Screening and active surveillance in prostate cancer: prognostic and short-term outcomes of active surveillance and quality of life aspects

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Academic Dissertation

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To My Family
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1. ABBREVIATIONS

ADC  Apparent diffusion coefficient  
5-ARI  5-alpha reductase inhibitor  
AS  Active surveillance  
ATFS  Active treatment-free survival  
AUA  The American Urological Association  
BPH  Benign prostatic hyperplasia  
BT  Brachytherapy  
CaPSURE  The Cancer of the Prostate Strategic Urological Research Endeavor  
CSAP  Cryosurgical ablation of the prostate  
cT  Clinical T-class  
CT  Computed tomography  
cTNM  Clinical Tumor-Node-Metastasis-stage  
DCE-MRI  Dynamic contrast-enhanced magnetic resonance imaging  
3D-CRT  Three-dimensional conformal radiation therapy  
DRE  Digital rectal examination  
DW-MRI  Diffusion-weighted magnetic resonance imaging  
EAU  The European Association of Urology  
EBRT  External beam radiation therapy  
ER  Emotional role  
ERSPC  The European Randomized Study of Screening for Prostate Cancer  
%fPSA  Free/total PSA ratio  
FPXI  The FinnProstate Study XI  
HDR-BT  High-dose rate brachytherapy  
HGPIN  High-grade prostatic intraepithelial neoplasia  
HIFU  High-intensity focused ultrasound  
HRQL  Health-related quality of life  
IGRT  Image-guided radiotherapy  
IIEF-5  The International Index of Erectile Function  
IMRT  Intensity-modulated external-beam radiotherapy  
IPSS  The International Prostate Symptom Score  
ISUP  International Society of Urological Pathology  
LDR-BT  Low-dose rate brachytherapy  
LHRH  Luteinizing hormone-releasing hormone  
MRI  Magnetic resonance imaging  
mRNA  Messenger ribonucleic acid  
MRSI  Magnetic resonance spectroscopy imaging  
PASS  The Prostate Active Surveillance Study  
PC  Prostate cancer  
PCA3  Prostate cancer antigen 3  
PCPT  The Prostate Cancer Prevention Trial
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<td>PIVOT</td>
<td>The Prostate Cancer Intervention Versus Observation Trial</td>
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<tr>
<td>PLCO</td>
<td>The Prostate, Lung, Colorectal and Ovarian cancer screening trial</td>
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<tr>
<td>PR</td>
<td>Physical role</td>
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<tr>
<td>PRIAS</td>
<td>The Prostate Cancer Research International: Active Surveillance Study</td>
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<td>ProtecT</td>
<td>The Prostate testing for cancer and Treatment trial</td>
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<tr>
<td>PSA</td>
<td>Prostate-specific antigen</td>
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<td>PSAD</td>
<td>PSA density</td>
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<td>PSADT</td>
<td>PSA doubling time</td>
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<td>PSAV</td>
<td>PSA velocity</td>
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<td>pTNM</td>
<td>Pathological Tumor-Node-Metastasis-stage</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<td>RARP</td>
<td>Robot-assisted radical prostatectomy</td>
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<td>REDEEM</td>
<td>The Reduction by Dutasteride of Clinical Progression Events in Expectant Management trial</td>
</tr>
<tr>
<td>REDUCE</td>
<td>The Reduction by Dutasteride of Prostate Cancer Events trial</td>
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<tr>
<td>RP</td>
<td>Radical prostatectomy</td>
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<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results program</td>
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<tr>
<td>SPCG-4</td>
<td>The Scandinavian Prostate Cancer Group Study Number 4</td>
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<tr>
<td>STUMP</td>
<td>Stromal tumour of uncertain malignant potential</td>
</tr>
<tr>
<td>TNM-stage</td>
<td>Tumor-Node-Metastasis-stage</td>
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<tr>
<td>TRUS</td>
<td>Transrectal ultrasound</td>
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<tr>
<td>TURP</td>
<td>Transurethral resection of prostate</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WW</td>
<td>Watchful waiting</td>
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2. LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:


II. Hanna Vasarainen, Utku Lokman, Mirja Ruutu, Kimmo Taari and Antti Rannikko: Prostate cancer active surveillance and health-related quality of life: results of the Finnish arm of the prospective trial. BJU Int 2011; 109:1614-1619.


V. Hanna Vasarainen, Jolanda Salman, Heidi Salminen, Riccardo Valdagni, Tom Pickles, Chris Bangma, Monique Roobol and Antti Rannikko: Predicting adverse rebiopsy findings, deferred treatment and radical prostatectomy findings with %fPSA in men on a prospective active surveillance program (PRIAS). Submitted.
3. ABSTRACT

Prostate cancer (PC) is a significant health problem worldwide. It is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among men. The wide use of prostate-specific antigen (PSA) has led to increased detection of PCs in its early stages. Active surveillance (AS) has emerged as an alternative management option to that of immediate radical treatments of these potentially overdiagnosed PCs. The aim of AS is to avoid or at least delay the side effects of immediate treatments.

The objective of this study was to evaluate the feasibility of AS as a management option for low-risk PC and determine how AS affects the quality of life (QOL) of low-risk PC patients. The more specific aims of the present study were to evaluate the short-term outcomes of the prospective AS cohort, analyse the effects of AS on the QOL during screening and AS overall, assess the respective roles of diffusion-weighted magnetic resonance imaging (DW-MRI) and a free/total PSA ratio as diagnostic and prognostic tools in AS.

The PRIAS (Prostate cancer Research International: Active Surveillance) study is an international prospective AS trial that originates from the European Randomized Study of Screening for Prostate Cancer (ERSPC). ERSPC is a multicenter, population-based and randomized screening trial that is being conducted in eight European countries. In study I, the outcomes of the 500 first PRIAS patients were analysed, the main outcome parameter was active treatment-free survival. Secondary endpoints included reasons for discontinuing AS, findings in the standard 1-year rebiopsies, and outcomes after radical prostatectomy. For the health-related quality of life (HRQL) analyses, the Finnish version of the RAND 36-Item Health Survey was used in both QOL studies. In addition, participants also received IPSS and IIEF-5 questionnaires in study II to analyse possible voiding symptoms and erectile function. In study III, RAND-36 QOL questionnaires were delivered to a total of more than 2000 screening participants of the Finnish arm of the ERSPC trial in five phases of the first screening round. In study IV, 80 men who had enrolled in the Finnish arm of the PRIAS study underwent DW-MRI before standard 1-year rebiopsy. In study V, the global PRIAS study cohort was used with the initial free PSA value available in 939 patients to assess the role of free/total PSA ratio (%fPSA) as a prognostic tool in AS.

Strict AS criteria of the PRIAS protocol resulted in a quarter of the patients stopping surveillance within two years after PC diagnosis. The main reason for discontinuation was adverse findings in the standard 1-year rebiopsy. Biopsy results were independent of the PSA-doubling time (PSADT). AS did not provoke major short-term QOL changes as assessed by standardized questionnaires and none of the patients on AS discontinued due to anxiety or distress. The HRQL of study patients was even better than that for the general age-stratified Finnish male population. Moreover, the PC screening did not have substantial effects on the short-term QOL of participants. This study population also had similar or slightly higher HRQL scores compared to the reference values obtained from the age-stratified general Finnish male population. DW-MRI, as interpreted in a routine clinical setting and performed in this study, could not predict treatment change or adverse rebiopsy or radical prostatectomy findings. PCs were small and rather well-differentiated, making it challenging to visualize these tumours using MRI. Free/total PSA ratio
(fPSA) at diagnosis could not predict outcomes of AS, although median %fPSA values were significantly lower in patients with treatment change after one year of surveillance. However, %fPSA kinetics may predict future treatments.

AS is a feasible management option for patients with low-risk PC. Short-term analyses revealed that a quarter of men discontinue AS, mainly because of reclassification of PC in standard rebiopsy, which highlights the importance of accurate diagnostics. Neither screening nor AS seemed to provoke short-term disturbances in QOL in the PC continuum. Small low-grade PCs are a challenge for non-spezialized radiologists to visualize accurately by DW-MRI. Change of %fPSA over time may have a value as a prognostic tool in AS.
4. INTRODUCTION

Prostate cancer (PC) is currently the most common malignancy in males in Finland and other Western countries (Jemal et al. 2011; Pukkala and Rautalahti 2013). The number of new cases reported has increased dramatically in recent years, which is mainly due to active and widespread use of prostate-specific antigen (PSA) in the diagnosis of PC. It has been estimated that up to half of all PCs, detected by PSA testing are clinically insignificant, which indicates that even if PC was not diagnosed, these tumours would not cause any symptoms during the men’s lifetimes (Draisma et al. 2003). The detection of clinically insignificant cancers leads to substantial overdiagnosis of PCs and overtreatment of patients. Overtreated patients are unnecessarily exposed to the side effects of radical treatments that provide no survival benefit but which may have an unfavourable effect on quality of life (QOL).

Active surveillance (AS) has emerged as an alternative strategy for managing these potentially overdiagnosed PCs. The idea of AS is to initially withhold radical treatments (i.e. surgery or radiation therapy), but reserve the opportunity for deferred treatment with curative intent in the case of disease progression or reclassification during follow-up.

AS takes advantage of the long natural history of PC and the good prognosis associated with localized low-grade disease. AS strategy is based on defined triggers to detect and predict higher risk PC in patients during follow-up. Currently diagnostic PSA, Gleason score at prostate biopsy and Tumor-Node-Metastasis-stage (TNM-stage) have been widely studied and they have established their position as significant prognostic factors for PC. During follow-up, patients are closely monitored using tools such as PSA, clinical examinations such as digital rectal examination (DRE) and prostate rebiopsies, and when any signs of disease progression occur, deferred radical treatment is given (Parker et al. 2004).

Hitherto, data related to AS are scarce and outcome of long-term follow-up is lacking. In addition, prospective and randomized trials, in which AS is compared with immediate radical treatment have not been published. The present research project investigates the feasibility of AS as a management option for low-risk PC within the framework of the PRIAS (Prostate cancer Research International: Active Surveillance) study (van den Bergh et al. 2007). The PRIAS-trial is an international prospective AS-trial that originates from the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Schröder et al. 2003). The PRIAS study was initiated in 2006 in the Erasmus University Medical Center in the Netherlands and it is still ongoing. PRIAS is currently the largest prospective AS study in existence. The study design of this prospective cohort study does not include randomization, since the differences in survival benefits between immediate radical treatments and AS would probably appear minor and a large patient cohort in addition to long follow-up would be needed, thus making such a study difficult to conduct.

The objectives for study of this thesis were to investigate the feasibility of AS as an expectant management strategy for low-risk PC and to analyse outcomes of follow-up on short-term after PC diagnosis. The specific aim was also to analyse the QOL during the screening and the subsequent AS after the diagnosis of low-risk PC. One of the main challenges to using the AS approach is to find those cancers that
progress and offer these patients a curative treatment in time. A substantial part of this thesis was to clarify the role of magnetic-resonance imaging (MRI) and free/total PSA ratio (%fPSA) as possible additional prognostic tools for AS.
5. REVIEW OF LITERATURE

5.1 The Prostate

The prostate is a walnut-sized exocrine gland and a part of the male reproductive system. It is located in the pelvis, just below the bladder, anterior to the rectum and it surrounds the proximal urethra. The prostate can be divided into central, peripheral and transition zones (Fig.1). The transition zone is the common area for benign prostatic hyperplasia and a peripheral zone for PC. Approximately two thirds of the prostate consist of glandular tissue and one third of fibromuscular tissue. The main function of this gland is the excretion of fluid that forms one-fifth the volume of the semen ejaculate. This prostatic fluid helps to carry and nourish the sperm. The smooth muscles of the prostate have an essential role in controlling the flow of semen during ejaculation. PC is a malignant disease of the prostate, but several benign conditions, such as benign prostatic hyperplasia and prostatitis commonly and coincidently occur in the prostate (Campbell-Walsh Urology 2007).

![Diagram of the prostate gland divided into zones.](https://via.placeholder.com/150)

*Figure 1.* The prostate gland divided into zones.
5.2 Epidemiology

Prostate cancer (PC) is a significant health problem worldwide. PC is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among men worldwide with an estimated 903,500 new diagnoses and 258,400 deaths in 2008, this represents 14% of all new cancer cases and 6% of all cancer deaths in males (Jemal et al. 2011). The incidence rates of PC vary by more than 25-fold worldwide. Elderly men are more often affected by PC, which makes the disease a considerable health problem in developed countries. Thus, the highest estimated PC incidence rates (age standardized rate per 100,000, in 2008) are observed in the highest resourced areas of the world, in North America (85.6), Australia/New Zealand (104.2), Western Europe (93.1), Northern Europe (73.1), and the lowest in South-Central Asia (4.1). 72% of the PC cases and 53% of the PC deaths occur in developed countries (all regions of Europe, North America, Australia/New Zealand, and Japan), which have <20% of the world population (Center et al. 2012). However, the highest estimated PC mortality rates are seen elsewhere, primarily in the Islands of the Caribbean (26.3/100,000), and in Southern Africa (19.3/100,000). The lowest mortality rates are found in Eastern Asia (2.5/100,000) (Ferlay et al. 2010).

Between the mid-1980s and early 1990s, after the introduction of the PSA test, PC incidence rates increased in many high-income countries (Potosky et al. 1995; Etzioni et al. 2002; Baade et al. 2009; Bray et al. 2010). Although there is still no clear declining incidence trends in sight, most of the registries in developed countries have shown signs of a stabilization (Center et al. 2012). In contrast to the increasing incidence of PC, the PC mortality rates have decreased in many high-income areas (North America, Oceania, Northern and Western Europe) (Center et al. 2012). In the United States this decrease has been particularly noticeable and over the last decade the mortality rates have decreased by as much as 4.3% (9.9/100,000) in 2008 (Jemal et al. 2010). There are several reasons for the declining mortality rates, but the main factors are early and increased detection rates of PC, in combination with advances and changes in treatments (Collin et al. 2008; Etzioni et al. 2008).

