# Active Surveillance and Prostate Cancer Screening

Stijn H. de Vries

ISBN: 978-90-8559-595-3

Cover: dormant, smoking and erupting volcanoes illustrating the prostate cancer spectrum.
Design: Michiel de Nijs
Layout and printing: Optima Grafische Communicatie, Rotterdam
Active Surveillance and Prostate Cancer Screening
S.H. de Vries
e-mail: jericholaan103@zonnet.nl

# Active Surveillance and Prostate Cancer Screening

## Actief afwachtend beleid en vroegopsporing van prostaatkanker

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
woensdag 2 december 2009 om 13:30 uur

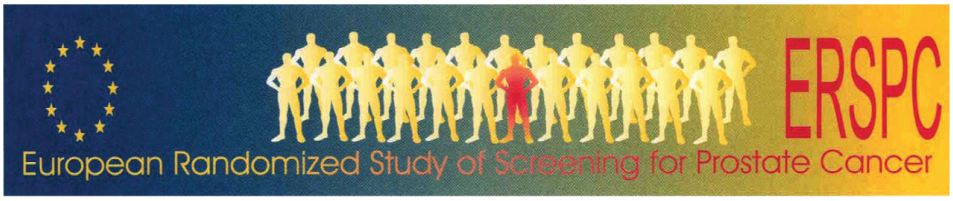
door
Stijn Hiëronymus de Vries

geboren te Paramaribo, Suriname

**PROMOTIE COMMISSIE**

| | |
|---|---|
| Promotoren: | Prof. dr. F.H. Schröder |
| | Prof. dr. C.H. Bangma |
| Overige leden: | Prof. dr. R.C.M. Pelger |
| | Prof. dr. J.W.W. Coebergh |
| | Dr. R.H.N. van Schaik |

The studies reported in this thesis were performed at the department of Urology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands as an integrated part of the European Randomized study of Screening for Prostate Cancer (ERSPC). The ERSPC is funded by grants from the European Union, the Dutch Cancer Society and ZonMW.



**CONTENTS**

# List of Abbreviations

| | |
|---|---|
| AS | active surveillance |
| DRE | digital rectal examination |
| DT | deferred treatment |
| EBRT | external beam radiation therapy |
| EM | expectant management |
| ERSPC | European Randomized Study of Screening for Prostate Cancer |
| PCa | prostate cancer |
| PSA | prostate specific antigen |
| BPSA | benign PSA |
| FPSA | free PSA |
| IPSA | inactive PSA |
| pPSA | precursor PSA |
| PSAD | PSA density |
| PSADT | PSA doubling time |
| PSAV | PSA velocity |
| RP | radical prostatectomy |
| TNM | tumour node metastasis classification system |
| TRUS | transrectal ultrasound |
| TURP | transurethral resection of the prostate |
| WW | watchful waiting |

# Part I:
# Introducing active surveillance

# Chapter 1

## Aim and Outline of the Thesis

**The aim of this thesis is to contribute to the evaluation of active surveillance as an option for selected men with adenocarcinoma of the prostate.**

Active surveillance (AS) entails an active observation policy for men with presumably curable prostate cancer (PCa) at diagnosis. The concept of AS is to avoid unnecessary treatment, with its inherent side effects and costs, while preserving the window of cure with active surveillance, in these males with PCa. Though it sounds and even feels contradictory to delay treatment in a PCa patient, the rationale of AS can be explained by several convincing arguments.

Firstly, PCa has a huge impact on health care systems in western societies. For example: 9,516 men were diagnosed with PCa in the Netherlands in the year 2006, a fifth of all cancers detected [1] and this number is estimated to increase to 12,032 in the year 2010 [2]. Likewise one in six males born in the USA today will be diagnosed with PCa some time during their life [3]. Secondly, prostate cancer screening, apart from other possible pitfalls, has to cope with overdiagnosis, i.e. detection of disease that never will cause symptoms and thus will not lead to death. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam, it is calculated that just over half the cancers detected will extremely unlikely give rise to symptomatic disease [4]. Even if only a subset of men with screen detected PCa can be managed on an AS policy this would drastically improve the quality of life in individual patients as they will have delayed or no side effects of the treatment. Moreover AS could also hugely reduce health care costs associated with treatment and recovery.

The key questions in active surveillance thus are:

- Which patients are suitable candidates for an AS policy?
- How can we select these men?
- How to monitor these men in order not to lose the window of cure?

This thesis does not answer all these questions, but it does represent the start of the development of an AS policy within the ERSPC, section Rotterdam. The data of this thesis are derived from the ERSPC study which was designed to answer the question whether screening has an effect on prostate cancer mortality [5]. This thesis, for all clarity, does not attempt to answer that question.

First of all background information on the prostate, PCa and PCa screening is essential to understand the window of opportunity for AS in selected prostate cancer patients. The introduction explains the effects of PSA driven screening on PCa epidemiology

like, stage migration, lead-time, and overdiagnosis as well as providing more detailed information about the different parameters used in the following chapters.

Chapter 3 is an overview of the different approaches to expectatively treat PCa and, summarizes the different selection and monitoring criteria used at the time, ending with a policy proposal for AS. It clearly illustrates the absence of universal nomenclature for AS at the time of writing. The term watchful waiting was used which is nowadays commonly replaced with AS. The goal of this chapter is to illustrate all aspects of the relative new approach of AS. It discusses the needs for proper identification of candidates, the development of monitoring techniques and trigger mechanisms for the management of PCa patients on AS and to stress the difference compared to expectative management modalities, which apply palliative treatment to patients when they develop symptoms.

To identify a subgroup of candidates suitable for AS, the outcomes of patients with clinically and screen detected prostate cancer are compared in chapter 4. The results show the differences in outcomes between both cohorts making patients with screen detected PCa, because they have more favourable characteristics at diagnosis and are unlikely to die of PCa within the first five years after the diagnosis, more apt candidates for an AS policy.

To further enhance selection of patients possibly fit for an AS policy the use of experimental blood tests was investigated. In chapter 5 PSA precursor forms are evaluated as a possible future tool to identify candidates for an AS policy with promising results.

The next chapter deals with a part of the monitoring puzzle. Chapter 6 depicts the natural course of PSA levels in ERSPC patients currently managed on an AS policy and its value as a monitoring tool to trigger deferred treatment is addressed.

# Chapter 2

## Introduction

## GOAL

The goal of this thesis is to contribute to the evaluation of active surveillance (AS) as a safe strategy in selected men with organ confined prostate cancer (PCa) at diagnosis. To investigate the feasibility of an AS policy the key questions in AS were addressed;

- Who are suitable candidates?
- How to select and monitor these men?
- When to treat these patients without compromising the chance of cure?

## SUMMARY

Active surveillance (AS) entails an active observation policy for men with localized prostate cancer. The concept of AS is to avoid unnecessary treatment, with its inherent side-effects and costs, while preserving the window of cure with deferred treatment. To explain the rationale of active surveillance in patients with a possible lethal disease several aspects will be highlighted:

- anatomy of the prostate and details of prostate specific antigen,
- epidemiology and natural history of prostate cancer (PCa),
- the relative slow natural progression of disease in most cases and,
- the differences between screen- and clinically detected PCa.

## THE PROSTATE

The prostate is vital for reproduction, not for life. The prostate is a male accessory reproductive exocrine gland and requires testicular function for its development, growth and role in reproduction. Its reproductive function is to expel a complex proteolytic secretion into the urethra during ejaculation. This ejaculate contains proteases (prostate specific antigen or PSA) the enzyme amylase, semenogelin, minerals (calcium and zinc), proteins of unknown function and is rich in acid phosphatase and citric acid. The enzymes liquify the semen after ejaculation while the phosphatases and salts modify the vaginal environment to enhance sperm mobility, survival and fertilisation chances.

## ANATOMY

A normal prostate gland is about the size of a chestnut, weighs 18 grams and measures 3 cm in length, 4 cm in width and 2 cm in depth [6]. The prostate is located distal from

the bladder around the proximal part of the urethra, and has a somewhat conical shape. Figure 1 [7].

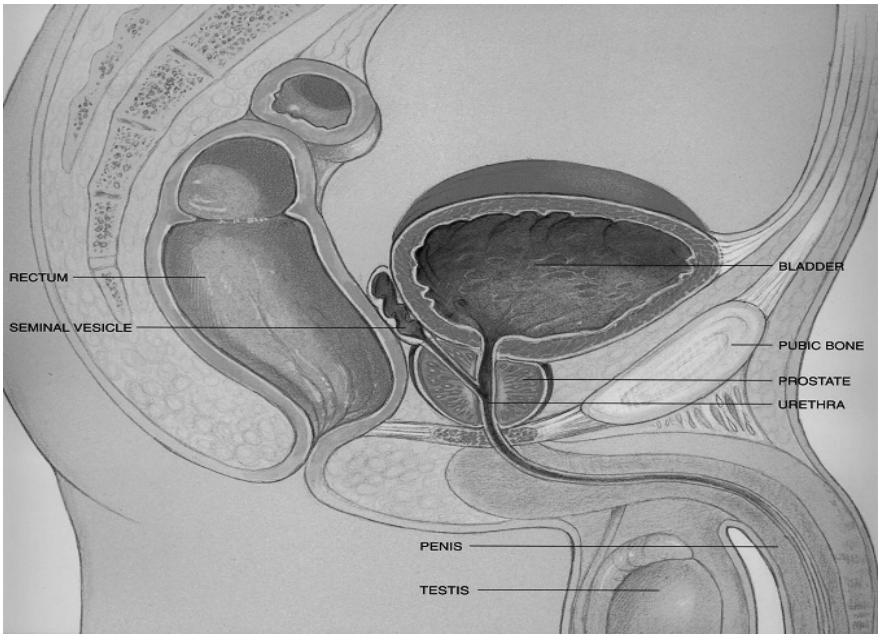



**Figure 1.** Anatomy of the prostate adapted from [7].

The base (basis prostatæ) is directed upward, and is anteriorly adjacent to the bladder neck and posteriorly to the seminal vesicles and the deferential ducts. The urethra penetrates the prostate closer to its anterior than its posterior border. The apex (apex prostatæ) is directed downward, and is continuous with the striated urethral sfincter. The urethra emerges again from a little above and in front of the apex. The posterior surface (facies posterior) is flattened from side to side and slightly convex from above downward, and lies about 4 cm. from the anus. The prostate is separated from the rectum by its sheath and some loose connective tissue. Near its upper border there is a depression through which the two ejaculatory ducts enter the prostate. The posterior surfaces sometimes presents a shallow median furrow, which imperfectly separates it into a right and a left lateral lobe. These two lobes form the main mass of the gland and are directly continuous with each other behind the urethra. The anterior surface (facies anterior) is placed about 2 cm. behind the pubic symphysis, from which it is separated by a plexus of veins and a quantity of loose fat. The lateral surfaces are prominent, and are covered by the anterior portions of the levatores ani muscles, which are separated from the gland by a plexus of veins, the lateral division of the dorsal vein complex. The cavernosal nerves run posterolateral to the prostate. The prostate is connected to the

pubic bone on either side by the puboprostatic ligaments, which together with the superior fascia of the urogenital diaphragm and the anterior portions of the levatores ani muscles hold the prostate it in its position.

The prostate gland has been divided into four zones by McNeal [8]. A transition zone, a central zone, a peripheral zone and the anterior fibromuscular stroma that separates the transition zone from the remaining glandular zones. Clinically the most interesting zones are the transitional and the peripheral zone. The transition zone commonly gives rise to benign prostatic hyperplasia and approximately 20% of the prostatic adenocarcinomas originate in this compartment. The peripheral zone is the preferential site of chronic prostatitis and the origin of around 80% of the prostatic adenocarcinomas [6].

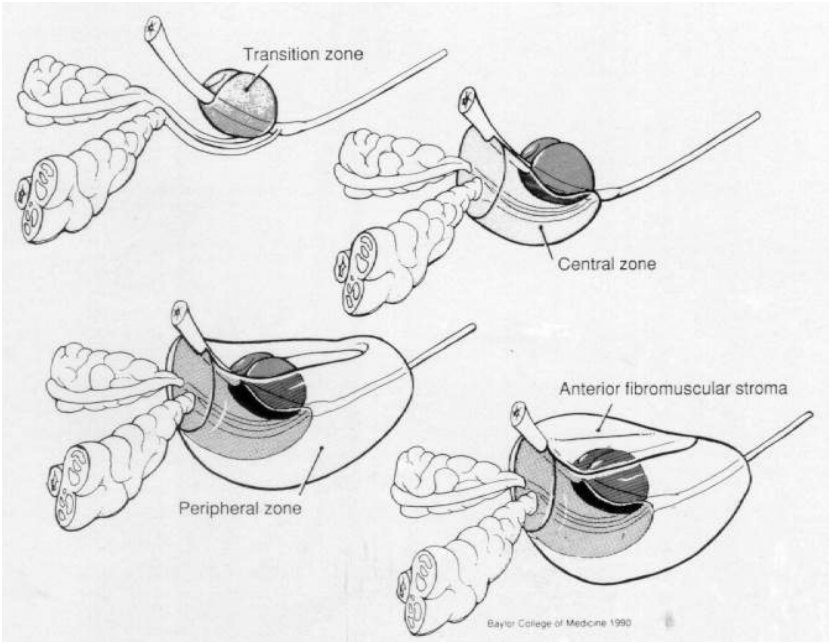



**Figure 2.** Zones of the prostate adapted from [6].

## PROSTATE SPECIFIC ANTIGEN (PSA)

PSA is a protease almost exclusively produced by the prostatic ductal and acinar epithelium. The function of PSA is to cleave semenogelin I and II in the seminal coagulum and thus to help with the liquefaction of the ejaculate [9]. Its widespread use in urological oncology is explained by improving prostate cancer detection rates when combined with the physical examination (digital rectal examination) [10]. However PSA is organ

specific and not cancer specific, meaning that an elevation of PSA can be caused by several prostatic diseases including prostate cancer [10-14].

The PSA molecule consists of 237 amino acids and weighs 33 kDalton. It was first purified and characterized in 1979 [15]. PSA belongs to the family of human tissue kallikrein proteases which digest high-molecular-weight proteins to release bioactive peptides. In total 15 tissue kallikrein genes have been identified [16]. PSA, also known as human kallikrein 3 (hK3) is formed in the secretory epithelial prostatic cells and secreted into the lumen in an inactive form containing a 7 amino acid precursor protein [17]. This precursor PSA (pPSA) is effectively removed extracellularly by hK2 and possibly by hK4 or trypsin and then secreted into the seminal plasma. In males with normal healthy prostates less than one per million PSA molecules enter the peripheral blood circulation [18]. Disruption of the basal membrane, i.e. in prostate cancer or, of the normal architecture (prostatitis or benign hyperplasia) of the prostate results in an excessive escape of PSA into the circulation [19, 20].

PSA is found in the peripheral blood circulation in two forms; a complexed and a non-complexed or free form. 70-90% of the PSA molecules entering the circulation will either bind to the protease inhibitor alpha-1 antichymotrypsine to form the PSA-ACT complex or form a stable complex with alpha2-macroglobulin [21, 22]. Complexes with other protease inhibitors as c protein inhibitor and alpha1-antitrypsin occur in minor amounts [23]. Complexed PSA is around 90 kDalton and thus too large to be cleared by glomerular filtration and most probably metabolized by the liver [24] with a half-life of 2.2 to 3.2 days [11, 25].

Free PSA (FPSA) constistute 10 to 30% of all the PSA in the circulation and does not form complexes with protease inhibitors due to internal cleavages which have rendered it catalytically inactive. FPSA has a biexponential clearing phase, with a rapid initial half-life rangin from 0.8 to 2.2 hours and a terminal phase ranging 16 to 33 hours and is thought to be cleared by the kidneys [26-29]. Clinically used immunoassays detect PSA-ACT and FPSA. The ratio of FPSA, thus the %FPSA in PSA might be used to increase both the sensitivity and specificity of PSA testing [30-33].

FPSA circulates in at least three different forms; precursor PSA, benign PSA and inactive PSA. Discussing all the PSA derivates is beyond the scope of this thesis however, in chapter 4 isoforms of FPSA are evaluated and the following section provides background information.

### Precursor PSA (pPSA)

The native precursor PSA is the PSA enzyme plus a 7-amino-acid pro-peptide leader. Theoretically seven forms of pPSA could be detectable if the precursor amino acids are removed one by one ([-7]pPSA, [-6]pPSA, [-5]pPSA etc). Thus far [-7]pPSA, [-5]pPSA, [-4] pPSA. [-2]pPSA, [-1]pPSA have been detected [34-36].

The [-7], [-5]pPSA and to a lesser extend [-4]pPSA are rapidly converted into mature active PSA by hK2 and trypsin in vitro [37-39]. The most stable pPSA form, [-2]pPSA, is not activated by hK2 or trypsin and appears to correlate more consistently with prostate cancer [40]. Typically, all the pPSA forms together constitute one third of the FPSA in cancer serum [41]. Precursor PSA forms have only been identified in plasma, never in the seminal plasma, suggesting that, in prostate cancer, the impairment of the architecture of the prostatic ductal system will result in an enrichment of pPSA forms and will force the pPSA forms into the serum [40]. In clinical studies, pPSA forms improved the clinical prostate cancer detection rate and have shown a correlation with aggressive cancers [42-44].

### Benign PSA (BPSA)

Another fraction of FPSA is BPSA. BPSA is a degraded form of PSA due to two internal cleavages and, as can be seen in figure 3, BPSA is associated with benign prostatic hyperplasia (BPH) tissue and prostatic volume and therefore called benign PSA [45-48]. This theory is based on the findings that men with an elevated PSA and a prostatic biopsy outcome negative for prostate cancer had significantly elevated BPSA levels, and that BPSA was predominantly found in the transition zone tisue [45, 49]. Though BPSA might not directly be associated with prostate cancer it could be useful to monitor patients on BPH related therapies. BPSA, in contrast to pPSA, is found in both seminal plasma and in blood [50].

### Inactive PSA (IPSA)

Inactive or IPSA is the third form of free PSA found in the circulation. IPSA is a group of intact, but enzymatically inactive PSA forms that does not form complexes with ACT most probably due to internal cleavage at Lys145-Lys146 [51]. Currently no assay can selectively detect the IPSA [52], and the clinical value of IPSA remains to be determined. However, indirect estimation of the IPSA level by subtracting the sum of the total BPSA and pPSA from the FPSA seems to have some relation with prostate cancer. Though results of studies evaluating the adjuvant clinical use of pPSA subforms are promising

the assays used are still in the research phase and the results should therefore be interpreted with caution [44].

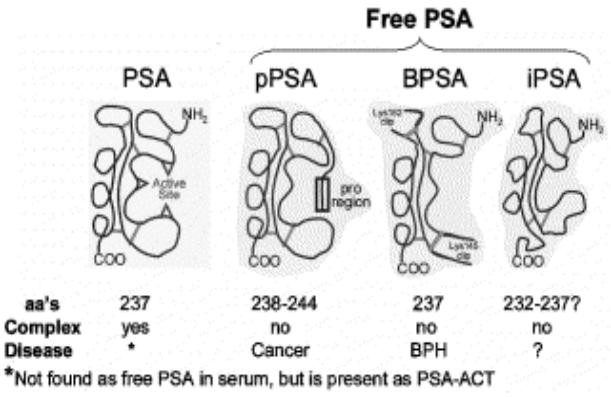



**Figure 3.** Molecular forms of PSA and FPSA, adapted from [51].
Legend: aa's amino acids.

## PROSTATE CANCER EPIDEMIOLOGY

Adenocarcinoma of the prostate, apart from basal cell carcinoma, is currently the most frequently diagnosed malignancy in males in Northern America and Western Europe including the Netherlands [3, 53]. For example 9,516 men were diagnosed with PCa in 2006 in the Netherlands, over a fifth of all cancers diagnosed [1]. This number is calculated to increase to 12,032 in the year 2010 [2]. In the United States, on January 1, 2005 there were approximately 2,106,499 men alive who had a history of PCa, and it is estimated that 186,320 men will be diagnosed with and 28,660 men will die of PCa in 2008 [3].

Though the exact aetiology of adenocarcinoma of the prostate remains unknown [54-56], the incidence of PCa rises with age. In one study 34% of males in their forties dying from competing causes had microscopic evidence of PCa [57]. The prevalence of PCa in autopsy studies rises to 80% in males aged 80 years or older [58]. Environmental and ethnicity factors most likely also play a role as the highest incidence of PCa is found in the United States in African Americans and the lowest incidence is found in Asia [59]. Though males with a brother or father with PCa have a substantial elevated risk of developing PCa, heriditary PCa does not seem to have a more aggressive biology [60]. Recent investigations suggest a relation of PCa with inflammation as this is thought to incite carciogenesis by causing cell and genome damage, promoting cellular turn over

and creating a tissue microenvironment that can enhance cell replication, angiogenesis and tissue repair [61].

The impact of PCa on males and the health care system is reflected by the observation that one in every six males born in the USA today will be diagnosed with PCa some time during their life [3]. The lifetime risk of dying from prostate cancer in the USA is currently 2.8% [62]. In the period before PSA driven screening the lifetime risk of developing PCa was around 8% [63], while the lifetime risk of dying of prostate cancer was 3.6% [64]. Thus the risk of being diagnosed with prostate cancer increased with time while the percentage of males succumbing to the disease slightly diminished. Though this could partially be due do new and improved treatment strategies and modalities it is most probably the result of PSA driven screening [65-70]. The profound effects of PSA driven screening on PCa epidemiology will be addressed later.

## PROSTATE CANCER DIAGNOSIS

The diagnosis of PCa requires histological evaluation of prostatic tissue. In the clinical setting, an arbitrarily defined serum PSA threshold level, or suspicious digital rectal examination prompts a prostatic biopsy. The biopsy procedure is performed transrectally and guided by ultrasound. However, PCa can also be found in tissue chips from a trans-urethral resection of the prostate or as an incidentaloma in a cystoprostatectomy specimen in patients with bladder cancer.

The Gleason scoring system for PCa is currently the gold standard [71], and has replaced other systems such as the MD Anderson grading system [72]. The Gleason scoring system is based on architectural acinar and glandular patterns of prostatic tissue and cytological features play no role. Figure 4 [71]. A Gleason pattern can range from 1 (highly differentiated) to 5 (poorly differentiated). The Gleason sum is the sum of the most prevalent pattern observed and the second most prevalent pattern. When only one pattern is present, the pattern is doubled. The Gleason score can thus range from 2 (1+1) to 10 (5+5). A higher Gleason score represents more aggressive PCa and a worse prognosis [73-77]. In a Gleason sum important information may be lost as it is unclear for a sum of seven whether the most prevalent pattern was 4 or 3. This information is clinically important since patients with a Gleason sum of 3+4 have a better prognosis than those with a Gleason sum of 4+3 [78]. In the ERSPC, section Rotterdam, a Gleason pattern of 1 or 2 is no longer assigned on a prostatic biopsy core due to the relatively limited amount of tissue available for pathological examination [79, 80]. The minimal

Gleason sum in the ERSPC is thus 3+3 = 6. All data in this thesis are derived from the ERSPC and scored following protocol [79].

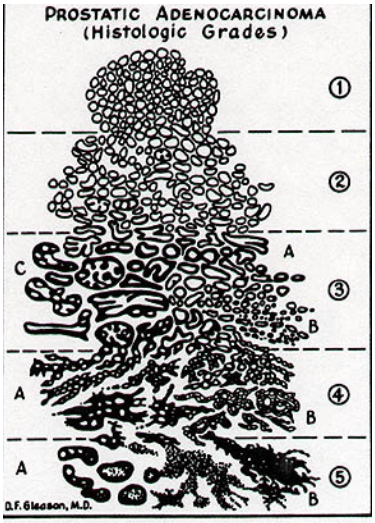



**Figure 4.** Gleason grading system. Adapted from [71].

## CLINICAL STAGING OF PCA

Apart from the histological diagnosis, PCa is also clinically staged. In the ERSPC, the clinical stage is based on the 1992 tumour node metastasis (TNM) classification for PCa [81]. The TNM classification is determined by the digital rectal examination (DRE), the transrectal ultrasound (TRUS) and radiographic studies when indicated. Since 1992 a new classification was introduced for patients with non palpable, PSA driven, detected PCa, stage T1C, see table 1 [81].

During a DRE the physician palpates the prostate with the index finger which is inserted in the rectum. Assessment of the prostate is thus limited to its dorsal side and the origin of the vesiculae seminales.

With a TRUS of the prostate a two dimensional image of the whole prostate can be created. PCa cannot always be visualized [82] and it is under discussion whether it should be used in staging screen detected PCa [83, 84]. In the ERSPC hypo-echogenic lesions in the peripheral zone of the prostate, if visible in both the sagital as the longitudinal plane, are assigned the according clinical tumour stage.

**Table 1.** 1992 Tumour node classification system for prostate cancer [81].

| | | |
|---|---|---|
| T0 | | No pathological evidence of cancer |
| T1 | | Clinically invisible/impalpable tumour |
| | T1a | incidentally <5% of tissue at transurethral contains cancer |
| | T1b | Incidentally >5% of tissue at transurethral contains cancer |
| | T1c | Cancer identified by needle biopsy due to elevated PSA |
| T2 | | Confined within the prostate |
| | T2a | Cancer in half of the lobe or less |
| | T2b | Cancer in more than one half of one lobe but not both lobes |
| | T2c | Cancer involves both lobes |
| T3 | | Extraprostate extension |
| | T3a | Extension outside of the prostate on one side |
| | T3b | Extension outside of the prostate on both sides |
| | T3c | Extension into one or both seminal vesicles |
| T4 | | Invasion of other organs |
| | T4a | Invasion of bladder neck and/or rectum |
| | T4b | Invades of levator muscles and/or fixation to pelvic wall |
| N | | Regional lymph nodes |
| | Nx | Lymph node invasion cannot be assessed |
| | N0 | No lymph node metastasis |
| | N1 | Metastasis in single lymph node <2 cm in greatest dimension |
| | N2 | Metastasis in single lymph node >2cm but <5 cm |
| | N3 | Metastasis in regional lymph node, either multiple or >5 cm |
| M | | Systemic spread |
| | Mx | Metastasis cannot be assessed |
| | M0 | No distant metastasis |
| | M1 | Distant Metastasis<br>M1a non-regional lymphnodes<br>M1b bone metastasis<br>M1c metastasis to other site. |

## NATURAL HISTORY OF CLINICALLY DETECTED PCA

The diagnosis of PCa will usually trigger both patients and physicians to find a way to eliminate all cancerous tissue. However PCa, unlike most other malignancies is a slowly

progressive disease in most cases. The relatively protracted natural course of PCa can be estimated by using prognostic tables such as those created by Albertsen et al. [85]. Figure 5 [85] shows the cumulative disease specific mortality (black band), mortality due to other causes (grey middle band) and the overall survival (white lower band) up to 20 years after diagnosis of 767 males stratified for age and Gleason Score at diagnosis.

All men in this study had clinically localized disease and received palliative treatment when developing symptoms. The males were diagnosed between 1971 and 1984 and were aged 55 to 74 years at diagnosis. Median follow-up is 24 years. Diagnosis was made without the use of PSA testing and was mainly based on transurethral resection material (60%) and needle biopsy findings (26%). When looking at the patients with well-differentiated PCa, indicated by a Gleason score of two to five, two to sixteen percent died of PCa after 20 years, while 55 to 95% did die of other causes. In the patients with a moderate to poorly differentiated PCa, i.e. a Gleason score of seven and higher, the percentage of males dying from PCa increases, though in the older age groups 40-60% will die of other causes. Another study monitored 223 patients with clinically diagnosed organ confined PCa without evidence of disseminated disease on an expectative policy with palliative hormonal therapy [86]. The mean follow-up of this study was 21 years. Of the 148 patients with grade 1 disease, 14 (9%) died of PCa while 118 (80%) died of other causes. In comparison: all nine patients with grade 3 died and five (56%) of them from PCa. Grade 1 PCa can be compared to a Gleason score of 3+3 or less, while grade 3 PCa measures up to a Gleason sore of 4+4 or higher. Moreover, 80% of the patients in this study had a repeat biopsy resulting in a grade change in only 31 patients (17%) resulting in a less favourable differentiation for 24 males. None of the patients diagnosed with clinically organ confined disease showed dedifferentiation over time. Grade did only change for patients diagnosed by TURP (in 73%) or after a prostatectomy (92%). Both these reports indicate that patients with favourable disease are unlikely to die of PCa and that dedifferentiation of PCa is rare. Moreover, even clinically diagnosed patients with poorly differentiated PCa can die of competing causes especially when they are diagnosed after 70 years of age.

## PROSTATE CANCER SCREENING AND THE ERSPC, SECTION ROTTERDAM

The goal of the ERSPC is to show or exclude a 20% decrease in PCa mortality based on PSA screening of asymptomatic individuals [5]. Ideally, advancing the diagnosis by screening detects PCa at an earlier stage and combined with timely treatment this offers a better hope of cure [87].

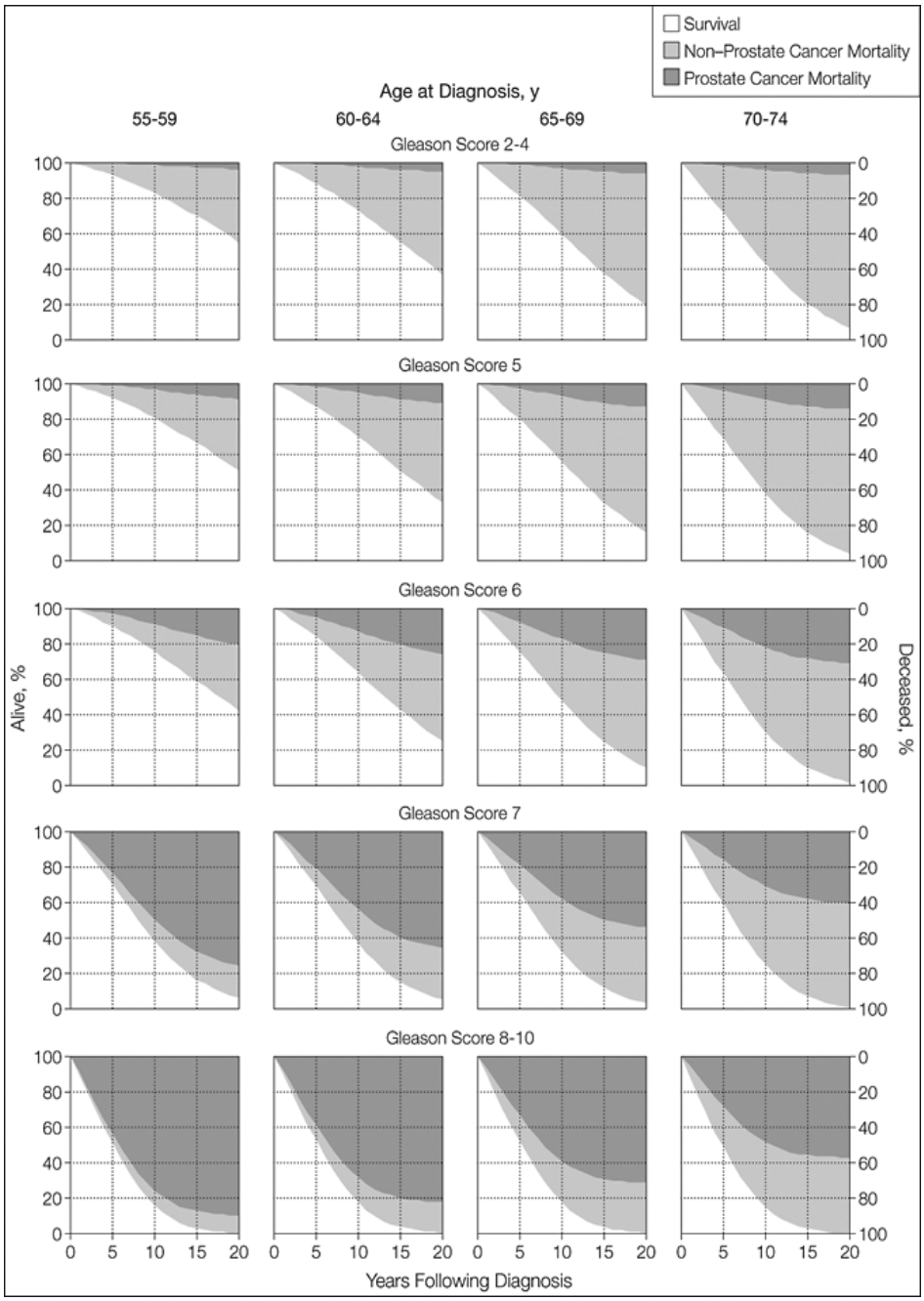



**Figure 5** shows the cumulative disease specific mortality (black band), mortality due to other causes (grey middle band) and the overall survival (white lower band) up to 20 years after diagnosis of 767 males stratified for age and Gleason Score at diagnosis. Adapted from [85].

The ERSPC is a multi-centre randomized controlled trial with 267,994 men participating in eight different European countries. Pilot studies started in 1993. Of the 42,376 men aged 55-74 years, from the ERSPC, section Rotterdam 21,166 participants were allocated to the intervention arm. After initial protocol changes these men are, since 1997 invited for a PSA test every four years. A PSA level of 3.0 ng/mL or higher prompts a TRUS and TRUS-guided lateral sextant biopsy of the prostate. Detailed descriptions of the screenprotocol and results are provided in the following chapters of this thesis and in a supplement of the British Journal of Urology International [88].

Though long-term natural history data of patients diagnosed in the PSA era are not yet mature, the introduction of PSA as a test for PCa screening has drastically changed the epidemiology of prostate cancer [65, 67, 89, 90]. Recent studies provide growing evidence for a PSA induced risk migration towards more favourable PCa characteristics at diagnosis [67-69, 91]. A favourable shift of prognostic factors is also documented within the ERSPC, section Rotterdam [92]. This risk factor migration can be explained by effects of PSA driven PCa screening, namely lead-time and length-time.

Lead-time is the time gained by forwarding the diagnosis with a screen test. Figure 6 [93]. If forwarding the diagnosis of PCa does not lead to an improvement of survival, a lead-time bias is generated. In all screen studies comparisons with unscreened cohorts should be adjusted for lead-time.

Lenght-time bias reflects the effect that slow growing cancers are more likely to be detected in a screening program, as they remain longer in the preclinical detectable phase than fast growing tumours. Figure 7. A relative overrepresentation of these slow growing and probably favourable prognostic PCa positively biases the survival results, especially if fast growing aggressive PCa are not detected by the screening tools or in the screen interval of PCa screening studies.

Preliminary estimates for lead-time in both hypothetical cohorts and prospective randomized screening studies for the detection of PCa range from 5-12 years, depending on the definition used [4, 94-98]. Lead-time is presumably shorter for aggressive cancers and older males while it is longer for less aggresssive cancers and younger patients. The mean lead-time for the ERSPC, Rotterdam, using several 4 year interval screen rounds in males aged 55 to 75 years old is approximately 10.3 years [4]. Thus the diagnosis PCa is made about 10 years earlier with PSA driven screening in the ERSPC section Rotterdam when compared to a clinically detectable disease.

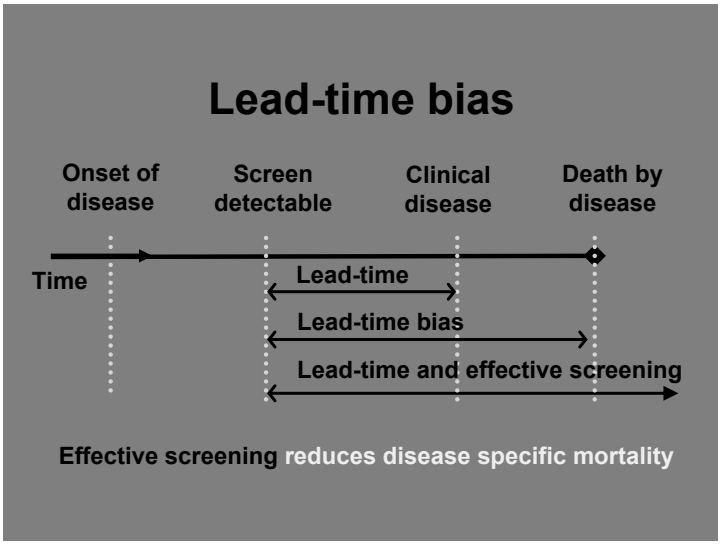



**Figure 6.** Time is depicted as the dark line, the dotted lines represent the onset of the disease, the time at which the disease is screen or clinically detectable and time of disease specific mortality. Lead-time is the time gained by forwarding the diagnosis with a screen test. Screening is effective if subsequent treatment postpones or even eliminates disease specific mortality. Adapted from [93].

