Active Surveillance For Low Risk Prostate Cancer

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ACTIVE SURVEILLANCE FOR LOW RISK PROSTATE CANCER
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Active Surveillance For Low Risk Prostate Cancer

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'The race of life'

Different comorbidities are competing.
Will prostate cancer reach the finish line first?

Voor mijn ouders en grootouders

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PART I

GENERAL INTRODUCTION

Objective

Background

Research questions

OBJECTIVE

This thesis aims to explore the feasibility of active surveillance for prostate cancers that have been diagnosed but have a low risk of causing any symptoms during lifetime when remaining untreated. Active surveillance is a strategy of initial expectant management of the disease, but with intensive monitoring and the option to switch to radical treatment at the moment progression occurs instead. The aim of the strategy is to delay or avoid the risk of side effects of radical treatments.

BACKGROUND

THE PROSTATE

The prostate is part of the male genitourinary tract. It is a walnut-sized gland, located underneath the urinary bladder, enveloping the proximal part of the urethra. The main function of the prostate is the excretion of a fluid that forms part of the semen, but it also has an important role in controlling the flow of semen at the moment of ejaculation.

PROSTATE CANCER

Cancer of the prostate is a major health issue, it is mainly found in elderly men. In the United States, as an example for most Western countries, prostate cancer (PC) is the most frequently diagnosed non-skin cancer and is the second leading cause of cancer-related mortality in men[1]. A total of 192.280 new cases are estimated to be detected and 27.360 men are estimated to die of this disease in 2009 in the United States[1]. This means that 1 out of every 6 men will be diagnosed with the disease during their lifetime and 1 out of every 35 will die of it[2]. The impressively high frequency of PC is further illustrated by autopsy studies, which show that as much as 55% of men in their fifties and 64% of men in their seventies harbour the disease[3].

Table 1 presents the 2002 version of the TNM (tumour, node, metastasis) classification system used in PC[4]. The different stages of PC are further illustrated in Figure 1[5]. PC initially develops within the prostate gland itself (stage ≤T2), but, when remaining untreated, may grow outside the prostatic capsule (stage T3), into surrounding organs (T4) such as the urinary bladder or the rectum. The disease metastasizes to the lymph nodes and other parts of the body, eventually causing death. The skeleton is another common location of metastases of PC.

PC is different from benign prostatic hyperplasia. This is also a very frequently seen condition in elderly men that causes urinary complaints, but comprises a non-malignant enlargement of the prostate only. The first clinical symptom of PC usually is pain due to skeletal metastases and not urinary symptoms.

DIAGNOSTIC MODALITIES

Figure 2 presents the most commonly used modalities in the diagnosis of PC[5,6]. The serum level of prostate specific antigen (PSA) can be measured by a blood test (Figure

Table 1: Tumour, node, metastasis (TNM) classification of prostate cancer (2002 version)

T: Evaluation of the (primary) tumour
- TX: cannot evaluate the primary tumour
- T0: no evidence of tumour
- T1: tumour present, but not detectable clinically or with imaging
  - T1a: tumour was incidentally found in less than 5% of prostate tissue resected (for other reasons)
  - T1b: tumour was incidentally found in greater than 5% of prostate tissue resected
  - T1c: tumour was found in a needle biopsy performed due to an elevated serum PSA
- T2: the tumour can be felt (palpated) on examination, but has not spread outside the prostate
  - T2a: the tumour is in half or less than half of one of the prostate gland's two lobes
  - T2b: the tumour is in more than half of one lobe, but not both
  - T2c: the tumour is in both lobes
- T3: the tumour has spread through the prostatic capsule (if it is only part-way through, it is still T2)
  - T3a: the tumour has spread through the capsule on one or both sides
  - T3b: the tumour has invaded one or both seminal vesicles
- T4: the tumour has invaded other nearby structures

It should be stressed that the designation "T2c" implies a tumour which is *palpable* in both lobes of the prostate. Tumours which are found to be bilateral on biopsy only but which are not palpable bilaterally should not be staged as T2c.

N: Evaluation of the regional lymph nodes
- NX: cannot evaluate the regional lymph nodes
- N0: there has been no spread to the regional lymph nodes
- N1: there has been spread to the regional lymph nodes

M: Evaluation of distant metastasis
- MX: cannot evaluate distant metastasis
- M0: there is no distant metastasis
- M1: there is distant metastasis
  - M1a: the cancer has spread to lymph nodes beyond the regional ones
  - M1b: the cancer has spread to bone
  - M1c: the cancer has spread to other sites (regardless of bone involvement)

2A). PSA is a glycoprotein that liquefies the semen that is formed almost exclusively by prostate tissue and is partly secreted into the blood stream. Serum PSA is a marker for PC[7]; the higher the serum PSA level, the higher the chance of finding PC and the more advanced the stage of PC that will be found[8]. The level of the PSA may range from <0.1 ng/ml in men without PC to even more than 5000 ng/ml in men with metastasized PC.

The dorsal part of the surface of the prostate can be checked for abnormalities such as indurations or lumps via the rectum with a digital rectal examination (DRE) (Figure 2B). An abnormal DRE increases the chance of finding PC[9].

The prostate can also be examined using transrectal ultrasound (TRUS) (Figure 2C). Abnormal (hypoechoic) lesions seen during TRUS have been associated with PC[10].

When there is a suspicion of PC, which may be based on the PSA level, or on DRE, TRUS, or other findings, the only way to make the definite diagnosis is to obtain prostatic tissue for histological examination by the pathologist. The most frequently applied

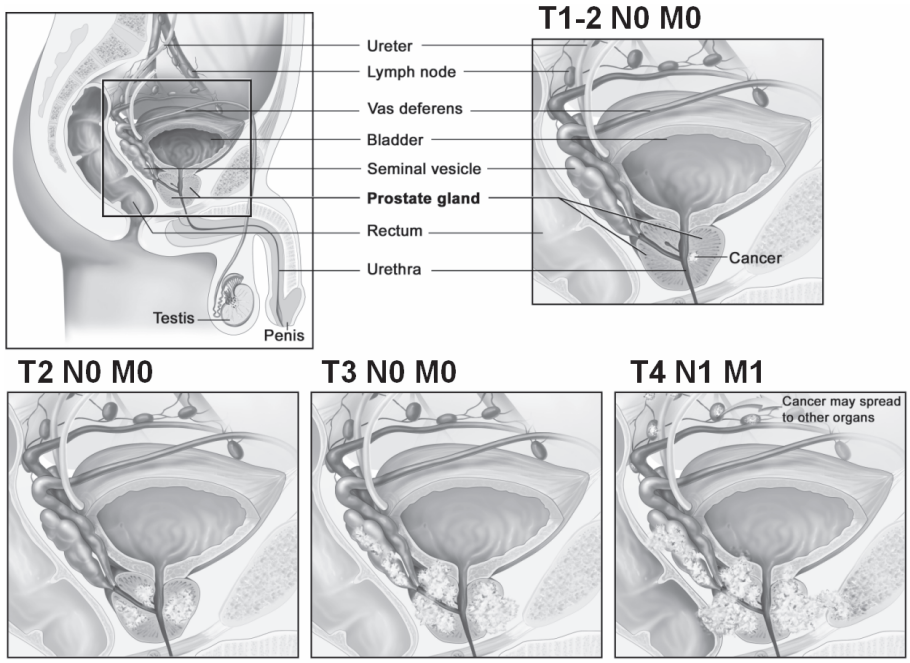


Figure 1: Prostate cancer disease stages

method is to take a number of prostate needle biopsy cores under TRUS-guidance using a hollow needle and a biopsy gun (Figure 2D). The number of positive biopsy cores, the extent to which the malignant tissue involves the biopsy cores, and the degree of histological (de)differentiation are examples of parameters at biopsy to assess disease aggressiveness[11-13]. The most commonly used measure of the state of histological differentiation seen in PC cells is the Gleason score, ranging from 2-10[14]. The Gleason score is the sum of the most commonly seen and the second most commonly seen Gleason pattern, ranging from 1-5.

EARLY DETECTION PROGRAMS

Mass screening for cancer has become part of everyday medical practice and has the aim to diagnose aggressive cancers in a still curable stage. In the early 1990s, research programs were initiated to study whether the early detection of PC has a favourable effect on disease specific mortality, but also whether a population-based screening program would be feasible in terms of costs and quality of life. The largest of these

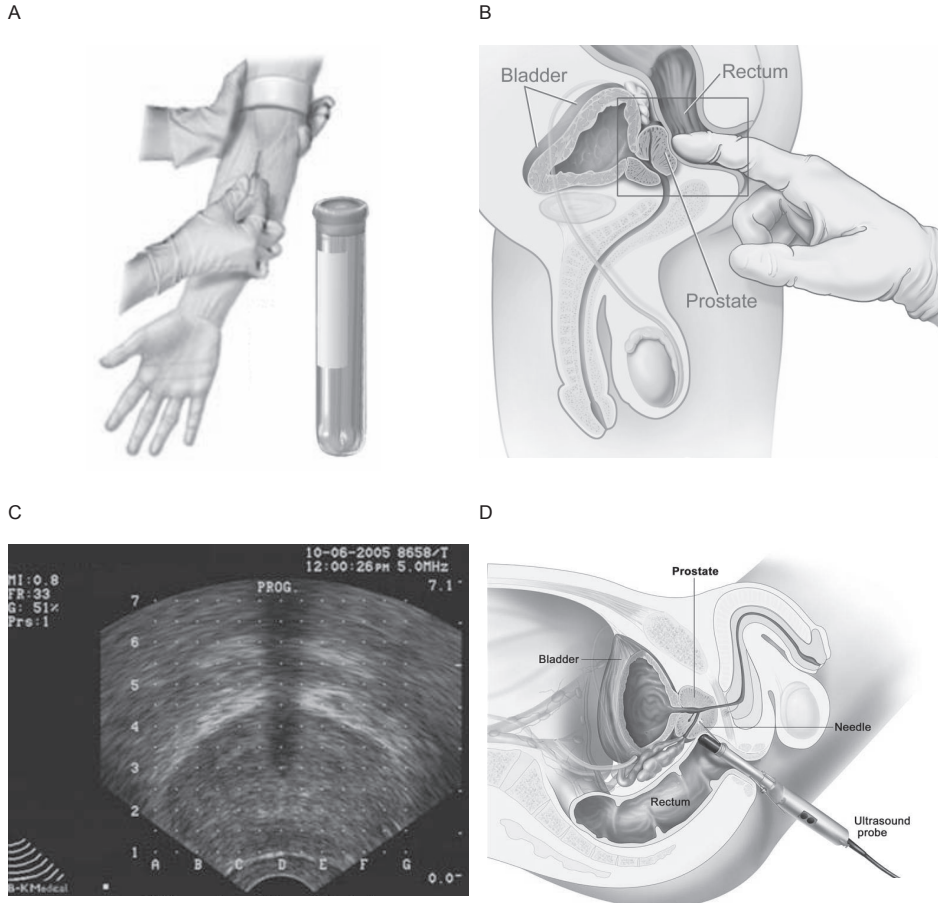


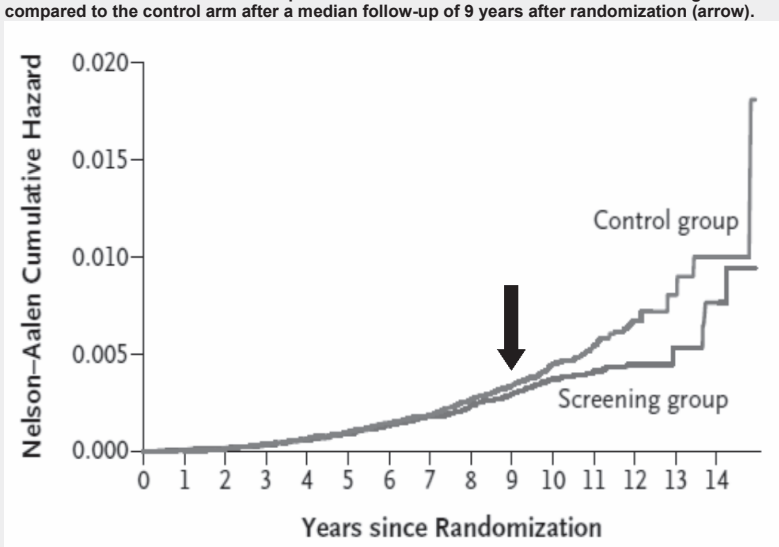
Figure 2: Diagnostic modalities used in diagnosing prostate cancer. A: Prostate specific antigen blood test, B: digital rectal examination, C: transrectal ultrasound (transverse image of the prostate), D: transrectal ultrasound-guided prostate biopsies.

PC screening trials was the European Randomized Study of Screening for Prostate Cancer (ERSPC), which found a significantly favourable effect of screening on the PC specific mortality[15,16]. More information on the ERSPC can be found in Panel 1. Another large PC screening trial, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) was done during the same period in the United States[17]. PSA is the most important diagnostic basis of most PC early detection programs, but other diagnostic measures such as DRE are also used in addition.

PANEL 1: THE EUROPEAN RANDOMIZED STUDY OF SCREENING FOR PROSTATE CANCER

The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in 1994, after the potential was discovered of prostate specific antigen (PSA) for the early detection of prostate cancer (PC)[18]. The main research questions were whether screening for PC could actually lower the disease specific mortality and whether population-based screening would be feasible in terms of costs and quality of life. Only a large randomized research effort would be able to answer these issues. The first pilot studies were conducted in Belgium and the Netherlands and showed that a large European screening trial for PC would be feasible. Centres in France, Finland, Italy, Spain, Sweden, and Switzerland also joined the study later. Men participating in the ERSPC were randomized either to the screening arm, in which men were invited for frequent screenings, or to the control arm, in which men were not invited for screening. The core age group of men included in the study was 55-69 years; this group consisted of 162.243 men. The main screening protocol consisted of PSA measurements every 4 years, with a (mainly lateralized six-core) prostate biopsy done when a PSA ≥4.0 ng/ml or later ≥3.0 ng/ml was found. A standardized causes of death evaluation was applied, an independent data monitoring committee was appointed, and multiple committees (on epidemiology, PSA, pathology etc.) were established to guarantee the quality of the study and data[19-21]. In 2009, at the third interim study analysis, with a median follow-up of 9 years after randomization, a significant reduction of 20% in the relative risk of death from PC was found in the screening arm, as compared to the control arm[16]. A total of 214 PC deaths were seen in the screening group, versus 326 in the control group (Figure). This resulted in a number needed to screen of 1410 and an additional number needed to treat of 48 to prevent 1 death due to PC. Although these numbers are comparable to screening programs for breast cancer, overdiagnosis and overtreatment are vastly more common in a PC screening program. A reduction in relative risk of death of PC of 27% was reported for men who actually were screened (adjustment for non-compliance), which amounted to 31% when adjustment for the diluting effect of screening taking place in the control arm (contamination) was also performed[22]. With a longer follow-up after randomization available in the future, the difference in mortality rates between arms may be larger (Figure). A certain amount of heterogeneity between the different centres exists regarding the screening interval, the age groups of invited men, the screening tests that were used in addition to PSA, and the applied biopsy schemes, but in all centres a trend was seen towards a favourable effect of PC screening on PC mortality. However, before possibly introducing screening for PC on a population level in the future, overdiagnosis, overtreatment, quality of life, and cost-effectiveness must be taken into account. Website: www.erspc.org.

Cumulative risk of death from prostate cancer in the ERSPC study arms. A significant reduction in the rate of death from prostate cancer of 20% was found in the screening arm compared to the control arm after a median follow-up of 9 years after randomization (arrow).



TREATMENTS FOR PROSTATE CANCER

In general, PC that is still confined to the prostate gland (stage ≤T2) may be treated with the following two groups of local treatments:

Surgery:

· Open radical prostatectomy

· Laparoscopic radical prostatectomy

· Robot-assisted laparoscopic radical prostatectomy

Radiation therapy:

· External beam radiation therapy

· Brachytherapy

· A combination of external beam radiation therapy and brachytherapy

Surgery comprises complete removal of the prostate gland and seminal vesicles, with the aim to remove all malignant tissue and to achieve cure of the disease, while preserving sexual and urinary functions as much as possible[23]. Radiation therapy aims to

cure the disease by eradicating the cancer by radiation of the entire prostate gland and seminal vesicles[24]. Other treatment modalities are also being investigated and include high intensity focused ultrasound and cryosurgery[25,26]. These have the option to treat the tumour focally.

Radical therapy has a favourable effect on the PC specific mortality rates. A significant but small difference of around 5% in the cumulative incidence of death due to PC was found with 10 years and more follow-up in favour of surgery, when comparing radical prostatectomy with watchful waiting in clinically-detected localized PC[27,28]. Data from randomized clinical trials are lacking concerning survival outcomes of radical prostatectomy versus radiation therapy. Long-term survival outcomes of other, more modern treatment modalities are available neither.

Metastasized PC cannot be cured and will in time always lead to death unless comorbidity causes interfere earlier. The median time between metastasis and death may be as long as 7 years and even much longer in individual cases[29]. Temporary suppression of the disease is possible using different forms of hormonal therapy[30]; chemotherapy is an option in the terminal phase of the disease.

In men in whom curative radical treatment is not an option due to age or comorbidity and in whom hormonal therapy is not yet necessary, watchful waiting is a possibility. This palliative strategy constitutes an initial expectant management of the disease; with hormonal therapy being started at the moment clinical symptoms occur. This approach is different from the strategy of active surveillance, in which deferred radical treatment has a curative intent.

SIDE EFFECTS OF RADICAL TREATMENT

When comparing men treated for PC to PC-free men, all traditional treatments for localized PC result in specific physical side effects, also on the long-term after treatment[31-33]. The main adverse outcomes after surgery are worsening of continence and erectile functions. At 52 months after surgery, urinary leakage was observed in 31% (pre-treatment 12%) and erectile dysfunction in 88% (pre-treatment 31%)[34]. Radiation therapy mainly leads to a decline in potency and to bowel problems. At 52 months after radiation therapy, erectile dysfunction was seen in 64% (pre-treatment 40%) and bowel bother in 11% (pre-treatment 3%)[34]. At two years after radical prostatectomy or radiation therapy, complete incontinence was seen in 10% and 4% and impotence in 80% and 62%, respectively[35]. Brachytherapy may lead to similar long-lasting urinary irritation, and bowel and sexual symptoms. When giving hormonal therapy adjuvant to radical therapy even worse outcomes are seen in most domains[31]. The adverse effects of radical prostatectomy and radiation therapy on health-related quality of life may be

reduced by nerve-sparing procedures or increasing the selectivity of delivered radiation, respectively[31,36].

RADICAL TREATMENT AND QUALITY OF LIFE

Patients may commonly have difficulty in making the decision for a specific treatment for PC and decision-related distress may persist over time[37]. Despite an obvious worsening of urinary, sexual, and bowel domains after radical therapy, mental health and overall well-being were however shown to be similar in men who had either been randomized to watchful waiting or to radical prostatectomy[38]. Also, despite differences in the size of adverse effects after different radical treatments (radical prostatectomy, radiation therapy, and observation alone, no differences in the effect on general health-related quality of life have been found[32,35].

Despite the frequently observed side effects, anxiety levels were lower and satisfaction was higher after radical treatment when compared to watchful waiting, although a selection bias cannot be excluded[39,40]. But even when compared with a control group of men without cancer, similar or even better scores for mental health and health-related quality of life scores have been observed in long-term survivors of PC in all different treatment groups (best scores seen after radical prostatectomy), despite worse scores for general health perception[41]. This discrepancy between disease specific quality of life aspects (worse scores on urinary, sexual, and bowel domains) and generic quality of life may however be caused by the fact that men experience urinary, erectile, and bowel function as less serious after they have become patients who learned to expect and accept these side effects. Other reasons may be that patients do not perceive these as health issues or that patients accept these side effects after having been treated for a life-threatening disease[42,43]. Other mechanisms may include the positive effects of the trauma and crisis of the diagnosis of PC and the resulting treatment, the fact that patients may naturally attempt to identify benefit from adversity, and the experience of positive change due to cancer survivorship[44,45].

NATURAL HISTORY OF PROSTATE CANCER

The different grades of PC aggressiveness result in a striking heterogeneity in clinical behaviour and outcomes when remaining untreated[46], as illustrated by Figure 3. PC 'competes' with other possible causes of death. Some aggressive forms of PC are almost always lethal, although in case of a short life expectancy, only symptomatic disease levels are reached (black arrow, Figure 3). Relatively non-aggressive PC almost always remains

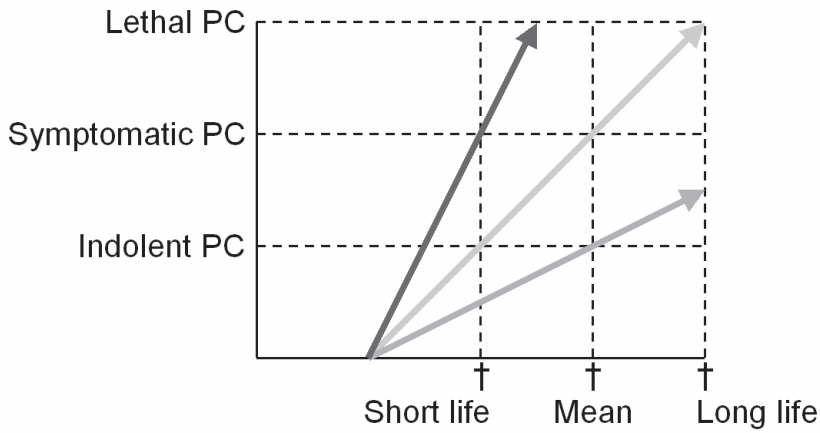


Figure 3: Schematic representation of the heterogeneity in clinical outcomes of PC due to differences in aggressiveness. The y-axis represents the disease stage of PC, the x-axis represents the lifespan (dependent of death causes unrelated to PC). Black arrow: aggressive PC; middle, light grey arrow: intermediately aggressive PC; dark grey arrow: relatively non-aggressive PC.

indolent (non-harmful) except in case of a long life expectancy (dark grey arrow). The clinical stage that intermediately aggressive PC reaches is directly dependent on the life expectancy (middle, light grey arrow). In patients who are older at the moment of diagnosis, fewer years are left for PC to develop to lethal stages and other causes of death will compete with PC as a cause of death. All cancers theoretically have a time interval in which cure may be reached by radical treatment ('window of curability'), which can be thought of as the period before the tumour metastasizes. This window of curability is longer in relatively non-aggressive PCs.

An important predictor of the disease specific outcome of untreated clinically-detected localized PC is the Gleason score[13]. In tumours with a Gleason score 2-4, 6, and 10 for example, the 20-year PC specific mortality rates are around 5%, 30%, and 55%, respectively[13]. After a reclassification of the Gleason scoring system, the scores 2-5 are almost never being given any more at biopsy, to compensate for the frequent upgrading of these scores at radical prostatectomy. This has caused a statistical artefact known as the Will Rogers phenomenon, resulting in an apparent improvement in clinical outcomes of the remaining Gleason scores (6-10)[47]. A contemporary Gleason score 6 PC has a more favourable prognosis than the mortality rates presented above.

INCIDENCE AND MORTALITY TRENDS

The incidence of PC has been rising during last decades in the Western world[48,49]. Figure 4 presents the age-standardized rates (European Standardized Rate) for incidence and mortality of PC in the Netherlands between 1970 and 2006. A rise of 40-50 in the beginning of the 1980s to 90-110 per 100.000 person years after 2000 is observed. Reasons for the rising incidence include:

· An aging population
· Increased life expectancy
· The increased awareness of the disease by patients and physicians
· The possibility and use of opportunistic screening (mainly PSA)
· The use of lower PSA thresholds for taking prostate biopsies
· More intensive biopsy-core schemes

Mortality rates have more or less remained stable at around 30 per 100.000 person years, although a slight decrease is seen since the early 1990s. This decrease is especially clearly observed in the United States population[1]. The specific reasons for this trend are uncertain, but may include improvements in treatment and the advent of PSA screening (Panel 1).

STAGE AND GRADE MIGRATION

While the incidence of PC has been rising, the mean grade and stage of detected tumours is decreasing[50-52]. The mean age at diagnosis of PC has also decreased during the last decades, implying that tumours are detected earlier in the natural history of the disease[53]. While 30% of the tumours that were diagnosed between 1989 and 1992 in the United States could be defined as low risk and have a favourable prognosis (T1c/T2a, PSA ≤10.0 ng/ml, and a Gleason score ≤6), this percentage was 45% between 1999 and 2001. Figure 4 illustrates the difference in the proportion of PCs with a favourable (dark grey arrow) and an unfavourable (black arrow) prognosis between the current 'PSA-era' and 2 decades ago. The absolute and relative number of non-aggressive PC (presented in Figure 3 as the dark grey arrow, defined in Figure 4 as PC that will not cause death) has increased vastly.

CLINICALLY- VERSUS SCREEN-DETECTED PROSTATE CANCER

Screening is one of the main reasons for the more frequent detection of small, well-differentiated, localized PC at younger age[18]. Screening for PC causes the tumour to be

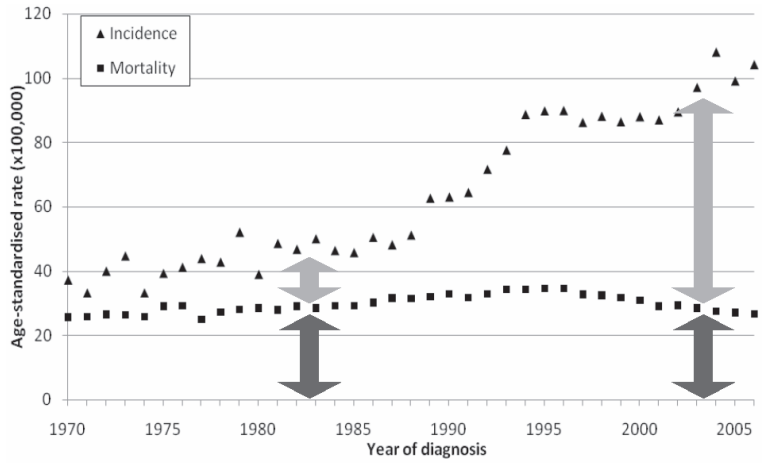


Figure 4: Age-standardized rates (European Standardized Rate) for incidence and mortality of prostate cancer in the Netherlands between 1970 and 2006 and schematic representation of the proportion of diagnosed cancers with a relatively favourable prognosis (dark grey arrows) and a relatively unfavourable prognosis. (black arrows)

detected at an earlier moment than the moment the diagnosis would have been made when the same tumour would have surfaced clinically due to symptoms. The period by which the diagnosis is advanced due to screening is called leadtime. The lower the stage and grade at the moment the tumour is detected by screening, the longer the leadtime and vice versa. The leadtime within the ERSPC has been estimated at 13, 9, and 8 years for clinical stages T1, T2, and T3 tumours respectively, and 12, 10, and 4 years for Gleason score <7, 7, and >7 tumours, respectively[54].

OVERDIAGNOSIS AND OVERTREATMENT

Some prostate tumours are diagnosed that would not have surfaced clinically during lifetime. This is called overdiagnosis. The current ratio between detection and mortality of PC has resulted in a high incidence of tumours with a favourable prognosis of which many are being overdiagnosed[55]. The exact rates of overdiagnosis are dependent of definitions, calculation methods, and study populations[56]. In the screening setting of the ERSPC, which is largely comparable to current clinical practice, these have been estimated at 69%, 38%, and 30% for clinical stages T1, T2, and T3 tumours, respectively, and 62%, 40%, and 8% for Gleason score <7, 7, and >7 tumours, respectively[54]. Figure 5 presents a schematic overview of the relation between prevalence of PC at autopsy (other cause of death than PC), diagnosed PC, and PC deaths[57]. Many more tumours

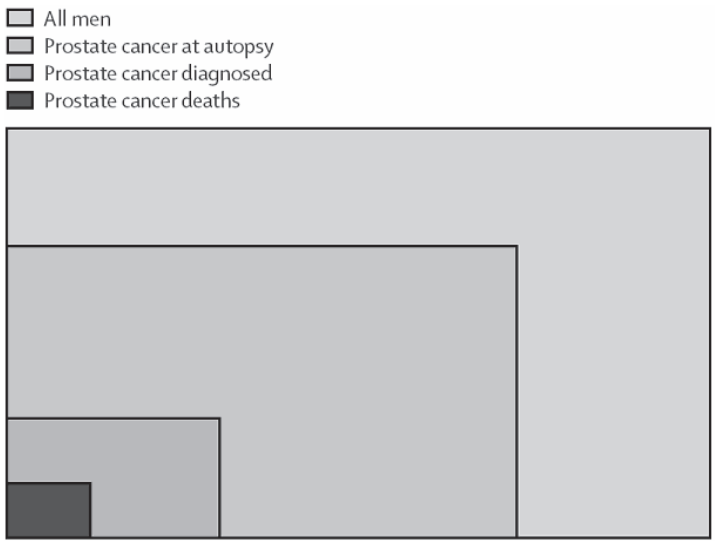


Figure 5: Relation between prevalence of prostate cancer at autopsy (other death cause than prostate cancer), diagnosed prostate cancer, and prostate cancer deaths.

are detected than the number of men dying from the disease, of which a large number would not even have surfaced or would have negatively affected the life expectancy. Expectant management of these tumours would result in the same mortality outcomes as radical therapy. Still, despite the rising incidence of these tumours, most detected PCs are treated radically, while expectant management is less frequently applied[58]. When radical therapy is instituted in an overdiagnosed PC, patients are unnecessarily subjected to the risk of side effects. This is called overtreatment. Overtreatment may lead to substantial costs and has ethical objections ('primum non nocere'; first do no harm).

ACTIVE SURVEILLANCE FOR LOW RISK PROSTATE CANCER

In this era of frequent and early PC detection, active surveillance has emerged as an alternative strategy for managing overdiagnosed PC that would not have surfaced clinically during lifetime if left undiagnosed, because patients will die due to other causes at an earlier moment. Active surveillance has the aim to delay or even avoid overtreatment of these tumours and resulting adverse side effects[59,60]. Active surveillance consists of initially withholding radical treatment such as surgery or radiation therapy, but monitoring the disease instead according to a fixed pattern of frequent investigations.

When the first indications arise that disease progression occurs, the switch to radical treatment with curative intent and within the window of curability is advised.

Active surveillance is different from the traditional strategy of watchful waiting in that it entails a strict follow-up program and that as soon as early progression is observed the switch is made to radical therapy with curative intent. Also, men who are candidates for active surveillance are healthy and potentially fit for curative radical treatment such as surgery or radiation therapy. Watchful waiting also entails expectant management but has a palliative intent, the switch to hormonal therapy is made only at the moment clinical symptoms develop, it has a less intensive monitoring program, and is mainly indicated for older men with comorbidity.

All patients with a prostate tumour that will supposedly not surface clinically when left untreated theoretically are candidates for active surveillance. The problem is their proper identification. Tumours are selected for active surveillance based on favourable parameters available at diagnosis such as early clinical stage, low PSA value, low PSA-density, early number of positive cores, low percentage of tumour involvement of the biopsies, and low Gleason score. Using these parameters, the tumours with a predicted favourable natural history and favourable outcomes after surgery are selected[13,61,62]. These tumours are followed by frequently repeating diagnostic measures such as PSA (PSA kinetics), DRE, or TRUS-guided biopsies to assess whether progression occurs. The aim is to detect progression early, so that a curative treatment is still possible and gives no different outcomes from when radical therapy would have been given directly.

Expectant management of PC may avoid the risk of side effects due to radical treatment, but has been reported in watchful waiting cohorts to affect the health-related quality of life and has been associated with lower satisfaction, and increased anxiety and distress in patients who have to live with the idea of having PC that is not treated radically[39,40,63,64]. These aspects have been found to be associated with the switch to active therapy, while this is not advised by the follow-up protocol[65,66]. Also, sexual function and physical scores have been reported to decrease more than expected from the aging process alone during watchful waiting[21]. The effects mentioned here may theoretically also be seen during active surveillance.

RESEARCH QUESTIONS

RETROSPECTIVE ANALYSIS

It is unknown for which prostate tumours an initial strategy of active surveillance is suitable and safe. To study this first question, participants of the European Randomized Study of Screening for Prostate Cancer (ERSPC) who had been diagnosed with low risk PC based on the literature were analysed retrospectively. First, the overall and the disease specific mortality outcomes of these men who also all initially chose for expectant management will be presented (Chapter 1). The potential harm of a treatment delay in the patients who received radical therapy later after an initial period of active surveillance will also be studied by comparing outcomes after radical prostatectomy to similar men who received immediate surgery (Chapter 2). Then, the possibilities of improving the selection for active surveillance are explored regarding outcomes after immediate radical prostatectomy (Chapter 3). Finally, possibilities for extending the current criteria for active surveillance will be studied by focusing on the mortality outcomes of a group of men with Gleason score 7 PC (Chapter 4).

PROSPECTIVE APPROACH

Although active surveillance may be feasible based on retrospective data, it is largely unknown how this strategy should be applied prospectively. Prospective evidence is needed to evaluate and optimize the criteria for inclusion and follow-up and to develop guidelines for active surveillance in the future. A prospective study protocol for active surveillance was developed to answer this second question and will be presented (Chapter 5). The short-term outcomes of patients participating in this protocol will be studied to get a first impression of the feasibility and the safety of this protocol (Chapter 6). The possibilities and disadvantages of using PSA kinetics during active surveillance will also be discussed (Chapter 7).

QUALITY OF LIFE ISSUES

The effects of expectantly managing PC on patients' quality of life have been studied in patients on watchful waiting but have never been explored in an active surveillance setting. This is the basis of the third question of this thesis. A study was initiated that comprised sending questionnaires to participants in a prospective active surveillance

program at multiple moments after the diagnosis. The patients' perception of active surveillance and their knowledge of the disease will be studied (Chapter 8). The levels of anxiety and distress in these men on active surveillance (Chapter 9), as well as the changes of these levels after diagnosis will also be analysed (Chapter 10). Finally, the Dutch version of a questionnaire measuring PC specific anxiety was validated and will be presented (Chapter 11).

PART II

RETROSPECTIVE ANALYSIS

Chapter 1
Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly
(European Urology 2009)

Chapter 2
Is delayed radical prostatectomy in men with early screen-detected prostate cancer associated with a higher risk of unfavourable outcomes?
(Cancer 2009)

Chapter 3
Rule-based versus probabilistic selection for active surveillance for prostate cancer and outcomes after radical prostatectomy
(Submitted)

Chapter 4
Gleason score 7 screen-detected prostate cancers initially managed expectantly: Outcomes in 50 men
(BJUI 2009)

Chapter 1

Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly

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ABSTRACT

Background

The incidence of small, localized, well-differentiated prostate cancer (PC) is increasing, mainly due to screening. Many of these cancers will not progress, while radical therapy may lead to substantial overtreatment. Active surveillance (AS) has emerged as an alternative.

Objective

To retrospectively validate the currently used criteria for eligibility for AS.

Design, setting, and participants

For this cohort study, data of 616 men who were diagnosed with PC between 1994 and 2007 at a mean age of 66.3 years in four centres of the European Randomized Study of Screening for Prostate Cancer (ERSPC) were combined. Patients all fit criteria for AS (PSA ≤10.0 ng/ml, PSA-density <0.2 ng/ml/ml, stage T1C/T2, Gleason-score ≤3+3=6, ≤2 positive biopsy cores) and initially were managed expectantly. Median follow-up was 3.91 years.

Measurements

Disease specific-, overall-, and treatment-free survival were studied. Present PSA-characteristics were assessed and also compared between men switching to deferred active therapy during follow-up and men remaining untreated.

Results and limitations

The calculated (Kaplan-Meier) 10-year PC specific survival (21 patients at risk) was 100%, which sharply contrasted with 77% overall survival. Men still alive showed favourable PSA-characteristics. Although the calculated 10-year treatment-free survival was only 43%, objective signs of progression often did not indicate the shift to radical treatment. The cohort consisted of men on AS as well as on watchful waiting; information on comorbidity or psychological distress was not available.

Conclusions

AS seems justified in selected men with screen-detected PC. Prospective protocol-based AS-programs are necessary to optimize selection criteria and to find the appropriate trigger points for switching to active therapy. Possible negative psychological reactions with AS against improved quality of life by withholding side effects from radical treatment should be considered.

INTRODUCTION

The incidence of prostate cancer (PC) has been rising during the last two decades[67]. PSA (prostate specific antigen) driven screening is probably the most important underlying reason for this trend[68]. Besides other effects, present screening leads to a more frequent detection of small, localized, well-differentiated malignancies[8,51].

With death due to other causes often occurring before these tumours become harmful, radical treatment may have no effect on these patients' PC specific survival[13]. At present, most of these early cancers are radically treated, carrying a chance of serious side effects[69-71].

Active surveillance (AS) is an emerging treatment strategy aiming to avoid overtreatment in these PC-patients. AS consists of initially following men with early PC and yet starting curative surgery or radiation therapy (RT) only when progression occurs. AS delays treatment in some men and avoids it completely in others[59,60]. The criteria for inclusion and for switching towards active therapy are not yet evidence-based[46].

The present multicenter study aims to validate the currently used criteria for eligibility for AS, by retrospectively studying outcome measures in men with screen-detected PC fitting these criteria and who were managed expectantly.

PATIENTS AND METHODS

Men included in this study all participated in the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC), had been diagnosed with PC, and initially had elected expectant management. The data cohorts of 4 centres in 3 countries were combined, i.e. Rotterdam in The Netherlands, Gothenburg in Sweden, and Helsinki and Tampere in Finland.

The ERSPC screening protocol (applied to men aged 50-75) consists of PSA-measurements (threshold 3.0 or 4.0 ng/ml), and/or transrectal ultrasound (TRUS), and/or digital rectal examination (DRE), at 2- or 4-year intervals. Abnormal findings lead to sextant prostate biopsies, the Finnish centres later changed to 10 or 12 biopsy cores[72]. Prostatic volume is measured by planimetric calculation during TRUS. After a PC-diagnosis men are referred to the regular medical circuit (which may be the ERSPC centre) where decisions on treatment are made[73].

A selection was made of men with baseline tumour characteristics fitting current eligibility criteria for AS (PSA ≤10.0 ng/ml, PSA-density <0.2 ng/ml/ml, stage T1C/T2, Gleason-score ≤3+3=6, ≤2 positive biopsy cores). Men with known positive lymph nodes or distant metastases at the time of diagnosis were also excluded. These thresholds are used in the prospective PRIAS-study on AS originating from the ERSPC and mainly are

similar to the inclusion criteria used in the first protocol-based prospective study on AS in Canada[66,74].

PC specific survival (time to death of PC, censoring time to death due to other causes or time to last follow-up in men still alive), overall survival (time to death of all causes, censoring time to last follow-up in men still alive), and treatment-free survival (time to deferred active treatment, censoring time to death or last follow-up in untreated men still alive) were analysed using Kaplan-Meier (KM) analysis. Furthermore, we assessed the PSA and PSA-doubling time (PSA-DT) of men in our study cohort who were alive at the moment of this analysis, applied the criteria for PSA-failure after treatment in men who received deferred radical prostatectomy (RP)[75] or RT[76], and also compared PSA-characteristics between men shifting to active treatment during follow-up and those remaining untreated.

Deferred active therapy was divided into 3 groups: RP, RT, and hormonal therapy (HT) (anti-androgens, luteinizing hormone-releasing hormones, and orchiectomy). For the purpose of simplicity, no difference was made between administering adjuvant HT or not in the RP and RTgr group. Treatments due to coexistent BPH (5-alpha-reductase-inhibitors and TURP) were not considered as active therapy for PC in this analysis.

For risk-stratification of patients based on their PSA-characteristics, the arbitrary threshold for PSA of 10.0 ng/ml and for PSA-DT of 3 years were chosen, the first being a cut-off value for inclusion and the second a trigger parameter to switch to deferred radical treatment in current AS-programs[66,74]. PSA and PSA-DT before and after treatment were separately assessed.

The PSA-DT was calculated in all patients with two or more PSA measurements available (≥2 post-treatment PSAs in men who received deferred treated), by plotting the base 2 logarithm of the PSA-value against time since diagnosis. The DT can be calculated as the reciprocal value of the slope of the regression line through these points.

Follow-up data were collected from patient charts; mortality information was retrieved by linkage with the national registries. In The Netherlands, an independent committee performed the review of all deceased PC-patients who separately judge the anonymized patient charts, in Sweden causes of death are based on death certificates, and in Finland both methods are applied[77].

For statistical analysis the commercially available software Statistical Package for the Social Sciences, version 14.0 (SPSS, Inc, Chicago, IL, USA) was used. Comparisons between centres were made using the non-parametric Kruskal-Wallis test. P values <0.05 were considered statistically significant.

RESULTS

In total, 988 men were primarily managed expectantly after PC diagnosis; of those, 616 (62.3%) conformed to the PRIAS-criteria for AS. Of the 372 (988-616) excluded men, 49 had a PSA >10.0 ng/ml (12 unknown), 130 had a PSA-density ≥0.2 ng/ml/ml (89 unknown), 4 had disease stage >T2 (24 unknown), 54 had Gleason-score >3+3=6 (24 unknown), and 108 had >2 positive biopsy cores (93 unknown). One man had positive lymph nodes at the time of diagnosis and one had distant metastasis.

Patient characteristics per ERSPC-centre are presented in Table 1. Small, but significant differences between centres were found in mean age (p <0.001), PSA at diagnosis (p <0.001), time to deferred active therapy (p 0.04), last PSA before deferred treatment was instituted (p 0.002), and the number of PSA-measurements per patient per year (p <0.001).

In all KM-analyses 39 men were excluded due to a lack of follow-up data because of recent diagnosis. Thus these analyses start with 577 patients at risk.

Figure 1 shows the PC specific and overall survival KM-curves. The mean follow-up was 4.35 years (range 0-11.63); median 3.91 (25-75p 1.85-6.61). One man died due to PC 11.22 years after diagnosis at the age of 59. In this patient treatment was postponed despite a PSA rising for over 7 years up to 880. The calculated 10-year PC specific survival was 100%. Death due to any cause occurred in 53 patients, after a mean of 4.25 years (0.45-10.99). The calculated 10-year overall survival was 77%. One man (last known PSA 17.7, PSA-DT 3.1 years, 4.5 years after diagnosis) had confirmed distant metastases during follow-up, detected 3.5 years after diagnosis. RT had been instituted with a delay of 0.8 year after PC-diagnosis.

Table 2 shows the last PSA and PSA-DT of all men alive at the time of analysis. Of the 381 alive untreated men, 27 had a PSA of ≥10.0, 27 had a PSA-DT ≤3 years, and 8 (2.1%) men had both. Of the 182 alive men who had undergone deferred active treatment, 2 had a PSA of ≥10.0, 11 had a PSA-DT ≤3 years, and 1 (0.5%) man had a combination of both. During follow-up after deferred RP (without adjuvant HT), 7 out of 81 men showed a PSA >0.2 ng/ml a median of 3.4 years (25-75p 1.7-5.3) after treatment. During follow-up after deferred RT (without adjuvant HT), 6 out of 78 men showed a rise of 2 ng/ml or more above nadir a median of 4.4 years (25-75p 3.2-5.1) after treatment.

PSA-DT was unknown in 77 patients, because only one PSA-measurement was available after diagnosis or after treatment.

Figure 2 shows the treatment-free survival KM-curve. During follow-up, 197 men switched to RP, RT, or HT, after a mean of 2.55 years (range 0.29-10.86). The calculated 10-year deferred treatment-free survival was 43%. After 7.75 years 50% of men had received treatment. The median treatment-free survival is 2.50 years (25-75p 1.11-5.05). Of the 197 men treated during follow-up 84 underwent RP (42.6%), 95 RT (48.2%), and

Table 1: Study group characteristics at diagnosis and during follow-up, per ERSPC-centre. All 616 men conformed to the PRIAS criteria for active surveillance and were initially treated expectantly.