In Finland, PC has been the most common cancer diagnosed among males since 1993 with 4715 new diagnoses (31.4% of all new cancer cases) in 2011 (Fig.2a) (Pukkala and Rautalahti 2013). Since the middle of the 1980s PC has been the second leading cause of cancer death with 882 deaths attributed to PC (14.4% of all cancer deaths) in 2011 (Fig.2b) (Pukkala and Rautalahti 2013). The incidence of PC has remained stable in Finland during the most recent years, but mortality has decreased by 3.1% per year since 2000 (Center et al. 2012).
Figure 2. Cancer incidence (a) and mortality trends (b) including PC (with prediction) among Finnish males (Finnish Cancer registry) (Pukkala and Rautalahti 2013) (Copyright permission 7.1.2014).
5.3 Risk factors

At present, three well-established risk factors for developing clinical PC have been identified. First, older age is a significant risk factor. In post-mortem studies a microscopic foci of PC was found in 15-29% of men aged 30-40 years. By the age of 70, a histological PC was identified in 60% of men and this rose to 80% who had some form of PC by the age of 80 (Sakr et al. 1993; Sakr et al. 1994). Second, ethnicity is a well-established risk factor for PC. For example, in the United States African Americans have a higher PC incidence rate than the white population. The results from Surveillance, Epidemiology, and End Results (SEER) program showed, that age-adjusted PC incidence between 2002 and 2006 for the white population was 153.0/100 000 as compared to 239.8/100 000 for the African American population (Horner et al. 2009). Third, heredity is also an established risk factor for PC. Men with an affected first-line relative (i.e. father or brother) have at least a doubled risk for PC (Steinberg et al. 1990). If two or more first-line relatives have this disease, the risk increases approximately 5 to 11 -fold (Bratt 2002; Hemminki 2012; Jansson et al. 2012). It has been estimated that in about 9% of men with PC, the disease has a true hereditary background with a strong genetic component. The definition of ‘hereditary PC’ includes the criteria that three or more relatives are affected or at least two relatives have early-onset PC before 55 years of age (Hemminki 2012).

There also exists a wide range of additional and exogenous factors, such as alcohol and food consumption, chronic inflammation, pattern of sexual behaviour, ultraviolet radiation exposure, that may be potential risk factors for PC, but have not produced definitive evidence of the association (Gronberg 2003; Schmid et al. 2007).

5.4 Classification

5.4.1 Histology

Prostatic adenocarcinoma is the most common malignancy in the prostate and it comprises over 90% of cases (Bostwick 1989). Although the majority of PCs are typical acinar adenocarcinomas, between 5-10% can be considered as variants (Grignon 2004; Mazzucchelli et al. 2008), i.e. mucinous adenocarcinoma, ductal adenocarcinoma and intraductal carcinoma. There are also several other primary and secondary tumours that may involve the prostate, but they are rare. Other primary tumour types, from the epithelial origin, are small cell carcinoma, basal cell carcinoma, urothelial carcinoma and mucin-producing urothelial type adenocarcinoma. Tumour types of mesenchymal origin are prostatic stromal tumours of uncertain malignant potential (STUMP) and prostatic stromal sarcoma (Osunkoya 2012). Other variants of prostatic adenocarcinoma include pseudohyperplastic adenocarcinoma, adenosquamous carcinoma, atrophic adenocarcinoma, foamy gland adenocarcinoma, adenocarcinoma with carcinoid-like morphology, adenocarcinoma with Paneth-like neuroendocrine differentiation, adenocarcinoma with sarcomatoid differentiation, signet ring cell adenocarcinoma and adenocarcinoma with neuroendocrine differentiation. Neuroendocrine differentiation in PC tumour has
been reported to follow androgen deprivation therapy and it has been hypothesized to be involved in the progression to castrate-resistant and metastatic PC (Alberti 2010). The treatment of unusual variants of PCs may be challenging as some of these subtypes can behave aggressively and do not respond to conventional therapies, such as hormonal therapy (Osunkoya 2012).

The most common secondary malignancy that involves the prostate through direct extension is that of the urinary bladder. In radical cystoprostatectomy series the incidence of prostatic involvement with urothelial carcinoma of the bladder is reported to be 12-48% (Schellhammer et al. 1977; Revelo et al. 2004). From other sites, the metastases to the prostate typically arise from the lung, gastrointestinal tract, kidney, skin, testicle or endocrine organs. The incidence of secondary tumours in the prostate is 0.1-6.0% (Johnson et al. 1974; Zein et al. 1985; Bates et al. 2002).

High-grade prostatic intraepithelial neoplasia (HGPIN) is presumed to be a premalignant lesion for PC. This is based on its common presence adjacent to PCs. HGPIN is defined as architecturally benign prostatic ducts and acini lined by atypical or dysplastic epithelial cells. In the prostate biopsy the expected incidence of HGPIN is 5-8% and the median risk for PC following HGPIN on needle biopsy is estimated to be 24% (Epstein et al. 2006).

### 5.4.2 Grading, Gleason score

The current standard for histological grading of prostatic adenocarcinoma is based on the Gleason score system (Gleason 1966). It replaced the previously widely used World Health Organisation (WHO) differentiation grading system that is still generally used for grading other malignant tumors. The Gleason grading system is based on the pattern of tumour growth, not just single nuclei or cells. The Gleason grade ranges from 1 (the least aggressive) to 5 (the most aggressive). The Gleason score that consists of two summed grade patterns, ranges from 2-10. The Gleason grading system was updated by the International Society of Urologic Pathology (ISUP) consensus conference held in 2005. According to the current standard for Gleason grading, the most extensive and the highest grade should be incorporated into Gleason score in prostate biopsy, not the two most common patterns as in the earlier version (Epstein et al. 2005). In radical prostatectomy (RP) specimens the most and the second most common Gleason grade should be reported in addition to the presence and proportion of the tertiary grade (Epstein et al. 2005). Two well-known problems related to the Gleason grading are the tendency for upgrading from prostate biopsy to the RP specimen and interobserver variability (Iczkowski and Lucia 2011).

The Gleason score is currently the most important prognostic factor for PC (Epstein 2010). A variety of different nomograms and prediction models have been created to be able to predict more accurately the status and prognosis of disease. In case of PC, Kattan nomograms and Partin tables can be considered the most commonly known nomograms and with PSA value, clinical stage and Gleason score of the tumour, it is possible to predict the presence of an indolent cancer (Kattan et al. 2003) or draw up the risk classification of the progression of PC (Partin et al. 2001).
5.4.3 Staging, TNM classification

The extent of PC is commonly classified by the TNM -staging system. Table 1 presents the 2009 TNM classification (Sobin et al. 2009). Clinical TNM (cTNM) stage is estimated at the time of diagnosis and pathological TNM (pTNM) stage can be issued only after surgical treatment as tissue samples are required for pTNM staging. The definition of clinical T stage is currently based on DRE and transrectal ultrasound (TRUS). Positron emission tomography/computed tomography (PET/CT), MRI and novel TRUS techniques are not routine practice in PC staging (Turkbey et al. 2009). Accurate staging is essential for prognosis assessment. In addition, treatment selection differs for localized (T1-T2N0M0), locally advanced (T3-4, NX-N0, MX-M0) and metastasized (T1-4, N1 or M1) PCs.

Table 1. TNM classification of PC (version 2009) (Sobin et al. 2009).

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<th>N - Regional lymph nodes</th>
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<th>M – Distant metastasis</th>
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5.5 Diagnosis

The most commonly used modalities in the diagnostics of PC are a measurement of serum PSA, DRE, and TRUS-guided biopsies (Heidenreich et al. 2013).

5.5.1 Prostate-specific antigen and other markers

PSA was characterized in 1970s (Ablin et al. 1970; Wang et al. 1979) and after mid-1980s it became available for clinical use as an important tumour marker and potential screening tool for the detection of PC (Stamey et al. 1987; Catalona et al. 1991). PSA is a kallikrein-like serine protease that liquefies semen and is secreted by the epithelial cells of the prostate. A higher level of PSA indicates a higher risk for PC (Schröder et al. 2008). PSA is an organ-specific and not a cancer-specific tumour marker, also other conditions such as benign prostatic hyperplasia (BPH), prostatitis, ejaculation, urinary retention, prostate biopsy, and transurethral resection of prostate (TURP) may elevate the levels of serum PSA at least temporarily (Dalton 1989; Brawn et al. 1991; Neal et al. 1992; Yuan et al. 1992; Oesterling et al. 1993b; Nadler et al. 1995; Herschman et al. 1997; McNeill and Hargreave 2000).

Although PSA concentration is a continuous variable, a cut-off point of 4 ng/ml was originally considered to be the upper limit for a normal PSA value (specificity 59% and sensitivity 79%) (Catalona et al. 1991). Currently, a PSA value of 3 or 3.1 microg/l should be considered for World Health Organization (WHO)-calibrated assays in order to have the same sensitivity/specificity (Stephan et al. 2009). The positive predictive value of PSA values for PC > 4.0 ng/ml has been estimated to be 32% (Catalona et al. 1994). The results from the Prostate Cancer Prevention Trial (PCPT), suggest a cut-off point of 4.0 ng/ml, whereby up to 15% of PCs may be left undetected. Notably, 15% of these PCs were graded as Gleason 7 or higher (Thompson et al. 2004). Age-adjusted reference values have been proposed instead of a single PSA cut-off value. These age-adjusted values take into account the increase in PSA due to BPH with advancing age (Oesterling et al. 1993a).

The percentage of free PSA (%fPSA) in serum is calculated as the free to total PSA ratio, which has been shown to improve the specificity of PSA testing in PC detection conditions and low free PSA percentage is associated with a higher risk of PC (Catalona et al. 1995; Luderer et al. 1995; Chen et al. 1996; Elgamal et al. 1996; Partin et al. 1996; Van Cangh et al. 1996; Catalona et al. 1998). Generally, the free to total PSA ratio has been considered an especially useful marker in patients with a total PSA concentration range between 2.1-10 ng/ml (Kobori et al. 2008). A number of derivatives of serum PSA value, such as PSA density (PSAD) (Benson et al. 1992), PSA doubling time (PSADT) (Schmid et al. 1993) and PSA velocity (PSAV) (Carter et al. 1992) have been considered to improve the diagnostic accuracy of PSA testing and to enhance early detection of PC. Previous prospective studies indicate that the use of these in everyday clinical practice has not been demonstrated to be superior compared to the use of serum total PSA value alone (O’Brien et al. 2009; Vickers et al. 2009; Heidenreich et al. 2013).

Messenger RNA (mRNA) of the PC antigen 3 (PCA3) gene is found to be overexpressed in >95% of primary PC cells (Bussemakers et al. 1999). PCA3 is therefore used as a biomarker and is measured in urine sediment after prostatic massage. It has been suggested to be marker independent of the serum PSA level,
prior prostate biopsy or prostate volume (Deras et al. 2008). PCA3 has shown potential as an adjunct marker in PC diagnostics, but due to its lack of sensitivity it cannot replace the PSA test in clinical practice and its value as a first-line diagnostic test is indefinitely limited (Roobol 2011). The PCA3 score may be combined with the serum PSA value and other clinical risk factors into a nomogram, that may be used in decision-making concerning biopsy/rebiopsy (Auprich et al. 2011).

5.5.2 Digital rectal examination

Before the PSA era, DRE was practically the main method for detection of PC (Gerber et al. 1993; Kavasmaa et al. 2013). Approximately every fifth PC (18%) is detected by a suspicious DRE finding alone, regardless of the PSA value (Carvalhal et al. 1999). DRE is not very specific, since only 40-50% of cases with abnormal DRE findings have PC on biopsy (Philip et al. 2005). The risk of PC is higher in cases of an abnormal DRE finding, and especially when combined with an increased serum PSA value (Carvalhal et al. 1999; Gosselaar et al. 2008a). An abnormal DRE finding is also associated with high-grade PCs (Okotie et al. 2007).

5.5.3 Transrectal ultrasound and prostate biopsies

TRUS is the most common imaging method to examine the prostate. Abnormal areas in TRUS have been associated with PC (Dahnert et al. 1986; Lee et al. 1986; Gosselaar et al. 2008b). The classic finding of PC on gray-scale ultrasound is described as a hypoechoic lesion, but cancer foci may also be visualized as being isoechoic or even hyperechoic (Muldoon and Resnick 1989; Flanigan et al. 1994; Tzai et al. 1995). It has been estimated that over 40% of PC lesions are isoechoic and approximately 5% appear as hyperechoic (Ellis and Brawer 1994). Sensitivity and specificity for conventional gray-scale TRUS are 39-75% and 40-82%, respectively (Heijmink et al. 2011). Standard TRUS technique has a limited role in detecting or staging early PC (Onur et al. 2004), because of particularly low accuracy (52-62%) (Heijmink et al. 2011). Many PCs are not visible on standard TRUS and the positive predictive value of hypoechoid lesions is only in the 25-30% range (Rifkin et al. 1990). Colour Doppler scanning combined with TRUS can improve the detection of PC (Rifkin et al. 1993). Some new ultrasound techniques have also been developed to improve the detection of PC. These innovative techniques, such as ultrasound with contrast agents, 3-D and 4-D sonography and elastography have shown promising results compared with standard TRUS in PC diagnosis (Balaji et al. 2002; Halpern et al. 2005; Miyanaga et al. 2006; Yi et al. 2006; Abul et al. 2007).

TRUS-guided prostate biopsy is the standard method for histopathological diagnosis of PC (Hara et al. 2008; Takenaka et al. 2008). The basic sextant biopsy protocol was introduced in the late 1980s to enhance the accuracy of PC diagnosis (Hodge et al. 1989). The PC detection rates can be improved by increasing the number of targeted regions and biopsy cores (Eskew et al. 1997; Babaian et al. 2000;
Ravery et al. 2000; Emiliozzi et al. 2004; Eskicorapci et al. 2004). Moreover, the extended biopsy scheme with 12 biopsy cores has replaced the sextant biopsy protocol. Despite increasing the number of cores, the risk of adverse events (i.e. bleeding, infection, voiding dysfunction, pain) is not increased (Eichler et al. 2006). A 12-core systematic prostate biopsy scheme, that includes apical and far-lateral core sampling in a template distribution, has been shown to be a compromise between maximal detection of PCs, whilst avoiding rebiopsies and it provides sufficient information about the disease (Bjurlin et al. 2013). Taking more than 12 biopsy cores does not seem to increase the benefit substantially (Eichler et al. 2006), but in selected cases it may be reasonable to increase the number of biopsy cores. Typically, saturation biopsies (i.e. template with ≥20 and transition zone included) are considered, when prostate biopsies are repeatedly negative, but when there is still a high suspicion of PC (Scattoni et al. 2010). In selected cases saturation biopsy can be performed with transperineal approach to improve the detection of PC (Moran et al. 2006).