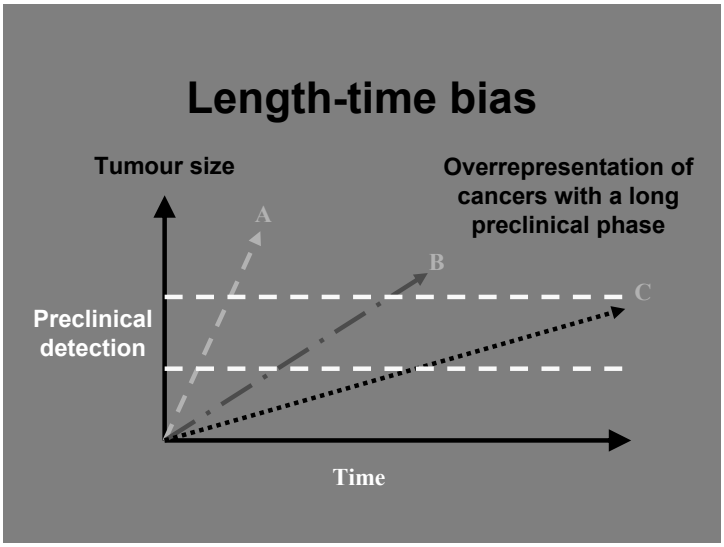



**Figure 7.** The y axis depicts tumor size, the x axis time. Smaller tumors can be detected earlier, at a preclinical stage, with screening. Fast growing tumors (A) are relatively short and slowly growing tumors (C) relatively long in the preclinical detection phase. At any point in time there will thus be a larger proportion of slowly growing tumors compared to fast growing tumors. The overrepresentation of these slowly progressive cancers in a screen cohort can cause a length-time bias. Adapted from [93].

### Overdiagnosis

While the goal of screening for cancer is to detect the disease at an early stage to improve survival, it will also detect asymptomatic PCa that would never have been detected clinically if PSA had not been used as a screening test [99]. These cancers could be categorized as overdetected or clinically insignificant. The definition of overdetection used in most studies is the proportion of cancers that would not have been diagnosed during lifetime, in the absence of screening. Calculations of overdetection range from 24 to 93%, obviously increasing with age and depending of the definition used [4, 95, 97, 100]. The calculated overdetection rate for multiple four year screen intervals with the ERPSC algorithm in Rotterdam is estimated at 54% [4]. This means that more than half of the patients diagnosed with PCa would have never developed symptoms of PCa if the disease had not been detected by PSA screening. Another study based on population based PCa screening, as indicated by medical claims and disease incidence reported by cancer registries, showed a calculated age adjusted lead-time of 4.5 years with an overdetection rate of 34% [101]. The lower lead-time and overdetection rate can be explained by the different study populations, i.e. a screen versus a clinical cohort, but also by the fact that in the latter study a PSA cut-off of 4.0 ng/mL was used compared to the ERSPC cut-off of 3.0 ng/mL.

Men with overdiagnosed PCa are ideal candidates for an active surveillance strategy as PCa treatment with curative intent is not without morbidity and even mortality. Or more explicitly, the only treatment effects overdiagnosed patients can experience are side-effects, as overtreatment per definition has a 100% cure rate. Moreover, treatment of these clinically insignificant cancers will favourably bias the disease specific survival after radical treatment (length-time bias).

## PROSTATE CANCER TREATMENT WITH CURATIVE INTENT

Males diagnosed with organ confined PCa (clinical TNM stage ≤ T2) have three curative treatment options:

- surgical removal (laparoscopic or open) of the prostate,
- destruction of all PCa tissue by radiation therapy, or
- an active surveillance policy with either option as deferred treatment.

Most patients and the majority of the physicians will instinctively prefer option 1 or 2; immediate eradication of all cancerous tissue. This line of thought is further fuelled by the current impressive ten year disease specific survival rates of up to 99% for organ confined prostate cancer immediately treated with curative intent [91, 102, 103]. Long-

term survival rates of patients with well differentiated organ confined disease treated in the pre PSA era (ranging from 90 to 94%) show no clear survival benefit for patients treated with either treatment modality with curative intent or with delayed palliative treatment [104-107].



Up to day, only one study prospectively compared open radical prostatectomy (RP) and expective management. In 2002, prospective randomised data of 695 clinically detected patients men showed that the disease specific survival was statistically significantly better for the men treated with RP compared to patients with expective therapy and delayed endocrine therapy. However seventeen patients needed to be treated to save one male from PCa death, at a median follow-up of 6.2 years. The overall survival did not differ between groups [108]. This report was recently updated and at a median follow-up of almost 11 years 47 patients in the RP arm (13.5%) and 68 in the expectative therapy arm (19.5%) died of PCa. The difference was again statistically significant and the absolute risk reduction of 5.4% shows that 19 patients need to be treated to prevent one prostate cancer death [109]. In a subgroup analysis it was shown that overall mortality, PCa mortality and the risk of developing metastasized disease was only statistically significantly reduced in patients younger than 65 years of age at diagnosis and not present the older men. However, these data should not easily be extrapolated to the current screen era with its risk migration towards more favourable PCa characteristics at diagnosis, and associated lead- and length-time [109, 110].

For example, in the study of Holmberg et al. [108], 12% of the men had stage T1C disease, 60% had a Gleason sum of 6 or lower, and 47% had a PSA level of 10 ng/mL or higher. In the first round of the ERSPC Rotterdam 35% of men had T1C disease which increased to 60% in the second screen [92]. Likewise the percentage of men with a biopsy Gleason score of 3+3 or lower or PSA level of 10 ng/mL or lower increased from 62% to 78% and respectively 68% to 93%. Still, apart from lead- and length-time differences, a third point can be made: a conservative management with delayed hormonal therapy is not the same as active surveillance as used in this thesis [111].

Surgical removal of the prostate, a radical prostatectomy (RP), is not without morbidity. Due to the anatomical position of the prostate deep in the pelvis, its close relations with the bladder, blood vessels, nerve bundles, external sphincter and the need to reconnect the bladderneck to the urethra, side-effects of this procedure are not uncommon. Most reported long-term side-effects after radical surgery are incontinence and erectile dysfunction [112-114], though uncommon peri-operative mortality does occur in around 0.2% [115]. Comparing laparoscopic and open radical prostatectomy at a single institution it was shown that 35% in the laparoscopic RP group versus 15% of the patients in the open RP group still had urinary incontinence after 2 years. Continence was defined

by not experiencing leakage of urine or the absence of using protective pads, by self administered patient questionaires [116].

Likewise, external beam radiotherapy, or radioactive prostatic seed implants (brachytherapy) will not only affect the tumour but also damage healthy surrounding tissue like the bowel, the bladder and the nerve bundles resulting in corresponding side-effects. Even mortality, though uncommon, occurs in 0.3% of patients within 30 days after radiation therapy [117].

The five year results of the prostate cancer outcomes study show that 14 to 16% of patients were incontinent after RP compared to 4% after external beam radiation therapy (EBRT) [118]. Likewise, 79.3% of the patients had erectile dysfunction after a RP compared to 63.5% of the EBRT group, but patients with EBRT had more bowel complaints than patients treated with a RP. This report did not compare side-effects with patients who did not receive treatment. Steineck et al. [119] looked at the quality of life of patients with organ confined disease randomized between RP and deferred palliative treatment. They found that 49% of the patients after a RP had urinary leakage after four years compared to 21% for patients with deferred palliative treatment. The figures for erectile dysfunction were 80% for the RP group versus 45%. The large variation of these numbers between the reports can be explained by the different definitions used but are useful to illustrate that curative treatment for prostate cancer can have serious long-term side-effects.

Some patients are clearly willing to cope with these side-effects or reduced quality of life especially if the treatment prolongs life. However, currently no data of completed randomized clinical trials, in the PSA era, comparing treatment modalities are present to show a survival benefit of any strategy in patients with well differentiated disease, but trials have been initiated and are starting to compare different treatments for localized prostate cancer which include screen detected PCa cases [110, 120, 121]. More detailed information is provided in the general discussion.

## ACTIVE SURVEILLANCE

Active surveillance entails a pro-active observation policy for men with localized prostate cancer, while reserving the possibility of deferred curative treatment. The rationale of AS is to avoid unnecessary treatment, with its inherent side-effects and costs in patients with PCa, who are not likely to progress to clinical disease during their lifetime, while offering these selected patients a possible cure at a later time.

AS thus clearly differs from regimens that provide delayed palliative treatment in previously untreated males. These regimens will be called expectant management (EM), because with palliative treatment there is no intention to cure. At the start of this thesis no consensus had yet been reached for the nomenclature for both types of conservative management in the literature and in the original publications watchful waiting was used [108, 122-125]. However, nowadays active surveillance has replaced the term watchful waiting [126].

Still a number of open questions result:
1) Who are suitable candidates for an active surveillance policy?
2) How can they be selected?
3) How to monitor these men in order not to lose the window of cure?
4) When should deferred treatment with curative intent take place?

### Selection of patients

Because AS offers patients deferred treatment with curative intent, males with slowly progressive, small volume and well differentiated organ confined disease at diagnosis are the best candidates [127]. At present time a large portion of these males will have been (over)diagnosed with PCa due to screening. Chapter 3 gives an overview of the conservative policies in the literature including AS and discusses selection and monitoring criteria. In the following section follows a short introduction of the different parameters used.

### Follow-up of patients

After the identification of minimal PCa deferred treatment only is a viable option if tumour dynamics can be monitored. PCa is by definition a progressive disease and progression can arise on three levels, biochemically, histologically and clinically.

### Biochemical progression

With surgery the whole prostate gland and the vesiculae seminales are removed. Therefore no production of PSA should be present and PSA should not be detectable in serum. When PSA levels become detectable after surgery there is either recurrence of disease, metastasized disease or the resection was incomplete. The most widely used definition of biochemical progression of PCa after radical surgery is a confirmed measurable PSA level [12, 13]. The definition used for biochemical progression of disease in the thesis are: three consecutive rising PSA levels after radiotherapy according to the recommenda-

tions of the American Society for Therapeutic Radiology and Oncology (ASTRO) [13]. No definitions are currently available for patients treated with an AS regimen, however PSA kinetics over time might provide useful information. Based on the assumption that PSA is correlated with PCa volume [128], and that prostate cancer cells continue to produce PSA which is shed into the bloodstream due to disruption of the basal membrane [19, 20], sequential PSA measurements over time could reflect tumour growth. It has been stated that one Ml of benign hyperplastic prostatic epithelium produces 0.3 ng PSA while the same amount of PCa tissue generates 3.5 ng PSA [11].

PSA velocity (PSAV) is the absolute rise of the serum PSA level in ng/mL per year [129]. For example a PSA level of 4 ng/mL at diagnosis rising to 4.2 and 4.3 ng/mL after respectively three and six months gives an absolute rise of 0.3 ng/mL in six months and a PSAV of 0.6 ng/mL/yr.

PSA doubling time (PSADT) is the time in years needed to double the original PSA level [128]. The use of PSADT is based on the assumption that PSA levels rise linearly in males without PCa, whereas these levels will rise exponentially, in line with cancerous growth, in PCa patients. To calculate PSADT the 2log(PSA) levels (2log(PSA) = 10log(PSA)/log(2)) are plotted against time since diagnosis. The PSADT is the reciprocal coefficient of the linear regression line through these points. The 2log(PSA) is used to minimize differences in PSA levels at diagnosis. Ideally at least three PSA values taken at a minimal three month interval are used. A PSADT of 10 years or greater is assumed to reflect indolent PCa whereas as PSADT of two years or shorter probably represents aggressive fast growing PCa.

Figure 8 shows an example of a patient with a rising PSA from 2 ng/mL to 4, 8 and 16 ng/mL in three years time. This corresponds to a PSAV of (16-2)/3 = 4.6 ng/mL/year. Likewise the PSADT is 1 as the coefficient of the line through the 2log(PSA) values is one. If the PSA would rise in from 2 to 16 ng/mL in one year the PSADT would ¼ yr or 3 months.

### Histological progression

The only way to monitor histological progression is to perform repeat prostatic biopsies or a (radical) prostatectomy. Histological progression can occur on two levels, namely, the tumour load increases due to growth, i.e. more biopsy tissue with PCa or, the tumour dedifferentiates into a higher Gleason pattern, i.e. from 3 to pattern 4 or 5.

Pitfalls in interpreting biopsy data can occur on two levels [130]. Firstly, prostatic biopsies are a sample of the whole prostate and thus sample errors can occur. As PCa is

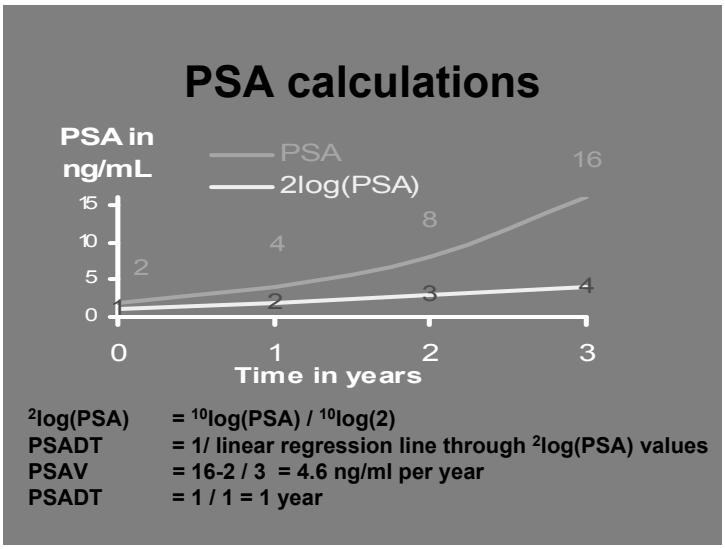



**Figure 8.** PSA calculations.

a multifocal disease it can happen that the most predominant Gleason pattern is not represented in the biopsied cores, or that the amount of PCa is too limited to clearly discriminate the two most prevalent patterns, especially in larger prostates. This is called reverse sampling. In a sample error an entire focus of PCa is missed. The risk of error increases with the size of the prostate as the chance of missing a focus rises. Currently the number of biopsies that should be taken is subject to discussion. Multiple groups state that PCa detection rates increase with the number of biopsies taken, ranging from 6 to up to 32 cores per session [131-133]. A recent review however, showed that with 12 cores harvested there is balance in the cancer detection rate and adverse events [132]. On the other hand one prospective randomized study showed no statistical significant difference in cancer detection rates comparing a lateral guided sextant biopsy and a regimen where twelve lateral biopsies were taken [134]. In the ERSPC a lateral directed sextant biopsy procedure is used, added with an extra lesion directed biopsy when a hypoechoic lesion is visible in both the sagital and the longitudinal plane at TRUS. The cancer detection rate with the lateral sextant biopsy is 85% [135]. In the first round of the ERSPC, section Rotterdam, 436 (23.7%) men having a biopsy, had a hypoechogenic lesion and an additional biopsy. In these men, 230 cancers were detected (52.8%), but only in 3.5% (eight of 230) it was solely this lesion directed core that showed malignancy [136]. Though the prostate cancer detection rate from the biopsy cores taken from the suspect lesion in the ERSPC section Rotterdam are low [136], an analysis of men undergoing a biopsy procedure at the second screen visit and a benign biopsy session 4 years before revealed no indication to change the biopsy protocol in the Rotterdam section [137].

Secondly, interpretations of pathologist can differ which is called inter-observer variability [138]. This variability is limited in the ERSPC, section Rotterdam, as all cancers are reviewed by one uro-pathologist (ThvdK) and according to a manual with guidelines on assigning Gleason Scores to prostatic biopsies [79].

In a clinical setting, Gleason grade progression in 241 patients with stage T1C PCa at diagnosis was uncommon [139]. All patients received annual repeat biopsies and grade progression occurred in 18.7 %. In 24 out of 45 males (53.3%) grade progression could be explained due to a sample error as degrading occurred within two years of diagnosis.

### Clinical progression

Clinical progression can be local or caused by metastatic lesions. Progression of local clinical stage can be evaluated by a physical exam or, the DRE. For example, a previously impalpable disease transforms into a palpable lesion. This lesion, however, might also be the result of a previously performed biopsy procedure.

If the PCa in its continuous expansion impairs voiding, by compressing or growing into the prostatic part of the urethra, some patients might need a transurethral resection of the prostate (TURP). Likewise it can grow into the urinary bladder, the pelvic floor, the external anal sphincter and less frequently into the rectum all of which can cause local symptoms.

Untreated aggressive prostate cancer will metastasize, firstly to the regional lymph nodes and from the non regional lymph nodes to preferably the bone, though visceral metastasis can occaisonally occur. Pain at preferential sites as the spinal column, the pelvis or ribs can be caused by an osteoblastic metastatic PCa lesion and can be visualized with radiographic studies as CT-scan, nucleotide bone scan or X-ray studies.

## SUMMARY

Active surveillance (AS) entails an active observation policy for men with localized prostate cancer. The concept of AS is to avoid unnecessary treatment, with its inherent side-effects and costs, while preserving the window of cure with active monitoring. Patients with screen detected PCa seem to be the most apt candidates due to the generated lead- and lenght-time associated with PCa screening. PSA kinetics as PSA velocity and PSA doubling time might be useful in monitoring patients on an AS policy.

# Chapter 3

## Watchful waiting in prostate cancer: review and policy proposals

F.H. Schröder and S.H. de Vries and C.H. Bangma

*B.J.U. International 2003, vol 92, 851-859*

## INTRODUCTION

Prostate cancer used to be diagnosed in men aged ≈ 70 years; with the advent of PSA-based early diagnostic regimens the lead-time (the period between screen detection and presumed clinical diagnosis) is increased and the age at diagnosis declines to ≈ 60 years. Because men are relatively elderly at the time of diagnosis there is an obvious chance of intercurrent death, which was ≈ 2:1 in the past. Table 1 shows the incidence and mortality estimates, and the calculated ratio of the age-standardized rates in Western Europe, North America and worldwide [140]. In all geographical areas referred to, the ratio between incidence and mortality has increased over time. However, this change is much more drastic in North America, where screening for prostate cancer is highly prevalent. Here, based on statistics for 2000, one in almost six men diagnosed with prostate cancer was likely to die from the disease.



**Table 1:** Incidence and mortality estimates of prostate cancer in 2000
Adapted from [140].

| Region | Cases (N) | ASR* | Deaths (N) | ASR* | Ratio ASR |
|---|---|---|---|---|---|
| Europe, West | 84,856 | 54.9 | 30,777 | 19.3 | 2.85 |
| North America | 211,950 | 102.2 | 39,919 | 17.8 | 5.74 |
| World | 542,990 | 21.2 | 204,313 | 7.9 | 2.68 |

Legend
ASR, age standardized range.

How do these epidemiological data translate to the clinical situation? Can those patients who are unlikely to die from their disease be identified with reasonable certainty? Is it possible to avoid unnecessary treatment safely and how can that be achieved? The present review attempts to give answers to these questions.

## NATURAL HISTORY AND A REVIEW OF RECENT DATA

Almost all available data relating to the natural history of prostate cancer are based on clinically detected cases. Natural history data on screen detected cases of prostate cancer are at present unavailable but will be created as a result of the large ongoing screening studies worldwide. A more comprehensive review is given by Klotz et al. [125]. Diagnosis in the cited series was usually by biopsy and in some cases by TURP. As a result of this, focal and incidental prostate cancer derived from the transition zone of the prostate is included in an unknown proportion. Because of the resulting uncertainties in assigning clinical stage, most studies have given preference to the use of histologi-

cal and cytological grade as the most important prognostic variable for stratification. Table 2 summarizes some of the results [75, 104, 106]. Data on overall survival are not age-corrected and therefore reflect to a large part the intercurrent mortality. Data on cancer-specific survival and mortality may be flawed by the uncertainties of the clinical determination of death from prostate cancer. However, the data are informative. There is a steep decline in the 5-, 10- and 15- year cancer-specific survival with increasing grade and, in [75], a steep increase in cancer-specific mortality with increasing Gleason scores. It is important to realise that most cases diagnosed with present diagnostic techniques fall into the moderately differentiated group (grade 2, Gleason 6). Cancer-specific 10-15-year mortality of moderately differentiated cases in the data cited in table 2 is 18-30%. Obviously, the favourable group of prostate cancer which may not require immediate treatment must primarily be found within the groups of men diagnosed with grade 1 and 2 or Gleason 4-6 cancers. However, biopsy grade alone does not discriminate sufficiently. In using biopsy-based grading the lack of correlation between biopsy grade and the true histological grade determined on radical prostatectomy (RP) specimens must be considered. Narain et al. [141] found that a biopsy Gleason score of < 7 identified the same grading only in 54.8% of cases; 40.9% and 4,3% were found to have Gleason 7 or Gleason >7 tumours in their RP specimens. Kaplan Meier curves constructed according to Gleason grade < 7 in biopsy and RP specimens showed a small but statistically significantly difference in disease free survival against the biopsy grade. Despite of these limitations the cited natural history data show that there are subgroups of patients who are not at risk of dying from prostate cancer even within 15 years. The identification of cancers which can be treated by watchful waiting (WW) with acceptable safety, the pattern and duration of follow-up, and the trigger points for treatment will be crucial elements for developing policies aiming at delaying or completely avoiding aggressive treatment.

## A ' WINDOW FOR CURE'

With the application of early detection measures such as PSA-driven screening for prostate cancer the diagnosis is advanced in time, i.e. the lead-time is increased. The lead-time is influenced by multiple factors, e.g. the sensitivity of screening tests, the speed of tumour development and age. The ongoing randomized screening studies worldwide lend themselves to the calculation of lead-time which, in this context can be defined as the elapsed period of time after which the yield of both the number and variety of prostate cancers in the subsequent round of screening is equal to that in the first round of screening. Auvinen et al. [94] calculated a mean lead-time of 5-7 years, which corresponds to a preclinical detectable phase of 10-14 years assuming that the

**Table 2:** Survival and cancer specific survival of conservatively managed prostate cancer by grade (from selected references)

| | | Survival, overall/cause specific, % (range) at | | |
|---|---|---|---|---|
| Reference | N | 5 years | 10 years | 15 years |
| [104]* Grade | | | | |
| 1 | 9,804 | -/- | 54 (52-56)/ 93 (91-94) | -/- |
| 2 | 6,198 | -/- | 38 (36-41)/ 77 (74-80) | -/- |
| 3 | 2,236 | 45 (41-50)/ 69 (56-78)**/ 63 (44-77)*** | 17 (14-20)/ 45 (40-51) | -/- |
| [75] Gleason score | | | | |
| 2-4 | 138 | -/- | -/- | -/4-7**** |
| 5 | 118 | -/- | -/- | -/6-11 |
| 6 | 294 | -/- | -/- | -/18-30 |
| 7 | 137 | -/- | -/- | -/42-70 |
| 8-10 | 80 | -/- | -/- | -/60-87 |
| [106] Grade | | | | |
| 1 | 492 | -/98 (96-99) | -/87 (81-91) | -/- |
| 2 | 265 | -/97 (93-98) | -/87 (80-92) | -/- |
| 3 | 63 | -/67 (51-79) | -/34 (19-50) | -/- |

Legend
*All data according to intention to treat;
**AJCC stage 1;
***AJCC stage 2;
****% of men dying within 15 years from prostate cancer according to the age range.

mean lead-time represents its midpoint. Draisma et al. [4] applied a micro-simulation model based on individual case histories of screen detected cases to the calculate lead-time and over-diagnosis. They found that the lead-time is strongly dependent on age but amounted to 12.3 years in a screening program of men aged 55-67 years. It must be assumed that the lead-time is shorter for aggressive and longer for indolent cancers. This information will become available from the ongoing randomised screening studies in Europe and in the USA.

The increment in lead-time by applying early-detection measures is associated with a significant stage shift towards more locally confined and less aggressive cancers [142].

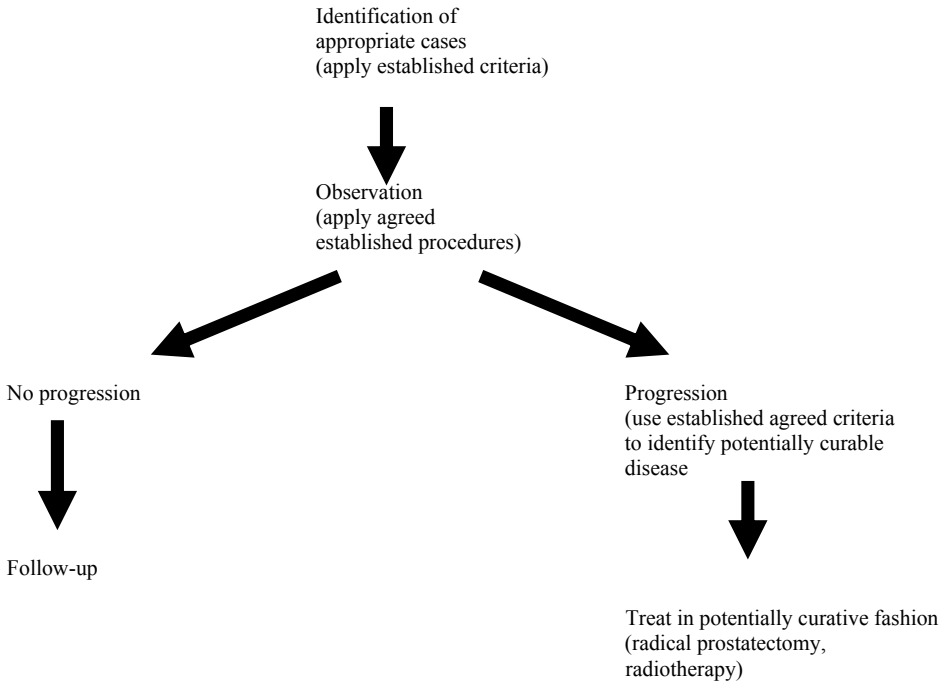
The long lead-time, stage reduction and natural history data cited above indicate that at least for properly selected cases there should be a long 'window' of time during which observation is appropriate without losing the opportunity for cure. This is also supported by available evidence from nomograms, prognostic tables and by the only available randomized study of observational treatment against RP. Holmberg et al. [108] randomized 695 patients with clinically diagnosed, non screen detected prostate cancer (TNM stage T1b, T1c and T2) including 35 cases with Gleason 8-10, between RP and observation. With observation alone (not followed by potentially curative measures) at a median follow-up of 6.2 years, 8.9% (31 of 348) men died from prostate cancer. Considering this same obviously relatively short observation period, 17 men needed to be treated to save one cancer death. The Partin tables [76] relate the occurrence of extraprostatic extension diagnosed on the RP specimen to clinical stage, PSA and biopsy Gleason score. In this context the event of extraprostatic extension is likely to limit or exclude curability. Clinical T2a disease, a PSA value of 2.5-4.0 ng/mL and a Gleason score of 5-6 is associated with extracapsular extension in 27% (range 23-31%) of cases. A rise of PSA to 4.1-6.0 and 6.1-10.0 ng/mL increases this probability by 5% for each step. These data illustrate the risk taken if, in a WW policy, a rise of PSA to 6.0 or 10.0 ng/mL is accepted. If, as will be shown later, doublings of PSA may occur within <1 year or > 10 years, information used in prognostic tables and nomograms is likely to be helpful in designing WW strategies.

## DEFINITIONS

WW should be clearly differentiated from 'observational' treatment as used in the natural history studies and the control arm of the Scandinavian Prostate Cancer Group study 4 [108]. Treatment by observation does not aim at the eventual cure of a given patient but at the determining the proper timing for instituting of endocrine (palliative) treatment. Such policies were previously based on doubts about the effectiveness of curative forms of management of localized disease e.g. RP and radiotherapy. Observational treatment may be indicated in men with prostate cancer whose life-expectancy is limited due by age or concomitant disease. This option entails that these two factors must considered in each treatment decision. Estimates of comorbidity are possible according to well established scoring systems. WW entails the observation of selected patients to determine which cancers should be treated by potentially curative measures and at when. The expected result is that some men, because they do not have aggressive disease, may not require any treatment because their cancer does not progress to clinical disease during their lifetime. The steps to be taken in WW are schematically indicated in Fig. 1. A logical consequence of the definitions given above is that patients who are not eligible for potentially curative management because of age or poor general health should not

be managed according to WW but according to observational regimens. The latter issue is beyond the scope of this review.

**Figure 1.** Flow diagram for WW in patients with prostate cancer






## CRITERIA FOR SELECTION

Criteria for selecting of patients for WW have not been established. Ideally, patients should be selected who either will not show progression during their lifetime or, if they show progression, will still be eligible for curative management with a high chance of success. The necessity for further research in this area and for determining prospectively evaluated appropriate criteria comes from the need to avoid unnecessary treatment, with its inherent side-effects and costs.

## PROSPECTIVE AND RETROSPECTIVE STUDIES

Several reports on prospective and retrospective studies are available; the selection criteria used in six recent papers [122-124, 143-145] are summarized in Table 3. A broad spectrum of available prognostic factors were included, but their role is often overruled

by considerations of comorbidity and age. In this respect only one study [145] and possibly another [122] represent prospective evaluations of WW. Post et al. [146] describe a 3-year overall survival of 89% in patients with prostate cancer with no concomitant disease, using an adapted Charlson classification, which deteriorated statistically significantly to 73% in patients with two or more concomittant diseases. The authors calculated multivariate hazard ratios (95% CI) for dying of 2.0 (1.0-4.3) and 7.2 (3.1-16.6) in patients aged 60 with one and ≥ 2 concomitant diseases, respectively. In this study, comorbidity was the most significant prognostic factor, especially in patients aged < 70 years in the first 3 years after diagnosis, followed by histological grade. Fowler et al. [147] describe a 5.7 times greater age-adjusted risk of comorbid death in men with severe comorbidities compared to those with none in patients with T1b and T2NXM0 prostate cancer treated with surgery or radiation therapy. Barry et al. [105] reported that the Charlson score in their retrospective analysis of patients with clinical M0 disease was an independent predictor of worse outcome in terms of a shorter overall survival, whether patients were treated with RP, radiotherapy or expectant management. In no treatment method did the Charlson score remain an independent predictor of cancer-specific death. However, evaluating prognostic factors at entry relative to disease progression contributes importantly to a better understanding and to better future choice of entry criteria. McLaren et al. [143] found that only initial PSA and PSA doubling time (PSADT) obtained during the follow-up correlated significantly with clinical progression and other endpoints. In the study by Choo et al. [122] none of the pretreatment variables correlated significantly with PSADT, which was a predictor of progression in that series. Stephenson et al. [123] found a significant correlation between 'clinically significant' histology, T-stage and findings at repeat biopsy, but not with Gleason score and PSADT, which also in that study was the most important prognosticator during the follow-up. Zietman et al. [144] found that age was the most important determinant of remaining free from therapeutic intervention. Only the work by Carter et al. [145] addressed systematically the relation between disease progression and prognostic factors at entry. Only PSA density (PSAD) and free/total PSA (f/tPSA) had a significant correlation. Age, PSA at diagnosis, prostatic volume and PSA velocity did not correlate. However, the overlap of data relating to PSAD and f/tPSA also limited, in the view of the authors, the usefulness of these two variables in selecting patients.

## PROGNOSTIC VALUE OF BIOPSY FINDINGS

In line with the development of PSA derivatives, biopsy variables like the Gleason score, the number of positive cores, total length of cancer invasion in one core or the maximum percentage of core length invaded by cancer, are described as having predictive

**Table 3** Selection variables for WW

| Reference | Variables, median range | Status of study | N men | Median (range) follow-up |
|---|---|---|---|---|
| [143] | Age 75 (49-85)<br>T1a-T3c, PSA 5.8 (0.2-21) ng/mL<br>MD Anderson grade 1-3, Gleason scores 2-7<br>Comorbidity, patient request | Prospective | 113 | 14 (0-58) months |
| [122] | Age 70 (49-84), stages T1b-T2b<br>PSA 6.5 (0.3-14.6) ng/mL<br>Gleason scores 3-7 | Prospective | 206 | 29 months |
| [124] | Age 75 (44-87), stage T1-T2*<br>PSA 7.4 ng/mL (mean 12.3)<br>Gleason scores 2-10 | Prospective (CaPSURE database) | 329 | - |
| [123] | Age 69 (51-86), T1a-T3<br>Mean PSA 7.4 (0.9-25.2) ng/mL<br>Gleason scores 2-10<br>Clinically significant/insignificant 68/20%<br>Mean PSA density 0.19 (0.02-0.55) | Prospective | 104 | 33 months |
| [144] | Age 71, T1a-T2c, PSA < 20 ng/mL (median 6.6)<br>Gleason scores ≤ 8, comorbidity | Retrospective | 199 | 3.4 years |
| [145] | Age 65 (52-72), T1c 'small volume'<br>Gleason 4-6, ≤ 2 biopsies with cancer or <half cancer in any core | Prospective | 81 | > 1 year (12-58 months) |

Legend
* >95% T1 or T2

value in estimating biochemical recurrence of disease [148-150]. A major pitfall in using biopsy-derived variables, as adressed elsewere in this review, is the representativeness of tumour characteristics, especially the Gleason score, in biopsy cores compared with the reference standard, the RP specimen [74, 141, 150-152]. Some groups [153] find a better correlation when extending the number of biopsies while others cannot detect this improved correlation [154, 155]. On the other hand Bastacky et al. [156] stated that perineural invasion on the biopsy in patients with clinical stage B disease correlated with extracapsular disease in 93% of RP specimens. Bonin et al. [157] showed that perineural invasion in a biopsy core was associated with biochemical recurrence of disease after three-dimensional conformational radiation therapy. Biopsy cores with higher tumour yield, e.g. tumour present in more than half of one core, more than three positive cores, or > 3 mm length of tumour invasion in one core, predicted biochemical progression in up to 90% of patients within 18 months after RP [74, 148, 158]. These patients should therefore be excluded from entering a WW policy.

Peller et al. [159] identified 92% of organ-confined disease using RP specimens when one biopsy was positive. Others [148, 160] found that 80 % and, respectively, > 90% of patients had no biochemical progression 2 years after RP if the total length of invasion of cancer was <15%, or respectively, <20% of the total length of biopsy cores minus peri-

prostatic tissue. Epstein et al. [150] stated that prostate cancer was insignificant if the maximal length in any core was < 3 mm, Gleason score <7 and a PSAD < 0.15, or a PSAD < 0.1 with a Gleason < 7 and if fewer than three cores had cancer invasion in a maximum of half of any core. The algorithms of others also include PSA or PSA-derived variables, a Gleason score < 7 and minimal biopsy findings, thereby clearly illustrating the correlation between greater tumor load and recurrence of disease [73, 161-163]. Eligible for a WW policy on the basis of biopsy findings could be patients with; (i) a Gleason score <7 combined with a PSAD of < 0.1 ng/mL/g and (ii) only one biopsy core positive for cancer, a length of < 3 mm, respectively, 30% of cancer in that core or <20% cancer invasion of the total biopsy length. When the results from ongoing randomized screening studies are available these criteria will probably need adjusting.

## POLICY PROPOSAL I: PATIENT SELECTION

Selecting patients for WW should be differentiated from selecting them for delayed palliative treatment (observation). This entails that a high ASA score or Charlson score, or an age-related condition that precludes surgery or radiotherapy should exclude patients from WW regimens. As indicated above, WW aims to identify those men who do not progress or who, if progression occurs, can be identified in a potentially curable state.

Data from available studies, which allow the determination of patient selection for WW, are scarce. A proposal is given in Table 4. Patients who are too old or too sick for treatment do not qualify for WW policies but for observational treatment. In most centres patients up to 75 years old would be eligible for RP if they have > 10 years of life expectancy; other centres would choose radiotherapy if the tumour is aggressive in older patients. Good general health with an ASA score ≤ 3 and a Charlson score ≤ 2 at the time of diagnosis can be considered a prerequisite for the future consideration of surgical management. The eligibility for radiotherapy may include men in poorer health. Carter et al. [145] chose the T1c classification as entry criterion for their study, but Choo et al. [164] and others also suggest that also palpable, locally confined disease, specifically T2a included cases with very low rates of progression. As for the PSA threshold, Carter et al. [165] showed that when the initial PSA level was greater than 5.0 ng/mL 30% of 317 cancers were incurable (pT3). In the experience of the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam, a PSA of 8 to 10 ng/mL was associated with 25% of T3-4 and 25% of pT3-pT4 cases. PSA density and f/tPSA might be of additional value in using PSA values in this context. Considering the data by Albertsen et al. [75] and the choice made by Carter et al. [145] a Gleason score < 7 seems a reasonable threshold. These considerations can be overruled by patient request if quality-of-

life considerations, mainly the risk of loss of potency, become a dominant factor in the clinical situation. A threshold relating to the amount of cancer found in biopsies was not explored in any of the studies. Suggestions could be derived from the information given in the section on the prognostic value of biopsy findings.