	Rotterdam (NL)	Gothenburg (SE)	Helsinki (FI)	Tampere (FI)	Total
Number	234	241	123	18	616
			AT DIAGNOSIS		
Mean age (yr) (range)	68.6 (56.9-76.5)	64.3 (51.2-70.2)	65.7 (55.1-72.1)	66.4 (58.6-71.9)	66.3 (51.2-76.5)
Mean PSA (ng/ml) (range) *	3.93 (1.20-9.50)	4.30 (3.00-9.72)	4.88 (3.00-9.00)	5.02 (2.60-9.90)	4.30 (1.20-9.90)
Mean prostate volume (ml) (range)	46.7 (19.0-150.0)	41.6 (18.8-107.0)	40.7 (18.0-127.0)	43.2 (21.0-67.0)	43.4 (18.0-150.0)
Mean PSA-density (ng/ml/ml) (range) *	0.09 (0.03-0.20**)	0.11 (0.04-0.20**)	0.13 (0.06-0.20**)	0.12 (0.07-0.18**)	0.11 (0.03-0.20**)
T-stage *					
- T1C (%)	185 (79.1)	222 (92.1)	118 (95.9)	18 (100)	543 (88.1)
- T2A (%)	42 (17.9)	16 (6.6)	5 (4.1)	0 (0)	63 (10.2)
- T2B (%)	2 (0.9)	2 (0.8)	0 (0)	0 (0)	4 (0.6)
- T2C (%)	5 (2.1)	1 (0.4)	0 (0)	0 (0)	6 (1.0)
Gleason-score *					
- 3+3=6 (%)	214 (91.5)	235 (97.5)	73 (59.3)	11 (61.1)	533 (86.5)
- Lower (%)	20 (8.5)	6 (2.5)	50 (40.7)	7 (38.9)	83 (13.5)
Positive biopsy cores *					
- 1 (%)	178 (76.1)	189 (78.4)	95 (77.2)	15 (83.3)	477 (77.4)
- 2 (%)	56 (23.9)	52 (21.6)	28 (22.8)	3 (16.7)	139 (22.6)
Total number of biopsy cores (range)	6.13 (6-7)	5.97 (2-10)	8.52 (3-13)	7.72 (5-13)	6.59 (2-13)
			DURING FOLLOW-UP		
Mean follow-up (yr) (range)	4.31 (0.0 – 10.88)	4.41 (0.0 – 11.63)	4.30 (0.0 – 10.39)	4.29 (0.0 – 8.07)	4.35 (0.0 – 11.63)
Mean number of PSA-measurements per patient per yr	1.72 (total 1735)	1.53 (total 1629)	2.04 (total 1081)	1.84 (total 142)	1.71 (total 4,587)
PC-death (%)	0 (0)	1 (0.4)	0 (0)	0 (0)	1 (0.2)
Mean time to PC-death (yr) (range)	- (-)	11.22 (-)	- (-)	- (-)	11.22 (-)
Overall death (%)	21 (9)	19 (8)	10 (8)	3 (17)	53 (9)
Mean time to overall death (yr) (range)	4.45 (0.45 – 8.93)	4.67 (0.92 – 11.22)	3.78 (1.55 – 8.92)	4.08 (1.19 – 6.45)	4.38 (0.45 – 11.22)
Deferred treatment (%)	63 (27)	81 (34)	47 (38)	6 (33)	197 (32)
Mean time to deferred treatment (yr) (range)	2.35 (0.29 – 9.18)	2.62 (0.52 – 10.86)	2.83 (0.33 – 7.82)	1.36 (0.55 – 2.51)	2.55 (0.29 – 10.86)
Last PSA pre-treatment (ng/ml) (range)	7.26 (1.30 – 17.0)	16.69 (1.90 – 880.0)	7.81 (3.30 – 20.0)	6.30 (2.90 – 9.40)	11.28 (1.30 – 880.0)

ERSPC European Randomized Study of Screening for Prostate Cancer
PRIAS Prostate Cancer Research International Active Surveillance
NL The Netherlands
SE Sweden
FI Finland
PSA prostate specific antigen
PC PC
* eligibility parameter for active surveillance
** rounded up

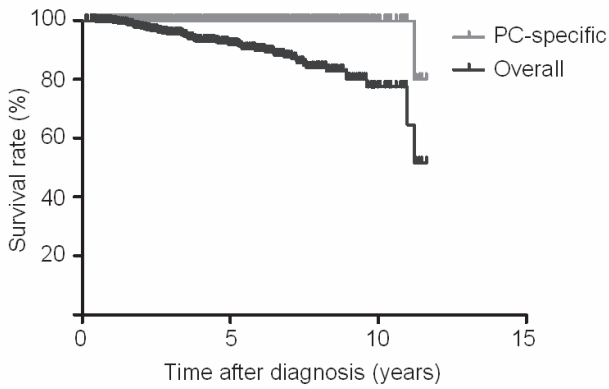

Figure 1: PC specific and overall survival

Years	0	1	2	3	4	5	6	7	8	9	10	11	12
# at risk	577	518	455	371	301	247	188	134	92	52	21	5	0
Cumulative # PC specific death (survival rate %)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	1 (80)
Cumulative # overall death (survival rate %)	0 (100)	2 (100)	13 (97)	21 (95)	30 (93)	33 (92)	38 (90)	42 (88)	47 (84)	50 (80)	51 (77)	52 (64)	53 (52)

Table 2: Last known PSA and PSA-DT characteristics of men still alive (563; 53 of 616 died) in our study cohort at time of analysis, per treatment-group

		Total	Untreated	Treated			
				All Tx	RP	RT	HT
Number		563	381 (68%)	182 (32%)	80	89	13
Last known PSA (ng/ml)	0-5	400	237 (59%)	163 (41%)	79	74	10
	5-10	119	116 (97%)	3 (3%)	0	2	1
	10-15	21	21 (100%)	0 (0%)	0	0	0
	15-20	6	4 (67%)	2 (33%)	0	2	0
	20-50	2	2 (100%)	0 (0%)	0	0	0
	>50	0	0 (0%)	0 (0%)	0	0	0
	Unknown	15	2 (13%)	13 (87%)	1	11	1
Last known PSA-DT * (yr)	0-1	6	3 (50%)	3 (50%)	1	2	0
	1-3	32	24 (75%)	8 (25%)	1	5	2
	3-5	33	27 (82%)	6 (18%)	3	3	0
	5-7	43	40 (93%)	3 (7%)	0	3	0
	7-10	46	45 (98%)	1 (2%)	0	1	0
	>10	144	84 (58%)	60 (42%)	55	4	1
	Neg	182	113 (62%)	69 (38%)	10	54	5
	Unknown	77	46 (60%)	31 (40)	10	17	4

Tx treatments
RP radical prostatectomy
RT radiotherapy
HT hormonal therapy
PSA prostate specific antigen
PSA-DT prostate specific antigen doubling time
Neg negative
* Calculated over all (>1) known PSA-values if untreated, over values after treatment only if treated

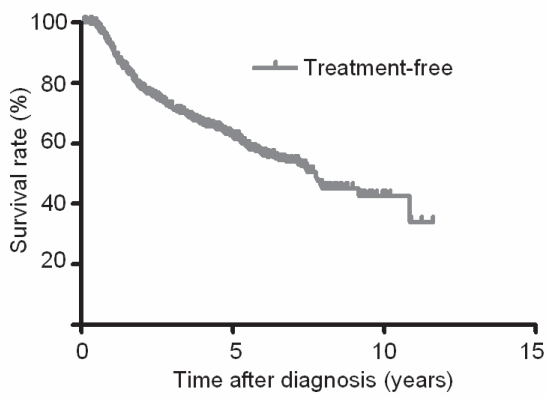

Figure 2: Treatment-free survival

Years	0	1	2	3	4	5	6	7	8	9	10	11	12
# at risk	577	477	360	271	204	158	109	74	38	19	8	2	0
Cumulative # treated	0	42	112	137	157	168	182	186	195	195	196	197	197
(survival rate %)	(100)	(92)	(78)	(72)	(66)	(62)	(56)	(54)	(45)	(45)	(43)	(34)	(34)

18 HT (9.1%). Men treated during follow-up were significantly younger at diagnosis than men remaining untreated (64.7 vs. 67.0; p <0.001) and men receiving RP (62.7) were younger than those receiving RT (66.1; p <0.001) or HT (67.4; p <0.001).

Table 3 shows the PSA and PSA-DT of men remaining untreated (last measurements) during follow-up compared to men switching to active therapy (last pre-treatment measurements). Of the 419 untreated men, 30 had a PSA ≥10.0, 29 had a PSA-DT ≤3 years, and 8 had both, making them candidates for active therapy. Of the 84 men before RP, 80 had a PSA <10.0, 59 had a PSA-DT >3 years, and 56 both; for the 95 before RT these numbers were 80, 58, and 47; and for the 18 before HT 7, 13 and 7. This results in a total of 110 (56+47+7) out of 197 men (55.8%) who received deferred treatment despite a favourable PSA and PSA-DT.

Finally, we checked whether clinical or pathological progression was observed in the period before the switch to active therapy. DRE-information during follow-up was available in a subgroup of 345 men (56.0%; Rotterdam, Helsinki, and Tampere), rebiopsy information in 142 men (22.9%; Helsinki and Tampere; not all 142 men underwent rebiopsies, 29 of 142 patients received a total of 33 rebiopsies). In the 110 men shifting to active treatment despite favourable PSA and PSA-DT, DRE was known in 53 men and played a role in 9 (17.0%), information on rebiopsies was known in 27 and played a role in 0 (0%).

Table 3: Pre-treatment PSA and PSA-DT characteristics of men in our study cohort, per treatment-group

		Total	Untreated	Treated			
				All Tx	RP	RT	HT
Number		616	419 (68%)	197 (32%)	84	95	18
Last known PSA pre-treatment (ng/ml)	0-5	315	259 (82%)	56 (18%)	37	17	2
	5-10	241	130 (54%)	111 (46%)	43	63	5
	10-15	47	24 (51%	23 (49%)	4	12	7
	15-20	8	5 (63%)	3 (37%)	0	1	2
	20-50	2	1 (50%)	1 (50%)	0	0	1
	>50	1	0 (0%)	1 (100%)	0	0	1
	Unknown	2	0 (0%)	2 (100%)	0	2	0
Last known PSA-DT * pre-treatment (yr)	0-1	13	4 (31%)	9 (69%)	3	4	2
	1-3	78	25 (32%)	53 (68%)	19	31	3
	3-5	83	28 (34%)	55 (66%)	22	27	6
	5-7	60	42 (70%)	18 (30%)	6	11	1
	7-10	67	49 (73%)	18 (27%)	9	6	3
	>10	121	101 (83%)	20 (17%)	12	6	2
	Neg	145	126 (87%)	19 (13%)	10	8	1
	Unknown	49	44 (90%)	5 (10%)	3	2	0

Tx treatments
RP radical prostatectomy
RT radiotherapy
HT hormonal therapy
PSA prostate specific antigen
PSA-DT prostate specific antigen doubling time
Neg negative
* Calculated over all (>1) known PSA-values if untreated, over values before treatment only if treated

DISCUSSION

We retrospectively studied PC specific-, overall-, and treatment-free survival of men with screen-detected PC initially managed expectantly, who would have been suitable for AS according to contemporary practice. In the first screening round of the Rotterdam section of the ERSPC, 21.8% of all men that might have been suitable for AS were actually treated expectantly[78].

Differences between the four centres in patient selection and follow-up were small, but significant. These can be traced back to cultural and traditional differences, and to differences in ERSPC screening protocols[73]. A protocol-based AS program was not applied.

The most prominent observation (Figure 1) is the favourable 10-year disease specific survival of 100%, in contrast with an overall survival of 77%. Of all men still alive remaining untreated 12% (46 out of 381) had a high last PSA or a quickly rising PSA, with the option for active therapy still open. Of all men still alive who received deferred treatment, 6.6% (12/182) had a high last PSA or a quickly rising PSA-DT. After RP 9% (7 out of 81) and after RT 8% (6 out of 78) showed PSA failure, but with HT started in 6 of them, none of them had a high PSA and short PSA-DT.

Although the thresholds that we used to risk-stratify patients based on PSA are arbitrary, we aimed to show that there is a high probability of a persistently favourable PC specific survival in the near future[79]. These results look encouraging, however longer follow-up is needed to conclude that AS is a safe approach. Furthermore, ongoing prospective protocol-based AS-programs, such as the PRIAS-study, are necessary to optimize criteria for eligibility[66,74,80].

These findings are in line with the previous knowledge on the favourable prognosis of up to 20 years of clinically-detected small, localized, well-differentiated PC[13,81,82], the leadtime of >10 years in these early tumours when screen-detected[54], and the improvement in mortality for all Gleason-score categories due to the Will Rogers phenomenon that has occurred last decades[47]. The concurrent observation of this study that a considerable number of men die due to other causes before PC surfaces, justifies expectant management. On the long-term PC-death rates may however still increase[81].

A second central finding (Figure 2) is that a considerable part of the men do not 'comply' with the expectant management regimen (10-year treatment-free survival 43%). The sudden drop in the treatment-free survival KM-curve shows that the highest rate of switching to deferred active treatment is seen within two years after diagnosis. Men choosing early treatment soon (within 1 or 2 years), were not statistically different from men receiving active therapy later during follow-up, regarding age, last PSA, or PSA-DT pre-treatment.

Although the achieved delay in treatment itself can be considered very precious for a healthy patient in avoiding side effects of radical treatment, the main benefit of an expectant management is life long avoidance of active therapy in men who do not need this. In line with the observations of other authors we observed that an initial expectant management often results in delay, not in avoidance of radical treatment, especially in younger patients at diagnosis[83]. So far, treatment was avoided completely in almost half of our patients. In the remainder it was deferred, often for many years. However, no follow-up protocol as used in current prospective AS-programs was applied in these patients[66,74,80]. Furthermore, switching to treatment can be seen as the whole idea of AS; to delay treatment in those who for various reasons are not candidates for immediate treatment at the moment of diagnosis and keep the option for curative treatment open.

Based on PSA-characteristics of all 616 patients, we found that a small fraction of 1.9% (8 of 419) of patients remaining untreated may be (or have been) better candidates for active treatment, while 55.8% (110 of 197) of men who did receive active therapy, were not obvious candidates for radical treatment. DRE or rebiopsies did not seem to explain this discrepancy. Factors such as anxiety, urologic complaints, or comorbidity information may have been more decisive, but these were not available[65].

These data show that at least a part of the deferred treatments could possibly have been avoided if a strict follow-up protocol had been applied. As we do not know the

efficacy of AS and the underlying (psychological) reasons for switching to active therapy, it is however not given that avoidance of treatment is the ultimate goal. It is undoubtedly essential for ongoing protocolized prospective AS studies to develop medical thresholds for application of deferred treatment in this group of men in the future[66,74,80]. A standardized approach and equally important providing mental support to patient and physician may extend the delay of active therapy and further diminish overtreatment.

Weak points of our study are that patient follow-up was not standardized and that our data mainly focus on survival, treatment, and PSA. The role of DRE and rebiopsies could only be assessed in a subgroup of patients, though it is unlikely that our findings are different for the entire cohort. As said, it was not possible to assess psychological factors or information on comorbidity or urologic complaints.

A second point of critique is that the very favourable PC specific survival we found may not be the effect of successful patient selection, but actually of the large number of deferred active therapies. With our retrospective non-randomized study design, we are not able to overturn this possibility. Following clinical logic, treatments have been performed more often in men within the relatively unfavourable PSA and PSA-DT ranges when compared with the untreated men, which possibly improves prognosis for the entire cohort. However with the presented data, we also hope to show that there is an important overlap in PSA-characteristics between men remaining untreated and men receiving deferred treatment, and that both groups show a favourable PC specific prognosis. This observation makes it unlikely that all instituted deferred treatments have saved men from death due to PC. It may be more reasonable to believe that many active therapies have not increased survival of patients in our cohort and therefore could be considered medically unnecessary.

Finally, our cohort consisted of a heterogeneous group of men either on watchful waiting (WW) with palliative intent (as studied by Albertsen et al. and Johansson et al.[13,81]) or on AS with curative intent, between which our retrospective data cannot distinguish. Older men with a high comorbidity scores are more likely to have been selected for WW. The mean age of 66.3 years (mean remaining life expectancy of ~15 years[84]) and the fact that 90.9% (84+95/197) of deferred treatments had curative intent (RP/RT) would however imply that many men are on an AS-like treatment. The border between these strategies is not black and white; men will naturally shift from AS to WW, especially after an extended follow-up.

A strong point of this study is its multicenter set-up and the size of our study group, in combination with a considerable follow-up period in quite a large number of men, with an abundant number of PSA-values (4,587) available. Furthermore, as our study cohort is a selection of men diagnosed with PC within the ERSPC, pathological examination of biopsy specimens was standardized, the follow-up data collection of patients has been organized in a structured method, and objective assessment of the causes of death are implemented.

CONCLUSIONS

This retrospective ERSPC multicenter study confirms that expectant management is a part of the clinical management of screen-detected PC. The border between AS and WW is not distinct. Men with screen-detected PC fitting current criteria for AS have a very favourable PC specific prognosis, after initially choosing an expectant management; after 10 years of follow-up 100% survived their PC, while almost one quarter had died due to other causes. Based on present PSA-characteristics, it is also unlikely that this observation will change in the near future. An expectant management for this group of PC-patients seems justified, also if the life expectancy exceeds 10 years.

The majority of men in our study received deferred treatment during follow up; after 10 years, only 43% was still untreated. Although the treatment delay itself is also valuable, we believe that with the right support, more patients are suitable to avoid active therapy, as objective signs of progression often did not play a role in the shift to active treatment.

Prospective AS studies should aim to explore whether AS does not increase risk for PC-death on the long term or constitutes a psychological terror for patients. Also, the selection criteria for an expectant management of PC should be optimized, incorporating comorbidity and life expectancy parameters. Furthermore, the best medical triggers for switching to active treatment and psychological aspects should be investigated, subjecting only those men to the chance of side effects of radical treatment who really benefit from this.

Chapter 2

Is delayed radical prostatectomy in men with low risk screen-detected prostate cancer associated with a higher risk of unfavourable outcomes?

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ABSTRACT

Background

Strategies of active surveillance (AS) of low risk screen-detected prostate cancers (PC) have emerged, since the balance between survival outcomes and quality of life issues when radically treating these malignancies is disputable. Delay before radical treatment caused by AS may be associated with an impaired chance of curability.

Methods

Men diagnosed with low risk (T1c/T2, PSA ≤10.0, PSA-density <0.2, Gleason score 3+3=6, 1-2 positive biopsies) PC in the Swedish section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) who received radical prostatectomy (RP) were studied. One group received immediate RP; one group received delayed RP after an initial period of expectant management. We compared these groups regarding histopathological and biochemical outcomes, correcting for baseline differences.

Results

Mean follow-up after diagnosis was 5.7 years (sd 3.2). The immediate RP group (N=158) received RP a mean of 0.5 (sd 0.2) years after diagnosis; the delayed RP group (N=69) after 2.6 (sd 2.0) years (p ≤.001). After adjustment for small baseline dissimilarities, no differences in RP frequencies of Gleason score >6 (OR 1.54 p .221), capsular penetration (OR 2.45 p .091), positive margins (OR 1.34 p .445), in RP tumour volume (difference 0.099 p .155), or in biochemical progression rates (p .185, p .689) were found between groups, although all data were in favour of immediate RP.

Conclusion

With limited patient numbers available for analysis, differences in intermediate outcomes between immediate RP and delayed RP were non significant. The delayed RP group may be subject to a selection bias. Prospective evaluation of AS protocols is essential.

INTRODUCTION

The incidence of small, localized, well-differentiated prostate cancer (PC) has risen during the last two decades, mainly due to a more widespread use of PSA (prostate specific antigen) screening[67]. Many of these tumours will remain non-harmful during lifetime and radical treatment of all these men will result in tremendous overtreatment[13,85]. The significant but modest favourable effect on PC specific survival of radical treatment when compared to watchful waiting has to be weighed against the risk of important side effects on an individual basis[28,31]. This issue has even become more important since a large screening trial recently reported a positive effect of screening[16].

Strategies of initial active surveillance (AS) have emerged, which consist of selecting men with a favourable prognosis based on tumour characteristics and initially withholding potentially curative radical treatment, but instead closely monitoring the disease[59]. When signs of progression occur, radical treatment is recommended. In retrospective analyses, PC specific mortality is very low, while some men die of other causes during follow-up[85]. AS may thus decrease overtreatment of PC and the risk of side effects by sparing surgery or radiation therapy in some men. In others however, radical treatment is merely delayed. A crucial question surrounding AS strategies is whether delaying curative treatment is associated with an impaired chance of curability.

In this retrospective study we compared histopathological and biochemical outcomes of men with screen-detected low risk PC between those receiving immediate radical treatment after diagnosis and those receiving delayed radical treatment after an initial period of expectant management.

PATIENTS AND METHODS

Men included in this study all participated in the screening arm of the Swedish section (Gothenburg) of the European Randomized Study of Screening for Prostate Cancer (ERSPC)[15] for which they provided written informed consent. The Swedish ERSPC study protocol randomized 20.000 men between 50 and 66 years of age. After approval of the ethical committee in 1994, men randomized to the screening arm have since the beginning in 1995 been offered PSA measurements every 2 years[86]. All men with a PSA ≥3.0 ng/ml were candidates for a digital rectal examination (DRE), transrectal ultrasound (TRUS), and lateralized sextant prostate biopsies; additional biopsy-core(s) were performed in case hypoechoic lesion(s) were seen during TRUS. Prostatic volume was measured by planimetric calculation from the TRUS recorded measurement of the prostate using the ellipsoid formula. After a PC-diagnosis, decisions on treatment were made after discussing potential treatment options between the physician and the

patient, including expectant management if applicable. Treatments were mainly performed in the ERSPC study centre itself (Sahlgrenska University Hospital, Gothenburg, Sweden). More detailed information on the ERSPC and the study protocol have been previously published[73].

We selected all clinical stage Ic/II (TNM: T1c/T2, N0/X, M0/X) PC, with a PSA at diagnosis ≤10.0 ng/ml, a PSA-density (PSA divided by prostatic volume) <0.2 ng/ml/cc, a Gleason score (pathological dedifferentiation) of 3+3=6 or more favourable, and 1 or 2 positive biopsy cores. Men with known positive lymph nodes or distant metastases at the time of diagnosis were excluded. The decision to perform a lymph node dissection was made on a patient specific basis and consisted of removing all lymphatic tissue in the angle between the obturator nerve and the external iliac vein. This combination of parameters is used as the criteria for eligibility in the international prospective PRIAS-study (Prostate cancer Research International: Active Surveillance) on AS originating from the ERSPC[74] and is largely similar to the inclusion criteria used in the first protocol-based prospective study of AS in Toronto in Canada[66]. All patients with PC with a Gleason sum score <6 were categorized as Gleason 6.

From this group we selected all individuals who received radical prostatectomy (RP). These patients consisted of one group of men who received RP as their initial treatment ('immediate RP group') and another group in whom initially an expectant management was elected but who changed to RP later during follow-up ('delayed RP group'). These two groups were compared in this study.

No standardized protocol for expectant management was applied in the delayed RP group, but surveillance was generally based on regular (typical 6 months) PSA measurements, with repeat-biopsies in men with increasing PSA, especially in those who preferred to remain on surveillance. After RP men were checked every 6 months with PSA. The criteria by Freedland et al. were used to define PSA relapse, i.e. a PSA value >0.2[75]. All prostate biopsy cores and RP specimens were reviewed by the same uropathologist (CGP). Follow-up data were collected from patient charts.

First, we compared baseline characteristics and histopathological outcomes after RP between the immediate RP group and the delayed RP group using the T-test for continuous variables and the Chi-square test for categorized variables. The following histopathological RP outcomes were assessed: Gleason score >6 (yes/no), capsular penetration (yes/no), positive margins (yes/no), and tumour volume (continuous). As the two study groups were not randomized and thus expected to differ in baseline characteristics, separate logistic and linear regression models were also used for analysis of potential differences in outcome variables. Two separate multivariable analyses were done, one to adjust for potential differences at the moment of diagnosis and one for the moment of RP. We also assessed whether the time between diagnosis and RP was associated with any of the outcome variables and whether in the delayed RP group

the PSA doubling time (PSA-DT) was associated with any outcomes, using univariate analyses in the two separate study groups. Third, we compared time to biochemical progression (BCP) after RP between groups using Kaplan-Meier, Log-Rank, and Breslow analysis (tests equality of survival functions by weighting all time points by the number of cases at risk at each time point), both using moment of diagnosis and moment of RP as t=0, since the immediate RP group likely has a longer follow-up after RP to show biochemical progression, thus possibly introducing a bias. Then, we assessed whether study group was predictive for time to BCP using Cox regression analysis, correcting for differences in variables at the moment of diagnosis as well as at the moment of RP. Finally, we analysed whether time between diagnosis and RP was predictive for BCP after RP in separate analyses for the immediate RP group and the delayed RP group.

Parameters not further analysed due to small number of events were mortality (3 men died in the delayed RP group, none of them due to PC) and seminal vesicle invasion (SVI; one man showed SVI in the immediate RP group).

Combining the data of different ERSPC study centres was considered, but rejected because of the small differences in screening protocols that would result in heterogeneity in the study population.

P values (2-sided) <0.05 were considered statistically significant. For statistical analysis the commercially available software Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc, Chicago, IL, USA) was used.

RESULTS

Table 1 presents study group patient characteristics at the moment of diagnosis and at the moment of RP, follow-up between diagnosis and RP, and histopathological outcomes after RP. Our study group consisted of 227 men who had been diagnosed with low risk prostate cancer for which they received RP, with a mean follow-up time since diagnosis of 5.7 years. Of these 227 men, 158 (69.6%) primarily elected RP as the initial treatment option, were operated a mean of 0.5 years after diagnosis, and were followed a mean of 5.7 years after diagnosis; 69 (30.4%) first had elected expectant management as the initial treatment option, switched to RP later, were operated a mean of 2.6 years after diagnosis, and were followed a mean of 5.8 years after diagnosis. Of all men diagnosed in the Swedish section of the ERSPC with PC fulfilling the PRIAS criteria up until the moment of this study analysis, the initial treatments were surveillance in 53%, RP in 42%, and radiation therapy in 5%. An overlap in the distribution of time intervals between diagnosis and RP was seen between men in the immediate RP group (range 0.1-1.1 years) and men in the delayed RP group (range 0.6-8.9 years). However, as the intent of treatment was different (i.e. first monitor the disease during follow-up

Table 1: Immediate RP and delayed RP study group baseline characteristics and comparisons (N=227)

	Immediate RP			Delayed RP			p*
N	158			69			-
TIME OF DIAGNOSIS							
Age (year) (mean, median, sd)	62.8	62.6	3.8	62.3	62.1	3.9	.375
PSA (ng/ml) (mean, median, sd)	4.3	4.0	1.1	4.2	3.8	1.3	.703
Prostate volume (cc) (mean, median, sd)	37.7	35.1	11.5	42.1	42.0	13.0	**.011**
PSA-density (ng/ml/cc) (mean, median, sd)	0.12	0.12	0.03	0.11	0.10	0.04	**.007**
Gleason score	3+3=6 100%			3+3=6 100%			-
Number of positive biopsies (mean, median, sd)	1.4	1.0	0.5	1.2	1.0	0.4	**.002**
Number of total biopsies (mean, median, sd)	6.0	6.0	0.4	6.0	6.0	0.3	.623
mm PC tissue (mean, median, sd)	3.4	2.7	2.8	2.4	1.5	2.7	**.013**
mm benign tissue (mean, median, sd)	70.4	71.9	17.8	72.3	71.8	18.2	.719
T stage	81.6% T1c 18.4% T2			94.2% T1c 5.8% T2			**.014**
TIME OF RADICAL PROSTATECTOMY							
Age (year) (mean, median, sd)	63.2	63.0	3.8	64.9	64.9	3.6	**.002**
PSA (ng/ml) (mean, median, sd)	4.3	4.0	1.1	5.7	5.0	2.3	**<.001**
FOLLOW-UP BETWEEN DIAGNOSIS AND RADICAL PROSTATECTOMY							
Time between diagnosis and RP (years) (mean, median, sd)	0.5	0.4	0.2	2.6	1.8	2.0	**<.001**
PSA-DT before RP (years)	-			0-3 24.6% 3-10 40.6% >10 18.8% Negative 15.9%			-
OUTCOMES AFTER RADICAL PROSTATECTOMY							
Gleason >6	22.7%			27.9%			.404
Capsular penetration	8.0%			11.8%			.372
Positive margins	20.0%			20.6%			.920
Tumour volume (cc)	0.7	0.5	0.7	0.8	0.5	0.8	.602
Total follow-up time since diagnosis (year) (mean, median, sd)	5.7	5.5	3.2	5.8	5.4	3.2	.737
Total follow-up time since surgery (year) (mean, median, sd)	5.2	4.9	3.1	3.2	2.1	3.0	**<.001**

* Student's T test was used for continuous variables, Chi square was used for categorized variables.
RP radical prostatectomy
PSA prostate specific antigen
PC prostate **cancer**
PSA-DT prostate **specific antigen doubling time**

before RP versus immediate RP), we maintained this division in initial treatment choice as derived from the patient charts in our analyses. Some men who elected RP as the initial treatment still had a considerable delay (1 patient >1 year) until actual surgery due to patients' delay in making the treatment decision. When compared to patients

Table 2: Odds ratios and difference in outcomes of the delayed RP group versus the immediate RP group; unadjusted, adjusted for parameters that are different between groups at the moment of diagnosis, and adjusted also for parameters that are different between groups at the moment of RP.

	Unadjusted			Adjusted (at diagnosis) *			Adjusted (at RP) **		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Gleason >6	1.32	0.69-2.53	.405	1.54	0.77-3.08	.221	1.47	0.70-3.09	.310
Capsular penetration	1.53	0.60-3.94	.375	2.45	0.87-6.93	.091	2.48	0.80-7.68	.114
Positive margins	1.037	0.51-2.10	.920	1.34	0.63-2.86	.445	1.21	0.54-2.75	.642
	Diff.	95% CI	p	Diff.	95% CI	p	Diff.	95% CI	p
Tumour volume (cc)	0.055	-0.26-0.15	.602	0.099	-0.058-0.36	.155	0.008	-0.210-0.236	.909

OR odds ratio
CI confidence interval
* adjusted for volume, mm pc, and T stage
** adjusted for volume, mm pc, T stage, age at RP, and PSA at RP
RP radical prostatectomy
Logistic regression was used for categorized variables, linear regression was used for continuous variables.

in the immediate RP group, patients in the delayed RP group had a significantly higher prostate volume and resulting lower PSA-density, less positive biopsies, less mm PC tissue, a higher frequency of nonpalpable (T1c) tumours, a higher age and PSA at the moment of RP, a longer time between diagnosis and RP, and a shorter total follow-up time since surgery. Besides PSA values, specific reasons for switching to RP during expectant management were unavailable for analyses; 65.2% of men in the delayed RP group had a relatively quickly rising PSA with a PSA-DT of 0-10 years, while 34.8% was operated while having a favourably slowly rising or falling PSA. Of all patients suitable for PRIAS who (eventually) received RP, 69% received a lymph node dissection, of which 2% was positive.

No significant differences were found in the frequency of RP outcome variables Gleason score >6, capsular penetration, positive margins, or in tumour size. No RP Gleason sum scores higher than 7 were observed.

Table 2 presents the odds ratios for RP Gleason score >6, capsular penetration, and positive margins, and the differences in RP tumour volume, as well as confidence intervals and p values, for the immediate RP versus the delayed RP group. Unadjusted univariate models, adjusted models incorporating the parameters at the moment of diagnosis, and adjusted models also incorporating the parameters at the moment of RP are presented. Adjusted ORs for both multivariable models for Gleason score >6 were 1.54 and 1.47, for capsular penetration 2.45 and 2.48, and for positive margins 1.34 and 1.21; difference in RP tumour volume .099 and .008 cc. No significant association of study group (immediate RP versus delayed RP) was found with any of the outcome variables in the unadjusted univariate or in any of the two adjusted multivariable models.

Neither in the immediate RP group nor in the delayed RP group did the time between diagnosis and RP show a univariate significant association with any of the outcome

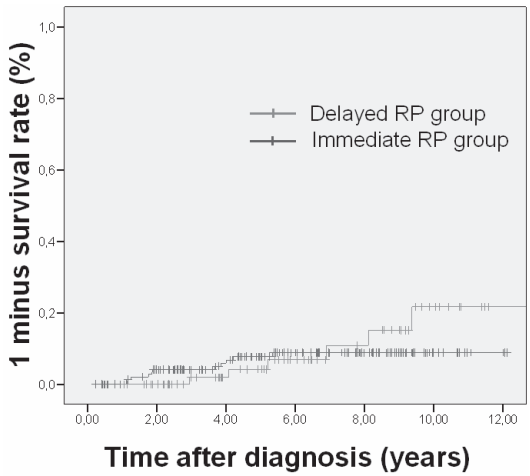

Figure 1A: Kaplan-Meier curves for biochemical progression after RP since moment of diagnosis in the immediate RP group and in the delayed RP group (Log Rank 0.689).

Years FU	0	2	4	6	8	10
Immediate RP (11 cases were not used in this analysis due to short-follow-up)						
Cumulative number events	0	6	8	11	11	11
Number at risk	147	135	104	72	47	12
BC progression (%)	0	4	6	9	9	9
Delayed RP (16 cases were not used in this analysis due to short-follow-up)						
Cumulative number events	0	0	1	3	4	6
Number at risk	53	53	43	30	21	9
BC progression (%)	0	0	2	7	11	22

RP radical prostatectomy
FU follow-up
BC biochemical

variables. The PSA-DT between diagnosis and RP neither was associated with the any of the outcome variables, neither when stratified in groups (0-3, 3-10 >10 year, or negative) nor as a continuous variable (with negative values set at 50 years or at 100 years). These findings did not change when only men with 3 or more pre-treatment PSA values available were analysed. When comparing men in the delayed RP group with a short PSA-DT (0-10 years) at the moment of RP with those with a favourable PSA-DT (>10 years or negative), no differences in outcomes were found.

Figure 1 presents the Kaplan-Meier curves for BCP after RP in the immediate RP group versus the delayed RP group with the moment of diagnosis as t=0 (Figure 1A) and the moment of RP as t=0 (Figure 1B). In neither figures a significant difference was seen between the BCP curves (10-year biochemical progression 9% vs. 22% and 9% vs. 35%, Log-Rank p .185 and .689, Breslow P .630 and .573, respectively). In Cox regression analysis study group (immediate RP versus delayed RP) was not a significant predictor of biochemical progression, neither when entering parameters at diagnosis in the

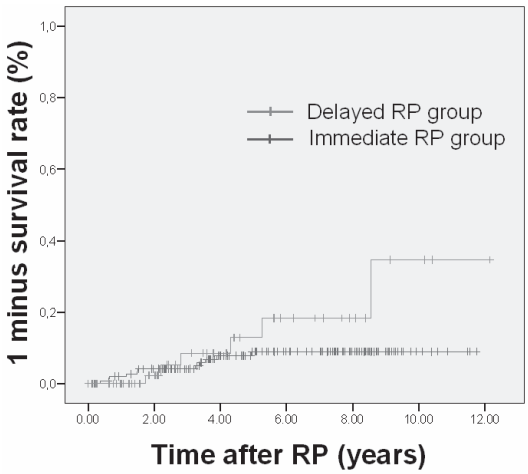

Figure 1B: Kaplan-Meier curves for biochemical progression after RP since moment of RP in the immediate RP group and in the delayed RP group (Log Rank 0.185).

Years FU	0	2	4	6	8	10
Immediate RP (11 cases were not used in this analysis due to short-follow-up)						
Cumulative number events	0	6	8	11	11	11
Number at risk	147	135	104	72	47	12
BC progression (%)	0	4	6	9	9	9
Delayed RP (26 cases were not used in this analysis due to short follow-up)						
Cumulative number events	0	1	3	5	5	6
Number at risk	43	38	23	12	7	3
BC progression (%)	0	2	9	18	18	35

RP radical prostatectomy
FU follow-up
BC biochemical

model (p .138; correcting for volume, mm pc, and T stage) nor when adding parameters at moment of RP to the model (p value 0.087; correcting for age at RP, PSA at RP, volume, mm pc, and T stage). When assessing the immediate RP group and the delayed RP group in separate Cox regression analyses, time between diagnosis and RP was not significantly predictive of biochemical progression after RP in either model.

The above results did not change when we defined our immediate RP and delayed RP group on the basis of a shorter or longer than 0.5 years delay between diagnosis and RP, instead of the treatment choice as retrieved from the patient charts.

DISCUSSION

In the limited setting of this study, no significant differences were found in adverse intermediate outcomes after RP between men who received immediate RP and those

who received RP after an initial period of expectant management, for small, well-differentiated, localized PC. Time between diagnosis and RP was not correlated with any of the outcome parameters.

However, with larger patient numbers and longer follow-up the results of our analysis might have shown significant results. All data seem in favour of the immediate RP group. The most striking number is the almost 2.5 times higher odds for capsular penetration after RP in the delayed RP group (Table 2). Still, it should be noted that the ideal study design would include comparisons between the outcomes of the immediate RP group and the outcomes of the delayed RP group *plus* men who start on expectant management and *stay* on expectant management at the time of analysis. Patients in this virtual third study group did however not receive RP and can therefore not be included in our analysis. While in the immediate RP group all men receive direct surgery, men in the delayed RP group may have switched to RP because of an unfavourable follow-up, which may be associated with unfavourable outcomes. Specific reasons for the switch are unknown, but 65.2% had a quickly rising PSA (other reasons probably include patient and physician's desire, anxiety, changes in clinical stage, and or repeat prostate biopsies). It could then be hypothesized that those men with a favourable follow-up, who remain out of consideration in the current study, also have favourable outcomes and that if all would receive RP and the results would be added to the delayed RP group, this would have a 'diluting' effect on the frequency of unfavourable findings in the delayed RP group. A study design in which the immediate RP and the delayed RP groups are randomized and in which the delayed RP group comprises all men who started on expectant management and all received RP after a fixed time interval is difficult to realize.

To illustrate the proportion of men diagnosed with low risk PC who switch to active therapy (RP, radiation therapy, hormones) during follow-up after initially starting on an expectant management, Figure 2 presents the treatment-free survival Kaplan-Meier curve of 200 Swedish men diagnosed with low risk (similar criteria as used in this study) PC in the ERSPC, who all initially elected an expectant management for their disease. Although this is a different group of men than the group that is the main focus of the current study, the proportion of these 200 men who switched to RP during follow-up comprise the current delay group of 69 men. The 10-year treatment-free survival was 40.4%; after 2.6 years (which is the mean follow-up of the 'delayed RP' group in the current study) this was 67.9%. This means that for every man who switched to active therapy, 2.1 men remain on expectant management (32.1% versus 67.9%).

Besides biological tumour progression during expectant management, the potential selection bias as described here above may also partly cause differences in unfavourable outcomes between the two groups. Our study does not allow for distinguishing in causality between these two hypotheses.

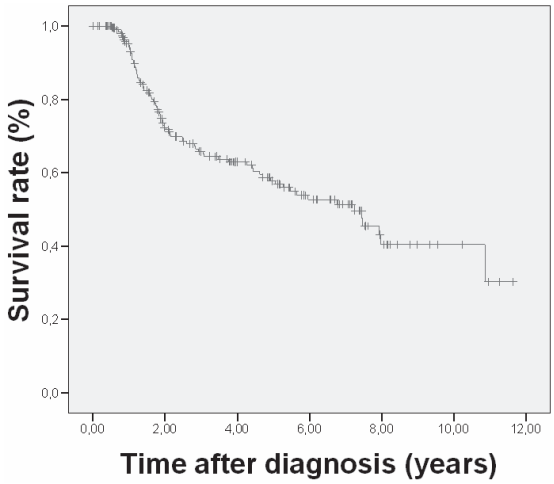

Figure 2: Treatment-free survival Kaplan-Meier curve of 200 men diagnosed with small, localized, well-differentiated PC in the Swedish section of the ERSPC, who initially chose expectant management. An event was defined as the switch from expectant management to radical treatment; cases were censored at the time of death or last known-follow-up when no event had occurred before. Although this is a different group of men than the group that is the main focus of the current study, the proportion of these 200 men who switched to RP during follow-up comprise the current delay group of 69. After a delay of 2.6 years (similar to the mean of the delayed RP group in our study) almost 2.1 times more men remain untreated than actively treated (32.1% versus 67.9%).

In the delayed RP group, side effects of therapy were avoided over a mean period of 2.6 years. In this period, the psychological burden of the disease may have been elevated. The potential favourable effect of expectant management on quality of life due to the avoidance of side effects such as impotence or incontinence must be weighed against the potential difference in outcomes and burden of living with 'untreated' cancer. Anxiety and distress levels of men participating in a prospective active surveillance program have been reported to be favourable[87]. However, besides possible worse pathological and biochemical outcomes, delaying radical treatment may also decrease the chance of quality of life sparing therapies, such as nerve-sparing RP.

The lack of an association between PSA kinetics (doubling time) before RP and outcome variables makes the use of this parameter during AS doubtful. This finding may be counterintuitive, but is in line with the conclusions of a review by Vickers et al. who did not find a predictive value of PSA kinetics beyond PSA alone in untreated patients[88]. Fall et al. also found that, although being prognostic factors, PSA value and rate of PSA change both are poor predictors of lethal prostate cancer among untreated patients with localized PC. Still, PSA-DT may prove to hold value in monitoring disease status in men on AS[89].

Due to the findings presented above and the knowledge of the mean leadtime of more than 10 years in these low risk prostate tumours[54], we believe that the harmful effect of initially delaying radical treatment as may be caused by AS protocols is small, which is in line with the conclusion of other reports[90,91]. Furthermore, since the length of delay between diagnosis and RP is not a predictor of adverse outcomes, the treatment of low risk screen-detected PC is unlikely to be a matter of emergency. The effect of delay on hard endpoints however is for now unknown, although the favourable effect of radical treatment on hard endpoints such as 10-year PC specific survival is only 5% in clinically-detected PC[28]. Importantly, patients and physicians who choose AS should be aware that when tumours with an unfavourable follow-up are selected for radical treatment, patients may comprise a selected group, with outcomes that may be different when compared to men who are operated immediately after diagnosis.

When compared to the available literature, Warlick et al. performed a similar analysis, although in a smaller patient cohort[91]. The outcomes of 38 men who had been included in a prospective expectant management protocol with T1c, PSA-density <0.15 (still, 11 out of 38 had a PSA-density ≥0.15), ≤2 positive cores, no Gleason pattern 4 or 5, <50% of any core involved with cancer - PC after delayed surgical intervention (median delay 26.5 months) were compared to 150 matched patients who received immediate surgical intervention (median delay 3.0 months). Outcome was defined as a <75% nomogram-derived chance of biochemical recurrence-free 10-year post-RP survival. The nomogram incorporated RP Gleason score, PSA, and RP organ-confinement status. A significant difference (23% of patients scored <75% in the delayed group versus 16% in the matched group) was not found.

Khatami et al. performed an exploratory case-control analysis of 28 Swedish men in an AS setting, also included in the current delayed RP group[92]. Initial surveillance with radical treatment at the moment of progression did not seem to compromise curability. Patel et al. also concluded that radical treatment at the time of progression after initial expectant management is effective[93].

Freedland et al. studied the association of time between diagnosis and surgery between 1988 and 2004 at a population level within the SEARCH database in 895 men with a PSA less than 10 ng/ml diagnosed with prostate cancer with a Gleason score of 6 or less, dividing the interval between diagnosis and surgery to 90 days or less, 91-180 days, or greater than 180 days[90]. It was not reported whether this cohort concerns screen-detected or clinically-detected patients or whether the delay was 'intended', as in an AS like strategy. No significant differences were found in high-grade disease, positive surgical margins, or extraprostatic extension. Men with more than 180 days delay however did show an increased risk of BCP (p .002).

In a similar retrospective population-setting, Nam et al. found a possible relationship between a delay of >3 months and adverse outcomes of 645 RPs performed between 1987 and 1997[94]. Finally, Khan et al. found no impact on cancer control after a delay of >60 days of 926 RPs performed between 1989 and 1994[95].

Weaknesses of our study include the lack of using a standardized follow-up protocol during expectant management, such as used in current prospective AS studies[66,74], resulting in a situation in which specific reasons for men to switch to radical treatment were unknown. Second, the mean follow-up time was only 5.7 years and intermediate outcome variables instead of hard endpoints such as PC specific mortality could only be assessed. However, this endpoint may well never be reached in men with such a favourable form of PC[85]. Finally, as stated above, this study design is surrogate for a randomized study in which RP would be performed after a fixed time interval in one group. A strength of our study is that it concerns a contemporary and representative cohort of patients within the controlled and standardized study environment of the ERSPC.

In the future, besides studying longer follow-up of retrospective data, it is essential to study the findings at and after RP of men who participate in current ongoing prospective active surveillance protocols that aim to filter out early (e.g. not longer than 1 year delay) during follow-up the men that need active therapy, to assess the safety of these protocols[66,74].

CONCLUSIONS

In men with small, localized, well-differentiated screen-detected PC, a statistically significant difference in the frequency of unfavourable histopathological and biochemical outcomes after RP was not found between men who received immediate surgery and men who received surgery after an initial period of expectant management after diagnosis. The time interval between diagnosis and RP was not significantly predictive for any adverse outcomes within these two groups. The harmful effect of treatment-delay in PC patients eligible for AS is therefore most likely to be limited. Still, patients and physicians who choose expectant management as the initial treatment strategy should understand that if RP is indicated later based on follow-up, a selection bias may cause a higher frequency of unfavourable outcomes. At this moment, AS is most appropriate for men older than 65 years at diagnosis; in younger men it should be recommended only to selected cases, as the long time risk is unknown. Results of prospective AS studies should be awaited.

Chapter 3

Rule-based versus probabilistic selection for active surveillance for prostate cancer and outcomes after radical prostatectomy

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ABSTRACT

Introduction

The currently applied inclusion criteria for active surveillance (AS) for prostate cancer (PC) may select men with significantly histopathological disease at RP. We explored the effect of further tightening rule-based criteria for AS and the alternative of using probabilistic selection using a nomogram on the frequency of indolent PC at radical prostatectomy (RP).

Patients and methods

Swedish and Dutch patients participating in the European Randomized Study of Screening for Prostate Cancer (ERSPC) who were diagnosed with PC and received RP were studied. The frequency of indolent disease at RP (<0.5 ml, confined, no Gleason pattern 4 or 5) and biochemical progression during follow-up was assessed. The performance regarding these outcomes was assessed of rule-based selection criteria for AS, with additional strict thresholds, and of nomogram application, with increasing risk thresholds.