5.5.4 Imaging

CT and MRI have generally been considered to have a limited role in detecting and staging PC. Despite high specificity (>80%), CT has low sensitivity (<30%) in the local staging of PC (Tarcan et al. 1996; Yu and Hricak 2000) and a minor role in terms of detection and staging PC (Platt et al. 1987; Hricak et al. 2007). The MRI allows a functional assessment with modalities such as diffusion-weighted MRI (DWI-MRI), magnetic resonance spectroscopy imaging (MRSI), dynamic contrast-enhanced MRI (DCE-MRI) and these MRI techniques can be used for the detection and staging of PC (Ravizzini et al. 2009). The sensitivity and specificity of PC detection and local staging with MRI vary considerably with the population and the technique used (Turkbey et al. 2009). Indefinitely, PET scanning does not play a significant role in the detection or localization of PC due to its invasive nature, high costs and availability of other imaging modalities such as MRI (Heijmink et al. 2011). However, if TRUS-guided biopsies and MRI are negative, PET scanning can be used and it may provide additional advantages especially when combined with other imaging modalities, such as MRI (Heijmink et al. 2011). CT and MRI are currently the main imaging modalities commonly used for staging nodal PC, although they have similar, equally low sensitivity for evaluation of lymph node metastases (Hovels et al. 2008). Radionuclide bone scan (scintigraphy) after a technetium-99m injection is the current standard method for investigating potential bone metastasis in high-risk PC patients. The guidelines of The European Association of Urology (EAU) have recommended bone scanning in those cases of poorly differentiated PC (Gleason score ≥7) and locally advanced disease (≥cT3), irrespective of the serum PSA level. For patients with a PSA value <20 ng/ml bone scanning is recommended in the presence of symptoms or poorly differentiated tumour (Heidenreich et al. 2008). Despite the high sensitivity of scintigraphy, it suffers from a lack of specificity, and therefore other imaging modalities, such as 18F-choline PET/CT are under active evaluation (Even-Sapir et al. 2004; Jadvar 2013).
5.6 Prostate cancer screening

The objective of PC screening is to reduce overall and PC-specific mortality and to improve men’s QOL by preventing locally advanced and metastatic disease (Baum 2013). Elevated PSA is the most important diagnostic tool of PC in early detection programmes although other diagnostic measures, such as DRE have been used. Currently, there is no general consensus about recommended population-based screening for all men to detect early PCs (Ilic et al. 2011).

Two major randomized controlled studies are ongoing that evaluate population-based PC screening. The European Randomized Study of Screening for Prostate Cancer (ERSPC) (Schröder et al. 2003; Schröder et al. 2009) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) (Andriole et al. 2009) have the capacity to evaluate better the efficacy of PC screening. Both ERSPC and PLCO trials were initiated in the early 1990’s. ERSPC is a multicenter trial conducted in eight European countries. In practice, ERSPC consists of several smaller screening trials each of which has its own criteria for the age of participants, screening intervals, threshold for a positive screening result and type of recruitment. In general, the ERSPC trial included a total of 162 243 men aged 55-69 years and they were randomized to the PSA screening group (offered PSA measurement about once every 4 years) or to unscreened control group (Schröder et al. 2009). The PLCO was initiated in the USA and has more congruent criteria. The PLCO randomized 76 693 men to receive annual screening with PSA and DRE or standard care as the control (Andriole et al. 2009). The main end-point of these two major studies is PC-specific mortality, but in addition, QOL and cost-effectiveness are also analyzed.

Both ERSPC and PLCO reported their interim data in 2009. The ERSPC trial showed a significant reduction of 20% in PC mortality in the screening group after a median follow-up of nine years (Schröder et al. 2009). After adjustment for contamination (i.e. control group participants who sought opportunistic PSA screening) and noncompliance (i.e. men in the screening group who did not participate in the screening), the mortality reduction was shown to be up to 31% (Roobol et al. 2009). The cumulative incidence of PC was 8.2% in the screening group and 4.8% in the control group. The results showed the absolute risk difference to be 0.71 death per 1000 men, that is 1410 men would have to be screened and 48 additional PC cases would have to be treated to prevent one death from PC (Schröder et al. 2009). Moreover, the updated analysis after a median follow-up of 11 years showed a decrease in both of these numbers; based on recent results, 1055 would have to be screened and 37 treated to prevent one PC death. The relative risk reduction for PC-specific death was shown to be 21% in favour of PC screening (Schröder et al. 2012).

The Swedish part of the ERSPC, the Göteborg screening trial, published the mortality results separately (Hugosson et al. 2010). This trial was initiated in 1994 as an independent study, but joined the ERSPC soon after. With a follow-up of 14 years, the study detected a mortality reduction of 44% in the screening arm, accompanied by a significant risk of over-diagnosis. The differences compared to the ERSPC and also the probable reasons for different results are longer follow-up, younger age at screening, shorter screening interval (2 years) and lower PSA threshold (3.0 ng/ml).
The PLCO trial did not find a PC mortality benefit in the screening arm. This result has been explained by contamination of the control arm. The contamination was extensive in the control arm since over a third of participants had undergone PSA testing and DRE within the first year of the study and half of the participants had PSA testing during the trial (Andriole et al. 2009).

The results of the ERSPC and the PLCO trials, as evaluated by the major urologic societies indicated that widespread population-based mass screening for PC is not recommended at present. The EAU recommends early detection of PC (i.e. opportunistic screening) in well-informed men instead of mass screening. A baseline PSA level should be determined at the age of 40 and screening intervals should be adapted to this baseline PSA serum concentration thereafter. An interval of 8 years might be appropriate for screening in men with baseline levels of ≤ 1 ng/ml. PSA testing is not recommended in men > 75 years as early detection of PC would not have any impact clinically (Heidenreich et al. 2013). The American Urological Association (AUA) do not recommend PSA screening for the following categories: men < 40 years, men 40-54 years of age at average risk, men > 70 years of age or life expectancy less than 10-15 years. They recommend shared decision making for men 55-69 years of age and a screening interval of ≥ 2 years (Carter et al. 2013).

5.6.1 QOL aspects related to the PSA screening process

PC screening has been shown to reduce PC-related mortality and the rate of advanced disease. Reduction in mortality from PC is the primary endpoint in the screening trials, but QOL is also a major aspect, and often expressed as quality-of-life adjusted gain in life years (QALYs). The problem of overdiagnosis related to screening has already been emphasized (Djulbegovic et al. 2010; Ilic et al. 2011). However, more confirmed data from randomized trials is needed as reports about the benefits and harmful effects of PSA screening have varied widely and are rather inconsistent (Ilic et al. 2007; Crawford and Abrahamsson 2008). Recently, data from the ERSPC trial concluded that the benefit of PSA screening was diminished by the loss of QALYs owing to post diagnosis long-term effects. Before more general recommendations regarding PSA screening can be made, data from longer-term follow-up, data on long-term effects of PC treatments, and AS data on QOL are also needed (Heijnsdijk et al. 2012).

Previous studies have shown that PSA screening participants do not experience any significant increases in anxiety levels, even with an abnormal PSA result (Essink-Bot et al. 1998; Brindle et al. 2006). The screening process does not seem to affect substantially the health status of individuals in the short-term; the exception to this is the short-lasting side effects of having a prostate biopsy (Essink-Bot et al. 1998). In addition, only men who have a tendency to anxiety have experienced higher levels of anxiety and distress during the screening process (Essink-Bot et al. 1998). In general, men seem to cope well through the PSA screening process, although a minority of participants experience distress at the time of prostate biopsy, which is not entirely resolved even by a negative screening result (Macefield et al. 2010). Screening for disease does not appear to have long-term negative emotional impact on participants (Collins et al. 2011) and the screening process itself has only little if any effect on participant’s psychological health (Awsare et al. 2008; Macefield et al. 2010).
5.7 Treatment options with curative intent

At present there are various treatment options available for PC, depending on the clinical stage of the disease. The options for localized PC with curative intent are AS, radical prostatectomy (RP), external beam radiotherapy (EBRT), brachytherapy (BT) and focal therapy. AS is hereafter discussed in the review as a separate entity. Currently the lack of randomized controlled trials makes the comparison of treatment modalities difficult.

5.7.1 Radical prostatectomy

RP is a surgical procedure to remove the prostate gland. Open retropubic RP has been the most commonly used technique, but recently robot-assisted radical prostatectomy (RARP) has become a commonly used option for open surgery (Novara et al. 2012b). Patients with a life expectancy of over 10 years and local disease are generally considered suitable, and the goal for RP is the eradication of PC while saving urinary continence and potency if possible (Bianco et al. 2005). Data from the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database has showed that RP is at present the most common treatment in men with localized PC and approximately half of these patients undergo RP procedure in the US (Cooperberg et al. 2010). A carefully selected patient population with high-risk and more advanced PC (PSA>20 ng/ml with clinical stage T3 and/or Gleason score 8-10 in biopsy) may also benefit from RP (Spahn et al. 2010; Gontero et al. 2011).

Two prospective randomized trials reported a PC-specific survival benefit from RP compared with watchful waiting (WW). The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) reported that compared to WW a reduction in the rate of death from PC, and at 15 years the absolute risk reduction was 6.1% following randomization to RP (Holmberg et al. 2012). The subanalysis of this study clarified, that individual prediction of benefit of RP varies widely depending on age and PC characteristics. The absolute 10-year PC mortality reduction in the RP group was 4.5% for low-risk versus 17.2% for high-risk patients, in men at 65 years of age (Vickers et al. 2012). The other randomized trial, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) showed a benefit attributable to RP in men < 65 years of age, but only in those who had only an intermediate or high risk of PC progression (Wilt et al. 2012).

It would be more acceptable to treat all PC patients when radical treatment did not cause any side effects or decrease QOL. Nevertheless, each treatment modality for localized PC has side effects, even in the long-term after treatment (Sanda et al. 2008; Litwin et al. 1995; Mols et al. 2009). The improvement in surgical techniques including the introduction of RARP, have resulted in advantages in postoperative recovery and functional outcomes (Novara et al. 2012b; Novara et al. 2012a; Ficarra et al. 2012a; Ficarra et al. 2012b). However, urinary incontinence and erectile dysfunction remain significant parts of the side effect profile of RP. The rates of urinary incontinence and erectile dysfunction after surgery vary widely between published reports. Approximately 8% of men that have undergone RP, have persisting urinary incontinence a year after the operation (Murphy et al. 1994).
Nerve-sparing techniques can be considered in a patient with organ-confined disease and reported potency rates after bilateral nervesparing RP varied between 31 and 86% (Dubbelman et al. 2006).

5.7.2 External beam radiation therapy

EBRT is one of the primary treatment modalities for patients with localized or locally advanced PC. It is also commonly used in cases that suggest a greater likelihood of non-organ-confined disease. Radiotherapy continues to be an important and valid alternative to surgery as a radical treatment for PC. In EBRT, radiation is delivered to the prostate gland via an external energy source. Three-dimensional conformal radiation therapy (3D-CRT) has been the gold standard for EBRT in many countries, and if possible, intensity-modulated external-beam radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is currently recommended (Bauman et al. 2012; Heidenreich et al. 2013). IMRT is an optimized form of 3D-CRT and by using implanted fiducial markers in the gland it enhances the ability to escalate radiation dosage without additional toxicity. To optimize outcomes of EBRT, a dose of ≥74 Gy is recommended for treating low-risk PC (Kupelian et al. 2005). For intermediate- and high-risk PC a dose escalation from 76 to 81 Gy has been shown to have a significant positive impact on 5-year progression-free survival (Kupelian et al. 2008; Krauss et al. 2011). One possibility for treatment of intermediate- or high-risk PC, is the combination of EBRT with low- or high-dose brachytherapy. Androgen-deprivation therapy is also recommended to be combined with EBRT to improve overall survival in patients with high-risk localized PC (D’Amico et al. 2008; Jones et al. 2011). The risk for side effects of EBRT increases with dose-escalation and patients are informed about potential later gastrointestinal or genitourinary toxicity, and possible adverse effects of EBRT on erectile function. The most typical side effects related to radiation therapy include gastrointestinal symptoms such as rectal bleeding and proctitis and genitourinary symptoms such as urgency, haematuria and incontinence (Budaus et al. 2012; Mohammed et al. 2012; Schmid et al. 2012). According to retrospective surveys, the effects of radiotherapy on erectile function are reported to be less than those of RP (Fowler et al. 1996). One of the long-term effects and risks related to radiotherapy is the development of radiation induced secondary malignancy, such as rectal or bladder cancer (Murray et al. 2013)

5.7.3 Brachytherapy

BT refers to the treatment of PC using ionizing radiation that is delivered via radioactive seeds placed in the prostate gland. The low-dose rate brachytherapy (LDR-BT) approach is transperineal and done under TRUS guidance. In LDR-BT, permanent low-energy radioactive implants, i.e. iodine-125 or palladium-103, are inserted into the prostate. LDR-BT is indicated in patients with low-risk PC (Ash et al. 2000). The updated consensus guidelines for LDR-BT in patient selection, optimal technique and follow-up, were recently published (Davis et al. 2012). In high-dose rate brachytherapy (HDR-BT) iridium-192 high-radiation source is
implanted temporarily into the gland. HDR-BT can be used in combination with EBRT for more aggressive and advanced PC tumours. The analyses of a BT series demonstrated good results for the oncological outcome (Sylvester et al. 2011; Morris et al. 2013). The main side effect profile of BT includes a risk of urinary retention (1.5-22%), incontinence (0-19%) and a risk for post-implantation transurethral resection of the prostate (required in up to 8.7% of cases) (Budaus et al. 2012). Erectile dysfunction develops in about 40% of men 3-5 years after BT (Heidenreich et al. 2013).

### 5.7.4 Focal therapies

The number of smaller PCs detected at an earlier stage, has increased during the past two decades due to the screening. Focal treatment, such as cryosurgical ablation of the prostate (CSAP) and high-intensity focused ultrasound (HIFU) therapy, has emerged as a treatment option in men with clinically localized small focus PC and for whom RP is not indicated (Babaian et al. 2008; Crouzet et al. 2010; Warmuth et al. 2010). Although recent studies have shown promising results (Donnelly et al. 2010), the long-term efficacy data are still lacking (Heidenreich et al. 2013). Known complications related to CSAP include acute urinary retention, erectile dysfunction (45-100%), urethral sloughing (0-6%), incontinence (2-4%), and fistula formation (<1%). Potential complications after HIFU are erectile dysfunction (13-53%), incontinence (1-15%), urethral stricture (4-14%), urinary retention (1-9%) and rectourethral fistulae (0-3%) (Nguyen and Jones 2011).