**Table 4:** Policy proposals for WW

| | |
|---|---|
| I Selection | |
| | Patients < 75 years, life expectancy > 10 years<br>Good general health (ASA score ≤2, Charlson score ≤1)<br>T1a, T1c or T2a<br>PSA < 5-8 ng/mL (and/or PSAD < 0.1 and/or f/tPSA ≥ 19%?)<br>Gleason score ≤ 6, no Gleason pattern 4<br>Patient request (quality of life considerations), applicable to higher risk after proper information<br>≤ one core positive for cancer with < 30% cancer involvement |
| II Follow-up recommendations | |
| Timing | 3-6 months, 3 monthly during year 1 and 2 |
| Physical | DRE - exclude T-progression |
| Laboratory | PSA and PSADT, creatinine |
| Imaging | TRUS yearly and upon indication, possibly together with biopsy (support for DRE, volume) |
| Biopsy | Every 12-18 months (grade progression?)<br>Option: biopsy after 3 months |
| III Trigger points for treatment | |
| | 1. Patient request<br>2. Local T progression (DRE or TRUS)<br>3. PSADT < 2 years<br>4. Grade progression on biopsy (≥ two Gleason scores, or Gleason pattern 4)<br>5. Any combination of items 2-4 |

PSAD, PSA density; DRE, digital rectal exam PSADT, PSA doubling time; PSAV, PSA velocity; TRUS, transrectal ultrasound.

## FOLLOW-UP OF WW

Ideally, the procedures used in selection and follow-up of patients assigned to WW regimens should be correlated with recognised outcome parameters, e.g. overall and cancer specific survival. Unfortunately such information is not currently available. In attempts

to still evaluate selection and follow-up procedures authors have chosen to consider the relationship of entry criteria and, in some instances, PSA and clinical progression rates, with information obtained during follow-up. Trigger points for treatment are often the result of arbitrary choices. Their effect on surrogate outcome variables will be reviewed later.

Table 5 gives a summary of follow-up regimens used in the watchful waiting studies chosen for review [122, 123, 143-145]. Most authors considered a follow-up interval of 3-6 months adequate and safe. A 3-monthly interval, at least during the initial period of follow-up, offers the advantage of accumulating many PSA values which gives the opportunity to consider biological variation and to calculate the PSA doubling time (PSADT). All authors perform a rectal examination during the follow-up visits, the main purpose being to detect progression of the originally assigned T-category. PSADT is also used within all studies and was found to correlate with clinical progression [123, 143, 144]. Several groups reported no correlation between PSADT and baseline variables [122, 123, 166]. A repeat biopsy, with the main goal being to detect grade progression, was taken either 6-monthly, yearly or 18-monthly, or on indication by four groups [122, 123, 144, 145]; biopsy protocols vary from six to 12 cores. In two of the cited references there was a weak correlation with either PSAV or f/tPSA and progression and/or baseline characteristics [145, 166].

**Table 5** Follow-up regimens used in WW studies

| Reference | Regimen |
|---|---|
| [143] | 3-6 monthly visits, PSA, PSADT, DRE, clinical progression increase in T-category |
| [122] | 3-monthly for 2 years, then 6 monthly, prospective evaluation, PSADT, f/tPSA, prostatic acid phosphatase creatinine, TRUS (6-monthly), re-biopsy after 12-18 months, bone scan after 1 and 2 years then every 2 years, with PSA >15 n/mL every year |
| [123] | 3-6 monthly follow-up, PSA, DRE, bone scan 'if indicated' sextant biopsies yearly, PSADT |
| [144] | 4-6 monthly follow-up, PSA, DRE, repeat biopsy upon indication, PSA increase |
| [145] | 6-monthly follow-up, PSA, DRE, TRUS an biopsy yearly (≥ 12 cores), PSADT, PSAD, PSAV, f/tPSA |

Legend
DRE, digital rectal exam; PSAD, PSA density; PSADT, PSA doubling time; PSAV, PSA velocity; TRUS, transrectal ultrasound.

In summary, most authors feel that patients on WW should be followed at 3 to 6-monthly intervals, and 3-monthly during the first 1 to 2 years. All authors used PSA and rectal examination; serum creatinine and free PSA was recommended by some. Bone scans are carried out on clinical indication or if the PSA increases to > 15 ng/mL. It is well documented that for a serum PSA of 20-50 ng/mL the rate of positive bone scans is ≈ 8%; at > 50 ng/mL the rate is 16% [167]. Clinical progression is diagnosed with an increase of

the T-category, a rise in serum creatinine caused by ureteric obstruction, an increase in Gleason score on re-biopsy, or if there are cancer-related specific complaints.

This information is summarized in Table 4; obviously, follow-up regimens need to be viewed against the background of the available outcome data. These will be referred to in the discussion of trigger points for treatment.

## INDICATIONS FOR TREATMENT



Almost all aspects of the application of WW to locally confined prostate cancer are still investigational. Candidate prognostic indicators for triggering treatment decisions are usually arbitrary, often governed by uncertainties and the patient's wishes resulting from the psychological stress of slowly rising PSA levels. While future research will also consider the prognostic factors available at the time of diagnosis, important information can be gained during follow-up which is likely to identify those cases that tend to progress to a potentially incurable stage. The candidate criteria listed in table 4 are now assessed as potential indicators for treatment or continued observation for patients who have chosen WW.

## PSA CHANGE OVER TIME

Many attempts have been made to correlate PSA change over time in various clinical situations to outcome parameters. Davidson et al. [168], in a multivariate analysis correlating progression in lymph-node positive disease to outcome, reported that a 20% increase in PSA was the most sensitive and specific indicator of progression. Carter et al. [169] using data from the Baltimore longitudinal study of ageing defined PSA velocity as the increase of PSA per year, noted that a change in the very slow increase in PSA in patients with benign disease, of 0.04 ng/mL/year to a PSA velocity of 0.75 ng/mL/year occurred 7.3 years prior to the diagnosis of clinical prostate cancer. This group also found that many observations over a period of ≥ 2 years were necessary to take account of the biological variation of serum PSA when calculating PSA slope and doubling times. In comparison, Ciatto et al. [170] found an average PSA velocity (two values) in healthy subjects of 0.07 ng/mL/year. Several groups have addressed the best way of determining of PSA rise and there seems to be growing consensus that PSA doubling time (PSADT) is the most suitable parameter. Choo et al. [164] used the following equations:

$$PSA(t) = PSA(0)\, e^{\lambda t}$$
$$\ln PSA(t) - \ln PSA(0) + \lambda t$$
$$Td = \ln 2/\lambda$$

where PSA (0) is the initial PSA, PSA (t) the PSA at time t after PSA (0), and λ is the slope; the rate constant does not correlate with baseline variables age, PSA, T category or Gleason score.

Schröder et al. [171] have proposed a fitting procedure in determining PSA slope; a similar procedure was described by Guess et al. [172]. Unfortunately, apart from visually estimating doubling time from grafts or groups of data, exact calculations are complex and currently difficult to use in the outpatient setting.

All considerations of PSA change with time are based on the assumption that PSA levels are related to tumour mass. It is recognised that clinical progression, usually of hormone unresponsive prostate cancer under endocrine treatment, may occur with no rise in PSA level. This issue was recently reviewed and quantified by new data by Collette et al. [173]. Several authors have attempted to establish a relationship between serum PSA levels and the volume of prostate cancer. Stamey et al. [174] found a significant correlation ($r = 0.7$) between pretreatment PSA and prostate cancer volume. Schmid et al. [128] indicated from the same database that 1 mL of prostate cancer on average correlated with 3.6 ng/mL of serum PSA. However, more recent data [175] do not reproduce the original data. There was no relevant or significant correlation between prostate cancer volume and pretreatment PSA, and the original data could not be reproduced. This is in line with other reports [145, 164] that PSADT does not correlate with pretreatment prognostic factors. Despite of these uncertainties, increasing evidence is emerging that increase in the PSA with time, especially expressed as PSADT, is a valuable prognostic factor. Clinical progression in locally confined disease with no increase in PSA seems to be extremely rare.

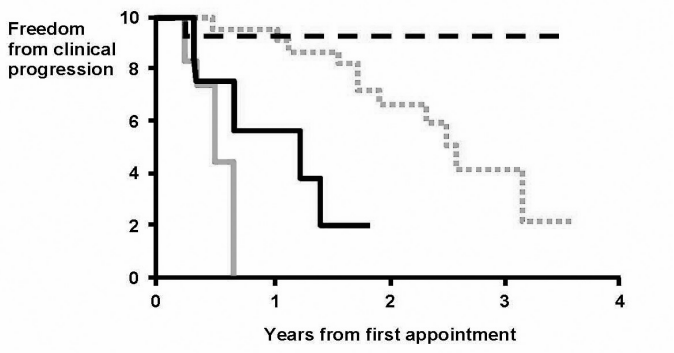
## PSA CHANGE WITH TIME AND PROGRESSION UNDER WATCHFUL WAITING

There are many reports of PSA as an indicator of progression and outcome after the potentially curative management of prostate cancer. Several authors have addressed the predictive value of the PSADT beforehand for progression after treatment. Hanks et al. [176] reported on 99 patients with T1-3 prostate cancer in whom the pretreatment PSADT was assessed. With a PSADT of < 1 year and > 1 year, 47% and 11% had PSA progression after 18 months. Goluboff et al. [177] assessed 150 patients in whom the

PSADT was calculated prior to radical prostatectomy. 56 patients had 3 or more PSA measurements before RP; 56 had three or more PSA measurements before treatment. With a follow-up time of 17.3 months PSADT did not correlate with PSA failure, the final PSA value or the Gleason score of the RP specimen.

The PSADT during WW situation is extremely variable; Choo et al. [164] in 134 patients with a median (range) of 24 (1-52) months and a median of seven PSA measurements, reported that the PSADT varied < 2 years to > 50 years in 27 of them. Carter et al. [169] estimated a normal PSADT with no cancer amounting to 54 ± 30 years at a baseline age of 40 years. Three of the available and reviewed reports on WW related PSA change over time to clinical progression. Stephenson et al. [123] reported in their study of 104 cases that a PSADT < 10 years correlated with disease progression on rectal examination and repeat biopsy, and with the presence of «significant cancer' at the initial evaluation; 48% of the men had a PSADT < 10 years. A PSADT < 4 years in 27% of the men correlated significantly with T progression established by rectal examination. McLaren et al. [143] in 113 cases reported a strong correlation of PSADT with several different thresholds of the time and rate of clinical progression. Their data are reproduced in Fig. 2. A multivariate analysis included PSADT and pretreatment variables (tumour grade, Gleason grade, initial PSA, T-classification). Only the PSADT remained significant in a multivariate analysis for predicting progression. PSA progression was not assumed to be clinical progression in this study. Carter et al. [145] found that PSA density was significantly higher and f/tPSA was significantly lower in men with disease progression, which occurred in 25 of 81 men (31%). Progression was determined by digital rectal examination and annual repeat biopsies. Age, PSA, prostate volume and PSA velocity were not statistically significantly related; the PSADT was not reported.

**Figure 2:** The Kaplan-Meier curves for PSADT as a predictor of activity during WW for PSADTs of <1.5 years (gray line), 1.5– 3 years (black line), > 3 years (gray dotted line) and static or decreasing (dashed black line). Adapted from [143].



Available data indicate that PSADT is a powerful predictor of clinical progression in patients managed by WW. The clinical utility needs to be established prospectively in larger series of men. The possibility of clinical progression with no PSA progression as reported by Stephenson et al. [123] has to be taken into account. Carter et al. [145] reported the outcome of RP in their follow-up series. Of 81 men with minimal T1c disease 25 had unfavourable biopsy findings indicating disease progression. Thirteen underwent RP within a median (range) time to progression of 14 months (12-52). 12 of these had curable disease.

## DIGITAL RECTAL EXAMINATION

There is consensus that progression of T-stage on a DRE must be considered clinical progression [122, 123, 143, 144]; this is specifically true if impalpable disease (T1c) progresses to a palpable lesion. Usually the impression on a DRE will be confirmed by biopsy. Stephenson et al. [123] reported a disappointing correlation between clinical progression on DRE, biopsy and PSADT.

## REPEAT BIOPSY

Repeat biopsies are recommended by most investigators after periods of 3-18 months [122, 123, 145, 178]. It is well established that repeat biopsy may not show cancer at all [179], but if there is upgrading this may be a result of having missed the less differentiated parts of a prostate cancer with several architectural patterns. At present, considering the available reports, the repeat biopsy can be selected as an integral part of the follow-up procedures in WW. Multivariate analysis of the progression variables available during follow-up must establish their relative and absolute value in the future, making use of larger and well defined series of patients.

## PATIENT REQUEST FOR TREATMENT CHANGE

In all WW series a large proportion of patients choose treatment because of the uncertainties about a slow but steady rise in PSA level; psychological stress is important in this context. This decreases the value of the time to and the rate of change in treatment as a potential endpoint.

Currently it is impossible to develop an evidence-based policy proposal for treatment indications. Recommendations are summarized in Proposal III in Table 4. The patient's request must be honoured. A short PSADT of probably < 2 years should provoke a consideration of treatment or further evaluation. A histological upgrade by two Gleason scores or more at repeat biopsy has been used in several of the WW studies. Other variables are listed in Table 4.

## CONCLUSIONS



WW and observational treatment should be differentiated. Despite of considerable uncertainties about the risks and potential benefits of WW and the procedures applied for case selection, follow-up and delayed treatment, WW is used with an increasing frequency. In this review we have assessed the existing information relating to case selection, follow-up and treatment indications. The preliminary data on the natural history of screen detected and clinically detected cancers suggest a long 'window of treatment opportunity'. Considering the few available data on final outcome (progression to incurable disease) this risk seems to be small with the selection and follow-up procedures recommended in the policy proposals in Table 4.

Future research must concentrate on the evaluation of entry criteria and follow-up procedures to establish the appropriate trigger points for treatment. In this respect observation studies and watchful waiting studies need to be separated. The ongoing randomized studies of screening for prostate cancer offer a good opportunity to develop this field further because they allow prospective observations in screen detected cases.

# Part II:
# Selecting patients for active surveillance

**Chapter 4**
Overall and disease-specific survival of patients with screen detected prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam
*Eur Urol. 2007 Feb; 51(2): 366-74*

**Chapter 5**
Additional use of [-2]precursor prostate specific antigen and "benign" PSA at diagnosis in screen detected prostate cancer
*Urology. 2005 May; 65(5): 926-30*

# Chapter 4

## Overall and disease specific survival of patients with screen detected prostate cancer in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam

Stijn H. de Vries, Renske Postma, René Raaijmakers, Stijn Roemeling, Suzie Otto, Harry J. de Koning, F.H. Schröder

*Eur. Urol. 51 (2007) 366-374*

## ABSTRACT

**Introduction:**
This report describes survival data of participants of the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam, diagnosed with prostate cancer (PCa) during the first round of screening, the prevalence screen.

**Patients and methods:**
PCa characteristics from cases diagnosed during the first screening round from December 1993 to March 2000 are shown. During follow-up, data were collected by semiannual patient chart review for the first 5 yr and annually thereafter. The causes of death are scored according to the diagnosis of the treating physician and are not based on the review of the independent causes-of-death committee. Overall and disease-specific survival graphs are shown in Kaplan-Maier projections and compared with expected survival outcomes for males in the same age categories from the Dutch provinces of North Holland and Flevoland. Statistical evaluation was based on Cox regression analysis.

**Results:**
During the prevalence screening, 1014 patients were diagnosed with PCa. Median follow-up was 55 mo, 126 (12.4%) patients died, 20 (2.0%) of PCa. Overall 5-yr observed and expected disease-specific survival was 97.7% and 82%, respectively. In the multivariate analysis, a Gleason sum of 4+4 or higher ($p = 0.025$) was predictive of PCa death.

**Conclusions:**
The observed survival data are in line with the literature and the expected favourable outcome for a screened population. The proportion of men dying from PCa is still small, and a 10-yr follow-up period for the final evaluation of the ERSPC may be too short.

## INTRODUCTION

Prostate cancer (PCa), unlike most other malignant diseases, has a protracted natural course in the majority of cases. Treatment after an early diagnosis of PCa, facilitated by screening, could possibly improve disease-specific survival [180]. Currently two large prospective randomized trials are investigating the effect of PCa screening on disease specific mortality [181]. While a beneficial effect of screening has yet to be determined, a shift towards more favourable tumour characteristics at diagnosis has been reported [67, 182]. This report describes, for the first time, the overall and disease-specific survival rates of patients diagnosed with PCa during the first round of screening in the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam. The goal of this early study of outcome parameters of PCa patients identified at the first screen in the ERSPC, Rotterdam is to put survival rates into perspective with the literature and with regional mortality data.

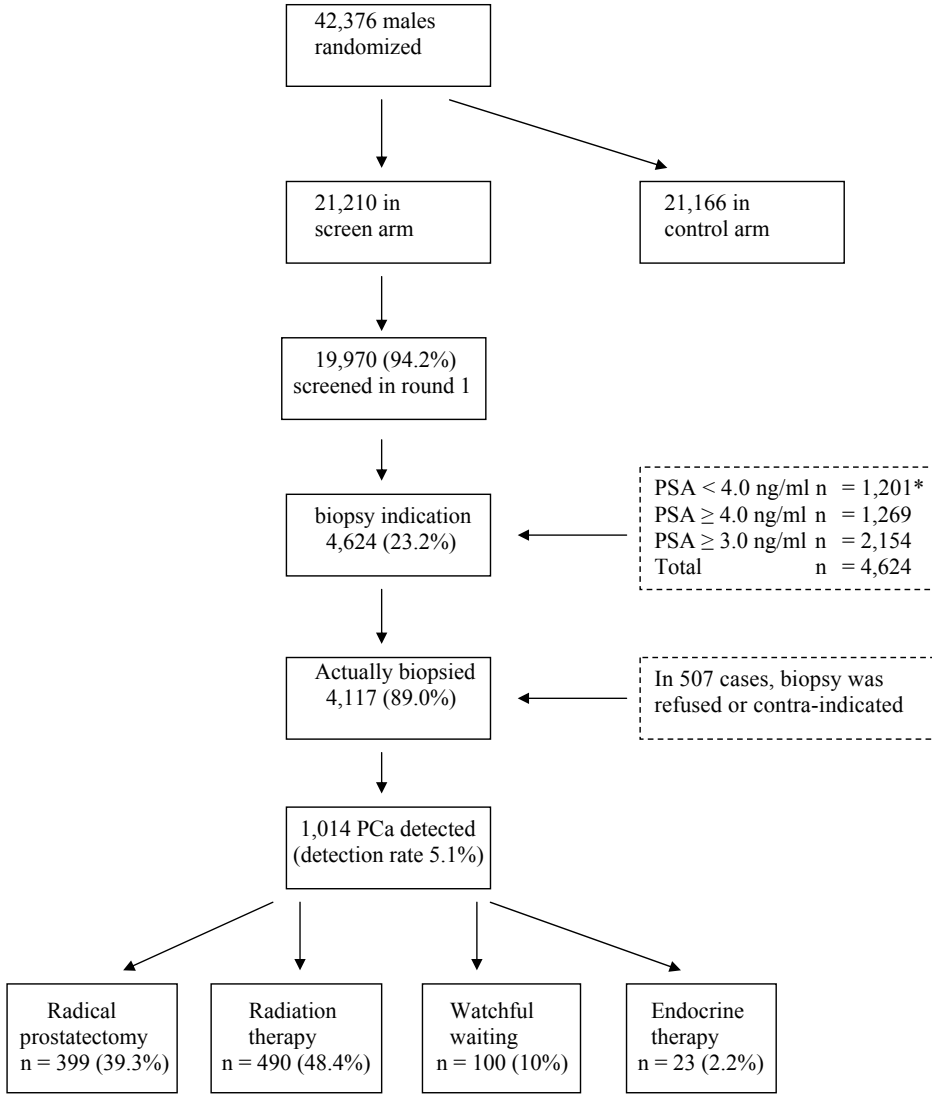


## PATIENTS AND METHODS

Patients diagnosed with PCa during screening in the prevalence screen of the ERSPC, section Rotterdam, were included. The first round started in December 1993 after four pilot studies; recruitment and randomization ended in December 1999. A detailed overview of the inclusion criteria and test procedures used was recently published elsewhere [88]. Fig. 1 shows the flowchart of the ERSPC, Rotterdam screening round 1. In short, 21,210 males were randomized into the screen arm and 19,970 patients (94.2%) were actually screened. Clinical staging in the ERSPC is done according to the 1992 UICC TNM classification [81]. The Charlson score was used to estimate the comorbidity status at diagnosis [183]. During follow-up data, were collected from semi-annual patient chart review for the first five yr and annually thereafter. Charts were checked for medical history, physical examinations, dissemination studies, and prostate-specific antigen (PSA) tests. To compare outcomes, we divided cases into three widely used prognostic groups [184]. In the study of D'Amico et al. [184] clinical stage is solely based on digital rectal examination (DRE) findings. Metastatic disease was diagnosed in case of new or increased radiographic evidence of metastases during follow-up.

Within the ERSPC all deceased PCa cases are reviewed by a national independent cause-of-death committee using predefined flowcharts or by an international committee if no consensus is reached [185]. All cases are reviewed blinded for personal information and trial arm; therefore these data are not yet available. However, during patient chart review, a preliminary cause of death is scored according to the diagnosis of the treating

**Fig. 1** Flowchart for the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam. Adapted from [88].




* These 1201 patients with an abnormal DRE or TRUS are 13.5% of all patients with a PSA level < 4 ng/ml.

physician; these scores were used for the survival analysis. Expected overall mortality for every subsequent year was calculated by multiplying the Dutch age-specific mortality quotient in the period 1996 to 2000 with the number of men in the cohort. For the first year the mortality quotient of the age group of 66.5 yr was used (median age study cohort: 66.7); for the second year the mortality quotient in the age group of 67.5-year-old men was taken, and so forth. The number of deceased males was subtracted from

the cohort before the next calculation. The expected disease specific mortality is the reported disease-specific survival of Dutch males diagnosed with PCa at 60 to 74 yr of age during the periods 1988-1991, 1992-1995, 1996–1998, and 1999-2001, in the Dutch provinces of North Holland and Flevoland [186]. The absolute numbers of patients diagnosed in these periods were 1,787, 1,525, and 1,690 respectively. The reason for using these data was that disease-specific survival was provided per year. A regression trendline for each category was plotted for illustrative purposes.

### Statistics

Distribution of parameters between the different treatment modalities is calculated with the use of the Pearson-Chi square test for categorical variables and the Kruskal-Wallis test for all continuous variables. Kaplan-Meier analysis was used for overall and disease-specific survival. The Cox proportional hazards regression model was used to calculate hazard ratios (HRs) and 95% confidence intervals for prognostic factors. A HR can vary from zero to any positive value and gives the relative risk for one unit increase in the predictor at any time. For example, the HR of age at diagnosis as a continuous variable is 1.07, which means that a patient aged 67 yr at diagnosis has 1.07 times the risk of dying of any cause compared with a 66-year old patient at any time of follow-up. After 5-mo follow-up, this hazard has exponentially increased to [100%*(1.07 $^{5}$)]-100% = 40.3% for the 67-year-old man. The HR in the categorical variables reflects the relative hazard, compared to the reference group. The largest groups, which in this study also had the most favourable PCa characteristics, were made the standard. All analyses were performed with the commercially available Statistical Package for the Social Science software, version 12.0 (SPSS Inc, Chicago, IL, USA).

## RESULTS

During the prevalence screening, 1,014 males were diagnosed with PCa. One patient retracted his written consent, and, in one patient, treatment modality is not yet known. Median follow-up was 55.1 mo. Table 1 shows the baseline data of 1,013 cases. All patient characteristics shown in table 1 were distilled into three prognostic groups and were statistically significantly different ($p < 0.001$) between the treatment groups (Table 2). The majority of cases (87.7%) directly received treatment with curative intent (Fig. 1). During follow-up a total of 126 (12.6%) patients died, including 20 from PCa. The 5-yr observed cumulative survival in the screen cohort was 88.3% while the expected 5-yr overall survival was 85.7%. Initially, the observed overall survival was higher than expected overall survival, but with extended follow-up both survival projections were

similar (Fig. 2A). The observed 5-yr disease-specific survival in the ERSPC, section Rotterdam, was 97.6%, which was higher than the 82% in the cohort of men diagnosed between 1996 and 1998, or the 76% of men diagnosed between 1992 and 1995 in the Dutch provinces of North Holland and Flevoland (Fig. 2B).

**Table 1** Baseline characteristics of the cases detected in the prevalence screen of the ERSPC, section Rotterdam

| | | Total | (% or range) | p value # |
|---|---|---|---|---|
| Patient n (%) | | 1013 | (100) | |
| Age at diagnosis (yr, median range) | | 66.7 | (55 - 75) | <0.001 |
| Follow-up (mo, median range) | | 55.1 | (0 -114) | <0.001 |
| PSA (ng/mL, median range) | | 5.7 | (0.3 - 315) | <0.001 |
| Clinical PSA group | ≤ 4^ | 262 | (25.8) | <0.001 |
| | 4-10 | 518 | (51.2) | |
| | >10 | 233 | (23.0) | |
| T stage [194] | T1C^ | 357 | (35.2) | <0.001 |
| | T2 | 468 | (46.2) | |
| | T3 | 177 | (17.5) | |
| | T4 | 11 | (1.1) | |
| Biopsy Gleason sum | ≤ 3+3^ | 635 | (62.6) | <0.001 |
| | 7* | 284 | (28.1) | |
| | ≥ 4+4 | 82 | (8.1) | |
| | unknown | 12 | (1.2) | |
| Charlson score | 0^ | 532 | (52.5) | <0.001 |
| | 1 | 314 | (31.0) | |
| | ≥2 | 167 | (16.5) | |
| Prognostic groups [184] | Favourable^ | 461 | (45.4) | <0.001 |
| | Intermediate | 291 | (28.8) | |
| | High risk | 261 | (25.8) | |

Legend
ERSPC: European Randomized Study of Screening for Prostate Cancer; PSA: prostate specific antigen.
* Including 18 patients with a Gleason score of 4+3.
# p values for continuous variables as age, PSA and follow-up are calculated with the Kruskal-Wallis test for the remaining categorical variables the Pearson chi-square test was used.
^ Reference category in Cox-regression analysis.

Table 3 shows the number of men treated by radical prostatectomy (RP), radiotherapy (RT), watchful waiting (WW), and endocrine treatment (ET) stratified into three prognostic groups. The numbers of PCa and intercurrent deaths are provided. Because of limited events, only the PCa-specific survival for the high-risk prognostic group could be calculated (Fig. 3).

All baseline characteristics shown in Table 1 were tested in univariate and multivariate analysis for their predictive value of overall mortality. The results are summarized in Table 4. Statistically significant predictors at diagnosis for overall death in the univariate analysis were age (p< 0.001), a Charlson score of 1 (p=0.003) or 2 (p<0.001), a clinical stage T3 disease (p=0.003), a biopsy Gleason sum of 4+4 (p<0.001), or patients in the high-risk prognostic group (p<0.001). The hazard ratio of 3.2 for patients with a Charlson score of two or higher, for example, means that, at any point during follow-up, these patients have a 3.2-fold increased risk of dying, compared with patients with a Charlson score of zero, who functioned as the reference group. The other reference groups are listed in Table 1. In the multivariate analysis age (p=0.013), a Charlson score of 1 (p=0.029) or 2 (p<0.001), clinical stage T3 disease (p=0.026) and a biopsy Gleason score of 4+4 or higher (p=0.036) remained statistically significant predictors for overall mortality.



PCa death occurred in 4 patients after RP (2 of perioperative complications), in 10 after RT and in 6 after ET. Of the 20 PCa deaths, 17 cases had high-risk PCa characteristics. The patient with favourable PCa characteristics died of perioperative complications. Of the two patients with intermediate characteristics dying of PCa, one appeared to have tumour growing into the bladder at pathologic examination. The other patient, who was treated with RT, had organ-confined PCa at DRE, but within a year after therapy capsular penetration was seen on transrectal ultrasound evaluation as well as a fast rising PSA level for which ET was started. No patient initially managed with a WW policy died of PCa, although during current follow-up 15 patients received deferred treatment with curative intent after an initial WW policy (RP= 3 and RT= 12). Moreover of the remaining 85 males, 6 patients currently have ET, 3 had metastatic disease at diagnosis that became symptomatic, 2 had local progression and 1 had a rising PSA.

Testing the baseline PCa characteristics in the univariate analysis for PCa-specific mortality, PSA as a continuous variable (p<0.001), patients with a PSA level > 10 (p=0.009), a biopsy Gleason score of 4+3 (p=0.003), a clinical stage T3 (p=0.025), or T4 (p<0.001), and patients with high-risk PCa characteristics (p=0.001) were at increased risk of dying of PCa. The corresponding HRs (95 confidence intervals [CIs]) are 1.01 (1.01-1.02), 7.3 (1.7-32.6), 22 (2.9-169), 13.5 (1.4-130), 30 (8.5-106) and 30.4 (4-229) for patients with high-risk PCa characteristics. In the multivariate analysis only males with a Gleason score of 4+4 (p=0.025) remained at a statistically significantly increased risk of 7.0 (1.3-37.7) of dying of PCa compared with patients with a biopsy Gleason sum of 3+3.

**Table 2** - Distribution of comorbidity and prostate cancer characteristics between treatment groups

| | RP n=399 | % | RT n=490 | % | WW =100(%) | ET n=23 | % | Total n=1012 | % |
|---|---|---|---|---|---|---|---|---|---|
| Charlson Score = 0 | 257 | (64.4) | 218 | (44.5) | 44 (44) | 12 | (52.2) | 531 | (52.5) |
| 1 | 96 | (24.1) | 176 | (35.9) | 36 (36) | 6 | (26.1) | 314 | (31.0) |
| >1 | 46 | (11.5) | 96 | (19.6) | 20 (20) | 5 | (21.7) | 167 | (16.5) |
| "Favourable" PCa [184] | 223 | (55.9) | 160 | (32.7) | 75 (75) | 2 | (8.7) | 460 | (45.4) |
| "Intermediate" PCa | 119 | (29.8) | 156 | (31.8) | 15 (15) | 1 | (4.3) | 291 | (28.8) |
| "High risk" PCa | 57 | (14.3) | 174 | (35.5) | 10 (10) | 20 | (87.0) | 261 | (25.8) |

Legend
Favourable PCa: T1C or T2A and PSA ≤ 10 ng/mL and Gleason score ≤ 3+3
Intermediate PCa: T2B or PSA < 20 ng/mL or a Gleason score of 7
High risk PCa: ≥T2C, PSA > 20 ng/mL or a Gleason score ≥ 8
PCa: prostate cancer; PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiotherapy; WW: watchful waiting; ET: endocrine treatment.

**Fig.2**
**Fig. 2A** Observed versus expected overall survival.

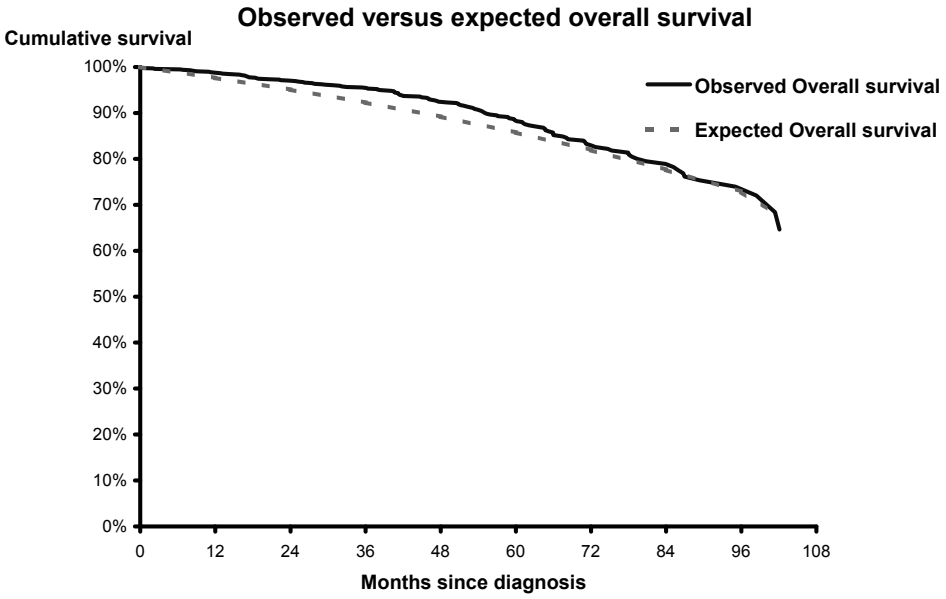


**Fig. 2B** Comparision of disease-specific survival of the European Randomized Study of Screening for Prostate Cancer (ERSPC) prevalance screen cohort with the observed PCa- specific mortality of Dutch males diagnosed at the age of 60-74 yr during four different time periods [186].

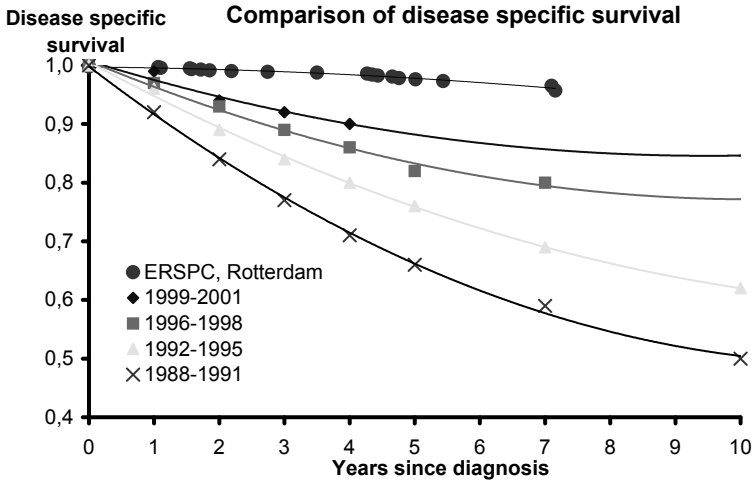





**Table 3** - Distribution of cases by received treatment and in three prognostic groups

| Prognostic group [184] | | | Cause of Death | | | |
|---|---|---|---|---|---|---|
| | | | Alive | PCa death | Intercurrent death | Total |
| Favourable | | RP | 212 | 1 | 10 | 223 |
| | | RT | 137 | 0 | 23 | 160 |
| | | WW | 69 | 0 | 6 | 75 |
| | | ET | 2 | 0 | 0 | 2 |
| | Total | | 420 | 1 | 39 | 460 |
| Intermediate | | RP | 109 | 1 | 9 | 119 |
| | | RT | 133 | 1 | 22 | 156 |
| | | WW | 13 | 0 | 2 | 15 |
| | | ET | 1 | 0 | 0 | 1 |
| | Total | | 256 | 2 | 33 | 291 |
| High risk | | RP | 54 | 2 | 1 | 57 |
| | | RT | 135 | 9 | 30 | 174 |
| | | WW | 9 | 0 | 1 | 10 |
| | | ET | 12 | 6 | 2 | 20 |
| | Total | | 210 | 17 | 34 | 261 |

Legend

ET: endocrine treatment; PCa: prostate cancer; RP: radical prostatectomy; RT: radiotherapy; WW: watchful waiting.