Results

Our study cohort consisted of 1011 men, with a median follow-up of 7.1 years after diagnosis. A total of 26% had indolent PC at RP. Criteria for suitability for AS and for the nomogram increased this number to 40-48%, with 40-50% of men remaining suitable. Stricter rule-based criteria and higher thresholds of the risk of indolent disease resulted in a higher frequency of indolent disease that was included (up to 61-67%), but at the cost of a decrease in the number of men suitable for AS (down to 2-17%). These refinements in selection did not have a significant effect on biochemical progression rates.

Conclusions

Even when applying the most stringent criteria using rule-based or probabilistic selection for AS, men with histopathologically significant PC are included. The adverse effects on morbidity and mortality of an initial misclassification within an AS protocol may be limited.

INTRODUCTION

The incidence of low risk prostate cancer (PC) has been rising[58]. Despite the favourable natural history of most of these tumours, the majority is treated with surgery or radiation therapy[13,58,85]. Although radical treatment of localized PC has a significantly favourable effect on mortality rates when compared to watchful waiting, all available active therapies bring an immediate risk of side effects[27,31,58].

Active surveillance (AS) has emerged as a potentially feasible strategy to decrease the overtreatment of low risk PC[59]. AS consists of selecting men with a supposedly indolent prostate tumour, initially withholding radical therapy, and strictly monitoring the disease instead. The option remains to switch to active therapy with curative intent at the moment progression occurs. Retrospective analyses show very favourable 10-year mortality outcomes in expectantly managed tumours that are considered suitable for AS[85].

The frequency of indolent cancer at radical prostatectomy (RP) and outcomes during follow-up after surgery observed in men who receive direct RP but who are also considered to be suitable for AS may be surrogate endpoints to assess the performance of the inclusion criteria of different prospective AS protocols[66,74,80,93,96-101]. Although all these protocols apply combinations of rule-based criteria for patient selection (e.g. prostate specific antigen (PSA) ≤10.0 ng/ml, ≤2 positive biopsies, etc.), probabilistic selection using a nomogram that incorporates the parameters into a calculation model may be preferable. The PRIAS study (Prostate cancer Research International: Active Surveillance) is one of the ongoing AS studies, applying intermediately wide rule-based inclusion criteria[74]. PRIAS originates from the ERSPC (European Randomized Study of Screening for Prostate Cancer)[16,102].

We studied the frequency of indolent cancer and biochemical progression after RP in men with screen-detected PC who received RP. We then assessed the effect on these frequencies of using more stringent rule-based criteria and we explored the effect of using probabilistic selection with a nomogram.

PATIENTS AND METHODS

Patients

Men included in this study participated in the screening arm of the ERSPC[16]. All provided written informed consent. For this study, the data cohorts of the ERSPC centres in Gothenburg (Sweden) and Rotterdam (The Netherlands) were combined. All men were diagnosed with PC and received RP as the primary treatment.

In Sweden men were screened with an interval of 2 years, in The Netherlands with an interval of 4 years. All men with a PSA ≥4.0 ng/ml and later ≥3.0 ng/ml were candidates for digital rectal examination (DRE), transrectal ultrasound (TRUS), and lateralized sextant prostate biopsies. An additional biopsy core was performed in case a hypoechoic lesion was seen during TRUS. Prostatic volume was measured by planimetric calculation from the TRUS recorded measurement of the prostate using the ellipsoid formula in Sweden and by planimetric calculation in The Netherlands. Further details of the ERSPC screening protocols in both countries have been published previously[21,86].

After a PC diagnosis, patients were referred back to regular healthcare were decisions on treatment were made and treatments were performed. In Sweden, these treatments were mainly performed in the ERSPC study centre itself (Sahlgrenska University Hospital, Gothenburg). Depending on hospital and treating physician, patients underwent open, laparoscopic, or robot-assisted laparoscopic RP.

Men with positive lymph nodes or distant metastases at the time of diagnosis or at the time of surgery were excluded for this analysis.

Methods

First we assessed the frequency of indolent PC at RP in our study cohort. Indolent PC was defined as a tumour volume less than 0.5 cc, AND confined to the prostate, AND with no Gleason pattern 4 or 5[62,103]. Significant PC was defined as a tumour volume larger than 0.5 cc, OR a non-confined tumour, OR presence of a Gleason pattern 4 or 5.

Second, we selected men from our study cohort with low risk PC and who therefore also would have been eligible for AS and studied the frequency of indolent cancer in this group. A low risk tumour was defined according to the rule-based criteria as used in the PRIAS study: clinical stage T1c/T2, AND a PSA ≤10.0 ng/ml, AND a PSA-density (PSA divided by prostatic volume) <0.20 ng/ml/cc, AND a Gleason score of 3+3=6 or more favourable (no pattern 4 or 5), AND 1 or 2 positive biopsy cores. We then explored which baseline diagnostic parameters were associated with the presence of (non-)indolent PC at RP within this group of men fitting the PRIAS criteria using logistic regression analysis. Only parameters with a statistically significant association in univariate analysis were used in multivariable models. PSA and volume were not analysed separately, but PSA-density was included. Also, the length of PC and benign tissue in the prostate biopsy were not included, but the percentage of malignant tissue per core was used instead.

Third, we used the parameters that showed a significant association with indolent PC within the PRIAS group to tighten the rule-based thresholds and assessed the effect on the frequency of indolent PC at RP. The chosen thresholds for this analysis were partially derived from the protocols of other AS studies or from reports on predicting insignificant or low-risk PC (PSA-density <0.15[62,104]; and percentage of PC per positive core <50%[62,105]) and partially were based on published literature on the relation of these

thresholds with outcomes after RP (PSA-density <0.10[106]; 1 positive biopsy core[107]). The performance of the different sets of criteria for selecting indolent PC was presented as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the percentage of the total study cohort still remaining suitable for AS.

Fourth, we explored the use of risk indications derived from a previously developed nomogram (by Steyerberg et al.) for indolent PC at RP in screen-detected men to select men who might be suitable for AS[12]. We assessed the effect of the criteria for eligibility for the nomogram (clinical stage T1c/T2a, AND PSA ≤20.0 ng/ml, AND Gleason score ≤3+3=6 (no pattern 4 or 5), AND ≤50% positive cores, AND ≤20 mm PC, AND ≥40 mm benign tissue in all cores) and also of different thresholds in the predicted chance of harbouring indolent PC (P-ind).

Finally, the time to biochemical progression (BCP) after RP was also studied using the Kaplan-Meier method. The criteria proposed by Freedland et al. were used to define BCP, i.e. a PSA value after RP >0.2 ng/ml[75]. Different combinations of rule-based selection criteria and P-ind cut-off points were compared using the Log-Rank test.

P values (2-sided) <0.05 were considered statistically significant. For statistical analysis the commercially available software Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc, Chicago, IL, USA) was used.

RESULTS

Our study cohort consisted of 1011 PC patients (62% Dutch, 38% Swedish) who received RP, with a median follow-up of 7.1 years available after diagnosis. Table 1 presents the study cohort characteristics and outcomes after RP. A total of 248 (26%) tumours at RP could be defined as indolent and 694 (74%) as significant; conclusions on the (in) dolence of the tumour could not be made in 69 men. Nomogram risk indications could be made in 479 (47%) men; the median P-ind was 58% and 40% actually did harbour indolent disease.

In univariate analysis, study centre, PSA-density, number of positive biopsies, and percentage PC per core showed a significant association with harbouring indolent PC within the group of men fitting the PRIAS criteria. Table 2 shows the logistic regression analysis with these variables entered. All remained statistically significantly related to indolent PC at RP. Swedish centre, higher PSA-density, more positive cores, and a higher percentage of PC per positive core were associated with a lower chance of indolent PC.

Table 3 presents the sensitivity, specificity, PPV, and NPV for indolent PC at RP of different sets of rule-based criteria for AS. The following criteria were used to narrow the PRIAS criteria: a PSAD threshold of <0.15 ng/ml/cc and <0.10 ng/ml/cc instead of <0.20 ng/ml/cc, a maximum number of positive biopsy cores of 1 instead of 2, and a maximum

Table 1: Study cohort characteristics and outcomes after radical prostatectomy. (N=1011)

DIAGNOSIS			
ERSPC study center	Netherlands	629	62%
	Sweden	382	38%
Follow-up (years) (median, 25-75p)	7.1	4.2-9.5	
Age (years) (median, 25-75p)	64.2	61.0-67.0	
Clinical disease stage	T1c	583	58%
	T2a	251	25%
	T2b	67	7%
	T2c	51	5%
	T3a	46	4%
	T3b	3	0.5%
	Unknown	4	0.4%
PSA (ng/ml) (median, 25-75p)	4.7	3.5-6.9	
Prostate volume (cc) (median, 25-75p)	34.8	28.4-45.0	
PSA-density (ng/ml/cc) (median, 25-75p)	0.13	0.09-0.20	
Number of positive cores (median, 25-75p)	2	1-3	
Total benign tissue (mm) (median, 25-75p)	65.3	53.9-74.4	
Total PC tissue (mm) (median, 25-75p)	5.5	2.4-11.6	
Percentage cancer per positive core (median, 25-75p)	44%	21-94%	
Gleason sum score	≤6 (no pattern 4)	748	74%
	>6	262	26%
	Unknown	1	
Prediction indolent cancer (median, 25-75p) (N=479 suitable for nomogram)	58%	40-76%	
RADICAL PROSTATECTOMY			
Tumour volume	<0.5 cc	361	39%
	≥0.5 cc	563	61%
	Unknown	87	
Extracapsular extension	No	785	80%
	Yes	203	20%
	Unknown	23	
Gleason sum score	≤6 (no pattern 4)	618	62%
	>6	374	38%
	Unknown	19	
Indolent cancer *	Yes	248	26%
	No	694	74%
	Unknown	69	

ERSPC European Randomized Study of Screening for Prostate Cancer
25-75p 25-75th percentile
PSA prostate specific antigen
PC prostate cancer
* Tumour volume less than 0.5 cc, confined to the prostate with no focal or established extracapsular extension, and with no Gleason grade 4 or 5.

percentage of biopsy core tumour involvement of 50% instead of no threshold. The positive predictive value for indolent PC of the PRIAS criteria was 48%. By tightening the PRIAS criteria a decrease in sensitivity from 73% down to 39%; a decrease in NPV from 88% down to 81%; an increase in specificity from 72% up to 91%; and an increase in

Table 2: Multivariable logistic regression analysis for indolent prostate cancer at radical prostatectomy. Only parameters shown to have a statistically significant association in univariate analyses were included in the model.

	p	Exp(B)
Study centre	<0.001	0.390
PSA-density	<0.001	0.000
Number of positive cores	0.009	0.500
% PC per core	0.010	0.143

PSA prostate specific antigen
PC prostate cancer

Table 3: Sensitivity and specificity of diagnostic PRIAS criteria for selecting indolent prostate cancer at radical prostatectomy and the effect of adding stricter thresholds. (N=937) In 74 men conclusions on the (non-) suitability for the PRIAS criteria could not be made.

	Total included	Total missed	% included	Indolent included	Indolent missed	Sens	Significant included	Significant missed	Spec	PPV	NPV
Total cohort	937	-	100%	246	-	-	691	-	-	-	-
PRIAS suitable	373	564	40%	180	66	73%	193	498	72%	48%	88%
STRICTER THRESHOLDS IN ADDITION TO PRIAS CRITERIA											
PSAD <0.15	298	641	32%	157	89	64%	141	552	80%	53%	86%
PSAD <0.10	156	783	17%	95	151	39%	61	632	91%	61%	81%
Only 1 positive core	227	713	24%	131	115	53%	96	598	86%	58%	84%
<50% PC per positive core	284	629	31%	151	82	65%	133	547	73%	53%	87%

Sens sensitivity
Spec specificity
PPV positive predictive value
NPV negative predictive value
PSAD prostate specific antigen density
PC prostate cancer

PPV from 48% up to 61% could be achieved. However, the percentage of men included fell from 40% down to 17%. Table 4 presents the performance of different thresholds of P-ind. The positive predictive value for indolent PC of suitability for nomogram calculations was 40%. By using higher P-ind thresholds a decrease in sensitivity from 77% down to 4%; a decrease in NPV from 88% down to 75%; an increase in specificity from 60% up to 99%; and an increase in PPV from 40% up to 67% could be achieved. However, the percentage of men included fell from 50% down to 2%. The performance of the PRIAS criteria was similar to the P-ind thresholds between 30 and 40%, also regarding the percentage of men eligible for AS.

Table 4: The effect of applying different thresholds of the nomogram risk of harbouring indolent PC on the numbers of indolent and significant PC included and missed. (N=892) In 119 men conclusions on the (non-) suitability for nomogram calculations could not be made.

	Total included	Total missed	% included	Indolent included	Indolent missed	Sens	Significant included	Significant missed	Spec	PPV	NPV
Total cohort	892	-	100%	231	-	-	661	-	-	-	-
Suitable for nomogram *	443	449	50%	178	53	77%	265	396	60%	40%	88%
Pind >10%	434	452	49%	173	54	76%	261	398	60%	40%	88%
Pind >20%	413	473	46%	171	56	75%	242	417	63%	41%	88%
Pind >30%	375	511	42%	168	59	74%	207	452	69%	45%	88%
Pind >40%	323	563	36%	157	70	69%	166	493	75%	49%	88%
Pind >50%	267	619	30%	137	90	60%	130	529	80%	51%	85%
Pind >60%	207	679	23%	112	115	49%	95	564	86%	54%	83%
Pind >70%	144	742	16%	84	143	37%	60	599	91%	58%	81%
Pind >80%	78	808	9%	49	178	22%	29	630	96%	63%	78%
Pind >90%	15	871	2%	10	217	4%	5	654	99%	67%	75%

Sens sensitivity
Spec specificity
PPV positive predictive value
NPV negative predictive value
Pind nomogram prediction for indolent cancer

Figure 1A presents the time to BCP curves stratified for men with PC not suitable for PRIAS, men suitable for PRIAS, and men suitable for PRIAS with all extra-added more stringent criteria. The last two groups were not statistically different (p 0.935), but both were significantly different from the first curve (p <0.001 and p 0.002). Figure 1B presents the time to BCP curves stratified for men with PC that was not suitable for nomogram calculation and in men with a nomogram P-ind of 0-30%, 30-70%, and 70-100%. All three P-ind curves were not statistically significantly different (p between 0.212 and 0.894), but all three were significantly different from the first curve of men not suitable for the nomogram (p <0.05).

DISCUSSION

In a group of Dutch and Swedish patients with screen-detected PC based on sextant biopsy who all received initial RP, indolent PC was seen in 26%. When applying criteria for eligibility for AS or criteria for nomogram suitability, this number increased to 40-48%. Both more stringent rule-based inclusion criteria for AS as well as stricter nomogram probability thresholds further decrease the rate of misclassified tumours in

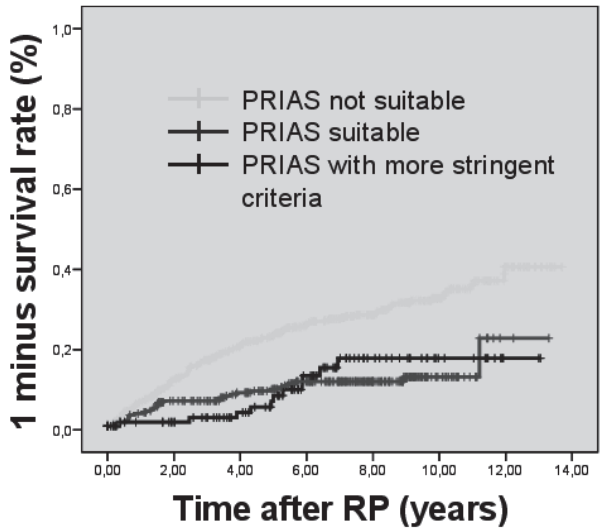

Figure 1A: Time to biochemical progression (>0.2 ng/ml) after radical prostatectomy in men with PC not suitable for PRIAS, suitable for PRIAS, and suitable for PRIAS with more stringent criteria.

PRIAS prostate cancer research international active surveillance
RP radical prostatectomy

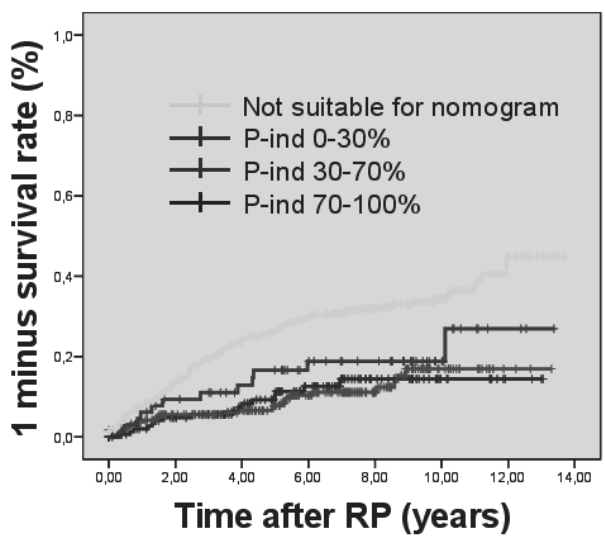

Figure 1B: Time to biochemical progression (>0.2 ng/ml) after radical prostatectomy in men with prostate cancer not suitable for nomogram calculation and in men with a nomogram P-ind of 0-30%, 30-70%, and 70-100%.

P-ind nomogram prediction of harbouring indolent prostate cancer
RP radical prostatectomy

an equal fashion, but at the cost of a similarly substantial number of patients no longer considered suitable for this strategy. Both approaches to further refine the criteria did not lead to a significant decrease in BCP rates after RP.

A PC that is suitable for AS comprises a tumour that is indolent, i.e. that will not cause morbidity or mortality when left untreated. AS protocols aim to include only these tumours, but also have the option to identify and radically treat tumours that appear to be misclassified later during follow-up. An indolent PC according to the criteria of Epstein et al.[62] is a tumour with a volume <0.5 cc, that is confined to the prostate, and has no Gleason pattern 4 or 5. The effect of different sets of inclusion criteria for AS on the outcomes after RP have been extensively studied in large RP series[99-101]. How the addition of different specific extra inclusion parameters or the use of a nomogram might be used to improve the selection of men for AS was never studied.

Although no large differences in the performance between rule-based selection and probabilistic selection were found in this study, using a nomogram may be the best-evidence method and is preferable. However, as mentioned by Vickers et al., in the clinical implementation of a prediction model the benefits should be weighed against the preferred choice of patients who opt for direct treatment, despite an only small benefit.

Even when applying the strictest rule-based criteria or the highest nomogram risks of harbouring indolent disease, some included tumours appear to be significant. Perfect patient selection for AS using the currently available parameters seems therefore impossible. Although concerns on the feasibility of AS have been expressed regarding the issue of misclassification, some remarks should be made in this. Including a man with histopathologically significant disease for AS is unwanted. However, direct surgery instead of AS would not have saved these men from adverse characteristics, as surgery already was the initial treatment. Also, the strict AS follow-up protocols including standard repeat biopsies would most likely identify the unfavourable within the window of curability. The delay of treatment this strategy may cause was previously found not to be related with a higher frequency of adverse outcomes[91,108]. Also, a significant PC may still show a non-significant disease course due to comorbidity and age of the patient. Unfavourable outcomes after RP or the presence of indolent disease also are not always associated with an unfavourable disease specific outcome[110]. Finally, very favourable disease specific outcomes have been observed in similar men, even when an initial expectant management was chosen[85]. Our inability to perfectly stratify at the moment of diagnosis men between those who need radical therapy and those in whom active surveillance is indicated does not justify an 'all or nothing' approach in which all detected PC receives radical therapy.

Different other studies have retrospectively applied criteria for AS on findings after RP[99-101]. However, the combined criteria for indolent PC were not always used[62,103]. In these studies Gleason upgrading was seen in 19-35% (most stringent criteria 16-28%), extracapsular extension in 5-14% (most stringent criteria 0-7%), and seminal vesicle invasion is seen in 1-3% (most stringent criteria 0-2%). Within the PRIAS suitable men in the current study, these numbers were 20%, 7%, and 1%. Reasons for the observed variations may include differences in inclusion criteria, method of detection (screening or clinical), number of biopsy cores performed, pathological processing and review. These differences might have an effect on later endpoints such as morbidity and mortality, but these should be studied in future analyses. Most importantly, the percentages presented above add to the findings of the current study that the frequency of unfavourable outcomes after RP is generally low, and that even the most stringent criteria for AS are unable to entirely rule out the chance of harbouring PC with unfavourable characteristics at RP.

A limitation of this study is that our cohort has been based on sextant biopsy only, which today is not the standard of clinical practice. Furthermore, the follow-up time of our study cohort is too short to assess mortality outcomes and relate these to baseline selection criteria. Also, our patients were operated in different centres and countries, by different surgeons, using different techniques for RP. Finally, a number (N=247) of cases used for this analysis were also included in the validation and construction of the nomogram that we used, which may lead to an overestimated performance of the nomogram P-ind. A strength of this study is that all participants were diagnosed with PC within the ERSPC, resulting in standardized pathological review and follow-up assessment.

Although mortality outcomes are not yet available for analysis, based on the current findings, we do not feel it is indicated to narrow the inclusion criteria we are using in the PRIAS study. Patients deciding on AS should however be informed on the fact that there is a considerable chance of harbouring unfavourable PC when RP would be done, despite the favourable disease characteristics at diagnosis. A balance should be found between the number of men suitable for AS, the rate of undersampling, and the intensity of the diagnostic evaluation of a patient. Taking more biopsy cores for example results in lower rates of tumour upstaging[111], but may also result in more overdiagnosed cases. Also the incorporation of a standard repeat biopsy has been mentioned[112]. New imaging techniques such as magnetic resonance imaging (MRI) and novel biomarkers may also lead to improvement in the staging of PCs to discriminate between tumours suitable for AS and tumours which should undergo radical therapy[113,114].

CONCLUSIONS

Probabilistic selection using a nomogram may be an alternative to the currently applied combination of rule-based criteria to select men for AS. However, even when applying the most stringent criteria using both methods a substantial number may still have histopathologically significant PC, while this considerably decreases the number of men who are considered suitable for AS. The adverse effects on morbidity and mortality of an initial misclassification of a tumour within an AS protocol may be limited.

Chapter 4

Gleason score 7 screen-detected prostate cancers initially managed expectantly: Outcomes in 50 men

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ABSTRACT

Objective

Active surveillance (AS) instead of radical treatment may be an appropriate initial strategy in selected men who are presently diagnosed with prostate cancer (PC), as many tumours will not progress during a patient his lifetime. Are men newly diagnosed with Gleason 7 PC also eligible for this strategy?

Patients and methods

PC specific-, overall-, and treatment-free survival were retrospectively analysed in men with Gleason score 7 PC, who were initially managed expectantly. All were screen-detected in four centres of the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Results

In a total of 50 men active therapy was initially withheld in presence of Gleason 7 disease; 29 of 50 (58%) would otherwise have been suitable for AS (PSA ≤10.0 ng/ml, PSA-density <0.2 ng/ml/ml, stage T1C/T2, ≤2 positive biopsy cores); 44 of 50 (88%) had a Gleason score 3+4=7. The mean age was 69.5 years (range 59.6-76.2); median follow-up was 2.6 years (25-75p 0.8-5.0); mean ASA-score was 1.8. The 6-year PC specific survival (9 patients at risk) was 100%, which sharply contrasted with 68% overall survival. Men alive at the time of study analysis showed a favourable PSA and PSA-doubling time. The 6-year treatment-free survival was only 59%, with most patients switching to active therapy justified on basis of their PSA. However, men with otherwise favourable tumour characteristics and Gleason score 3+4=7 remained treatment-free significantly longer than their counterparts with unfavourable other tumour features and Gleason score 4+3=7.

Conclusion

In select patients with screen-detected Gleason 3+4=7 PC, AS may be an option, especially in those with comorbidity and/or a short life expectancy.

INTRODUCTION

Active surveillance (AS) is an emerging treatment strategy for men with small, localized, well-differentiated prostate cancer (PC), aiming to avoid the radical treatment with the risk of side effects of non-harmful tumours[59]. AS consists of monitoring the disease and only switching to curative active therapy when progression is observed. Criteria for eligibility and follow-up are prospectively studied in ongoing studies[66,74,80].

Patients with PC are eligible for expectant management when they harbour disease that has the potential to remain sub-clinical during their remaining lifetime. Research now focuses on the identification of prostate tumours that have a long indolent natural history, in order to select men for AS even when diagnosed with PC at a relatively young age[114]. It is also useful to explore the feasibility of an expectant management in patients at the other end of the spectrum, i.e. with fewer remaining life years due to higher age and/or comorbidity. Here, AS with curative intent and palliative watchful waiting (WW) merge.

Regarding the Gleason score of a prostate tumour, a score of 3+3=6 or more favourable is generally considered to be suitable for AS[74,115,116]. However, some AS protocols also include selected men with a Gleason score of 7[66,80].

In this article, we present the outcomes of 50 men with screen-detected PC with Gleason score 7 who initially were managed expectantly. Using this limited material, we aim to explore the feasibility of AS in a group of PC patients that is considered to be on the borderline of eligibility for this strategy.

PATIENTS AND METHODS

Men included in this study all participated in the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC). They all had been diagnosed with PC, and initially elected an expectant management strategy. The data sets of 4 different centres in 3 countries were combined, i.e. Rotterdam in The Netherlands, Gothenburg in Sweden, and Helsinki and Tampere in Finland.

The ERSPC screening protocol (applied to men aged 50-75) consists of PSA measurements (threshold 3.0 or 4.0 ng/ml), and/or transrectal ultrasound (TRUS), and/or digital rectal examination (DRE), at 2- or 4-year intervals. Variations per centre and during the development of ERSPC occurred and were agreed upon. Abnormal findings lead to sextant prostate biopsies; the Finnish centres later changed to 10 or 12 biopsy cores[72]. Prostatic volume is measured by planimetric calculation or prostate ellipsoid formula during TRUS. After a PC-diagnosis men are referred to regular healthcare (which may also be the ERSPC centre) where decisions on treatment are made[73].

First, a selection was made of men on expectant management who had been diagnosed with a Gleason 7 tumour, both 3+4=7 and 4+3=7, independent of other tumour characteristics. Second, this group was divided into men who besides the Gleason score were suitable for AS (PSA ≤10.0 ng/ml, PSA-density <0.2 ng/ml/ml, stage T1C/T2, ≤2 positive biopsy cores) and men who were not. These thresholds are used in the prospective PRIAS-study on AS originating from the ERSPC and are largely similar to the inclusion criteria used in the first protocol-based prospective study of AS in Canada[66,74]. Men with known positive lymph nodes or distant metastases at the time of diagnosis were also excluded. A division between primary Gleason pattern 3 and 4 was also made.

PC specific survival (time to death of PC, censoring time to death due to other causes or time to last follow-up in men still alive), overall survival (time to death of all causes, censoring time to last follow-up in men still alive), and treatment-free survival (time to deferred active treatment, censoring time to death or last follow-up in untreated men still alive), were analysed using the Kaplan-Meier (KM) analysis and plots. Furthermore, we assessed the PSA and PSA doubling time (PSA-DT) of men in our study cohort who were alive at the moment of these analyses in order to get information on their current disease status. Next to this we compared PSA-characteristics between men shifting to active therapy during follow-up and those remaining untreated in order to get insight into the justification of their switch-over to active therapy based on PSA level and PSA-DT.

Deferred active therapy was divided into 3 groups: radical prostatectomy (RP), radiotherapy (RT), and hormonal therapy (HT). In the RP- and RT-group, no difference was made between administering adjuvant HT or not.

For risk-stratification of patients based on their PSA-characteristics, the arbitrary thresholds for PSA of 10.0 ng/ml and for PSA-DT of 3 years were chosen, the first being a cut-off value for inclusion and the second a trigger parameter to switch to deferred radical treatment in current AS-programs[66,74]. PSA-values before and after treatment were separately assessed.

To calculate PSA-DT, the base 2 logarithm of the PSA value was plotted against time since diagnosis. The DT can be calculated as the reciprocal value of the slope of the regression line through these points.

Follow-up data were collected from patient charts; mortality information was retrieved by linkage with the national registries. In The Netherlands, an independent committee performed the review of all deceased PC-patients. The committee individually reviews the anonymized patient charts. In Sweden causes of death are based on death certificates, and in Finland both methods are applied, at least to selected parts of the population[77].

For statistical analysis the commercially available software Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc, Chicago, IL, USA) was used.

RESULTS

In total 50 men with Gleason 7 disease chose an expectant management. Patient characteristics are presented in Table 1. Mean age was 69.5 (range 59.6-76.2); mean PSA at diagnosis was 5.7 ng/ml (range 2.5-15.9). Based on other tumour characteristics besides the Gleason score, 21 men would have been suitable for AS, 29 also had other unfavourable characteristics. Mean ASA (American Society of Anaesthesiologists) comorbidity score, information which was available in 54% of our cohort, was 1.8 (3 was the highest score observed in our cohort (N=4).

Figure 1 shows the PC specific and overall survival Kaplan-Meier-curves. The mean follow-up was 3.4 years (range 0.0-11.6); median 2.6 (25-75p 0.8-5.0). No patient in our cohort died due to PC during follow-up; the calculated 6-year PC specific survival was

Table 1: Study group characteristics at diagnosis and during follow-up

Number	50	
AT DIAGNOSIS		
Mean age (yr) (range)	69.5	(59.6-76.2)
Mean PSA (ng/ml) (range) *	5.7	(2.5-15.9)
Mean prostate volume (ml) (range)	34.8	(15.5-68.0)
Mean PSA-density (ng/ml/ml) (range) *	0.18	(0.05-0.54)
T-stage *		
- T1C (%)	40	(80)
- T2 (%)	9	(18)
- T3 (%)	0	-
- Unknown (%)	1	(2)
Gleason score		
- 3+4=7 (%)	44	(88)
- 4+3=7 (%)	6	(12)
Positive cores *		
- 1-2 (%)	32	(64)
- 3-4 (%)	10	(20)
- Unknown (%)	8	(16)
Total number of biopsy cores (range)	6.7	(5-12)
Mean ASA score (range)	1.78	(1-3)
DURING FOLLOW-UP		
Mean follow-up (yr) (range)	3.4	(0.0-11.6)
Mean number of PSAs per patient per year	1.8	(299 total)
Prostate cancer death (%)	0	-
Intercurrent death (%)	7	(14)
Mean time to intercurrent death (yr) (range)	4.3	(0.9-6.9)
Deferred active therapy (%)	15	(30)
Mean time to deferred active therapy (yr) (range)	1.6	(0.5-6.2)
Mean last PSA pre-treatment (ng/ml) (range)	12.0	(5.9-31.8)

PSA prostate specific antigen
ASA American Society of Anaesthesiologists (comorbidity score)
* Eligibility parameter for active surveillance (besides Gleason score)

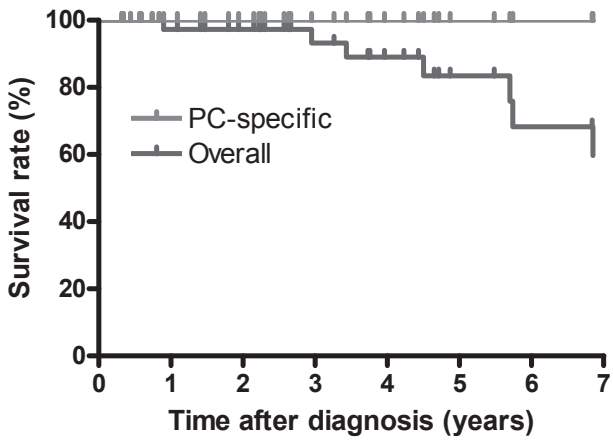

Figure 1: PC specific and overall survival of men with screen-detected Gleason 7 prostate cancer initially managed expectantly (N=44)

Years	0	1	2	3	4	5	6	7
Numbers at risk	44	36	31	23	18	12	9	7
Cumulative PC specific death (% survival)	0 (100)	-	-	-	-	-	-	0 (100)
Cumulative overall death (% survival)	0 (100)	1 (97)	1 (97)	2 (93)	3 (89)	4 (83)	6 (68)	7 (60)

100%. Death due to any cause in this period occurred in 7 patients, after a mean of 4.3 (0.9-6.9) years; the calculated 6-year overall survival was 68%.

Of the total group of 50 men, 43 were still alive at the time of this study analysis. Table 2 shows the last known PSA and PSA-DT of these men. Of these 43, 30 remained untreated during follow-up and 13 had undergone deferred active treatment. Of the living untreated men, 3 (10%) had a PSA of >10.0, 1 (3%) had a PSA-DT <3 years, and no man had a combination of these two. Of the living treated men, 0 (0%) had a PSA of ≥10.0, 2 (15%) had a PSA-DT <3 years, and no man had a combination of these two. PSA-DT was unknown in 10 patients (6 untreated, 4 treated), because only one PSA-measurement was available due to recent diagnosis or treatment.

Table 2 also shows the *pre-treatment* PSA and PSA-DT of all 50 men in our study cohort, divided into those remaining untreated during follow-up (last known PSA) and those switching to deferred treatment (last PSA pre-treatment). Of the 35 untreated men, 3 (9%) had a PSA ≥10.0, 2 (6%) had a PSA-DT <3 years, and no man had a combination of these two. Of the 15 men undergoing RP, RT, or HT, 7 (47%) had a last PSA pre-treatment ≥10.0, 9 (60%) had a last pre-treatment PSA-DT <3 years, and 5 (33%) had a combination of these two.

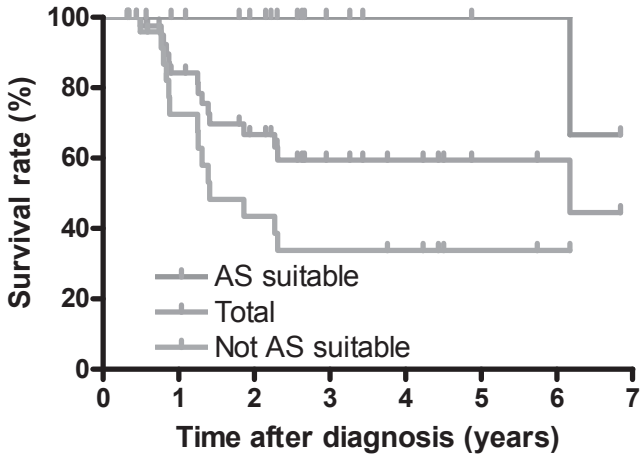

Figure 2: Treatment-free survival for the total cohort (N=44), for the subgroup of men who have favourable tumour characteristics (AS suitable, N=19), and for the subgroup of men who have unfavourable tumour characteristics (Not AS suitable, N=25)

Years	0	1	2	3	4	5	6	7
TOTAL								
Numbers at risk	44	30	21	12	9	5	4	2
Cumulative number treated - Total (% survival)	0 (100)	6 (84)	12 (67)	14 (59)	14 (59)	14 (59)	14 (59)	15 (45)
AS SUITABLE								
Numbers at risk	19	16	13	6	4	3	3	1
Cumulative number treated - AS suitable (% survival)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	1 (67)
NOT AS SUITABLE								
Numbers at risk	25	14	8	6	5	2	1	1
Cumulative number - Not AS suitable (% survival)	0 (100)	6 (71)	12 (41)	14 (31)	14 (31)	14 (31)	14 (31)	14 (31)

AS active surveillance

Figure 2 shows the treatment-free survival KM-projection for the total study cohort (middle curve). Furthermore, the curve is split up into patients who regarding the tumour characteristics next to the Gleason score were suitable for AS (N=21, upper curve) and those with other unfavourable tumour characteristics (N=29, bottom curve). During follow-up, 15 men switched to deferred treatment, after a mean of 1.6 years (range 0.5-6.2); 1 of the otherwise AS suitable, and 14 of the non-AS suitable group. Men otherwise not suitable for AS switched significantly (p 0.0004) earlier to deferred active therapy than with other favourable features (upper curve versus bottom curve). The calculated 6-year deferred treatment-free survival is 59% for the total group, 100% in the AS suitable group, and 34% in the non-AS suitable group. The median treatment-free survival is 1.4 years (25-75p 0.7-3.0). Of 15 men treated during follow-up 3 underwent RP (20%), 8 RT (53%), and 4 HT (27%). Mean PSA pre-treatment was 12.00 (5.90-31.80),

Table 2: The last known PSA and PSA-DT characteristics (I) of the 43 men alive at the time of study analysis (seven of 50 had died); the PSA levels and PSA-DT are those after treatment for the 13 men who received deferred active therapy; and (II), the PSA and PSA-DT characteristics before treatment of the 15 men who had received deferred active therapy during follow-up vs the last known PSA and PSA-DT of the 35 men who remained untreated during the follow-up. Values are n (%) or n (for small totals)

Variable		Total	Untreated	Treated			
				All	RP	RT	HT
I. Men alive at analysis							
Number		43	30 (70)	13 (30)	2	8	3
Last known PSA (ng/ml)	0-2	9	0	9	2	6	1
	2-5	16	16	0	0	0	0
	5-10	13	11	2	0	1	1
	>10	** 3	3	0	0	0	0
	Unknown	2	0	2	0	1	1
Last known PSA-DT * (yr)	0-1	1	0	1	0	1	0
	1-3	2	1	1	0	1	0
	3-10	15	13	2	0	1	1
	>10	3	3	0	0	0	0
	Negative	12	7	5	1	3	1
	Unknown	10	6	4	1	2	1
II. Deferred active therapy vs treatment-free							
Number		50	35 (70)	15 (30)	3	8	4
Last known PSA pre-treatment (ng/ml)	0-2	0	0	0	0	0	0
	2-5	18	18 (100)	0	0	0	0
	5-10	22	14 (64)	8 (36)	2	5	1
	>10	10	3	7	1	3	3
	Unknown	0	0	0	0	0	0
Last known PSA-DT * pre-treatment (yr)	0-1	1	0	1	0	1	0
	1-3	10	2	8	1	4	3
	3-10	16	14	2	1	0	1
	>10	5	3	2	0	2	0
	Negative	11	10	1	0	1	0
	Unknown	7	6	1	1	0	0

Tx treatments
RP radical prostatectomy
RT radiotherapy
HT hormonal therapy
PSA prostate specific antigen
PSA-DT prostate specific antigen doubling time
Neg negative
* Calculated over all known (two or more) PSA values if untreated, over values post-treatment only if treated
** Absolute values 10.1, 23.0, and 23.0.

mean PSA post-treatment was 0.90 (0.10-3.10). Men treated during follow-up did not differ significantly in age from men remaining untreated (p 0.368).

When comparing the treatment-free survival of patients with Gleason score 3+4=7 disease with patients with Gleason score 4+3=7 disease, the second group was treated earlier than the first, although the numbers were too small to test this statistically. After 1, 2, and 3 years the treatment-free survival in the 3+4 group was 88%, 74%, and 66%; it was 67%, 22%, and 22% in the 4+3 group (0% after 7 years).

DISCUSSION

We retrospectively studied PC specific-, overall-, and treatment-free survival in a special group of 50 men with screen-detected Gleason score 7 PC that was initially managed expectantly.

An important finding is the favourable 6-year disease specific survival of 100%, in contrast with an overall survival of 68%. These results look encouraging, but should not be interpreted as a justification for expectant management in all men with Gleason score 7 disease. Longer follow-up and more observations are needed to establish AS a feasible approach in this group, in first instance for men with a limited life expectancy.

In an attempt to predict longer-term outcome of our study cohort, we assessed the last-known PSA and PSA-DT in men living at the time of study analysis. Considering a PSA >10.0, or a PSA-DT <3 years as unfavourable, 6 out of 43 (14%) (4 out of 30 untreated men, 2 out of 13 men after deferred active therapy) men had an unfavourable current disease status. Still, as no man had a combination of a high PSA and a quickly rising PSA, it may be assumed that none of them will die due to PC on short-term.

In a subgroup analysis of the only study which randomized between expectant management and RP for mainly clinically-detected PC[27], Holmberg et al. found that the Gleason score is the best parameter to separate low- and high-risk groups. However, the magnitude of the benefit of RP in terms of disease specific mortality differs only according to age group (young men benefit more from RP than older men; no benefit was seen above 65 years) and not according to the Gleason score[117].

Albertsen et al. studied the natural course of PC; a subgroup of 43 patients had Gleason score 7 disease and were aged 65-69 at diagnosis[13]. When comparing our 50 patients with a mean age of 69.5 years with his study, we found the 6-year PC specific survival to be more favourable (0% versus ~20%) among our patients. This discrepancy may be caused by the potentially favourable effect of the option to switch to surgery or radiation therapy during follow-up (11 out of all 15 treated patients), instead of androgen withdrawal therapy only[27]. Other reasons may be the leadtime due to screening of almost 10 years in Gleason 7 PCs[54] and the improvement in mortality which occurred for all Gleason score categories due to the 'Will Rogers phenomenon', a grade shift in prognosis of biopsy specimens due to omitting scores 2-5[47]. The overall survival in our group is less favourable when compared to the group of Albertsen et al. (32% versus ~20%)[13], implying that our patients already had a shorter life expectancy at diagnosis.

A second central finding is that a large part of the men received deferred treatment, and thus do not 'comply' with the initial expectant management regimen. After 6 years, the treatment-free survival was only 59%. Considering a PSA >10.0 or a PSA-DT <3 years as a medically justified treatment indication, 11 (2+4+5) out of 15 men (73%) received active therapy in line with PSA or PSA changes. On the other hand, of men remaining

untreated a much smaller proportion of 5 (3+2) out of 35 men (14%) are potential candidates for active therapy. Thus, the choice between deferred treatment or not was justified in most cases. We chose to include all eligible men in our analysis, independent of the follow-up period, resulting in a realistic picture of the treatment-free survival, also on the short-term.

The most important benefit of an expectant management strategy is the avoidance of radical treatment with its side effects. Though, in line with the observations of other authors on watchful policies, it seems that treatment in many of our patients is merely delayed, not avoided[83]. Treatment delay however is also valuable and furthermore, the switch to active therapy is inherent to an AS-like protocol and not unexpected as such.

A third finding of this study was that the treatment-free survival was higher in men with otherwise favourable tumour characteristics and in men with a primary Gleason pattern 3. As mentioned before, the withholding of active therapy was justifiable in most of these men, regarding the PSA and PSA-DT.

Prospective AS studies currently including men with Gleason 3+4=7 are those of Choo et al. (N=21)[118] and Van As et al. (N=39)[119]. Outcomes in these specific patient groups have not been presented.

The most essential weak point of this study is the small size of our study group, which limits the value of our findings and statistical testing. Also, in 6 of the 50 patients no follow-up data was available. The selection based on tumour characteristics resulted in even smaller subgroups. However, data on outcomes in this group of men with screen-detected intermediate risk PC who are also managed expectantly is very scarce.

Second, patient follow-up was not standardized and our data mainly focus on survival, treatment, and PSA. The role of other medical factors such as DRE, rebiopsies, and comorbidity, and psychological factors such as anxiety and urologic complaints, was not assessed in this study, but may have been more decisive in the shift to deferred active treatment during follow-up than PSA characteristics. On the other hand, in most of our patients the PSA and PSA-DT at the time of deferred treatment fitted the common clinical practice to switch to deferred active therapy with high or rapidly rising PSA and the continuation of expectant management with a low or slowly rising PSA.

Third, the PSA and PSA-DT thresholds we used to risk-stratify our patients are arbitrary. Ongoing protocol-based prospective AS studies explore whether these cut-off points are useful in selecting the appropriate candidates for switching to radical treatment[66,74,80].

Fourth, the very favourable PC specific survival we found may not be the effect of correct and safe patient selection, but actually of the large number of deferred active therapies still given later during follow-up. In men with otherwise favourable tumour characteristics and a Gleason score of 3+4=7 the switch to deferred active therapy was observed much less frequently.

Finally, our cohort consisted of a mixed group of men either on WW (as studied by Albertsen et al. and Johansson et al.[13,81]) or AS. Many of the patients probably have comorbidity or choose themselves not to have active therapy. Of the subjects in this study in whom this information was available, 37% were healthy patients (ASA score 1), 48% had mild (ASA score 2), and 15% had severe systemic disease (ASA score 3). In both AS and WW, deferred treatment is chosen when progression of the PC is suspected, but with palliative intent in the former and curative intent in the latter. This may result in differences between patients in the monitoring regimen and the applied thresholds to switch to active therapy. In clinical practice an important overlap exists between the two strategies; AS may merge into WW during follow-up. The mean age in our cohort of 69.5 years (mean remaining life expectancy of >12 years[84]), a mean ASA score of 1.8, and the fact that 11 out of 15 (73%) deferred treatments were RP or RT (mainly given to men who do not have very significant comorbidity) would imply that a large part were better candidates for AS.

A strong point of this study is its multicenter set-up. Also, a large number of PSA values (299 in total) were available in the follow-up of our patients. Furthermore, as our study cohort is a selection of men diagnosed with PC within the ERSPC, pathological examination of biopsy specimens was standardized, the follow-up data collection of patients has been organized in a structured way, and objective assessment of the causes of death are implemented.