### 5.8 Hormonal therapy

Hormonal therapy is mainly used in patients with locally advanced or metastasized PC, in postponing clinical progression and reducing symptoms. The principle behind endocrine therapy is to eliminate androgens (by chemical or surgical castration) or androgen action (antiandrogens) and hence achieve an inhibitory effect on PC cells. When prostate cells are deprived of androgenic stimulation they undergo apoptosis. The elimination of androgens can be achieved by suppressing the secretion of testicular androgens, i.e. surgical castration or with chemical castration by using luteinising hormone-releasing hormone (LHRH) agonists, with or without antiandrogens. In recent years LHRH antagonists have also become available for chemical castration. Immediate androgen deprivation therapy compared with deferred therapy initiated at the time symptomatic progression occurs, gives a modest improvement in overall survival, but not in disease-specific survival, except in patients with aggressive PC (Studer et al. 2013). Data of SPCG-7/SFUO-3 trials suggest that when androgen deprivation therapy in combination with radiotherapy is compared with endocrine treatment alone, it halves the 10-year PC-specific mortality and decreases overall mortality in men with locally advanced disease or high-risk local PC (Widmark et al. 2009). Hormonal treatment can also be used as a neoadjuvant or adjuvant therapy. In cases of locally advanced PC, for which
immediate androgen suppression with LHRH agonists given during and for three years after EBRT, improved disease-free and overall survival (Bolla et al. 2002).

There are many side effects related to hormonal therapy. Castration is associated with hot flushes, loss of energy, loss of libido, loss of potency, osteoporosis, weight gain, nausea, vomiting and mood swings. Patients on long-term conventional androgen deprivation therapy may also have a higher risk of cardiovascular disease (Bourke et al. 2012). The main side effects associated with antiandrogens are gynecomastia and breast pain (Iversen et al. 2010).

5.9 Active surveillance

5.9.1 Rationale for active surveillance

Over the last two decades, the proportion of low-risk PCs in which earlier detection did not change the prognosis, has increased (Welch and Black 2010). This phenomenon is described by the term overdiagnosis. The most significant evidence for PC overdiagnosis comes from randomized screening trials. PSA-based PC screening has led to the overdiagnosis of indolent tumours in up to 50% of cases (Draisma et al. 2003). AS has emerged as an alternative strategy for managing these potentially overdiagnosed PCs. The objective of this strategy is to avoid, or postpone the treatment of PC, and thereby diminish the possible adverse effects of radical treatments (Parker 2004). Radical treatment of all men with low-risk PC, would cause a considerable amount of unnecessary side effects, such as incontinence and impotence (Pardo et al. 2010) that have adverse effects on QOL (Sanda et al. 2008).

The specific approach of AS is to initially withhold radical treatments (i.e. surgery or radiation therapy), but reserve the opportunity to deferred treatment with curative intent in the case of disease progression or recategorification observed during follow-up. During AS, patients are intensively monitored using such tools as repetitive PSA measurements, clinical examination including DRE and prostate biopsies.

The basis for using the AS strategy is the substantial evidence and knowledge of the long natural history of PC. Post-mortem studies have shown that the prevalence of indolent PCs is high in aging men; in about 50% of men in their fifties harbour histological evidence of PC and the rate increases with age (Sakr et al. 1994). Such tumours are not likely to progress or their growth potential is so slow that these patients are likely to die of other causes than PC. Widespread PSA-based screening and extended-pattern biopsy schemes have led to an increasing trend in overdiagnosis (Draisma et al. 2003; Welch and Black 2010).

A Gleason score of 6 for PC has been seen as a part of the aging process (Sakr et al. 1994). A Gleason score of 6 PC has been shown not to have the characteristic hallmarks of many other cancers, which are: apoptosis resistance, sustained angiogenesis, local tissue invasion/metastasis, unlimited replicative potential, insensitivity to antigrowth signals and self-sufficiency to growth signals (Guo et al. 1997; Skacel et al. 2001; Padar et al. 2003; Pasquali et al. 2006; True et al. 2006; Susaki and Nakayama 2007; Mucci et al. 2009; Hanahan and Weinberg 2011; Ross et al. 2011; Bismar et al. 2012; Fleischmann et al. 2012). The 20-year outcomes following conservative management, based on the Albertsen WW cohort before the PSA testing era, reported a mortality rate of 22% for Gleason score of 5 or
6 PC (Albertsen et al. 2005b). However, ERSPC data indicate that screen-detected PCs are diagnosed approximately 10 years earlier (Schröder et al. 2010). The Gleason grading system was changed in 2005 (Epstein et al. 2005), which resulted in the relative upgrading of the disease; it has been estimated that one-third of patients (with a Gleason score 6 PC) in the Albertsen study would be upgraded according to the current grading system (Albertsen et al. 2005a). Of importance is that, the grading of the tumours in the WW series is based on biopsy rather than surgical staging, which is known to underestimate the proportion of higher grade PCs. A study of 12,000 men with pathologically confirmed Gleason score 6 PC after RP, found that 0.2% progressed to the metastatic phase during the 20-year follow-up, but after the re-analysis the same individuals of this group upgraded to Gleason 4 pattern (Eggenger et al. 2011). Similar results were reported for a RP series of 14,000 men with a Gleason score 6 cancer of which only 22 had lymph node metastases and these PCs upgraded into Gleason score ≥7 after re-analysis (Ross et al. 2012). It could be concluded that the prevailing current thinkings suggest Gleason score 6 cancer to be only a risk factor for clinically significant PC rather than a cancer with metastatic potential itself.

5.9.2 Watchful waiting versus active surveillance

AS emerged from the experience of WW. The term ‘watchful waiting’ is used to describe the conservative approach to management of PC. The rationale for this observational strategy is the finding that PCs often progress slowly and are diagnosed in elderly men with high incidence of comorbidity. WW aims to avoid or at least delay treatment and the related side effects, and thus helps maintain the QOL. When treatment is required, it is palliative only. By contrast, patients on AS should be initially fit for radical treatment. The AS strategy aims to diagnose clinically significant disease and if it occurs during follow-up, offer deferred radical treatment with curative intent only when needed. Hence, avoidance of unnecessary morbidity from overtreating PCs is a desired objective. This observational strategy was first described in 2002 (Choo et al. 2002).

5.9.3 Definition of clinically insignificant prostate cancer

The aggressiveness of PC is partly defined by its pathological characteristics, i.e. pathological stage, differentiation grade and tumour volume. The terms ‘indolent’ and ‘clinically insignificant’ have been widely used for low-risk asymptomatic PCs. These terms are often used interchangeably. However, the term ‘insignificant’ takes the clinical aspect more into account, whereas the term ‘indolent’ refers to the pathological features (Ploussard et al. 2011b). Frequently used criteria for indolent PC include pathological stage T2, absence of Gleason pattern 4/5 and tumour volume less than 0.5ml in a RP specimen (Epstein et al. 1994). The tumour volume threshold of <0.5 ml is based on only a modest series of cystoprostatectomies taken before PSA testing era ensured (Stamey et al. 1993). Recent ERSPC trial data suggest a cancer volume of 1.3 ml as a cut-off point for indolent Gleason score 6 (stage ≤T2) PC (Wolters et al. 2011).
Clinical criteria that combines clinical and biopsy findings were based on histological data. Currently, the definition for low-risk PC as described by D’Amico is the most widely accepted: i.e. a PSA of less than 10 ng/ml, Gleason score of 6 or less, and nonpalpable tumour or palpable in less than half of one lobe of the prostate (i.e. T1c or T2a) (D’Amico et al. 1995). A more strict definition (Epstein criteria) distinguishes the very low-risk PC into separate category, as defined as a PSAD of <0.15 ≤50% PC involvement of any biopsy core, and maximum of two positive biopsy cores (Epstein 2011), the other low-risk PCs fulfill the D’Amico criteria. Various nomograms have also been developed to assess the probability of indolent or low-risk PC (Bangma et al. 2009).

5.9.4 Patient selection for active surveillance

The most effective AS programme would reliably be able to recognize the patients with the more aggressive disease and the need for active treatment early after diagnosis. Although there exists no randomized trials that compare selection criteria for AS, several prospective AS series have provided a feasible basis for indentifying appropriate patients using this management strategy (Dall’Era et al. 2008; van As et al. 2008; Klotz et al. 2010b; Soloway et al. 2010; Adamy et al. 2011; Tosoian et al. 2011; Bul et al. 2013b). Patients who are considered candidates for AS should be fit for radical treatment, thus comorbidities and age are essential issues in the AS decision-making process. Eventually, treatment decision for patients with localized early stage PC should take into account several things such as age, comorbidities, personal preferences, estimation of the aggressiveness of the PC and potential benefits and risks of radical treatments (Smith 2011). Although the specific inclusion criteria for AS vary by institution and there is also a wide range of criteria, the majority of criteria are similar and offer a common basis for patient selection. These include low clinical stage (T1-T2), low PSA (<10-15 ng/ml), well-differentiated PC (Gleason score< 7 in most series) and small volume tumour in the biopsy. The inclusion criteria of largest prospective AS trials are listed in Table 2.

<table>
<thead>
<tr>
<th>Institution</th>
<th>PSA</th>
<th>Clinical stage</th>
<th>Gleason score</th>
<th>PC positive biopsy cores</th>
<th>Single core positivity</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIAS (van den Bergh et al. 2007)</td>
<td>≤ 10</td>
<td>T1-T2</td>
<td>≤ 3+3</td>
<td>≤ 2</td>
<td>NR</td>
<td>PSAD &lt; 0.2</td>
</tr>
<tr>
<td>University of Toronto (Klotz et al. 2010b)</td>
<td>≤ 10</td>
<td>T1c</td>
<td>≤ 3+3</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>University of Miami (Soloway et al. 2010)</td>
<td>≤ 10</td>
<td>≤ T2a</td>
<td>≤ 3+3</td>
<td>≤ 2</td>
<td>≤ 20%</td>
<td>-</td>
</tr>
<tr>
<td>UCSF (Dall’Era et al. 2008)</td>
<td>≤ 10</td>
<td>≤ T2a</td>
<td>≤ 3+3</td>
<td>≤ 33%</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>Johns Hopkins (Tosoian et al. 2011)</td>
<td>-</td>
<td>T1c</td>
<td>≤ 3+3</td>
<td>≤ 2</td>
<td>≤ 50%</td>
<td>PSAD ≤ 0.15</td>
</tr>
<tr>
<td>Royal Marsden Hospital (van As et al. 2008)</td>
<td>≤ 15</td>
<td>≤ T2a</td>
<td>≤ 3+4</td>
<td>≤ 50%</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>MSKCC (Adamy et al. 2011)</td>
<td>≤ 10</td>
<td>≤ T2a</td>
<td>≤ 3+3</td>
<td>≤ 3</td>
<td>≤ 50%</td>
<td>-</td>
</tr>
</tbody>
</table>

* Until 2000 for men over 70: GS3+4, PSA<15
MSKCC = Memorial Sloan Kettering Cancer Center; NR=not recorded; PSAD=PSA-density; UCSF = University of California, San Francisco
Most of the AS protocols accept only patients with a Gleason score of 6 PC and the presence of Gleason pattern 4 is considered a contraindication for AS. However, previous studies have shown promising results, and suggest that a small amount of Gleason pattern of 4 might still be categorized as indolent disease and these patients should also be considered as candidates for AS, since the progression rates have not differed significantly from Gleason score 6 PCs (Choo et al. 2002; Cooperberg et al. 2011b; Bul et al. 2012b). This approach may be more applicable in older patients (over >65 years) or in men with short life expectancy and comorbidities (Klotz 2013).

### 5.9.5 Monitoring and triggers for intervention

The aim of intensive monitoring during AS is to identify those patients with biologically aggressive PC missed initially or PCs that have developed during surveillance, but which are still at a curable stage. Each AS protocol has its own follow-up strategy and there is no preferable way of monitoring. Contemporary AS protocols monitor potential progression by means of PSA testing, clinical examination by DRE and by prostate biopsy. Monitoring includes repetitive measurements of serum PSA (e.g. at 3-month intervals) and based on these measurements the PSADT or PSAV values can be calculated. A rebiopsy is performed at one year of surveillance and in most AS protocols biopsy are repeated at least every 3 to 4 years. The common triggers for intervention (Table 3) include Gleason progression to ≥7 or higher tumour volume in prostate rebiopsy, short PSADT (a cut-off value ranging between ≤2 and ≤4 years), increasing PSA velocity, changes on serial imaging or patient’s request mainly due to increased anxiety.

<table>
<thead>
<tr>
<th>Institution</th>
<th>Triggers for intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIAS (van den Bergh et al. 2007)</td>
<td>PSADT&lt;3 years; GS≥7; &gt;2 positive cores</td>
</tr>
<tr>
<td>University of Toronto (Klotz et al. 2010b)</td>
<td>PSADT≤3 years; T stage progression; GS upgrade</td>
</tr>
<tr>
<td>University of Miami (Soloway et al. 2010)</td>
<td>GS ≥7; increase of positive cores, increase of core involvement</td>
</tr>
<tr>
<td>UCSF (Dall'Era et al. 2008)</td>
<td>GS≥7; PSAV&gt;0.75ng/ml per year</td>
</tr>
<tr>
<td>Johns Hopkins (Tosoian et al. 2011)</td>
<td>GS≥7; &gt;2 positive cores; &gt;50% core involvement</td>
</tr>
<tr>
<td>Royal Marsden Hospital (van As et al. 2008)</td>
<td>Primary GS≥4; PSAV&gt;1ng/ml per year; &gt;50% core involvement</td>
</tr>
<tr>
<td>MSKCC (Adamy et al. 2011)</td>
<td>PSA≥10; GS≥7; ≥3 positive cores; &gt;50% core involvement</td>
</tr>
</tbody>
</table>

| GS=Gleason score; PSADT=PSA doubling time; PSAV=PSA velocity |
| MSKCC = Memorial Sloan Kettering Cancer Center; UCSF = University of California, San Francisco |

Changes of serum PSA value over time seem to be a trigger for treatment less often than upgrading the classifications or Gleason scores in rebiopsies (Dall'Era et al. 2008). PSADT is a trigger for active treatment in about 10-20% of cases (Bul et al.
2012c) and a short PSADT (i.e. ≤3 years) has been shown to be associated with adverse rebiopsy findings (Bul et al. 2012a). However, some recent studies have questioned the association between PSA kinetics and reclassification or adverse rebiopsy results in the short-term (Ross et al. 2010; Whitson et al. 2011), and therefore PSA kinetics are often combined with information from DRE and biopsy. In addition to being an invasive procedure with potential morbidity, prostate biopsy often underestimates the grade and stage of the disease (Stav et al. 2007). This creates the need for the development of novel biomarkers and imaging technology, such as MRI, to improve AS.