**Fig. 3** – Prostate cancer-specific survival of high-risk prostate cancer patients (n = 261).

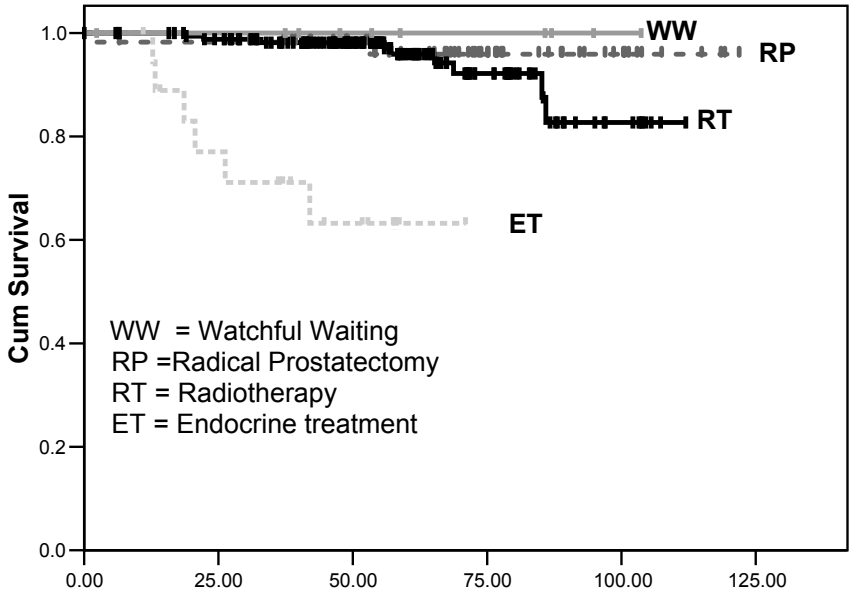



**Table 4** Uni- and multivariate analysis of prostate cancer characteristics on overall survival (n = 1012)

| | | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | | | HR | 95% CI | | |
| | | | Lower | Upper | p value | | Lower | Upper | p Value |
| Age (yr) | | 1.07 | 1.03 | 1.11 | <0.001 | 1.05 | 1.01 | 1.09 | 0.013 |
| PSA (ng/mL) | | 1.00 | 0.99 | 1.01 | 0.103 | 1.00 | 0.99 | 1.01 | 0.824 |
| PSA group | 0-4* | | | | | | | | |
| | 4-10 | 0.73 | 0.48 | 1.12 | 0.149 | 0.68 | 0.43 | 1.07 | 0.094 |
| | >10 | 1.13 | 0.71 | 1.79 | 0.613 | 0.77 | 0.45 | 1.35 | 0.366 |
| Charlson score | 0* | | | | | | | | |
| | 1 | 1.90 | 1.25 | 2.88 | 0.003 | 1.60 | 1.05 | 2.45 | 0.029 |
| | 2 | 3.22 | 2.06 | 5.05 | <0.001 | 3.08 | 1.95 | 4.86 | <0.001 |
| T stage | T1C* | | | | | | | | |
| | T2 | 1.29 | 0.83 | 2.02 | 0.264 | 1.18 | 0.74 | 1.90 | 0.486 |
| T3 | T3 | 2.14 | 1.30 | 3.51 | 0.003 | 2.07 | 1.09 | 3.93 | 0.026 |
| T4 | T4 | 2.29 | 0.55 | 9.60 | 0.258 | 1.68 | 0.30 | 9.50 | .0555 |
| Gleason score | ≤ 3+3* | | | | | | | | |
| | 3+4 | 1.17 | 0.77 | 1.78 | 0.467 | 0.96 | 0.56 | 1,63 | 0.876 |
| | 4+3 | 1.39 | 0.34 | 5.79 | 0.648 | 0.82 | 0.19 | 3.52 | 0.789 |
| | ≥4+4 | 2.76 | 1.72 | 4.12 | <0.001 | 2.10 | 1.05 | 4.22 | 0.036 |
| Prognostic Group [184] Favourable* | | | | | | | | | |
| | Intermediate | 1.22 | 0.77 | 1.92 | 0.394 | 1.04 | 0.57 | 1.87 | 0.906 |
| | High risk | 2.15 | 1.41 | 3.27 | <0.001 | 0.87 | 0.40 | 1.89 | 0.723 |

Legend

HR: hazard ratio; 95%CI: confidence interval.

* Reference group to which other groups are compared. The reference group per definition has a HR of 1.

## DISCUSSION

### Overall Survival

The 6-yr overall survival rate of 83.3% of this report concurs with the report of Holmberg et al. [108], which showed that 115 of 695 (16.5%) patients treated with either RP or palliative ET, died during a median follow-up of 6.2 yr. The finding that observed overall survival for cases was initially better than expected overall survival for Dutch males is in line with a recent report from Otto et al. [187]. These authors showed that, after an average follow-up of 2.8 yr of all randomized cases in the ERSPC, section Rotterdam, overall survival was statistically significantly better, compared to the general Dutch population. This observation seems to hold ground during the first 60 mo after diagnosis, even in the subgroup of cases diagnosed with PCa, and may be due to "healthy screenee bias". With increasing follow-up this advantage gradually disappeared as the observed overall survival curve approximated the expected overall survival.



### Disease specific survival

The 97.6% 5-yr overall disease-specific survival found in this screen cohort is in line with recent international reports [63, 188, 189] for localized PCa in the PSA era. The small number of cases with advanced disease and a worse disease-specific survival had only minimal impact on the overall disease-specific survival. The 5-yr disease-specific survival of the cohort of males aged 60 to 75 yr from the northern part of the Netherlands was 82% for males diagnosed between 1996 and 1998. However, this cohort cannot be considered to be identical to the control group of the ERSPC; thus, this finding should be interpreted with great caution because it is subject to several biases. A comparison with the real ERSPC control group at this time is prohibited by obvious trial rules and is not possible because these data are still blinded. The survival curve of the screen cohort with high-risk PCa, as shown in Fig. 3, is calculated with the use of the Kaplan-Maier method and is positively biased by lead-time, length-time and overtreatment, which are inherent to screening [4, 94, 95, 97]. The Kaplan-Maier analysis is not the most appropriate method to evaluate the effect of screening on disease-specific survival because the number at risk decreases with intercurrent mortality and thus influences the curve. Still the Kaplan-Maier technique was chosen because those studies, reported in the literature of men who were recruited in the PSA era, also used this method [188, 189]. Differences between curves do not provide treatment comparisons but most likely reflect the impact of patient selection. No quantitative statistics were therefore applied.

The prevalence round of the ERSPC, section Rotterdam, is associated with a mean overdiagnosis rate of 48.7%, and a mean lead-time of 9.1 yr for males aged 55 to 75 yr [4] (personal communication). This finding means that half of the screen detected cancers in Rotterdam would not have lead to clinical symptoms, even if they had not been detected, and that the PCa diagnosis is forwarded in time on an average of 9 yr. The impact of forwarding the diagnosis in time with screening could be reflected by the observation that, in the screened population 20 (2.0%) patients died of PCa, compared with 47 (6.8%) PCa deaths in the report of Holmberg et al. [108], where most of the patients were clinically diagnosed. Treatment of an overdiagnosed patient will false-positively favour disease-specific survival because overdiagnosed men by definition have a 100% disease specific survival rate. Moreover lead-time could suggest an increased disease-specific survival, even if an early diagnosis and subsequent treatment do not alter disease-specific survival prospects. Another uncertainty in this study, which will not be present in the final evaluation, is that the causes of death were not independently reviewed. Often a death certificate is not filled out by the attending physician because > 50% of deaths occur outside office hours [89], which could result in a reported cause of death that differs from the clinical picture [190]. Comparing cause of death of medical hospital patient charts with information on the death certificate in 201 patients who died of PCa Albertsen et al. [191], found a discrepancy of 10 - 20%, indicating the need for an independent committee reviewing the causes of death.

Furthermore the extent of opportunistic screening for PCa in the control population (contamination) will influence this comparison because a higher contamination rate will decrease the difference between both groups and influence the statistical power [5]. In a recent report the effective contamination, defined as an elevated PSA test prompting a prostatic biopsy, within the control arm of the ERSPC Rotterdam was calculated to be 7%; this led to a diagnosis of PCa in 3% [192]. Although exact numbers for contamination for this group are not available it can be assumed that contamination in this region was lower because PSA testing was done less frequently in the rest of the Netherlands, compared with the patients included in the trial during 1997 and 2000 [192]. The disease-specific survival rates of the different cohorts of Dutch males diagnosed with PCa between 60 and 74 yr of age increased with time (fig. 2B), which could be explained by improved treatments strategies and also by the production of lead-time due to increasing use of PSA-based testing in the Netherlands. Survival curves for males diagnosed between 1992 to 1998 in the surrogate control cohort dropped faster initially, compared with the screen cohort; however, with extended follow-up they show a stabilizing trend. The initial drop reflects the fact that, around 20% of the males in this "control" cohort had clinical stage T4 disease at diagnosis [186], compared to 1.1% in the screen cohort, while the subsequent stabilizing trend mirrors the relatively favourable prognosis of most PCa

patients [75, 86]. If these projections are correct, the cumulative disease-specific survival will continue to increase but at an invariably decreasing rate. When all these observations and biases are taken into consideration, the estimated 10-yr follow-up for the final evaluation of the ERSPC trial may be too short.

Regardless of whether one is in favour or opposed to PCa screening, patients currently diagnosed with PCa have a longer life expectancy attributable to lead-time, which is bound to go accompanied with a rise of mortality attributable to competing causes, especially in patients with favourable PCa characteristics [193]. This favourable group will have the highest rate of overdiagnosis, and the patients might not only be burdened unnecesarily with the diagnosis of PCa but might even suffer from side-effects after treatment. PCa screening in the general population should not be advocated until an effect of PCa mortality has been shown and reliable tools to identify the lethal but curable from the overdiagnosed cancers become available. If screening is desirable, the decision should be made after objective information has been provided, explaining the pros, cons and uncertainties associated with PCa screening.



## CONCLUSIONS

Although the ERSPC was not designed originally to compare treatment modalities, preliminary overall and disease-specific survival results reflect current trends in literature. Patients with screen detected PCa are very unlikely to die of PCa within 5 yr, and had a better disease-specific survival, compared with the simulated control cohort. Because of the limited number of PCa deaths and the biases associated with PCa screening, a 10-yr follow-up period of the final evaluation of the ERSPC may be too short.

*Acknowledgements*
This study was funded by the Dutch Cancer Society (grant no. EUR-94-869, EUR-98-1757); The Netherlands Organization for Health Research and Development (ZONMw) (grant no. 002-22820 2000-2-1016); the European Union (grant no. QLRI-2000-01741); and Europe Against Cancer. We thank Bert Blijenberg for processing the PSA samples, Theo van der Kwast for reviewing all Gleason scores, and Mark Wildhagen for assisting with the statistical analysis.

## EDITORIAL COMMENTS

*Marcos Luján, Hospital de Getafe. Madrid, Spain*
*marcoslujan@terra.es*
*European Urology 51 (2007) 374*

This important paper by De Vries and colleagues contributes to the increasing evidence about survival rates when considering prostate cancer natural history and therapy options. This study has been performed in the context of the European Randomized Study of Screening for Prostate Cancer (ERSPC).We are aware that all participant centers in this study follow a strict protocol in all phases of the screening detection process, and also with the assignment of causes of death. Local and multicenter committees exert a close monitoring for all those processes. In this paper, screening detected prostate cancer patients have a 97% chance of avoiding prostate cancer death after 5 years. Although five year survival rates are somewhat preliminary when considering screening detected cancers, results of overall and disease- specific survival are in line with the existing literature, either when radical prostatectomy [195], radiation therapy [196] or watchful waiting [85] are considered. Again, Gleason score seems to establish the difference with regard to outcomes, no matter which therapy option is chosen. Unfortunately, there is still much work to do in the field of localized prostate cancer. No discussion that Gleason score (and other tools) may help to identify the highest risk cases, but even more has to be done with regard to therapy. First, differences between therapy options (aggressive or conservative) to date have shown to be small in terms of survival [85, 195, 196]. Second, when a randomized trial with a design like ERSPC needs a sample size of nearly 200,000 recruited men to demonstrate a potential survival benefit between the active way (screening tests and therapy) and the conservative way (no tests, hence no therapy), one must consider the possibility that the real survival difference underlying in the target population, if existing, may be not so important as many believe.

### Do We Need the Final Results of the ERSPC Trial?

*Peter Albers*
*Department of Urology, Klinikum Kassel GmbH, Mönchebergstraße 41-43, D-34130 Kassel, Germany*
*European Urology 51 (2007) 291–292*

The oncologic community eagerly awaits the final results of the two important international screening studies for prostate cancer (Prostate, Lung Colorectal and Ovary [PLCO] and European Randomized Study of Screening for Prostate Cancer [ERSPC]). In

the report by de Vries et al.[197] in the current issue of the journal, the investigators of the ERSPC trial publish for the first time results regarding overall and disease-specific survival in the screening arm of the Rotterdam section of the trial compared to historical controls. The 1,014 patients with prostate cancer detected by screening are compared with a control group from the Dutch cancer registry of the same region. After a median follow-up of 5 yr, only 20 patients (2%) had died from prostate cancer. The comparison with the control group of patients diagnosed with prostate cancer between 1996 and 1998 reveals a difference of 15.6% in favour of the screened population. Of importance, this control group is not at all identical with the ERSPC control group. However, the 97.7% rate of disease-free survival of the 1,014 patients is in line with the currently published rates in patients with localised disease [198]. The authors conclude that patients within a screening program have a higher overall survival, which is not surprising because the patients see physicians more frequently. They further conclude that patients with screening-detected cancers are most unlikely to die from prostate cancer within 5 yr. This again is not surprising because the ERSPC investigators have already stated that the rate of favourable tumours within screening-detected cancers is much higher compared to the control group [199]. Therefore, this effect is completely explained by lead-time bias. Their last conclusion is that due to the limited number of prostate cancer deaths because of the high numbers of favourable cancers, the final evaluation of the ERSPC program may take longer than 10 yr. This, of course, is disappointing for the urologic community. This conclusion describes the problems of a trial that started randomisation in 1993 and finished enrolment in 1999. Within this time period, the 5-yr disease-specific survival rates of prostate cancer patients had improved significantly. This is nicely shown in Fig. 2B of the article [197] in the current issue. From an approximately 70% disease-free survival (DFS) rate in the population 1988–1991, this percentage increased to 82% DFS for the population 1996–1998 and 88% in the population diagnosed at the end of the enrolment (1999–2001). The DFS of the ERSPC control group is not revealed yet for obvious reasons, but the main problem will be that there is an increasing contamination of the control group by prostate-specific antigen (PSA) testing from the early 1990s to 2000. In the final years of the enrolment, the control group certainly did not differ from the screened group as it did 6 yr before. This may diminish the difference in DFS rates. The second problem may be the high rate of detection of favourable tumours by screening as described earlier [182, 199]. The third problem is the high rate of treatment in patients who may be candidates for active surveillance. At the time when the trial started, only a few patients were offered active surveillance. After the publication of the Canadian group regarding the favourable results of surveillance, this treatment strategy emerged [200]. Nearly one third of patients in this ERSPC group with screening-detected cancers would have been candidates for active surveillance [201]. However, 90% of patients chose active treatment with a somewhat higher chance of side- effects. For example,

of the 20 patients who have died from prostate cancer in this publication, 4 died after radical prostatectomy but 2 of these 4 died perioperatively. Seventeen of 20 patients who died from prostate cancer had highrisk features. Only 10% (n = 100) of patients voted for watchful waiting. Therefore, the changing treatment options in the last 5 yr will certainly become a problem in the interpretation of the ERSPC trial results. If the trial fails to show a superiority of screening in terms of mortality, people will argue that in recent years many had an opportunistic screening (currently an estimated 7%). If the trial shows the superiority of screening in terms of mortality, people will argue whether a rigorous active surveillance strategy instead of a mere control group would be the easiest solution for the problem and that this strategy had been underused during the time of enrolment. With an even longer follow-up, the problems will not disappear. Of importance, this trial delivers repeatedly valuable information on the changes of prostate cancer management in the 1990s with strong implications for treatment. Before the final results will be published, this trial yields results that influence treatment decisions of today, for example, baseline PSA, frequency of PSA values to exclude progression, and cut-off levels of PSA. Nearly all patients who are in danger of dying from prostate cancer within 5 yr have Gleason 4 + 4 or higher differentiation, only 15% of patients with favourable parameters and active surveillance need deferred treatment, and thus the overall disease-specific survival at 5 yr currently is nearly 100% [198]. Screening or not is mainly a health policy issue. For most men, an early PSA value at the age 40–45 yr is important [202]. With standardisation in the diagnosis and implementation of active surveillance, most of the important problems appear in the patients with locally advanced or metastatic disease. During the last years the number of patients with the primary diagnosis of a metastatic prostate cancer has decreased. Thus, at the time when the screening results are available, the potential screening population will have changed with most of the men already knowing their PSA value and acting accordingly. The ERSPC trial has already provided the uro-oncologic community with such valuable information that the planned publication should not be delayed. Remember the Holmberg data that were derived from a completely different staging era when the diagnosis by transurethral resection was common [195]. At the time of publication this time lag certainly influenced the interpretation of the results in terms of translation to the current clinical situation. This should be kept in mind if the conclusion is drawn that the final results of the screening trials will take longer then expected.

# Chapter 5

## Additional use of [-2] precursor prostate-specific antigen and "benign" PSA at diagnosis in screen-detected Prostate Cancer

Stijn H. de Vries, René Raaijmakers, Bert G. Blijenberg, Stephan D. Mikolajczyk, Harry G. Rittenhouse and F. H. Schröder

*Urology 65:926-930, 2005*

## ABSTRACT

### Objectives

To evaluate the adjuvant clinical use of [-2]precursor prostate-specific antigen ([-2]pPSA), which is associated with prostate cancer (PCa), and "benign" PSA, related to benign prostatic hyperplasia, in selecting a treatment strategy in patients with screen-detected PCa.

### Methods

Research-use immunoassays (Beckman Coulter) were used to measure [-2]pPSA, sum [-7, -5, -4, and -2]pPSA, and benign PSA from the frozen serum of participants from the screen arm of the European Randomized Study of Screening for Prostate Cancer, section Rotterdam, diagnosed with PCa with a serum PSA level lower than 15 ng/mL. We compared men with relatively benign PCa (Epstein's criteria; group 1) and men with arbitrarily defined aggressive PCa characteristics (Gleason score greater than 4 + 4 and more than four cores with PCa invasion or pT3C disease; group 2).

### Results

The data of 61 patients were evaluated. The median age in both groups was 68 years. Total PSA performed best in a univariate analysis, although in the multivariate analysis, the combination of pPSA and percent free PSA could correctly predict 95.5% of group 1 and 82.4% of group 2. The pPSA and percent free PSA forms remained statistically significant in the multivariate analysis of a subgroup of 30 participants normalized for PSA level and prostate volume; combined they correctly identified 89.5% and 54.5% of patients identified as having relatively favourable and aggressive PCa characteristics, respectively.

### Conclusions

Adjuvant clinical use of pPSA over traditional parameters in selecting treatment strategies for men with PCa cannot yet be definitely determined. However, the promising results in a subgroup analysis warrant further investigation.

## INTRODUCTION

In the continuing quest for a better, more reliable, and informative marker for prostate cancer (PCa), varying prostate-specific antigen (PSA) derivatives have been evaluated and tested for clinical utility. Recently discovered molecular precursors forms of PSA (pPSA), appear to correlate with PCa [41, 51, 209]. Native pPSA contains a 7 amino acid N-terminal pro-peptide, but multiple forms of pPSA with truncated pro-peptides are found in serum [34, 35, 44]. In vitro, the most stable of the five currently identified pPSA forms is [-2]pPSA, the PSA molecule plus two precursor amino acids [40]. The [-2]pPSA form also shows the most cancer specificity by immunostaining [210]. Pro-PSA together with benign PSA (BPSA) and inactive PSA, constitute the free PSA fraction of PSA (FPSA) [51]. Although BPSA is not directly associated with PCa, it was significantly elevated in biopsy-negative men with a raised PSA level, and might thus be a marker for benign prostatic hyperplasia [46, 51]. In this study, we evaluated the adjuvant clinical value of the combination of [-2]pPSA and BPSA in predicting the PCa characteristics in patients with screen-detected PCa using research assays (Beckman Coulter, for research use only; not intended for use in diagnostic procedures). We hypothesized that a high [-2]pPSA level and a low BPSA level would reflect relatively poor prognosis PCa, with the reverse associated with relatively favourable PCa prognostic factors. If true, this [-2]pPSA / BPSA ratio could then be used in determining therapy.



## MATERIAL AND METHODS

Research-use immunoassays (Beckman- Coulter, San Diego, Calif) were used to retrospectively estimate the [-2]pPSA, sum [-7, -5, -4 and -2]pPSA (designated as pPSA) [209], and [44] levels, in addition to total PSA(tPSA) and FPSA from the frozen serum of men with histologically proven, screen-detected PCa from the screen arm of the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. The blood samples of participants were assayed for tPSA within 3 hours and the remaining serum stored at –80 °C. The samples were stored on dry ice during shipment (Biologistic Services, The Netherlands, www.biologistic.nl) to San Diego where they were processed. The conditions and algorithm of the European Randomized Study of Screening for Prostate Cancer have been described in detail elsewhere [211-213]. In brief, after giving written informed consent, 21,210 of 42,376 men aged 55 to 74 years were randomized into the screening arm. The participants underwent three screening tests: PSA measurement, digital rectal examination, and a transrectal ultrasonography. The biopsy indication was set at a PSA level of 4.0 ng/mL or greater, or suspicious findings on digital rectal examination or transrectal ultrasonography. After April 1997, a PSA level of 3.0 ng/mL or greater prompted

sextant biopsy. Lateral sextant biopsies were taken in line with the recommendations of Eskew et al. [131]. In the case of a hypoechogenic lesion on transrectal ultrasonography, a seventh, lesion-directed biopsy, was taken. Because of two side studies, during the second round some men were also offered biopsy if they had a PSA level of 1.0 to 2.9 ng/mL. Clinical staging was done throughout the whole study according to the International Union Against Cancer TNM classification of 1992 [81]. The prostate biopsy cores are labeled and processed individually. The exact processing of lateral sextant biopsy results has been described elsewhere [203]. Patients with relatively favourable prognostic factors were selected from the group of men initially followed up with a watchful waiting policy, using the biopsy-derived criteria of Epstein et al. [150] for minimal PCa (T1c disease, PSA density (PSAD) less than 0.15 ng/mL/cm$^3$, no Gleason pattern 4, less than 50% invasion per core, and 2 cores maximum with PCa invasion). Patients from the prevalence screen with a biopsy Gleason score of 4+4 or greater and more than four biopsy cores with PCa invasion or pathological Stage T3c were arbitrarily considered to represent poor prognosis PCa. Men with a PSA level at diagnosis of greater than 15 ng/mL were excluded to minimize the difference of PSA fractions due to tPSA values. Figure 1 shows a flowchart of the current study. To exclude a possible tPSA to volume bias, a second analysis for cases in the 4 to 10 ng/mL PSA range combined with a prostate volume (PV) smaller than 60 cm$^3$ was performed.

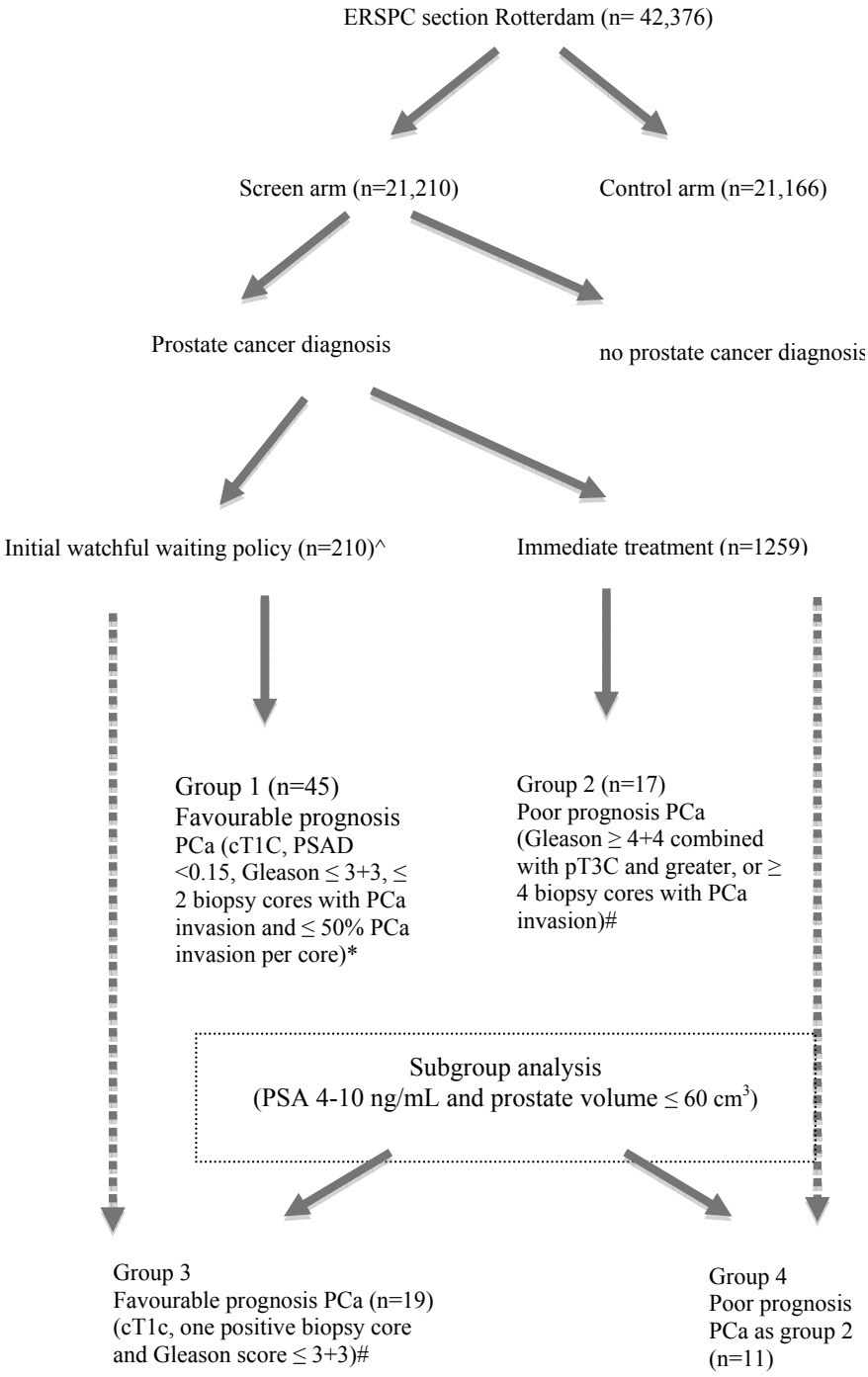
Patients were selected from the original watchful waiting cohort and the previously defined aggressive PCa cohort. The patients in the favourable group all had clinically T1c disease, combined with one biopsy core invaded with well-differentiated PCa, (Gleason 3+3 or lower). In both analyses, absolute total values of all PSA subforms, as well as the fractions of the PSA subforms, in FPSA were compared.

Statistical analyses were performed using the commercially available Statistical Package for Social Sciences software, version 12.0 (SPSS, Chicago, Ill). Two sided P values were calculated with the Mann-Whitney U tests for all variables. A significance cutoff of 5% was used. In the initial analysis only, all PSA derivates were a candidate for entry into the forward logistic regression multivariate analysis. TPSA, PV, and PSAD were not candidates, because selection for the favourable prognostic group was partly based on the PSAD. In the subgroup analysis, PSA, and all PSA subforms were candidates.

## RESULTS

Of 201 patients with screen-detected PCa initially treated on a watchful waiting policy, 44 had favourable prognostic characteristics. The data of PSA, additional FPSA and FPSA subforms, were compared with the results of 17 patients who had the previously defined aggressive PCa characteristics. The results for both groups, with univariate analysis-

**Figure 1**




Legend Figure 1: Flowchart of European Randomized Study of Screening for Prostate Cancer. * Until June 2002. * Epstein criteria [150] # arbitrarily defined criteria

**Table 1** Patient characteristics at diagnosis

| | Favourable PCa (n= 44) | | | Poor PCa (n = 17) | | | Total (n=61) | |
|---|---|---|---|---|---|---|---|---|
| | Median | Minimumimim | Maximum | Median | Minimum | Maximum | Median | p value |
| Age (yr) | 68 | 57 | 75 | 68 | 58 | 74 | 68 | 0.778 |
| PSA (ng/mL) | 4.0 | 1.4 | 9.3 | 7.0 | 3.5 | 14.8 | 4.5 | <0.001 |
| Prostate volume ($cm^3$) | 45.60 | 21.40 | 129.50 | 34.50 | 19.90 | 68.20 | 42.40 | 0.005 |
| PSAD | 0.08 | 0.03 | 0.15 | 0.21 | 0.10 | 0.53 | 0.09 | <0.001 |
| FPSA | 0.66 | 0.29 | 2.69 | 0.78 | 0.43 | 1.51 | 0.72 | 0.032 |
| [-2]pPSA | 0.032 | 0.013 | 0.251 | 0.065 | 0.018 | 0.103 | 0.037 | <0.001 |
| pPSA | 0.273 | 0.077 | 0.790 | 0.420 | 0.148 | 0.742 | 0.290 | 0.006 |
| BPSA | 0.172 | 0.035 | 1.233 | 0.264 | 0.095 | 0.541 | 0.199 | 0.043 |
| [-2]pPSA/BPSA ratio | 0.181 | 0.027 | 0.966 | 0.228 | 0.082 | 0.428 | 0.211 | 0.043 |
| %FPSA | 0.165 | 0.093 | 0.297 | 0.109 | 0.044 | 0.248 | 0.153 | <0.001 |
| pPSA / FPSA ratio | 0.430 | 0.175 | 0.817 | 0.503 | 0.283 | 0.830 | 0.453 | 0.054 |
| [-2]pPSA/FPSA ratio | 0.050 | 0.019 | 0.290 | 0.082 | 0.041 | 0.122 | 0.058 | 0.001 |
| BPSA/FPSA ratio | 0.284 | 0.122 | 0.961 | 0.284 | 0.181 | 0.566 | 0.284 | 0.520 |

Legend: PCa: prostate cancer; PSA: prostate-specific antigen; PSAD: PSA density; FPSA: freePSA; [-2]pPSA: fraction of precursor PSA; pPSA: precursor PSA; BPSA: benign PSA; %FPSA: percent FPSA.

related P values are shown in table 1. The differences in tPSA, planimetric PV, PSAD, and absolute levels of FPSA, [-2]pPSA, BPSA, and pPSA were statistically significant between groups. After calculating the different ratios of the FPSA subforms in FPSA, only the difference in the fraction [-2]pPSA in FPSA (P =0.001) remained statistically significant. As expected, the difference in the percent FPSA (%FPSA) was statistically significant between the two groups. None of the PSA derivates alone could outperform tPSA, because the tPSA had the best ROC curve at any point (data not shown). The [-2]pPSA to BPSA ratio reached borderline statistical significance (P = 0.043). The statistical difference of tPSA and PV was at least partially due to the use of a cutoff value for the PSAD (less than 0.15 ng/mL/$cm^3$) for the favourable group, who were, therefore, not entered in the multivariate analysis. In the multivariate logistic regression analysis, pPSA and %FPSA remained statistically significant predictors, with P = 0.001 and P < 0.001, respectively (Table 2). In combination, they predicted 42 of the 44 "favourable" patients (sensitivity 95.5%) and missed 3 of 17 patients with poor characteristics (specificity 82.4%).

To minimize the influence of tPSA level and PV on the PSA subforms, we did a subgroup analysis in the group of men with PSA level between 4 and 10 ng/mL and a PV smaller than 60 $cm^3$. The 19 patients in group 3 were compared with the 11 men with poor prognostic PCa characteristics. Table 3 shows the results of the subgroup analysis. Now only the absolute value (in ng/mL) of pPSA, as well as its fraction in FPSA and the [-2]pPSA/BPSA ratio, were statistically significantly different between groups (P= 0.030, P=0.027, and P=0.033, respectively). PSAD remained statistically significantly greater in the poor

**Table 2.** Multivariate analysis results

| | Included | p-value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Odds ratio | 95 CI |
|---|---|---|---|---|---|---|---|---|
| "Favourable" vs. "poor" | pPSA<br>%FPSA | 0.001<br><0.001 | 95.5%<br>(42 of 44) | 82.4%<br>(14 of 17) | 93.3% | 87.5% | $1.0*10^{6}$<br><0.001 | $414 - 2.4*10^{8}$<br>$7.6*10^{-29}$ - $1.5*10^{-9}$ |
| subgroup "favourable" vs. "poor" | pPSA<br>%FPSA | 0.015<br>0.053 | 89.5%<br>(17 of 19) | 54.5%<br>(6 of 11) | 77.3% | 75% | $2.5*10^{4}$<br><0.001 | $7.5 - 8.7*10^{7}$<br>$1.5*10^{-18}$ - 1.3 |

Legend: PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval; other abbreviations as in Table 1

**Table 3.** Patient characteristics in the PSA 4-10ng/ml range

| | "Favourable" PCa (n=19) | | | "Poor" PCa (n= 11) | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Median | Minimum | Maximum | Median | Minimum | Maximum | Median | p value (Two-Tailed) |
| Age (yr) | 68 | 57 | 75 | 68 | 58 | 74 | 68 | 0.591 |
| PSA (ng/mL) | 5.8 | 4.1 | 8.7 | 6.4 | 5.0 | 9.5 | 6.2 | 0.106 |
| Prostate volume ($cm^3$) | 39.9 | 22.7 | 58.0 | 32.6 | 20.6 | 46.3 | 35.2 | 0.162 |
| PSAD | 0.15 | 0.08 | 0.28 | 0.20 | 0.14 | 0.35 | 0.17 | 0.033 |
| FPSA | 0.730 | 0.360 | 2.380 | 0.930 | 0.430 | 1.510 | 0.748 | 0.518 |
| [-2]pPSA | 0.049 | 0.013 | 0.251 | 0.067 | 0.039 | 0.103 | 0.051 | 0.055 |
| pPSA | 0.367 | 0.121 | 0.696 | 0.588 | 0.230 | 0.742 | 0.417 | 0.030 |
| BPSA | 0.234 | 0.122 | 1.389 | 0.287 | 0.095 | 0.541 | 0.247 | 0.813 |
| [-2]pPSA/BPSA | 0.196 | 0.016 | 0.966 | 0.308 | 0.191 | 0.428 | 0.231 | 0.033 |
| %FPSA | 0.149 | 0.041 | 0.301 | 0.110 | 0.069 | 0.248 | 0.142 | 0.189 |
| pPSA / FPSA | 0.478 | 0.055 | 0.817 | 0.571 | 0.360 | 0.830 | 0.497 | 0.027 |
| [-2]pPSA / FPSA | 0.054 | 0.009 | 0.290 | 0.082 | 0.047 | 0.122 | 0.068 | 0.074 |
| BPSA / FPSA | 0.301 | 0.178 | 0.584 | 0.247 | 0.181 | 0.566 | 0.287 | 0.175 |

Legend as in Table 1.

prognostic group (P=0.033). In the forward multivariate logistic regression analysis, only the entering PSA and PSA subforms, pPSA and %FPSA, remained significant predictors and together reached a sensitivity of 89.5% with a specificity of 54.5% (Table 2).

## COMMENT

PCa remains an unpredictable disease capable of killing patients. In the current PSA screening era, however, the vast majority of detected cancers are well differentiated and clinically organ confined and can be treated with a curative intent [77]. However,

because of overdiagnosis, which has been shown to be present in 50% of patients or more with screen-detected PCa [4, 95], not all patients with PCa will need immediate radical treatment. The decision regarding therapy is often based on predictors estimating tumour aggressiveness and the patient's wishes. Commonly used parameters such as the biopsy Gleason score, PSAD and clinical stage, although validated and clinically useful, are subject to error because of interobserver and intraobserver variability [76, 141, 214]. A reliable biochemical parameter reflecting tumour characteristics could aid both clinicians and patients in more objectively choosing a therapy modality. In this study, we evaluated the use of pPSA forms combined with BPSA as a possible future aid in making treatment decisions. Bangma et al. [215] investigated the value of [-5,-7]pPSA and human kallikrein-2 but not [-2]pPSA and BPSA as possible serum markers for PCa grading. Using a different assay system for [-5,-7]pPSA [215], the investigators did not find any correlation between these serum markers and the pathological grade or stage. Catalona et al. [42], and Sokoll et al. [216] initially demonstrated that the ratio of pPSA in FPSA (%pPSA) significantly increased the specificity for cancer detection in the 2 to10 ng/mL PSA range and outperformed tPSA and %FPSA. The measurement of [-5,-7]pPSA alone, however, did not add significant clinical utility in those studies, in agreement with Bangma et al. [215]. In a more recent study, Catalona et al. [43] reported the tumour characteristics of the same cohort and determined that %[-2]pPSA was the best discriminator to identify aggressive cancers in the 2 to 4 ng/mL PSA range and %pPSA was the best predictor in the 4 to 10 ng/mL range [43]. The investigators defined an aggressive cancer as one with a biopsy or pathological Gleason score of 7 or greater or a pathologic stage T3. The median values for %pPSA in 4 to 10 ng/mL range in the current report were greater than those observed by Catalona et al. [43] and Sokoll et al. [216], which could be explained by the different selection criteria used. The differences in the absolute values of FPSA, pPSA forms, %FPSA, and %pPSA were statistically significant between groups in the current initial analysis, as was the tPSA. The combination of pPSA and %FPSA correctly predicted 42 of 44 men with favourable PCa and 14 of 17 patients with arbitrarily defined poor PCa characteristics (Table 2), This impressive result, however, could also be attributed to the significantly greater tPSA and lower PV in the poor characteristics group, because both parameters can influence the pPSA and BPSA levels [48, 215]. Moreover, by using the Epstein criteria to select the group of patients with relatively favourable PCa characteristics, a PSA to PV bias was introduced.