Concluding, the appropriateness of decisions on specific treatments in patients who have been diagnosed with early PC is a topic of much debate in the present urologic scientific literature. With the lack of solid predictive parameters, it is difficult in these patients to objectively balance age and comorbidity against tumour characteristics. Ongoing prospective protocol based AS studies will hopefully be able to elucidate some of the uncertainties of this relatively new strategy regarding criteria for eligibility. Based on the current retrospective observations, men with screen-detected Gleason 3+4=7 PC with otherwise favourable tumour characteristics may be suitable for AS, certainly if they have a limited life expectancy.

PART III

PROSPECTIVE APPROACH

Chapter 5
Prospective validation of active surveillance in prostate cancer: the PRIAS study.
(European Urology 2007)

Chapter 6
Short-term outcomes of the prospective multicenter PRIAS study (Prostate Cancer Research International: Active Surveillance)
(BJUI 2009)

Chapter 7
Prostate specific antigen kinetics in clinical decision-making during active surveillance for early prostate cancer - A review.
(European Urology 2008)

Chapter 5

Prospective validation of active surveillance prostate cancer: The PRIAS-study

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The incidence of prostate cancer (PC) has risen in most Western and Eastern countries during the last 15 years. Most detected tumours have a lower grade and stage than in the past. The increasing number of biopsies, the increasing number of cores per biopsy, the increasing overall life expectancy and most importantly the increasing use of PSA-measurements as a screening test, with lower thresholds for biopsy, are accountable for this development[51]. The majority of these screen-detected tumours have favourable characteristics, with a beneficial long-term survival[120]. Many of these malignancies would most probably not have caused any symptoms during lifetime if they had remained undiagnosed. This so-called overdiagnosis due to screening often results in overtreatment, subjecting men to unnecessary costly and invasive treatment with the risk of important side effects[121,122]. Men screened for prostate cancer should be protected against this. The replacement of initial active treatment with active surveillance in patients with small, localized, well-differentiated prostate cancer contributes to achieving this aim. Quality of life might also be preserved longer with this strategy. Because screening for prostate cancer is frequently applied, the attention to this approach in this specific subgroup of men with prostate cancer has increased. There is a rising demand for an evidence-based approach, but unfortunately until this day it is not yet available. Uncertainties currently exist concerning the risk of missing the window of curability in prostate cancer and criteria to rely on for changing from active surveillance to curative therapy in time to avoid or minimize that risk[46].

The Rotterdam section of the ERSPC (European Randomized study of Screening for Prostate Cancer[15]) and the Department of Urology of the Erasmus Medical Center in Rotterdam have initiated the prospective, observational PRIAS-study (Prostate cancer Research International: Active Surveillance) to validate the management of prostate cancer with active surveillance. A previous article shows that retrospectively 261 out of 1,014 men (25.7%) detected with prostate cancer in the first round of screening in the Rotterdam section of the ERSPC were suitable for active surveillance, when applying the clinical, histological, and biochemical criteria used in the PRIAS-study, which are described below. In practice in only 64 of these 261 men (24.5%) a watchful strategy was chosen[60]. In patients in whom active surveillance was actually elected, a very beneficial outcome was observed, with a cause specific survival of 100%[78].

The PRIAS-study is entirely web-based. The website www.prias-project.org offers patients information on the study and after login can be used by physicians to enter patient inclusion and follow-up data. Using this tool offers many benefits for daily urological clinical practice. Each time the urologist enters data of a follow-up visit, a graphical survey of the PSA-measurements is presented and the PSA-doubling time (PSA-DT) is calculated. Furthermore, based on the follow-up criteria (Figure 1), a recommendation is automatically presented on whether the patient should continue on active surveillance or whether to discontinue and choose for active treatment

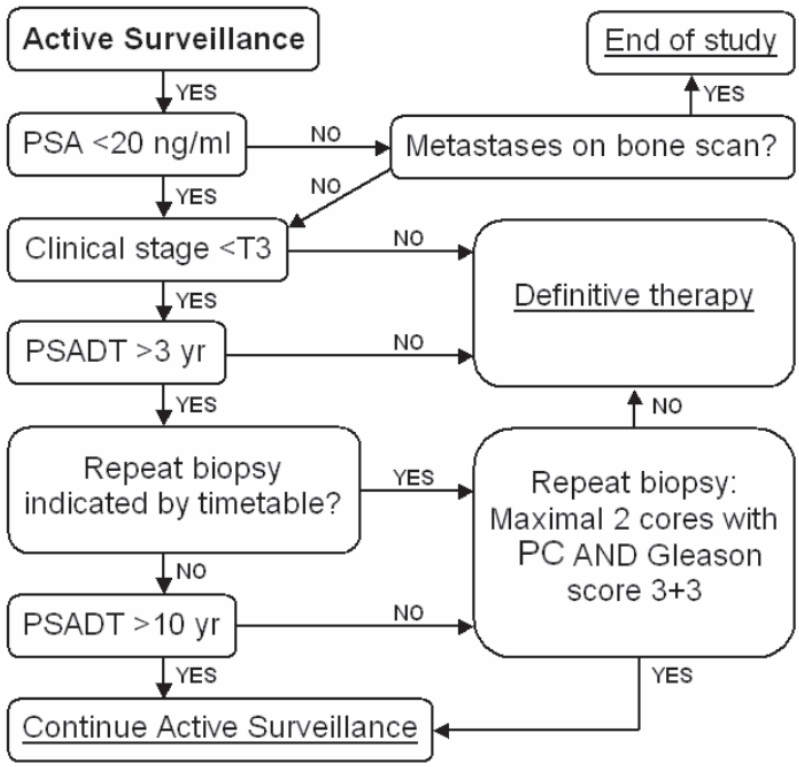

Figure 1: Follow-up criteria decision tree.

PSA	prostate-specific antigen
PSADT	PSA doubling time
PC	prostate cancer

(Figure 2). Most importantly the website offers support in clinical practice, by facilitating evidence-based decisions when considering active surveillance.

With the inclusion criteria of the PRIAS-study (Table 1) an attempt is made to select men with insignificant organ-confined tumours who have a favourable prognosis[13,61,115,123,124]. The criteria are: (1) men should have a histologically proven adenocarcinoma of the prostate, they should be fit for possible curative treatment, be willing to attend the follow-up visits, and they should not have received former therapy; (2) clinical stage is T1C or T2; (3) Gleason-score is ≤6 and ≤2 biopsy cores must be invaded with prostate cancer; (4) PSA is ≤10 ng/ml and PSA-density is ≤0.2 ng/ml/ml. The percentage of cancer-invasion in a biopsy core has not been taken up in our present inclusion criteria, although it does provide additional information on the probability of the presence of a minimal focus of prostate cancer[125]. It is currently not a standard procedure in all

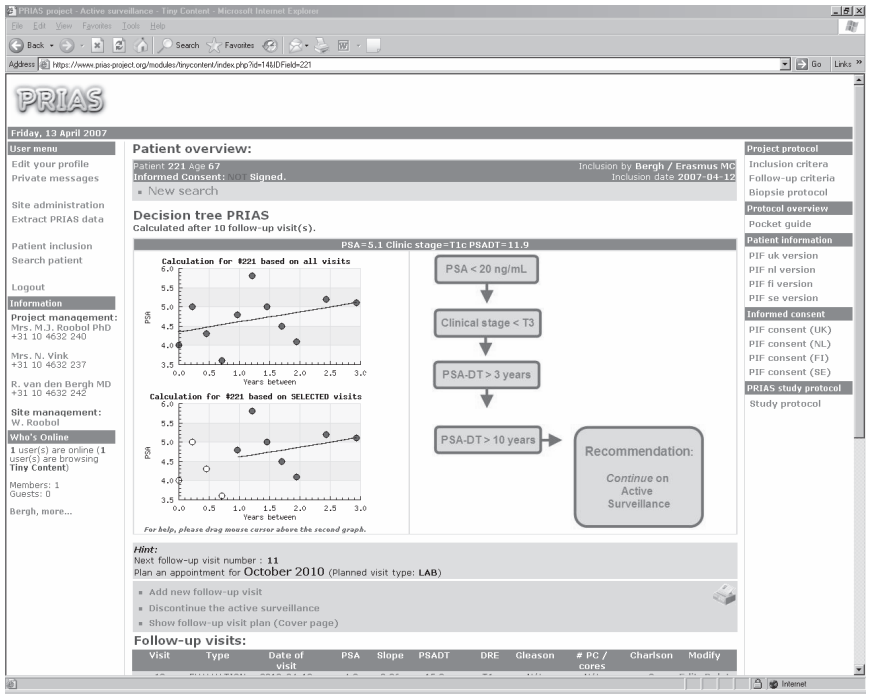

Figure 2: Screen shot of the web site www.prias-project.org

centres for pathologists to evaluate each specific core to this detail. Implementation of this criterion at this time would therefore strongly reduce the general feasibility and participation to our protocol.

The follow-up protocol, combining visits according to a timetable with standardized follow-up criteria, is formulated to timely detect the fast growing tumours, which are aggressive and therefore not suitable for active surveillance.

The timetable consists of 3-monthly PSA-measurements and biannual clinical examinations during the first two years, and biannual PSA-measurements and annual

Table 1: Inclusion criteria

1. Men should:
· Have histologically proven adenocarcinoma of the prostate
· Be fit for curative treatment
· Be willing to attend the follow-up visits
· Not have received former therapy for prostate cancer
2. Clinical stage is T1C or T2
3. Gleason score is ≤6 and ≤2 biopsy cores are invaded with prostate cancer
4. PSA is ≤10 ng/ml and PSA-density is <0.2 ng/ml/ml

clinical examinations in the subsequent years. Repeat biopsies are standard and are planned after 1, 4, 7 and 10 years of surveillance. These are essential in correcting for possible undersampling during the initial biopsies and for detecting true progression of tumour grade[52,126].

The follow-up criteria of the PRIAS-study are: (1) patient is content with active surveillance; (2) clinical stage remains <T3; (3) Gleason-score remains ≤6 and ≤2 of the repeat biopsy cores are invaded with prostate cancer; (4) PSA-DT is favourable and remains longer than 3 years. A PSA-DT <3 years is considered unfavourable and leads to an advice to choose for deferred active treatment. If the PSA-doubling time is in the 'grey' area between 3 and 10 years, it is recommended to perform a repeat biopsy additional to the standard protocol, unless this is already indicated in the same year according to the timetable[127,128]. Decisions on continuing or discontinuing active surveillance are based on the value of the PSA-DT only after a patient was in study during one full year. A reliable estimate of the PSA-DT can then be made, based on 5 single PSA-measurements. Later on during follow-up the physician can select the PSA-measurements on which the calculation of the PSA-DT is based. Whenever the serum PSA exceeds 20, a bone scan is advised[129].

When taking biopsies in a PRIAS-study candidate, it is advised to use the guideline for the number of biopsy cores to be taken in a certain prostate volume (8 in <40 cc, 10 in 40-60 cc, and 12 in >60 cc)[130,131]. If the number of obtained biopsy cores used for inclusion is lower than instructed it is advised, not obligatory, to perform a repeat biopsy within 8 weeks after inclusion.

At this moment the PRIAS-study is applied in a collaborative effort between centres in the region of Rotterdam in The Netherlands and in Helsinki in Finland. Soon the application of the protocol will be extended internationally, including North America. The aim of the study is to provide a highly needed evidence-based guideline for active surveillance in prostate cancer in order to prevent overtreatment. Future results can be used to study PSA-changes (PSA-doubling time, PSA-velocity, PSA-density) and pathological findings in radical prostatectomy specimens of prostate cancers considered suitable for active surveillance. With longer follow-up the data can be related to hard endpoints such as clinical progression and PC specific survival. Furthermore the effect of active surveillance on the quality of life and the validity of the use of a web-based decision tool in actively surveying patients with prostate cancer are investigated.

Chapter 6

Short-term outcomes of the prospective multicenter PRIAS study (Prostate Cancer Research International: Active Surveillance)

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ABSTRACT

Objective

Active surveillance (AS) for early prostate cancer (PC) may provide a partial solution to the current overtreatment dilemma in this disease. We evaluated the short-term outcomes of the prospective international PRIAS (Prostate cancer Research International: Active Surveillance) study (Dutch Trial Register NTR1718).

Patients and methods

The first 500 (of >850) participants with asymptomatic T1c/T2 PC, PSA ≤10.0 ng/ml, PSA-density <0.2 ng/ml/cc, Gleason score ≤3+3=6, and 1-2 positive biopsy cores were analysed. The follow-up protocol consists of frequent PSA measurements, digital rectal examinations, and standard repeat biopsies (first after 1 year). Primary outcome: active therapy-free survival. Secondary endpoints: reasons for stopping AS, findings in 1-year repeat biopsies, and outcomes after radical prostatectomy (RP).

Results

Patients were included between December 2006 and July 2008. Median follow-up after diagnosis was 1.02 yr (25-75th percentile: 0.6-1.5). The 2-year active therapy-free survival rate was 73%. Of the 82 men who changed to active therapy during follow-up, 83% (68/82) did so based on protocol. Of the 261 repeat biopsies available for analysis, 34% (90/261) showed no cancer, while 22% (57/261) showed Gleason score >6 or >2 positive biopsy cores. A relatively unfavourable PSA-DT of 0-10 years was seen in 53% (102/194) and 62% (33/53) of men with favourable and unfavourable rebiopsy results, respectively. After RP, 17% (4/24) showed T3 disease and 50% (12/24) Gleason score >6.

Conclusion

AS seems feasible, but survival outcomes are unknown. A strict follow-up protocol including standard 1-year repeat biopsies results in 1 out of 4 men stopping AS after 2 years.

INTRODUCTION

Screening for prostate cancer (PC) has the potential to decrease disease specific mortality, but also results in overdiagnosis[16]. Many men who are currently being diagnosed with PC will never develop symptoms during their lifetime if left untreated[60,85]. Radical treatment, which brings an immediate risk of side effects, thus is not always indicated[31].

Active surveillance (AS) has emerged as an alternative treatment option[59]. AS aims to avoid overtreatment in men with small, localized, well-differentiated PC by initially withholding radical treatment. Instead, the tumour is closely monitored with the purpose of switching to active local therapy with curative intent if progression occurs.

AS programs have been initiated in order to acquire evidence for the currently used selection and surveillance criteria, which are based on retrospective data[66,80,97,105,116,132]. The PRIAS study (Prostate Cancer Research International: Active Surveillance)[74] is an international prospective observational study originating from the European Randomized Study of Screening for Prostate Cancer (ERSPC)[15]. PRIAS offers a protocol for the inclusion and a follow-up of men who are considered suitable for AS, which is applied by a web-based instrument[133].

In this article, we assess the effect on active therapy-free survival of applying the PRIAS protocol for AS on 500 men diagnosed with early PC.

PATIENTS AND METHODS

Study design

The PRIAS study centre accrual and patient inclusion started in December 2006 and is still ongoing. At the moment of manuscript submission (May 2009), >800 patients had been included. This article presents the first study interim analysis, based on the first 500 study inclusions.

The main outcome parameter was active therapy-free survival; secondary endpoints include reasons for stopping AS, findings in the standard 1-year repeat biopsies, and outcomes after radical prostatectomy (RP). Furthermore, PSA doubling time (DT) distributions, findings at DRE (digital rectal examination), and preliminary survival details are discussed.

PRIAS study protocol

The criteria for eligibility for PRIAS aim to select asymptomatic, small, localized, well-differentiated PC and consist of: histologically proven adenocarcinoma of the prostate, no previous treatment, fit for curative treatment, clinical stage T1C or T2, a PSA level of

10.0 ng/ml or less, a PSA-density of less than 0.2 ng/ml, Gleason score 3+3=6 or more favourable, and 1-2 biopsy cores invaded with PC[74].

The PRIAS follow-up scheme consists of PSA measurements every 3 months and DRE every 6 months during the first 2 years after diagnosis; thereafter PSA measurements every 6 months and yearly DRE. Repeat biopsies are standard and are performed after 1, 4, and 7 years. Whenever during follow-up the PSA doubling time (PSA-DT) is 0-3 years, the clinical stage exceeds T2, or the rebiopsies show >2 positive biopsy cores or Gleason score >3+3=6, the protocol advises to switch to active therapy. When the PSA-DT is in the intermediate area of 3-10 years, yearly repeat biopsies are advised, instead of the standard schedule. PSA-DT is advised to be used only after 1 year of follow-up, with 5 singular PSA measurements available. Whenever the PSA exceeds 20.0 ng/ml, a bonescan is advised.

A prostate volume-dependent number of random biopsy cores is advised, but is not obligatory: <40cc: 8, 40-60cc: 10, >60cc: 12 biopsies[131]. Biopsy cores containing high-grade prostatic intraepithelial neoplasia or atypical lesion are considered to be negative.

The medical ethical committee of the Erasmus University Medical Centre and, dependent of local regulations, local committees approved the PRIAS study (MEC number 2004-339). All participants provided written informed consent.

PRIAS website

The PRIAS study website can be found at www.prias-project.org[133]. Study documents, screenshots, and general information are open for the public. Physicians login using a personal account and use the website to include and follow-up their AS patients. PSA-DT is calculated automatically and presented in graphs. Furthermore, automatic individualized recommendations based on the protocol are provided (Figure 1). The coordinating study centre (Erasmus MC, Rotterdam, The Netherlands) monitors and checks the website database every 3 months.

Analysis

Active therapy-free survival was assessed using Kaplan-Meier analysis. Reasons for stopping AS and treatments chosen are entered by the treating physicians. Potential predictors of adverse findings in repeat biopsies were explored using multivariate logistic regression analysis. PSA-DT was calculated by plotting the base 2 logarithm of the PSA-value against time since diagnosis. The DT can be calculated as the reciprocal value of the slope of the regression line through these points. PSA values that were measured during infection or shortly after biopsy (as mentioned by the treating physician) were excluded from calculation. Local pathologists reviewed RP specimens.

Men who were already under surveillance at the moment of inclusion were only included if the diagnosis was not longer than 2 years before and if the PRIAS follow-up

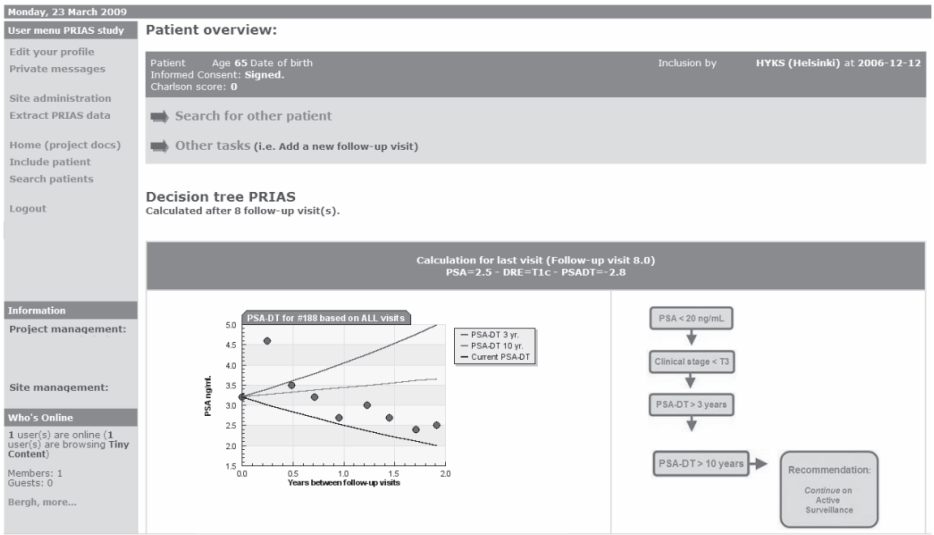

Figure 1: Screenshot of the website www.prias-project.org showing the patient follow-up screen with PSA doubling time graphs and automatic recommendations on follow-up.

protocol was applied in this period. Patients using 5-alpha-reductase inhibitors (5-ARIs) were excluded from the current analysis.

For statistical analysis the Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc, Chicago, IL, USA) was used.

RESULTS

Study group characteristics

Table 1 presents those centres that included 10 or more of the first 500 patients in PRIAS. Table 2 presents the baseline and follow-up characteristics of our study cohort. Patients were included between December 2006 and July 2008. Median follow-up time was 1.02 (25-75 percentile 0.6-1.5) year.

Active therapy-free survival

Figure 2 shows the total active therapy-free survival curve, as well as the curves stratified for reason of stopping AS (PSA-DT-related, biopsy-related, or other). A prominent drop is seen in the biopsy-related, PSA-DT-related, and total curve around 1 year of follow-up, which corresponds with the standard 1-year rebiopsies and the use of the PSA-DT as an exclusion factor when 5 measurements are available after 1 year, as indicated by the protocol.

Table 1: Participating PRIAS centres and study inclusion numbers (N=500) *

Country	City	Centre	Inclusions
The Netherlands	Rotterdam	Erasmus University Medical Centre	63
	Amsterdam	The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital	55
	Dordrecht	Albert Schweitzer Hospital	44
	Rotterdam	St. Franciscus Hospital	41
	Hengelo	Hospital Group Twente	33
	Goes	Oosterschelde Hospital	17
	Delft	Reinier de Graaf Hospital	11
	Breda	Amphia Hospital	10
	Other **		49
Finland	Helsinki	University Hospital	72
	Other **		8
Canada	Vancouver	British Columbia Cancer Agency	37
Italy	Milan	Fondazione IRCCS, Istituto Nazionale dei Tumouri	31
France	Reims	Centre Hospitalier Universitaire Robert Debré	10
	Other **		19
		TOTAL	500

* Countries and centres are only included in this table if 10 or more of the first 500 PRIAS patients have been included in this centre.

** Other participating centres in the PRIAS study are Antonius Hospital, Nieuwegein; Hospital Bernhoven, Veghel; Canisius-Wilhelmina Hospital, Nijmegen; Catharina Hospital, Eindhoven; Diakonessenhuis, Utrecht; Hospital Gelderse Valei, Ede; Haga Hospital, Den Haag; Ikazia Hospital, Rotterdam; Maasstad Hospital, Rotterdam; Medical Centre, Alkmaar; Medical Spectrum Twente, Enschede; Red Cross Hospital, Beverwijk; Rivas, Gorinchem; Ruwaard van Putten Hospital, Spijkenisse; Slingeland Hospital, Doetinchem; Spaarne Hospital, Hoofddorp; St. Jans Gasthuis, Weert; University Medical Centre, Utrecht; Tweesteden Hospital, Tilburg; Vlietland Hospital, Schiedam; VU University Medical Centre, Amsterdam; Westfries Gasthuis, Hoorn (The Netherlands); Kuopio University, Kuopio; Mikkeli; Oulu University; Päijät-Häme; Seinäjoki (Finland); Emco Klinik, Salzburg; Universitätsklinik für Urologie und Andrologie, Salzburg (Austria); Virgen del Camino, Pamplona (Spain); Wilhelms University, Münster (Germany); University Hospital, Gent (Belgium); Groupe Hospitalier Bichat, Paris (France).

Reasons for stopping active surveillance

Table 3 presents the specific reasons for 82 men stopping AS, as well as the active therapies they elected. Men stopped AS based on medical parameters according to protocol in 83% (68/82) and based on patient anxiety and/or request in 17% (14/82). A biopsy-related reason for stopping AS was observed in 56% (38/68) of the protocol-based decisions; a PSA-DT-related reason was seen in 62% (42/68); in 13 of these men both factors were simultaneous reasons for stopping. All patients received radical treatments; palliative hormonal therapy only was not given.

Table 2: Study group characteristics (N=500)

	Median	25 - 75 percentile
	DIAGNOSIS	
Age (year)	66.0	60.7 - 70.4
PSA (ng/ml)	5.3	3.9 - 6.7
Prostate volume (ml)	42.6	35.0 - 56.0
PSA-density (ng/ml/cc)	0.12	0.09 - 0.16
Total biopsy cores (number)	8.0	6.0 - 11.0
Positive biopsy cores (number)	1 core 68.6% 2 cores 31.4%	
Gleason score	3+3=6 95.0% Lower 5.0%	
DRE	T1c 79.2 % T2a 19.2% T2b 1.2% T2c 0.4%	
	FOLLOW-UP	
Follow-up (year)	1.02	0.6 - 1.5
Number of visits (number)	4	2 - 6

PSA prostate specific antigen
DRE digital rectal examination

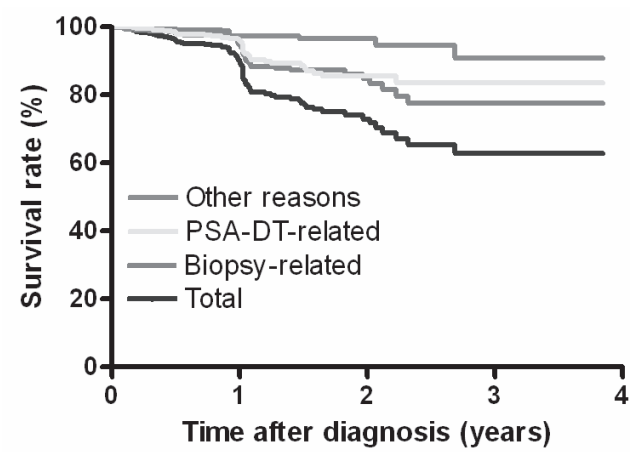

Figure 2: Active therapy-free survival; total and stratified for reason of stopping active surveillance (N=500)

Years follow-up	0	0.5	1	1.5	2	2.5	3	3.5	4
No. at risk	500	415	263	125	60	34	19	10	6
Cumulative no. treated TOTAL (survival rate %)	0 (100)	19 (96)	38 (90)	70 (78)	76 (73)	81 (65)	82 (63)	82 (63)	82 (63)

Table 3: Deferred active therapies and reasons for stopping AS (N=82)

	Deferred active therapies				
	Radical prosta-tectomy	External beam radiation therapy	Brachy-therapy	Unknown/ other	TOTAL
Reasons for switching to active therapy					
Protocol-based					
PSA-DT, rebiopsy number of positive cores, and rebiopsy Gleason score	1	-	-	-	1
PSA-DT and rebiopsy number of positive cores	4	2	-	1	7
PSA-DT and rebiopsy Gleason score	1	2	1	1	5
Rebiopsy number of positive cores and Gleason score	5	5	1	1	12
Rebiopsy number of positive cores	6	1	5	-	12
Rebiopsy Gleason score	2	-	3	-	5
PSA-DT only	7	4	12	2	25
T stage only	-	-	-	1	1 *
Psychological					
Anxiety	4	3	-	1	8
Other					
Did not want follow-up anymore	-	2	1	1	4
Unknown	1	-	1	-	2
TOTAL	31	19	24	8	82

* At patient's own request a MRI was made, revealing clinical stage T3a.
PSADT prostate specific antigen doubling time
AS active surveillance

Repeat biopsies

Of the 170 men with >1.25 yr follow-up (taking into account repeat biopsy being 'late' 1 follow-up visit), 14% (24/170) did not comply to having any repeat biopsy. A total of 261 men had standard repeat biopsies, depicted in Table 4 by the PSA-DT calculated using the available PSA values at that time. Biopsies were taken a median of 1.02 years (25-75p: 1.0-1.1) after diagnosis. The median number of prostate biopsy cores in the rebiopsy was 10 (25-75p: 8-12). No histological PC, 'PRIAS suitable' PC (1-2 positive biopsies, Gleason score ≤3+3=6), and more unfavourable PC (>2 positive biopsies and/or Gleason score >3+3=6) were found in 34% (90/261), 44% (114/261), and 22% (57/261), respectively. PSA-DT was unknown in 5% (14/261) of these patients. In men with favourable rebiopsy findings a PSA-DT of 0-3, 3-10, >10 years, and negative DT were seen in 28% (54/194), 25% (48/194), 8% (15/194), and 40% (77/194) respectively. In men with unfavourable rebiopsy findings a PSA-DT of 0-3, 3-10, >10 years, and negative DT were seen in 28% (15/53), 34% (18/53), 6% (3/53), and 33% (17/53) respectively. PSA-DT was not significantly different between men who showed upgrading in the biopsy characteristics and not (Mann-Whitney P 0.411).

Table 4: Standard rebiopsy after 1 year findings in relation to PSA doubling time at the time of biopsy (N=261)

	Favourable findings N=194			Unfavourable findings N=53				
Rebiopsy findings	A. No PC	B: 'PRIAS suitable': 1-2 biopsy cores and Gleason =<3+3=6)	*A + B*	C: >2 biopsy cores, Gleason =<3+3=6	D: 1-2 biopsy cores, Gleason >3+3=6	E: >2 biopsy cores and Gleason >3+3=6	*C + D + E*	TOTAL
PSA-DT								
0-3 yr	24 (28%)	30 (28%)	54 (28%)	7 (24%)	5 (50%)	3 (21%)	15 (28%)	**69 (28%)**
3-10 yr	18 (21%)	30 (28%)	48 (25%)	12 (41%)	1 (10%)	5 (36%)	18 (34%)	**66 (27%)**
>10 yr	7 (8%)	8 (7%)	15 (8%)	1 (3%)	2 (20%)	0 (0%)	3 (6%)	**18 (7%)**
Negative	37 (43%)	40 (37%)	77 (40%)	9 (31%)	2 (20%)	6 (43%)	17 (33%)	**94 (39%)**
Unknown	4	6	10	3	0	1	4	**14**
TOTAL	**90 (34%)**	**114 (44%)**	**204 (78%)**	**32 (12%)**	**10 (4%)**	**15 (6%)**	**57 (22%)**	**261 (100%)**

PC prostate cancer
PRIAS Prostate Cancer Research International Active Surveillance
PSA-DT prostate specific antigen doubling time

In univariate analysis (data not shown) the number of positive biopsy cores at initial diagnostic biopsy (2 versus 1) was the only parameter showing a positive relation to unfavourable repeat biopsy findings. Unfavourable rebiopsy findings were observed in 17% (32/183) of men with 1 positive biopsy at diagnosis and in 32% (25/78) of men with 2 positive biopsies (Chi-square p 0.014). Age, clinical stage, PSA, PSA-DT (neither slope of the regression line, PSA-DT divided in groups, nor PSA-DT with negative values set at 50 years), prostate volume, time to rebiopsy, number of biopsy cores taken at diagnosis, at rebiopsy, difference in number of biopsy cores, or the ratio between the initial number of biopsy cores and the repeat number of cores (even though a median number 2 more cores was taken at rebiopsy) did not show any significant association.

Radical prostatectomy

Of the 27 men who underwent RP after a median of 1.0 (25-75 percentile: 0.5-1.1) after starting on AS within PRIAS, histopathological outcomes were available in 24 (89%), as presented in Table 5. These patients chose RP based on: PSA-DT only (N=6), rebiopsy findings only (N=10), a combination (N=6), or other reasons (N=5). In the four T3 tumours the rebiopsy already showed both >2 positive biopsies as well as Gleason score >6 in 3 cases and >2 positive biopsies in 1 case. Of the twelve cases showing Gleason upgrading in the RP specimen, rebiopsies were performed previously in 11 and in all these unfavourable characteristics were found (Gleason >6 in 7, >2 positive biopsies

Table 5: Histopathological findings after radical prostatectomy of patients who started on active surveillance and switched to surgery during follow-up (N=24)

pT-stage (TNM2002)	pT2a	3	(12%)
	pT2b	2	(8%)
	pT2c	15	(63%)
	pT3a	4	(17%)
Capsular penetration	No	19	(79%)
	Yes	5	(21%)
Gleason score	3+3=6	12	(50%)
	3+4=7	10	(42%)
	4+3=7	1	(4%)
	3+5=8	1	(4%)
Positive margins	No	15	(62%)
	Yes	9	(38%)
Lymph nodal stage	pN0	7	(29%)
	pNX	17	(71%)
First PSA post-RP (ng/ml)	<0.1	18	(95%)
	≥0.1	1	(5%)
	Unknown	5	

PSA prostate specific antigen
RP radical prostatectomy

in 8, and a combination in 4). No significant association was found of any inclusion parameter or PSA-DT with adverse findings on RP.

PSA doubling time

A total of 2080 PSA measurements were performed during follow-up (mean 4.2 per patient). Considering the cumulative follow-up time of our study cohort, accounting for the difference in frequency of PSA measurements between 0 and 2 years after diagnosis and in the period thereafter, 2026 PSA measurements could be expected (mean 4.1 per patient). With more PSAs available for PSA-DT calculation, decreasing proportions of very unfavourable (0-3 yr) and very favourable (negative) PSA-DTs are seen due to a regression to the mean effect and due to the protocol advise of switching to active therapy in case of a fast rising PSA (data not shown).

Digital rectal examination

A total of 23 men showed upstaging in clinical stage on DRE of cT1c to cT2 during follow-up; none to cT3. Men with DRE upstaging had a longer follow-up after diagnosis (T test p 0.009), but were not significantly different from other men regarding baseline characteristics (all p >0.05). Rebiopsies (in 19/23 men) showed no PC, PRIAS suitable PC, or upgrading/upstaging in 26% (5/19), 47% (9/19), and 26% (5/19) respectively. PSA-DTs in this group were 0-3, 3-10, >10 years, or negative in 43% (10/23), 22% (5/23), 22% (5/23), and 13% (3/23) respectively.

Survival

Our data do not allow for a survival analysis. During the available follow-up period, no man died due to PC; 2 patients died due to other causes (abdominal aneurysm 1.4 years after diagnosis and myocardial infarction 2.2 years after diagnosis); lymph node metastases were detected in one patient one year after diagnosis.

DISCUSSION

This study presents the largest prospectively analysed cohort of patients in an AS program with good protocol compliance. We found that applying a strict AS follow-up protocol on selected patients with early PC resulted in 1 out of 4 men stopping AS after 2 years of follow-up. An important reason for stopping AS was the finding of adverse characteristics in standard repeat biopsies in 1 out of 5 patients. No difference was seen between PSA-DTs at the moment of rebiopsies with favourable and unfavourable outcomes. The men with unfavourable findings at RP already had an unfavourable rebiopsy result.

Finding a way out of the overtreatment dilemma of overdiagnosed PC, as is aimed by AS, has further gained importance since the European Randomized Study of Screening for Prostate Cancer (ERSPC) recently found that screening has the potential to decrease PC mortality[16]. The short-term observations presented in this study are important to monitor the effects and safety of applying in men with early PC a selection and follow-up AS protocol based on retrospective studies[13,85]. Longer follow-up is however needed to assess survival outcomes.

A considerable number of men stopped AS during follow-up (treatment-free survival 73% after 2 years). The rate of men stopping AS appears to slow down after an initial period of selection between tumours with a favourable and tumours with an unfavourable clinical behaviour, longer follow-up however is needed. The 2-year treatment-free survival rates as reported by other AS study groups vary from 67% to as high as 95%, depending on patient selection and follow-up criteria, and the prospective or more retrospective nature of these studies[66,105]. Although the aim of AS is to eventually avoid active therapy, switching to radical treatment during follow-up when progression occurs is an essential part of this strategy.

Psychological factors may influence decisions on treatment receipt of men with expectantly managed PC[65]. The main reason for stopping AS in our cohort was protocol-based and not due to psychological factors. Other studies have reported a larger role for non-medical reasons to stop AS[66]. Anxiety and distress levels in (Dutch) men participating in

the PRIAS study have been previously reported to be mostly favourable[87]. Anxiety of the physician was not recorded as a reason for stopping AS in our cohort[134].

Biological progression may be a reason for standard repeat biopsy upgrading, but are mainly caused by initial undersampling. Choo et al. studied the upgrading in Gleason scores and number of positive biopsies in standard repeat biopsies during AS[118]. The median number of prostate biopsy cores was 6 on initial and repeat biopsy, compared to 8 and 10 in PRIAS. Repeat biopsy compliance was also lower: 64% versus 86% in PRIAS. Upgrade in Gleason score >3+3=6 of men with an initial Gleason score of ≤3+3=6 such as included in the PRIAS study was observed in 38% (32/84); increase in the number of positive biopsies >2 in 37% (39/105). These numbers were only 10% (25/261) and 18% (47/261) in PRIAS. The difference may be explained by the lower number of biopsy cores and by the lower rebiopsy compliance rate. Probably, mostly men with unfavourable characteristics were rebiopsied, and men with a favourable disease status were not. In contrast to our findings, another study has found a relation between PSA kinetics and adverse findings in repeat biopsies[135]. However, the repeat biopsies in this study were not performed standard, but dependent of clinical changes. We did not find an association between the number of biopsy cores obtained at initial and repeat biopsy and the numbers of biopsy upgrading during follow-up[111].

Although the number of RP specimens is too limited for definitive analysis, histopathological findings after deferred RP are in line with the outcomes reported after immediate RP in similar selections of PC patients. Suardi et al. studied the pathological features of prostate specimens after RP performed between 1992 and 2007 in 2345 men with T1c/T2a, Gleason ≤6, PSA ≤10.0 ng/ml PC at diagnosis[101]. Although patient characteristics differ from the PRIAS criteria (PSA-density and number of biopsy cores was not assessed, and T2b/T2c disease was not included), this study does give an indication of the true nature of PCs included in PRIAS. A Gleason score >6 was found in 35.3%. Extracapsular extension, seminal vesicle invasion, and lymph node involvement were seen in respectively 13.5%, 2.9%, 0.9%. In a similar study design, Conti et al. found rates of Gleason upgrading of 23-35% and extracapsular extension of 7-11% when applying AS criteria mainly corresponding to PRIAS[99]. Active surveillance may result in a selection process in which mainly men with unfavourable follow-up characteristics receive surgery and therefore show more adverse outcomes after RP, while the patients with a favourable follow-up remain untreated[108].

This study has some weaknesses. First, a randomized control group receiving initial radical treatment is not included. Recently, the START-trial has been initiated in North-America, which aims to study difference between expectant management and radical treatment in men with early PC in a randomized fashion[136]. Difficulties in setting up a randomized trial include: 1) the expected survival benefit of RP and RT likely is small[28],

2) the number of patients needed is very large, and 3) the follow-up time needed is very long. Survival outcomes could not be analysed in our study due to a short follow-up. Further, a selection bias may be present in a number of our patients; because physicians may tend to delay inclusion of a patient into PRIAS until for example a second favourable PSA measurement is available. Finally, the percentage of tumour involvement in the biopsy cores was not included in the inclusion and follow-up criteria in order to widen the applicability of our protocol to peripheral hospitals where this is not standard measured, although at the cost of the predictive value for adverse findings after RP[137]. For this reason, nomogram scores for harbouring indolent PC[12] can not be applied in all patients. A future subgroup analysis however is a possibility.

A strength of this paper is the large patient number. PRIAS has included more patients than any other prospective AS study reported. Furthermore, the protocol adherence is strong, likely due to web-based inclusion and follow-up.

Based on the current analysis, no direct indications regarding patient safety can be found to tighten the criteria for AS as currently used in PRIAS. If a higher active therapy-free survival is desirable, possible adaptations to the protocol may be an option. Patients with only one positive biopsy-core have a lower chance of adverse findings at repeat biopsy and may therefore remain on AS for a longer period. Eggener et al. also have reported that this parameter is associated with therapy-free survival[112]. Another possibility is to include a standard repeat biopsy in the inclusion criteria for AS. The importance of repeat biopsies during AS has been emphasized by other study groups[112,135].

Definitive outcomes of AS will not only be defined by tumour-, but also by patient characteristics, in relation with life expectancy and comorbidity scores. Future research, which can partly be done within the PRIAS study, should aim to study long-term survival outcomes of AS when compared to other treatment options, optimize AS inclusion and follow-up criteria, clarify the role of PSA kinetics during AS, assess the effect of 5 ARIs during AS, incorporate new biomarkers and imaging techniques, and study the effect on quality of life during AS when compared to other treatments.

In conclusion, AS for early PC using a web-based tool is a feasible strategy to avoid overtreatment on short-term after diagnosis. Applying the strict PRIAS inclusion and follow-up protocol results in 1 out of 4 men who start on AS switching to active therapy within 2 years after diagnosis. This is mainly due to the fact that 1 out of 5 standard repeat biopsies one year after diagnosis show adverse findings, which is independent of the PSA-DT. Based on the current short-term analysis, the protocol seems not to comprise curability. In the future, PRIAS may provide data to optimize AS protocols, as well as long-term survival and quality of life outcomes of AS.

Chapter 7

Prostate specific antigen kinetics in clinical decision making during active surveillance for early prostate cancer – A review

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ABSTRACT

Context

The kinetics of prostate specific antigen (PSA) are generally assumed to be indicative of tumour progression and are therefore used in clinical decision-making in men on active surveillance for early prostate cancer.

Objective

This review aims to provide support in exploiting PSA kinetics in an active surveillance setting.

Evidence acquisition

We searched the Medline database and reviewed the evidence on both the relation between PSA kinetics before radical treatment for prostate cancer and outcome, as well as the role of PSA kinetics during active surveillance. Furthermore, the benefits and setbacks of different derivatives of PSA kinetics, minimal required time interval and number of measurements, practical recommendations, and pitfalls of the use in clinical practice are discussed.

Evidence synthesis

The evidence concerning the prognostic value of the PSA velocity and PSA doubling time is sparse, especially in active surveillance. PSA kinetics alone should therefore not be used as the trigger for deferred radical treatment or repeat prostate biopsies. There seems to be consensus between several reports on the unfavourable outcome relating to a PSA doubling time <3-4 years and on the favourable prognostic value of a doubling time >10 years or a decreasing PSA level. Online tools provide help in calculations and insight in disease development. The best method of calculation, number of measurements, and time interval between measurements is unknown for now.

Conclusions

Despite the current deficits in our understanding of the natural behaviour of early prostate cancer and its relation with serum PSA levels, and despite several secondary factors playing a role in PSA kinetics, it is currently a practical parameter we can offer men on active surveillance to assess the status of their disease.

INTRODUCTION

Active surveillance is presently a frequently practiced strategy to decrease the current overtreatment of early prostate cancer, specifically in Europe. It is as such, besides surgery and radiation therapy, part of guidelines for the treatment of early prostate cancer. Overdiagnosis and the resulting overtreatment are determined by tumour characteristics on one, and life expectancy of a patient on the other side. As the greater part of men with a small, localized, and well-differentiated prostate tumour will die with and not of their disease, active surveillance saves men with an insignificant form of this disease from the chance of serious side effects of surgery or radiation therapy. Furthermore, ethical and economical issues are associated with this strategy. An important setback of active surveillance may be the psychological burden of living with 'untreated' prostate cancer in some men.

Active surveillance consists of an initial selection of tumours with apparently favourable features and of subsequent monitoring of these malignancies. Criteria for insignificant disease used in prospective active surveillance studies are presented in Table 1. Radical treatment with curative intent is preferably only chosen when the prostate cancer seems to progress, but before the tumour becomes noncurable; however it is currently not clear which trigger points are most suitable[46]. Deferring radical treatment in these patients appears not to alter natural history[91].

The serum level of prostate specific antigen (PSA) is indicative of prostate size and cancer growth. In different phases before and after treatment of prostate cancer the change in time of PSA is considered to be an important parameter to assess the relatively favourable or unfavourable development of a prostate tumour. PSA kinetics measured 10-15 years before diagnosis, when the effect of benign prostate hyperplasia is small, are even associated with cancer specific survival 25 years later[138]. On the other hand, it was found that PSA velocity has no additional value in a screening protocol for prostate cancer[139].

Table 1: Inclusion parameters used in prospective active surveillance studies to predict insignificant prostate cancer.

	Van den Bergh[74]	Klotz[66]	Carter[116]
PSA (ng/ml)	≤10.0	≤10.0 (patients >70 yr: ≤15.0)	-
PSA-density (ng/ml/ml)	<0.20	-	<0.15
Clinical stage	T1c or T2, N0, M0	T1C or T2A, N0, M0	T1C, N0, M0
Number of positive biopsies	<3	-	<3
Gleason-score	≤3+3=6	≤3+3=6 (patients > 70 yr: ≤3+4=7)	≤3+3=6
% core invasion	-	-	<50%

PSA prostate specific antigen

PSA kinetics are also an easy to apply and logical tool in clinical decision-making during active surveillance[128]. A high PSA velocity (PSA-V; absolute PSA increase per time interval) or short PSA doubling time (PSA-DT; time interval for doubling-up of initial PSA) are related with an unfavourable outcome and should lead to performing an additional prostate biopsy or to deferred radical treatment during follow-up of active surveillance. A low PSA-V or a long PSA-DT are associated with a non-aggressive course of the disease and may justify a more conservative attitude. (It should be noted that the use of PSA in this setting is different from the use of PSA as a diagnostic test, as the diagnosis prostate cancer has already been made.)

Different retrospective studies have confirmed that men who have a rapidly rising PSA during active surveillance choose deferred radical treatment more often, especially younger patients[83,140]. The triggers to be used in a prospective manner to select men with a medical indication for radical treatment are however subject to investigation.

In this article we first review the different available derivates of PSA kinetics, the literature on the relation between PSA kinetics before treatment for prostate cancer and outcome, and furthermore the literature on the role of PSA kinetics during active surveillance. As the aim of active surveillance is to timely switch to deferred radical treatment during follow-up when necessary, retrospective studies on the relation between PSA kinetics before surgery or radiation therapy and outcome provide valuable information in this setting. Finally, we aim to provide directions and cut-off values to make the most out of PSA kinetics in clinical practice, by discussing the differences between PSA velocity and PSA doubling time, the minimal requirements for obtaining objective calculations, practical recommendations, and pitfalls of the use of this parameter.