5.9.6 Outcomes of active surveillance studies

5.9.6.1 Treatment free-survival, PC-specific mortality and overall mortality

Despite the varying inclusion criteria of AS studies, PC-specific and overall mortality rates are low in the short-term (Table 4). The longest median follow-up (6.8 years) of AS was reported for the Toronto cohort, in which the 5- and 10-year PC-specific survival rates were 99.7% and 97.2%, respectively (Klotz et al. 2010b). This patient cohort includes men with low-risk and intermediate-risk (30%) PCs. Men > 70 years had PSA values of up to 15 ng/ml and Gleason scores ≤ (3+4). The median age of patients in this AS series was relatively high (70.3 years), which probably explains the high all-cause mortality rate (overall survival 78.6%). AS study by Johns Hopkins University reported results with no PC deaths or metastatic cases, after a median follow-up of 2.7 years (Tosoian et al. 2011). In this study the patients fulfilled strict criteria for very low-risk PC, i.e. the Epstein criteria. A retrospective study from the ERSPC, on 988 participants and a median follow-up of 3.91 years, reported 10-year PC-specific survival of 100% (van den Bergh et al. 2009b). The prospective PRIAS AS study reported a treatment-free survival of 77.3% after 2 years, a median follow-up of 1.6 years and PC-specific survival of 100% (Bul et al. 2013b).

5.9.6.2 Outcomes from deferred treatment

As PC progress or is reclassified beyond the initial inclusion criteria, deferred radical treatment is often recommended. The results from PRIAS data showed, that patients who discontinued AS due to protocol deviations, 14% had a Gleason score of ≥4+3 and 19% extracapsular extension (Bul et al. 2012c). This is in concordance with previous studies. Several previous studies have examined RP series that compared deferred to immediate treatments and no significant differences were observed in pathological outcome or in biochemical recurrence rates (Warlick et al. 2006; van den Bergh et al. 2010b; Holmstrom et al. 2010; Dall’Era et al. 2011). Furthermore, a nationwide cohort study in the United States showed similar rates for PC mortality in men with low-risk PC who chose deferred treatment on AS and those who were treated immediately (Shappley et al. 2009). The majority of AS patients, about 2/3 remain treatment free, and metastatic cases and PC mortality are shown to be rare in
prospective AS trials (van As et al. 2008; Dall’Era et al. 2008; Klotz et al. 2010a; Tosoian et al. 2011). However, the longest AS cohort study from Toronto reported a biochemical recurrence rate of 50% in radically treated men, which represented 13% of the total patient cohort (Klotz et al. 2010b).

Table 4. Summary of survival results of AS series.

<table>
<thead>
<tr>
<th>Institution</th>
<th>Size of cohort</th>
<th>Median follow-up (months)</th>
<th>Median age (years)</th>
<th>ATFS (%)</th>
<th>OS (%)</th>
<th>CSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIAS (Bul et al. 2013b)</td>
<td>2494</td>
<td>19</td>
<td>65</td>
<td>76</td>
<td>97.1</td>
<td>100</td>
</tr>
<tr>
<td>University of Toronto (Klotz et al. 2010b)</td>
<td>453</td>
<td>82</td>
<td>70</td>
<td>70</td>
<td>78.6</td>
<td>97.2</td>
</tr>
<tr>
<td>University of Miami (Soloray et al. 2010)</td>
<td>230</td>
<td>32</td>
<td>64</td>
<td>86</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>UCSF (Dall’Era et al. 2008)</td>
<td>321</td>
<td>47</td>
<td>64</td>
<td>54</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Johns Hopkins (Tosoian et al. 2011)</td>
<td>769</td>
<td>32</td>
<td>66</td>
<td>54</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Royal Marsden Hospital (van As et al. 2008)</td>
<td>326</td>
<td>22</td>
<td>67</td>
<td>73</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>MSKCC (Adamy et al. 2011)</td>
<td>238</td>
<td>22</td>
<td>64</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ATFS = active treatment-free survival; OS = overall survival; CSS = cancer-specific survival
MSKCC = Memorial Sloan Kettering Cancer Center; UCSF = University of California, San Francisco

5.9.6.3 Rebiopsy outcomes

Most of the AS trials include prostate rebiopsy as a part of surveillance strategy. This is based on the assumption that the Gleason grade is a significant predictor for PC prognosis. The data from radical prostatectomy specimen showed that preoperative clinical undergrading is common, it is estimated to be 20-30% with a standard 12-biopsy core system (Conti et al. 2009; Smaldone et al. 2010; Suardi et al. 2010). In most cases, Gleason classification upgrading is likely to be due to the more accurate resampling than true disease progression (Porten et al. 2011). The results from the PRIAS study indicated the risk of reclassification towards higher risk of PC in 21.5% of men in 1-year rebiopsies (Bul et al. 2012a). Higher PSAD and number of positive biopsy cores at diagnosis (2 versus 1) were predictive of a higher grade and a higher volume PC at rebiopsy. Several other studies have reported reclassification rates between 13-55% (Venkitaraman et al. 2007; Ng et al. 2009; Ross et al. 2010; Tseng et al. 2010; Adamy et al. 2011; Isharwal et al. 2011; San Francisco et al. 2011; Whitson et al. 2011). In many of these studies PSAD has also shown to be a significant baseline predictor for reclassification in rebiopsy (Venkitaraman et al. 2007; Ng et al. 2009; San Francisco et al. 2011).
5.9.7 Psychological and QOL aspects

The principal aim of AS is to avoid or delay side effects of radical treatment, but one concern is the possible psychological burden on the patient caused by the knowledge of having an untreated cancer. Men with low-risk PC may experience anxiety during AS and this may have negative effects on their QOL (Bacon et al. 2001; Galbraith et al. 2001; Litwin et al. 2002). Men on a surveillance-like strategy may be unsettled due to a perception of danger and this may negatively influence their QOL (Wallace 2003). However, recent studies showed that patients with low-risk PC and on AS, do not seem to have higher anxiety or distress levels in the short-term. During a nine-month period, anxiety and distress levels remained relatively low, but those patients with a more neurotic personality and lower physical health scores reported higher anxiety and distress levels (van den Bergh et al. 2009a; van den Bergh et al. 2010a). Previous studies also suggest that AS is not significantly associated with psychological distress when compared to immediately treated patients who received radiotherapy with or without hormonal therapy (Burnet et al. 2007). Patients on AS have been shown to have comparable generic- and disease-specific health-related quality of life (HRQL) dimensions compared to patients treated with EBRT. Patients on AS had fewer problems with bowel function than patients who had received radiation therapy. Patients treated by radiation therapy also reported significantly more problems with erectile function. HRQL of patients on surveillance was comparable to age- and sex- matched normative population up to 10 years after diagnosis (Thong et al. 2010). Surveillance, unlike immediate treatment, was associated with QOL benefits as a long-term decrease in the risk of urinary incontinence and impotence. QOL outcomes were not worse in patients who had delayed treatment after initial surveillance compared to those who had immediate treatment (Kasperzyk et al. 2011). AS has also been reported to have the highest quality-adjusted life expectancy, when compared with radiation therapy, brachytherapy or radical prostatectomy (Hayes et al. 2010). Serial prostate rebiopsies may have an adverse effect on erectile function, but no significant effect on lower urinary tract symptoms has been observed (Fujita et al. 2009).

The majority of the patients seem to be satisfied with the choice of surveillance and only a limited number of men were reported to be afraid of PC progression (Latini et al. 2007). Communication, education and peer-support groups can be beneficial to ease anxiety concerning AS (Pickles et al. 2007). Discontinuation of AS and a change to deferred radical therapy are not often due to anxiety or distress (Cooperberg et al. 2011a). The patients who have chosen expectant management (WW) as their treatment option, have similar or even better HRQL scores compared to men without PC at the beginning of the surveillance, but many of HRQL domains are affected by increasing age and scores decrease over time (Arredondo et al. 2008). Longer follow-up is needed to be able to assess the long-term psychological and QOL effects of AS. Ongoing studies, such as the Prostate testing for cancer and Treatment (ProtecT) study that randomize treatments of patients with low-risk PC, may offer more information about QOL effects of AS (Lane et al. 2010).
5.9.8 Imaging

The role of imaging in AS patients is currently under extensive investigation. MRI seems to be the most promising imaging modality. Since the early 1980s, MRI has been used to evaluate the anatomy of the prostate and PC disease (Steyn and Smith 1982). The utility of MRI is its accurate representation of soft tissue anatomy, high spatial resolution, and the possibility for functional measurements to be taken, e.g. spectroscopy. These advantages have led to the active evaluation of the role of MRI in the diagnosis and staging of PC (Lindner et al. 2010). T2-weighted MRI was initially used for tumour localization, but benign conditions (i.e. prostatitis, haemorrhage) were found to have a similar appearance. T2-weighted MRI has a varying sensitivity (46-96%) and a low specificity (54-82%) in tumour localisation (Wefer et al. 2000; Engelbrecht et al. 2002; Kirkham et al. 2006). Hence, other MRI modalities were developed namely: diffusion weighted MRI (DW-MRI), which measures the diffusion of water molecules in tissue; dynamic contrast-enhanced MRI (DCE-MRI), which utilizes the microvascular properties of tissue and MR spectroscopy (MRSI), which measures metabolite levels (creatine, choline, citrane, polyamides) in tissue. The multiparametric approach i.e. combinations of these modalities (T2 weighted imaging combined DW-MRI and/or DCE-MRI and/or MRSI) accurately rules out clinically important lesions, and has negatively predictive values for high grade PCs (Villers et al. 2006; Delongchamps et al. 2011; Somford et al. 2013). A large cancer lesion under MRI in a patient with PC has a high predictive value for clinically significant disease (Futterer et al. 2009; Villeirs et al. 2011). A study reported that multiparametric MRI also has a significant correlation with Gleason score, but significant overlap between different grades still existed (Hambrock et al. 2011).

Multiparametric MRI has been used to target biopsies at suspicious lesions. Previous results report PC detection rates of 41% with (median 4 cores) MRI guided targeted biopsy in men with previous negative TRUS-guided 12-core random biopsies (Hoeks et al. 2012). The majority of cancers detected (87%) were clinically significant. Multiparametric MRI in combination with MRI guided biopsy may thus have a role in risk classification at diagnosis and during follow-up in AS patients. The role of MRI in AS has not yet been fully determined, although it has been shown to aid in the detection of the anteriorly located tumours (Lawrentschuk et al. 2010). Guidelines have been developed for prostate MRI including imaging acquisition protocols and a structurized reporting system to improve the reproducible and reliability of MR images with standardised methods and technologies (Barentsz et al. 2012; Moore et al. 2013). Accurate interpretation of MRI is challenging and requires experience that can result in significant interobserver variability (Mussurakis et al. 1996). MR imaging is not assumed to replace the histological verification of PC, but to help decrease the frequency of rebiopsy and biopsy-related morbidity in patients on AS (Turkbey et al. 2011b; Turkbey et al. 2012).

5.9.9 Biomarkers

Potential serum and urine biomarkers for PC have been intensively studied in basic research laboratories for the past decade. Future novel biomarkers may make it possible to improve the risk rating of PC at an early stage. Unfortunately, no
clinically relevant markers have been validated as relevant prognostic factors in AS as yet. Isoforms of PSA, such as combination of free PSA and -2ProPSA (Isharwal et al. 2011) are under evaluation. Prostate cancer antigen 3 (PCA3) was initially promising, as it was shown to be associated with PC volume (Ploussard et al. 2011a). However, results about its accuracy in predicting stage and grade of PC were contradictory (Roobol 2011). The PCA3 marker has also been studied in an AS cohort, but no association was found with biopsy progression after a short follow-up (Tosoian et al. 2010). Further evaluation is needed to clarify the role of PCA3 in AS.

5.9.10 The role of 5-Alpha Reductase Inhibitors

Two randomized, placebo-controlled trials, The Prostate Cancer Prevention Trial (PCPT) (Thompson et al. 2003) and The Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE) (Andriole et al. 2010) found an approximately 25% reduction in overall PC incidence in men taking 5-alpha reductase inhibitors (5-ARI). These results suggest that men on AS may benefit from using 5-ARI, but these two studies also reported a 0.5% increase in high-risk PC in 5-ARI users. A retrospective study on 5-ARI use in men on AS found, that men with low-risk PC, who were using 5-ARI had a favourable prognosis compared to those without 5-ARI medication (Finelli et al. 2011). A prospective study, The Reduction by Dutasteride of Clinical Progression Events in Expectant Management trial (REDEEM), randomized men on AS between dutasteride and placebo. The results showed a reduced risk of PC progression in 5-ARI users and no increase in high-grade PC after 3 years (Fleshner et al. 2012). This study suggests that men on AS may benefit from the use of 5-ARI in reducing the risk of reclassification on rebiopsy.
6. **AIMS OF THE STUDY**

Active surveillance is an alternative option for immediate radical treatments in patients with low-risk PC. The aim of this initial expectant management strategy is to avoid or postpone the risk of side effects from radical treatment. The overall objective of the present study was to evaluate the feasibility of AS as a management option for low-risk PC and further analyse the QOL issues during the continuum of the PC disease.

The specific aims of the study were:

I. to evaluate the short-term outcomes of the prospective international PRIAS study (study I).

II. to analyse the effects of AS on the HRQL and urinary and erectile function (study II).

III. to observe the short-term effects of various phases of PC screening on HRQL (study III).

IV. to assess the role of DW-MRI interpreted in a routine clinical setting, as a diagnostic and prognostic tool in AS (study IV).

V. to evaluate the utility of a free/total PSA ratio as a prognostic tool in AS (study V).
7. MATERIALS AND METHODS

PRIAS is an international prospective trial that originates from the ERSPC. In this dissertation the data from the PRIAS study is used in two articles (I, V), and the data from the Finnish arm of the PRIAS study is used in two articles (II, IV). The data from the Finnish arm of ERSPC is used in one article (III).

7.1 Study populations

7.1.1 The Finnish arm of the ERSPC trial (study III)

ERSPC is a multicenter, population-based and randomized PC screening trial that commenced in the early 1990’s and is conducted in eight European countries. In the first screening round (1996-1999) in Finland, 80 144 men were identified from the population registry and randomized into screening (31 866) or into the control arm (48 278). The men were born between 1929-1944 and were living in the Helsinki or Tampere metropolitan areas. Men who had emigrated, or deceased prior to the screening invitation, and with previous PC diagnosis (identified from the Finnish Cancer Registry) were excluded. A PSA blood sample was drawn from 20 793 participants (30 190 invited, response 69%).