To test the hypothesis that the combination of [-2]pPSA and BPSA could differentiate between relatively favourable and poor PCa characteristics, a subgroup analysis of patients with comparable tPSA values and PV at diagnosis was done. Although the numbers were limited, this analysis showed a statistically significantly lower [-2]pPSA/BPSA ratio (P=0.033) in men with favourable PCa characteristics compared with those with poor PCa characteristics, in line with our hypothesis. The pPSA and %pPSA remained

significantly greater in the poor prognostic subgroup. In the multivariate analysis, the combination of pPSA and %FPSA reached a sensitivity of 89.5% and specificity of 54.5%. This means that 17 of 19 men with arbitrarily defined favourable PCa characteristics were correctly identified as having relatively favourable prognostic PCa characteristics on the basis of a combination of these serum markers. Owing to the low specificity of the test, the positive predictive value of the test was 77.3%, meaning that roughly three quarters of the patients identified as "favourable" by this marker combination did have favourable prognostic characteristics and one quarter actually had "poor" prognostic characteristics. Although promising, this result should be interpreted with caution. First, the groups were small and arbitrarily defined and compared populations of PCa with rather extreme differences in prognostic characteristics. Second, clinical, and not pathologic, tumour characteristics were used to design the patient groups, and those are known to underestimate the highest cancer grade present in the prostate. Third, conserved frozen samples were tested with a research-use assay that may not be as robust as fully validated assays. Despite these potential limitations, in our opinion, the results warrant further study of these new tumour markers.



## CONCLUSIONS

The adjuvant clinical usefulness of pPSA forms and BPSA in identifying aggressive from less aggressive PCa, compared with traditional parameters, cannot yet be definitively determined. However, the promising results in a subgroup analysis warrant additional study.

# Part III:
# Monitoring patients on active surveillance

**Chapter 6**
Prostate cancer characteristics and prostate specific antigen changes in screen detected patients initially treated with a watchful waiting policy
*J Urol. 2004 Dec; 172: 2193-6*

# Chapter 6

## Prostate Cancer Characteristics and Prostate Specific Antigen changes in Screening detected Patients initially treated with a Watchful Waiting Policy

Stijn H. de Vries, René Raaijmakers, Ries Kranse, Bert G. Blijenberg and F.H. Schröder *J. Urol. 2004 Dec;172:2193-2196*

## ABSTRACT

**Purpose:**
We evaluated prostate cancer (PCa) characteristics at diagnosis and changes in prostatic specific antigen (PSA) with time in males with screening detected PCa that was initially managed with a watchful waiting policy.

**Materials and Methods:**
Patients with histologically proven PCa and PSA less than 10 ng/mL were selected from the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. The choice of initiating a watchful waiting policy was patient desire or physician advice. PSA slope and PSA doubling time (PSADT) were calculated in patients with 3 or more PSA test results available.

**Results:**
A total of 191 patients were included. Mean age at diagnosis was 69 years and mean PSA was 3.9 ng/mL. Of the patients 92.6% had a Gleason score of 3 + 3 or lower, 133 had a follow-up of greater than 12 months (mean 40) and 35 (29.2%) had a negative PSA slope. Mean PSADT was 9.7 years (range 0.3 to 155) in 85 males with a positive PSA slope. During follow-up 30 patients changed therapy.

**Conclusions:**
Watchful waiting remains a controversial prostate cancer treatment strategy. In select screening detected patients with PCa, there appears to be a subgroup with stable or even decreasing PSA values with time. These males could profit from a watchful waiting policy with possible deferred treatment. Together with conventional tumour parameters at diagnosis PSADT and PSA slope during follow-up could be used to monitor tumour activity and possibly aid in determining the time of deferred treatment. Further follow-up is mandatory to validate these results.

## INTRODUCTION

The primary goals of the European Randomized Study of Screening for Prostate Cancer (ERSPC) are to show a significant decrease in prostate cancer (PCa) mortality between the screening and control arms, and evaluate screening algorithms [88]. The ERSPC was not primarily designed to compare different treatment modalities. In the Dutch (Rotterdam) screening arm of the ERSPC males with a histologically proven PCa are referred to their general practitioner after discussing diagnosis and treatment options during an outpatient clinic visit at the study site. Patients are free to choose the treatment modality as well as the specific health care center. In some select patients the physician of choice might not advise immediate radical therapy, while some patients do not desire immediate treatment. We outline preliminary results in patients in the screening arm of the ERSPC, section Rotterdam with watchful waiting as initial treatment.

## PATIENTS AND METHODS

After four pilot studies the ERSPC, section Rotterdam started in June 1994 with a four-year screening interval. The conditions and algorithm of the ERSPC have been previously described in detail [88]. Briefly, 21,210 of 42,376 men 55 to 74 years old were randomized into the screening arm after providing written informed consent. Participants underwent 3 screening tests, namely PSA measurement, digital rectal examination (DRE) and transrectal ultrasound (TRUS). Biopsy indication was set at PSA 4.0 ng/mL or greater, or suspicious findings on DRE or TRUS. After April 1997, PSA 3.0 ng/mL or greater prompted sextant biopsy. Lateral sextant biopsies were performed, in line with the findings of Eskew et al. [131]. In case of a hypoechogenic lesion on TRUS a seventh, lesion directed biopsy was obtained. Due to 2 side studies during the round 2 some men were also offered biopsy in the PSA 1.0 to 2.9 ng/ml range [88]. Patients in the screening arm with a histologically proven PCa who had started on a watchful waiting policy between September 1994 until August 2002 were selected. Excluded were patients with PSA at diagnosis greater than 10 ng/mL due to a lower probability of organ confined disease. PSA at diagnosis was determined with the Beckman-Coulter Hybritech Tandem E Assay; (Hybritech, San Diego, California). Since January 2000, the Access automated version has been used (Beckman- Coulter, Fullerton, California). No statistically significant difference was found between these assays in the PSA range of less than 10 ng/mL. Clinical staging is done throughout the whole study according to the 1992 UICC TNM classification [81]. Prostate biopsy cores are labeled and processed individually [203]. To estimate comorbidity status at diagnosis the Charlson score was used [183]. Because follow-up regimens varied among local practices, data for this study were collected from semiannual patient

chart review for the first 5 years and annually thereafter. Charts were assessed for medical history, physical examination (DRE), dissemination studies and PSA tests. To minimize PSA level outcome differences, the PSA values of other assays were corrected for known differences with the Hybritech assay using the regression method of Passing and Bablok (see appendix) [204, 205]. Indications and patient characteristics are provided for those who changed therapy. To calculate PSA doubling time (PSADT) the base 2 logarithm of the PSA value was calculated using the formula, 2log(PSA) = 10log(PSA) / 10log(2) [206], and plotted against time since diagnosis (date of PSA measurement to date of diagnosis). The linear regression line through these points estimates the PSA slope. The doubling time can be calculated as the reciprocal value of a positive slope, while a negative or decreasing slope represents a PSA half-life. PSA slopes were only calculated in patients with 3 or more PSA values acquired prior to a possible therapy change.

## RESULTS

In the ERSPC screening arm 1,514 males were diagnosed with adenocarcinoma of the prostate between September 1994 to August 2002 and 201 were initially managed by a WW policy that is 13.3% of all screening detected cancers. We excluded 10 males due to a PSA greater than 10 ng/mL at diagnosis. Table 1 shows results in the 10 excluded patients. Shortly after the PCa diagnosis 1 excluded patient died of a pulmonary embolism after tumour nephrectomy.

**Table 1.** Excluded patients with PSA greater than10.0 ng/mL

| Patient | Age at diagnosis | PSA at diagnosis (ng/mL) | PSA density (ng/mL/cm$^3$) | Gleason pattern | No. pos cores | PSADT (yrs) | Follow-up (mos) | Treatment Change | last PSA (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 75.3 | 24.8 | 0.27 | 3+3 | 1 | 3.1 | 89.7 | ET after 80.5 mos | 1.7 |
| 2 | 74.7 | 10.4 | 0.17 | 3+4 | 4 | 4.9 | 44.6 | no change | 17 |
| 3 | 73.9 | 10.3 | 0.38 | 3+3 | 1 | 9.2 | 63.4 | no change | 14 |
| 4 | 71.2 | 13.1 | 0.25 | 3+4 | 3 | -3.0 | 50.1 | EBRT after 19.4 mos | 1.8 |
| 5 | 66.5 | 315.7 | 5.80 | 4+4 | 3 | 0.8 | 85.8 | ET after 18.7 mos | 1.9 |
| 6 | 72.4 | 13.2 | 0.29 | 3+3 | 4 | 9.2 | 57.4 | no change | 8.6 |
| 7 | 72.8 | 16.6 | 0.15 | 3+4 | 4 | | 0.0 | no change | died |
| 8 | 74.0 | 12.0 | 0.56 | 3+3 | 1 | 4.0 | 20.9 | no change | 15.3 |
| 9 | 58.6 | 55.0 | 1.82 | 4+4 | 7 | 5.1 | 28.9 | no change | 76 |
| 10 | 64.4 | 11.0 | 0.22 | 3+3 | 2 | -6.4 | 33.0 | no change | 7.5 |

legend
ET= Endocrine Treatment
EBRT= External Beam Radiation Therapy

Table 2 shows the characteristics at diagnosis of the 191 included males. Of the included men 103 were diagnosed with PCa in round 1, including 8 after repeat biopsy 1 year later, while 87 were diagnosed in round 2 and 1 was diagnosed in round 3. Mean age at diagnosis was 69 years. The majority of concomitant diseases were related to the cardiovascular/cerebrovascular systems. In 76 patients (39.8%) the physician suggested WW, while 73 patients (38.2%) preferred a watchful waiting policy. In 42 patients (22%) these data are not yet available. A total of 32 males (16.6%) had a PSA less than 3.0 ng/mL.

DRE was abnormal in 47 patients (24.6%). Of the patients 28 had T2A, 2 had T2B, 11 had T2C and 6 patients had T3 palpable disease, which was T3A in 5 and T3C in 1.

In 154 men (80.6%) the biopsy Gleason sum was 6 (3+3), while 23 (12%) had a Gleason sum of less than 6. One patient had a Gleason score of 4+3, 9 had a Gleason score of 3+4 and the remaining 4 men had a 4+4 Gleason pattern. A total of 106 patients (88.3%) with 1 positive core had less than 30% invasion of that core, while 4 (3.3%) had greater than 50% invasion in that single positive core. Follow-up for 12 months (mean 40, range 13 to 100) was available on 133 patients and 120 underwent 3 or more PSA tests (median, range 3 to 15) before changing therapy. In these patients the mean PSA slope was 0.11 2log(ng/mL) yearly (median 0.09, range -0.91 to 3.0), which corresponds to a mean PSADT of 11.6 years (median 6.9, range 0.3 to 101) in patients with a positive slope. Table 3 shows the distribution of PSADT, PSA half-life, and related treatment decisions.

During follow-up 30 patients changed therapy. A total of 20 patients received subsequent radiation therapy with curative intent, including 2 who received adjuvant endocrine treatment. Five men underwent radical prostatectomy (RP). Five males are being treated with endocrine treatment (ET), 2 have other malignancies (urothelial cell carcinoma and metastasized bladder cancer, respectively) and 1 who progressed to clinical T3A stage elected to start endocrine treatment. The remaining patient was intentionally scheduled for curative radiation therapy, but computerized tomography guided punction confirmed PCa metastasis. He has been on luteinizing releasing hormone analogues since November 1997 and still has PSA less than 1 ng/mL. The remaining patient uses the 5a-reductase blocker finasteride. Median time to treatment change was 19 months (mean 27, range 7 to 82) with a mean follow-up after treatment of 27 months (median 20, range 2 to 86) (table 4). Of the 30 patients with subsequent treatment 1 currently has signs of biochemical recurrence. He underwent RP 7 months after diagnosis, when PSA increased from 2.4 ng/mL at diagnosis to 3.5 ng/mL. Trigger points for deferred therapy were patient desire without signs of biochemical or local progression in 5 males. Two males had PSA plus local progression. In 22 males the treating physician interpreted the PSA increase with time as biochemical progression, and 1 patient seemed to have local progression without PSA progression.

**Table 2.** Characteristics at diagnosis in 191 included males

| | No. Pts | (%) |
|---|---|---|
| Age at diagnosis (mean 68.6 median 69.3): | | |
| 55-59 | 8 | 4.2 |
| 60 - 64 | 33 | 17.3 |
| 65 - 69 | 64 | 33.5 |
| 70 - 74 | 82 | 42.9 |
| Older than 75 | 4 | 2.1 |
| Charlson score: | | |
| 1 or Less | 153 | 80.1 |
| Greater than 1 | 22 | 11.4 |
| Unknown | 16 | 8.4 |
| PSA at diagnosis ng/mL ( mean 3.9 median 3.6): | | |
| Less than 4 | 108 | 56.5 |
| 4-10 | 83 | 46.3 |
| PSA density ng/mL/ $cm^3$ (mean 0.11 median 0.09): | | |
| 0.15 or Less | 154 | 83.2 |
| Greater than 0.15 | 37 | 16.8 |
| Clinical stage: | | |
| T1C | 144 | 75.4 |
| T2 | 41 | 21.5 |
| T3 | 6 | 3.1 |
| No. pos cores: | | |
| 1 | 120 | 62.8 |
| 2 | 43 | 22.5 |
| 3 or Greater | 28 | 14.7 |
| Gleason sum: | | |
| 6 or Less | 177 | 92.7 |
| 7 | 10 | 5.2 |
| 8 or Greater | 4 | 2.1 |
| Therapy choice: | | |
| Physician suggestion | 76 | 39.8 |
| Patient choice | 73 | 38.2 |
| Unknown | 42 | 22.0 |

Mean follow-up was 40 months (median 37, range 13.5 to 99.8 in 133 patients with greater than12 months of follow-up.

During follow-up 6 patients in the overall group have died of intercurrent causes. None have died of prostate cancer, as coded by the independent Causes of Death Committee [88].

**Table 3.** PSADT in patients with 3 or more PSA test before treatment change and PSA half-life in those with negative slope

| | No.Treatment Change | | | |
|---|---|---|---|---|
| **PSADT (yrs)** | **No** | **Yes** | **Total (n=)** | **Total (%)** |
| 0 - 1.99 | 1 | 4 | 5 | 4.2 |
| 2 - 2.99 | 5 | 4 | 9 | 7.5 |
| 3 - 3.99 | 5 | 2 | 7 | 5.8 |
| 4 - 4.99 | 9 | 3 | 12 | 10.0 |
| 5 - 9.99 | 20 | 2 | 22 | 18.3 |
| 10 - 19.99 | 17 | 2 | 19 | 15.8 |
| > 20 | 9 | 2 | 11 | 9.2 |
| | 66 | 19 | 85 | 70.8 |
| **PSA half-life (yrs)** | | | | |
| > 10 | 17 | 1 | 18 | 15.0 |
| 5 - 9.99 | 7 | | 7 | 5.8 |
| 3 - 4.99 | 8 | | 8 | 6.7 |
| 1 -2 | 2 | | 2 | 1.7 |
| subtotals | 34 | 1 | 35 | 29.2 |
| Total | 100 | 20 | 120 | 100.0 |

**Table 4.** Characteristics of patients with subsequent treatment.

| | Median RP | Median RT | Median ET | Totals |
|---|---|---|---|---|
| No. Pts. | 5 | 20 | 5 | 30 |
| Age at diagnosis (years) | 68 | 67.5 | 73.7 | 67.7 |
| PSA at diagnosis ng/mL (range) | 3.4 (2.4 - 7.3) | 4.8 (1.4 - 7.6) | 3.6 (3.1 - 5.2) | 4.4 (1.4 - 7.6) |
| Months before treatment | 9.1 (6.9 - 53) | 19.1 (12.0 - 58.6) | 23.9 (14.8 - 60.5) | 19.1 (6.9 - 60.5) |
| Mos follow-up after treatment (range) | 47.5 (4.7 - 85.5) | 19.0 (2.9 - 57.2) | 8.2 (0 - 55.7) | 20.5 (0 - 85.8) |

**Table 5.** PSADT in patients with positive slope

| | No change | Change | Totals |
|---|---|---|---|
| Mean yrs* | 12.6 | 8.0 | 11.6 |
| Median (range) | 7.9 (1.9-101) | 3.4 ( 0.3-44 ) | 6.9 ( 0.3-101 ) |
| total (n) | 66 | 19 | 85 |

* p= 0.006

## DISCUSSION

Organ confined adenocarcinoma of the prostate can be managed in 3 ways, namely by surgery, radiation therapy or watchful waiting. In surgery and radiation therapy the goal is to eliminate the primary tumour. However, in this effort normal structures are sometimes damaged, and unwanted side effects can occur. The combination of slow PCa progression in most screening detected cases [4, 94], the suspected overdiagnosis of PCa in this opportunistic (PSA) screening era [4], and these possible side effects explain renewed interest in watchful waiting [108, 122, 145]. The rationale of watchful waiting should be to avoid unnecessary treatment with its inherent side effects and costs in patients with PCa, who are not likely to progress to clinical disease during their lifetime, while offering these select patients a possible cure later. Thus, the key to successful watchful waiting is based on 2 pillars.

It must become possible to identify patients with organ confined PCa who have latent or minimal PCa and are not likely to progress or who might even never have symptoms of the disease.

Objective and reliable parameters of PCa activity must become available to monitor this cohort not to lose the opportunity of treatment with curative intent when required or desired.

In the literature PSA at diagnosis less than 10 ng/mL, clinical stage T2A and a Gleason score of 3+3 or lower are usually used to identify males with favourable PCa characteristics. In the current study 161 males (84%) had such favourable characteristics.

Although earlier studies suggested an advantage of RP over radiotherapy [188], recent reports show similar 5 and 8-year biochemical-free survival rates of up to 90% for either therapy modality in patients with favourable prognostic PCa characteristics [77, 189]. Although biochemical-free survival is a surrogate endpoint, these impressive results might well be positively biased by a number of males with screening detected PCa that might not have become clinically apparent during the normal lifetime [4, 95], since by definition overtreatment has a 100% disease specific survival rate.

Carter et al. selected 81 patients with presumed small volume cancers [145] based on the Epstein criteria, T1C, PSAD 0.15 ng/ml/cm$^3$ or less, 2 or fewer cores with cancerous invasion, less than 50% cancer invasion in any core and no Gleason pattern

greater than 3 for watchful waiting [150]. Follow-up consisted of semiannual PSA tests and annual repeat biopsy (greater than 12 cores). Of 25 patients with progression on prostatic needle biopsy 12 had curable cancers after RP [145]. Of the 100 males in this study complying with Epstein selection criteria 2 underwent RP and 5 received radiation therapy. In the Rotterdam region repeat prostate biopsy to evaluate histological PCa characteristics is not a routine investigation. Still, during follow-up in the current study 16 patients underwent repeat biopsy. In 7 sextant biopsies PCa histology was found, which led to subsequent treatment in 2 males. The remaining 9 biopsies did not show histological evidence of PCa. Apart from histological progression, PSA tests can be done during follow-up in patients with PCa. This is based on the assumption that PCa volume correlates with PSA [128]. The PSA increase with time, that is PSADT, then reflects tumour activity. In the prospective study Choo et al. defined disease progression based on repeat prostate needle biopsies, clinical progression and PSADT [122]. They arbitrarily used a PSADT less than 2 years as a criterion for treatment. In the current study 5 males had PSADT less than two years, of whom 4 changed therapy.

Furthermore they found that 42% of males (72) had PSADT greater than 10 years, suggesting slowly progressive tumours [122]. When calculating PSA slope, we found a negative slope in 35 of 120 men (29.1%)(table 3). Because PCa is by definition a progressive disease, this remarkable finding, which has also been described by others [207], should be interpreted rather as result of the natural or biochemical variation of PSA [205, 208]. This phenomenon can also be explained by assay variation and, therefore, it most likely represents stable or minimally progressive PCa. A third explanation could be that with time PCa is dedifferentiating and produces less PSA. However, this seems less likely since most males in this study had favourable PCa characteristics at diagnosis. The finding that 25 of 35 patients had a negative slope of –0.2 to 0 ng/mL yearly, corresponding with a PSA half-life of greater than 5 years, is in line with reported biological PSA variation [208]. In this study 30 patients (25%) had PSADT greater than 10 years, thus, suggesting indolent disease, which increases to 54.1% when the 35 with a negative slope are added to this group. This value is higher than the findings of Choo et al. [122]. However, they did not describe a subgroup with a decreasing PSA with time also, when comparing mean PSA slope and PSADT in patients with and without subsequent treatment, PSADT was significantly higher in those receiving subsequent treatment (p=0.006) (table 5).

Several aspects must be considered when interpreting these results. 1) Study follow-up is too limited to show differences in outcome after deferred treatment with curative intent. 2) Because follow-up is done at different centers, various PSA assays were used. Although regression equations to correct for assay type were used to calculate PSA change with time, we still found a wide interpatient range of PSA slope and PSADT. In a further attempt to minimize this variation we calculated PSA slope and PSADT while excluding the PSA value at diagnosis, without using the regression equations, assuming

that during follow-up the same assay was used. Of the 96 males with 3 or more PSA tests before treatment change in this subgroup 24 (25%) still had a decreasing PSA slope and 19 (18.7%) had PSADT greater than 10 years. This finding is more in line with the findings of Choo et al. [122], and it again supports the possibility that there is a group of patients with favourable PCa characteristics that has slow progressive or even latent disease. 3) These patients were selected from 2 subsequent rounds of a PCa detection program and might not resemble an average population. However, as PSA driven screening becomes more prevalent in western countries, more males with comparable favourable PCa characteristics will also be detected outside of a screen program.

The results of this study show that at least in screening detected PCa there is an identifiable population of males who have stable or even decreasing PSA with time. These patients could possibly benefit from a watchful waiting policy with possible deferred therapy at a later time. Further analyses of these data with longer follow-up could aid in coming to an evidence-based decision, justifying a watchful waiting policy with possible deferred treatment in select patients. Objective clinical parameters, such as PSA slope or PSADT activity, may be useful indicators for monitoring PCa.

## CONCLUSIONS

Watchful Waiting remains a controversial topic in prostate cancer treatment. However, in carefully selected screening detected patients with PCa it appears safe to delay curative treatment or even refrain from treatment. Together with conventional tumour parameters at diagnosis PSADT or PSA slope could be used to monitor tumour activity during follow-up and possibly aid in determining the time of deferred treatment. Further follow-up is mandatory to validate these results.

Conja Franken-Raab provided follow-up data.

*Acknowledgements*
Supported by grants EUR-94-869 and EUR-98-1757 (to Erasmus University Rotterdam) from the Dutch Cancer Society and grants 002-22820 and 2000-2-1016 (to Erasmus University Rotterdam) from The Netherlands Organization for Health Research and Development (ZONMw), by 5th Framework program grant QLRI-2000-01741 (to Erasmus University Rotterdam) from the European Union, and by Europe Against Cancer.

**Appendix.** Regression equations converting used PSA assay values into Hybritec Tandem-E values [204, 205].

y (Elecsys) = 1.03(Tandem E) - 0.02
y (Immulite) = 0.99(Tandem E) - 0.19
y (Access) = 1.03(Tandem E) - 0.08
y (IMx) = 0.89(Access) +0.01 Until Februari 1998 another reagent was used and no regression equation available for the Tandem-E assay.
y (Tandem E) = 1.09(IMx) -0.06

# Part IV:
# General discussion

**Chapter 7**
General discussion

# Chapter 7

## General discussion

The goal of this thesis is to contribute to the evaluation of active surveillance (AS) as a safe strategy in selected men with organ confined prostate cancer (PCa) at diagnosis. To investigate the feasibility of an AS policy the key questions in AS were addressed;

- Who are suitable candidates?
- How to select and monitor these men?
- When to treat these patients without compromising the chance of cure?

In the general discussion the outcomes of the previous chapters are evaluated and compared with the current perspectives on AS because continuous progress has occurred in recent years in both the fields of prostate cancer and of active surveillance.

## RATIONALE FOR ACTIVE SURVEILLANCE

The concept of AS is to avoid or delay unnecessary treatment, with its inherent side-effects and costs, while preserving the window of cure in these patients. As explained in the introduction PCa screening is associated with a shift towards more favourable PCa characteristics at diagnosis, lead-time bias, lenght-time bias and overdiagnosis of PCa [4, 65, 142]. Thus PCa is diagnosed at an earlier age, at a more favourable stage and will in some patients never develop into clinical disease. These findings triggered the development of an AS protocol within the ERSPC, section Rotterdam [217]. **Chapter 3** is the result of an inventory of the different protocols used at the time. The expression "watchful waiting" was originally chosen to describe this policy as no international consensus was yet reached how to describe such a pro-active monitoring policy. Nowadays, watchful waiting as used in this thesis is replaced by the term "active surveillance"[126]. **Chapter 3** stands at the beginning of the development of an AS regimen in the Rotterdam region and led to a first policy proposal in November 2003 at the Rotterdam Comprehensive Cancer Registration (IKR) meeting. After regional introduction, the policy proposal was published in the magazine of the Dutch Urological Association [218]. This proposal has evolved into an international prospective, observational study "Prostate Cancer Research International: Active Surveillance study", (PRIAS, www.prias-project.org) [219, 220]. More detailed information on the multicentre PRIAS study and other AS research endeavours is provided further down.

## SELECTING PATIENTS FOR AN ACTIVE SURVEILLANCE POLICY

In **chapter 4** the overall survival (OS) and disease specific survival (DSS) of screen detected PCa patients are compared to a non screened cohort [197]. After a median follow-up of 55 months the five year OS and DSS were 88.3% and 97.5% respectively in the screen cohort compared to a DSS of 82% in the cohort of men from the northern part of the Netherlands aged 60 to 75 years and diagnosed between 1996 and 1998. In the prevalence screen cohort 81.4% of the patients had organ-confined disease and 45.4% had favourable prognostic PCa characteristics. PCa death after a median follow-up of 55.1 months occurred almost exclusively in the group of men with poor prognostic characteristics and none of the patients on an expectant management policy died of PCa. This finding is helpful in selecting patients for AS in the future. Firstly, PCa death was very uncommon during the first five years especially in the favourable risk group of the screen cohort. Future AS candidates should thus be recruited using the characteristics of this group. Furthermore, screen detected cases had a better DSS compared to clinically detected cases which may identify a healthy screenee bias. As candidates for an AS policy these men may benefit longer from avoiding the side-effects of active treatment. It also becomes clear from the limited number of PCa deaths in this prevalence screen detected cohort of prostate cancers that follow-up of long duration is necessary to validate any treatment modality for organ confined screen detected PCa.

## ACTIVE SURVEILLANCE POLICIES OVER TIME

Results of a prospective randomized controlled trial of AS in the current PSA screen era are not yet available, therefore level one evidence based criteria for selecting, monitoring and timing deferred treatment in active surveillance are non existent. The identification criteria most widely used for prostate cancers that may be considered clinically "non significant" were proposed more than ten years ago [150, 221]. For example, the definition that clinically insignificant cancer should be smaller than 0.5 cc was suggested in 1993 [221]. It is based on 55 men (40%) out of 139 patients who had undergone a radical cystoprostatectomy for bladder cancer and had incidental PCa at pathological examination. 80% of these cancers were smaller than 0.5 cc and were classified as clinically insignificant on the basis of epidemiological considerations. Another commonly used definition to predict insignificant cancer based on biopsy results and PSA density was introduced in 1994 [150]. Though this definition has been successfully tested with surgical specimens [222, 223] no validation study correlating biopsy outcome with the natural history of PCa is currently available.

**TABLE 1**

| | | Choo.et al[122, 228, 232] | Vd Berg et al.[227] | Soloway et al. [229] | Carter et al.[230] |
|---|---|---|---|---|---|
| Study type | | Prospective, single centre cohort since 1995 | Retrospective validation | Retrospective single centre cohort 1992-2007 | Prospective longitudinal single centre cohort since 1995-2006 |
| Number of patients | | 331 | 616 | 99 | 407 |
| Mean follow-up | | 8 yr (2-11) | 4.3 yr (0-11) | 3.7 yr (1-14) | 3.4 yr (0.2-12) |
| Region | | Toronto Canada | ERSPC centers The Netherlands, Sweden and Finland | Miami, USA | Baltimore, USA |
| Inclusion criteria | PSA in ng/ mL | ≤10 (≤ 15)* | ≤10 | ≤ 15 | Mean 5 (range 0.3-24) |
| | T Stage | T1C-T2A | T1C-T2 | ≤T2 | T1C |
| | PSAD in ng/ml/ cc | Not used | ≤ 0.2 | Not used | ≤ 0.15 |
| Prostate biopsy characteristics | Gleason Score | ≤ 3+3 (3+4)* | ≤ 3+3<br>≤ 2 positive cores | ≤ 3+3<br>≤ 2 positive cores, max 50% invasion | ≤ 3+3<br>≤ 2 positive cores, max 50% invasion |
| Follow-up | | PSA, DRE 3-monthly, after 2 yrs 6-monthly | Varying per centre | PSA, DRE 3-monthly, after 2 yrs 6-monthly | PSA, FPSA, DRE 6 monthly |
| | Repeat biopsy | After 1 year and 3-5 yearly thereafter | Not predefined | After 6-12 mths and on clinical suspection thereafter | Yearly |
| Indications for treatment | | Patient wish (10%)<br>PSADT <3 yr (20%)<br>Grade progression (5%) | Patient wish<br>PSADT ≤ 3 yr<br>PSA > 10<br>Stage progression | Patient wish<br>PSADT (no predefined cutoff)<br>Grade progression<br>Stage progression | Patient wish<br>Grade progression<br>> 50% of PCa invasion in a single biopsy core |
| Progression after deferred treatment (DT) | | 3 cases died of PCa despite deferred RP within a year of diagnosis | 12% PSA failure (13 of 159 cases 7/81 after RP 6/78 after RT | 0/2 RP Thus no progression<br>0/3 RT<br>0/3 HT | Not available, though 2 men had lymph node involvement at deferred RP |
| %DT | | 35% (n= 101) | 55% at 10 yr | 8% (n= 8) | 25% (n=103) |
| Without DT** | | Not available | 43% at 10 yr | 85% at 5 yr | 59% at 3.4 yr |
| Disease specific survival | | 99% (n=3) | 10 yr 100% | 100% | 100% |
| Overall survival | | 85% | 10 yr 77% | Not available | 98% |
| Remarks | | AS appears to be safe in selected men | 110 of 197 men with DT had favourable PCa characteristics at the time of DT | In 65% initial repeat biopsy revealed no PCa. AS appears to be safe in selected men without compromising curability | 20% of pt with deferred RP had adverse pathological findings but this is consistent with patients immediately treated. [293]<br>DT not based on PSA kinetics or stage progression |

* if age over 70 years at diagnosis

** excluding those patients lost to follow-up or withdrawn from the study

Since the arbitrarily defined criteria for selection, follow-up and deferred treatment provided in **chapter 3**, numerous studies have appeared [122, 224-231]. Table 1 shows a selection of the key AS studies and their outcomes thus far.

The median follow-up of the first prospective protocol-based report on AS [122] currently amounts to about 8 years [228, 232]. The DSS of the 331 men on AS was 99.3%. Three men died of PCa; all had deferred treatment within a year of diagnosis due to rapid rise in PSA levels and developed bone metastasis in the same year of treatment, succumbing to the disease within 5.5 years after diagnosis. The overall survival was 85% and 35% received deferred treatment [228, 232].

A report combining data from different ERSPC centres showed that at a median follow-up of 4.3 years, none of the 616 men with favourable PCa initially managed on a AS policy died of PCa and 32% received deferred treatment [227]. Extrapolating the results to ten years after diagnosis, the DSS still was 100%, with a corresponding OS of 77% and 43% of the patients continuing on AS. 13 out of 159 males (12.2%) treated with curative intent have biochemical recurrence of disease. One patient died of PCa 11 years after diagnosis and one man did develop metastases despite deferred RT within a year of diagnosis.

Soloway et al. report that out of 99 patients on AS 8 had deferred treatment and none of these men had evidence of biochemical recurrence at a three years of follow-up after treatment [229]. No patient died of PCa and 85% of the men continued on AS after five years. 63% of the patients had an initial 10 core repeat biopsy 6 to 12 months after diagnosis which showed no evidence of PCa at pathological examination in 65% of the men. During follow-up of these males with undetectable disease subsequent repeat biopsies demonstrated a Gleason score of 3+3 or greater in 25%, including two patients with a Gleason score of 3+4.

Experience with AS at the Johns Hopkins Institute again shows 100% DSS with a probability of remaining on AS after 8 years of 49%, the OS was not reported [230]. Two patients had lymph node invasion at RP more than five years after diagnosis and 20% of 49 men undergoing a deferred RP had adverse pathological characteristics corresponding with a risk of 25% or more of biochemical recurrence at 10 years of follow-up.

Other active surveillance reports show similar excellent disease specific mortality ranging from 99% to 100% with follow-up ranging from three to seven years for patients with favourable disease [231, 233-237]. The follow-up periods are clearly too short to apply final judgement.

As appears from the data just reviewed, most inclusion criteria suggested in **chapter 3** remain unchanged. For example, most investigators still select PCa patients with clinical stage T1C or T2A with a Gleason score of 3+3 or less for AS [219, 234, 238]. However, the maximum level of PSA at diagnosis is now commonly extended to 10 ng/mL in com-

parison to 5-8 ng/mL as proposed in **chapter 3**. Likewise, a tendency towards accepting two cores with PCa invasion as long as less than half of that cores is invaded with PCa and accepting a PSAD of 0.15 to 0.2 ng/mL/cc compared to 0.1 ng/mL/cc can be seen [219, 224, 226, 229, 230]. The main pitfalls of all the reports on AS is that none of the reported studies has a prospective randomized design and that follow-up is relatively short, especially if a lead-time of approximately 10 years associated with PCa screening [4, 239] is considered.

## COMPARING TREATMENT MODALITIES

Men eligible for an AS policy should be selected among the patients with favourable PCa characteristics as indicated above. While the ERSPC is not designed to compare treatment modalities several studies have attempted to compare the results of different treatments for localized prostate cancer [104, 109, 240-243].

Only the Scandinavian Prostate Cancer Group Study *4* (*SPCG-4*) study is a prospectively randomized study and shows a small though statistically significant advantage in DSS and OS for clinically detected patients treated with RP compared to patients treated with expectant management and palliative hormonal therapy after 12 years of follow-up as discussed in the introduction [109]. The Prostate cancer Intervention Versus Observation Trial (PIVOT) has just published its baseline results from 731 men recruited from 1994 till 2002 [120]. Like the SPCG-4 study it is designed to compare surgery and watchful waiting defined as deferred palliative treatment. In the PIVOT trial 76% of men had a PSA driven PCa diagnosis compared to 5% in the Swedish study. In the PIVOT trial more men had a lower PSA and well differentiated disease (25% versus 13%) at diagnosis. First results are expected in 2010

Though currently no data are available comparing treatment related outcome in patients with only favourable screen detected PCa, prospectively randomized controlled trials have been initiated. In the United Kingdom the multicenter Prostate Testing for Cancer and Treatment (ProtecT) study has started in September 2001. The ProtecT study aims to evaluate the effectiveness, cost-effectiveness and acceptability of different treatments for men with localised prostate cancer. The three treatments are active surveillance, radical prostatectomy and external beam radiotherapy. The major objective will be to assess survival at 5, 10 and 15 years following treatment [244]. The Surveillance Therapy Against Radical Treatment (START) trial will also only include men with favourable PCa and is designed to compare outcome for AS against surgery, external beam radiation or brachytherapy. This study is still in the feasibility phase [120, 200, 239], but aims to enroll and follow 2,130 newly diagnosed patients with low-risk prostate cancer

in Canada, the U.S.A., England, and Europe. Results of these trials will undoubtedly hugely improve knowledge on selection, monitoring and timing of deferred treatment.