EVIDENCE ACQUISITION

The Medline database was searched for English articles using the search terms ‘PSA’; and ’velocity’, or ‘doubling time’, or ‘kinetics’; and ‘radical prostatectomy’, or ‘radiation therapy’, or ‘brachytherapy’, or ‘active surveillance’, or ‘watchful waiting’. This search resulted in 269 hits, of which 8 articles relating PSA velocity or PSA doubling time with outcome after radical treatment and 8 articles relating PSA kinetics during active surveillance for early prostate cancer with outcome were extracted. Retrieved articles originated from 1993 to 2007, 81% of the studies from the last 10 years. Reference lists of retrieved articles were scrutinized for additional relevant articles.

During this process, special attention was paid to information on the benefits and setbacks of different derivates of PSA kinetics, to the minimal time intervals and number of measurements upon which calculations of PSA kinetics were based, and on

practical recommendations and pitfalls of the use of PSA velocity and PSA doubling time in clinical practice.

EVIDENCE SYNTHESIS

PSA mathematics

The change in PSA over time is most commonly defined as either PSA velocity or PSA doubling time. PSA-V is the absolute increase or decrease in PSA in a specified period. It is independent of the starting value, but increasing with time when considering the exponential growth of a malignant process. PSA-V is usually defined as ng/ml per year. PSA-DT is the time period it takes the PSA to double in value, which is stable when considering an exponential rise in PSA, but dependent of the starting value. It is usually presented in years or months. Both parameters are further illustrated in Figure 1 and Figure 2, and an example patient is provided in Table 2. With a stable PSA-DT, PSA-V will increase over time.

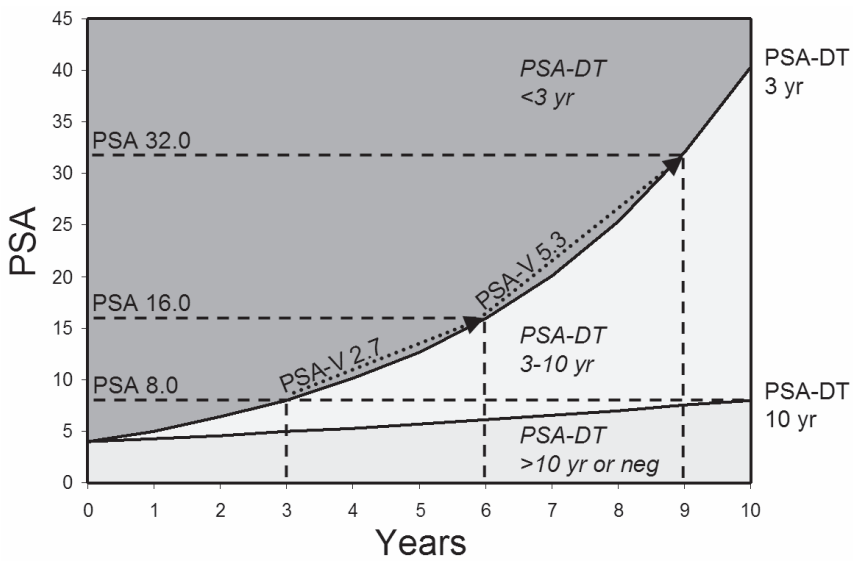

Figure 1: PSA doubling time reference lines of 3 and 10 years (based on a PSA starting value of 4.0 ng/ml, over a total period of 10 years), dividing the possible course of PSA values over time in three fractions (areas from top to bottom): An unbeneficial (PSA-DT <3 yr), a less beneficial (PSA-DT 3-10 yr), and a beneficial (PSA-DT >10 yr or negative) PSA course. PSA velocity (dotted arrows) of two different periods in time within the reference line of PSA-DT 3 years are also drawn; with a stable PSA-DT, PSA velocity increases over time.

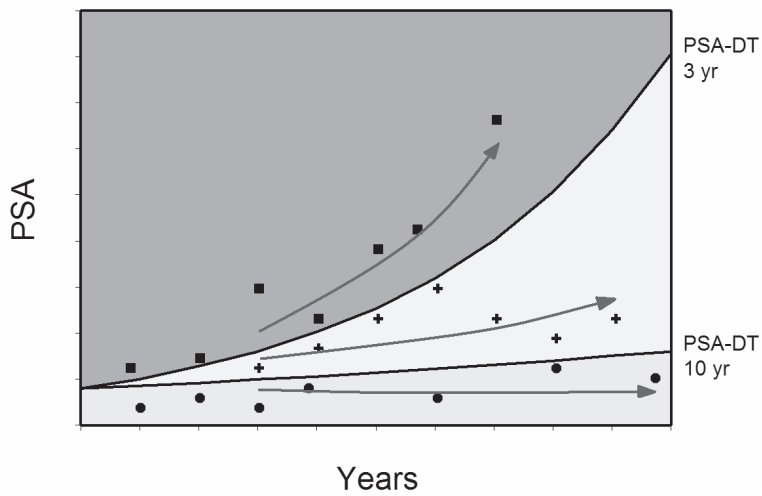

Figure 2: Examples of the PSA pattern of three fictive patients (based on a PSA starting value of 4.0 ng/ml): The lines correspond with an unbeneficial (<, quickly rising, PSA-DT ≅ 2 yr), less beneficial (+, slowly rising, PSA-DT ≅ 9 yr), and beneficial (·, slowly falling, PSA-DT ≅ -20 yr) PSA course.

Different methods of calculating PSA velocity and PSA doubling time are available (e.g. based on the first and the last measured value only or on a regression line through all available measurements, based on normal or logarithmic values), but only small differences in predictive value have been found between these derivatives[128]. Connolly et al. found that using all available PSA measurements in a linear regression analysis should be the method of choice for calculating PSA velocity. When using the first and last measurement only, these should at least be separated by a sufficiently long time period[141] .

The relative PSA velocity is a logarithmic derivate of PSA velocity. Combining the relative PSA velocity and PSA amplitude (intercept with the y-axis of the regression line through all logarithmic PSA values) is suggested to result in a more powerful predictive ability for patients at risk of progression in an active surveillance group. Another option is to use subtracted PSA-DT, which is the doubling time of the singular PSA values of which the baseline PSA value has been subtracted[142]. Finally, PSA-V risk count has been proposed as a method of interpreting PSA history by Carter et al., which is the number of times the PSA velocity exceeds a threshold along time[143].

PSA kinetics before radical treatment

The speed of rise in PSA level prior to radical treatment for prostate cancer has been associated with predictions of outcome. The evidence for this relation may still be scarce and sometimes differing between studies, but has been reported after radical prostatectomy (RP), external beam radiation therapy (EBRT), and brachytherapy.

Table 2: Cumulative and periodic PSA velocity and doubling time in an example patient, with half-yearly PSA measurements. After initial oscillations in both parameters due to a limited number of measurements, PSA velocity tend to rise over time, while PSA doubling time tends to remain stable, especially when assessing the first and last time periods.

Measurement No	1	2	3	4	5	6	7	8	9	10	11
Date	Jan '08	Jul '08	Jan '09	Jul '09	Jan '10	Jul '10	Jan '11	Jul '11	Jan '12	Jul '12	Jan '13
PSA	3.9	4.2	4.8	5.0	5.3	5.6	6.2	6.9	7.3	7.5	8.1
Cumulative PSA velocity (ng/ml/yr)	-	0.6	0.9	0.78	0.72	0.69	0.73	0.8	0.84	0.83	0.84
Cumulative PSA doubling time (yr)	-	4.7	3.3	3.9	4.4	4.8	4.7	4.5	4.5	4.7	4.7
PSA velocity over period (ng/ml/yr)	0.69					0.96					
PSA doubling time over period (yr)	4.8					4.9					

PSA prostate specific antigen

D'Amico et al. studied 1,095 men with localized prostate cancer who had undergone RP and found that men whose PSA level had increased by more than 2.0 ng/ml during the year before the diagnosis, had a higher risk of PC specific death[144]. The proportion of patients with this PSA velocity was 24%. The results of a study by King et al. confirmed the association of a similar preoperative rise in PSA with relapse after radical prostatectomy[145]. D'Amico found the threshold of 2.0 ng/ml/yr to be also associated with a significantly higher risk of death due to prostate cancer following external beam radiation therapy in 358 men; he found similar results for low and high-risk prostate cancer[146]. Eggener et al. further confirmed that a PSA-V of 2.0 ng/ml/yr before intervention was predictive for cancer progression following EBRT or brachytherapy in a group of 130 men[147]. Of the men above this threshold 38% had cancer progression, against 12% who were under 2.0 ng/ml/yr.

Goluboff et al. found a relation between pretreatment PSA doubling time and positive margins and seminal vesicle invasion at radical prostatectomy, but PSA-DT did not correlate with PSA failure, final PSA, or Gleason score[148]. Hanks et al. however did find a relation between PSA-DT and biochemical progression-free survival, in 99 patients with T1-3, NX, and M0 prostate cancer after external beam radiation therapy[149]. A pretreatment PSA-DT of <1 year was considered as aggressive and >5 years as favourable. Egawa et al. retrospectively calculated the PSA doubling time prior to surgery of 62 patients with prostate carcinoma and found that stage pT3 disease was significantly more common in patients with a PSA-DT of ≤3 years than in those with a doubling time >3 years. This group also found that biochemical failure was more common in patients with a rapid PSA-DT before RP[150].

In contradiction to the above, Freedland et al. assessed 331 men after radical prostatectomy and found that neither preoperative PSA velocity nor doubling time was a predictor of adverse pathologic findings or biochemical recurrence after RP[151].

Summarizing, there seems to be substantial evidence that PSA kinetics before radical treatment predict outcomes, a quickly rising PSA being associated with worse results. Most studies assess large patient numbers and have acceptable levels of evidence. However, due to the retrospective nature of these articles, there is no proof that the prospective use of PSA kinetics thresholds can identify men with an unfavourable prognosis at the time when curative treatment is still possible. PSA velocity or doubling time may merely be an unfavourable prognostic factor. Furthermore, a quickly rising PSA is more common in men with a high starting PSA level. This proportion of men is expected to be much smaller in a screened cohort than in a clinically diagnosed cohort.

Characteristics of studies relating PSA kinetics before radical treatment with outcome are presented in Table 3.

PSA kinetics in active surveillance

As active surveillance is an emerging strategy, the prospectively acquired evidence for the relation between PSA kinetics during active surveillance and outcome such as prostate cancer specific mortality is still preliminary. As compared to the predictive thresholds found in articles on the role of PSA kinetics before treatment, the cut-off values for clinical decision-making in active surveillance of PSA velocity should be lower and of those of PSA doubling time should be higher to be sure that these are always on the 'safe' side.

The guidelines of the European Association of Urology mention a 'rising serum PSA level' as an indication for tumour activity, but do not suggest cut-off values in PSA, PSA velocity, or PSA doubling time that can be used in clinical practice[152]. The National Comprehensive Cancer Network considers a PSA velocity >0.75 ng/ml/yr or a PSA doubling time <3 year as a sign of progression in its guidelines of expectant management in early prostate cancer[153].

A large prospective study on active surveillance, describing almost 300 men, reported that in their group 42% had a PSA-DT >10 years, 23% had a PSA-DT <3 years and 35% of the men in the group with a PSA-DT between 3 and 10 years[154]. A similar wide spread of doubling times in a comparable cohort of men was retrospectively found by Roemeling et al. and by Carter et al., despite narrow inclusion criteria for favourable disease at diagnosis[60,116].

Several studies found a relation between a short PSA doubling time in active surveillance and an unfavourable prognosis. Schmid et al. observed that a shortening of PSA-DT is correlated with increasing cancer volume and stage[155]. McLaren et al. found that a PSA-DT of <2 years in a group of 113 patients in a watchful waiting program

Table 3: Characteristics of studies relating PSA kinetics before radical treatment with outcome

Author	Year	Kinetics	PSA (ng/ml)	N	Age (yr)	Tx	Endpoint	Significant relation	Threshold
King [12]	2007	PSA-V	Median 6.1 (IQR 4.5 – 9.4)	471	Median 62.0	RP	Relapse	Yes	2.0 ng/ml/yr
Eggener [14]	2006	PSA-V	<4.0: 34%; 4.0-10.0: 61%	130	Mean 59.0	EBRT, BT	Progression	Yes	2.0 ng/ml/yr
D'Amico [13]	2005	PSA-V	Median 8.0 (range 0.5 – 124.5)	358	Median 71.2	EBRT	PC death	Yes	2.0 ng/ml/yr
D'Amico [11]	2004	PSA-V	Median 4.3 (range 0.3 – 58.2)	1095	Median 64.7	RP	PC death	Yes	2.0 ng/ml/yr
Freedland [18]	2001	PSA-V; PSA-DT	Median 7.2	86	Median 64.0	RP	Pathological stage; biochemical progression	No	-
Egawa [17]	2000	PSA-DT	Median 9.0 (range 1.8-86.4)	62	Median 67.0	RP	Pathological stage	Yes	3 yr
Goluboff [15]	1997	PSA-DT	<10.0: 66%; 10.0-20.0: 29%	56	Mean 61.0	RP	Pathological stage	Yes	-
Hanks [16]	1996	PSA-DT	<10.0: 47%; 10.0-20.0: 21%	99	Mean 70.0	EBRT	Biochemical freedom of disease	Yes	<1 yr: unfavourable; >5 yr: favourable

PSA-V prostate specific antigen velocity
PSA-DT prostate specific antigen doubling time
RP Radical prostatectomy
EBRT External beam radiation therapy
BT Brachytherapy
PC prostate cancer
IQR interquartile range

with otherwise favourable clinical features indicates a high likelihood of developing locally advanced disease, so the optimal threshold of PSA-DT for intervention should be around 3 years. In the study cohort, 20-25% of patients initially classified as low risk are nevertheless at risk of disease progression based on a PSA-DT of less than 3 years[128]. Furthermore, Khan et al. observed that PSA velocity could be useful to predict which men will have unfavourable findings in their repeat biopsies[156]. In the Swedish section of the European Randomized Study of Screening for Prostate Cancer, Khatami et al. observed that PSA-DT was a statistically significant predictor of PSA relapse after treatment in 104 men who were initially managed with active surveillance, with a mean follow-up time of 63 months. In the 70 patients who underwent radical prostatectomy, PSA relapse was observed in 9, of which 7 had a PSA-DT <2 years. As none of the 37 men with a PSA-DT >4 years had PSA relapse, it was concluded that a man with a PSA-DT <4 year is not an optimal candidate for active surveillance[157]. Stephenson et al. concluded in a group of 94 men that a PSA-DT of less than 10 years correlates with a higher chance of disease progression[158].

In contradiction to this, Patel et al. did not find a correlation between PSA-DT and progression in a cohort of small (78% T1C, most only 1 positive biopsy) tumours, whilst these are the tumours that are diagnosed increasingly often and are particularly suitable for active surveillance[93]. Neither did Carter et al. prospectively find a difference in PSA velocity between men treated expectantly who had progression to noncurable disease and those who did not[116].

In a study of Fall et al. different cut-off points of the relative PSA velocity were used to assess its value in differentiating men on active surveillance between high and low risk groups of eventually dying of prostate cancer. Although a quickly rising PSA was clearly positively associated with increased risk for prostate cancer death, the authors did not find one cut-off point that was specific and sensitive enough for use in clinical practice. PSA change was predictive of lethal prostate cancer, but was a poor predictor of lethal prostate cancer among patients with localized prostate cancer who are managed by watchful waiting[159]. Finally, this group stated that although PSA level and its kinetics are clearly associated with the behaviour of individual prostate cancers, they are not sensitive or specific enough to be used alone to identify the tumours that will eventually cause harm to a patient.

In summary, the studies available so far that relate PSA kinetics during active surveillance with outcome, are based on relatively small numbers of patients, the follow-up time is limited, and the results are sometimes contradictory. A striking similarity however is seen between two studies in the cut-off value of PSA-DT below which there is a high chance of adverse outcome, being <2 year to <4 year[128,157]. Prospective studies on active surveillance use a similar cut-off value as a trigger point for deferred treatment[66,74]. On the other side, a PSA-DT >10 years, a static course of the PSA values, or a negative PSA doubling time is generally associated with a good prognosis[66,158]. Ongoing prospective studies on active surveillance aim to validate these findings by applying these cut-off values as trigger points for deferred treatment in case of a quickly rising PSA or repeat biopsies in case of moderately rising PSA in larger groups of men[66,74]. The variation in the existence of and in the level of predictive cut-off values of PSA kinetics found in different articles may be based on a variance in selecting men with low-risk prostate cancer, or on the number of PSA measurements and measurement period. The thresholds presented above leave a grey area between a PSA-DT 4-10 years in which there is least consensus of the value of this parameter and where it seems to have lowest discriminating value. In this area, additional repeat biopsies may be helpful. The safest option is to for the present always use a combination of PSA kinetics and tumour-related factors such as clinical stage or Gleason progression for the assessment of the status of prostate cancer during active surveillance. A complicated situation however may arise when despite a quickly rising PSA, repeat biopsies show favourable characteristics. Prospective active surveillance studies should clarify these issues[74,116].

Characteristics of studies relating PSA kinetics during active surveillance with outcome are presented in Table 4.

Clinical use of PSA kinetics in active surveillance

Velocity versus doubling time

At this moment no preference exists for applying velocity, doubling time, or other PSA kinetics derivate in actively monitoring men with early prostate cancer, a head-to-head comparison has never been performed. The (degree of rise in) PSA velocity in time may have a different predictive value for identifying significant prostate cancer progression than PSA doubling time (which tends to remain stable in an exponential PSA increase),

Table 4: Characteristics of studies relating PSA kinetics during active surveillance with outcome

Author	Year	Kinetics	PSA (ng/ml)	N	Age (yr)	FU (yr)	Endpoint	Significant relation	Threshold (yr)
Fall [29]	2007	PSA-V	<4: 17.2%; 4.0-6.9: 18.0%; 7-9.9: 16.9%; 10.0-20.0: 30%; >20.0: 18.0%	267	<60: 15.7%; 60-64: 30.3%; 65-69: 36.7%; >70: 17.2%	Mean 8.5 +- 2.7	Lethal prostate cancer	Yes	-
Khatami [26]	2006	PSA-DT	Median 4.2 (3.0-27.8)	270	Median 64.6	Mean 5.25 (0.9-10.0)	Disease progression	Yes	4
Patel [28]	2004	PSA-DT	Mean 5.9 (0.09-30.2)	88	Mean 65.3	Median 3.7 (0.6-14.3)	Progression	No	-
Khan [25]	2003	PSA-V	ND	78	ND	ND	Small volume disease	Yes	-
Carter [23]	2002	PSA-V	Median 5 (1-13)	81	Median 65	Median 1.9 (1-4.8)	Progression to noncurable disease	No	-
Stephenson [27]	2002	PSA-DT	Mean 7.4 (0.9-25.2)	94	Mean 69	Mean 2.8 (1-10)	Disease progression	Yes	10
McLaren [5]	1997	PSA-DT	Median 5.8 (0.2-21)	113	Median 75	Median 1.2 (0-4.8)	Clinical or stage progression	Yes	1.5
Schmid [24]	1993	PSA-DT	ND	43	ND	ND	Disease stage and grade	Yes	-

PSA-DT prostate specific antigen doubling time
PSA-V prostate specific antigen velocity
ND No data
FU Follow-up

depending on the time period after prostate cancer diagnosis in which it is being assessed. Further research should aim to compare the value of both parameters.

PSA-V and PSA-DT share the similar underlying idea that PSA changes in time have additional value over using the PSA level alone on an individual basis. No conclusive evidence however exists to support this hypothesis, neither that PSA kinetics are not useful.

Minimal number and timing of PSA measurements

There is no consensus on the minimal and maximal number of PSA measurements and the time period on which calculation of PSA velocity or doubling time should be based during active surveillance. More measurements, over a longer period of time result in more stable and more objective results, but could also result in a longer delay before these could be interpreted. The appropriate number of measurements needed may therefore depend on the speed of rise of PSA. Minimal requirements differ from 3 points in at least one half year to 5 points in one year[66,74]. A method of 'progressive omission' (i.e. leaving out the older PSA measurements') in PSA kinetics calculations will result in a more up to date result, which is then however subject to more oscillations.

Practical recommendations

Internet-based tools may provide important help in applying PSA kinetics in individuals with early prostate cancer on active surveillance. Numerous instruments nowadays are available on the internet that offer calculations of velocity or doubling time, or that also integrate automatic recommendations during follow-up of patients on active surveillance. Such web-based tools are presented in Table 5.

Pitfalls

When using PSA doubling time or PSA velocity in an individual patient, caution should be remained for a number of practical pitfalls. We will mention six points here. First, as with respect to a singular PSA measurement, transitory PSA outliers may be due to infection, or following DRE or prostate biopsies, which may lead to a higher PSA value and result in a higher velocity and shorter doubling time. Oscillations up to 20-30% in men aged >50 years in the PSA range 0.1 – 20 ng/ml may be due to biological variation[160]. In connection with this, PSA kinetics calculated early during follow-up may fail to predict future PSA progression patterns, reflecting the possible unpredictable variations of this parameter[161]. Evidently unreliable PSA values, with a proper explanation of 'outliers', should not be included in calculations of PSA kinetics, avoiding a medically unnecessary choice for deferred treatment during follow-up of active surveillance. Second, the use of different detection assays may be an important other cause of variation in PSA level. A difference of 11% has recently been reported between two different assays[162].

Table 5: Examples of different available PSA kinetics calculation tools on the Internet

Website	Developer	Remarks
www.mskcc.org/mskcc/ applications/ nomograms/ PSADoublingTime.aspx	Memorial Sloan-Kettering Cancer Centre, New-York, United States	Part of an extended program of prostate cancer prediction tools and nomograms
psakineticss.sunnybrook.ca/ pg_ application_PSA_ calculator.cfm	Sunnybrook Health Sciences Centre, Toronto, Canada	-
www.pcngcincinnati.org/ psa/calculator. html	Prostate Cancer Networking Group of Greater Cincinnati, United States	-
www.prias-project.org	Erasmus MC, Rotterdam, The Netherlands	Integrated tool for active surveillance

Third, the observation period necessary for obtaining a valid calculation of velocity or doubling time that is not disturbed by considerable short-term fluctuations may be too long or the number of PSA-measurements may be too high for use in clinical practice. The minimal requirements used in current studies are mere estimations. Fourth, as PSA arises from both benign and malignant tissue, the predictive value of PSA velocity or doubling time for cancer progression may be lower in certain groups of patients, making it an unusable parameter in clinical practice during active surveillance. This may be the case in men with large prostates in whom the PSA shed into the blood as a result of benign prostatic hyperplasia exceeds the PSA levels caused by the prostate cancer, or in men who have small prostate tumours or tumours that shed little PSA into the bloodstream, causing, if any, only small oscillations in PSA. The characteristic PSA doubling time of men aged 60 has been described to be 74 years in men without prostatic disease and 12 years in men with BPH. In these two groups, doubling times increase with higher age. In the same study, men with localized and metastatic PC had a median doubling time of 3.0 and 2.0 years respectively[163]. Fifth, both PSA-V as well as PSA-DT may not correlate with early tumour progression, but could be merely indicators of aggressive disease for which the window of curability has already closed, as is presumed by the group of Carter. Finally, the effect of commonly used 5-α-reductase inhibitors on the predictive value of PSA kinetics for tumour progression is uncertain. As 5-α-reductase inhibitors are known to decrease the PSA level with about 50% and mostly suppress the benign components of PSA secretion, they may enhance the utility of PSA and its kinetics in an active surveillance population[164]. The potential of this medication to delay tumour progression in this group of patients is also subject of investigation[165].

CONCLUSIONS

In the absence of better alternatives, PSA kinetics are an important and a very practical parameter we can nowadays offer men on active surveillance to be used when assessing

the status of their prostate cancer. A number of limitations should however be kept in mind when applying PSA velocity or doubling time in clinical practice, including the current deficits in our understanding of the natural behaviour of prostate cancer, the exact relation of true tumour progression with PSA levels, the scarceness of prospectively collected evidence with long follow-up, and several secondary factors influencing singular PSA values.

The best objective evidence from PSA kinetics during active surveillance can be distilled from singular PSA measurements by using internet-based tools and by applying standardized cut-off points. This will provide support during active surveillance and also increases insight, overview, and compliance in both patient and physician. The best evidence on the role of PSA kinetics during active surveillance is available on the PSA doubling time, which seems to correspond significantly with tumour growth. At least 3 measurements over a period of at least 6 months should be used for calculations. A PSA doubling time of more than 10 years can be considered favourable; a PSA doubling time of less than 3-4 years should lead to the advice to switch to radical treatment. PSA kinetics should always be combined with other diagnostics such as digital rectal examination and standard repeat prostate biopsies in an active surveillance program, especially in the 'grey' area between these cut-off values.

Ongoing prospective research is likely to provide further evidence on the value of PSA kinetics during active surveillance, by following large groups of men with early prostate cancer. These efforts should aim to elucidate the role of the (PSA value derived) inclusion criteria for active surveillance, the frequency of PSA measurements, and predictive value of different PSA kinetics and trigger points for prostate cancer progression. Better markers for prostate cancer may offer accurate predictions in the future. Furthermore, co-morbidity aspects and age may be incorporated in active surveillance in the initial selection criteria and trigger points for secondary treatment during follow-up, further enhancing this evolving strategy.

PART IV

QUALITY OF LIFE ISSUES

Chapter 8
Disease insight and treatment perception of men on active surveillance for early prostate cancer
(BJUI 2009)

Chapter 9
Anxiety and distress during active surveillance for early prostate cancer
(Cancer 2009)

Chapter 10
Do levels of anxiety and distress increase during active surveillance for early prostate cancer?
(Submitted)

Chapter 11
Prostate cancer specific anxiety in Dutch patients on active surveillance: Validation of the Memorial Anxiety Scale for Prostate Cancer
(Quality of Life Research 2009)

Chapter 8

Disease insight and treatment perception of men on active surveillance for early prostate cancer

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ABSTRACT

Objective

Active surveillance (AS) for early prostate cancer (PC) instead of radical treatment may partly solve the overtreatment dilemma in this disease, but may be experienced as a complex and contradictory strategy by patients. We investigated the levels of knowledge of PC and the perception of AS in men on AS.

Patients and methods

A total of 150 Dutch men recently diagnosed with early PC participating in a prospective protocol-based AS program (PRIAS study) received questionnaires, including a 15-item measure on general knowledge of PC, and open-ended questions on the most important disadvantages and advantages of AS and on the specific perception of AS. We assessed knowledge scores, and explored potentially associated factors, stated (dis)advantages, and specific perceptions.

Results

The questionnaire response rate was 86% (129/150). Participants provided correct answers to a median of 13 (25-75 percentile: 12-14) out of 15 (87%) knowledge items. Younger and higher educated men showed higher knowledge scores. In line with a priori hypotheses, the most frequently reported advantage and disadvantage of AS were the delay of side effects and the risk of disease progression, respectively. Specific negative experiences included the feeling of losing control over treatment decisions, distress at follow-up visits, and the desire for a more active participation in disease management. No conceptually wrong understandings or expectations of AS were identified.

Conclusions

We found adequate knowledge of PC levels and realistic perceptions of the surveillance strategy in patients with early PC on AS. These findings suggest adequate counselling by the physician or patient self-education.

INTRODUCTION

Active surveillance (AS) is a new treatment strategy for early prostate cancer (PC), consisting of initially withholding radical treatment. Instead, the disease is strictly monitored and active therapy with curative intent is considered at the moment progression occurs. By delaying side effects of surgery or radiation therapy in some and avoiding it completely in others, AS has the potential to partly solve the overtreatment dilemma, which is mainly a result from the overdiagnosis due to screening[59,85].

Better patient knowledge and understanding of disease and treatment has been reported to be associated with better self-management and coping, with improved patients' satisfaction with their care, and increased adherence[166-170].

AS may be perceived as a complex or even contradictory treatment strategy by patients, especially by men with low knowledge of their disease. Disease insight and perception of the treatment strategy may be underexposed but important aspects of treatment satisfaction in patients on AS.

We assessed the level of knowledge of PC and associated factors, and we explored perceived advantages and disadvantages of AS and specific perceptions of this treatment strategy in a group of patients with early PC on AS.

PATIENTS AND METHODS

PRIAS study

All patients included in the present study participated in the protocol-based AS program of the international prospective observational PRIAS study (Prostate Cancer Research International: Active Surveillance)[74]. Men are eligible for the PRIAS study if they have a diagnosis of adenocarcinoma of the prostate with a prostate specific antigen (PSA) level of 10.0 ng/ml or less, a PSA-density (PSA divided by prostate volume) of less than 0.2 ng/ml/cc, T1c or T2 disease, and 1-2 positive prostate needle biopsy cores, with a Gleason score of 3+3=6 or more favourable. After the PC diagnosis and consultation with the urologist, a shared decision is made on the initial treatment strategy. If AS is elected and if a patient subsequently wants to participate in the PRIAS study, written informed consent is provided. The medical ethical committee (MEC) of the Erasmus University Medical Centre approved the PRIAS study (MEC number 2004-339), as did the MECs of the participating 12 non-university hospitals, depending on the local regulations. PRIAS is coordinated from the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC)[16].

Quality of life study in the Dutch part of the PRIAS study

In the period between May 2007 and May 2008, all Dutch men (N=150) with a recent (no longer than 6 months) diagnosis of PC who were included in the PRIAS-study, received a baseline quality of life (QoL) questionnaire by mail at their home address. If the questionnaire was not returned within 1 month, patients were reminded once by telephone. The questionnaire contained measures for psychological, demographical, and other variables. A second follow-up questionnaire was sent at 9 months after diagnosis to those men who had returned the first.

Questionnaire measures included in the current study

Knowledge of PC was assessed using a 15-item measure with 3 response options each (*'True, not true, don't know.'*). Per correctly provided answer, 1 point was added to the total 'Knowledge of PC' score. The total score can range from 0-15, with 15 indicating maximum knowledge on PC. The specific content of all 15 items can be found in Table 2. The measure was based on a 20-item knowledge of PC measure that was previously used to study the effectiveness of an information leaflet on PC screening published by the Dutch Cancer Foundation ('KWF Kankerbestrijding'), from which 5 non-relevant questions in an AS setting were excluded. The measure was similar in size and sort of questions to other knowledge of PC measures as used in other studies[171-173]. A conceptual overlap with items used in these studies was noted in 8 out of 15 (53%) items.

Advantages of AS over other treatment options as perceived by participants were assessed using one open-ended item (*'Which are for you the most important advantages of active surveillance? Start with the most important aspect.'*) with space for 3 possible responses. A similar item was included on the disadvantages of AS.

Specific perceptions of AS were extracted from the open comments section at the end of the questionnaire (*'This is the end of this questionnaire. If you have any comments, please write them down below. Also, if any special personal circumstances influenced your response to the items in this questionnaire please mention these below.'*). Completing this item was optional. Comments provided in the second questionnaire (9 months after diagnosis) were also included in this analysis and was the only item from this follow-up questionnaire that was used in the current study.

Educational level was assessed using 1 item with 6 response options and was divided into two groups defined as 'low education' (primary, secondary education, and/or high school) or 'high education' (professional education, college, and/or university). Employment status was defined as 'employed' or 'otherwise'. Civil status was defined as 'married/living together' or 'otherwise'.

Patient specific information

Medical information (PSA, clinical stage, number of positive biopsies, age) and hospital type were derived from the PRIAS study database. Clinical disease stage was defined as 'T1C' or 'T2'. Age was categorized into <60, 60-70, and >70 years. Hospital type was defined as 'university/specialized' in case a patient was under AS in an academic or specialized-oncologic centre, or as 'other hospital'.

Analysis

Scores on knowledge were assessed and related to educational level, employment status, civil status, age, and hospital type. We hypothesized men with high educational level, employed status, who were married, young age, and under surveillance in a university hospital, to show higher scores on knowledge of PC, with educational level to show the strongest relation. Parameters found to be statistically significantly associated in a univariate regression analysis were entered in a multivariable model. Hypotheses regarding sizes and directions of the potential relationships between these parameters were based on published literature (educational level, civil status, and age)[173,174] and on logical reasoning (employment status, hospital type) that these were potentially relevant in this patient group.

Advantages and disadvantages, and specific perceptions mentioned by participants were extracted, grouped, and counted independently by two of the authors (RCNvdB, MLEB). We hypothesized that the most frequently reported advantage included the delay or avoidance of side effects of radical treatment and that the most frequently reported disadvantage included fear of disease progression.

A p value <0.05 (alpha) was considered statistically significant. For statistical analysis the commercially available software Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL, USA) was used.

RESULTS

Patient population

Of the 150 questionnaires sent, 129 (response rate 86%) were completed and returned a median of 2.4 (25-75 percentile: 1.3-3.9) months after diagnosis. Table 1 presents general, medical, and demographical details of our study cohort. Median age was 64.6 (25-75p: 60.2-70.4) years; 92% were married or living together. Information on ethnicity was not available in our study, but based on surnames of participants, we estimated our cohort to be of >95% Dutch origin.

Table 1: General, medical, and demographical characteristics of the study population (N=129)

General		
Age in years (median, 25-75 percentile)	64.6	30.2 - 70.4
Time in months between baseline questionnaire completion and diagnosis (median, 25-75 percentile)	2.4	1.3 - 3.9
Medical		
PSA in ng/ml (median, 25-75 percentile)	5.7	4.6 - 7.0
Clinical stage		
T1C (%)	91	70.5
T2 (%)	38	29.5
Number of positive biopsies		
1 (%)	79	61.2
2 (%)	50	38.8
Demographical		
Education		
Low (%)	86	67.2
High (%)	42	32.8
Missing	1	
Employed		
Yes (%)	50	39.7
No (%)	76	60.3
Missing	3	
Hospital		
University/specialized (%)	61	47.3
Other (%)	68	52.7
Civil status		
Married/living together (%)	119	92.2
Other (%)	10	7.8

PSA prostate specific antigen

Knowledge of prostate cancer

Table 2 presents the 15 items on PC knowledge we used in this study, answers considered correct, and percentages of men answering correctly. Participants answered a median of 13 (25-75 percentile: 12-14) items correctly (87%); 11 men (9%) answered all 15 items correctly. Despite overall high scores, more than 50% of men thought that metastasized PC is still curable while in reality this is impossible; more than 30% thought that PC does not recur after radical treatment while there is a relevant chance of disease recurrence; and almost 30% of men thought that treating early PC does not cause any urinary incontinence while this is an important side effect of primary treatment, or thought that PC is the second deadliest cancer while the prognosis of PC in general is mainly favourable.

Table 3 presents the univariate and multivariable regression analysis of knowledge of PC score. In univariate regression analysis higher educational level, married status, and younger age were significantly ($p < 0.05$) associated with a higher PC-knowledge score. At multivariable analysis educational level and age remained statistically significantly

Table 2: Question items on prostate cancer in general that were used in this study, answers considered correct, and percentage of study population answering correctly. Per correct answer, 1 point was added to the total 'Knowledge of PC' score (score range 0-15). (N=129)

Question	Answer	Answered Correctly
1.The prostate is situated at the bottom of the abdominal cavity	True	89.1%
2.The risk of being diagnosed with prostate cancer decreases with increasing age	False	94.6%
3. Prostate cancer is more common in men aged 70 than in men aged 40	True	89.1%
4. Prostate cancer may lead to death	True	83.7%
5. Most men diagnosed with prostate cancer will not die of prostate cancer	True	82.2%
6. If prostate cancer has metastasized, curative treatment is no longer possible in most cases	True	44.2%
7. The treatment of early detected prostate cancer may cause unwanted incontinence	True	73.6%
8. After surgery for prostate cancer, side effects may arise, such as erectile problems	True	95.3%
9. Treating prostate cancer through radiation therapy does not cause any side effects	False	83.7%
10. After treatment, prostate cancer stays away in all cases	False	69.0%
11. A man may have prostate cancer, even though he never has symptoms	True	96.9%
12. If prostate cancer is found in an early stage, it may be treated well	True	96.9%
13. Prostate cancer is the second most deadly type of cancer	False	71.3%
14. Urinary problems in elder men are most commonly caused by a benign enlargement of the prostate	True	85.3%
15. It may occur that prostate cancer is detected that would never have caused any problems	True	87.6%

Table 3: Univariate and multivariable analysis of factors associated with the knowledge of PC score

	Univariate		Multivariable	
	β	p value	β	p value
Educational level (low vs. high)	.256	.004	.209	.016
Employment status (employed vs. other)	.075	.407	-	-
Civil status (married/living together vs. other)	-.176	.045	.132	.124
Age at diagnosis (<60, 60-70, >70 years)	-.235	.007	-.197	.022
Hospital type (university/specialized vs. other)	.054	.544	-	-

related with knowledge of PC, with the strongest relation for educational level (β 0.209; P 0.016).

Perceived advantages and disadvantages of active surveillance

Table 4 presents the advantages and disadvantages of AS mentioned by participants. A first, a second, and a third advantage were provided by 120 (93%), 51 (40%), and 20 (16%) out of 129 respondents, respectively. Nine (7%) men did not provide any advantage of AS. A first, a second, and a third disadvantage were provided by 103 (80%), 29 (22%), and 7 (5%) out of 129 respondents, respectively. Twenty-six men (20%) did not provide any

Table 4: Advantages and disadvantages of active surveillance mentioned by participants; total number and percentage of total study cohort. (More than 1 answer could be given by a single participant) (N=129)

Advantage of active surveillance	Number	%
- Delay of any side effects due to physical damage after radical treatment such as incontinence and impotence, so that quality of life and lifestyle are not altered	80	62
- Delay unnecessary radical treatment (no specific reason mentioned)	42	33
- Insight in the clinical behaviour of the disease by frequent checkups and by doing so buying time for the most appropriate decision on treatment	23	18
- No burden and risks of stressful treatment and hospital admission	15	12
- Better treatment options may be available in the future	2	2
- Family situation did not allow for radical treatment	1	1
- Contribution to scientific research	1	1

Disadvantage of active surveillance	Number	%
- Risk of unfavourable consequences on disease status, such as clinical stage progression or the development of metastases	39	30
- Uncertainty and distress (no specific reason mentioned)	25	19
- Frequent checkups, including 3 monthly PSAs, and yearly bothersome prostate biopsy	13	10
- Psychological burden of carrying 'untreated' prostate cancer and being a patient	13	10
- Active surveillance is merely a delay of radical treatment instead of avoidance	6	5
- Contradiction of waiting while having been diagnosed with cancer	6	5
- Active surveillance protocol may not be not adequate to timely detect progression	2	2
- Risk that nerve-sparing surgery is no longer possible in the future	1	1

No advantage was mentioned by 7%, no disadvantage was mentioned by 20% ($p < 0.01$).

disadvantage of AS. Significantly more men failed to provide any disadvantage than any advantage ($p < 0.01$).

The most frequently reported advantage of AS included the delay or avoidance of any side effects of radical treatment, with or without stating the specific reason of being able to continue normal lifestyle. The most frequently reported disadvantage of AS included the potential risk of disease progression, resulting in uncertainty and distress.

Patient perceptions

Out of 129 respondents, 39 (30%) provided comments in the open comments section at the end of the baseline questionnaire; 52 (49%) in the comments section of the 106 available follow-up questionnaires. No conceptually wrong perceptions were identified. Most comments could be assigned as related to the treatment decision, to PC as a disease, and to AS as a treatment strategy. Table 5 presents the specific illustrative statements of 17 different patients.

Table 5: Statements made by men with early prostate cancer on active surveillance related to treatment decision, to PC as a disease, or to AS as a treatment strategy, and patient details (N=17)

Statement	Age (yrs)	Education	Time since diagnosis
TREATMENT DECISION-RELATED			
Confidence in putting the treatment decision in the hands of the physician:			
- 'Because I am a layman only, my choice for active surveillance is mainly based on my confidence in my treating urologist, the decisions he makes, and the (active surveillance) follow-up protocol.'	57	high	4 months
Feeling of losing control over treatment decision:			
- 'I received little to no advice on the treatment-options for my disease; the choice for active surveillance had actually already been made by my urologist.'	55	low	19 days
- 'Living with prostate cancer is something you have to learn. I feel I am handed over to the medical world. Due to a lack of knowledge, it is very hard for me to make decisions on my own.'	55	low	9 months
Important role of a patient's spouse:			
- 'At part 1 of the questionnaire, WE felt unable to give an adequate answer.'	62	low	8 months
PROSTATE CANCER-RELATED			
Varying levels of anxiety and distress due to the diagnosis early PC:			
- 'I am not sure whether I am a 'real' cancer patient, as my PSA fluctuates somewhere around 6 and only a few malignant cells have been found.'	75	high	9 months
- 'It doesn't help to worry about these things. So we just continue on the path we have chosen.'	70	low	9 months
- 'I am depressed, and I am using medication. I am afraid of having cancer at other sites in my body as well, in my abdomen etc..'	49	low	9 days
Unexpected side effects of the diagnosis:			
- 'In general, the knowledge of having prostate cancer isn't causing too much (of) trouble, however, unintentionally, it does influence my sexual interest, which seems to have decreased since the diagnosis.'	57	low	9 months
Other events overshadowing the impact of the diagnosis PC:			
- ' (my experience of prostate cancer) is strongly influenced by the fact that I have lost my wife recently due to the results of pancreatic cancer.'	71	high	4 months
ACTIVE SURVEILLANCE STRATEGY RELATED			
Wish to be in control over the disease:			
- 'Because my PSA kept rising during the last three measurements, I am thinking of getting a PSA test earlier then scheduled according to the active surveillance protocol.'	61	low	9 months
- 'Whenever the PSA level will reach 10.0 ng/ml, I will quit active surveillance and switch to radical treatment.'	64	high	9 months
Difficulties in monitoring PC during AS:			
- 'I do not understand why PSA values vary so much, could this be related to dietary or lifestyle factors?'	60	high	9 months
The possibility of changing from AS to other treatment options:			
- 'I feel well, also physically. Life is still a challenge for me. My religion plays a major role in this. The thought of being under close surveillance for my disease with the possibility of switching to radical treatment when this is necessary is very comforting.'	76	low	8 months
The rise or fall of the PSA values:			
- 'Because the PSA value has been rising over the last three measurements, I am increasingly worried.'	55	low	1 month
- 'As the last 2 measurements clearly showed a lower PSA value, I have become more positive on expectant management, although deep inside the anxiety remains.'	55	low	9 months
- ' Every time my PSA is measured, I am very stressed.'	63	unknown	9 months
Burden of the intensive follow-up regimen:			
- 'The prostate biopsies are painful investigations and have side effects afterwards. I am reluctant to undergo this again, especially since the PSA value is not rising'.	62	low	3 months

DISCUSSION

We found an adequate knowledge of PC and a realistic perception of the treatment strategy AS in a group of men with early PC participating in a prospective AS study, with highly educated and especially younger men having highest knowledge scores. Only a few deficiencies in comprehension in background and treatment of PC and in the treatment strategy AS were identified.

To our knowledge, this is the first study that measures knowledge of PC in men on AS and that explores specific patients' expectations and perceptions of this treatment strategy. The median knowledge score of 13 out of a maximum of 15 may be considered as adequate, although there is no reference for what constitutes 'adequate knowledge' and our study design did not allow for direct comparisons with other patient cohorts receiving other treatments. The incorrectly answered questions suggest that these patients may expect somewhat too much of the possibilities and results of PC treatments. Besides the lack of any association of knowledge with employment status or hospital type, the size and direction of correlations of factors with knowledge were in line with a priori hypotheses.

The most frequently mentioned advantages and disadvantages of AS by participants were also in line with the authors' hypotheses. Our finding that significantly more men provided any advantage of AS than any disadvantage, could be caused by the fact that the advantages of AS may be more emphasized than disadvantages in patient-physician discussions at the moment of treatment-decisions or in the provided patient information, that these are simply remembered better by patients, or that this is a result of a selection bias. Men who are better aware of the disadvantages of AS may tend to choose another treatment-option earlier. No conceptually wrong (dis)advantages were reported, although *'Better treatment options may be available in the future'* (N=2) may not be a realistic consideration.

Various patient specific positive and negative perceptions of the treatment decision, the diagnosis early PC, and the treatment strategy AS were identified. Again, no conceptually wrong ideas or expectations were identified.

We previously found no evidence for an association of anxiety and distress levels with disease knowledge in men on AS[87]. Still, men with less knowledge of PC may be more confused by the treatment strategy AS. Other factors such as physician attitude and advice may play a more decisive role in the eventual choice for and perception of AS[175,176]. We believe that especially in this specific patient group who is living with 'untreated' cancer, adequate knowledge of PC and the treatment strategy AS is essential to understand the advantages and disadvantages of expectant management when compared to radical therapies for localized PC such as surgery or radiation therapy. Reasons for the adequate knowledge of PC levels and realistic perceptions of AS found in our study (even with the

same protocol being applied in different hospitals) remain unknown, but may include counselling by the physician, patient self-education, or a selection bias of men with adequate knowledge choosing AS earlier than men with low knowledge.

Various groups have measured knowledge of PC in different cohorts[171-173,177-179]. Disease knowledge levels were found to be associated with important decisions such as the participation in screening programs[171]. Our finding that younger and higher educated men show higher knowledge of PC scores is in line with other reports[173,177]. Socio-economic group and ethnicity have also been reported to be associated with knowledge levels[178,179], but our study design did not allow for analysis of these parameters.