7.1.2 The PRIAS study (studies I, II, IV and V)

In 2006 the PRIAS study was initiated in the Erasmus University Medical Center in the Netherlands and between December 2006 and July 2008 the first 500 international patients were included in the PRIAS trial (I). The PRIAS study is still ongoing and the number of participating countries and centres has also increased (Figure 3). In Finland, the PRIAS commenced in Helsinki University Central Hospital and since 2007, the PRIAS study expanded under the name of the national FinnProstate Study XI (FPXI) into eight other clinics in Finland. Between December 2006 and May 2009, the first 124 patients had been included in the study; 80 of these participants had been followed for at least a year by May 2009 (II). Between February 2009 and May 2011, 80 of Finnish PRIAS patients underwent DW-MRI in Helsinki University Central Hospital (IV). Men were included between December 2006 and October 2013 from the international PRIAS data, a free PSA value was determined in 939 patients at the study enrolment (V). The RP data used in the analysis was available from the Finnish arm of the PRIAS study (V).
7.2 Study protocols and study design

7.2.1 Study III the Finnish arm of the ERSPC trial

Men were invited for a blood test to determine their serum PSA concentration in the screening arm. Men with PSA 3.0-3.9 ng/ml were referred to DRE, and since 1998 a determination of the free/total PSA ratio was used as an ancillary test in these screening participants. Men with a PSA value over 4 ng/ml were referred to a full clinical examination, whereas DRE was used as an ancillary standalone test for men with marginally elevated PSA values. Men with a PSA ≥ 4 ng/ml or a suspicious finding in DRE or free/total PSA ratio < 0.16 were referred for diagnostic examination i.e. TRUS with prostate biopsy. In the screening arm, men received a re-invitation to the second and third screening rounds that were arranged four and eight years after the first round. The men were invited for the latter rounds, regardless of previous participation or non-response to screening.

7.2.2 Studies I, II, IV and V protocol

The protocols for studies I, II, IV and V are based on the PRIAS study. The PRIAS inclusion criteria are histologically confirmed adenocarcinoma of the prostate with a PSA level ≤ 10 ng/ml, clinical T –class (cT) ≤ 2, a Gleason score ≤ 6, a maximum of two positive biopsies and PSA density < 0.2 ng/ml. A patient should be fit for
curative treatment and have no history of previous PC treatments to be considered a candidate for the PRIAS study. The patients in studies I, II, IV and V were intensively monitored during AS. PSA was measured every 3 months and DRE every 6 months during the first two years after diagnosis. Thereafter, PSA was measured every 6 months and DRE was performed annually. Prostate rebiopsies were standard and were taken 1, 4 and 7 years after enrolment in the study. If PSADT was between 3 to 10 years, annual rebiopsies were advised. The criteria for discontinuation of surveillance and deferred active treatment were PSADT less than 3 years, cancer in more than two rebiopsy cores or Gleason score higher than 6. If PSA exceeded over 20 ng/ml, a bonescan was recommended (Fig.4).

![Flowchart](image)

*Figure 4.* Studies I, II, IV and V based on the PRIAS protocol.

A prostate volume-dependent number of random biopsies was also advised, but not obligatory. The recommendation for the number of biopsies was: prostate volume < 40 ml 8 biopsies, 40-60 ml 10 biopsies, > 60 ml 12 biopsies (Vashi et al. 1998). In Finland, 12 TRUS-guided random biopsies were routinely taken. The measurement of free PSA was not mandatory according to the study protocol, but many of the participating centres had incorporated free PSA measurement into the study visit plan (V).
In the analysis of the first 500 PRIAS patients (I), the main outcome parameter was active treatment-free survival. Secondary endpoints included reasons for discontinuation of AS, findings in the standard 1-year rebiopsies, and outcomes after RP. Distributions of PSADT, DRE findings and preliminary survival were also analysed.

### 7.2.3 PRIAS internet website

The PRIAS trial has its own website that can be found at www.prias-project.org. The site offers general information about AS of PC and the PRIAS study itself and is available to the public. The web-based tool within the website is used for the inclusion and follow-up of study participants. After logging in using a personal account, physicians have access and can include new patients and search for follow-up details of their own study participants. PSADT is calculated automatically and the site also generates a graph presenting the patient’s PSA values over time. The PRIAS website provides automatic individualized recommendations, such as whether continuation of AS is indicated according to the protocol or not. The Erasmus University Medical Center in Rotterdam is the co-ordinating study centre that maintains the PRIAS website.

### 7.2.4 RAND 36 – Item Health Survey (II, III)

The Finnish version of RAND 36-Item Health Survey (Hays et al. 1993) was used in two studies (II, III) to analyse HRQL. The RAND-36 questionnaire is validated and had good reproducibility in the Finnish population (i.e. Cronbach’s α 0.80-0.94). Age-stratified reference values were also available, which made the comparison with the general population possible (Aalto et al. 1999). The RAND-36 questionnaire included 36 items that were further divided into eight subscales: physical functioning, bodily pain, general health perceptions, mental health, role limitations due to physical and emotional problems, social function and vitality. Each of the eight subscales was scored from 0 to 100 and a higher score indicated better HRQL.

The PRIAS protocol does not require the use of any particular standard quality of life-survey. In Helsinki University Hospital, the RAND-36 questionnaire was chosen to evaluate effects of AS on participants’ general QOL and to allow comparisons across different treatments and diseases. QOL is monitored at the study inclusion and in surveillance at 3, 5, and 7 years. One year QOL questionnaire was answered by the patients before the first rebiopsy. At the same time, points relating to voiding symptoms and erectile function were also evaluated using the well-validated and standardized IPSS and IIEF-5 questionnaires (II).

The quantification of the impact of the screening process on HRQL was achieved when RAND-36 questionnaires were delivered to the screening participants at each of the five phases of the first screening round: 500 at invitation, 500 after a PSA test, 500 after the PSA result, 314 after DRE (before information of its result, but aware of the PSA value); and >300 after TRUS and biopsy (before information of its result, but aware of the PSA value)(Fig.5). Additional copies of questionnaires were made and delivered without keeping track of the exact numbers in one department. Consequently, the exact number of delivered questionnaires after TRUS
and biopsy is not available. Participants were different in each of the five phases and were asked to fill in RAND-36 questionnaires. Information on sociodemographic and behavioural factors was also collected at invitation, attendance and partly at PSA result phases, but was not ancillary to either the screening test by DRE or the diagnostic examination (TRUS/biopsy) phases. The questionnaires were delivered with the invitation letter, which also included information about the study and PC in general (III).

Figure 5. Flow chart of the recruitment of study (III) participants

7.2.5 MRI (IV)

MRI is not a mandatory part of the PRIAS protocol, but in Helsinki University Central Hospital, DW-MRI was incorporated into the follow-up protocol and patients had the opportunity to have DW-MRI after a year of AS, before the first rebiopsy (IV). MRI was performed with 3T T2-W MRI (Philips Medical Systems) with using a body-array coil. Echo-planar DW-MRI images (with b-values 0 s/mm²,
300 s/mm², 600 s/mm²) were obtained transverse to the prostate parallel to the corresponding set of T2-W images. The analysis of T2-W MRI images was quantitative and for the analyses the prostate was divided into seven regions (right apex, middle, basis, left apex, middle, basis and anterior part). Low T2 signals in the peripheral zone and in the central area were considered suspicious for malignant lesion. T1 images were also analysed to rule out benign processes (e.g. prostate hyperplasia or haemorrhage) and to ensure that high signal areas did not exist in the same locations. DW-MRI images and apparent diffusion coefficient (ADC) maps were compared with each other and the appearance of the lesion in bright contrast in DW-MRI and low signal intensity on ADC, was considered suspicious for malignancy. MRI images were interpreted by two genitourinary radiologists and results were made available, as a written report, to the clinicians at the patient’s first rebiopsy follow-up visit.

7.2.6 Statistics

The Statistical Package for the Social Sciences (SPSS) was used for data analyses. The cut-off level of statistical significance was set at p=0.05 in all tests. Values are expressed as median and range, unless stated otherwise.

The differences in means of the RAND-36 questionnaire scores were analysed using the paired/non-paired t-test, or when non-parametric by the Mann-Whitney U-test, depending on the groups and distribution of the data. A ‘half SD rule’ was used to interpret the QOL data, i.e. a change in QOL variables more than 0.5 SD was considered clinically significant (Norman et al. 2003). Correlation analysis and Pearson chi-squared test clarified the associations between patients’ characteristics and HRQL variables. Binary and ordinal logistic regression analyses further interpreted the associations between HRQL variables and assumed HRQL predicting factors (II, III). Spearman’s rank coefficient correlation analysis and Pearson chi-squared test were used to assess the associations between clinical variables/rebiopsy findings and DW-MRI results. Logistic regression was used to analyse assumed predictors of deferred radical treatment (IV) and to explore potential predictors of adverse rebiopsy findings (I, V). Active treatment-free survival was assessed using the logrank test and graphically displayed by the Kaplan-Meier survivorship method (I, V). Time to treatment change and association of patients’ baseline characteristics and adverse RP findings were analysed using the Cox regression (V). Hazard ratios were estimated together with the associated 95% confidence interval and p-values (V).

7.2.7 Ethics

The Ethics Committees of Helsinki University Central Hospital and Tampere University Hospital approved The Finnish Prostate Cancer Screening Trial protocol. The PRIAS study protocol was approved by The Ethics Committee of Helsinki University Central Hospital in 2006. In other PRIAS centers (I, V), the study protocol was approved by the respective ethics committees in each participating country.
8. RESULTS

8.1 The short-term outcomes of the first 500 PRIAS patients (study I)

Table 5 shows the baseline characteristics of the first 500 patients in the PRIAS study (I). At the time of analysis the median follow-up was 1.02 years. The 2-year active treatment-free survival (ATFS) rate was 73%. Figure 6 presents the total ATFS and also stratifies the reasons for discontinuing AS. A considerable drop in the survival curve was observed for all reasons, at biopsy and also at PSADT at 1 year of follow-up.

Table 5. The characteristics of study patients (study I).

<table>
<thead>
<tr>
<th>Variable</th>
<th>At diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (25-75 percentiles)</td>
</tr>
<tr>
<td>Age, year</td>
<td>66.0 (60.7-70.4)</td>
</tr>
<tr>
<td>PSA, ng/ml</td>
<td>5.3 (3.9-6.7)</td>
</tr>
<tr>
<td>PSAD, ng/ml/cc</td>
<td>0.12 (0.09-0.16)</td>
</tr>
<tr>
<td>Prostate volume, cm3</td>
<td>42.6 (35.0-56.0)</td>
</tr>
<tr>
<td>DRE</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>79.2%</td>
</tr>
<tr>
<td>T2a</td>
<td>19.2%</td>
</tr>
<tr>
<td>T2b</td>
<td>1.2%</td>
</tr>
<tr>
<td>T2c</td>
<td>0.4%</td>
</tr>
<tr>
<td>Positive biopsy cores</td>
<td></td>
</tr>
<tr>
<td>1 core</td>
<td>68.6%</td>
</tr>
<tr>
<td>2 cores</td>
<td>31.4%</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
</tr>
<tr>
<td>=6</td>
<td>95.0%</td>
</tr>
<tr>
<td>&lt;6</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; DRE = digital rectal examination

Figure 6. ATFS for discontinuing in AS (total and stratified for reason).
At the time of analysis 82/500 (16%) men had already discontinued AS; 83\%(68/82) due to protocol-based reasons and 17\%(14/82) because of anxiety and/or by request. The reasons for the discontinuations in protocol were adverse rebiopsy findings (Gleason score >6 and/or >2 PC positive rebiopsy cores) for 43\%(29/68), PSADT for 37\%(25/68) and for both reasons combined 19\%(13/68). Table 6 lists the specific reasons for discontinuation of AS and the active treatments chosen.

Table 6. Reasons for discontinuation of AS (n=82) and deferred active treatments (study I).

<table>
<thead>
<tr>
<th>Reason for active treatment</th>
<th>Deferred active treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP</td>
</tr>
<tr>
<td>Protocol-based</td>
<td></td>
</tr>
<tr>
<td>PSADT (only)</td>
<td>7</td>
</tr>
<tr>
<td>Number of positive cores at rebiopsy and Gleason score</td>
<td>5</td>
</tr>
<tr>
<td>Number of positive cores at rebiopsy</td>
<td>6</td>
</tr>
<tr>
<td>Gleason score at rebiopsy</td>
<td>2</td>
</tr>
<tr>
<td>PSADT, number of positive cores at rebiopsy and Gleason score</td>
<td>1</td>
</tr>
<tr>
<td>PSADT, number of positive cores at rebiopsy</td>
<td>4</td>
</tr>
<tr>
<td>PSADT and Gleason score</td>
<td>1</td>
</tr>
<tr>
<td>T stage (only)</td>
<td>-</td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Request to discontinue on AS</td>
<td>-</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
</tr>
</tbody>
</table>

*MRI was performed, revealing clinical stage T3a

BT=brachytherapy; PSADT=prostate-specific antigen doubling time; RP=radical prostatectomy; RT=external beam radiation therapy;

In total, 261/500 (52\%) of study patients had standard rebiopsy and biopsies were taken a median of 1.02 (25-75 percentiles: 1.0-1.1) years after PC diagnosis. In the rebiopsy the median number of biopsy cores was 10 (25-75 percentiles: 8-12). No cancer was found in 34\%(90/261), favourable result (i.e. Gleason score ≤6, ≤2 positive biopsy cores) in 44\%(114/261) and unfavourable result (i.e. Gleason score >6 and/or >2 positive biopsy cores) in 22\%(57/261). Rebiopsy results in relation to PSADT at the time of biopsy are shown in Table 7. PSADT was not available in 14/261 (5\%) patients. When PSADT was compared in patients with favourable and
unfavourable biopsy results, the difference between the groups was not statistically significant ($p=0.411$). The univariate analysis revealed that only variable predicting unfavorable rebiopsy findings was the number of PC positive biopsy cores at diagnostic biopsy (two versus one). 17% (32/183) of men with one PC positive biopsy at diagnosis also had unfavourable rebiopsy findings and 32% (25/78) of men with two positive biopsy cores ($p=0.014$). Age, prostate volume, PSA, PSADT, clinical stage, time to rebiopsy and number of diagnostic/rebiopsy cores had no significant association with unfavourable rebiopsy findings.

Table 7. Rebiopsy findings after 1 year of AS in relation to PSA doubling time at the time of biopsy (n=261) (study I).