## IMPROVING SELECTION CRITERIA

While the results of prospective randomized trials comparing AS to immediate treatment with curative intent mature, patients, in current-day practice, need to be advised on treatment decisions right away. Together with the clinical stage, PSA level and prostatic volume, prostatic biopsy characteristics can be used in nomograms to predict whether a cancer will be indolent [127, 245-250].While these nomograms are currently the best we have, they still define an indolent cancer as an index tumour of smaller than 0.5 cc with no Gleason pattern four or five based on data from the early nineties [221]. Using a nomogram one should appreciate the fact that up to 20% of cases are wrongly being classified as having indolent disease despite a predictive accuracy of 80 to 90% for having indolent cancer [127, 251].

Another, more user friendly tool, is the Cancer of the Prostate Risk Assessment (CAPRA) score [252]. It was originally designed to improve pre-treatment risk assessment. The CAPRA score was initially tested in patients treated with RP [252] and it has been externally validated [253-255], The CAPRA ranges from 0 to 10 points and a higher score predicts a higher risk of recurrence of PCa. The score is based on PSA level, primary and secondary Gleason pattern, age, tumour stage, and percentage of biopsy cores invaded by PCa. In June 2009, the CAPRA score was successfully tested to predict clinical endpoints as development of metastasis, DSS and OS for patients with localized PCa treated with surgery, radiation therapy, AS or expectative management, making it a useful tool for current-day practice [91]. For a man with CAPRA score 1 this resulted in an estimated 10 year metastasis free survival, DSS and OS of 99%, 98.2% and 76.7%, respectively.

The keys to success for AS are parameters that can accurately identify and monitor indolent disease. Otherwise a patient with organ-confined disease at diagnosis might progress to metastasized disease while being on an AS with only palliative treatment remaining. Or even better, a marker or algorithm which avoids screening and diagnosis in potentially indolent PCa could dramatically enhance the effectivity of population based screening which currently has to cope with overdiagnosis. In the still continuing quest for such a "holy grail", precursor PSA (pPSA) was investigated in **chapter 5** Though groups were arbitrarily defined and on contrary ends of the PCa characteristics spectrum, combination of pPSA forms and %freePSA were able to predict a PCa with favourable characteristics in 77.3% [256]. Since then major steps in development have

been made. A fully automated though still research only [-2]pPSA assay has been developed and tested [257, 258]. Moreover, when analysing sera of patients with and without PCa, the authors found that incorporating %[-2]pPSA, %pPSA, total PSA and age in an artificial neural network delivered an area under the curve (AUC) of 0.84 with 95% confidence intervals of 0.80-0.87 compared to an AUC of 0.56 (0.51-0.61) for total PSA [257]. A neural network is a non-linear statistical data-modelling tool, which can be used to model complex relationships between inputs and outputs. However, the authors did not consider in this comparison the fact that most PCa are diagnosed through elevated PSA values, and that therefore the ROC analysis is subject to attribution bias. In this neural network, contrary to earlier reports [259, 260], the digital rectal examination and the prostatic volume, which are more subjective parameters, did not improve the AUC and were therefore omitted. Another report using data from both the ERSPC, section Rotterdam as well as the university of Innsbruck showed that %[-2]pPSA at 95% sensitivity reached a 22% specificity compared to 9% for %FPSA and tPSA within the tPSA range of 2-10 ng/mL [261]. Furthermore, %[-2]pPSA showed greater selectivity for detecting more aggressive cancers within the tPSA range of 4-10 ng/mL [261].

These promising findings based only on objective measurable serum values will lead to the release of an automated multiplex precursor PSA assay in the third quarter of 2009 (personal communication Claude Darte from Beckman Coulter®). This will allow the validation and further exploration of these markers in randomized trials and might even establish the use of %pPSA in predicting dedifferentiation of PCa in patients on AS.

Several other biomarkers for PCa detection and management are under evaluation [262-264]. One study suggests that early prostate cancer antigen 2 (EPCA-2) has an equal or higher sensitivity for PCa detection but a statistically significantly better specificity than PSA. Moreover EPCA-2 appeared able to differentiate between organ and non-organ confined disease [265]. Likewise human glandular kallikrein 2 (hK2) [266, 267], prostate secretory protein 94 (PSP94) [268] prostate stem cell antigen (PSCA) [269, 270] amongst others [271, 272] may be able to differentiate between aggressive and relatively favourable PCa some even in PSA ranges lower than 10 ng/mL. As not all investigators found these promising results [273], and groups were still small future randomized trials are needed to show which markers are safe for selection of patients.

In the new field of metabolomics, in which all small molecule metabolites within a biological sample are evaluated, a metabolite called sarcosine has received attention [274]. Sarcosine levels were immeasurable in benign prostatic tissue, elevated in prostate cancer tissue but significantly increased in patients with metastasized PCa. In a limited validation set of urines sarcosine was measurable in urine and differentiated "benign" biopsies from patients with biopsy proven PCa. While sarcosine might thus be a

marker for aggressive prostate cancer the authors also suggest that it could provide new leads for monitoring and targeted treatment strategies as sarcosine and its regulatory enzymes seem to modulate PCa progression. While sarcosine is still far away from any clinical utility the PCA3 urine test only introduced in 2003 is currently available for PCa detection after initially negative biopsies and investigated for its possible prognostic use [275, 276]. Moreover, PCA3 is independent of prostatic volume, serum PSA and prior negative biopsies and could be used in a nomogram to improve prediction of biopsy outcome [277]. In the effort to improve test characteristics PCA3 was sucesfully combined with the prostate-specific and androgen regulated transmebrane protease-serine fusion transcript (TMPRSS2-ERG) in urinary sediments [278]. In a cohort of 78 men with biopsy proven PCa, the PCA3 test alone was positive in 48 urine samples, thus reaching a sensitivity of 62%, which improved to 73% in combination with the TMPRSS2-ERG test, without compromising specificity. Though this was a first feasibility study to combine these new markers others have also shown improvement of test results with multiplex assays combining several tests [264, 279], which in the future might even be used to predict a positive prostate biopsy outcome and tumour characteristics.

## MONITORING DISEASE

In **chapter 6** PSA measurements over time are evaluated as a possible tool for monitoring patients on an active surveillance policy. Sixty-five men (54.4%) had a stable or even slightly declining PSA with time suggesting indolent PCa [217]. In the Swedish section of the ERSPC only men with a PSA doubling time (PSADT) of four years or faster during their active surveillance experienced a PSA relapse after deferred treatment with a radical prostatectomy [280]. Few other reports have been published relating other outcomes observed in AS patients to PSA kinetics in screen detected prostate cancer [235, 281].

However fast rising PSA levels, mostly defined as a PSA velocity (PSAV) of 2 ng/mL/year in the year before surgery or radiotherapy, were significant predictors for biochemical relapse or disease specific mortality [282-284]. Sengupta et al. showed in a retrospective cohort of over two thousand men treated with surgery for PCa that pre-treatment PSAV was a better predictor of biochemical progression, while PSADT was a stronger predictor of clinical progression and death from PCa [285].

In the Baltimore Longitudinal Study of Aging PSAV did while PSADT did not correlate with high risk or fatal disease in a statistically significant fashion [286]. Another report showed that PSAV was a better predictor than PSADT for adverse pathological findings at repeat prostatic biopsy in men with untreated PCa [287]. Though both were statistically significant predictors, the area under the receiver-operating curve was 0.70 for PSAV and

0.63 for PSADT. Other reports showed no relation of PSAV or PSADT with outcome [177, 288, 289].

The usefulness of PSADT as a predictive marker after therapy is illustrated by the fact that a workgroup has published suggestions how to report on PSADT data [290]. No such uniformity has yet been reached for active surveillance strategies. Most AS protocols suggest that PSADT greater than ten years or declining PSA over time reflects a good prognosis [122, 123, 219, 291]. Likewise, these ongoing AS strategies consider a PSADT faster than two to four years an indication for deferred treatment or at least for a repeat prostatic biopsy. To calculate PSADT is more difficult than to calculate PSAV, but a number of free of charge web based calculators exist that compute PSADT. In the PRIAS study such a tool is integrated and automatically provides PSADT. Evaluation of data of the PRIAS and other AS protocols will clarify the definitive role of PSADT and PSAV in AS.

## SAFETY OF ACTIVE SURVEILLANCE

The chance of losing the window of cure during AS appears to be small, but AS is not a rose without thorns. As described in the section AS policies over time, the risk of biochemical recurrence of disease after deferred treatment is small and ranges from 0 to 20% [227, 228, 230, 292]. The number of 20% is based on the pathological features of patient with deferred RP [230, 293]. This group presumes that males with a Gleason score of 4+3 or higher, pathological stage T3, positive surgical margins or nodal involvement will have less than 75% probability of remaining free of biochemical recurrence 10 years after surgery and should be considered having non curable PCa. A report from the same group investigating the effect of deferred therapy compared to immediate treatment with curative intent showed that delayed therapy did not compromise curability [293]. Though this result is of great value in the decision process whether or not to embark on an AS policy at the same time it shows that 20 to 23% [230, 293] of men eligible for an AS policy had these adverse finding at surgery indicating the need for better selection criteria. Other reports concur with the finding that deferred treatment does not alter disease specific outcome [280, 289, 294]. Out of 80 patients on AS at the Royal Marsden institute followed for 42 months on average, none of the 11 patients with deferred treatment had signs of biochemical recurrence of PCa with a median follow-up of 20 months after treatment. Furthermore no patient had yet developed metastasis or started on palliative hormonal treatment [292].

When combining the data on outcome of AS in the current PSA era, it appears to be safe at least in the short term for the majority of males and deferred treatment is not associated with deterioration of PCa prognosis. Considering the long natural history of

PCa in the groups of men selected for AS, long term observations are mandatory to allow final judgement.

## ACTIVE SURVEILLANCE AND PROSTATE CANCER SCREENING

The ERSPC with over 250,000 recruited men in eight different countries and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) in the USA with 76,705 men are evaluating the effect of screening with PSA and digital rectal examination on prostate cancer specific mortality [181, 295]. In March, 2009 the ERSPC group showed a statistically significantly 20% relative mortality reduction at a third interim analysis based on the predefined core group of over 160,000 men aged between 55 and 69 years in favour of the intervention arm [296]. During a median follow-up of nine years, 5,990 cases of PCa (8.2%) were detected and 214 (0.29%) men died of the disease in the screen cohort. In the control arm 4,307 (4.8%) cases were diagnosed with PCa and 326 (0.37%) men succumbed to PCa, resulting in a statistically significant absolute reduction of 0.71 PCa deaths per 1,000 men in favour of screening in the intention to screen analysis. Or put in another way 1,410 men needed to be screened to prevent one prostate cancer death, with an average of 1.7 screening visits within a nine-year period. Screening however increased prostate cancer incidence with 34 per 1,000 men so that 48 men (1,410/1,000x34) need to be treated to prevent one prostate cancer death at nine years of follow-up.

The PLCO study with over 38,000 men in the screen arm between the age of 55 to 74 years and a median follow-up of 11.5 years was published at the same time because of continuing lack of a significance of the death rate between the two arms and information suggesting harm from screening [297]. At ten years of follow-up 3,452 (9.0%) men were diagnosed with and 92 died of PCa in the intervention arm. The numbers of the control group were 2,974 (7.8%) and 82 respectively resulting in a relative rate ratio (death rate of the screen group divided by the death rate in the control group) of 1.11 (95% confidence interval 0.83-150), implying a non-statistically significantly increase in prostate cancer mortality in the intervention arm [297].

These contradictory results can possibly be explained by differences in trial protocol [88, 298], selection bias, geographical differences [88] [299], compliance rates and PSA testing outside the trial [192, 298, 300-302], however this lies beyond the scope of this thesis.

An important result for AS is the confirmation in both studies that death was relatively uncommon during follow-up, with rates of PCa deaths per 10,000 person years of 2.0 for the screen arm and 1.7 for the control group in the PLCO study at seven years. In

the ERSPC trial these numbers varied from 1.9 to 5.8 for the men aged 55 to 69 yr in the screen arm and 2.5 to 7.9 in the control group. This again confirms the relatively indolent natural course of many screen detected PCa. Together with the knowledge that

- patients with screen detected prostate cancer have a significantly higher chance (49%) of harbouring clinically insignificant cancer compared to clinically diagnosed males (13%) [127];
- the chance of having insignificant PCa rises at a subsequent screen [300, 303] translating into more favourable PCa characteristics [236, 304];
- patients diagnosed with PCa after a previous negative screen have a better outcome compared to men diagnosed at a prevalence screen even after correcting for T stage, Gleason score and initial PSA level [305];
- currently, in the USA, 91% of diagnosed PCa is organ confined, the vast majority has PSA driven diagnosed, non palpable, PCa with a small focus well differentiated Gleason sum 3+3 PCa and a PSA level of 10 ng/mL or less, with an associated relative 5 year disease specific survival of 100% [69, 306];
- the ERSPC has a calculated 54% overdiagnosis rate with an associated lead-time of 10.3 years [4], and approximately one third of the screen detected cancers can be identified as potentially indolent with the use of nomograms based on clinical an pathological characteristics [280, 303];
- other series reported overdiagnosis rates of 7- 93% and lead-times ranging from 5 to 14.1 years with the longest lead-times for young men with well differentiated disease and the highest overdiagnosis rates for older men [94, 95, 100, 101, 307].

This can cumulate into an enormous pool of possible future AS candidates, making both AS and taking positions on offering screening a top priority in the urological and oncological practice.

Clear-cut advise on whether and who to screen cannot yet be provided, as, despite its statistically significant results, the ERSPC trial does not yet warrant population based screening as several aspects like population coverage, overdiagnosis, quality of life, cost and cost effectiveness have not yet been taken into account. Still the mortality reduction of 20% in favour of prostate cancer screening will probably only further fuel the already widespread use of opportunistic PSA driven PCa screening. On the other hand, men aged 70 to 74 years did not seem to benefit from screening in the ERSPC in an exploratory analysis, suggesting that screening for PCa should not be advisable in these men. Most urological and oncological societies do agree with testing as long as it is a shared initiative between patient and physician and both the potential benefits and limitations of prostate cancer early detection are discussed in advance, with those who favour testing [70, 308-312].

## QUALITY OF LIFE

This thesis did not directly address health related quality of life (HRQoL) aspects. With AS one hopes to defer or even refrain from radical therapy for potentially indolent PCa and thus to avoid unnecessary treatment related side-effects. However, the patient and his relatives need to cope with living with untreated cancer. This anxiety is well reflected by the fact that 10 to 50% of the men on an AS policy desire deferred treatment despite of the absence of clinical or biochemical progression of the disease [228, 236].

One randomized trial from the SPCG-4 initially showed no difference in psychological distress comparing patients treated with RP to men treated with watchful waiting [119], though after 6 to 8 years of follow-up distress seemed to grow in the watchful waiting group while it remained stable in the RP group even after filtering out patients on androgen deprivation [313]. Though a drawback of this study is that each man only once filled out an assessment where a longitudinal study would have been even better [314]. Another study also reported a difference in HRQoL between treatment groups over time with patients treated with RP performing best and those treated with radiation the worst leaving the patients on watchful waiting in between [315].

Though the reported data concerns clinically diagnosed patients on an expectant management strategy comparable effect on HRQoL are to be expected at longer follow-up in AS men. Another report showed that lifestyle interventions improving overall health positively impact HRQoL, showing that both physician and patient can manage some of the uncertainty and anxiety associated with AS successfully [316]. This important aspect of AS will have to play a role in the decision process of males considering AS. The PRIAS, ProtecT and START trials will all address and hopefully clarify HRQoL aspect in a contemporary cohort of men treated with AS in the future [200, 244, 317].

## FUTURE PERSPECTIVES

In the light of the recent results from the ERSPC showing a favourable effect on PCa specific mortality in favour of PCa screening it is to be expected that more men will demand PSA testing from their general practitioner or urologist. Awareness education explaining the potential benefits and limitations of prostate cancer seems warranted for patients as well as first and second line physicians. In the mean time investigations will need to focus on finding and optimizing reliable tools to predict indolent cancer based on non-invasive procedures. This would greatly enhance screening for PCa by reducing the number of prostatic biopsies and ideally making the detection of indolent PCa an exception rather than the rule, leaving only those patients who could benefit from curative treatment in terms of increased disease survival. During this quest for "the

holy grail" screen protocols will have to be perfected. Research for markers that predict indolent PCa even before diagnosis and markers that can timely predict progression of disease hopefully will be identified. A grant of 7.5 million euro from the Center for Translational Molecular Medicine was assigned in August 2009 for this purpose to three Dutch University Medical Centres, with the Erasmus MC leading the investigations, will surely boost this area of research. In the meantime with increasing follow-up of the current active surveillance research endeavours the true nature of screen detected PCa managed on AS will have to show its true value. Time can only tell whether PCa on active surveillance behaves as a dormant volcano not altering the natural course of life in patients or whether it will transform into an active volcano releasing a lava flow of PCa cells metastasizing into the human body without previously releasing detectable signals announcing activity.

In summary, active surveillance can provide a temporary refuge for both patients and physicians while the prostate cancer screening data matures into evidence based recommendations and tools to avoid screening in patients with indolent disease are being developed.

AS is still an evolving treatment modality but appears to be safe within the ERSPC in selected patients, though follow-up is still limited. There is a clear difference in PCa outcome between screen detected and clinically diagnosed PCa, making screen detected PCa patients more apt candidates for an AS policy. PSA kinetics, such as PSA doubling time, can be useful to monitor patients and timing deferred treatment. New biomarkers like precursor PSA are being extensively investigated to enhance pre-treatment decision-making. Current ongoing trials such as the PRIAS-project will boost improvements in selection and monitoring criteria for active surveillance protocols. Active surveillance could avoid unnecessary treatment, with its inherent side-effects and costs, in a time of overdiagnosis and overtreatment due to PSA driven screening, while preserving the window of cure. However active surveillance is not a rose without thorns as the window of cure could be lost during follow-up.

# References


[1] Comprehensive Cancer Centers of the Netherlands. Cancer sites 2006. [cited 24-05-2009]; Available from: http://www.ikcnet.nl/uploaded/FILES/Landelijk/cijfers/kerncijfers/VIKC_nkr_plaatje_nl1.jpg

[2] Kankerbestrijding KWF. http://www.kwfkankerbestrijding.nl/index.jsp?objectid=14886 (Dutch Cancer Society). 2004.

[3] Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al. SEER Cancer Statistics Review, 1975-2005,. 2008.

[4] Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003 Jun 18;95(12):868-78.

[5] de Koning HJ, Liem MK, Baan CA, Boer R, Schroder FH, Alexander FE. Prostate cancer mortality reduction by screening: power and time frame with complete enrollment in the European Randomised Screening for Prostate Cancer (ERSPC) trial. Int J Cancer. 2002 Mar 10;98(2):268-73.

[6] Campbell. Diagnosis and staging of Prostate Cancer. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, eds. *Campbell's Urology*. 8 ed. Philadelphia: Saunders 2003:3055-79.

[7] Anderson CJ. Prostate anatomy.jpg. 2008 [cited; Available from: http://www.keyholeurology.co.uk/prostatecancer.html

[8] McNeal JE. Normal histology of the prostate. Am J Surg Pathol. 1988 Aug;12(8):619-33.

[9] Lilja H, Oldbring J, Rannevik G, Laurell CB. Seminal vesicle-secreted proteins and their reactions during gelation and liquefaction of human semen. J Clin Invest. 1987 Aug;80(2):281-5.

[10] Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med. 1991 Apr 25;324(17):1156-61.

[11] Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987 Oct 8;317(15):909-16.

[12] Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. Jama. 1999 May 5;281(17):1591-7.

[13] Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. Int J Radiat Oncol Biol Phys. 1997 Mar 15;37(5):1035-41.

[14] Stamey TA, Kabalin JN, McNeal JE, Johnstone IM, Freiha F, Redwine EA, et al. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. J Urol. 1989 May;141(5):1076-83.

[15] Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of a human prostate specific antigen. Invest Urol. 1979 Sep;17(2):159-63.

[16] Yousef GM, Diamandis EP. The new human tissue kallikrein gene family: structure, function, and association to disease. Endocr Rev. 2001 Apr;22(2):184-204.

[17] Lundwall A, Lilja H. Molecular cloning of human prostate specific antigen cDNA. FEBS Lett. 1987 Apr 20;214(2):317-22.

[18] Stephan C, Jung K, Diamandis EP, Rittenhouse HG, Lein M, Loening SA. Prostate-specific antigen, its molecular forms, and other kallikrein markers for detection of prostate cancer. Urology. 2002 Jan;59(1):2-8.

[19] Bostwick DG. Prostate-specific antigen. Current role in diagnostic pathology of prostate cancer. Am J Clin Pathol. 1994 Oct;102(4 Suppl 1):S31-7.

[20] Nadler RB, Humphrey PA, Smith DS, Catalona WJ, Ratliff TL. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. J Urol. 1995 Aug;154(2 Pt 1):407-13.

[21] Lilja H, Christensson A, Dahlen U, Matikainen MT, Nilsson O, Pettersson K, et al. Prostate-specific antigen in serum occurs predominantly in complex with alpha 1-antichymotrypsin. Clin Chem. 1991 Sep;37(9):1618-25.

[22] Stenman UH, Leinonen J, Alfthan H, Rannikko S, Tuhkanen K, Alfthan O. A complex between prostate-specific antigen and alpha 1-antichymotrypsin is the major form of prostate-specific antigen in serum of patients with prostatic cancer: assay of the complex improves clinical sensitivity for cancer. Cancer Res. 1991 Jan 1;51(1):222-6.

[23] Balk SP, Ko YJ, Bubley GJ. Biology of prostate-specific antigen. J Clin Oncol. 2003 Jan 15;21(2):383-91.

[24] Agha AH, Schechter E, Roy JB, Culkin DJ. Prostate specific antigen is metabolized in the liver. J Urol. 1996 Apr;155(4):1332-5.

[25] Oesterling JE, Chan DW, Epstein JI, Kimball AW, Jr., Bruzek DJ, Rock RC, et al. Prostate specific antigen in the preoperative and postoperative evaluation of localized prostatic cancer treated with radical prostatectomy. J Urol. 1988 Apr;139(4):766-72.

[26] Bruun L, Savage C, Cronin AM, Hugosson J, Lilja H, Christensson A. Increase in percent free prostate-specific antigen in men with chronic kidney disease. Nephrol Dial Transplant. 2008 Nov 21.

[27] Bjork T, Ljungberg B, Piironen T, Abrahamsson PA, Pettersson K, Cockett AT, et al. Rapid exponential elimination of free prostate-specific antigen contrasts the slow, capacity-limited elimination of PSA complexed to alpha 1-antichymotrypsin from serum. Urology. 1998 Jan;51(1):57-62.

[28] Lilja H, Haese A, Bjork T, Friedrich MG, Piironen T, Pettersson K, et al. Significance and metabolism of complexed and noncomplexed prostate specific antigen forms, and human glandular kallikrein 2 in clinically localized prostate cancer before and after radical prostatectomy. J Urol. 1999 Dec;162(6):2029-34; discussion 34-5.

[29] Gregorakis AK, Malovrouvas D, Stefanakis S, Petraki K, Scorilas A. Free/Total PSA (F/T ratio) kinetics in patients with clinically localized prostate cancer undergoing radical prostatectomy. Clin Chim Acta. 2005 Jul 24;357(2):196-201.

[30] Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements. Jama. 1997;277(18):1452-5.

[31] Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. Jama. 1998 May 20;279(19):1542-7.

[32] Bangma CH, Rietbergen JB, Kranse R, Blijenberg BG, Petterson K, Schroder FH. The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. J Urol. 1997;157(6):2191-6.

[33] Raaijmakers R, Blijenberg BG, Finlay JA, Rittenhouse HG, Wildhagen MF, Roobol MJ, et al. Prostate cancer detection in the prostate specific antigen range of 2.0 to 3.9 ng/ml: value of percent free prostate specific antigen on tumor detection and tumor aggressiveness. J Urol. 2004 Jun;171(6 Pt 1):2245-9.

[34] Mikolajczyk SD, Grauer LS, Millar LS, Hill TM, Kumar A, Rittenhouse HG, et al. A precursor form of PSA (pPSA) is a component of the free PSA in prostate cancer serum. Urology. 1997 Nov;50(5):710-4.

[35] Peter J, Unverzagt C, Krogh TN, Vorm O, Hoesel W. Identification of precursor forms of free prostate-specific antigen in serum of prostate cancer patients by immunosorption and mass spectrometry. Cancer Res. 2001 Feb 1;61(3):957-62.

[36] Jansen FH, Roobol M, Jenster G, Schroder FH, Bangma CH. Screening for Prostate Cancer in 2008 II: The Importance of Molecular Subforms of Prostate-Specific Antigen and Tissue Kallikreins. Eur Urol. 2008 Nov 29.

[37] Kumar A, Mikolajczyk SD, Goel AS, Millar LS, Saedi MS. Expression of pro form of prostate-specific antigen by mammalian cells and its conversion to mature, active form by human kallikrein 2. Cancer Res. 1997 Aug 1;57(15):3111-4.

[38] Lovgren J, Valtonen-Andre C, Marsal K, Lilja H, Lundwall A. Measurement of prostate-specific antigen and human glandular kallikrein 2 in different body fluids. J Androl. 1999 May-Jun;20(3):348-55.

[39] Takayama TK, Fujikawa K, Davie EW. Characterization of the precursor of prostate-specific antigen. Activation by trypsin and by human glandular kallikrein. J Biol Chem. 1997 Aug 22;272(34):21582-8.

[40] Mikolajczyk SD, Marker KM, Millar LS, Kumar A, Saedi MS, Payne JK, et al. A truncated precursor form of prostate-specific antigen is a more specific serum marker of prostate cancer. Cancer Res. 2001 Sep 15;61(18):6958-63.

[41] Mikolajczyk SD, Rittenhouse HG. Pro PSA: a more cancer specific form of prostate specific antigen for the early detection of prostate cancer. Keio J Med. 2003 Jun;52(2):86-91.

[42] Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Amirkhan A, et al. Serum pro prostate specific antigen improves cancer detection compared to free and complexed prostate specific antigen in men with prostate specific antigen 2 to 4 ng/ml. J Urol. 2003 Dec;170(6 Pt 1):2181-5.

[43] Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Horninger W, et al. Serum pro-prostate specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/ml prostate specific antigen. J Urol. 2004 Jun;171(6 Pt 1):2239-44.

[44] Mikolajczyk SD, Catalona WJ, Evans CL, Linton HJ, Millar LS, Marker KM, et al. Proenzyme forms of prostate-specific antigen in serum improve the detection of prostate cancer. Clin Chem. 2004 Jun;50(6):1017-25.

[45] Mikolajczyk SD, Millar LS, Wang TJ, Rittenhouse HG, Wolfert RL, Marks LS, et al. "BPSA," a specific molecular form of free prostate-specific antigen, is found predominantly in the transition zone of patients with nodular benign prostatic hyperplasia. Urology. 2000 Jan;55(1):41-5.

[46] Linton HJ, Marks LS, Millar LS, Knott CL, Rittenhouse HG, Mikolajczyk SD. Benign prostate-specific antigen (BPSA) in serum is increased in benign prostate disease. Clin Chem. 2003 Feb;49(2):253-9.

[47] Wang TJ, Slawin KM, Rittenhouse HG, Millar LS, Mikolajczyk SD. Benign prostatic hyperplasia-associated prostate-specific antigen (BPSA) shows unique immunoreactivity with anti-PSA monoclonal antibodies. Eur J Biochem. 2000 Jul;267(13):4040-5.

[48] Naya Y, Fritsche HA, Bhadkamkar VA, Mikolajczyk SD, Rittenhouse HG, Babaian RJ. Volume-based evaluation of serum assays for new prostate-specific antigen isoforms in the detection of prostate cancer. Urology. 2004 Mar;63(3):492-8.

[49] Marks LS, Linton HJ, Gasior CL, Millar LS, Mikolajczyk SD, Rittenhouse HG, et al. BPSA is a potential serum marker for benign prostatic hyperplasia (BPH) (abstract). J Urol. 2001;165(2001):266.

[50] Mikolajczyk SD, Millar LS, Marker KM, Wang TJ, Rittenhouse HG, Marks LS, et al. Seminal plasma contains "BPSA," a molecular form of prostate-specific antigen that is associated with benign prostatic hyperplasia. Prostate. 2000 Nov 1;45(3):271-6.

[51] Mikolajczyk SD, Marks LS, Partin AW, Rittenhouse HG. Free prostate-specific antigen in serum is becoming more complex. Urology. 2002 Jun;59(6):797-802.

[52] Nurmikko P, Vaisanen V, Piironen T, Lindgren S, Lilja H, Pettersson K. Production and characterization of novel anti-prostate-specific antigen (PSA) monoclonal antibodies that do not detect internally cleaved Lys145-Lys146 inactive PSA. Clin Chem. 2000 Oct;46(10):1610-8.

[53] Visser O, Siesling S, van Dijck JAAM. Eleventh report of the Netherlands Cancer Registry: VIKC; 2003.

[54] Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. J Urol. 2004 Nov;172(5 Pt 2):S6-11; discussion S-2.

[55] Bonkhoff H, Remberger K. Morphogenetic concepts of normal and abnormal growth in the human prostate. Virchows Arch. 1998 Sep;433(3):195-202.

[56] van der Kwast TH, Tetu B, Suburu ER, Gomez J, Lemay M, Labrie F. Cycling activity of benign prostatic epithelial cells during long-term androgen blockade: evidence for self-renewal of luminal cells. J Pathol. 1998 Dec;186(4):406-9.

[57] Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. J Urol. 1993 Aug;150(2 Pt 1):379-85.

[58] Bostwick DG, Qian J, Schlesinger C. Contemporary pathology of prostate cancer. Urol Clin North Am. 2003 May;30(2):181-207.

[59] Gronberg H. Prostate cancer epidemiology. Lancet. 2003 Mar 8;361(9360):859-64.

[60] Roemeling S, Roobol MJ, de Vries SH, Gosselaar C, van der Kwast TH, Schroder FH. Prevalence, treatment modalities and prognosis of familial prostate cancer in a screened population. J Urol. 2006 Apr;175(4):1332-6.

[61] Vasto S, Carruba G, Candore G, Italiano E, Di Bona D, Caruso C. Inflammation and prostate cancer. Future Oncol. 2008 Oct;4(5):637-45.

[62] Ries LAG MD, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). Lifetime risk of death of cancer 2003-2005. 2008.

[63] Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, et al. Cancer statistics, 2004. CA Cancer J Clin. 2004 Jan-Feb;54(1):8-29.

[64] Ries LAG MD, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). Lifetime risk of dying of prostate cancer 1973-1993. 2008.

[65] Cooperberg MR, Lubeck DP, Mehta SS, Carroll PR. Time trends in clinical risk stratification for prostate cancer: implications for outcomes (data from CaPSURE). J Urol. 2003 Dec;170(6 Pt 2):S21-5; discussion S6-7.

[66] Feuer EJ, Mariotto A, Merrill R. Modeling the impact of the decline in distant stage disease on prostate carcinoma mortality rates. Cancer. 2002 Aug 15;95(4):870-80.

[67] Jani AB, Vaida F, Hanks G, Asbell S, Sartor O, Moul JW, et al. Changing face and different countenances of prostate cancer: racial and geographic differences in prostate-specific antigen (PSA), stage, and grade trends in the PSA era. Int J Cancer. 2001 Dec 20;96(6):363-71.

[68] Moul JW, Wu H, Sun L, McLeod DG, Amling C, Lance R, et al. Epidemiology of radical prostatectomy for localized prostate cancer in the era of prostate-specific antigen: an overview of the

Department of Defense Center for Prostate Disease Research national database. Surgery. 2002 Aug;132(2):213-9.

[69] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. CA Cancer J Clin. 2008 Mar-Apr;58(2):71-96.

[70] Heidenreich A, Aus G, Abbou CC, Bolla M, Joniau S, Matveev V, et al. EAU guideline Prostate Cancer, 2009 update. 2009.

[71] Gleason DF. Classification of prostatic carcinomas. Cancer Chemother Rep. 1966 Mar;50(3):125-8.

[72] Brawn PN, Ayala AG, Von Eschenbach AC, Hussey DH, Johnson DE. Histologic grading study of prostate adenocarcinoma: the development of a new system and comparison with other methods--a preliminary study. Cancer. 1982 Feb 1;49(3):525-32.

[73] Badalament RA, Miller MC, Peller PA, Young DC, Bahn DK, Kochie P, et al. An algorithm for predicting nonorgan confined prostate cancer using the results obtained from sextant core biopsies with prostate specific antigen level. J Urol. 1996;156(4):1375-80.

[74] D'Amico AV, Whittington R, Malkowicz SB, Wu YH, Chen M, Art M, et al. Combination of the preoperative PSA level, biopsy gleason score, percentage of positive biopsies, and MRI T-stage to predict early PSA failure in men with clinically localized prostate cancer. Urology. 2000;55(4):572-7.

[75] Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. Jama. 1998;280(11):975-80.

[76] Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology. 2001;58(6):843-8.

[77] Peschel RE, Colberg JW. Surgery, brachytherapy, and external-beam radiotherapy for early prostate cancer. Lancet Oncol. 2003 Apr;4(4):233-41.

[78] Chan TY, Partin AW, Walsh PC, Epstein JI. Prognostic significance of Gleason score 3+4 versus Gleason score 4+3 tumor at radical prostatectomy. Urology. 2000 Nov 1;56(5):823-7.

[79] van der Kwast TH, Lopes C, Santonja C, Pihl CG, Neetens I, Martikainen P, et al. Guidelines for processing and reporting of prostatic needle biopsies. J Clin Pathol. 2003 May;56(5):336-40.

[80] Epstein JI. Gleason score 2-4 adenocarcinoma of the prostate on needle biopsy: a diagnosis that should not be made. Am J Surg Pathol. 2000 Apr;24(4):477-8.

[81] Schröder FH, Hermanek P, Denis L, Fair WR, Gospodarowicz MK, Pavone-Macaluso M. The TNM classification of prostate cancer. Prostate Suppl. 1992;4:129-38.

[82] Terris MK, Freiha FS, McNeal JE, Stamey TA. Efficacy of transrectal ultrasound for identification of clinically undetected prostate cancer. J Urol. 1991 Jul;146(1):78-83; discussion -4.

[83] Ohori M, Kattan MW, Utsunomiya T, Suyama K, Scardino PT, Wheeler TM. Do impalpable stage T1c prostate cancers visible on ultrasound differ from those not visible? J Urol. 2003 Mar;169(3):964-8.

[84] Onur R, Littrup PJ, Pontes JE, Bianco FJ, Jr. Contemporary impact of transrectal ultrasound lesions for prostate cancer detection. J Urol. 2004 Aug;172(2):512-4.

[85] Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. Jama. 2005 May 4;293(17):2095-101.

[86] Johansson JE, Andren O, Andersson SO, Dickman PW, Holmberg L, Magnuson A, et al. Natural history of early, localized prostate cancer. Jama. 2004 Jun 9;291(22):2713-9.

[87] Walsh PC. Prostate cancer kills: strategy to reduce deaths. Urology. 1994 Oct;44(4):463-6.

[88] Roobol MJ, Schröder FH. The European Randomized Study of Screening for Prostate Cancer (ERSPC): rationale, structure and preliminary results 1994-2003. BJU Int. 2003;92(Supplement 2):1-122.

[89] Coebergh JW, Janssen-Heijnen ML, Louwman MLG, Voogd AC. Cancer Incidence, care and survival in the South of the Netherlands, 1995-1999; a report of the Eindhoven cancer registry with cross-border implications. Eindhoven: Comprehensive cancer center South (IKZ); 2001.

[90] Hoedemaeker RF, van der Kwast TH, Boer R, de Koning HJ, Roobol M, Vis AN, et al. Pathologic features of prostate cancer found at population-based screening with a four-year interval. J Natl Cancer Inst. 2001 Aug 1;93(15):1153-8.

[91] Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. J Natl Cancer Inst. 2009 Jun 16;101(12):878-87.