Denberg et al., after interviewing 20 men, found that treatment decisions in men with localized PC were not uncommonly based on misconceptions and anecdotes, instead of on realistic deliberations on survival and the risk of side effects[180]. This is in contrast with our findings.

Limitations of this study include the use of a non-validated measure on PC knowledge. Attempts to develop a reliable and valid questionnaire to test PC knowledge have been reported, but the use of these measures seems limited[181]. A recent study from the group of Litwin et al. used a self-designed measure, as was done in our study[173]. Second, our study design did not include other patient cohorts who received other treatments for PC, making comparisons impossible. Third, the optional type of items we included on (dis)advantages and on specific perceptions may have limited the value of the response.

A strength of this article is that it is the first to study disease knowledge, (dis) advantages of AS, and potential misunderstandings on AS in men with early PC on AS. Furthermore, extensive questionnaires were used, with a high response rate, completed without any help. Finally, the study was conducted within the controlled environment of the prospective PRIAS study.

Future research should further clarify the role of knowledge of their disease in men with PC and its relation with non-protocol-based decisions to stop AS should be investigated longitudinally[65]. Development of a standardized and validated knowledge of PC measure may also be useful.

In conclusion, this is one of the first studies to provide insight into the thoughts and feelings of patients on AS for early PC. Our cohort of patients recently diagnosed with early PC who participate in a prospective AS program have an adequate knowledge of their disease and report realistic expectations of AS. Although true misconceptions on PC or on AS were not identified, a variety of factors that influence the personal perception of AS were reported. Our findings suggest adequate counselling by the physician or patient self-education.

Chapter 9

Anxiety and distress during active surveillance for early prostate cancer

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ABSTRACT

Background

Patients on active surveillance (AS) for early prostate cancer (PC) may experience feelings of anxiety and distress while living with 'untreated' cancer. These feelings were quantified and their association with various psychological, medical, demographic, and decision-related factors was assessed.

Methods

Men recently diagnosed with PC who participated in a prospective protocol-based AS program (PRIAS study) received a questionnaire (N=150). Scores on decisional conflict (DCS), depression (CES-D), generic anxiety (STAI-6), and PC specific anxiety (MAX-PC) were compared with reference values and the literature. Associations with scores on physical health (SF-12 PCS), personality (EPQ), shared decision-making, knowledge of PC, and demographic and medical parameters were determined with univariate and multivariable linear regression analyses.

Results

The questionnaire response rate was 86% (129/150). Of all respondents 81%, 92%, 83%, and 93% scored better than reference values for clinically significant uncertainty about the treatment decision, depression, generic anxiety, and PC specific anxiety, respectively. Scores were comparable to, or more favourable than, those of men (reported in literature) who underwent other treatments for localized PC. In multivariable analysis, the following associations emerged: a perceived important role of the physician in shared decision-making with higher decisional conflict; better physical health with lower depression; neurotic personality with higher depression, generic and PC specific anxiety; and higher PSA with higher PC specific anxiety.

Conclusions

Men on protocol-based AS mainly report favourable levels of anxiety and distress. A neurotic personality score is associated with unfavourable scores. These findings may help to optimize patient selection for AS or in selecting men for supportive measures.

INTRODUCTION

The incidence of small, localized, well-differentiated prostate cancer (PC) is rising, mainly due to screening. As a result, the ratio between men dying *with* and *from* PC is increasing[67]. Nevertheless, the majority of men with low risk PC primarily undergo some form of radical treatment; this carries a risk of treatment specific side effects that may have a potentially unfavourable effect on quality of life (QoL)[31,34,50].

Active surveillance (AS) is emerging as a realistic strategy to avoid overtreatment by surgery or radiation therapy[66,74]. Men with a favourable disease specific prognosis are candidates for AS. After an initial selection process, radical treatment is withheld and, instead, the disease is closely monitored[59]. Curative active therapy remains an option, but is preferably only chosen when progression occurs. AS is different from the more traditional 'watchful waiting' option, in that the aim of the latter (i.e. optional deferred treatment) is purely palliative.

Apart from the current uncertainties surrounding the medical aspects of AS (long-term outcomes are still unknown), AS may be associated with psychological harms: i.e. patients may experience feelings of anxiety and distress while living with 'untreated' cancer[63]. Empirical data on the levels of such potentially negative emotions among men on AS are lacking, because it is a relatively new treatment option. It is also unknown whether particular men may be at increased risk of psychological distress. Such knowledge could be valuable for selection of the best candidates for AS, or for the initiation of supportive measures during AS.

This study aims to provide insight into the levels of decisional conflict surrounding the choice for AS, as well as the levels of depression, and generic and PC specific anxiety, in men participating in a protocol-based AS program. Secondly, to assess associations between these four variables and psychological, medical, demographic, and decision-related factors.

METHODS

PRIAS study

All patients included in the present study participated in the protocol-based AS program of the international prospective observational PRIAS study (Prostate Cancer Research International: Active Surveillance)[74]. Men are eligible for the PRIAS study if they have a diagnosis of adenocarcinoma of the prostate with a prostate specific antigen (PSA) level of 10.0 ng/ml or less, a PSA-density (PSA divided by prostate volume) of less than 0.2 ng/ml/ml, nonpalpable or localized disease, and no more than two positive prostate needle biopsy cores, with a Gleason score (measure of histological dedifferentiation) of

3+3=6 or more favourable. After the PC diagnosis and consultation with their urologist, patients first decide on AS and then also provide informed consent when they want to participate in the PRIAS study. The medical ethical committee (MEC) of the Erasmus University Medical Centre approved the PRIAS study (MEC number 2004-339), as did the MEC of the peripheral hospitals, depending on the local regulations.

Quality of life study in the Dutch part of the PRIAS study

In the period between May 2007 and May 2008, all Dutch men (N=150) with a recent (no longer than 6 months before) diagnosis of PC who were included in the PRIAS-study, received a QoL questionnaire at their home address. If the questionnaire was not returned within 1 month, patients were reminded once by telephone. The questionnaire contained measures for psychological, demographic, and other variables, and was combined with medical information retrieved from the PRIAS study.

Measures included in the questionnaire

Decisional conflict on the choice for AS was assessed with the Decisional Conflict Scale (DCS), consisting of 16 items with 5 response options each. The total score can range from 0-100, with 100 indicating maximum decisional conflict[182]. DCS scores lower than 25 are associated with implementing the decision, scores exceeding 37.5 are associated with decision delay or feeling unsure about implementation[183]. Subscales of the DCS were not analysed in this study.

Depression was assessed with the Center for Epidemiologic Studies Depression scale (CES-D), consisting of 20 items with 4 response options each. The total score can range from 0-60, with 60 indicating maximum depression[184]. A CES-D score of ≥16 defines an individual as clinically depressive[185].

Generic anxiety was assessed with the abridged State Trait Anxiety Inventory (STAI-6), consisting of 6 items with 4 response options each. The total score can range from 20-80, with 80 indicating maximum generic anxiety[186]. A STAI-6 score of over 44 defines an individual as highly anxious[187].

PC specific anxiety was assessed with the Memorial Anxiety Scale for Prostate Cancer (MAX-PC), consisting of 18 items with 4 response options each (score range per item 0-3). The total score can range from 0-54, with 54 indicating maximum PC specific anxiety[188]. A MAX-PC score of 27 has been applied as a cut-off in other studies to identify individuals with clinically significant PC specific anxiety, which represents an average score of 1.5 on each item[189]. The MAX-PC consists of 3 subscales: PC anxiety, PSA anxiety, and fear of recurrence.

General health was assessed using the short-form health-survey (SF-12), consisting of 12 items with 2-6 response options each. Two scores emerge from the SF-12, the physical component summary (PCS) and the mental component summary (MCS). Both

these total scores can range from 0-100, with 100 indicating best overall health[190]. The SF-12 scoring rules have been designed such that the mean score in the general US population is 50, with a standard deviation of 10. Due to conceptual overlap of the MCS with the CES-D, STAI-6, and MAX-PC, in the present study the MCS was not included in the analysis.

Personality was assessed using the Eysenck personality questionnaire (EPQ), consisting of 48 items with 2 response options each. The total score can range from 0-12 on 4 separate personality scales, with a score of 12 indicating the highest possible score for that specific personality trait[191]. The 4 personality scales are psychoticism, extraversion, neuroticism, and social desirability (of questionnaire response). In statistical analysis, scores on the first three personality scales should be corrected for social desirability[191].

Involvement of the physician in the decision-making process was assessed using a self-developed item: 'Who had the major part (i.e. who had the most influence) in the choice for active surveillance, you or your physician?' with 5 response options. The total score can range from 1-5, with 5 indicating that the decision for AS was made mainly by the physician.

Knowledge on PC was assessed using a self-designed measure (a validated alternative questionnaire on knowledge of PC does not exist), consisting of 15 items with 3 response options each, giving 1 point for each correct answer. The total score can range from 0-15, with 15 indicating maximum knowledge on PC in general. Cronbach's alpha for this measure of knowledge of PC was 0.58. Examples of items are 'Men can have prostate cancer, without having complaints.' and 'Urinary complaints in elder men are most commonly caused by a benign enlargement of the prostate.' ('True'/'false'/'don't know').

Clinical disease stage was defined as 'palpable localized disease' or 'nonpalpable disease'. Educational level was assessed using 1 item with 6 response options and was divided into two groups defined as 'low education' (primary, secondary education, and/or high school) or 'high education' (professional education, college, and/or university). Employment status was defined as 'employed' or 'otherwise'. Civil status was defined as 'married' or 'otherwise'. Hospitals were defined as 'university' in case a patient was under AS in an academic or specialized-oncologic centre, or as 'other hospital'. Other major life events in the period around PC diagnosis were assessed using an open-ended question in the comments section at the end of the questionnaire (coded as 'yes'/'no'). Sexual activity within the last 2 weeks was defined as 'yes' or 'no'.

Validated Dutch translations of the DCS[192], CES-D[193], STAI-6[194], SF-12[195], and EPQ[196] were used. DCS, CES-D, STAI-6, MAX-PC, SF-12, and EPQ were scored applying the official scoring system and regulations for missing values[182,184,186,188,190,191]. For the present study, the MAX-PC was adapted to the Dutch language using formalized forward and backward translation procedures[197]; Cronbach's alpha of the Dutch version was 0.77.

Analysis

First, score distributions of the 4 main variables of interest (DCS, CES-D, STAI-6, and MAX-PC, reflecting decisional conflict, depression, generic anxiety, and PC specific anxiety, respectively) were assessed. Mean scores were compared to reference values and to mean scores of cohorts of patients with localized PC who underwent other treatments (as reported in the literature). We determined the clinical relevance of the differences between the means of different groups using the minimal important difference, which was defined as half of a standard deviation (sd)[198].

Second, DCS, CES-D, STAI-6, and MAX-PC scores were used as dependent variables in separate univariate and multivariable linear regression analyses. We assessed associations of each of these 4 variables with physical health (SF-12 PCS) scores, personality scale scores (EPQ), shared decision-making score, knowledge on PC score, sexual activity, major recent life event, medical parameters (PSA, clinical stage, number of positive biopsy cores), and demographic parameters (age, education, employment, hospital type, and civil status). The underlying hypotheses for including variables in our analysis were partly based on previous studies in which these were shown to be associated with psychopathological features in PC patients[134,199] (physical health, personality, shared decision-making, sexual activity), and partly on intuitive assumptions that these are potentially relevant in this patient group (knowledge of PC, medical characteristics, demographics). We hypothesized that higher scores on knowledge of PC in general and, thus, of the generally favourable disease characteristics (lower PSA and number of positive biopsy cores, nonpalpable disease); higher education level; being employed; married civil status; and more intensive support in a university or specialized oncologic centre would reduce concerns and, thus, potentially would be associated with lower scores on anxiety and distress. Only variables shown to have significant associations in the exploratory univariate analysis were entered in the multivariable models. As recommended by the EPQ manual, the effect of adding a social desirability personality score to the multivariable analyses (independent of its significance in univariate assessment), was also assessed.

Finally, the discriminative power of the 4 resulting models for anxiety (STAI-6, MAX-PC) depression (CES-D), and decisional conflict (DCS) scores under or above the thresholds for clinical anxiety, depression, or decisional conflict were analysed using the are under the receiver operating curve (AUC) (c-statistic). An AUC of 0.50 indicates no discriminative power, and an AUC of 1.0 indicates maximum discriminative power.

A p value <0.05 (alpha) was considered statistically significant. In case variables were not normally distributed, log transformations were used. For statistical analysis the commercially available software Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL, USA) was used.

RESULTS

Patient population

Of the 150 questionnaires sent, 129 (response rate 86%) were completed and returned a mean of 2.7 (sd 1.7) months after diagnosis. These completed questionnaires were sent to patients a mean of 2.2 (sd 1.6) months after initial diagnosis and were completed a mean of 0.4 (sd 0.6) months later. Table 1 presents data on general, medical, demographic, and other patient population characteristics, as well as the scores on the questionnaire measures.

Analysis

The distributions of scores on the 4 main outcome variables (DCS, CES-D, STAI, and MAX-PC) are presented in Figure 1. The DCS, CES-D, STAI-6, and MAX-PC scores were all significantly correlated with each other (Pearson's correlation coefficients 0.19-0.66). Of all men, 81% (104/129) had DCS scores lower than the reference value for decision delay or feeling unsure about implementation (37% (81/129) also had scores below the reference value associated with problems in implementing the decision), 92% (119/129) had CES-D scores lower than the reference value for clinical depression, 83% (107/129) had STAI-6 scores lower than the reference value for clinical anxiety, and 93% (120/129) had MAX-PC scores lower than the reference value for clinically significant PC specific anxiety. In total, 83 men (64.3%) scored below the reference values on all 4 main variables. Three men did not complete the DCS, 1 did not complete the STAI-6.

Compared to the literature, mean DCS scores in our cohort were lower than in a group of 111 American men with localized PC who had decided on treatment (56% elected radical prostatectomy, 19% external radiotherapy, and 25% watchful waiting) 2 months earlier (27.5 versus 35.0; difference >0.5 sd; the sd of scores in our cohort were used)[200]. Mean CES-D scores were comparable with 118 Dutch men (mean age of 62.6 years) who had undergone radical prostatectomy 6 months earlier for mainly localized PC (5.7 versus 7.7; difference <0.5 sd); mean STAI scores were also comparable (35.9 versus 32.2; difference <0.5 sd)[201]. Mean CES-D scores in our cohort were also comparable with 181 Dutch men who had undergone radiotherapy 6 months earlier, also mainly for localized PC (5.7 versus 9.4; difference <0.5 sd); mean STAI scores were also comparable (35.9 versus 34.9; difference <0.5 sd)[201]. Finally, the mean MAX-PC score in our cohort was comparable to 367 mostly Caucasian, mostly married men with both organ-confined and advanced PC, who were awaiting routine clinical oncology appointments[189] (13.9 versus 13.0, respectively; difference <0.5 sd). However, the percentage of our men with MAX-PC scores above the reference value for clinically significant PC specific anxiety was lower (7.0% versus 10.6%, respectively).

Table 1: Characteristics (general, medical, demographic, other, and questionnaire measures) of the study population (N=129)

General						
Total no. of patients		129				
Age in years (mean/median/sd)	64.9	64.6	6.89			
Time in months between questionnaire completion and diagnosis (mean/median/sd)	2.7	2.4	1.7			
Medical						
PSA in ng/ml (mean/median/sd)	5.70	5.70	1.9			
Clinical stage						
Non-palpable (%)		91	70.5			
Localized (%)		38	29.5			
Number of positive biopsies						
1 (%)		79	61.2			
2 (%)		50	38.8			
Demographic						
Education						
Low (primary, secondary) (%)		86	67.2			
High (college, university) (%)		42	32.8			
Missing		1				
Employed						
Yes (%)		50	39.7			
No (%)		76	60.3			
Missing		3				
Hospital						
University/specialized (%)		61	47.3			
Other (%)		68	52.7			
Civil status						
Married/living together (%)		119	92.2			
Other (%)		10	7.8			
Other						
Major life event (not PC)						
Yes (%)		15	11.6			
No (%)		114	88.4			
Sexual active						
Yes (%)		93	72.7			
No (%)		35	27.3			
Missing		1				
Questionnaire measures				Clinical threshold	Observed range	Score range
DCS score (mean/median/sd) *	27.5	28.1	13.7	37.5	0 – 67.2	0 – 100
CES-D score (mean/median/sd) *	5.7	4.0	6.1	16	0 –24.0	0 – 60
STAI-6 score (mean/median/sd) *	35.9	35.0	9.0	44	20.0 – 66.7	20 – 80
MAX-PC score (mean/median/sd) *	13.9	14.0	8.8	27	0 – 39.0	0 – 54
· PC anxiety	9.3	8.0	6.8	-	0 – 29.0	0 – 33
· PSA anxiety	0.3	0.0	1.0	-	0 – 6.0	0 – 9
· Fear of recurrence	4.3	4.0	2.5	-	0 – 12.0	0 – 12
SF-12 PCS scores (mean/median/sd)	50.3	54.3	9.4		14.6 – 62.9	0 – 100

EPQ (mean/median/sd)					
Psychoticism	2.1	2.0	1.3	0 – 6	0 – 12
Extraversion	6.6	6.3	3.4	0 – 12	0 – 12
Neuroticism	3.3	3.0	2.7	0 – 12	0 – 12
Social desirability	8.0	8.0	2.4	0 – 12	0 – 12
Physician role in decision-making (mean/median/sd)	3.2	3.0	1.5	1 – 5	1 - 5
Knowledge of prostate cancer (mean/median/sd)	12.4	13.0	2.0	3 – 15	0 - 15

PSA prostate specific antigen
DCS decisional conflict scale (decisional conflict)
CES-D centre for epidemiologic studies depression scale (depression)
STAI-6 state trait anxiety inventory - 6 (generic anxiety)
MAX-PC memorial anxiety scale - prostate cancer (prostate cancer specific anxiety)
PC prostate cancer
SF-12 PCS short-form health-survey physical component summary (physical health)
EPQ Eysenck personality questionnaire (personality)
* Variable of main interest

Univariate analysis

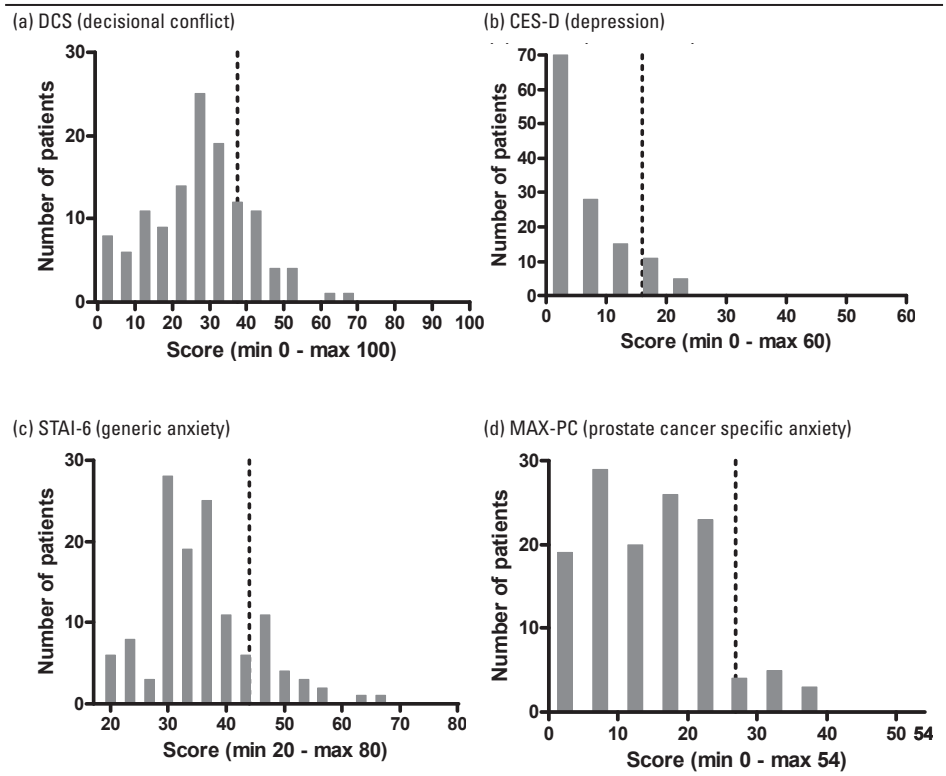
The EPQ neuroticism score and the score on the role of the physician in the shared decision-making process were associated with higher DCS scores, indicating that higher neuroticism scores and a large perceived role of the physician in the decision-making process were associated with increased decisional conflict on AS (Table 2). The EPQ-extraversion score and AS in a university/specialized hospital were associated with lower DCS scores, indicating that high extraversion and follow-up in a specialized centre were associated with lower scores. The EPQ neuroticism score and a recent major life event were associated with higher CES-D scores; the SF-12 PCS, the EPQ extraversion score, and sexual activity were associated with lower CES-D scores. The EPQ neuroticism score was associated with higher STAI-6 scores; the SF-12 PCS was associated with lower STAI-6 scores. The EPQ neuroticism score and PSA were associated with higher MAX-PC scores. No associations were found between any of the main variables of interest and EPQ psychoticism and social desirability scores, knowledge of PC, the time interval after diagnosis, age, clinical stage, number of positive biopsy cores, education, and employment and civil status.

Multivariable analysis

Table 3 gives data on multivariable regression analyses, with separate models for DCS, CES-D, STAI-6, and MAX-PC.

Scores on the role of the physician in the shared decision-making process remained associated with higher DCS scores. The EPQ neuroticism scores remained associated with higher CES-D scores; SF-12 PCS scores remained associated with lower CES-D scores. The EPQ neuroticism scores remained associated with higher STAI-6 scores. The EPQ neuroticism scores and higher PSA level remained associated with higher MAX-PC

Figure 1: Score distributions of (a) DCS, (b) CES-D, (c) STAI-6, and (d) MAX-PC (N=129). Dotted lines indicate reference values for (a) decision delay or feeling unsure about implementation, (b) depression, (c) high generic anxiety, and (d) clinically significant prostate cancer specific anxiety. In these figures, for the purpose of overview, the scores have been summarized in score groups.



DCS	decisional conflict scale
CES-D	centre for epidemiologic studies depression scale
STAI-6	state trait anxiety inventory - 6
MAX-PC	memorial anxiety scale - prostate cancer (total MAX-PC score)

scores. Addition of the EPQ social desirability scores to these models did not change these findings.

The model for predicting depression (CES-D) performed best (adjusted R^2 40%), while the model for predicting decisional conflict (DCS) performed worst (adjusted R^2 11%). Log transformations of scores did not change the above associations.

The AUC for discriminating between scores under and above the clinical threshold was 0.64 for the DCS (95% confidence interval (95% CI), 0.52-0.77), 0.89 for the CES-D (95% CI, 0.78-0.99), 0.74 for the STAI-6 (95% CI, 0.63-0.85), and 0.89 for the MAX-PC (95% CI, 0.79-0.99). Thus the independent variables that were included in the current study performed best in discriminating between high and low depression and PC specific anxiety, respectively.

Table 2: Univariate linear regression analyses of anxiety and distress outcome variables (N=129)

	DCS		CES-D		STAI-6		MAX-PC	
Variable	β	p value	β	p value	β	p value	β	p value
SF-12 PCS	.036	.695	-.396	***<.001**	-.202	***.025**	-.010	.914
EPQ								
- Psychoticism	.128	.153	-.016	.859	.016	.862	.012	.897
- Extraversion	-.178	***.047**	-.227	***.010**	.083	.351	.005	.953
- Neuroticism	.241	***.007**	.547	***<.001**	.430	***<.001**	.450	***.001**
- Soc. Desirability	-.098	.276	-.106	.232	.114	.200	.044	.621
Shared decision-making	.228	***.011**	.132	.139	.088	.332	.103	.251
Knowledge of PC	-.082	.363	-.027	.762	.119	.180	.033	.710
Time between diagnosis and questionnaire	-.093	.313	-.097	.285	-.101	.265	-.071	.433
Age	-.009	.919	.151	.087	-.019	.834	-.059	.504
PSA	.079	.377	.063	.475	.104	.241	.206	***.019**
T stage	-.045	.614	-.037	.677	.089	.319	.097	.277
+ biopsy cores	.059	.513	-.078	.380	-.008	.932	.041	.646
Education	.007	.939	.078	.383	-.064	.473	-.013	.885
Employment	.008	.931	-.145	.104	.005	.957	.077	.393
Hospital type	-.178	***.046**	-.051	.564	-.027	.758	-.156	.077
Civil status	-.017	.846	.137	.122	.069	.440	-.081	.363
Recent event	.013	.884	.211	***.017**	.077	.386	-.028	.756
Sexual activity	.032	.726	-.200	***.023**	-.085	.341	.068	.443

DCS decisional conflict scale (decisional conflict)
CES-D centre for epidemiologic studies depression scale (depression)
STAI-6 state trait anxiety inventory - 6 (generic anxiety)
MAX-PC memorial anxiety scale - prostate cancer (prostate cancer specific anxiety)
SF-12 PCS short-form health-survey physical component summary (physical health)
EPQ Eysenck personality questionnaire (personality)
PSA prostate specific antigen
* Significant ($p < 0.05$)

DISCUSSION

In the present study, the majority of men with early PC included in a protocol-based program for AS showed favourable anxiety and distress scores compared to reference values and to groups of patients with PC who underwent other treatments. A perceived important role of the physician in the shared treatment decision-making, a poor physical health score, a high neuroticism score, and a high PSA value were found to be significantly positively (which is the expected direction) associated with one or more (neuroticism scores) of the DCS, CES-D, STAI-6, and MAX-PC scores. It is interesting that, in the Questionnaire comments section, many men responded positively to filling in an extensive questionnaire (as used in the present study), appreciating the fact that these less-often discussed aspects of their disease were also investigated.

As expected, the 4 main variables of interest were all significantly intercorrelated, indicating that men who scored lower on the decisional conflict scale are, in part (64%

Table 3: Multivariable linear regression analyses of anxiety and distress outcome variables (N=129)

	DCS		CES-D		STAI-6		MAX-PC	
Variable	β	p value	β	p value	β	p value	β	p value
SF-12 PCS	-	-	-.293	*<.001	-.139	.094	-	-
EPQ								
- Extraversion	-.130	.137	-.071	.330	-	-	-	-
- Neuroticism	.168	.061	.462	*<.001	.418	*<.001	.459	*<.001
Shared decision-making	.199	*.025	-	-	-	-	-	-
PSA	-	-	-	-	-	-	.197	*.013
Hospital type	-.139	.109	-	-	-	-	-	-
Recent event	-	-	.121	.096	-	-	-	-
Sexual activity	-	-	-.096	.193	-	-	-	-

Model		p value		p value		p value		p value
R^2	.136	-	.424	-	.209	-	.241	-
Adjusted R^2	.107	-	.399	-	.195	-	.229	-
Model F	4.660	*<.001	16.963	*<.001	15.701	*<.001	19.852	*<.001

DCS decisional conflict scale (decisional conflict)
CES-D centre for epidemiologic studies depression scale (depression)
STAI-6 state trait anxiety inventory - 6 (generic anxiety)
MAX-PC memorial anxiety scale - prostate cancer (prostate cancer specific anxiety)
SF-12 PCS short-form health-survey physical component summary (physical health)
EPQ Eysenck personality questionnaire (personality)
PSA prostate specific antigen
* Significant (p <0.05)

scored below all 4 reference values), the same men who demonstrated low depression scores, generic anxiety, and PC specific anxiety, and vice versa.

Patients who perceived that the physician played the most important role in the shared decision-making process (27 of 129, i.e. 21% reported the maximum score of 5), were also those who had more doubts (high DCS score) about the choice for AS. This suggests that men who perceive that they have actively participated in the treatment decision-making show fewer doubts regarding their treatment decision.

The association between worse physical condition scores (SF-12 PCS) and worse mental health scores was previously reported by Litwin et al. in men with early-stage PC from the CAPSURE™ database[202]; this may be explained by the fact that men who are in good shape are less preoccupied with medical problems.

In our study, a neurotic personality score seemed to be an important determinant of anxiety and distress in men on AS, as this was significantly associated with 3 of the variables of interest. Persons scoring high on the neuroticism subscale are emotional instable, they are usually quickly afraid and can be described as 'worriers'. An important characteristic is that they are constantly preoccupied with things that could go wrong and react rather emotionally to various events, and also show this easily[191]. The perception that such men will show more anxiety and distress when living with 'untreated' cancer is supported by the results of the present study.

Of the measured biological parameters, PSA was the only one (positively) associated with levels of anxiety, this was previously reported by Litwin et al.[202]. Palpable versus nonpalpable disease, or 2 versus 1 positive prostate biopsy core showed no significant association. However, PSA did have the largest range of values.

Steineck et al. explored the effect of watchful waiting on well-being or subjective QoL compared to radical prostatectomy in men with localized PC randomized for treatment[38]. After a mean follow-up of 4 years, no significant differences in QoL scores were found between the watchful waiting and radical prostatectomy cohort. Litwin et al., however, found that men with early stage prostate carcinoma who underwent radical prostatectomy performed better than men on watchful waiting regarding general health-related QoL at 15 months after diagnosis[202]. AS is a relatively new approach and has a curative intent, which is in contrast with watchful waiting. Burnet et al., comparing men with localized PC managed with AS to patients during or after radiotherapy, found no differences in anxiety or distress[203].

Blank et al. observed that the long-term negative psychological effect of treatment for PC was low irrespective of the specific treatment and that it was mainly influenced by patient-bound factors (such as personality and behavioural strategies)[204], which is in line with the results of the present study. Bisson et al. found that the overall levels of psychopathology in men with early localized PC are low and that only a subgroup of men experience distress[205]. Although younger men are reported to show more psychological distress[202,205], this was not evidenced in our cohort.

Our study has some limitations. Firstly, it focused on a selected patient group who had already selected AS to be the initial treatment strategy for their disease. They may have made this decision *because* they experienced low levels of anxiety and distress. The results of the present study should therefore not be generalized to patients with early PC before the treatment decision.

Another limitation of this study is the lack of comparison groups within the same protocol. Instead, scores were compared with reference values and patient cohorts from the literature. A QoL study within a trial randomizing for treatment option, such as the ProtecT study[206], is indicated for this purpose.

Thirdly, we did not use an underlying explicit conceptual model for including the different variables in our intentionally exploratory analysis. Hypotheses for potential correlations were based on previous studies and on our intuitive assumptions.

Finally, because this study is based on cross-sectional data, no conclusions can be drawn about the causal relationship between the variables found to be significantly associated with anxiety and distress.

A longitudinal observational QoL study on AS is currently ongoing within the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Men who are diagnosed with PC and eligible for PRIAS are sent questionnaires

before they have made a decision regarding treatment and are then followed, independent of treatment choice. A longitudinal study approach will reveal whether decisions on treatment options or on switching to deferred radical treatment during AS are influenced by the levels of anxiety and distress, as was observed by Latini et al.[65]. Furthermore, such a study will reveal whether the small group of men who show higher levels of anxiety and distress during AS will actually show less negative emotions after they have received radical treatment. A man may rather be a 'bad patient to have PC', than be a bad candidate for AS specifically.

A strength of the present study is the high compliance rate (86%). In addition, we used an extensive questionnaire (consisting mainly of standardized measures), allowing the simultaneous collection of many different relevant parameters. Furthermore, implementing the QoL study within the prospective PRIAS study allowed a direct prospective approach to all participants. The relatively short follow-up after PC diagnosis (median 2.7 months) decreases the bias of selecting only those patients with a favourable clinical follow-up.

What is the relevance of these findings for clinical urological practice? Awareness that patient-related factors are associated with levels of anxiety and distress may be useful in the shared treatment decision-making process in general, or in the selection of patients for AS. Korfage et al. used the STAI score at diagnosis to screen for patients who were likely to experience high levels of anxiety and depression after treatment[201]. During AS, psychological support may be indicated in a selected group of patients. Interventions during expectant management for PC are premature, but lifestyle changes[207], interventions by frequent telephone calls from a nurse[208], and group support within a peer community setting[209] have been suggested. The predictive and discriminative value of the parameters found to have a significant association with levels of anxiety and distress in the present cross-sectional analysis should be investigated in future longitudinal studies.

CONCLUSIONS

The majority of men in our study population with early PC who chose AS in a protocol-based program show favourable levels of decisional conflict, depression, generic anxiety, and PC specific anxiety on the short-term after diagnosis. A perceived important role of the physician in the treatment-decision, poor physical health, high PSA, and especially a neurotic personality, are associated with less favourable levels of anxiety and distress. In future longitudinal analyses, these findings may prove useful in the initial shared decision-making process for treatment in men with early PC, in the specific patient selection for AS, or in the selection of patients on AS for supportive measures.

Chapter 10

Do levels of anxiety and distress increase during active surveillance for low risk prostate cancer?

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ABSTRACT

Purpose

Anxiety and distress may be present in patients with low risk prostate cancer (PC) on active surveillance (AS). This may be a reason to discontinue AS.

Materials and Methods

Dutch PC patients on AS within a prospective AS study (N=150) received questionnaires at inclusion (t=1) and 9 months after diagnosis (t=2). We assessed changes in scores on decisional conflict (DCS), depression (CES-D), generic anxiety (STAI-6), PC specific anxiety (MAX-PC), and self-estimated risk of progression. We explored the associations of the scores at t=2 with t=1 scores for physical health (SF-12 PCS), personality (EPQ), shared decision-making, knowledge of PC, demographics, and medical parameters, and PSA doubling time (DT) during follow-up.

Results

The t=1 and t=2 questionnaires were completed by 86% (129/150) and 90% (108/120) a median of 2.4 and 9.2 months after diagnosis, respectively. T=1 anxiety and distress levels were previously found to be generally favourable. Significant though clinically non-relevant decreases were seen in the mean scores of STAI-6 (p 0.016), MAX-PC fear of progression subscale (p 0.005), and self-estimated risk of progression (p 0.049). Levels of anxiety and distress at t=2 were mainly predicted by scores at t=1. Higher EPQ neuroticism score and an important role of the physician in the treatment decision had an additional unfavourable effect; good physical health, palpable disease, and higher age had a favourable effect. No association was seen with PSA-DT. Nine men discontinued AS; 2 due to non-medical reasons.

Conclusions

Levels of anxiety and distress generally remain favourably low during the first 9 months of surveillance.

INTRODUCTION

Active surveillance (AS) for low risk prostate cancer (PC) consists of initially withholding radical treatment after diagnosis and closely monitoring the disease instead[59]. The switch to active therapy with curative intent remains an option and is made at the moment progression occurs. AS aims to decrease the current overtreatment of PC by delaying side effects of radical treatment in some patients and avoiding them completely in others[58,85].

The levels of anxiety and distress in men who were recently diagnosed with low risk PC and chose AS have been found to be favourably low[87]. These levels may however increase during follow-up, as living with 'untreated' cancer during expectant management of PC has been shown to be associated with unfavourable levels of anxiety and distress[63,210]. Increased psychological distress may cause men to switch from AS to radical treatment while this is not indicated by the medical protocol[65].

In this study we aimed to assess the changes over time of the levels of anxiety and distress of men with low risk PC on AS and to explore factors associated with these levels during follow-up. Furthermore, we studied the motives of men who discontinued AS to reasons unrelated to progression of PC.

MATERIALS AND METHODS

All patients included participated in the protocol-based AS program of the international prospective observational PRIAS study (Prostate Cancer Research International: Active Surveillance)[74]. If AS is elected after diagnosis and if patients also choose to participate in the PRIAS study, written informed consent is provided. The medical ethical committee (MEC) of the Erasmus University Medical Centre approved the PRIAS study and quality of life (QoL) side study (MEC number 2004-339), as did the MEC of the peripheral hospitals, depending on local regulations.

In the period between May 2007 and May 2008, all Dutch men with a recent (no longer than 6 months before) diagnosis of PC who were included in the PRIAS-study (N=150), received a first QoL questionnaire at their home address by mail (t=1). If the questionnaire was not returned within 1 month, patients were reminded once by telephone. All patients who had returned the first questionnaire received a second questionnaire at 9 months after diagnosis (t=2).

Details of the measures and parameters included in the questionnaire have been described previously[87]. The t=1 questionnaire contained the Decisional Conflict Scale (DCS)[182], the Center for Epidemiologic Studies Depression scale (CES-D)[184], the State Trait Anxiety Inventory (STAI-6)[186], the Memorial Anxiety Scale for Prostate Cancer

(MAX-PC)[188], the physical component summary (PCS) of the short-form health-survey (SF-12)[190], and the Eysenck personality questionnaire (EPQ)[191]. Furthermore, the involvement of the physician in the decision-making process, knowledge on PC in general, self-estimated risk of disease progression, clinical disease stage, educational level, employment status, civil status, hospital type, other major life events in the period around PC diagnosis, and recent sexual activity were assessed. The PSA doubling time (DT) during follow-up was stratified in 4 groups: 0-3 years (most unfavourable), 3-10 years, >10 years, and negative (most favourable). The t=2 questionnaire sent at 9 months after diagnosis included the DCS, MAX-PC, STAI-6, CES-D, and self-estimated risk of progression.

The frequency of scores under or above the reference values at t=1 and t=2 were assessed. The differences in scores on DCS, CES-D, STAI-6, MAX-PC, and self-estimated risk of progression between the t=2 and the t=1 questionnaire were analysed using paired samples T test. The clinical relevance of differences was determined using the minimal important difference, defined as half a sd of the first measurement[198]. Second, the scores at t=2 (second questionnaire) of DCS, CES-D, STAI-6, MAX-PC, and self-estimated risk of progression were used as dependent variables in 5 separate multivariable linear regression analyses. These analyses were corrected for scores at t=1 (first questionnaire) to correct for autocorrelation. Associations with the following variables were explored, available at t=1: physical health (SF-12 PCS) scores, personality scale scores (EPQ; 4 subscales), shared decision-making score, knowledge on PC score, sexual activity, major recent life event, demographical parameters (age, education, employment, hospital type, and civil status), medical parameters (PSA, clinical stage, number of positive biopsy cores); registered during follow-up: PSA-DT, last known PSA. Finally, we identified men who switched to radical treatment while this was not covered by the medical protocol, and interviewed them point-by-point by telephone according to a fixed list of questions.

RESULTS

Table 1 presents the medical, demographic, and other characteristics of the total study patient population (N=129). Figure 1 presents the patient cohort follow-up flow diagram. Between the first and second questionnaire, 9 men (7%) switched to active therapy, of whom 2 due to reasons not covered in the protocol. Treatments consisted of radical prostatectomy in 5 patients (56%), brachytherapy in 2 (22%), external beam radiation therapy in 1 (11%), and an unknown treatment modality in 1 (11%). Twelve men who were still included in the protocol did not respond to the second questionnaire for unknown reasons. The t=1 and t=2 questionnaires were completed by 86% (129/150)

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

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

PSA prostate specific antigen
25-75p 25th – 75th percentile
PC prostate cancer

and 90% (108/120), at median of 2.4 months (25-75p: 1.3-3.9) and 9.2 months (25-75p: 9.0-9.6) after diagnosis, respectively. The 108 men who remained on surveillance and completed both the t=1 and the t=2 questionnaire were not statistically different at diagnosis from the group of 21 men who only completed the t=1 questionnaire (12 non-responders plus 9 discontinued AS) for all measured variables, except for a higher SF-12 PCS (51.4 (N=108) versus 45.2 (N=21)), a higher EPQ Psychoticism score (2.2 versus 1.6), and a higher PSA anxiety score (0.4 versus 0.05). The size of these differences however was small (<0.5 sd). The distribution of the PSA-DT during follow-up based on all the

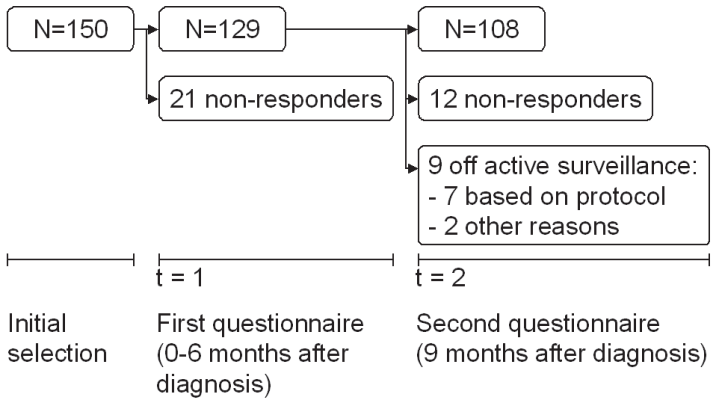

Figure 1: Patient cohort selection flow diagram

PSAs measured between diagnosis and t=2 in the 108 men were as follows: 31% (N=32) 0-3 years (fastest rising PSA levels), 11% (N=11) 3-10 years, 9% (N=9) >10 years, and in 50% (N=52) it was negative (in 4 patients the PSA-DT was unknown).

Table 2 presents the questionnaire scores at t=1 and t=2 of the 129 and 108 men who completed the first and second questionnaire, respectively. Significant decreases were seen in the mean scores on general anxiety (STAI-6) (p 0.016), PC specific anxiety (MAX-PC) fear of progression subscale (p 0.005), and self-estimated risk of disease progression (p 0.049). The decreases however were smaller than half a sd and therefore considered not to be clinically relevant. The percentage of men scoring above the clinical thresholds at t=1 and t=2 were 20% and 25% for DCS, 6% and 8% for CES-D, 17% and 12% for STAI-6, and 7% and 9% for MAX-PC, respectively. For DCS, 9/102 men with a t=1 score under the clinical threshold scored higher than the threshold at t=2, while 8/25 men with a t=1 score higher than the clinical threshold scored under the threshold at t=2. For CES-D, these numbers were 6/121 and 4/8, for STAI-6 5/106 and 10/22, and for MAX-PC total score 1/120 and 1/9, respectively.

Table 3 presents the multivariable linear regression analyses with the scores at t=2 on DCS, CES-D, STAI-6, MAX-PC, and self-estimated risk of progression as dependent variables, corrected for scores at t=1. Only parameters showing a significant association in univariate analysis were included. In all 5 multivariable analyses, the scores at t=1 remained significantly associated with scores at t=2. Furthermore, the following parameters showed an additionally statistically significant association with the scores at t=2: higher EPQ Neuroticism score and higher score for shared decision-making (large perceived role of the physician) with higher DCS scores; high SF-12 PCS scores with lower STAI-6 scores; and palpable disease and higher age with a lower self-estimated risk of progression. Among other non-significant parameters, the PSA-DT (divided into

Table 2: Questionnaire scores at t=1 (N=129) and t=2 (N=108)

			t=1 (N=129) (median 2.4 months after diagnosis)			t=2 (N=108) (median 9.2 months after diagnosis)			
	Score range	Clinical threshold	Mean	Median	25-75p	Mean	Median	25-75p	p *
DCS score	0 – 100	37.5	27.0	28.1	17.2-36.3	27.9	28.1	17.2-36.3	.377
CES-D score	0 – 60	16	5.4	4.0	0.0-9.0	5.3	3.0	0.0-8.8	.929
STAI-6 score	20 – 80	44	35.2	33.3	30.0-40.0	33.4	33.3	30.0-36.7	.016
MAX-PC total score	0 – 54	27	13.7	13.5	6.3-20.0	13.4	14.0	7.0-18.0	.550
- PC anxiety	0 – 33	-	9.1	8.0	3.0-14.0	9.5	9.0	4.0-13.0	.385
- PSA anxiety	0 – 9	-	0.3	0.0	0.0-0.0	0.3	0.0	0.0-0.0	.675
- Fear of progression	0 – 12	-	4.2	4.0	2.0-6.0	3.5	4.0	2.0-5.0	.005
Self-estimated risk of progression	-4 – 4	-	0.2	0.0	0.0-1.0	0.05	0.0	0.7	.049
SF-12 PCS scores	-	-	51.4	54.3	48.9-55.9	-	-	-	-
EPQ									
- Psychoticism	0 – 12	-	2.2	2.2	1.0-3.0	-	-	-	-
- Extraversion	0 – 12	-	6.6	6.3	4.0-9.0	-	-	-	-
- Neuroticism	0 – 12	-	3.2	3.0	4.0-5.0	-	-	-	-
- Social desirability	0 – 12	-	8.1	8.0	7.0-10.0	-	-	-	-
Physician role in decision-making	1 – 5	-	3.1	3.0	3.0-3.3	-	-	-	-
Knowledge of prostate cancer	0 – 15	-	12.5	13.0	12.0-14.0	-	-	-	-

25-75p 25-75th percentile
DCS decisional conflict scale (decisional conflict)
CES-D centre for epidemiologic studies depression scale (depression)
STAI-6 state trait anxiety inventory – 6 (generic anxiety)
MAX-PC memorial anxiety scale - prostate cancer (prostate cancer specific anxiety)
PC prostate cancer
PSA prostate specific antigen
SF-12 PCS short-form health-survey physical component summary
EPQ Eysenck personality questionnaire
* Paired samples t-test

groups) during follow-up showed no significant relation with anxiety and distress levels at t=2, in contrast to our a priori hypothesis. These results did not change when using the difference between first and last known PSA or the PSA-DT as a continuous variable with negative values set to 50 years instead.