<table>
<thead>
<tr>
<th>Rebiopsy Findings</th>
<th>Favourable (n=194)</th>
<th>Unfavourable (n=53)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No PC</td>
<td>1-2 positive cores and Gleason 6</td>
<td>&gt;2 positive cores, Gleason ≤6</td>
</tr>
<tr>
<td><strong>PSADT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 years</td>
<td>24/ (26%)</td>
<td>30/ (28%)</td>
<td>54/ (28%)</td>
</tr>
<tr>
<td>3-10 years</td>
<td>18/ (21%)</td>
<td>30/ (28%)</td>
<td>48/ (25%)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>7/ (8%)</td>
<td>8/ (7%)</td>
<td>15/ (8%)</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>37/ (43%)</td>
<td>40/ (37%)</td>
<td>77/ (40%)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>90/ (34%)</td>
<td>114/ (44%)</td>
<td>204/ (78%)</td>
</tr>
</tbody>
</table>

PSADT = prostate-specific antigen doubling time

Of the 27 men who underwent RP, 24 (89%) results were available. Patients underwent RP a median of 1.0 (25-75 percentile: 0.5-1.1) year after PC diagnosis and the study enrolment. The reasons for surgical treatment were: PSADT <3 years only (6/27), adverse rebiopsy findings only (10/27), combination of these two protocol-based reasons for discontinuation (6/27) and other reasons (5/27). In all four cases of T3 tumors, in rebiopsy more than two PC positive cores were found and in three of these Gleason scores were also upgraded >6. In 50% (12/24) of RP specimens Gleason scores were upgraded; in the rebiopsies of 11 men taken previously, unfavorable biopsy characteristics were found in all of them. No significant association could be observed between adverse RP findings (Gleason >6 or T3) and PRIAS inclusion variables or PSADT.

The present data do not allow for a mortality analysis. During follow-up, no one died of PC. Two patients died due to other reasons and in one patient PC lymph node metastases were detected.
8.2 Short-term HRQL effects of AS (study II)

In study II, of the enrolled 124 Finnish PRIAS patients (in the area of Helsinki University Central Hospital), 105/124 (85%) had completed and returned the baseline RAND-36 questionnaire and 19/124 (15%) had not responded by the time of analysis. 80 patients had been followed for at least a year and 75 of these (94%) had completed the questionnaires at the study inclusion and after one year of follow-up. The response rates for IPSS and IIEF-5 questionnaires were 80% (60/75) and 56% (42/75), respectively. The patient characteristics of the study group (75 men with baseline and follow-up questionnaires available) and the non-respondent group (19) are shown in Table 8. The only significant difference between the groups was in the educational background; the respondents had a significantly higher level of education ($p=0.02$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group (N=75)</th>
<th>Non-respondents (N=19)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years (median, 25th-75th percentiles)</td>
<td>64 (60-69)</td>
<td>64 (60-69)</td>
<td>0.9</td>
</tr>
<tr>
<td>Initial PSA, ng/ml</td>
<td>5.1 (2.0-10.0)</td>
<td>5.0 (1.4-9.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Initial free PSA, ng/ml</td>
<td>0.7 (0.0-2.8)</td>
<td>0.7 (0.2-1.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Clinical stage T1 at diagnosis</td>
<td>75 (100)</td>
<td>19 (100)</td>
<td></td>
</tr>
<tr>
<td>One positive biopsy at diagnosis</td>
<td>53 (71)</td>
<td>12 (63)</td>
<td>0.5</td>
</tr>
<tr>
<td>Two positive biopsies at diagnosis</td>
<td>22 (29)</td>
<td>7 (37)</td>
<td>0.5</td>
</tr>
<tr>
<td>Higher education (college/university)</td>
<td>23 (50)</td>
<td>1 (10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Married/living with a partner</td>
<td>51 (67)</td>
<td>13 (68)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

After one year of AS, no significant differences in mental (mental health, physical role, social function, vitality) or in physical health dimensions (bodily pain, general health, physical function, physical role) were observed (Table 9). Slightly inferior results were noted in two domains of eight HRQL subgroups, but the differences were not statistically significant: bodily pain ($p=0.149$) and physical function ($p=0.608$) decreased during AS. After follow-up the scores of three HRQL domains, i.e. social function, emotional and physical role, were slightly better than at the study enrolment. The only statistically significant improvement was observed for physical role ($p=0.010$), but the change was not clinically significant (<0.5 SD). The correlation and regression analyses revealed that the assumed HRQL predicting factors (i.e. age, diagnostic PSA, PSA change during follow-up at any time point) did not correlate or associate with any of the eight HRQL domains at the study enrolment or during AS. Compared to the reference values obtained from the general Finnish male population (aged 55-64 and 65-74), mean HRQL scores among men on AS were significantly better in all eight subgroups of RAND-36 ($p<0.05$) at diagnosis and after follow-up (Figures 7 & 8).
During AS follow-up, total IPSS score increased slightly (mean 7.9 vs 9.2, \( p = 0.121 \)). In total IIEF-5 score, significant change was not observed (mean 18.8 vs 19.5, \( p = 0.583 \)).

**Table 9.** Mean (SD) HRQL in AS patients, measured by RAND-36 questionnaire (study II).

<table>
<thead>
<tr>
<th>RAND-36 questionnaire score</th>
<th>Baseline, at the study inclusion mean (SD)</th>
<th>After a year of AS mean (SD)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>65 (15.2)</td>
<td>65 (16.3)</td>
<td>0.780</td>
</tr>
<tr>
<td>Physical function</td>
<td>91 (13.6)</td>
<td>90 (12.9)</td>
<td>0.608</td>
</tr>
<tr>
<td>Mental health</td>
<td>81 (14.9)</td>
<td>81 (14.1)</td>
<td>0.696</td>
</tr>
<tr>
<td>Social function</td>
<td>91 (14.4)</td>
<td>93 (14.0)</td>
<td>0.279</td>
</tr>
<tr>
<td>Vitality</td>
<td>76 (15.7)</td>
<td>76 (16.0)</td>
<td>0.582</td>
</tr>
<tr>
<td>Body pain</td>
<td>90 (15.6)</td>
<td>87 (18.7)</td>
<td>0.149</td>
</tr>
<tr>
<td>Role physical</td>
<td>81 (34.2)</td>
<td>89 (25.7)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Role emotional</td>
<td>82 (32.6)</td>
<td>88 (29.0)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

* \( p < 0.05 \) statistically significant cut-off

**Figure 7.** RAND-36 scores in men aged 55–64 (study II).

(PF, physical function; PR, physical role; ER, emotional role; VT, vitality; MH, mental health; SF, social function; BP, body pain; GH, general health)

**Figure 8.** RAND-36 scores in men aged 65–74 (study II).

(PF, physical function; PR, physical role; ER, emotional role; VT, vitality; MH, mental health; SF, social function; BP, body pain; GH, general health)
8.3 Short-term HRQL effects of PC screening (study III)

During the first screening round, the RAND-36 questionnaire was delivered to a total of more than 2000 participants in five discrete phases. At the invitation phase 293/500 men (59%, 4 excluded due to incompletely filled questionnaires) responded, at screening 386/500 men (77%, 9 exclusions), at PSA result 271/500 men (54%, 12 exclusions) and at DRE 217/314 men (69%, 6 exclusions). The exact number of questionnaires delivered after the diagnostic examination phase (i.e. TRUS and biopsy) is not known, because additional copies of the questionnaires were made and delivered without keeping track of the actual numbers at one participating department. In total 319 responders were evaluated for this screening phase. In the RAND-36 questionnaires, the item ‘non-response rate’ was 0.5-1.5% at each of different screening phases. A range of 8.8-12.5% of screening participants did not respond to one or more questions.

The range of mean ages of the participants for the different phases was 60-63 years (Table 10). Information on sociodemographic and behavioral factors was collected at phases 1 to 3 (i.e. invitation, PSA blood test and partly at PSA result group), but not at the DRE and TRUS/biopsy phases. No significant differences were noted between the screening participants in the sociodemographic and behavioral factors at different screening phases (Table 11).

Table 10. Mean ages of questionnaire respondents at different phases of the PC screening process (study III).

<table>
<thead>
<tr>
<th>Screening phase</th>
<th>Mean age, years (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Invitation</td>
<td>60.2 (4.6)</td>
</tr>
<tr>
<td>2) PSA blood test</td>
<td>60.7 (4.4)</td>
</tr>
<tr>
<td>3) PSA result</td>
<td>60.8 (4.5)</td>
</tr>
<tr>
<td>4) Digital rectal examination</td>
<td>62.3 (4.3)</td>
</tr>
<tr>
<td>5) TRUS and biopsy</td>
<td>62.8 (4.3)</td>
</tr>
</tbody>
</table>

The highest HRQL response scores of the RAND-36 questionnaire (medians of 90-100) were related to the emotional role, physical role, physical function and social function. The lowest scores of RAND-36 were consistently found for general health (median 65) at each screening phase and followed by energy/fatigue. No major or systematic changes in HRQL could be detected during the screening process (Table 12). However, a decrease was observed in the emotional role subscale ($p=0.005$) at the ancillary screening test (DRE) phase and a minor but statistically significant decrease was found in social function after receiving the PSA result ($p=0.035$). After diagnostic examination (TRUS/biopsy) the pain HRQL score was higher than after DRE ($p=0.003$).

HRQL scores were higher in patients with abnormal PSA values (PSA ≥3) than those with normal PSA values (PSA <3), which was unexpected. No significant differences were found between these groups when general health and mental dimensions were compared.

The ordinal regression analysis showed results that were largely unremarkable. Significant associations ($p<0.01$) between age and poorer physical function were detected. In contrast, physical exercise with better physical function,
energy and general health, improved energy and mental health, and also education with physical function and physical role were reported. At DRE phase an unexpected association between a higher serum PSA level and better general health scores was observed among other findings of borderline significance.

The comparison of HRQL scores to the reference values (for the subscales) of general Finnish age-stratified male population (aged 60-64), showed no significant differences; HRQL was similar or slightly better among screening participants (Figure 9).

Table 11. Socio-demographic and lifestyle factors among study participants (study III).

<table>
<thead>
<tr>
<th></th>
<th>Invitation N (%)</th>
<th>PSA blood test N (%)</th>
<th>PSA result N (%)</th>
<th>Pearson Chi-Square (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full/Part time employed</td>
<td>131 (45)</td>
<td>141 (37)</td>
<td>105 (39)</td>
<td>p=0.173</td>
</tr>
<tr>
<td>Unemployed</td>
<td>25 (9)</td>
<td>52 (13)</td>
<td>26 (10)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>104 (36)</td>
<td>141 (37)</td>
<td>107 (39)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>33 (11)</td>
<td>52 (13)</td>
<td>33 (12)</td>
<td></td>
</tr>
<tr>
<td><strong>Position</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White collar</td>
<td>84 (29)</td>
<td>90 (23)</td>
<td>75 (28)</td>
<td>p=0.508</td>
</tr>
<tr>
<td>Blue collar</td>
<td>73 (25)</td>
<td>104 (27)</td>
<td>62 (23)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>116 (40)</td>
<td>178 (46)</td>
<td>121 (45)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>20 (6)</td>
<td>14 (4)</td>
<td>13 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>183 (63)</td>
<td>242 (63)</td>
<td>175 (65)</td>
<td>p=0.556</td>
</tr>
<tr>
<td>Yes</td>
<td>107 (37)</td>
<td>142 (37)</td>
<td>96 (35)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>15 (5)</td>
<td></td>
<td>25 (7)</td>
<td>*NA</td>
</tr>
<tr>
<td>Married/Cohabitation</td>
<td>240 (82)</td>
<td>317 (82)</td>
<td></td>
<td>p=0.457</td>
</tr>
<tr>
<td>Divorced</td>
<td>30 (10)</td>
<td>29 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widow</td>
<td>8 (3)</td>
<td>15 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary/Secondary school</td>
<td>118 (41)</td>
<td>152 (39)</td>
<td>*NA</td>
<td>p=0.681</td>
</tr>
<tr>
<td>Secondary school graduate</td>
<td>3 (1)</td>
<td>7 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocational school/institute</td>
<td>75 (26)</td>
<td>107 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>7 (2)</td>
<td>12 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>56 (19)</td>
<td>66 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>34 (11)</td>
<td>42 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exercise ≥ ½ hours (leisure time)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>7 (2)</td>
<td>10 (3)</td>
<td>*NA</td>
<td>p=0.298</td>
</tr>
<tr>
<td>Occasionally</td>
<td>72 (25)</td>
<td>80 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regularly once a week/ less frequently</td>
<td>40 (14)</td>
<td>35 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regularly twice a week</td>
<td>48 (16)</td>
<td>71 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 3 times a week</td>
<td>121 (42)</td>
<td>183 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>2 (1)</td>
<td>7 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NA = Not available
**Table 12.** HRQL as RAND-36 scores (median, 25th–75th percentiles) at five screening phases (study III).

<table>
<thead>
<tr>
<th>RAND-36 subgroup</th>
<th>Invitation Phase 1</th>
<th>PSA blood test Phase 2</th>
<th>PSA result Phase 3</th>
<th>Digital rectal examination Phase 4</th>
<th>Transrectal ultrasound and biopsy Phase 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>65 (50-75)</td>
<td>65 (50-75)</td>
<td>65 (50-75)</td>
<td>65 (45-75)</td>
<td>65 (50-75)</td>
</tr>
<tr>
<td>Physical function</td>
<td>90 (80-95)</td>
<td>90 (80-100)</td>
<td>90 (80-95)</td>
<td>90 (80-95)</td>
<td>90 (80-95)</td>
</tr>
<tr>
<td>Mental health</td>
<td>84 (69-92)</td>
<td>84 (72-92)</td>
<td>80 (72-92)</td>
<td>84 (72-92)</td>
<td>84 (68-82)</td>
</tr>
<tr>
<td>Social function</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
<td>95 (75-100) *</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
</tr>
<tr>
<td>Energy/Fatigue</td>
<td>70 (55-85)</td>
<td>75 (60-85)</td>
<td>75 (60-85)</td>
<td>75 (60-85)</td>
<td>75 (60-85)</td>
</tr>
<tr>
<td>Pain</td>
<td>90 (68-100)</td>
<td>90 (68-100)</td>
<td>90 (68-100)</td>
<td>80 (68-100)</td>
<td>**90 (78-100) ***</td>
</tr>
<tr>
<td>Physical role</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
<td>100 (75-100)</td>
</tr>
<tr>
<td>Emotional role</td>
<td>100 (67-100)</td>
<td>100 (67-100)</td>
<td>100 (67-100)</td>
<td>94 (67-100) **</td>
<td>100 (67-100)</td>
</tr>
</tbody>
</table>

* p = 0.035; 3 vs. 2; ** p = 0.005; 4 vs. 3; *** p = 0.003; 5 vs. 4

**Figure 9.** RAND-36 results at testing compared with age-stratified (60-64) of the general Finnish male population (study III).