[92] van der Cruijsen-Koeter IW, Vis AN, Roobol MJ, Wildhagen MF, de Koning HJ, van der Kwast TH, et al. Comparison of screen detected and clinically diagnosed prostate cancer in the European randomized study of screening for prostate cancer, section rotterdam. J Urol. 2005 Jul;174(1):121-5.

[93] De Vries SH, Bangma CH, Schroder FH. Chapter 13. The role of conservative policies in the treatment of prostate cancer. In: Bowsher W, Carter A, eds. *Challenges in prostate cancer*. 2 ed: Blackwell Publishing 2006:153-66.

[94] Auvinen A, Maattanen L, Stenman UH, Tammela T, Rannikko S, Aro J, et al. Lead-time in prostate cancer screening (Finland). Cancer Causes Control. 2002 Apr;13(3):279-85.

[95] Etzioni R, Penson DF, Legler JM, di Tommaso D, Boer R, Gann PH, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst. 2002 Jul 3;94(13):981-90.

[96] Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. Jama. 1995 Jan 25;273(4):289-94.

[97] McGregor M, Hanley JA, Boivin JF, McLean RG. Screening for prostate cancer: estimating the magnitude of overdetection. Cmaj. 1998 Dec 1;159(11):1368-72.

[98] Pearson JD, Carter HB. Natural history of changes in prostate specific antigen in early stage prostate cancer. J Urol. 1994 Nov;152(5 Pt 2):1743-8.

[99] Schroder FH, Alexander FE, Bangma CH, Hugosson J, Smith DS. Screening and early detection of prostate cancer. Prostate. 2000 Aug 1;44(3):255-63.

[100] Zappa M, Ciatto S, Bonardi R, Mazzotta A. Overdiagnosis of prostate carcinoma by screening: an estimate based on the results of the Florence Screening Pilot Study. Ann Oncol. 1998 Dec;9(12):1297-300.

[101] Telesca D, Etzioni R, Gulati R. Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends. Biometrics. 2008 Mar;64(1):10-9.

[102] Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol. 2002 Feb;167(2 Pt 1):528-34.

[103] Brenner H, Arndt V. Long-Term Survival Rates of Patients With Prostate Cancer in the Prostate-Specific Antigen Screening Era: Population-Based Estimates for the Year 2000 by Period Analysis. J Clin Oncol. 2004 Nov 30.

[104] Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer. Lancet. 1997;349(9056):906-10.

[105] Barry MJ, Albertsen PC, Bagshaw MA, Blute ML, Cox R, Middleton RG, et al. Outcomes for men with clinically nonmetastatic prostate carcinoma managed with radical prostactectomy, external beam radiotherapy, or expectant management: a retrospective analysis. Cancer. 2001;91(12):2302-14.

[106] Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, et al. Results of conservative management of clinically localized prostate cancer. N Engl J Med. 1994;330(4):242-8.

[107] Aus G, Hugosson J, Norlen L. Long-term survival and mortality in prostate cancer treated with noncurative intent. J Urol. 1995 Aug;154(2 Pt 1):460-5.

[108] Holmberg L, Bill-Axelson A, Helgesen F, Salo JO, Folmerz P, Haggman M, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med. 2002 Sep 12;347(11):781-9.

[109] Bill-Axelson A, Holmberg L, Filen F, Ruutu M, Garmo H, Busch C, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst. 2008 Aug 20;100(16):1144-54.

[110] Wilt TJ. SPCG-4: a needed START to PIVOTal data to promote and protect evidence-based prostate cancer care. J Natl Cancer Inst. 2008 Aug 20;100(16):1123-5.

[111] Parker C. The Scandinavian Prostate Cancer Group Study: the case for conservative management. BJU Int. 2005 Nov;96(7):952-3.

[112] Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. Jama. 2000 Jan 19;283(3):354-60.

[113] Korfage IJ, Essink-Bot ML, Borsboom GJ, Madalinska JB, Kirkels WJ, Habbema JD, et al. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer. 2005 Aug 20;116(2):291-6.

[114] Madalinska JB, Essink-Bot ML, de Koning HJ, Kirkels WJ, van der Maas PJ, Schroder FH. Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. J Clin Oncol. 2001 Mar 15;19(6):1619-28.

[115] Gilbert SM, Dunn RL, Miller DC, Daignault S, Ye Z, Hollenbeck BK. Mortality after urologic cancer surgery: impact of non-index case volume. Urology. 2008 May;71(5):906-10.

[116] Touijer K, Secin FP, Cronin AM, Katz D, Bianco F, Vora K, et al. Oncologic Outcome after Laparoscopic Radical Prostatectomy: 10 Years of Experience. Eur Urol. 2008 Nov 6.

[117] Alibhai SM, Leach M, Warde P. Major 30-day complications after radical radiotherapy: a Population-Based Analysis and Comparison With Surgery. Cancer. 2009 Jan 15;115(2):293-302.

[118] Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst. 2004 Sep 15;96(18):1358-67.

[119] Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlen BJ, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med. 2002;347(11):790-6.

[120] Wilt TJ, Brawer MK, Barry MJ, Jones KM, Kwon Y, Gingrich JR, et al. The Prostate cancer Intervention Versus Observation Trial:VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. Contemp Clin Trials. 2009 Jan;30(1):81-7.

[121] Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. Bmj. 2002 Oct 5;325(7367):766-70.

[122] Choo R, Klotz L, Danjoux C, Morton GC, DeBoer G, Szumacher E, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol. 2002 Apr;167(4):1664-9.

[123] Stephenson AJ, Aprikian AG, Souhami L, Behlouli H, Jacobson AI, Begin LR, et al. Utility of PSA doubling time in follow-up of untreated patients with localized prostate cancer. Urology. 2002;59(5):652-6.

[124] Koppie TM, Grossfeld GD, Miller D, Yu J, Stier D, Broering JM, et al. Patterns of treatment of patients with prostate cancer initially managed with surveillance: results from The CaPSURE database. Cancer of the Prostate Strategic Urological Research Endeavor. J Urol. 2000;164(1):81-8.

[125] Klotz LH, Choo R, Morton G, Danjoux C. Expectant management with selective delayed intervention for favorable- risk prostate cancer. Can J Urol. 2002;9 Suppl 1:2-7.

[126] Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. Lancet Oncol. 2004 Feb;5(2):101-6.

[127] Steyerberg EW, Roobol MJ, Kattan MW, van der Kwast TH, de Koning HJ, Schroder FH. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. J Urol. 2007 Jan;177(1):107-12; discussion 12.

[128] Schmid HP, McNeal JE, Stamey TA. Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. Cancer. 1993;71(6):2031-40.

[129] Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. Jama. 1992 Apr 22-29;267(16):2215-20.

[130] Ruijter E, van Leenders G, Miller G, Debruyne F, van de Kaa C. Errors in histological grading by prostatic needle biopsy specimens: frequency and predisposing factors. J Pathol. 2000 Oct;192(2):229-33.

[131] Eskew LA, Bare RL, McCullough DL. Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. J Urol. 1997 Jan;157(1):199-202; discussion -3.

[132] Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. J Urol. 2006 May;175(5):1605-12.

[133] Stewart CS, Leibovich BC, Weaver AL, Lieber MM. Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. J Urol. 2001 Jul;166(1):86-91; discussion -2.

[134] Naughton CK, Miller DC, Mager DE, Ornstein DK, Catalona WJ. A prospective randomized trial comparing 6 versus 12 prostate biopsy cores: impact on cancer detection. J Urol. 2000 Aug;164(2):388-92.

[135] Presti JC, Jr., O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol. 2003 Jan;169(1):125-9.

[136] Gosselaar C, Roobol MJ, Roemeling S, Wolters T, van Leenders GJ, Schroder FH. The value of an additional hypoechoic lesion-directed biopsy core for detecting prostate cancer. BJU Int. 2008 Mar;101(6):685-90.

[137] Roobol MJ, van der Cruijsen IW, Schroder FH. No reason for immediate repeat sextant biopsy after negative initial sextant biopsy in men with PSA level of 4.0 ng/mL or greater (ERSPC, Rotterdam). Urology. 2004 May;63(5):892-7; discussion 7-9.

[138] Renshaw AA, Schultz D, Cote K, Loffredo M, Ziemba DE, D'Amico AV. Accurate Gleason grading of prostatic adenocarcinoma in prostate needle biopsies by general pathologists. Arch Pathol Lab Med. 2003 Aug;127(8):1007-8.

[139] Sheridan TB, Carter HB, Wang W, Landis PB, Epstein JI. Change in prostate cancer grade over time in men followed expectantly for stage T1c disease. J Urol. 2008 Mar;179(3):901-4; discussion 4-5.

[140] Ferlay J BF, Pisani P, Parkin DM. GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide, IARC press, Lyon 2001. 2001.

[141] Narain V, Bianco FJ, Jr., Grignon DJ, Sakr WA, Pontes JE, Wood DP, Jr. How accurately does prostate biopsy Gleason score predict pathologic findings and disease free survival? Prostate. 2001;49(3):185-90.

[142] Rietbergen JB, Hoedemaeker RF, Kruger AE, Kirkels WJ, Schroder FH. The changing pattern of prostate cancer at the time of diagnosis: characteristics of screen detected prostate cancer in a population based screening study. J Urol. 1999;161(4):1192-8.

[143] McLaren DB, McKenzie M, Duncan G, Pickles T. Watchful waiting or watchful progression?: Prostate specific antigen doubling times and clinical behavior in patients with early untreated prostate carcinoma. Cancer. 1998 Jan 15;82(2):342-8.

[144] Zietman AL, Thakral H, Wilson L, Schellhammer P. Conservative management of prostate cancer in the prostate specific antigen era: the incidence and time course of subsequent therapy. J Urol. 2001;166(5):1702-6.

[145] Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. J Urol. 2002 Mar;167(3):1231-4.

[146] Post PN, Hansen BE, Kil PJ, Janssen-Heijnen ML, Coebergh JW. The independent prognostic value of comorbidity among men aged < 75 years with localized prostate cancer: a population-based study. BJU Int. 2001;87(9):821-6.

[147] Fowler JE, Jr., Terrell FL, Renfroe DL. Co-morbidities and survival of men with localized prostate cancer treated with surgery or radiation therapy. J Urol. 1996;156(5):1714-8.

[148] Ravery V, Chastang C, Toublanc M, Boccon-Gibod L, Delmas V. Percentage of cancer on biopsy cores accurately predicts extracapsular extension and biochemical relapse after radical prostatectomy for T1-T2 prostate cancer. Eur Urol. 2000;37(4):449-55.

[149] Nelson CP RM, Strawderman M, Montie JE, Sanda MG. Preoperative parameters for predicting early prostate cancer recurrence after radical prostatectomy. Urology. 2002;59(5):740-5; discussion 5-6.

[150] Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. Jama. 1994 Feb 2;271(5):368-74.

[151] Weldon VE, Tavel FR, Neuwirth H, Cohen R. Failure of focal prostate cancer on biopsy to predict focal prostate cancer: the importance of prevalence. J Urol. 1995;154(3):1074-7.

[152] Lattouf JB, Saad F. Gleason score on biopsy: is it reliable for predicting the final grade on pathology? BJU Int. 2002;90(7):694-8; discussion 8-9.

[153] San Francisco IF, DeWolf WC, Rosen S, Upton M, Olumi AF. Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. J Urol. 2003;169(1):136-40.

[154] Grossklaus DJ, Coffey CS, Shappell SB, Jack GS, Cookson MS. Prediction of tumour volume and pathological stage in radical prostatectomy specimens is not improved by taking more prostate needle- biopsy cores. BJU Int. 2001;88(7):722-6.

[155] Egevad L, Norlen BJ, Norberg M. The value of multiple core biopsies for predicting the Gleason score of prostate cancer. BJU Int. 2001;88(7):716-21.

[156] Bastacky SI, Walsh PC, Epstein JI. Relationship between perineural tumor invasion on needle biopsy and radical prostatectomy capsular penetration in clinical stage B adenocarcinoma of the prostate. Am J Surg Pathol. 1993;17(4):336-41.

[157] Bonin SR, Hanlon AL, Lee WR, Movsas B, al-Saleem TI, Hanks GE. Evidence of increased failure in the treatment of prostate carcinoma patients who have perineural invasion treated with three-dimensional conformal radiation therapy. Cancer. 1997;79(1):75-80.

[158] Huland H, Hammerer P, Henke RP, Huland E. Preoperative prediction of tumor heterogeneity and recurrence after radical prostatectomy for localized prostatic carcinoma with digital rectal, examination prostate specific antigen and the results of 6 systematic biopsies. J Urol. 1996;155(4):1344-7.

[159] Peller PA, Young DC, Marmaduke DP, Marsh WL, Badalament RA. Sextant prostate biopsies. A histopathologic correlation with radical prostatectomy specimens. Cancer. 1995;75(2):530-8.

[160] Freedland SJ, Csathy GS, Dorey F, Aronson WJ. Clinical utility of percent prostate needle biopsy tissue with cancer cutpoints to risk stratify patients before radical prostatectomy. Urology. 2002;60(1):84-8.

[161] Terris MK, Haney DJ, Johnstone IM, McNeal JE, Stamey TA. Prediction of prostate cancer volume using prostate-specific antigen levels, transrectal ultrasound, and systematic sextant biopsies. Urology. 1995;45(1):75-80.

[162] Elgamal AA, Van Poppel HP, Van de Voorde WM, Van Dorpe JA, Oyen RH, Baert LV. Impalpable invisible stage T1c prostate cancer: characteristics and clinical relevance in 100 radical prostatectomy specimens--a different view. J Urol. 1997;157(1):244-50.

[163] Haese A, Chaudhari M, Miller MC, Epstein JI, Huland H, Palisaar J, et al. Quantitative biopsy pathology for the prediction of pathologically organ-confined prostate carcinoma: a multiinstitutional validation study. Cancer. 2003;97(4):969-78.

[164] Choo R, DeBoer G, Klotz L, Danjoux C, Morton GC, Rakovitch E, et al. PSA doubling time of prostate carcinoma managed with watchful observation alone. Int J Radiat Oncol Biol Phys. 2001;50(3):615-20.

[165] Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. Jama. 1997;277(18):1456-60.

[166] Do V, Choo R, De Boer G, Klotz L, Danjoux C, Morton G, et al. The role of serial free/total prostate-specific antigen ratios in a watchful observation protocol for men with localized prostate cancer. BJU Int. 2002;89(7):703-9.

[167] Gleave M GS, Rennie P,. Recent advances in prostate cancer, BPH; Proceedings of the IV Congres on Progress and Controversies in Oncological Urology (PACIOU IV) held in Rotterdam, the Netherlands, April 11-13, 1996. In: FH S, ed.: Parthenon Publishing, New York, London 1996 1996:109-20.

[168] Davidson PJ, Hop W, Kurth KH, Fossa SD, Waehre H, Schroder FH. Progression in untreated carcinoma of the prostate metastatic to regional lymph nodes (stage t0 to 4,N1 to 3.M0,D1). European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol. 1995;154(6):2118-22.

[169] Carter HB, Morrell CH, Pearson JD, Brant LJ, Plato CC, Metter EJ, et al. Estimation of prostatic growth using serial prostate-specific antigen measurements in men with and without prostate disease. Cancer Res. 1992;52(12):3323-8.

[170] Ciatto S, Bonardi R, Lombardi C, Zappa M, Gervasi G, Cappelli G. Analysis of PSA velocity in 1666 healthy subjects undergoing total PSA determination at two consecutive screening rounds. Int J Biol Markers. 2002;17(2):79-83.

[171] Schroder FH, Kranse R, Barbet N, Hop WC, Kandra A, Lassus M. Prostate-specific antigen: A surrogate endpoint for screening new agents against prostate cancer? Prostate. 2000;42(2):107-15.

[172] Guess B, Jennrich R, Johnson H, Redheffer R, Scholz M. Using splines to detect changes in PSA doubling times. Prostate. 2003;54(2):88-94.

[173] Collette L, de Reijke TM, Schroder FH. Prostate specific antigen: a prognostic marker of survival in good prognosis metastatic prostate cancer? (EORTC 30892). Eur Urol. 2003 Aug;44(2):182-9; discussion 9.

[174] Stamey TA, Kabalin JN, Ferrari M, Yang N. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. IV. Anti-androgen treated patients. J Urol. 1989;141(5):1088-90.

[175] Stamey TA, Johnstone IM, McNeal JE, Lu AY, Yemoto CM. Preoperative serum prostate specific antigen levels between 2 and 22 ng./ml. correlate poorly with post-radical prostatectomy cancer morphology: prostate specific antigen cure rates appear constant between 2 and 9 ng./ml. J Urol. 2002;167(1):103-11.

[176] Hanks GE, Hanlon AL, Lee WR, Slivjak A, Schultheiss TE. Pretreatment prostate-specific antigen doubling times: clinical utility of this predictor of prostate cancer behavior. Int J Radiat Oncol Biol Phys. 1996;34(3):549-53.

[177] Goluboff ET, Heitjan DF, DeVries GM, Katz AE, Benson MC, Olsson CA. Pretreatment prostate specific antigen doubling times: use in patients before radical prostatectomy. J Urol. 1997;158(5):1876-8; discussion 8-9.

[178] Epstein JI, Walsh PC, Carter HB. Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage T1c disease. J Urol. 2001;166(5):1688-91.

[179] Vis AN, Boerma MO, Ciatto S, Hoedemaeker RF, Schroder FH, van der Kwast TH. Detection of prostate cancer: a comparative study of the diagnostic efficacy of sextant transrectal versus sextant transperineal biopsy. Urology. 2000;56(4):617-21.

[180] Aus G, Abbou CC, Bolla M, Heidenreich A, Schmid HP, van Poppel H, et al. EAU guidelines on prostate cancer. Eur Urol. 2005 Oct;48(4):546-51.

[181] de Koning HJ, Auvinen A, Berenguer Sanchez A, Calais da Silva F, Ciatto S, Denis L, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial. Int J Cancer. 2002 Jan 10;97(2):237-44.

[182] Postma R, van Leenders AG, Roobol MJ, Schroder FH, van der Kwast TH. Tumour features in the control and screening arm of a randomized trial of prostate cancer. Eur Urol. 2006 Jul;50(1):70-5.

[183] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

[184] D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. Jama. 1998 Sep 16;280(11):969-74.

[185] De Koning HJ, Blom J, Merkelbach JW, Raaijmakers R, Verhaegen H, Van Vliet P, et al. Determining the cause of death in randomized screening trial(s) for prostate cancer. BJU Int. 2003 Dec;92 Suppl 2:71-8.

[186] website CCR. Regional Cancer Registry North Holland/ Flevoland, The Netherlands. http://ww-wikcnetnl/system/image_viewer/indexphp?recID=805&image=1 2005 20-jan [cited; Available from: http://www.ikcnet.nl/page.php?id=224

[187] Otto SJ, Schroder FH, de Koning HJ. Low all-cause mortality in the volunteer-based Rotterdam section of the European randomised study of screening for prostate cancer: self-selection bias? J Med Screen. 2004;11(2):89-92.

[188] D'Amico AV, Whittington R, Malkowicz SB, Cote K, Loffredo M, Schultz D, et al. Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer. 2002 Jul 15;95(2):281-6.

[189] Kupelian PA, Elshaikh M, Reddy CA, Zippe C, Klein EA. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. J Clin Oncol. 2002 Aug 15;20(16):3376-85.

[190] Newschaffer CJ, Otani K, McDonald MK, Penberthy LT. Causes of death in elderly prostate cancer patients and in a comparison nonprostate cancer cohort. J Natl Cancer Inst. 2000 Apr 19;92(8):613-21.

[191] Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. J Urol. 2000 Feb;163(2):519-23.

[192] Otto SJ, van der Cruijsen IW, Liem MK, Korfage IJ, Lous JJ, Schroder FH, et al. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. Int J Cancer. 2003 Jun 20;105(3):394-9.

[193] Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel EL, et al. Differential prognostic impact of comorbidity. J Clin Oncol. 2004 Aug 1;22(15):3099-103.

[194] (UICC). IUaC. TNM classification of malignant tumours. 4th ed. 2nd revision ed. Berlin (Germany): Springer Verlag 1992.

[195] Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2005 May 12;352(19):1977-84.

[196] Roach M, Lu J, Pilepich MV, Asbell SO, Mohiuddin M, Terry R, et al. Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on Radiation Therapy Oncology Group clinical trials. Int J Radiat Oncol Biol Phys. 2000 Jun 1;47(3):609-15.

[197] de Vries SH, Postma R, Raaijmakers R, Roemeling S, Otto S, de Koning HJ, et al. Overall and disease-specific survival of patients with screen-detected prostate cancer in the European randomized study of screening for prostate cancer, section Rotterdam. Eur Urol. 2007 Feb;51(2):366-74; discussion 74.

[198] Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006 Mar-Apr;56(2):106-30.

[199] Roemeling S, Roobol MJ, Gosselaar C, Schroder FH. Biochemical progression rates in the screen arm compared to the control arm of the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Prostate. 2006 Jul 1;66(10):1076-81.

[200] Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol. 2005 Nov 10;23(32):8165-9.

[201] Roemeling S, Roobol MJ, Postma R, Gosselaar C, van der Kwast TH, Bangma CH, et al. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. Eur Urol. 2006 Sep;50(3):475-82.

[202] Loeb S, Roehl KA, Antenor JA, Catalona WJ, Suarez BK, Nadler RB. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology. 2006 Feb;67(2):316-20.

[203] Hoedemaeker RF, Kranse R, Rietbergen JB, Kruger AE, Schroder FH, van der Kwast TH. Evaluation of prostate needle biopsies in a population-based screening study: the impact of borderline lesions. Cancer. 1999 Jan 1;85(1):145-52.

[204] Passing H, Bablok. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. J Clin Chem Clin Biochem. 1983 Nov;21(11):709-20.

[205] Yurdakul G, Bangma CH, Blijenberg BG, van Zelst BD, Wildhagen MF, van der Kwast TH, et al. Different PSA assays lead to detection of prostate cancers with identical histological features. Eur Urol. 2002 Aug;42(2):154-8.

[206] René Raaijmakers MFW, Kazuto Ito, Alvaro Pàez, Stijn H. de Vries, Monique J. Roobol, Fritz H. Schröder. Prostate specific antigen change in the European Randomized study of Screening for Prostate Cancer: ERSPC (section Rotterdam). Urology. 2003.

[207] Egawa S, Matsumoto K, Suyama K, Iwamura M, Kuwao S, Baba S. Observations of prostate specific antigen doubling time in Japanese patients with nonmetastatic prostate carcinoma. Cancer. 1999 Aug 1;86(3):463-9.

[208] Prestigiacomo AF, Stamey TA. Physiological variation of serum prostate specific antigen in the 4.0 to 10.0 ng./ml. range in male volunteers. J Urol. 1996 Jun;155(6):1977-80.

[209] Niemela P, Lovgren J, Karp M, Lilja H, Pettersson K. Sensitive and specific enzymatic assay for the determination of precursor forms of prostate-specific antigen after an activation step. Clin Chem. 2002 Aug;48(8):1257-64.

[210] Chan TY, Mikolajczyk SD, Lecksell K, Shue MJ, Rittenhouse HG, Partin AW, et al. Immunohistochemical staining of prostate cancer with monoclonal antibodies to the precursor of prostate-specific antigen. Urology. 2003 Jul;62(1):177-81.

[211] Beemsterboer PM, Kranse R, de Koning HJ, Habbema JD, Schroder FH. Changing role of 3 screening modalities in the European randomized study of screening for prostate cancer (Rotterdam). Int J Cancer. 1999;84(4):437-41.

[212] Kranse R, Beemsterboer P, Rietbergen J, Habbema D, Hugosson J, Schroder FH. Predictors for biopsy outcome in the European Randomized Study of Screening for Prostate Cancer (Rotterdam region). Prostate. 1999;39(4):316-22.

[213] Schroder FH, Denis LJ, Kirkels W, de Koning HJ, Standaert B. European randomized study of screening for prostate cancer. Progress report of Antwerp and Rotterdam pilot studies. Cancer. 1995;76(1):129-34.

[214] Benson MC, Whang IS, Olsson CA, McMahon DJ, Cooner WH. The use of prostate specific antigen density to enhance the predictive value of intermediate levels of serum prostate specific antigen. J Urol. 1992 Mar;147(3 Pt 2):817-21.

[215] Bangma CH, Wildhagen MF, Yurdakul G, Schroder FH, Blijenberg BG. The value of (-7, -5)pro-prostate-specific antigen and human kallikrein-2 as serum markers for grading prostate cancer. BJU Int. 2004 Apr;93(6):720-4.

[216] Sokoll LJ, Chan DW, Mikolajczyk SD, Rittenhouse HG, Evans CL, Linton HJ, et al. Proenzyme psa for the early detection of prostate cancer in the 2.5-4.0 ng/ml total psa range: preliminary analysis. Urology. 2003 Feb;61(2):274-6.

[217] de Vries SH, Raaijmakers R, Kranse R, Blijenberg BG, Schroder FH. Prostate cancer characteristics and prostate specific antigen changes in screening detected patients initially treated with a watchful waiting policy. J Urol. 2004 Dec;172(6 Pt 1):2193-6.

[218] de Vries SH, Bangma CH, Schroder FH. Watchful waiting versus expectant management in prostate cancer. NTvU (Nederlands Tijdschrift voor Urologie. 2004 nov;12(4):101-5.

[219] van den Bergh RC, Roemeling S, Roobol MJ, Roobol W, Schroder FH, Bangma CH. Prospective validation of active surveillance in prostate cancer: the PRIAS study. Eur Urol. 2007 Dec;52(6):1560-3.

[220] PRIAS. [cited; Available from: https://www.prias-project.org/modules/news/

[221] Stamey TA, Freiha FS, McNeal JE, Redwine EA, Whittemore AS, Schmid HP. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. Cancer. 1993 Feb 1;71(3 Suppl):933-8.

[222] Epstein JI, Chan DW, Sokoll LJ, Walsh PC, Cox JL, Rittenhouse H, et al. Nonpalpable stage T1c prostate cancer: prediction of insignificant disease using free/total prostate specific antigen levels and needle biopsy findings. J Urol. 1998 Dec;160(6 Pt 2):2407-11.

[223] Jeldres C, Suardi N, Walz J, Hutterer GC, Ahyai S, Lattouf JB, et al. Validation of the contemporary epstein criteria for insignificant prostate cancer in European men. Eur Urol. 2008 Dec;54(6):1306-13.

[224] Bastian PJ, Carter BH, Bjartell A, Seitz M, Stanislaus P, Montorsi F, et al. Insignificant Prostate Cancer and Active Surveillance: From Definition to Clinical Implications. Eur Urol. 2009 Mar 6.

[225] Dall'Era MA, Carroll PR. Outcomes and follow-up strategies for patients on active surveillance. Curr Opin Urol. 2009 May;19(3):258-62.

[226] Dall'Era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, Klotz LH, et al. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer. 2008 Apr 15;112(8):1650-9.

[227] van den Bergh RC, Roemeling S, Roobol MJ, Aus G, Hugosson J, Rannikko AS, et al. Outcomes of Men with Screen-Detected Prostate Cancer Eligible for Active Surveillance Who Were Managed Expectantly. Eur Urol. 2008 Sep 17.

[228] Klotz L. Active surveillance for prostate cancer: trials and tribulations. World J Urol. 2008 Oct;26(5):437-42.

[229] Soloway MS, Soloway CT, Williams S, Ayyathurai R, Kava B, Manoharan M. Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. BJU Int. 2008 Jan;101(2):165-9.

[230] Carter HB, Kettermann A, Warlick C, Metter EJ, Landis P, Walsh PC, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol. 2007 Dec;178(6):2359-64; discussion 64-5.

[231] Stattin P, Holmberg E, Bratt O, Adolfsson J, Johansson JE, Hugosson J. Surveillance and deferred treatment for localized prostate cancer. Population based study in the National Prostate Cancer Register of Sweden. J Urol. 2008 Dec;180(6):2423-9; discussion 9-30.

[232] Klotz L. Active surveillance with selective delayed intervention for favorable risk prostate cancer. Urol Oncol. 2006 Jan-Feb;24(1):46-50.

[233] Suardi N, Capitanio U, Chun FK, Graefen M, Perrotte P, Schlomm T, et al. Currently used criteria for active surveillance in men with low-risk prostate cancer: an analysis of pathologic features. Cancer. 2008 Oct 15;113(8):2068-72.

[234] Dall'Era MA, Konety BR, Cowan JE, Shinohara K, Stauf F, Cooperberg MR, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. Cancer. 2008 Jun 15;112(12):2664-70.

[235] van den Bergh RC, Roemeling S, Roobol MJ, Aus G, Hugosson J, Rannikko AS, et al. Gleason score 7 screen-detected prostate cancers initially managed expectantly: outcomes in 50 men. BJU Int. 2009 Jan 9.

[236] Roemeling S, Roobol MJ, de Vries SH, Wolters T, Gosselaar C, van Leenders GJ, et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. Eur Urol. 2007 May;51(5):1244-50; discussion 51.

[237] Ercole B, Marietti SR, Fine J, Albertsen PC. Outcomes following active surveillance of men with localized prostate cancer diagnosed in the prostate specific antigen era. J Urol. 2008 Oct;180(4):1336-9; discussion 40-1.

[238] van As NJ, Parker CC. Active surveillance with selective radical treatment for localized prostate cancer. Cancer J. 2007 Sep-Oct;13(5):289-94.

[239] START. [cited; Available from: http://www.sunnybrook.ca/uploads/N070913.pdf

[240] Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med. 2008 Mar 18;148(6):435-48.

[241] Adolfsson J, Tribukait B, Levitt S. The 20-Yr outcome in patients with well- or moderately differentiated clinically localized prostate cancer diagnosed in the pre-PSA era: the prognostic value of tumour ploidy and comorbidity. Eur Urol. 2007 Oct;52(4):1028-35.

[242] Albertsen PC, Hanley JA, Penson DF, Barrows G, Fine J. 13-year outcomes following treatment for clinically localized prostate cancer in a population based cohort. J Urol. 2007 Mar;177(3):932-6.

[243] Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. Jama. 2008 Jul 9;300(2):173-81.

[244] Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, et al. Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. Health Technol Assess. 2003;7(14):1-88.

[245] Roobol MJ. Algorithms, nomograms and the detection of indolent prostate cancer. World J Urol. 2008 Oct;26(5):423-9.

[246] Makarov DV, Trock BJ, Humphreys EB, Mangold LA, Walsh PC, Epstein JI, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. Urology. 2007 Jun;69(6):1095-101.

[247] Kattan MW, Eastham JA, Wheeler TM, Maru N, Scardino PT, Erbersdobler A, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol. 2003 Nov;170(5):1792-7.

[248] Nakanishi H, Wang X, Ochiai A, Trpkov K, Yilmaz A, Donnelly JB, et al. A nomogram for predicting low-volume/low-grade prostate cancer: a tool in selecting patients for active surveillance. Cancer. 2007 Dec 1;110(11):2441-7.

[249] Dong F, Kattan MW, Steyerberg EW, Jones JS, Stephenson AJ, Schroder FH, et al. Validation of pretreatment nomograms for predicting indolent prostate cancer: efficacy in contemporary urological practice. J Urol. 2008 Jul;180(1):150-4; discussion 4.

[250] Bangma CH, Roobol MJ, Steyerberg EW. Predictive models in diagnosing indolent cancer. Cancer. 2009 Jul 1;115(13 Suppl):3100-6.

[251] Chun FK, Haese A, Ahyai SA, Walz J, Suardi N, Capitanio U, et al. Critical assessment of tools to predict clinically insignificant prostate cancer at radical prostatectomy in contemporary men. Cancer. 2008 Aug 15;113(4):701-9.

[252] Cooperberg MR, Pasta DJ, Elkin EP, Litwin MS, Latini DM, Du Chane J, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol. 2005 Jun;173(6):1938-42.

[253] Cooperberg MR, Freedland SJ, Pasta DJ, Elkin EP, Presti JC, Jr., Amling CL, et al. Multiinstitutional validation of the UCSF cancer of the prostate risk assessment for prediction of recurrence after radical prostatectomy. Cancer. 2006 Nov 15;107(10):2384-91.

[254] May M, Knoll N, Siegsmund M, Fahlenkamp D, Vogler H, Hoschke B, et al. Validity of the CAPRA score to predict biochemical recurrence-free survival after radical prostatectomy. Results from a european multicenter survey of 1,296 patients. J Urol. 2007 Nov;178(5):1957-62; discussion 62.

[255] Zhao KH, Hernandez DJ, Han M, Humphreys EB, Mangold LA, Partin AW. External validation of University of California, San Francisco, Cancer of the Prostate Risk Assessment score. Urology. 2008 Aug;72(2):396-400.

[256] de Vries SH, Raaijmakers R, Blijenberg BG, Mikolajczyk SD, Rittenhouse HG, Schroder FH. Additional use of [-2] precursor prostate-specific antigen and "benign" PSA at diagnosis in screen-detected prostate cancer. Urology. 2005 May;65(5):926-30.

[257] Stephan C, Kahrs AM, Cammann H, Lein M, Schrader M, Deger S, et al. A [-2]proPSA-based artificial neural network significantly improves differentiation between prostate cancer and benign prostatic diseases. Prostate. 2009 Feb 1;69(2):198-207.

[258] Sokoll LJ, Wang Y, Feng Z, Kagan J, Partin AW, Sanda MG, et al. [-2]proenzyme prostate specific antigen for prostate cancer detection: a national cancer institute early detection research network validation study. J Urol. 2008 Aug;180(2):539-43; discussion 43.

[259] Stephan C, Meyer HA, Kwiatkowski M, Recker F, Cammann H, Loening SA, et al. A (-5, -7) proPSA based artificial neural network to detect prostate cancer. Eur Urol. 2006 Nov;50(5):1014-20.

[260] Stephan C, Xu C, Brown DA, Breit SN, Michael A, Nakamura T, et al. Three new serum markers for prostate cancer detection within a percent free PSA-based artificial neural network. Prostate. 2006 May 1;66(6):651-9.

[261] Jansen FH, van Schaik RHN, Kurstjens J, Horninger W, Bektics J, Wildhagen MF, et al. Percent (-2) proPSA improves diagnostic accuracy in prostate cancer detection. *EUA 2009*. Stockholm, Sweden 2009.

[262] Shariat SF, Karam JA, Margulis V, Karakiewicz PI. New blood-based biomarkers for the diagnosis, staging and prognosis of prostate cancer. BJU Int. 2008 Mar;101(6):675-83.

[263] Sardana G, Dowell B, Diamandis EP. Emerging biomarkers for the diagnosis and prognosis of prostate cancer. Clin Chem. 2008 Dec;54(12):1951-60.

[264] Lin DW. Beyond PSA: utility of novel tumor markers in the setting of elevated PSA. Urol Oncol. 2009 May-Jun;27(3):315-21.

[265] Leman ES, Cannon GW, Trock BJ, Sokoll LJ, Chan DW, Mangold L, et al. EPCA-2: a highly specific serum marker for prostate cancer. Urology. 2007 Apr;69(4):714-20.

[266] Raaijmakers R, de Vries SH, Blijenberg BG, Wildhagen MF, Postma R, Bangma CH, et al. hK2 and free PSA, a prognostic combination in predicting minimal prostate cancer in screen-detected men within the PSA range 4-10 ng/ml. Eur Urol. 2007 Nov;52(5):1358-64.

[267] Steuber T, Vickers AJ, Haese A, Becker C, Pettersson K, Chun FK, et al. Risk assessment for biochemical recurrence prior to radical prostatectomy: significant enhancement contributed by human glandular kallikrein 2 (hK2) and free prostate specific antigen (PSA) in men with moderate PSA-elevation in serum. Int J Cancer. 2006 Mar 1;118(5):1234-40.

[268] Nam RK, Reeves JR, Toi A, Dulude H, Trachtenberg J, Emami M, et al. A novel serum marker, total prostate secretory protein of 94 amino acids, improves prostate cancer detection and helps identify high grade cancers at diagnosis. J Urol. 2006 Apr;175(4):1291-7.

[269] Raff AB, Gray A, Kast WM. Prostate stem cell antigen: A prospective therapeutic and diagnostic target. Cancer Lett. 2008 Oct 4.

[270] Han KR, Seligson DB, Liu X, Horvath S, Shintaku PI, Thomas GV, et al. Prostate stem cell antigen expression is associated with gleason score, seminal vesicle invasion and capsular invasion in prostate cancer. J Urol. 2004 Mar;171(3):1117-21.

[271] Rubin MA, Bismar TA, Andren O, Mucci L, Kim R, Shen R, et al. Decreased alpha-methylacyl CoA racemase expression in localized prostate cancer is associated with an increased rate of biochemical recurrence and cancer-specific death. Cancer Epidemiol Biomarkers Prev. 2005 Jun;14(6):1424-32.