Results from the interview by telephone of the 2 participants who discontinued AS due to non-medical reasons are presented in Table 4. Contradictory opinions of different physicians on AS and a lack of confidence in AS were the main motives for discontinuation.

Table 3: Multivariable linear regression analyses of anxiety and distress scores at t=2 (second questionnaire), corrected for scores at t=1 (first questionnaire) (N=108)

	DCS t=2		CES-D t=2		STAI-6 t=2		MAX-PC t=2		Self-estimated risk of progression t=2	
Variable	β	p	β	p	β	p	β	p	β	p
DCS t=1	.636	**<.001**	-	-	-	-	-	-	-	-
CES-D t=1	-	-	.316	**.027**	-	-	-	-	-	-
STAI-6 t=1	-	-	-	-	.561	**<.001**	-	-	-	-
MAX-PC t=1	-	-	-	-	-	-	.782	**<.001**	-	-
Self-estimated risk of progression t=1	-	-	-	-	-	-	-	-	.277	**.003**
T stage	-	-	-	-	-	-	-	-	-.239	**.011**
Age	-	-	-	-	-	-	-	-	-.225	**.016**
SF-12 PCS	-	-	-.176	.132	-.201	**.012**	-	-	-	-
EPQ-neuroticism	.636	**.044**	.208	.113	.090	.295	.015	.829	-	-
Shared decision-making	.152	**.035**	-	-	-	-	-	-	-	-
Knowledge	-	-	-	-	.075	.338	-	-	-	-
PSA-DT group	-	-	-.027	.836	-	-	-	-	-	-
Last PSA	-	-	-.168	.211	-	-	-	-	-	-
Model		p		p		p		p		p
R^2	.551	-	.368	-	.450	-	.622	-	.187	-
Adjusted R^2	.538	-	.312	-	.427	-	.615	-	.163	-
Model F	40.5	**<.0001**	6.6	**<.0001**	19.1	**<.0001**	83.2	**<.0001**	7.6	**<.0001**

DCS decisional conflict scale (decisional conflict)
CES-D centre for epidemiologic studies depression scale (depression)
STAI-6 state trait anxiety inventory – 6 (generic anxiety)
MAX-PC memorial anxiety scale - prostate cancer (prostate cancer specific anxiety)
SF-12 PCS short-form health-survey physical component summary (physical health)
EPQ Eysenck personality questionnaire (personality)
PSA-DT prostate specific antigen doubling time

DISCUSSION

We found that in a group of men with low risk PC who started and remained on AS during a follow-up period of 9 months, levels of anxiety and distress remained favourably low. Only 2 out of 129 men in our cohort discontinued AS due to non-medical reasons. Although the levels of anxiety and distress at t=2 were mainly predicted by scores already seen at t=1, a neurotic personality and an important role of the physician in the treatment decision had an additional unfavourable, and good physical health,

Table 4: Results of telephone interview with two participants who discontinued AS due to psychological reasons

	Participant 1	Participant 2
Age at discontinuing AS	70 years	65 years
Duration of surveillance	4 months	4 months
Active therapy	External beam radiation therapy	Brachytherapy
Perceived benefits of AS?	'I am not aware of any.'	'… no burden of radical treatment.'
Motives for discontinuing AS?	'Waiting while having cancer in your body will only worsen the disease.' 'My GP and the GP of my partner advised against expectant management. I consider their opinion more important than my urologist's advise.' 'A friend died recently within 0.5 year after being diagnosed with metastatic PC.'	'All physicians left the treatment-decision to me, which is very hard for me, because I am a layman only.' 'The physician did not stick to the follow-up protocol, for example the digital rectal examination was not performed.' 'There is a tumour there, it may be non harmful, but still I haven't got confidence in expectant management.'
Role of family friends during AS?	'They were not nervous, as I did not act nervously after being diagnosed with PC. ' 'My family is not specialized in PC, so I don't depend on their opinion too much.'	'I have discussed the switch from AS to active therapy with my spouse, but she did not have any influence on my decision.'
Role physician?	´My urologist advised AS and was perplexed when told him that I wanted to discontinue AS.´	-
Anxiety and distress during AS?	'No, if progression would have been seen, there was always the possibility to switch to surgery.'	'I found the active surveillance strategy a rather unsure situation.'
Other remarks	'The PSA may be low, but still it IS cancer.´ 'I have problems with my potency after EBRT and I have a rising PSA as well, but the idea of being checked every 3 months is very comforting.'	'I was very reluctant to undergo surgery, so I chose brachytherapy'

palpable disease and higher age had a favourable effect on these levels. PSA-DT showed no association.

In the initial treatment decision in a man diagnosed with supposedly low risk PC, the potential side effects of radical treatment should be weighed against the possible unfavourable effects of AS. These include a potentially unfavourable effect of the treatment delay on long-term PC specific mortality outcomes and the potential psychological burden of living with 'untreated' PC.

The levels of anxiety and distress in our cohort were favourable at t=1, as has been reported previously[87], and this situation did not change much during follow-up. The level of anxiety and distress measured in the second questionnaire had an important association with the levels measured in the first questionnaire. It is a well-known phenomenon that previously measured levels on QoL measures are strongly predictive

of the levels measured later[211]. A number of variables showed an additional predictive value for anxiety and distress levels at t=2 in our study. Men with a higher EPQ neuroticism score and a perceived important role of the physician in making the decision for AS showed higher DCS score at the second questionnaire than could be expected from the level at the first questionnaire alone (Table 3). Higher SF-12 PCS scores had a similar additional, but favourable effect on the STAI-6 score, and palpable disease and higher age had a favourable effect on the perceived risk of progression at t=2. However, the parameter that we mostly expected to be of importance, the PSA-DT, was not. Either the assessed follow-up time may be too short or medical parameters such as PSA-DT may play a minor role only in predicting changes in the level of anxiety and distress in patients on AS. Lack of physician's support, or peer or internal pressure to 'do' something may have a more important effect[175]. Factors that were previously found to be associated with higher levels of anxiety and distress at t=1 were poor physical health, EPQ neurotic personality score, an important role of the physician in the treatment decision, and higher PSA[87]. Physical health and EPQ Neuroticism score thus are associated with both the first measured scores as well as with the scores measured at the second questionnaire. Men in good physical condition and low neuroticism personality score who choose AS show favourable levels of anxiety and distress after diagnosis and show a further improvement later.

A thorough review of the psychosocial aspects surrounding expectant management for PC and AS in specific has been published by Pickles et al.[134]. Burnet et al. studied three groups of men with localized PC; the first was undergoing radiotherapy, the second already had received radiotherapy, and the third was on AS[203]. No differences in anxiety and distress levels between these groups were found. Blank et al. observed that mainly patient-bound factors such as personality and behavioural strategies influence the long-term negative psychological effect of treatment for PC[204]. The specific treatment modality played an inferior role.

Korfage et al. studied longitudinally anxiety and depression levels of 299 men with localized PC who were treated with radical prostatectomy or radiotherapy over a period of 5 years after treatment within the European Randomized Study of Screening for Prostate Cancer (ERSPC)[16,201]. STAI and CES-D mean scores decreased and SF-36 mean scores increased significantly after treatment. In the period thereafter, anxiety and distress levels mainly remained stable. The only longitudinal study of QoL aspects in expectantly managed PC patients was performed by Latini et al.[65]. It was found that both PSA kinetics as well as changes in cancer anxiety were related to decisions on treatment-receipt. We did not find a relation with PSA kinetics; the number of men switching to active therapy due to non-medical reasons was too small to analyse.

A limitation of this study is that it focuses on a selected patient group who already had selected AS as the initial treatment strategy for their disease. They may have made this decision *because* they experienced low levels of anxiety and distress. Also, reference scores were used as comparison. So although the favourable scores on anxiety and distress in our cohort look encouraging, direct comparisons with other treatment options for low risk PC are indicated. A QoL study within a trial randomizing for treatment modality, such as the ProtecT study, has the potential to assess these issues[206]. The potential selection bias of including mainly patients with favourable characteristics as described above may be reinforced during follow-up. We found no relevant differences in characteristics when comparing men who remained on AS and completed both questionnaires with men who did not respond to the second questionnaire or who discontinued AS (although the clinically non-relevant difference in the SF-12 PCS scores still might, the mean anxiety and distress scores in the latter groups may be elevated at the moment they discontinued the PRIAS study. Data of these men were not included in our analysis. Also, the follow-up time is short, with a limited time interval between both questionnaires; our findings may be different with a longer time after diagnosis available. Future studies should aim at providing longer-term data on QoL aspects of men with low risk PC on AS and compare these to the effect of other treatments. QoL studies ideally should include both physical parameters such as continence and potency scores, as well as the health-related perceived QoL and perceived anxiety and distress.

A strength of this study is the high compliance rates to the questionnaires. Also, we used an extensive questionnaire, mainly consisting of standardized measures, allowing the simultaneous collection of many different relevant parameters. Furthermore, implementing the QoL study within the prospective PRIAS study allowed direct prospective approach of all participants in this study. Finally, this is one of the first studies to assess longitudinal changes in anxiety and distress in men on AS who live with 'untreated' PC.

CONCLUSIONS

Patients with low risk PC who chose AS show favourably low levels of anxiety and distress from the moment of diagnosis up to 9 months afterwards, independent of the increase or decrease in PSA value. The most important predictors for the levels of anxiety and distress measured at the second questionnaire were the levels measured at the first questionnaire. Additionally, men with low neurotic personality and good physical health scores seem to psychologically perform best during AS.

Chapter 11

Prostate cancer specific anxiety in Dutch patients on active surveillance: Validation of the Memorial Anxiety Scale for Prostate Cancer

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ABSTRACT

Purpose

Men with prostate cancer (PC) may show specific disease-related anxiety. We evaluated the psychometric properties of the Dutch adaptation of the Memorial Anxiety Scale for Prostate Cancer (MAX-PC).

Methods

The MAX-PC was translated using standardized forward-backward procedures. Patients (N=150) on active surveillance, a strategy of initially withholding active therapy, for recently diagnosed early PC were mailed a questionnaire. Internal consistency was estimated using Cronbach's alpha. The scale structure was analysed using confirmatory factor analysis (CFA). Construct validity was evaluated by Pearson's correlations between MAX-PC scores and scores on decisional conflict (DCS), generic anxiety (STAI), depression (CES-D), and general mental health (SF-12 MCS).

Results

Data from 129 respondents was used (response rate 86%). Cronbach's alpha for the total score and the three subscales were 0.77, 0.91, 0.64, and 0.85 respectively. CFA largely confirmed the three-factor structure as used in the original publication (model fit: χ^2 149, p 0.051). The patterns of directions and sizes of the correlations (r=0.36–0.66) between MAX-PC scale scores and the other variables were in accordance with a priori hypotheses, except for the prostate specific antigen anxiety subscale. The relatively poor performance of this scale in the original version was replicated.

Conclusions

The structure and validity of the MAX-PC to quantify PC specific anxiety were largely confirmed in Dutch patients.

INTRODUCTION

Prostate cancer is the second largest cancer-related cause of death in men and accounts for 16% of all cancer diagnoses, with a rising incidence during the last years[48,212]. Active surveillance is a relatively new treatment strategy for men with early prostate cancer. It consists of initially withholding radical treatment, but instead monitoring the disease and switching to active therapy only when progression occurs. Active surveillance may reduce overtreatment, but may cause anxiety and distress while living with 'untreated' cancer.

It is important to have an instrument that adequately measures anxiety specifically related to prostate cancer. To assess prostate cancer specific anxiety, Roth et al. developed the Memorial Anxiety Scale for Prostate Cancer (MAX-PC)[188]. They found that the MAX-PC captured anxiety among men with prostate cancer that might be missed using other more general anxiety measures, while for example it is more strongly associated with changes in PSA (prostate specific antigen) level[189].

We assessed the validity of the Dutch adaptation of the MAX-PC in Dutch men on active surveillance.

METHODS

MAX-PC

The original US MAX-PC was developed for identifying and quantifying anxiety in men with prostate cancer and was designed for self-administration[188]. It consists of 18 items, divided into 3 subscales: 'prostate cancer anxiety' (11 items; example: 'Any reference to prostate cancer brought up strong feelings in me.' - *Not at all, rarely, sometimes, often*), 'PSA anxiety' (3 items; example: 'I have been so anxious about my PSA test that I have thought about delaying it.' - *Not at all, rarely, sometimes, often*), and 'fear of recurrence' (4 items; example: ´Because cancer is unpredictable, I feel I cannot plan for the future.' – *Strongly agree, agree, disagree, strongly disagree*). Total score ranges from 0-54, with 54 indicating maximum anxiety. Scores on the 3 scales range from 0-33, 0-9, and 0-12, respectively. The total MAX-PC was subdivided into the three subscales as it was designed to tap three specific aspects of prostate cancer-related anxiety, although the reliability of the 'PSA anxiety' subscale was found to be weak in the original publication[188]. To our knowledge, the MAX-PC has never been translated or used in an active surveillance setting[188,189,213,214].

Translation

The translation to Dutch followed standardized forward-backward procedures[197]. First, three forward translations by native Dutch with a medical background with fluency in English were performed and pooled into a common version after a consensus meeting. Second, a native English speaker fluent in Dutch and also with a medical background translated this provisional Dutch version back into English, while being blinded to the original version. This back translation showed some discrepancies with the source document, but these were mainly related to the wording and not to the specific meaning of items. Consensus was reached by discussion. The Dutch version of the MAX-PC was first tested face-to-face at the respondent's home in 5 participants, who completed the questionnaire while thinking aloud in the presence of a researcher. Afterwards, guided by a checklist, potential problems in acceptance or comprehension and time necessary for questionnaire completion were explored and discussed with the participant. Only minor problems, different for all 5 participants, were found during this process. These did not indicate a need to adapt the Dutch version of the MAX-PC. The Dutch version of the MAX-PC can be found a https://www.prias-project.org/modules/news/article.php?storyid=12

Patients

Our study group consisted of Dutch patients who had been recently diagnosed with prostate cancer, elected active surveillance as the initial treatment option, and who consented to participate in the prospective protocol-based PRIAS (Prostate Cancer Research International: Active Surveillance)-study on active surveillance[74]. If diagnosed between May 2007 and May 2008, these men received a questionnaire within 6 months after diagnosis. Men are medically eligible for the PRIAS study if they have small, localized, well-differentiated prostate cancer. The medical ethics committee at the Erasmus University Medical Centre in Rotterdam in The Netherlands (coordinating centre) approved this study (number 2004-339).

Questionnaire

Besides the MAX-PC, the questionnaire included the Decisional Conflict Scale (DCS, 16 items with 5 response options: total score 0-100, with 100 indicating maximum decisional conflict) to assess decisional conflict on the choice for active surveillance[182]; the Centre for Epidemiologic Studies Depression scale (CES-D, 20 items with 4 response options, total score 0-60, with 60 indicating maximum depression)[184]; the abridged State Trait Anxiety Inventory (STAI-6, 6 items with 4 response options, total score 20-80, with 80 indicating maximum generic anxiety)[186]; and the Short Form health survey 12 (SF-12, 12 items with 2-6 response options, mean score 50, with a standard deviation of 10 in the general US population) of which we used the Mental Component Summary (MCS) score[190].

Quality criteria

Floor or ceiling effects causing an abnormal score distribution were considered to be present when >15% of respondents had the lowest or the highest possible score, respectively[215].

We estimated the internal consistency by calculating the Cronbach's alpha coefficients for the total MAX-PC and the three subscales. An alpha of 0.7 is generally regarded as sufficient for group comparisons[216].

An initial confirmatory factor analysis (CFA) model was fitted in which each item was assigned to one of three underlying factors, similar to the original publication, to verify that the original factor structure was present in our data[188]. Correlated factors were allowed in this model. The fit of the model was improved by freeing fixed parameters according to the sequence implied by the modification indices. When we found equal or nearly equal modification indices, priority was given to freeing fixed parameters in the covariance matrix of the errors over for instance fixed factor loadings[217]. Model fit was assessed with the chi-square (χ^2) test, the root mean square error of approximation (RMSEA), and comparative fit index (CFI).

Construct validity was assessed by comparing MAX-PC total score and the three subscale scores with DCS, CES-D, STAI-6, and SF-12 scores using Pearson correlation coefficients. Correlations with r >0.3 were considered relevant[218,219]. We hypothesized higher scores on the total MAX-PC and subscales to be related to higher scores on DCS, CES-D, and STAI-6, and to lower SF-12 MCS scores; that correlations were highest with STAI-6, as this measure also is anxiety specific, and lower with DCS, CES-D, and SF-12 MCS; and that correlations with the 'PSA anxiety' subscale were lower, because this is a very specific subscale, previously found to show lower construct validity. We tested differences between correlations with MAX-PC total for significance with a bootstrap procedure to obtain standard errors[220]. At least 75% of the results should be in accordance with a priori hypotheses[215].

Statistical analysis

For statistical analysis the commercially available software Statistical Package for the Social Sciences, (version 15.0; SPSS, Inc, Chicago, IL, USA), S-Plus (version 8.0; TIBCO software, Palo Alto, CA, USA), and LISREL (version 8.72; Scientific Software International, Lincolnwood, IL, USA)[221] were used. A p value of ≤0.05 was considered statistically significant.

RESULTS

Out of the 150 questionnaires sent, 129 were completed at a mean of 2.67 months (sd 1.74) after diagnosis (response rate 86%). Patient characteristics are shown in Table 1, questionnaire scores and distributions in Table 2. All 129 men completed all 18 MAX-PC items. In 8 men the DCS, CES-D, STAI-6, or SF-12 score was discarded, as one or more items of one of these measures were missing.

Only CES-D and the 'PSA anxiety' subscale showed floor effects, with 25% and 85% of subjects exhibiting the most favourable low score, respectively. No ceiling effects were observed.

The Cronbach´s alpha coefficients for the 'prostate cancer anxiety' subscale, the 'PSA anxiety' subscale, the 'fear of recurrence' subscale, and the total MAX-PC were 0.91, 0.64, 0.85, and 0.77, respectively.

The initially fitted CFA model in which the items were assigned to the same factors as in the original publication did not fit very well (χ^2 271.81 with 132 df, $p < 0.001$, RMSEA = 0.081, CFI 0.95). However, the modification indices in the sequence of subsequently fitted models indicated that model fit could be substantially improved by freeing parameters

Table 1: General, medical, and demographical patient characteristics (N=129)

General		
Total number of patients	129	
Mean age (year) (sd)	64.9	(6.9)
Mean time (months) between questionnaire completion and diagnosis (sd)	2.7	(1.7)
Medical characteristics		
Mean prostate specific antigen level (ng/ml) (sd)	5.7	(1.9)
Clinical stage		
T1C (%)	91	(71)
T2 (%)	38	(29)
Demographics		
Education		
Low (primary, secondary) (%)	86	(67)
High (college, university) (%)	42	(33)
Missing	1	
Employed		
Yes (%)	50	(60)
No (%)	76	(40)
Missing	3	
Hospital		
Academic/referral centre (%)	61	(47)
Other (%)	68	(53)
Marital status		
Married/living together (%)	119	(92)
Other (%)	10	(8)

Table 2: Questionnaire scores and distributions (N=129)

	Mean	sd	Median	25-75 percentile	Possible score range	Observed score range	% Minimum score	% Maximal score
MAX-PC total	13.9	8.8	14.0	6-20	0-54	0 – 39	2	0
- Prostate cancer anxiety	9.3	6.8	9.0	3-14	0-33	0 – 29	5	0
- Prostate specific antigen anxiety	0.3	1.0	0.0	0-0	0-9	0 – 6	85	0
- Fear of recurrence	4.3	2.5	4.0	2-6	0-12	0 – 12	6	1
DCS	27.5	13.7	28.1	18.8-36.3	0-100	0 – 67.2	1	0
CES-D	5.7	6.1	4.0	0.5-9.2	0-60	0 – 24	25	0
STAI-6	35.9	9.0	35.0	30-40	20-80	20 – 66.7	5	0
SF-12 MCS	54.1	8.5	55.6	52.2-60.1	Mean 50, sd 10	25.5 – 67.1	0	0

MAX-PC Memorial Anxiety scale - Prostate Cancer (prostate cancer specific anxiety)
DCS Decisional Conflict Scale (decisional conflict)
CES-D Center for Epidemiologic Studies Depression scale (depression)
STAI-6 State Trait Anxiety Inventory – 6 (generic anxiety)
SF-12 MCS Short-Form health-survey Mental Component Summary score (general mental health)

Table 3: Factor loadings (and standard deviations) in the final adequately fitting confirmatory factor analysis model.

	Subscales		
Item	Prostate cancer anxiety	Prostate specific antigen anxiety	Fear of recurrence
1	0.59 (0.07)	-	-
2	0.58 (0.07)	-	-
3	0.62 (0.07)	-	-
4	0.77 (0.07)	-	-
5	0.64 (0.07)	-	-
6	0.52 (0.06)	-	-
7	0.71 (0.07)	-	-
8	0.39 (0.06)	-	-
9	0.38 (0.06)	-	-
10	0.64 (0.08)	-	-
11	0.66 (0.06)	-	-
12	-	0.36 (0.06)	-
13	-	0.14 (0.04)	-
14	-	0.21 (0.05)	-
15	-	-	0.48 (0.07)
16	-	-	0.48 (0.06)
17	-	-	0.60 (0.06)
18	-	-	0.67 (0.06)

Table 4: Construct validity. Pearson correlation coefficients between scores on validated questionnaires and the three domain scores and the total score of the MAX-PC.

Validated outcome scales	MAX-PC I Prostate cancer anxiety	MAX-PC II Prostate specific antigen anxiety	MAX-PC III Fear of recurrence	MAX-PC TOTAL
DCS	0.36 **	0.08	0.45 **	0.41 **
STAI-6	0.59 **	0.27 **	0.59 **	0.66 **
CES-D	0.46 **	0.18 *	0.40 **	0.48 **
SF-12 MCS	-0.36 **	0.04	-0.38 **	-0.39 **

* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)
MAX-PC Memorial Anxiety scale - Prostate Cancer (prostate cancer specific anxiety)
DCS Decisional Conflict Scale (decisional conflict)
CES-D Center for Epidemiologic Studies Depression scale (depression)
STAI-6 State Trait Anxiety Inventory – 6 (generic anxiety)
SF-12 MCS Short-Form health-survey Mental Component Summary score (general mental health)

in the error covariance matrix only, while leaving the factor structure unchanged. Adding 10 extra covariance parameters among a total of 153 of these parameters resulted in a just adequately fitting model (χ^2 148.61 with 122 df, p 0.051, RMSEA = 0.037, CFI 0.99) that had the same factor structure as the original. These freed parameters indicated the presence of small neglected factors. Table 3 presents the factor loadings and standard deviations of the final adequately fitting CFA model.

The correlation coefficients of the MAX-PC scores with DCS, CES-D, STAI-6, and SF-12 MCS are shown in Table 4. The 'PSA anxiety' subscale did not show any relevant correlations (r <0.3); all other correlations were >0.3. In line with prior hypotheses, the strongest correlations of the MAX-PC and the three subscales were seen with STAI-6. The p value for the difference between the correlation MAX-PC total - DCS (r = 0.41) and MAX-PC total - CES-D (r = 0.48) was 0.49, for MAX-PC total – DCS (r = 0.41) versus MAX-PC total – STAI-6 (r = 0.66) p was 0.008. All other possible differences between correlations were significant at the 0.001 level. Correlations were in line with hypotheses in >75%.

DISCUSSION

We largely reproduced the structure and the validity of the MAX-PC as a measure for prostate cancer specific anxiety in a sample of Dutch prostate cancer patients on active surveillance. To our knowledge, no other questionnaires for assessing prostate cancer specific anxiety are available.

The 'PSA anxiety' subscale performed relatively poorly with a Cronbach's alpha of 0.64 and with no relevant correlations with other scores. These problems with the 'PSA anxiety' subscale were also observed in the original version of the MAX-PC[188,189]. The

abnormal score distribution (85% of men in our population exhibited the lowest possible score) limits the value of the 'PSA anxiety' subscale in our study.

Compared to the internal consistency scores reported in other studies (alpha of the total MAX-PC 0.89-0.90; subscales 'prostate cancer anxiety', 'PSA anxiety', and 'fear of recurrence': 0.90-0.91, 0.54-0.64, and 0.82-0.85 respectively[188,189,213]), Cronbach's alpha for the total MAX-PC was somewhat lower in our cohort, but similar for the subscales.

CFA largely confirmed the three-factor structure as used in the original publication. Correlation analysis provided evidence for the construct validity of the total score and the 'prostate cancer anxiety' and 'fear of recurrence' subscales but not of the 'PSA anxiety' subscale. These findings are also in line with results found for the original version[188].

Our study has limitations. Future validation studies should incorporate test-retest reliability, because this is an important quality measure for questionnaires that have a discriminative purpose such as the MAX-PC, and longitudinal validity. Second, our data lack any psychiatric assessment or clinical diagnosis, so cut-off points for clinical prostate cancer specific anxiety could not be established. Finally, we evaluated only a specific subgroup of patients with prostate cancer, i.e. men who are on active surveillance and who received the diagnosis no longer than 6 months earlier. As clinimetric properties may vary between different study populations, it is recommended to further validate the MAX-PC in other prostate cancer patient cohorts, e.g. before and after surgery or radiation therapy. Only with a multiple-group model or a direct comparison with the original version of the MAX-PC, the above-mentioned assertions on the validity of the Dutch version of the MAX-PC can be confirmed.

In conclusion, we found positive evidence for the appropriateness of the MAX-PC to identify and quantify prostate cancer specific anxiety. It may allow for comparisons between Dutch patients and other international observations and for comparisons of the effect of treatments and/or supportive measures. However, some weaknesses in the original version, especially regarding the 'PSA anxiety' subscale, were also replicated in the adapted Dutch version. The 'PSA anxiety' subscale of MAX-PC may need to be revised.

NEDERLANDSE VERSIE MEMORIAL ANXIETY SCALE – PROSTATE CANCER (MAX-PC)

UW OORDEEL OVER PROSTAATKANKER EN PSA-TESTS (PROSTAAT SPECIFIEK ANTIGEEN)

Wij willen graag beter begrijpen hoe patiënten omgaan met de behandeling voor prostaatkanker en de onderzoeken die daarbij komen kijken.

Omcirkel op elke regel één getal.

I. Hieronder vindt u uitspraken van mannen over prostaatkanker. Geef aan hoe vaak elke uitspraak voor u van toepassing was: helemaal niet, zelden, af en toe, vaak.
Omcirkel het nummer van uw antwoord.
Denk aan de *afgelopen week*.

1. Elke verwijzing naar prostaatkanker riep sterke gevoelens in me op.
2. Hoewel het goed is om te doen, vond ik het beangstigend om mijn PSA te laten meten.
3. Elke keer als ik iets hoorde over een vriend of beroemdheid met prostaatkanker, werd ik bezorgder over het feit dat ik prostaatkanker heb.
4. Bij de gedachte aan het laten meten van het PSA, werd ik ongeruster over het feit dat ik prostaatkanker heb.
5. Andere dingen deden me steeds aan prostaatkanker denken.
6. Ik voelde me als het ware verdoofd als ik aan prostaatkanker dacht.
7. Ik dacht aan prostaatkanker zonder dat ik het wilde.
8. Ik had veel gevoelens over prostaatkanker, maar ik wilde ze niet onder ogen zien.
9. Ik viel moeilijker in slaap, omdat ik gedachten aan prostaatkanker niet van me af kon zetten.
10. Ik was bang dat de uitslag van mijn PSA-test zou aantonen dat mijn ziekte aan het verergeren was.
11. Alleen al bij het horen van het woord 'prostaatkanker' werd ik bang.

II. Geef bij de volgende drie vragen aan hoe vaak elke situatie *ooit* voor u van toepassing was.

12. Ik zag er zo tegen op om mijn PSA te laten controleren, dat ik erover dacht de test uit te stellen.

13. De uitslag van de PSA-test verontrustte mij zo, dat ik overwoog om de arts te vragen de test nog een keer te doen.
14. Ik zat zo in over de uitslag van mijn PSA-test dat ik overwoog de test voor de zekerheid bij een ander laboratorium over te laten doen.

III. Hieronder staan uitspraken over wat iemand van zijn eigen gezondheid kan vinden. Geef aan in hoeverre u het eens bent met elke uitspraak: helemaal eens, eens, oneens, helemaal oneens.
Omcirkel het nummer van uw antwoord.
Denk aan de *afgelopen week*.

15. Omdat kanker onvoorspelbaar is, voel ik mij niet in staat plannen te maken voor de toekomst.
16. Mijn angst dat de kanker erger wordt belemmert mij te genieten van het leven.
17. Ik ben bang dat de kanker erger wordt.
18. Ik ben meer gespannen sinds bij mij prostaatkanker is vastgesteld.

PART V

GENERAL DISCUSSION

Key findings

Perspective

Epilogue

Key findings

This thesis in the first place aimed to analyse in which patients with prostate cancer an initial strategy of active surveillance may be suitable and safe. A total of 616 men were studied who were diagnosed with low risk prostate cancer according to criteria based on the literature (defined as stage T1c of T2 disease, with a prostate specific antigen (PSA) ≤10.0 ng/ml, a PSA-density <0.2 ng/ml/cc, 1 or 2 positive biopsies, and a Gleason score of 3+3=6 or more favourable) and who were also initially managed expectantly[85]. These patients participated in one of the three included study centres of the ERSPC (European Randomized Study of Screening for Prostate Cancer) and were diagnosed between 1994 and 2007. A very favourable 10-year prostate cancer specific mortality of 0% was observed, while almost 1 out of 4 men had died in the same period due to other causes. Then, 69 men with the same tumour characteristics who also started on expectant management but switched to radical prostatectomy later (on average 2.6 years after diagnosis) were compared to 158 similar men who received immediate radical prostatectomy after diagnosis[108]. No significantly higher risk of unfavourable histopathological or biochemical outcomes after radical prostatectomy was seen. An initial strategy of active surveillance thus retrospectively seems suitable and for now acceptably safe in patients with screen-detected low risk prostate cancer. Taking the long natural history of these cancers into consideration however, longer follow-up is needed to draw definitive conclusions. In a number of patients with low risk prostate cancer, adverse histopathological outcomes are seen after radical prostatectomy, despite the fact that surgery was performed immediately after diagnosis[222]. Lowering the thresholds of diagnostic parameters used to define low risk prostate cancer or using a nomogram-derived risk indication to define low risk prostate cancer decreases, but would not exclude the number of incorrectly selected patients. At the same time, this would reduce dramatically the number of patients suitable for expectant management. Finally, indications were found that the inclusion criteria for active surveillance may be widened in select patients[223]. In a group of 50 men with Gleason score 7 prostate cancer a prostate cancer specific mortality of 0% was seen 6 years after diagnosis. The most important limitations of the retrospective analysis as described above are a non-randomized design, an incomplete short follow-up, a lack of using a fixed protocol for expectant management, and an overlap between patients on watchful waiting with palliative intent and active surveillance as applied in some centres.

Secondly, this thesis aimed to explore how a strategy of active surveillance should be applied prospectively. Offering an active surveillance protocol for inclusion and follow-up via a web-based decision tool is feasible[74]. This is being done in the prospective multicenter PRIAS study (Prostate Cancer Research International: Active Surveillance).

PRIAS uses the selection criteria for low risk prostate cancer as described above. The surveillance protocol consists of frequent PSA measurements, digital rectal examinations, and standard repeat prostate biopsies. Of the first 500 PRIAS patients included, 1 out of 4 had discontinued active surveillance and had switched to radical treatment at 2 years after diagnosis[102]. The main reason was a high frequency of adverse findings in the repeat biopsies. The PSA doubling time was not associated with the favourable or unfavourable outcome of the repeat biopsies. Although this parameter is widely considered to be suitable to monitor disease status during active surveillance, the evidence for the usefulness of PSA kinetics is currently limited and contradictory[89]. The main limitations of this prospective analysis of active surveillance are a non-randomized design and a limited follow-up time available.

The third aim of this thesis was to study the effects of active surveillance on patients' health-related quality of life. A questionnaire-based study was therefore performed. In 129 men on active surveillance who participated in the PRIAS study specific personal insights and experiences influenced the perception of prostate cancer[224]. The level of knowledge of prostate cancer was adequate in most patients and no misconceptions on the strategy active surveillance were found. In the same selected group of 129 patients, the levels of anxiety and distress while living with 'untreated' prostate cancer generally were favourably low when compared to reference scores and the literature[87]. Men with a neurotic personality and poor physical health showed less favourable scores. The levels of anxiety and distress remained favourable during a follow-up period of 9 months[225]. Finally, the structure and psychometric validity was confirmed of a Dutch translation of a questionnaire specifically on prostate cancer specific anxiety[226]. Limitations of these health-related quality of life studies include a non-randomized design, a selection bias due to including only men who had already made the choice for active surveillance, a lack of comparison groups who received other treatments within the same study, and the limited follow-up time.

Perspective

THE FOUNDATION OF EXPECTANT MANAGEMENT

'Cure might not be possible in those prostate cancer patients in whom it is needed.'[227] Screening has the potential to decrease prostate cancer (PC) specific mortality. By repeated screening over a period of 9 years, a reduction of 20% in PC specific mortality was achieved in the European Randomized Study of Screening for Prostate Cancer (ERSPC) intention-to-screen analysis[16]. This means that on a population level, 4 out of every 5 men who would have died due to PC without screening still do so. Although for some of these men the reason for this unfavourable course was that the diagnosis was made in an already advanced and incurable stage, the favourable effect of radical treatment on the natural history of localized PC also is only limited. Radical prostatectomy (RP) decreases PC specific mortality from 18% to 13% and development of metastasis from 26% to 19% when compared to expectant management with delayed hormonal therapy[28]. The favourable effect of radical treatment was limited to men aged <65 at diagnosis[117].

'Cure might not be needed in those PC patients in whom it is possible.'[227] PSA screening also is one of the main reasons for the overdiagnosis of PC. Rates have been estimated at 84% if life expectancy (PC specific mortality) is taken as the endpoint and 50% if PC diagnosis (symptomatic disease) only is considered[54,228]. Especially well-differentiated and confined tumours have only a very limited unfavourable effect on patients' life expectancy even when managed expectantly[13,81,229]. The very smallest 'indolent' tumours comprise as much as 32% of all cancers detected in a first-round screening setting, which may be comparable to modern urological practice[230]. Still, many overdiagnosed PCs unnecessarily receive radical treatment[58].

More selective screening holds the key to decrease the overdiagnosis of PC while minimising the number of significant PCs that are being missed. Research within studies such as the ERSPC should focus on using pre-diagnostic parameters to most accurately identify indolent cancer on one side and assess the risk of harbouring potentially lethal PC on the other side and adapt the indication to perform a biopsy accordingly. For this purpose, future screening protocols may be individualized based on additional medical parameters, age, and comorbidity, using nomograms or risk indicators[231,232].

Currently, the most important studies on the natural history of PC and the effect of radical treatment are still based on cohorts diagnosed in the pre-PSA era. Since then, the outcomes of PC detected in the screening era may have improved. The currently frequently applied active therapy of tumours that would not have altered life expectancy

may have diluted the favourable effect of radical treatment as found in the pre-PSA era. Trials randomizing for treatment modality in contemporary PC patients such as ProtecT[233], START[234], and PIVOT[235] will provide essential contemporary information on the natural history of screen-detected PC and the effect of radical treatment in general and in specific patient groups.

Key studies on PC screening, treatment, and risk reduction are presented Table 1.

SELECTION FOR ACTIVE SURVEILLANCE

Expectant management is justified in all PCs that can be safely identified as being indolent and thus would remain asymptomatic when remaining untreated. The pathological characteristics of indolent PC have been defined RP specimens as <0.5 ml, organ-confined, and with no Gleason pattern 4 or 5[103,115]. The incidence of these tumours is ~32% in patients receiving RP at first round of screening for PC[230]. The difficulty is that it is impossible at present to differentiate with certainty at the moment of diagnosis between those men who harbour indolent disease and those who do have

Table 1: Key studies on PC screening, treatment, and risk reduction

Acronym	Name	Location	Main study question/outcome
ERSPC	European Randomized Study of Screening for Prostate Cancer	Europe	Screening for PC reduces PC specific mortality with ~20%.
PCPT	Prostate Cancer Prevention Trial	US	Finasteride reduces the risk of PC with ~25%, though more high-grade disease is detected.
PIVOT	Prostate cancer Versus Observation Trial	US	Surgery vs. watchful waiting in screen-detected localized PC. - *Ongoing*
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	US	Screening for PC does not reduce PC specific mortality.
ProtecT	Prostate testing for cancer and treatment	UK	Surgery vs. radiotherapy vs. AS in screen-detected PC. - *Ongoing*
REDEEM	Reduction by Dutasteride of Clinical Progression Events in Expectant Management	US/Canada	Effect of Dutasteride on disease progression during AS. - *Ongoing*
REDUCE	Research Study To Reduce The Incidence Of Prostate Cancer In Men Who Are At Increased Risk	Worldwide	Dutasteride reduces the risk of finding PC by ~23%.
SPCG-4	Scandinavian Prostate Cancer Group Study 4	Scandinavia	Surgery has a favourable effect on PC specific mortality of ~5% vs. watchful waiting in clinically diagnosed patients.
START	Standard Treatment Against Restricted Treatment	Canada	Surgery or radiation therapy vs. AS. - *Ongoing*

PC prostate cancer
AS active surveillance
US United States
UK United Kingdom

significant PC. The fact that the (pre-operative) prediction of insignificant cancer is not perfect however is not an excuse to radically treat all diagnosed PCs in an 'all or nothing' approach. Parameters such as the Gleason score are highly predictive for mortality rates, but their discriminative value is limited. In selected subgroups of PC patients mainly very favourable disease specific outcomes are seen after expectant management (although longer term data should be awaited)[85]. The same selected men may however still die due to PC, even after aggressive treatment[222]. Risk assessment at the moment of diagnosis for the natural history of PC should thus be improved.

Studying the discriminative value of diagnostic parameters for the natural clinical outcomes of PC is difficult. First, as not treating curable cancer goes against the logical clinical sense, cohorts with expectantly managed patients are scarce[236]. Second, the available cohorts are made up mainly of the most favourable tumours. Third, the performance of the available diagnostics is limited. Certainty on the actual stage and grade of PC is only available after the prostate has already been removed and cannot be obtained by biopsy.

Different strategies may be applied to improve our risk assessment of whether a tumour will be lethal later or will remain asymptomatic. We have however to realize that we are in a learning curve with this process. First, the use of the available diagnostic parameters may be optimized. Currently ongoing active surveillance (AS) studies combine thresholds of clinical stage, PSA, PSA-density, number of positive biopsy cores, percentage of core involvement, and Gleason score[66,74,80,97,98,105,132]. Details of inclusion criteria of ongoing AS programs are presented in Table 2. By associating different combinations of different thresholds of inclusion criteria to the presence of indolent disease and to the natural history of PC, an optimal combination of parameters may be found to more accurately identify indolent disease[236]. If currently used inclusion criteria for

Table 2: Ongoing active surveillance studies and inclusion criteria

Coordinating centre	Country	Inclusion criteria
Sunnybrook, Toronto[66]	Canada	Stage T1c-T2a, if age <70: PSA ≤10, ≤3+4=7; if age >70: PSA ≤15, ≤6
Erasmus MC, Rotterdam[74]	The Netherlands	Stage T1c-T2, PSA ≤10, PSA-density <0.2, 1-2 positive biopsy cores, Gleason score ≤3+3=6 (PRIAS)
Royal Marsden, Surrey[80]	UK	Stage T1-T2a, PSA <15, <50% positive biopsy cores, Gleason score ≤3+4=7
University of San Francisco[97]	US	Stage T1-T2a, PSA <10, <33% positive biopsy cores, Gleason score ≤6
University of Miami[105]	US	Stage ≤T2, PSA ≤15, 1-2 positive biopsy cores, Gleason score ≤6, <50% PC tissue per core
Johns Hopkins, Baltimore[98]	US	Stage T1c, PSA-density ≤0.15, Gleason score ≤6, 1-2 positive biopsy cores, <50% PC tissue per core
University of Connecticut[132]	US	Stage T1c-2a, PSA <10, 1-2 positive cores, Gleason score ≤6, <50% PC tissue per core

PSA prostate specific antigen
PC prostate cancer
PRIAS Prostate Cancer Research International: Active Surveillance

AS turn out to be safe, the thresholds may be extended. Second, probabilistic selection for indolent PC using risk indications from nomograms may be used. This is preferable over (arbitrary) rule-based selection[12,237,238]. Rule-based selection includes subjects who have multiple parameters just below the thresholds and therefore are selected unjustifiably; a probabilistic selection includes subjects with one of the parameters just above the threshold, but should be selected justifiably. Figure 1 illustrates the difference in selection when using either a set of rule-based criteria or a nomogram (probabilistic selection). Multiple probabilistic selection tools (nomograms) have become available, using different parameters available at different steps in the clinical process to predict future findings. Figure 2 illustrates the different clinical steps in PC and examples of available nomograms. The 'ideal nomogram' would be one that uses non-invasive parameters, available in an early stage, to predict definitive outcomes after treatment or of the natural history of a tumour. The indication for expectant management is based on the balance between the chance of dying due to other causes and the chance of progression of PC. The third strategy is therefore to obtain an adequate indication of the life expectancy of patients. By modelling the time between diagnosis and symptoms for different risk predictions of indolent disease and combining these with life expectancy (using a wide margin on the 'safe side'), an individualized selection for expectant management would be possible[239-241]. In elderly patients, wider inclusion criteria for AS of PC may be applied. Fourth, new biomarkers that allow for more accurate estimations of the presence of indolent disease may be used. These will be discussed later.

ACTIVE SURVEILLANCE

AS aims to compensate for the imperfections in future risk assessment of PC at the moment of diagnosis by incorporating a strict follow-up protocol. Tumours that appear not to be suitable for expectant are aimed to be found timely so curative treatment may still be given. Parameters used during AS follow-up should ideally:

· Reflect significant changes in pathological tumour status
· Identify disease progression within the window of curability
· Balance the burden of frequency of diagnostics and the potential delay until treatment
· Leave minimal impact in terms of costs and quality of life

Currently ongoing AS studies mainly use PSA, digital rectal examination (DRE), transrectal ultrasound (TRUS), and repeat biopsies as follow-up parameters[66,74,80,97,98,105,132]. The time interval that is applied between PSAs is 1-6 months, between DREs and TRUS 3-12 months, and between standard repeat biopsies 6-36 months[62,74,93,97,105,119,238].

Although repeated measurements provide frequent new information on the status of the disease and may correct for previous undersampling, it is unknown with which

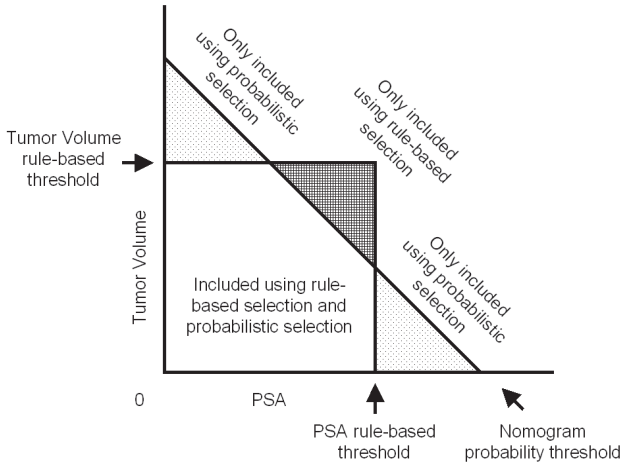

Figure 1: This graph explains the difference in selection when using either a set of rule-based criteria or a nomogram (probabilistic selection). A hypothetical model is presented, in which the parameters PSA value and tumour volume are used to select indolent prostate tumours. Rule-based selection includes subjects with a PSA and a tumour volume both just below the threshold, but who actually unlikely have an indolent tumour (dark grey); the nomogram includes subjects with a PSA or a tumour volume just above the threshold, but who still likely have an indolent tumour (light grey).

PSA prostate specific antigen

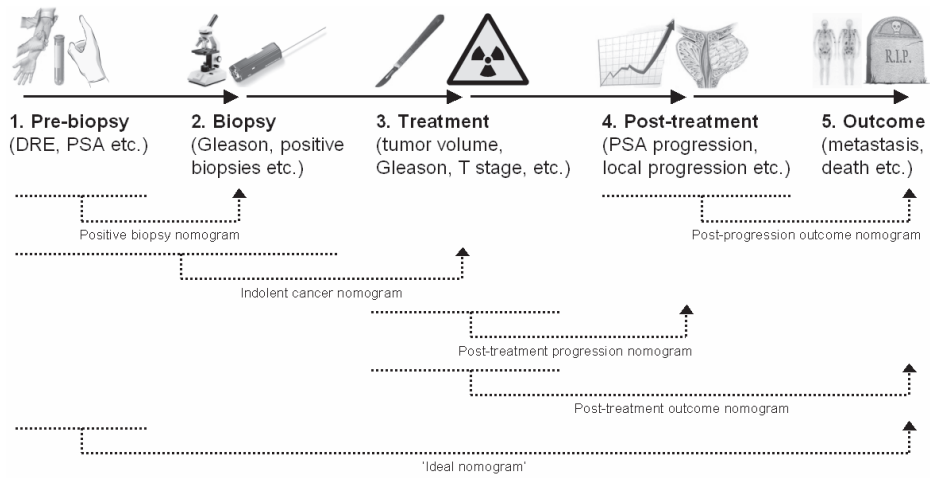

Figure 2: Schematic representation of the different clinical steps in prostate cancer, examples of relevant parameters, and examples of existing nomograms using available information to predict future steps. In an expectant management situation, steps 3 and 4 are skipped.