[272] Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature. 2002 Oct 10;419(6907):624-9.

[273] Wenske S, Korets R, Cronin AM, Vickers AJ, Fleisher M, Scher HI, et al. Evaluation of molecular forms of prostate-specific antigen and human kallikrein 2 in predicting biochemical failure after radical prostatectomy. Int J Cancer. 2009 Feb 1;124(3):659-63.

[274] Sreekumar A, Poisson LM, Rajendiran TM, Khan AP, Cao Q, Yu J, et al. Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression. Nature. 2009 Feb 12;457(7231):910-4.

[275] Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ, van Balken B, et al. DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. Eur Urol. 2003 Jul;44(1):8-15; discussion -6.

[276] van Gils MP, Hessels D, Hulsbergen-van de Kaa CA, Witjes JA, Jansen CF, Mulders PF, et al. Detailed analysis of histopathological parameters in radical prostatectomy specimens and PCA3 urine test results. Prostate. 2008 Aug 1;68(11):1215-22.

[277] Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, et al. PCA3: a molecular urine assay for predicting prostate biopsy outcome. J Urol. 2008 Apr;179(4):1587-92.

[278] Hessels D, Smit FP, Verhaegh GW, Witjes JA, Cornel EB, Schalken JA. Detection of TMPRSS2-ERG fusion transcripts and prostate cancer antigen 3 in urinary sediments may improve diagnosis of prostate cancer. Clin Cancer Res. 2007 Sep 1;13(17):5103-8.

[279] Laxman B, Morris DS, Yu J, Siddiqui J, Cao J, Mehra R, et al. A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. Cancer Res. 2008 Feb 1;68(3):645-9.

[280] Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. Int J Cancer. 2007 Jan 1;120(1):170-4.

[281] van den Bergh RC, Roemeling S, Roobol MJ, Wolters T, Schroder FH, Bangma CH. Prostate-specific antigen kinetics in clinical decision-making during active surveillance for early prostate cancer--a review. Eur Urol. 2008 Sep;54(3):505-16.

[282] D'Amico AV, Chen MH, Catalona WJ, Sun L, Roehl KA, Moul JW. Prostate cancer-specific mortality after radical prostatectomy or external beam radiation therapy in men with 1 or more high-risk factors. Cancer. 2007 Jul 1;110(1):56-61.

[283] D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med. 2004 Jul 8;351(2):125-35.

[284] King CR, Freedland SJ, Terris MK, Aronson WJ, Kane CJ, Amling CL, et al. Optimal timing, cutoff, and method of calculation of preoperative prostate-specific antigen velocity to predict relapse after prostatectomy: a report from SEARCH. Urology. 2007 Apr;69(4):732-7.

[285] Sengupta S, Myers RP, Slezak JM, Bergstralh EJ, Zincke H, Blute ML. Preoperative prostate specific antigen doubling time and velocity are strong and independent predictors of outcomes following radical prostatectomy. J Urol. 2005 Dec;174(6):2191-6.

[286] Loeb S, Kettermann A, Ferrucci L, Landis P, Metter EJ, Carter HB. PSA doubling time versus PSA velocity to predict high-risk prostate cancer: data from the Baltimore Longitudinal Study of Aging. Eur Urol. 2008 Nov;54(5):1073-80.

[287] Ng MK, Van As N, Thomas K, Woode-Amissah R, Horwich A, Huddart R, et al. Prostate-specific antigen (PSA) kinetics in untreated, localized prostate cancer: PSA velocity vs PSA doubling time. BJU Int. 2008 Oct 16.

[288] Freedland SJ, Dorey F, Aronson WJ. Preoperative PSA velocity and doubling time do not predict adverse pathologic features or biochemical recurrence after radical prostatectomy. Urology. 2001 Mar;57(3):476-80.

[289] Patel MI, DeConcini DT, Lopez-Corona E, Ohori M, Wheeler T, Scardino PT. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. J Urol. 2004 Apr;171(4):1520-4.

[290] Arlen PM, Bianco F, Dahut WL, D'Amico A, Figg WD, Freedland SJ, et al. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. J Urol. 2008 Jun;179(6):2181-5; discussion 5-6.

[291] Schroder FH, de Vries SH, Bangma CH. Watchful waiting in prostate cancer: review and policy proposals. BJU Int. 2003 Nov;92(8):851-9.

[292] Hardie C, Parker C, Norman A, Eeles R, Horwich A, Huddart R, et al. Early outcomes of active surveillance for localized prostate cancer. BJU Int. 2005 May;95(7):956-60.

[293] Warlick C, Trock BJ, Landis P, Epstein JI, Carter HB. Delayed versus immediate surgical intervention and prostate cancer outcome. J Natl Cancer Inst. 2006 Mar 1;98(5):355-7.

[294] Roemeling S, De Vries SH, Gosselaar C, Schroder F. Influence of deferred treatment with curative intent on progression free survival rates in prostate cancer. *EAU abstract*. Istanbul, Turkey 2005.

[295] Gohagan JK, Prorok PC, Hayes RB, Kramer BS. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials. 2000 Dec;21(6 Suppl):251S-72S.

[296] Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and Prostate-Cancer Mortality in a Randomized European Study. N Engl J Med. 2009 Mar 26;360(13):1320-8.

[297] Andriole GL, Grubb RL, 3rd, Buys SS, Chia D, Church TR, Fouad MN, et al. Mortality Results from a Randomized Prostate-Cancer Screening Trial. N Engl J Med. 2009 Mar 26;360(13):1310-9.

[298] Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000 Dec;21(6 Suppl):273S-309S.

[299] Barry MJ. Screening for prostate cancer--the controversy that refuses to die. N Engl J Med. 2009 Mar 26;360(13):1351-4.

[300] Grubb RL, 3rd, Pinsky PF, Greenlee RT, Izmirlian G, Miller AB, Hickey TP, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int. 2008 Dec;102(11):1524-30.

[301] Ciatto S, Zappa M, Villers A, Paez A, Otto SJ, Auvinen A. Contamination by opportunistic screening in the European Randomized Study of Prostate Cancer Screening. BJU Int. 2003 Dec;92 Suppl 2:97-100.

[302] Roemeling S, Roobol MJ, Otto SJ, Habbema DF, Gosselaar C, Lous JJ, et al. Feasibility study of adjustment for contamination and non-compliance in a prostate cancer screening trial. Prostate. 2007 Jul 1;67(10):1053-60.

[303] Roemeling S, Roobol MJ, Kattan MW, van der Kwast TH, Steyerberg EW, Schroder FH. Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations. Cancer. 2007 Nov 15;110(10):2218-21.

[304] Postma R, Schroder FH, van Leenders GJ, Hoedemaeker RF, Vis AN, Roobol MJ, et al. Cancer detection and cancer characteristics in the European Randomized Study of Screening for Prostate Cancer (ERSPC)--Section Rotterdam. A comparison of two rounds of screening. Eur Urol. 2007 Jul;52(1):89-97.

[305] Nguyen PL, Chen MH, Catalona WJ, Alexander BM, Roehl KA, Loeb S, et al. Biochemical recurrence after radical prostatectomy for prevalent versus incident cases of prostate cancer: implications for management. Cancer. 2008 Oct 17.

[306] Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol. 2007 Jun;177(6):2106-31.

[307] Parker C, Muston D, Melia J, Moss S, Dearnaley D. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. Br J Cancer. 2006 May 22;94(10):1361-8.

[308] American Urological Association. Policy statement on early detection of prostate cancer (website). http://wwwauanetorg/content/guidelines-and-quality-care/policy-statements/e/early-detection-of-prostate-cancercfm. 2008;Octobre.

[309] Nederlandse vereniging voor Urologie. Prostaatkanker. [cited; Available from: http://www.nvu.nl/patienten/aandoeningen-en-behandeling/aandoeningen-en-behandelingen/prostaatkanker-diagnostiek

[310] American Cancer Society. Recommendations for prostate cancer early detection 2008 [cited 23-05-2009]; Available from: http://www.cancer.org/docroot/CRI/content/CRI_2_6x_Prostate_Cancer_Early_Detection.asp?sitearea=

[311] National Cancer Institute PDQ Screening and Prevention Editorial Board. Prostate Cancer Screening (PDQ®). may 2008 [cited; Available from: http://www.cancer.gov/cancertopics/pdq/screening/prostate/healthprofessional/allpages

[312] National Comprehensive Cancer Network. Prostate Cancer Early Detection V.2.2007. 2007 [cited 16-02-2009]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/prostate_detection.pdf

[313] Johansson E, Bill-Axelson A, Holmberg L, Onelov E, Johansson JE, Steineck G. Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. Eur Urol. 2009 Feb;55(2):422-30.

[314] Korfage IJ. Editorial comment on: Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. Eur Urol. 2009 Feb;55(2):432.

[315] Litwin MS, Lubeck DP, Spitalny GM, Henning JM, Carroll PR. Mental health in men treated for early stage prostate carcinoma: a posttreatment, longitudinal quality of life analysis from the Cancer of the Prostate Strategic Urologic Research Endeavor. Cancer. 2002;95(1):54-60.

[316] Daubenmier JJ, Weidner G, Marlin R, Crutchfield L, Dunn-Emke S, Chi C, et al. Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. Urology. 2006 Jan;67(1):125-30.

[317] van den Bergh RC, van Vugt HA, Korfage IJ, Steyerberg EW, Roobol MJ, Schroder FH, et al. Disease insight and treatment perception of men on active surveillance for early prostate cancer. BJU Int. 2009 Jul 7.

# Summary

The goal of this thesis is to contribute to the evaluation of active surveillance (AS) as a safe strategy in selected men with organ confined prostate cancer (PCa) at diagnosis. To investigate the feasibility of an AS policy the key questions in AS were addressed;

- Who are suitable candidates?
- How to select and monitor these men?
- When to treat these patients without compromising the chance of cure?

The concept of AS is to avoid unnecessary treatment, with its inherent side-effects and costs, while preserving the window of cure in males with localized PCa. First the rationale of deferred treatment in a potential lethal disease is explained providing background information on the prostate, prostate specific antigen (PSA) and prostate cancer in the introduction. The window of opportunity for AS is provided by screening which forwards the diagnosis in time and causes a shift towards more favourable prostate cancer characteristics at time of diagnosis. Together with the known relatively latent natural history op PCa in most cases this leads to overdiagnosis. Overdiagnosis is the detection of asymptomatic PCa that would never have been detected clinically if PSA had not been used as a screening test. Due to the anatomical position of the prostate, treatment of PCA with curative intent is not without morbidity and even mortality. The goal of AS is to defer or even defy treatment for these men with overdiagnosed PCa while keeping the window of cure with a detailed follow-up regimen. Patients and physicians however will have to realize that active surveillance is still an empiric therapy. An overview of different selection parameters and follow-up criteria together with trigger points to time deferred treatment is given in **Chapter 3**.

**Chapter 4** shows overall and disease specific rates of males diagnosed with PCa in the first round of ERSPC, section Rotterdam. These data are compared to a cohort of Dutch males outside the screening program. It was shown that PCa slowly progresses in most screen detected PCa cases and that prostate cancer deaths were rare during a median follow-up of 55 months. PCa deaths, when present, were more common in the non screened cohort. In the ERSPC cohort only one patient, with favourable prognostic PCa characteristics died of prostate cancer due to peri-operative complications out of a total of 20 PCa deaths.

No patient initially managed on an active surveillance policy died during follow-up. This study showed the differences in outcome of a screen versus non-screen cohort making screen detected patients more apt AS candidates. Moreover due to the limited

PCa deaths it becomes clear that extensive follow-up is mandatory to compare treatment modalities in screen detected PCa patients.

In **chapter 5** experimental blood tests i.e. precursor PSA forms, are evaluated as a possible future selection tool to improve selection of patients for an active surveillance policy. As prostate specific antigen (PSA) is prostate specific and not PCa specific precursor forms of PSA, which form a part of the free PSA, and the so called benign PSA are investigated whether they can enhance sensitivity and specificity in identifying or excluding suitable patients for an active surveillance regimen. Frozen serum of screen detected cases with arbitrarily defined relatively latent PCa and aggressive tumour characteristics was used to retrospectively measure precursor PSA and benign PSA. The combination of precursor PSA and %free PSA in a multivariate analysis reached a very high sensitivity of 95.5% and a specificity of 82.4% but could be attributed to a difference in total PSA levels and prostatic volume in the two groups. In a subset of 30 patients normalized for PSA level and prostatic volume the combination of precursor PSA and %free PSA correctly identified 89.5% and 54.5% of the patients with relatively favourable and aggressive PCa characteristics respectively.

In **chapter 6** the natural course of PSA levels of ERSPC patients currently managed on an expectative management policy including patients on active surveillance and its value as a monitoring tool to time deferred treatment is addressed. The idea is that PSA measurements over time correlate with tumour characteristics and could be a useful monitoring tool in patients on AS. More than half of the 120 patients in whom PSA doubling time (PSADT) could be calculated had a PSADT of 10 years or longer or even declining PSA values over time suggesting indolent disease. Thus there seems to be a subset of men with screen detected prostate cancer who have stable or even declining PSA values over time who might be candidates for AS and PSADT could be used to monitor these patients.

In the general discussion these selection, and monitoring criteria are put into perspective and compared to the latest developments in the field of AS research. The selection and monitoring criteria proposed in **chapter 3** have generally remained stable though there is a tendency towards more liberal inclusion with regard to the PSA value at diagnosis and number of prostatic biopsy cores invaded with PCa. Prospective randomized controlled trials of AS comparing treatment modalities in screen detected PCa have been initiated. Results of these trials will undoubtedly hugely improve knowledge on selection, monitoring, timing of deferred treatment and the quality of life though follow-up will have to be extensive as PCa specific mortality is rare in patients with organ confined screen detected PCa. In the meantime AS as a treatment strategy for selected males

with organ confined PCa at diagnosis is gaining ground, indirectly showing that most clinicians and researchers believe it to be a safe treatment modality while the search for biomarkers optimizing selection of patients for AS or, even able to predict indolent PCa before diagnosis is ongoing. Moreover the contemporary results of AS cohorts do not show a deterioration of PCa prognosis in these men.

In conclusion, based on the current available evidence, active surveillance, though still an evolving treatment modality, seems to provide a safe temporary refuge for both patients and physicians while prostate cancer screening data mature into evidence based recommendations and tools to avoid screening in patients with indolent disease are being developed.

# Samenvatting

Het doel van dit proefschrift is bij te dragen aan de ontwikkeling van een actief afwachtend beleid (active surveillance, AS), een van de behandelstrategieën van prostaatkanker. De idee van dit actief afwachtend beleid is onnodige behandeling, en de daarmee geassocieerde bijwerkingen te voorkomen. Daarnaast blijft door intensieve follow-up de mogelijkheid bestaan om, indien nodig, alsnog een behandeling met curatieve intentie te geven.

Om de haalbaarheid van een actief afwachtend beleid te toetsen, zijn de volgende vragen onderzocht:

- Welke patiënten zijn geschikt voor een actief afwachtend beleid?
- Hoe kunnen deze patiënten geselecteerd en gevolgd worden?
- Wanneer is uitgestelde therapie nodig om de kans op genezing te behouden?

In het eerste deel is achtergrond informatie verstrekt over een actief afwachtend beleid. De rationale van een actief afwachtend beleid bij een potentieel dodelijke ziekte wordt uiteengezet in **hoofdstuk 1**.

**Hoofdstuk 2** geeft informatie over de prostaat, het prostaat specifiek antigeen (PSA), prostaatkanker en de effecten van vroegopsporing naar prostaatkanker. Met vroegopsporing wordt de diagnose prostaatkanker niet alleen eerder gesteld maar ook veel vaker. Bovendien heeft een dergelijk gediagnosticeerde prostaatkanker vaak relatief gunstige kenmerken en in de meeste gevallen een indolent natuurlijke verloop. Door vroegopsporing worden echter ook prostaatkankers opgespoord die nooit klachten zullen veroorzaken. Deze detectie van asymptomatische prostaatkankers wordt overdiagnose genoemd. Binnen de European Randomized Study of Screening for Prostate Cancer (ERSPC), sectie Rotterdam wordt geschat dat ongeveer de helft van alle gevonden prostaatkankers zeer waarschijnlijk nooit symptomen zal geven. Veel artsen en patiënten zullen mogelijk onnodig kiezen voor een behandeling met curatieve intentie. Deze overbehandeling geeft per definitie geen levensverlenging, maar heeft wel een risico op bijwerkingen. Het doel van AS is om, op een veilige manier, behandeling uit te stellen of wellicht overbodig te maken.

**Hoofdstuk 3** geeft een overzicht van de verschillende vormen van een actief afwachtend beleid. Allereerst wordt het verschil duidelijk gemaakt tussen een expectatief beleid met palliatieve therapie (expectant management) en een actief afwachtend beleid (active

surveillance). De criteria voor inclusie en vervolgen van patiënten voor een actief afwachtend beleid worden besproken. Ook wordt behandeld wanneer alsnog uitgestelde therapie nodig is. Het hoofdstuk eindigt met een voorstel voor een actief afwachtend beleid.

Het tweede deel gaat dieper in op de selectie criteria voor een actief afwachtend beleid. In **hoofdstuk 4** is de overleving weergeven van 1014 mannen, die in de eerste ronde van de ERSPC zijn gediagnosticeerd met prostaatkanker. Deze gegevens worden vergeleken met een patiëntencohort buiten het vroegopsporings-programma. Met een mediane follow-up van 55 maanden wordt aangetoond dat prostaatkanker ontdekt door vroegopsporing in de meeste gevallen een langzaam progressieve ziekte is. De prostaatkankerspecifieke mortaliteit is gering, maar hoger in het cohort zonder vroegopsporingsprogramma. In de studiegroep is één patiënt uit de groep met relatief gunstige prostaatkankerkenmerken door peri-operatieve complicaties overleden. 17 van de in totaal 20 prostaatkanker sterfgevallen zijn patiënten met slechte prognostische kenmerken bij diagnose. Niemand uit de AS groep is gedurende de studie periode overleden aan prostaatkanker. Dit onderzoek laat duidelijk de verschillen in overleving zien tussen mannen met vroegopgespoord en klinisch gedetecteerd prostaatkanker. Het verheldert ook waarom mannen gediagnosticeerd met prostaatkanker na vroegopsporing geschikter zijn voor AS. Daarnaast wordt duidelijk dat een langdurige follow-up noodzakelijk is gezien het indolente verloop van de meeste prostaatkankers ontdekt door vroegopsporing.

In **hoofdstuk 5** worden experimentele bloedtesten geëvalueerd. Omdat PSA prostaatspecifiek en niet prostaatkankerspecifiek is worden biochemische voorlopervormen van PSA (pPSA) onderzocht om de sensitiviteit en specificiteit om inclusie criteria voor AS te verbeteren. Deze pPSA-vormen maken onderdeel uit van het vrij PSA evenals het zogenoemde "benigne" PSA. Voor dit onderzoek zijn patiënten geselecteerd met ofwel relatief gunstige ofwel zeer ongunstige prostaatkanker eigenschappen. De combinatie van de pPSA-vormen en het percentage vrij PSA bereikte, in een multivariate analyse, een sensitiviteit van 95.5% met een specificiteit van 82.4%. Deze indrukwekkende waarden kunnen echter ook veroorzaakt zijn door het verschil in PSA waarden tussen de twee groepen. Derhalve is een subanalyse gedaan van 30 mannen waarbij gecorrigeerd is voor de PSA waarde en het prostaatvolume. In deze subanalyse is de voorspellende waarde voor een relatief gunstige prostaatkanker 89.5% en 54.5% voor een agressieve prostaatkanker. Geconcludeerd kan worden dat deze experimentele bloedtesten weliswaar veelbelovend zijn, maar verder onderzoek nodig is.

Het derde deel schetst de waarde van het beloop van PSA over een periode van tijd, de PSA verdubbelingstijd (PSADT). De gedachte hierachter is dat meerdere PSA metingen tijdens de follow-up de prostaatkankeractiviteit weerspiegelen en de PSADT gebruikt zou kunnen worden als leidraad. **Hoofdstuk 6** beschrijft 191 mannen die niet direct behandeld zijn voor hun prostaatkanker. Bij 120 patiënten kon een PSADT berekend worden. Meer dan de helft van deze groep heeft een PSADT van meer dan 10 jaar of zelfs een dalende PSA trend, hetgeen suggestief is voor indolent prostaatkanker. 30 mannen hebben alsnog therapie gekregen en 1 hiervan heeft aanwijzingen voor een oplopend PSA na behandeling. Tijdens de follow-up (mediaan 40 maanden) overleed geen enkele patiënt aan prostaatkanker. Er blijkt dus een subgroep van mannen met vroegopgespoord prostaatkanker te zijn die stabiele of zelfs afnemende PSA waarden hebben. Deze patiënten kunnen mogelijk voor AS in aanmerking komen en de PSADT lijkt een goed hulpmiddel om deze mannen te vervolgen of eventuele uitgestelde behandeling aan te bevelen.

In de **discussie** worden de verschillende selectie- en vervolgcriteria vergeleken met de huidige literatuur en in perspectief gezet met de laatste ontwikkelingen op het gebied van AS. Hieruit blijkt dat de geopperde selectiecriteria van hoofdstuk 3 over het algemeen in stand zijn gebleven. Er lijkt een tendens te bestaan naar het verhogen van de PSA waarde. Ook worden tegenwoordig patiënten geïncludeerd met meer dan één prostaatnaaldbiopt dat prostaatkanker bevat. Deze verruiming van de selectiecriteria heeft waarschijnlijk te maken met meer kennis omtrent het – in de meeste gevallen - indolente verloop van prostaatkanker ontdekt door vroegopsporing.

Prospectief gerandomiseerde onderzoeken, welke de verschillende behandelingen van vroegopgespoorde prostaatkanker (inclusief AS) gaan vergelijken, zijn geïnitieerd. Een van deze onderzoeken, de PRIAS (Prostate cancer Research International: Active Surveillance) studie (www.prias-project.org), is geëvolueerd uit een voorstel voor AS in de regio Rotterdam. De resultaten van deze onderzoeken zullen terdege bijdragen aan de kennis omtrent selectie, vervolgen en bepalen van het tijdstip van uitgestelde behandeling bij AS. Aan de andere kant zullen de definitieve resultaten pas na jaren beschikbaar zijn, gezien het indolente verloop in het merendeel van deze prostaatkankers. De meest recente resultaten van de ERSPC laten een significante daling van de prostaatkanker specifieke sterfte zien ten gunste van vroegopsporing. Derhalve zal, gezien de aan vroegopsporing gerelateerde overdiagnose, AS alleen maar actueler worden.

Het blijkt dat AS als behandeling bij geselecteerde mannen met prostaatkanker ontdekt door vroegopsporing steeds vaker voorkomt. Dit laat indirect zien dat zowel onderzoekers als clinici het een veilige behandeling vinden. Daarnaast laten de huidige resultaten van behandeling met AS geen verslechtering in prognose zien gedurende de follow-up.

Samenvattend is er een duidelijk verschil in prognose tussen klinisch gediagnosticeerd of na vroegopsporing ontdekt prostaatkanker. Vroegopgespoord prostaatkanker heeft een duidelijk betere ziekte-specifieke overleving. Op basis van de beschikbare literatuur, lijkt AS veilig voor geselecteerde mannen met prostaatkanker ontdekt door vroegopsporing. De zoektocht naar biomarkers, die de selectiecriteria voor AS verfijnen, het tijdstip van uitgestelde behandeling optimaliseren of, wellicht indolent prostaatkanker kunnen voorspellen voordat de diagnose gesteld wordt, is in volle gang. De resultaten van prospectieve studies zullen de definitieve waarde van AS aantonen terwijl de gegevens van de effecten van vroegopsporing naar prostaatkanker uitkristalliseren. In de tussentijd kan AS, bij overgediagnosticeerd prostaatkanker, onnodige behandeling, en de daaraan gerelateerde ongewenste bijwerkingen en kosten, voorkomen.

Zowel patiënten als behandelaars moeten zich bewust zijn het feit dat AS nog steeds een empirische behandeling is en dat gedurende een actief afwachtend beleid prostaatkanker van een slapende naar een actieve vulkaan kan transformeren en de mogelijkheid op genezing daarmee in rook is opgegaan.

# Publications

*2002* **De Vries SH**, Klijn AJ, Lilien MR, De Jong TP. Development of renal function after neonatal urinary ascites due to obstructive uropathy.
J Urol. 2002 Aug;168(2):675-8.

*2003* Schröder FH, **de Vries SH**, Bangma CH.
Watchful waiting in prostate cancer: review and policy proposals.
BJU Int. 2003 Nov;92(8):851-9.

*2004* **De Vries SH**, Bangma CH, Schröder FH
Watchful waiting versus expectant management at prostatic carcinoma.
NTvU 2004 Nov; 4: 101-105.

Raaijmakers R, Wildhagen MF, Ito K, Pàez A, **de Vries SH**, Roobol MJ, Schröder FH.
Prostate-specific antigen change in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam.
Urology. 2004 Feb;63(2):316-20.

Huang Foen Chung JW, **de Vries SH**, Raaijmakers R, Postma R, Bosch JL, van Mastrigt R.
Prostate volume ultrasonography: the influence of transabdominal versus transrectal approach, device type and operator.
Eur Urol. 2004 Sep;46(3):352-6.

**de Vries SH**, Raaijmakers R, Kranse R, Blijenberg BG, Schröder FH.
Prostate cancer characteristics and prostate specific antigen changes in screening detected patients initially treated with a watchful waiting policy.
J Urol. 2004 Dec;172(6 Pt 1):2193-6.

*2005* Postma R, **de Vries SH**, Roobol MJ, Wildhagen MF, Schröder FH, van der Kwast TH.
Incidence and follow-up of patients with focal prostate carcinoma in 2 screening rounds after an interval of 4 years.
Cancer. 2005 Feb 15;103(4):708-16.

**de Vries SH**, Raaijmakers R, Blijenberg BG, Mikolajczyk SD, Rittenhouse HG, Schröder FH.
Additional use of [-2] precursor prostate-specific antigen and "benign" PSA at diagnosis in screen detected prostate cancer.
Urology. 2005 May;65(5):926-30.

*2006* Roemeling S, Roobol MJ, **de Vries SH**, Gosselaar C, van der Kwast TH, Schröder FH.
Prevalence, treatment modalities and prognosis of familial prostate cancer in a screened population.
J Urol. 2006 Apr;175(4):1332-6.

**De Vries SH**, Bangma CH, Schröder FH.
The role of conservative policies in the management of Prostate cancer.
Book: Challenges in prostate cancer, chapter 13. 2nd edition.
Editor: Winsor Bowser

Gosselaar C, Roobol MJ, Roemeling S, **de Vries SH**, Cruijsen-Koeter I, van der Kwast TH, Schröder FH.
Screening for prostate cancer without digital rectal examination and transrectal ultrasound: results after four years in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam.
Prostate. 2006 May 1;66(6):625-31.

*2007* **de Vries SH**, Postma R, Raaijmakers R, Roemeling S, Otto S, de Koning HJ, Schröder FH.
Overall and disease-specific survival of patients with screen detected prostate cancer in the European randomized study of screening for prostate cancer, section Rotterdam.
Eur Urol. 2007 Feb;51(2):366-74;

Roemeling S, Roobol MJ, **de Vries SH**, Wolters T, Gosselaar C, van Leenders GJ, Schröder FH.
Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome.
Eur Urol. 2007 May;51(5):1244-50;

Raaijmakers R, **de Vries SH**, Blijenberg BG, Wildhagen MF, Postma R, Bangma CH, Darte C, Schröder FH.
hK2 and free PSA, a prognostic combination in predicting minimal prostate cancer in screen detected men within the PSA range 4-10 ng/ml.
Eur Urol. 2007 Nov;52(5):1358-64.

*2009* Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Berenguer A, Määttänen L,Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg BG, Moss SM, de Koning HJ, Auvinen A; **ERSPC Investigators**.
Screening and prostate-cancer mortality in a randomized European study.
N Engl J Med. 2009 Mar26;360(13):1320-8.

# Curriculum Vitae

Stijn Hiëronymus de Vries werd op 21 april 1976 op de wereld gezet door zijn vader in Paramaribo, Suriname. Met een MAVO/HAVO brugklasjaar op het Pierson College in 's-Hertogenbosch stapte hij over naar de tweede klas van het Gymnasium Beekvliet te St. Michielsgestel. Na het eindexamen in 1994 vertrok hij een jaar naar Salamanca, Spanje om de taal te leren. In 1995 werd hij ingeloot voor de studie geneeskunde te Groningen. Na het behalen van het artsexamen in 2002 begon hij als arts-onderzoeker bij professor Schröder op het prostaatkanker screeningsbureau. In 2005 startte hij met de opleiding tot uroloog. De eerste twee jaar vooropleiding heelkunde werden genoten in het Sint-Franciscus Gasthuis te Rotterdam bij dr. Wittens en dr. Kerver. In 2007 begon de vierjarige opleiding urologie in het Erasmus Medisch Centrum Rotterdam bij dr. Dohle. In 2008 keerde hij voor een jaar terug naar het Sint-Franciscus Gasthuis voor de urologie bij dr. Blom alwaar hij in 2010 ook zijn opleiding zal afronden, in 2009 geniet hij de opleiding in het Erasmus Medisch Centrum.

Stijn is in 2005 getrouwd met Quirine Ledeboer en in mei 2009 werd hun zoon Gijs geboren.

# Dankwoord

Net klaar met de opleiding geneeskunde en al een wetenschappelijke publicatie in de tas begon ik vol goede moed op 16 september 2002 aan dit promotieonderzoek. Ik zou dat varkentje wel eens wassen in twee jaar tijd.

Op 4 oktober 2009 mag het duidelijk zijn dat het wel wat anders is gelopen. Dat ik uiteindelijk toch nog dit dankwoord schrijf is dan ook zeker niet alleen mijn verdienste.

Professor Schröder, heel veel dank voor uw vertrouwen en begeleiding. Ondanks uw bevlogenheid en enorme "drive" weet u een bijna onevenaarbaar arbeids ethos ten toon te spreiden. U heeft de gave echt te luisteren, naar alle gelederen ook naar kritische opmerkingen, en ieder een eerlijk antwoord te geven waarbij diegene altijd in zijn waarde wordt gelaten. Een tijd lang zat ik zelfs in de kamer naast u in het Z-gebouw, waar u mij naast de wetenschappelijke vonk ook heeft besmet met uw power-naps. Het is een voorrecht om bij u te promoveren

Professor Bangma, beste Chris, dank voor je begeleiding. Ik hoop dat ik ooit op de helft van jouw capaciteiten kom om klinisch en wetenschappelijk werk te combineren. Ik waardeer zeer de integere manier waarop jij mij tijdens deze ultieme poging hebt begeleid.

De overige leden van de kleine commisie, professor Coebergh, professor Pelger en dr. Ron van Schaik wil ik bedanken voor de beoordeling van het manuscript, door uw suggesties is het beslist sterker geworden. Ook professor Witjes, hoewel zittend in de grote commissie wil ik bedanken voor zijn opmerkingen.

Natuurlijk mogen de ERSPC deelnemers en het screeningsbureau hier niet ontbreken. Eerst waren we gehuisvest in een zijkamer op de poli urologie, later een eigen verdieping aan de Rochussenstraat. Met Monique Roobol stevig aan het roer, die mij (en alle anderen promovendi) heeft geloodst door de diverse protocollen en databases. Daarnaast Wilma, altijd goed voor een dagje PSA prikken op lokatie, Conja, zonder jouw geen follow-up, Ellen en Lakshmi bedankt voor de fijne samenwerking. Ook Mark Wildhagen, professor van der Kwast, Ries, Gerrit en Bert dank voor het delen van jullie kennis. Daarnaast natuurlijk mijn generatie medepromovendi: Ingrid en René. René in een korte tijd zijn we goede vrienden geworden, mede door jou heb ik me snel in Rotterdam thuisgevoeld. Het was een eer om jouw paranimf te mogen zijn en super dat je nu mijn paranimf bent.

Het is ons gelukt! Natuurlijk ook mijn dank (en respect) voor goede samenwerking met de snellere generatie promovendi Stijn en Claartje die inmiddels al lang dr. zijn.

Ellen van de Berg en later Monique van der Linde die het altijd weer lukte om een gaatje in de agenda van de professor te vinden.

Michiel, VLF is misschien voor jou genoeg, toch wil ik je hier bedanken voor je trouwe vriendschap, ook in moeilijkere tijden was je er voor mij en Quirine. Ook nu ben je er weer voor mij. Trouwes woar bleft mun PDFje!!

Aat en Marcella, dank voor jullie steun en support de afgelopen tijd, en dan bedoel ik niet alleen rond het proefschrift. Samen met jullie hele gezin beschouw ik jullie een extra "warme kant".

Ferd, Lange, dank voor het vertrouwen, ik hoop dat je het niet erg vindt dat ik in plaats van een paarse kaft een grijze achtergrond heb genomen. Ik hou van jou.

Mama of liever Moesjk, ondanks alles heb jij mij mee kunnen geven dat het leven goed is. Ik sta elke keer weer versteld van je veerkracht. Ik ben dankbaar voor je opvoeding omdat jij voor een groot deel hebt gezorgd dat ik samen met Flore ben geworden zoals we zijn. Daar mag je trots op zijn.

Lieve Qui, Dikke, inmiddels zijn we allebei al ruim voorbij de bijna 23, maar ik ben nog steeds gek op jou. Sinds Groningen maak je me alleen nog maar gelukkiger. Samen hebben we al heel wat overwonnen en nu hebben we dan ook nog Gijs! Zonder jou had ik het niet gekund en ik beloof je vanaf nu minder computer en meer Q. time. Ik wil altijd jouw man zijn.

Gijs, al voor je er was heb je pappa aangezet tot het afronden van dit proefschrift. Ik ben benieuwd wat je nog meer in petto hebt. Je gulle lach was al een fantastische reden voor studieontwijkend gedrag!

# PhD Portfolio

Erasmus MC
Universitair Medisch Centrum Rotterdam

| | |
|---|---|
| Name PhD student: Stijn H. de Vries | PhD period: 2002-2004 |
| Erasmus MC Department: Urology | Promotors: Prof.Dr. F.H. Schröder |
| Research School: - | Prof.Dr. C.H. Bangma |
| | Supervisor: - |

| 1. PhD training | Year | Workload (Hours/ECTS) |
|---|---|---|
| General courses | | |
| Biomedical English Writing and Communication | | |
| Research Integrity | | |
| Laboratory animal science | | |
| Specific courses (e.g. Research school, Medical Training) | | |
| Medical training/ residency Erasmus University Rotterdam | | |
| Surgical/ Urological training | | |
| Presentations | | |
| Favourable development of renal function after neonatal urinary ascites due to obstructive uropathy. ESPU congres, Budapest, Hungary | 2002 | 5 |
| Indications for deferred treatment (watchful waiting) for prostate cancer Brachytherapie congres, Rotterdam | 2003 | 5 |
| Voorstel behandelingschema watchful waiting in de regio Rotterdam, Integraal Kankercentrum Rotterdam, werkgroep Urologische tumoren, Rotterdam | 2003 | 5 |
| Watchful waiting in the ERSPC, section Rotterdam and subsequent therapy change. Poster presentation AUA, San Francisco | 2004 | 5 |
| Development of PSA over time in males with screen-detected adenocarcinoma of the prostate following a watchful waiting policy. Poster presentation AUA, San Francisco | 2004 | 5 |
| Precursor en "benigne" PSA in screengedetecteerd PCa Presentation NVU voorjaarsvergadering | 2004 | 5 |
| Dalend PSA bij onbehandeld prostaatcarcinoom Presentation NVU najaarsvegradering | 2004 | 5 |
| Several presentations at international ERSPC meetings | 2002-2004 | |
| Seminars and workshops | | |
| Presentation and writing skills | 2002 | 5 |
| Methods of clinical research | 2003 | 5 |
| (Inter)national conferences | | |
| AUA, San Francisco | 2004 | |
| Several ERSPC meetings | 2002-2004 | |
| Several meetings of de Dutch Urological Association (NVU) | | |

The production of this thesis was financially sponsored by:

Abbot,

Astellas

Pharma BV,

Astra Zeneca,

Beckman Coulter,


GSK,


Novartis,

Olympus Nederland BV,

Pfizer,

Stichting Contactgroep Prostaatkanker,

Star MDC,


SUWO,

SWOP