DRE digital rectal examination
PSA prostate specific antigen

frequency these measurements should be repeated to identify disease progression within the window of curability. Future research should therefore aim to find which (changes in) parameters have the strongest relation with the presence of indolent or significant disease. Also, it should be studied at which frequency these measurements should be repeated to timely detect disease progression and which thresholds should be used as trigger points to switch from AS to radical treatment. When following men with PC, it is preferable for the intensity of the follow-up program to lean to overtreating some men, rather than to not actively treating some men with significant cancers. These issues may be studied by relating follow-up parameters to histopathological findings at repeat biopsies or at RP, or to morbidity and mortality outcomes within AS programs. Models of tumour growth and dedifferentiation may be used to get a better impression of the appropriate frequency at which measurements should be repeated during follow-up. If current AS protocols appear to be safe, the frequency of measurements and exclusion criteria may be relaxed. As holds true for the inclusion criteria, rule-based exclusion criteria during follow-up may also be replaced by probabilistic exclusion using nomograms. The speed of changes in nomogram risk assessments may then be used to continue or discontinue AS, taking age and comorbidity into account in order to individualize the follow-up to the specific patient. Potential new biomarkers may of course also be used during follow-up.

PSA KINETICS

As reviewed in this thesis, the evidence for a relation of the speed of rise of PSA during AS with definitive endpoints is limited and contradictory[89]. The physiological variation of PSA causes PSA-DT (doubling time) calculations to fluctuate and may be the most important cause of the lack of predictive value of the doubling time. In other chapters in this thesis, evidence neither was found for the relation of PSA kinetics during expectant management with histopathological RP findings, repeat prostate biopsy findings, or levels of anxiety and distress[102,108,225]. Still, PSA kinetics is used in most ongoing AS studies[66,74,80,97,105,132]. One AS protocol however has abandoned the PSA kinetics as a prognostic factor to monitor disease status, because the opinion of this research group is that the window of curability has already closed at the time PSA kinetics indicate disease progression[98]. The different AS programmes use either PSA-DT (time in which the PSA value doubles) or PSA velocity (absolute rise in PSA in a specified time interval). PSA-DT may better reflect exponential tumour growth and PSA rise than PSA velocity, but PSA velocity may still have a better predictive value for disease progression during AS[155,242].

There is a lack of knowledge on whether PSA kinetics during AS are predictive of morbidity and mortality later and whether disease progression can be detected on time. Furthermore, the best methods of calculation should be assessed[143,243], as well as the frequency of PSA measurements and the number of measurements needed for calculation. Most of the studies that have been performed on this subject were not done within prospective protocols for AS with frequent PSA measurements, but in retrospective cohorts of patients who received only a small number of PSA measurements over relatively long time intervals. The value of PSA kinetics during AS should therefore be studied within prospective AS studies[128]. Different derivates and calculations of PSA kinetics and trigger points to switch to active therapy should be compared and associated with findings in repeat biopsies, findings in deferred RP, biochemical progression after RP, metastases, and mortality. The predictive value of changes in other parameters during follow-up should also be explored, such as the change in PSA-density.

DIAGNOSTIC AND REPEAT BIOPSIES

Prostate needle biopsies are the golden standard to obtain prostatic tissue for histological evaluation and cancer diagnosis. Since prostate biopsies result in a random sample of tissue, an important problem of these biopsies is the frequent discrepancy between prostate biopsy findings and the 'real tumour' Gleason scores and tumour volume as found in RP. Incorporating standard repeat biopsies in the selection for AS may improve the initial undersampling. The repeat random biopsies however result in more tissue from same prostate regions. Higher-grade or larger tumour volume may however be present at other locations, such as the anterior region of the prostate[244]. Upgrading and downgrading between biopsy and prostatectomy Gleason score occurs in as much as 30-50%, although a discrepancy of 2 or more Gleason score points is much rarer[102,124,245]. The aim of prostate biopsies in an AS setting is to assess tumour disease stage and grade with enough certainty to safely start on AS. Repeat prostate biopsies may correct for undersampling in time or detect true biologic tumour progression. The burden of the frequency of the prostate biopsies and the number of biopsy cores should be minimized.

Future studies are important to determine the perfect biopsy schemes regarding biopsy site and number of cores in an AS inclusion and follow-up setting, dependent of prostate specific features such as volume. RP specimens of patients with supposedly low risk PC and of patients who started on AS and switched to surgery later should be investigated to study where tumours and missed high-grade parts of the tumour are located and how many random biopsy cores are needed to adequately sample these tumours. Models based on biopsies of RP specimens may provide the most appropriate

schemes[246]. The anterior region of the prostate may harbour the largest tumours during AS, as this region is under sampled during normal random biopsies[244]. The yield of a prostate biopsy series can be improved either by taking more biopsy cores or by increasing the sensitivity of biopsy cores. Taking more biopsies decreases but does not solve the problem of undersampling; Gleason score upgrading was still seen in 23.5% even when >18 cores were taken[111]. Including regions that are normally not sampled may be useful in an AS setting[244]. Saturation biopsy may also be useful for even more accurate staging, but may not be feasible within a repeat biopsies AS setting[247]. A better method may be to more selectively biopsy the prostate, increasing the yield of a single core. To do so, better imaging of the prostate may provide opportunities to visualize the tumour and guide biopsies to the lesion. The different imaging techniques will be discussed below. To assess whether the actual targeting by visualization or just the sampling of different areas of the prostate result in finding the tumour, random biopsies from these areas should also be taken as comparison[248]. The frequency and the indications for repeating prostate biopsies should be explored by comparing the frequency and extent of stage and grade upgrading within different AS protocols with longer time between biopsies.

NEW TUMOUR MARKERS

Novel biomarkers in tumour cells or products of tumour cells may be able to improve the accuracy with which to assess the risk of PC in an early stage. These markers may be added to the inclusion and follow-up criteria for AS or to nomograms predicting indolent disease. Currently ongoing basic research on this issue is diverse and the focus varies from tumour cells themselves, to products of tumour cells, to the body's immune response to tumour cells. Potential markers may be based on tumour secreted exosomes, auto-antibodies, metabolomic alterations (such as sarcosine), DNA changes (variations (SNPs) and methylation), micro RNAs, tumour metabolites, circulating tumour cells, and proteins (PSA and derivates)[249-256].

Observational AS programmes may provide an important opportunity to study the predictive value of future biomarkers. Available markers such as PCA3 and TMPRSS:ERG (although not found in all PC patients) are under study[257-259]. The predictive value of these markers at diagnosis and during follow-up can be studied by relating these to findings in repeat biopsies, PSA kinetics, histopathological findings in RP specimens, treatment-free survival, metastasis rate, and PC specific mortality. Biomarker research may also be done within ongoing trials randomizing for treatment. Markers may be associated with differences in treatment outcomes between arms and with the natural history of PC in the expectant management arms of these studies. Populations included in these studies are also more diverse than those included in AS studies. In both types

of studies, biobanks may be established. These allow for measuring newly discovered markers in large numbers of previously collected tissue samples, which can then retrospectively be associated with endpoints.

NEW IMAGING TECHNIQUES

New imaging techniques may improve our assessment of PC disease stage and grade. These diagnostics may be incorporated in AS protocols. Most AS protocols use DRE only to assess local disease stage, which is far from accurate[101,222]. One option is Magnetic Resonance Imaging (MRI), which as been reported to accurately image prostate tumours[119]. Diffusion weighed resonance imaging may be a non-invasive method to predict disease aggressiveness[260]. MR-guided biopsies may be used to target biopsies to suspicious lesions. MRI images may also be linked to TRUS by a computer, making it possible to take MRI-visualized-TRUS-guided biopsies, which is an easier to access technique[261]. Other promising imaging techniques include contrast enhanced TRUS and histoscanning[262,263].

Incorporated within an AS protocol, the value of these imaging techniques may be explored regarding: the number of supposedly low risk tumours that can be visualized, the potentially more accurate staging and grading, the effects on treatment-free survival, morbidity, and mortality, and the burden and feasibility of these procedures. In a collaborative research effort with the Radboud University in Nijmegen in The Netherlands, a MRI side study to PRIAS has been initiated. In this study, MR imaging and MR-guided biopsies have been added to the standard inclusion and follow-up protocol. Within the Erasmus MC in Rotterdam in The Netherlands, a protocol of histoscanning is being incorporated in PRIAS, in order to study the effect of this scan on staging and grading of supposedly low risk PC.

NEW THERAPIES

New therapies may cure PC while having a lower risk of side effects, making the indication for AS (i.e. avoidance of side effects) less strong. Traditional therapies such as laparoscopic RP, external beam radiotherapy, and brachytherapy are in constant development and improvement. Examples are the nerve-sparing procedures during RP and the increasing selectivity of conformal radiation therapy, sparing surrounding tissue and sparing erectile function and continence[31,36]. Focal therapies are also in development. Examples are high-intensity focused ultrasound and cryotherapy[25,26].

However, before becoming a feasible alternative to traditional treatments, long-term survival outcomes of these new treatment modalities should be studied, ideally in studies randomizing for treatment. The effect on the health-related quality of life (HRQoL) of the different treatments is equally important.

WEBSITE DEVELOPMENTS

Favourable experiences have been encountered with www.prias-project.org for: providing information to patients, applying a medical protocol for inclusion and follow-up of AS, and at the same time collecting data for the PRIAS study database[74]. The PRIAS study website may expand in the future and evolve into a diverse information portal on AS for low risk PC. Options include educational articles and movies, and the possibility for patients to ask questions online, with the aim to provide insight into the disease and to decrease potential anxiety and distress in patients. The physician's side of the website may be further improved by increasing user friendliness and implementation of a more versatile PSA kinetics calculator.

INTERVENTIONS DURING ACTIVE SURVEILLANCE

A period of AS may provide an important opportunity in which interventions may be started to delay or inhibit PC progression. Low risk PC may grow and dedifferentiate and evolve into higher risk cancer[52]. One option to intervene may be 5-alpha reductase inhibitors (5-ARIs). This drug (Dutasteride©) has shown to have a significantly favourable effect on the risk of finding PC in the PCPT and the REDUCE study[264]. 5-ARIs may also play a role in improving the yield of prostate biopsy and PSA kinetics during AS due to a reduction in the size of the prostate. The REDEEM study may prove whether endocrine prevention using Dutasteride© has a favourable effect on progression during AS[165]. In this study men with low risk PC on expectant management are randomized to the 5-ARI or control group and progression at repeat prostate biopsies is measured.

Dietary and lifestyle interventions may also favourably affect PC tumour biology and may be studied within an AS setting[265,266]. Among others, reported interventions include a low fat diet, vegan diet, low carbohydrate diet, low glycemic index diet, cholesterol diet, weight loss, vitamin supplements, soy diet, and lycopenes diet[267-269]. Men on AS may either be randomized to a control group or one of these interventions. Endpoints of these studies may be: findings in repeat biopsies and RP, PSA kinetics, morbidity, mortality, and HRQoL.

EFFECTS ON QUALITY OF LIFE

The effects of AS when compared to radical treatment on patients' HRQoL are a supposedly favourable effect on mainly urinary, sexual, and bowel domains and a potential unfavourable effect on anxiety and distress levels. In this thesis, HRQoL was defined as the physical, psychological, and social functioning and was used as an endpoint in different studies. HRQoL considerations should be taken into account in the treatment decision in men diagnosed with early PC in order to select the best candidates for AS, regarding psychopathology and protocol adherence.

Although the aim of AS is to avoid side effects of radical treatments, it may also have an unfavourable effect on physical domains. Sexual, bowel, and urinary function score have been found to decrease more than expected from the aging process alone during watchful waiting and it can be hypothesized that this decrease also occurs during AS[270]. The delay between diagnosis and treatment due to AS may not compromise mortality outcomes, but may close off opportunities to perform HRQoL preserving interventions such as nerve-sparing RP. This would result in a worsening of the urinary, sexual, and bowel domains of patients who start on AS. Evidence regarding the supposedly better scores on urinary, sexual, and bowel domains as provided by some retrospective studies is therefore necessary to strengthen the foundation of AS[271]. These effects on HRQoL of different treatment modalities for low risk PC, including AS, can be compared within randomized trials, such as the ProtecT study[233]. Because side effects after radical treatment may improve with longer follow-up after treatment and urinary, sexual, and bowel function scores during expectant management may worsen, long follow-up is necessary to assess the true effects of AS. HRQoL studies should ideally both include measures of PC specific domain scores and as well as measures of the effect of these domains on the perceived HRQoL, to account for the possibility of a response shift after radical treatment[42].

Besides these urinary, sexual, and bowel domains, anxiety and distress levels and predictors should also be compared between different treatment modalities. The short term anxiety and distress levels have been found to be favourable in men on AS in the studies presented in this thesis[87,225]. It is however important to also study the development of anxiety and distress after longer follow-up. Furthermore, qualitative studies of men who switch to radical therapy due to non medical reasons may identify the motives of these men[65]. If it is known why men switch to radical treatment due to non-medical issues, these can be anticipated for during follow-up with interventional strategies.

Only a limited number of men with low risk PC who are suitable for expectant management actually choose AS[58]. The aim should be to increase this percentage. To analyse the process of treatment decision and underlying reasons of men who have been diagnosed with localized PC, qualitative studies should be performed in this

group. Fear of progression to incurable disease is the most common reason to reject AS[175,272]. Knowledge of PC and AS, peer-pressure, demographical factors and attitude of the physician towards this strategy may be other important aspects[224]. Values on the potential advantages and disadvantages of AS may differ between patients and affect treatment decisions. If it is known what the main reasons are for choosing a specific treatment, adequately fitted decision support may be provided.

SUPPORT AND EDUCATION

Supportive and educational interventions may be used to optimize the treatment decision process in men with low risk PC or to decrease anxiety and distress during AS. Patients may need extra information regarding their disease[224]. Decision aids such as information leaflets and PC risk assessment tools such as the Prostate Cancer Risk Indicator[231,273] may be used in patients who have to chose between different treatments to provide insight in the disease, future risks, and treatment choices. During AS, changes in lifestyle such as increasing physical exercise may be initiated in order to improve the HRQoL[207]. Peer support groups have been evaluated positively by patients and may also be implemented[274]. Furthermore, cognitive-behavioural group intervention was also effective in improving HRQoL and these changes were associated significantly with intervention associated increases in perceived stress-management skills[275].

Future research may focus on the effect of support and education on the treatment decisions of men diagnosed with localized PC, acceptance rates of AS, the HRQoL of patients on AS, and on the compliance with the an AS protocol. By measuring anxiety, distress, knowledge, and treatment preferences before and after these interventions, their effects can be measured.

OUTCOMES OF ACTIVE SURVEILLANCE

The feasibility of AS may be measured by different endpoints, including: treatment-free survival, histopathological and biochemical outcomes after RP, rate of metastasis, PC specific mortality, HRQoL aspects, and costs. The feasibility and future role of AS will be defined by a combination of these outcomes. Comparing outcomes of AS with radical treatment in a randomized controlled trial may be difficult due to the expected small difference in disease specific survival, the very large number of patients needed, and the long follow-up time that is needed.

The treatment-free survival of different AS protocols is directly dependent of the follow-up protocol and selection criteria for AS[101], but also on the number of men who

discontinue AS due to psychological reasons[65]. Including standard repeat biopsies at inclusion for example may lower the number of patients included, but increase the treatment-free survival during follow-up. The reported treatment-free survival in ongoing AS studies varies from 67% to as high as 95%, reflecting differences in inclusion and follow-up criteria, and a possible selection bias in some studies[66,105]. In the PRIAS study, one out of 4 men had discontinued AS after 2 years[102].

Histopathological and biochemical outcomes after RP may provide intermediate outcomes and an indication of morbidity and mortality outcomes later. Findings in RP performed after an initial period of expectant management should always be compared with outcomes after immediate RP. The possibility should however be considered that a selection bias exists in a condensed group of men with more adverse findings because they have been selected for RP based on an adverse clinical follow-up[108]. Based on retrospective findings in this thesis and other articles, it is unlikely that the delay before treatment will cause substantial adverse outcomes in patients with low risk PC, however follow-up is too short to draw definitive conclusions on these outcomes within prospective AS protocols[91,108,276]. In an AS study with yearly repeat biopsies (PSA kinetics were not used in this study to monitor disease), 35% of men who received RP after initial expectant management showed extraprostatic extension and 48% showed a Gleason score >6; 27% had an indolent tumour at RP[244]. In PRIAS, 17% showed extraprostatic extension and 50% showed a Gleason score >6[102]. Worse outcomes of expectant management (although in a watchful waiting setting) may only surface even after very long follow-up[81]. Concerns have been expressed that a strategy of AS results in directly treating relatively aggressive tumours only, while waiting for the window of curability to close for the relatively less aggressive tumours, and that this might even compromise the benefits of early detection of PC (editorial comment[244])[16]. To assess these outcomes, future studies should include larger patient numbers and compare the effects of different inclusion and follow-up parameters on outcomes after RP.

Morbidity and mortality rates after AS in men with low risk PC should be compared to similar men who received immediate radical therapy such as RP or radiation therapy in randomized studies such as START[234]. These results will however be available only after many years, because both the leadtime of tumours and the very favourably long natural history must be awaited, before disease specific death rates may start to diverge between groups. In the meantime, the results of single arm studies such as PRIAS may provide insight into the outcomes of AS. Despite differences in inclusion criteria, all ongoing AS studies select screen-detected patients with PC that retrospectively have a very favourable disease specific outcome when expectantly managed. It is therefore unlikely that large differences in mortality will appear between ongoing AS protocols. For the same reason, it is most likely that the current AS programmes will merely show the safety of AS within the very selected groups of patients, but will not be able to provide

Table 3: Future research directions related to active surveillance

Subject	Objective
Screening	- To increase the selectiveness of screening procedures. - To individualize screening.
PC risk prediction	- To explore the natural history of screen-detected PC. - To study predictors of morbidity and mortality. - To study new biomarkers
Treatments for localized PC	- To study the effect of radical treatment of screen-detected PC on morbidity, mortality, and HRQoL, when compared to AS. - To identify subgroups in which radical treatment has a favourable effect. - To study the effect of new therapies on morbidity, mortality, and HRQoL.
Health-related quality of life	- To compare the effect on urinary, sexual, and bowel domains of different treatment options. - To compare effects on anxiety and distress levels over time between different treatment options. - To analyze treatment decisions of men diagnosed with PC with the purpose to systematically develop decision aids and evaluate their effectiveness. - To analyse non-medical reasons for discontinuing AS and to develop supportive interventions.
Selection for AS	- To study the use of probabilistic selection. - To individualize selection. - To optimize biopsy strategies. - To study the effect of incorporating imaging techniques.
Follow-up during AS	- To assess which parameters measured during follow-up are indicative of morbidity or mortality outcomes. - To study which trigger points should be used to switch to radical treatment. - To explore the feasibility of probabilistic follow-up.
Interventions during AS	- To explore the possibilities of chemoprevention, lifestyle and dietary interventions to decrease progression rates during AS. - To explore the effect of supportive and educational measures on treatment decisions and protocol adherence.

PC prostate cancer
AS active surveillance
HRQoL health-related quality of life

cut-off points to differentiate within all men diagnosed with PC who are definitely suitable and definitely unsuitable for AS. The expectant management arms of ongoing trials randomizing for treatment will provide more information.

The HRQoL outcomes of men who start on AS may be expressed as Quality Adjusted Life Years (QALYs). The QALYs of men with low risk PC should be compared between choosing AS and radical treatment within randomized studies. Special attention should be paid to patients who start on AS at a moment they are in good physical condition and who due to comorbidity during follow-up are no longer a candidate for radical treatment, and in whom progression of the prostate tumour is seen. In those men, the window of curative therapy has been missed due to patient specific factors, a situation which may have particular negative psychological and physical effects.

The cost aspect of AS when compared to radical treatment may also be an important consideration for the future feasibility of this strategy and its place in healthcare

policies. The total costs of AS are made up of: a strict surveillance program of frequent follow-up measurements in all patients, with radical treatment, resulting side effects, and post-treatment follow-up in some cases, with a potential slightly higher chance of metastasized disease. Costs of radical treatment include active therapy in all patients, resulting side effects, and post-treatment follow-up in all men, but with a potentially slightly lower chance of metastasized disease.

An overview of the future research directions related to AS as discussed above is presented in Table 3.

Epilogue

Screening for prostate cancer has the potential to decrease the number of deaths due to this disease, but also knocks off the lid of Pandora's Box. Many additionally diagnosed tumours now join in the competition of the race of life. Most of these however only have a very small chance to win, even when no attention is paid to them; they will not be a significant threat for life or cause any symptoms when remaining untreated. More selective screening methods should be found to partly close the lid. After a diagnosis of cancer 'doing nothing' may be hard to swallow, even the more because our knowledge of the natural history of prostate cancer is limited and our means to differentiate at an early moment between harmless slow growing and dangerous fast growing cancers are imperfect. The favourable effect on mortality of radical treatment however is only limited and at the same time all available options bring an immediate risk of side effects. As long as this situation exists, there is a role for active surveillance to attempt to provide a temporary solution for the overtreatment of overdiagnosed prostate cancer. Our knowledge of active surveillance regarding selection and follow-up criteria and effects on health-related quality of life should be expanded; we are only at the beginning of the learning curve. The ultimate destination is to diagnose and actively treat only those men who would develop symptoms of prostate cancer during life.

PART VI

APPENDICES

Summary
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Samenvatting (Dutch)
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References
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Summary

(PART I) The first part of this thesis introduces the objective, background, and research questions on which the thesis is based. The incidence of prostate cancer has been rising last years, mainly as a result of the increasingly frequently applied PSA (prostate specific antigen) screening. As a result, many men are being (over)diagnosed with prostate cancer that would not have become symptomatic when remaining undiagnosed. Radical (over)treatment of these low risk tumours brings an important risk of side effects and should therefore be avoided. Active surveillance has emerged as an alternative strategy. It consists of selecting supposedly low risk tumours and initially withholding radical treatment. Whenever during the following close surveillance progression seems to occur, deferred radical treatment is given. The feasibility of this strategy is explored in this thesis by performing a retrospective data analysis, by exploring a prospective approach, and by studying related quality of life issues.

(PART II) This thesis in the first place aimed to analyse in which patients with prostate cancer an initial strategy of active surveillance may be suitable and safe. (**Chapter 1**[85] →) A total of 616 men were studied who were diagnosed with low risk prostate cancer according to criteria based on the literature (defined as stage T1c of T2 disease, with a PSA ≤10.0 ng/ml, a PSA-density <0.2 ng/ml/cc, 1 or 2 positive biopsies, and a Gleason score of 3+3=6 or more favourable) and who were also initially managed expectantly. These patients participated in one of the three included study centres of the ERSPC (European Randomized Study of Screening for Prostate Cancer) and were diagnosed between 1994 and 2007. A very favourable 10-year prostate cancer specific mortality of 0% was observed, while almost 1 out of 4 men had died in the same period due to other causes. (**Chapter 2**[108] →) Then, 69 men with the same tumour characteristics who also started on expectant management but switched to radical prostatectomy later (on average 2.6 years after diagnosis) were compared to 158 similar men who received immediate radical prostatectomy after diagnosis. No significantly higher risk of unfavourable histopathological or biochemical outcomes after radical prostatectomy was seen. An initial strategy of active surveillance thus retrospectively seems suitable and for now acceptably safe in patients with screen-detected low risk prostate cancer. Taking the long natural history of these cancers into consideration however, longer follow-up is needed to draw definitive conclusions. (**Chapter 3**[222] →) In a number of patients with low risk prostate cancer, adverse histopathological outcomes are seen after radical prostatectomy, despite the fact that surgery was performed immediately after diagnosis. Lowering the thresholds of diagnostic parameters used to define low risk prostate cancer or using a nomogram-derived risk indication to define low risk prostate cancer decreases, but would not exclude the number of incorrectly selected patients. At the

same time, this would reduce dramatically the number of patients suitable for expectant management. (**Chapter 4**[223] →) Finally, indications were found that the inclusion criteria for active surveillance may be widened in select patients. In a group of 50 men with Gleason score 7 prostate cancer a prostate cancer specific mortality of 0% was seen 6 years after diagnosis. The most important limitations of the retrospective analysis as described above are a non-randomized design, an incomplete short follow-up, a lack of using a fixed protocol for expectant management, and an overlap between patients on watchful waiting with palliative intent and active surveillance as applied in some centres.

(**PART III**) Secondly, this thesis aimed to explore how a strategy of active surveillance should be applied prospectively. (**Chapter 5**[74] →) Offering an active surveillance protocol for inclusion and follow-up via a web-based decision tool is feasible. This is being done in the prospective multicenter PRIAS study (Prostate Cancer Research International: Active Surveillance). PRIAS uses the selection criteria for low risk prostate cancer as described above. The surveillance protocol consists of frequent PSA measurements, digital rectal examinations, and standard repeat prostate biopsies. (**Chapter 6**[102] →) Of the first 500 PRIAS patients included, 1 out of 4 had discontinued active surveillance and had switched to radical treatment at 2 years after diagnosis. The main reason was a high frequency of adverse findings in the repeat biopsies. The PSA doubling time was not associated with the favourable or unfavourable outcome of the repeat biopsies. (**Chapter 7**[89] →) Although this parameter is widely considered to be suitable to monitor disease status during active surveillance, the evidence for the usefulness of PSA kinetics is currently limited and contradictory. The main limitations of this prospective analysis of active surveillance are a non-randomized design and a limited follow-up time available.

(**PART IV**) The third aim of this thesis was to study the effects of active surveillance on patients' health-related quality of life. (**Chapter 8**[224] →) A questionnaire-based study was therefore performed. In 129 men on active surveillance who participated in the PRIAS study personal insights and experiences influenced the perception of prostate cancer. The level of knowledge of prostate cancer was adequate in most patients and no misconceptions on the strategy active surveillance were found. (**Chapter 9**[87] →) In the same selected group of 129 patients, the levels of anxiety and distress while living with 'untreated' prostate cancer generally were favourably low when compared to reference scores and the literature. Men with a neurotic personality and poor physical health showed less favourable scores. (**Chapter 10**[225] →) The levels of anxiety and distress remained favourable during a follow-up period of 9 months. (**Chapter 11**[226] →) Finally, the structure and psychometric validity was confirmed of a Dutch translation of a questionnaire specifically on prostate cancer specific anxiety. Limitations of these health-related quality of life studies include a non-randomized design, a selection bias

due to including only men who had already made the choice for active surveillance, a lack of comparison groups who received other treatments within the same study, and the limited follow-up time.

(**PART V**) The fifth part of this thesis discusses the key findings of and perspective to the presented studies, and presents an epilogue. The foundation and prerequisites for active surveillance and the rationale behind the strategy are discussed into more detail. Possibilities for improving the selection and follow-up of tumours during active surveillance are discussed. Improvements may be made in the use of already applied parameters such as PSA kinetics, and diagnostic and repeat biopsies. Furthermore, new tumour markers and imaging techniques may provide important opportunities and applications within the active surveillance research and may in the future prove useful in an active surveillance protocol. The time period during which a patient is on active surveillance may also provide an important opportunity to apply medical or psychological interventions. The effects of these on the tumour and patient should be studied. Finally, besides the long-term medical outcomes of active surveillance, quality of life aspects are equally important to enable objective assessment of the true feasibility of active surveillance in the future. Improvements in screening methods may lower the overdiagnosis rate and developments in curative treatments may lower the rate of side effects, which would make the active surveillance strategy obsolete.

(**PART VI**) The sixth and last part of the thesis is made up out of different appendices, both in English and in Dutch, including a summary, complete list of references, and curriculum vitae of the author.

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Education:

2000-2006:	Medical school University of Utrecht, The Netherlands
1994-2000:	Gymnasium in Amersfoort, The Netherlands

Work:

From 2010:	Resident in Urology
2007-2009:	PhD research 'Active surveillance for low risk prostate cancer.' Supervisors: professor C.H. Bangma, professor E.W. Steyerberg, professor F.H. Schröder, dr M.J. Roobol, and dr M.L. Essink-Bot.
2004-2006:	Employee at the medical website www.dokterdokter.nl
2004-2005:	Medication courier at a pharmacy
2004-2005:	Student-assistant in anatomy and practical skills courses at the medical faculty

Other activities:

2000-2006:	Member of the ´Utrechts Studenten Corps´
2005:	Amsterdam-Dakar Challenge, a car rally for charity.
2000-2001:	Pilot selection Royal Netherlands Air Force

Scientific experiences:

· PhD research ERSPC (European Randomized Study of Screening for Prostate Cancer), section Rotterdam, The Netherlands.
· Multiple scientific publications.
· Multiple (poster)presentations at medical conventions and meetings, including: EAU, AUA, ASCO, SiURO, NVU, ERSPC-meetings.

· Management of the international prospective PRIAS study on active surveillance for low risk prostate cancer.
· Book chapters on screening for prostate cancer.
· Award: *NVKZ 'Zorg voor morgen – prijs' 2008*
· Award: *EAU 'Best paper on clinical research published in the urological literature' 2008.*
· Award nominee: *NRC Handelsblad 'Academic Year Prize 2009'*

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Running, diving, skiing, model building, golf, rally, family, and friends.

Other:
- Academic Year Prize 2009 weblog: http://www.academischejaarprijs.nl/index.php?/site/weblogs/Prostaatkanker_zorgen_voor_morgen/
- 'Noorderlicht Nieuws' broadcast: http://player.omroep.nl/?aflID=10023092 (starting at minute 15:05)
- 'NOS Journaal' broadcast (March 18th, 2009): http://player.omroep.nl/?aflID=9116258 (starting at minute 17:55)

Conventions and meetings

International convention/meeting attended	Month	Year	City	Country
European Randomized Study of Screening for Prostate Cancer: Annual meeting	March	2007	Toledo	Spain
European Association of Urology: Annual meeting	March	2007	Berlin	Germany
European Association of Urology: European Multidisciplinary Meeting on Urological Cancers	November	2007	Barcelona	Spain
Congresso Nazionale Società Italiana di Urologia Oncologica	November	2007	Modena	Italy
American Society of Clinical Oncology: Genitourinary Cancers Symposium	February	2008	San Francisco	US
European Association of Urology: Annual meeting	March	2008	Milan	Italy
European Randomized Study of Screening for Prostate Cancer: Annual meeting	April	2008	Peschiera	Italy
American Society of Clinical Oncology: Genitourinary Cancers Symposium	February	2009	Orlando	US
European Association of Urology: Annual meeting	March	2009	Stockholm	Sweden
European Randomized Study of Screening for Prostate Cancer: Annual meeting	April	2009	Gothenburg	Sweden
American Urological Association: Annual meeting	April	2009	Chicago	US
Interdisciplinary Oncology Course: Urological Tumours	May	2009	Oviedo	Spain
European Society of Residents in Urology: Autumn meeting	October	2009	Ljubljana	Slovenia
European Association of Urology: European Multidisciplinary Meeting on Urological Cancers	November	2009	Barcelona	Spain

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Samenvatting

(**DEEL I**) Het eerste deel van dit proefschrift beschrijft het doel, de achtergrond en de onderzoeksvragen waarop de dissertatie is gebaseerd. De incidentie van prostaatkanker is de afgelopen jaren sterk gestegen, vooral als gevolg van de vroegopsporing met behulp van PSA (prostaat specifiek antigeen). Hierdoor worden veel mannen (over) gediagnosticeerd met een prostaattumor die geen klachten zou hebben gegeven wanneer deze niet-gediagnosticeerd was gebleven. Ook bij deze tumoren met een laag risico brengt radicale (over)behandeling echter een belangrijk risico op bijwerkingen met zich mee en de zin van deze behandelstrategie moet daarom worden overwogen. Een actief afwachtend beleid biedt een alternatieve strategie. Dit bestaat uit het selecteren van tumoren met een vermoedelijk laag risico en het in eerste instantie terughoudend zijn met radicale behandeling. Wanneer er tijdens het hierop volgende controleproces progressie van de ziekte lijkt op te treden, wordt er alsnog radicale behandeling gegeven. In dit proefschrift wordt de haalbaarheid van een actief afwachtend beleid onderzocht door een retrospectieve data analyse te verrichten, een prospectieve aanpak te verkennen en door gerelateerde kwaliteit van leven aspecten te bestuderen.

(**DEEL II**) Ten eerste had dit proefschrift als doel om te analyseren bij welke patiënten met prostaatkanker een initieel actief afwachtend beleid gerechtvaardigd en veilig is. (**Hoofdstuk 1**[85] →) Een groep van 616 mannen werd bestudeerd die gediagnosticeerd waren met prostaatkanker met een laag risico volgens criteria gebaseerd op gegevens uit eerdere literatuur (gedefinieerd als klinisch stadium T1c of T2, met een PSA ≤10.0 ng/ml, een PSA densiteit <0.2 ng/ml/cc, 1 of 2 positieve prostaatbiopten met een Gleason score van 3+3=6 of gunstiger), en die ook initieel een afwachtend beleid kozen. Al deze patiënten participeerden in een van de drie in deze analyse meegenomen studie centra van de ERSPC ('European Randomized Study of Screening for Prostate Cancer', Europese gerandomiseerde studie naar de vroegopsporing van prostaatkanker) en werden gediagnosticeerd tussen 1994 en 2007. Er werd een zeer gunstige 10-jaars prostaatkankerspecifieke mortaliteit van 0% gevonden, terwijl bijna 1 op de 4 mannen na deze tijd al was overleden aan hele andere oorzaken. (**Hoofdstuk 2**[108] →) Vervolgens werden 69 mannen met dezelfde tumorkarakteristieken en die ook in eerste instantie kozen voor een afwachtend beleid maar later overstapten naar een radicale prostatectomie (gemiddeld 2.6 jaar na diagnose) vergeleken met 158 vergelijkbare patiënten die meteen na diagnose een radicale prostatectomie hadden ondergaan. Er werd geen significant hoger risico op ongunstige histopathologische of biochemische uitkomsten na de operatie gezien. Een initiële strategie van actief afwachtend beleid lijkt dus retrospectief gezien gerechtvaardigd te zijn en vooralsnog afdoende veilig bij patiënten met een vroeg opgespoorde prostaattumor met een laag risico. Aangezien

het natuurlijk beloop van deze tumoren erg lang is, moet wel langere follow-up worden afgewacht om definitieve conclusies te kunnen trekken. (**Hoofdstuk 3**[222] →) Bij een aantal patiënten met prostaatkanker welke voldoet aan de criteria voor laag risico worden toch ongunstige histopathologische kenmerken gezien na radicale prostatectomie, ondanks het feit dat deze operatie direct na diagnose werd uitgevoerd. Het aanscherpen van de diagnostische parameters gebruikt om prostaatkanker te definiëren als laag risico of het gebruik van een nomogram verkleinen het aantal onterecht geselecteerde patiënten, maar sluit deze niet met zekerheid uit. Tegelijkertijd zou dit in sterke mate het aantal patiënten reduceren wat geschikt wordt geacht voor een afwachtend beleid. (**Hoofdstuk 4**[223] →) Tenslotte werden er aanwijzingen gevonden dat de criteria voor laag risico verruimd zouden kunnen worden bij geselecteerde patiënten. Ook bij een groep van 50 mannen met prostaatkanker met een Gleason score van 7 werd namelijk een prostaatkankerspecifieke overleving van 100% gezien 6 jaar na de diagnose. De belangrijkste beperkingen van de hierboven beschreven retrospectieve analyse zijn de niet-gerandomiseerde opzet, een incomplete korte follow-up, het ontbreken van een vast protocol voor afwachtend beleid en een overlap tussen patiënten op 'watchful waiting' met een palliatieve insteek en actief afwachtend beleid patiënten, zoals toegepast in sommige centra.

(**DEEL III**) Ten tweede had dit proefschrift als doel om te verkennen hoe een strategie van actief afwachtend beleid prospectief zou moeten worden toegepast. (**Hoofdstuk 5**[74] →) Het aanbieden van een protocol voor inclusie en controle voor actief afwachtend beleid met behulp van een beslishulp beschikbaar via internet is haalbaar. Deze aanpak wordt gevolgd in meerdere centra in het kader van de prospectieve PRIAS studie ('Prostate Cancer Research International: Active Surveillance', internationaal prostaatkankeronderzoek: actief afwachtend beleid). PRIAS hanteert de criteria voor laag risico zoals hierboven beschreven. Het controle protocol na diagnose bestaat uit frequente PSA metingen, rectaal toucher en standaard worden biopten van de prostaat herhaald. (**Hoofdstuk 6**[102] →) Van de eerste 500 patiënten geïncludeerd in de PRIAS studie waren 2 jaar na de diagnose 1 op de 4 gestopt met het actief afwachtend beleid en overgestapt op een radicale behandeling. De belangrijkste reden voor de overstap was de hoge frequentie van ongunstige bevindingen in de herhalingsbiopten. De PSA verdubbelingstijd liet geen associatie zien met een gunstige of ongunstige uitslag van de herhalingsbiopten. (**Hoofdstuk 7**[89] →) Alhoewel opeenvolgende PSA metingen in het algemeen beschouwd worden als een bruikbare parameter om de status van de ziekte te controleren tijdens een actief afwachtend beleid, is het bewijs voor het nut in deze situatie nog beperkt en tegenstrijdig. De belangrijkste beperkingen van bovengenoemde prospectieve analyse zijn de niet-gerandomiseerde opzet en de zeer beperkte beschikbare follow-up tijd.

(**DEEL IV**) Het derde doel van dit proefschrift was om de effecten van een actief afwachtend beleid op de gezondheidsgerelateerde kwaliteit van leven te bestuderen.

(**Hoofdstuk 8**[224] →) Er werd daarom een studie uitgevoerd met behulp van vragenlijsten. Bij 129 patiënten op actief afwachtend beleid die deelnamen aan de PRIAS studie bleken specifieke persoonlijke inzichten en ervaringen invloed te hebben op hun belevenis van prostaatkanker. Bij de meeste mannen was hun kennis van de ziekte voldoende en er werden geen misvattingen gevonden over de strategie van actief afwachtend beleid. (**Hoofdstuk 9**[87] →) Bij dezelfde selecte groep van 129 patiënten die leven met 'onbehandelde' prostaatkanker waren de mate van angst en onrust gunstig laag, vergeleken met referentiewaarden en de literatuur. Mannen met een neurotische persoonlijkheid en slechte fysieke gezondheid lieten de ongunstigste scores zien. (**Hoofdstuk 10**[225] →) Deze scores op schalen van angst en onrust bleven gunstig gedurende een follow-up periode van 9 maanden. (**Hoofdstuk 11**[226] →) Tenslotte werd de structuur en psychometrische validiteit bevestigd van een Nederlandse vertaling van een vragenlijst specifiek ontworpen voor het meten van prostaatkankerspecifieke angst. De beperkingen van de kwaliteit van leven studies waren onder andere de niet-gerandomiseerde opzet, het mogelijk bestaan van een selectiebias door alleen mannen te bestuderen die de keuze voor actief afwachtend beleid al hadden gemaakt, een gebrek aan vergelijkingsmateriaal van mannen die andere behandelingen hadden ondergaan binnen dezelfde studie en de beperkte follow-up periode.

(**DEEL V**) Het vijfde deel van dit proefschrift bediscussieert de belangrijkste bevindingen en de context van de gepresenteerde studies en presenteert een epiloog. De basis van en voorwaarden voor actief afwachtend beleid en de ratio achter deze strategie worden in verder detail behandeld. De mogelijkheden voor verbetering van de selectie en follow-up van tumoren voor actief afwachtend beleid worden hierbij besproken. Eventuele verbeteringen zouden kunnen worden gedaan in de toepassing van al gebruikte variabelen zoals PSA kinetica en prostaatbiopten op het moment van diagnose en tijdens de verdere controle. Verder zouden nieuwe tumormarkers en beeldvormende technieken belangrijke kansen en mogelijkheden kunnen bieden binnen het onderzoek naar actief afwachtend beleid en in de toekomst mogelijk hun plek kunnen vinden binnen een vast protocol voor actief afwachtend beleid. De periode van actief afwachtend beleid zou ook een belangrijke mogelijkheid kunnen bieden om medische of psychologische interventies toe te passen. De effecten hiervan op de tumor en op de patiënt zouden onderzocht moeten worden. Tenslotte zijn op de lange termijn de kwaliteit van leven aspecten even belangrijk als de puur medische uitkomsten van actief afwachtend beleid om uiteindelijk een objectieve inschatting kunnen maken van de werkelijke haalbaarheid van deze strategie in de toekomst. Verbeteringen in de methoden voor vroegopsporing zouden de overdiagnose kunnen verminderen; ontwikkelingen op het gebied van curatieve behandelingen zouden het aantal bijwerkingen kunnen beperken. Uiteindelijk zou een actief afwachtend beleid hierdoor overbodig kunnen worden.

(DEEL VI) Het zesde en laatste deel van dit proefschrift bestaat uit een aantal bijlagen, deels in het Engels en deels in het Nederlands, waaronder een samenvatting, een curriculum vitae van de auteur en een referentielijst.

Curriculum vitae

Roderick van den Bergh werd op 25 januari 1982 geboren in Zeist. Hij groeide op in Den Dolder met zijn broer Marnix, met schoolplein en bos om de hoek. Op het gymnasium in Amersfoort deed hij de middelbare school. Na het eindexamen in 2000 besloot hij de studie geneeskunde te gaan doen in Utrecht. In de 7 hierop volgende jaren studeerde hij daar met veel plezier en woonde op de Goedestraat en op de Hugo de Grootstraat. Tijdens zijn studie groeide de interesse en het enthousiasme voor het vak urologie en de wetenschappelijke achtergrond van dit vak. Het onderzoek en co-schap in het laatste jaar van zijn studie vielen dan ook binnen deze richting. In december 2006 studeerde hij af. Hierna kon hij beginnen met een baan als arts-onderzoeker bij de grote Europese screeningstudie naar prostaatkanker (ERSPC) in Rotterdam met een driejarig promotieonderzoek naar de haalbaarheid van een actief afwachtend beleid bij vormen van prostaatkanker met een laag risico. Dat onderzoek vormt de basis van dit boekje. Tijdens deze onderzoeksperiode participeerde hij aan vele congressen en bijeenkomsten. Ook ging hij in deze periode samenwonen met Carline van Amstel in Rotterdam. In januari 2010 zal Roderick beginnen met de opleiding tot uroloog in het cluster Utrecht. De vooropleiding heelkunde zal hij volgen in het Diakonessenhuis. Naast zich bezig te houden met prostaten, doet hij een poging tot golfen en hardlopen en, wanneer daar gelegenheid voor is, tot duiken, skiën, rallyrijden en modelbouwen, dit alles natuurlijk afgewisseld met (nog) minder inspannende activiteiten.

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Professor Steyerberg, het feit dat ik je vanaf dag 1 Ewout mocht noemen is tekenend voor je laagdrempeligheid. Niemand kan met zijn commentaar zo snel de vinger op de zere plek van een studie of onderzoek leggen als jij. Ik vond onze gesprekken altijd inspirerend en gezellig. Ik ben trots dat je mijn promotor bent.

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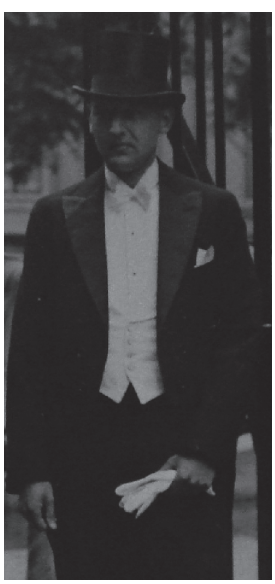
Carline, ik ben zo blij met je!

Roderick van den Bergh, september 2009.



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(ERSPC)

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PhD Portfolio

Summary of PhD training and teaching

Name PhD student:	PhD period: 2007 – 2009	
Roderick van den Bergh	Promotors:	Prof.dr. C.H. Bangma
Erasmus MC Department: Urology		Prof.dr. E.W. Steyerberg
Research School: -	Supervisors:	Dr. M.J. Roobol
		Dr. M.L. Essink-Bot

1. PhD training

	Year	Workload (ECTS)
General courses		
Biomedical English Writing and Communication	2007 – 2008	10
Nihes Classical Methods for Data analysis (CC02)	2008	5.7
Seminars and workshops		
Department Journal Club	2007 – 2009	1
Presentations		
Multiple presentations at different conventions and meetings	2007 – 2009	5
(Inter)national conferences		
Multiple poster and oral presentations at EAU, AUA, ASCO, NVU, ERSPC meetings	2007 – 2009	10
Other		
Clinical work urological ward	2009	2

2. Teaching

	Year	Workload (ECTS)
Lecturing		
Physician education web-based study decision tool (PRIAS) at multiple occasions	2007 – 2009	2

EAU	European Association of Urology
AUA	American Urological Association
ASCO	American Society of Clinical Oncology
NVU	Nederlandse Vereniging voor Urologie
ERSPC	European Randomized Study of Screening for Prostate Cancer
PRIAS	Prostate Cancer Research International: Active Surveillance