### 8.4 DW-MRI after a year of AS and before rebiopsy (study IV)

80 PRIAS patients in Helsinki University Central Hospital underwent DW-MRI after one year of follow-up but before the first rebiopsy. The characteristics of the study patients are shown in Table 13.
40/80 patients (50%) had a lesion suspicious for malignancy in T2-weighted MRI and 30 (75%) of these 40 patients also had a suspicious lesion on their ADC maps, generated from DW-MRI sequences. Neither the malignant suspicious lesion in MRI (i.e. MRI positivity) nor the tumour ADC revealed any significant correlations with clinical variables, such as age, PSA at diagnosis, free PSA, prostate volume, percentage of PC at diagnostic biopsy, PSA at discontinuation of AS or PSADT (Table 14). No significant associations were detected between MRI positivity/tumour appearance in ADC maps and diagnostic biopsy (number of PC positive cores, Gleason score), rebiopsy findings (number of PC positive cores, Gleason score) or discontinuation of AS (Table 15). Similarly, no significant associations were found in a separate analysis of the patient group (n=23) with adverse findings in rebiopsy (Gleason score >6 and/or number of PC positive cores >2) or discontinuation of AS.

Table 13. Characteristics of study patients (study IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study patients (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years), median (range)</td>
<td>64 (50-77)</td>
</tr>
<tr>
<td>PSA at diagnosis (ng/ml), median (range)</td>
<td>5.7 (1.4-10.0)</td>
</tr>
<tr>
<td>Free PSA at diagnosis (ng/ml), median (range)</td>
<td>0.9 (0.0-2.8)</td>
</tr>
<tr>
<td>Prostate volume (cc), median (range)</td>
<td>44.2 (16-100)</td>
</tr>
<tr>
<td>Clinical stage T1 at diagnosis (%)</td>
<td>80 (100)</td>
</tr>
<tr>
<td>One positive biopsy core at diagnosis (%)</td>
<td>56 (70)</td>
</tr>
<tr>
<td>Two positive biopsy cores at diagnosis (%)</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Gleason score 3+3=6 (%)</td>
<td>78 (97.5)</td>
</tr>
<tr>
<td>PC length at diagnostic biopsy, mm (mean % of total biopsy length)</td>
<td>2.1 (1.2)</td>
</tr>
<tr>
<td>Rebiopsy</td>
<td></td>
</tr>
<tr>
<td>No cancer (%)</td>
<td>30 (38.5)</td>
</tr>
<tr>
<td>Gleason score 6 (%)</td>
<td>37 (47.4)</td>
</tr>
<tr>
<td>Gleason score 7 (%)</td>
<td>10 (12.8)</td>
</tr>
<tr>
<td>Gleason score 9 (%)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>No repeat biopsy</td>
<td>2*</td>
</tr>
<tr>
<td>PC length at rebiopsy, mm (mean % of total biopsy length)</td>
<td>5.0 (2.6)</td>
</tr>
</tbody>
</table>

* One patient could not undergo rebiopsy due receiving an antithrombotic medication and one patient refused rebiopsy
PC = prostate cancer; PSA = prostate-specific antigen

Table 14. Spearman’s correlations between clinical variables and tumour appearance on MRI / ADC maps (study IV).

<table>
<thead>
<tr>
<th>Study population (N=80)</th>
<th>Age</th>
<th>Prostate volume</th>
<th>PSA at dg</th>
<th>% of PC at diagnostic biopsy</th>
<th>PSA-DT</th>
<th>PSA at discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.103</td>
<td>0.106</td>
<td>0.106</td>
<td>-0.222</td>
<td>-0.056</td>
<td>0.080</td>
</tr>
<tr>
<td>p value</td>
<td>0.361</td>
<td>0.351</td>
<td>0.349</td>
<td>0.069</td>
<td>0.411</td>
<td>0.560</td>
</tr>
<tr>
<td>ADC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.072</td>
<td>0.034</td>
<td>-0.018</td>
<td>-0.219</td>
<td>-0.037</td>
<td>0.015</td>
</tr>
<tr>
<td>p value</td>
<td>0.525</td>
<td>0.768</td>
<td>0.875</td>
<td>0.073</td>
<td>0.745</td>
<td>0.898</td>
</tr>
</tbody>
</table>

r = correlation coefficient; ADC = apparent diffusion coefficient
Table 15. Chi-squared analysis between clinical variables and MRI / ADC maps (study IV).

<table>
<thead>
<tr>
<th>Study population (N=80)</th>
<th>Gleason score at diagnostic biopsy</th>
<th>Cancer positive cores at diagnostic biopsy</th>
<th>Gleason score at rebiopsy</th>
<th>Cancer positive cores at rebiopsy</th>
<th>Discontinue on AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>r =correlation coefficient; ADC = apparent diffusion coefficient; AS = active surveillance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>0.000</td>
<td>1.000</td>
<td>0.109</td>
<td>0.329</td>
<td>-0.006</td>
</tr>
<tr>
<td>ADC</td>
<td>r =correlation coefficient; ADC = apparent diffusion coefficient; AS = active surveillance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>-0.041</td>
<td>0.712</td>
<td>-0.169</td>
<td>0.131</td>
<td>-0.055</td>
</tr>
</tbody>
</table>

Rebiopsy results were available for 78 (98%) of the study patients, including information on cancer length and location in biopsy cores. 30/78 (38.5%) patients had no cancer on the first rebiopsy. The only significant association for tumour location emerged between right middle lobe in MRI and right base on rebiopsy ($p=0.004$) (Table 16).

Table 16. Associations between MRI and carcinoma location in rebiopsy (Pearson chi-squared test) (study IV).

<table>
<thead>
<tr>
<th>MRI</th>
<th>Rebiopsy apex dx</th>
<th>mid dx</th>
<th>basis dx</th>
<th>apex sin</th>
<th>mid sin</th>
<th>basis sin</th>
</tr>
</thead>
<tbody>
<tr>
<td>apex dx</td>
<td>0.307</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mid dx</td>
<td>0.430</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>basis dx</td>
<td>0.977</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>apex sin</td>
<td></td>
<td>0.584</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mid sin</td>
<td></td>
<td></td>
<td></td>
<td>0.059</td>
<td>0.545</td>
<td></td>
</tr>
<tr>
<td>basis sin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.409</td>
<td></td>
</tr>
</tbody>
</table>

dx = right; sin = left

By the time of the analysis 23 patients had already discontinued AS; 19 of these were due to reclassification/progression in the first rebiopsy (Gleason score >6 and/or number of PC positive cores >2) and the remaining 4 were because of biochemical progression, i.e. PSADT<3 years. None of the patients discontinued AS due to MRI results or anxiety.

The only predicting variable for active treatment was higher PSA at discontinuation ($p=0.002$). Appearance of tumour suspicion (Table 17) on T2-W MRI ($p=0.273$) or on ADC maps ($p=0.691$) could not predict treatment change according to the logistic regression analysis (Table 17). The PPV and NPV for MRI findings in predicting treatment change were 30% and 73%, and for ADC maps 30% and 72%.

Table 17. Logistic regression analysis of overall treatment changes (study IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.057</td>
<td>0.9 (0.73-1.01)</td>
</tr>
<tr>
<td>PSA at diagnosis</td>
<td>0.371</td>
<td>0.8 (0.41-1.40)</td>
</tr>
<tr>
<td>PSA density</td>
<td>0.921</td>
<td>1.0 (0.99-1.01)</td>
</tr>
<tr>
<td>% of PC at diagnostic biopsy</td>
<td>0.199</td>
<td>1.8 (0.74-4.28)</td>
</tr>
<tr>
<td>PSADT</td>
<td>0.921</td>
<td>1.0 (0.99-1.01)</td>
</tr>
<tr>
<td>PSA at stopping AS</td>
<td>0.002</td>
<td>1.8 (1.23-2.59)</td>
</tr>
<tr>
<td>MRI/T2</td>
<td>0.273</td>
<td>3.4 (0.38-30.73)</td>
</tr>
<tr>
<td>ADC</td>
<td>0.691</td>
<td>0.6 (0.07-5.86)</td>
</tr>
</tbody>
</table>

ADC = apparent diffusion coefficient; OR = odds ratio; PSA = prostate-specific antigen
Results of RP specimen were available from 22 patients. All PCs in specimens were small (median cancer surface 5%; range 1-25%) and prostate confined (<pT3). Four patients had a Gleason score of 6, 12 patients Gleason scores of (3+4) and six patients Gleason score of (4+3) for PC. Of 22 operated patients, 50% (11) had a lesion suggestive of malignancy as indicated by DW-MRI and in eight patients the lesion also appeared malignant in the ADC map. No significant association was noted between cancer location in RP specimen and MRI.

8.5 Free/total PSA ratios in patients on AS (study V)

The diagnostic %fPSA value data of 939 PRIAS patients were obtained. Table 18 presents the characteristics of the study cohort. By the time of the analysis 438 men had been on AS for at least a year and these men provided data for the 12 months follow-up %fPSA measurements.

By the time of analysis 656/939 (69.9%) patients of study cohort were still on AS, because 283/939 (30.1%) had discontinued. Of these 283, 181 (64.0%) had discontinued AS for protocol-based reasons and 102 (36.0%) for non-protocol based reasons such as anxiety. The median surveillance was 17.2 (range 0.7-82.7) months. The median follow-up period until discontinuation (for all reasons) was 14.7 months (range 0.7-82.7) and for protocol-based discontinuation 14.9 (range 4.0-54.8) months. Of the discontinued patients, 153 (54.1%) had undergone RP (i.e. robot-assisted laparoscopic or open retropubic), 32 (11.3%) had EBRT, 40 (14.1%) BT and one (0.4%) patient underwent HIFU. 19 (6.7%) patients had changed AS to WW and in 38 (13.4%) patients another kind of management option was chosen or information about treatment was not available.

Table 18. Characteristics of the study patients (study V).

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=939)</th>
<th>No treatment (n=758)</th>
<th>Active treatment (n=181)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (25-75p)</td>
<td>64.9 (60.0-69.6)</td>
<td>65.2 (60.1-69.8)</td>
<td>64.4 (60.4-68.3)</td>
<td>0.290</td>
</tr>
<tr>
<td>Prostate vol, cm^3, median (25-75p)</td>
<td>44.0 (34.9-54.0)</td>
<td>44.0 (35.0-55.0)</td>
<td>43.7 (33.5-52.0)</td>
<td>0.176</td>
</tr>
<tr>
<td>PSA, ng/mL, median (25-75p)</td>
<td>5.6 (4.5-7.0)</td>
<td>5.6 (4.5-6.8)</td>
<td>5.8 (4.8-7.3)</td>
<td>0.063</td>
</tr>
<tr>
<td>%fPSA, median (25-75p)</td>
<td>14.5 (9.7-18.8)</td>
<td>14.7 (10.1-19.7)</td>
<td>13.5 (8.6-18.6)</td>
<td>0.068</td>
</tr>
<tr>
<td>PSAD, ng/mL/g, median (25-75p)</td>
<td>0.13 (0.10-0.16)</td>
<td>0.13 (0.10-0.16)</td>
<td>0.14 (0.11-0.17)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Clinical stage, no (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.451</td>
</tr>
<tr>
<td>T1c</td>
<td>863 (91.9)</td>
<td>699 (92.2)</td>
<td>164 (90.6)</td>
<td></td>
</tr>
<tr>
<td>T2a-c</td>
<td>76 (8.1)</td>
<td>59 (7.8)</td>
<td>17 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Biopsy cores median, no (25-75p)</td>
<td>12 (10-12)</td>
<td>12 (10-12)</td>
<td>12 (10-12)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Positive biopsy, no (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.050</td>
</tr>
<tr>
<td>1</td>
<td>649 (69.1)</td>
<td>534 (70.4)</td>
<td>115 (63.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>282 (30.0)</td>
<td>216 (28.5)</td>
<td>66 (36.5)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>8 (0.9)</td>
<td>8 (1.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant result (p<0.05)

25-75p = 25-75th percentile
PSA = prostate-specific antigen; fPSA% = free/total PSA ratio (%); PSAD = prostate-specific antigen density
First rebiopsy results were available for 595 of the study patients. PC reclassification occurred in 144 (24.2%). The predicting variables for adverse first rebiopsy findings (i.e. Gleason score >6 and/or >2 PC positive biopsy cores) were the number of cancer positive cores (one versus two) at the diagnostic biopsy \((p=0.000)\) and age at diagnosis \((p=0.002)\) (Table 19).

**Table 19.** Association of baseline characteristics with rebiopsy progression (study V).

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>1-year rebiopsy (n=595)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at dg</td>
<td>1.1 (1.02-1.09)</td>
<td>0.002*</td>
</tr>
<tr>
<td>PSA</td>
<td>0.96 (0.74-1.25)</td>
<td>0.79</td>
</tr>
<tr>
<td>%fPSA</td>
<td>1.0 (0.99-1.04)</td>
<td>0.41</td>
</tr>
<tr>
<td>PSAD</td>
<td>1.1 (0.95-1.22)</td>
<td>0.26</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>ref.</td>
<td>0.17</td>
</tr>
<tr>
<td>T2</td>
<td>1.62 (0.81-3.24)</td>
<td></td>
</tr>
<tr>
<td>Total Bx cores</td>
<td>0.98 (0.88-1.08)</td>
<td>0.64</td>
</tr>
<tr>
<td>Positive Bx cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>ref.</td>
<td>0.000*</td>
</tr>
<tr>
<td>2</td>
<td>2.06 (1.38-3.09)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant result \((p<0.05)\)

PSA = prostate-specific antigen; %fPSA% = free/total PSA ratio (%); PSAD = prostate-specific antigen density; OR = odds ratio; CI = confidence interval

In a multivariate analysis, baseline %fPSA could not predict the probability of treatment change, although after a year of AS the difference in median %fPSA values between those men still on AS compared to those who had discontinued was statistically significant \((p=0.031)\) (Table 20). The probability of discontinuing AS was significantly lower in men with a baseline of %fPSA ≥15 and a positive %fPSA velocity compared to men with a baseline of %fPSA <15 and a negative %fPSA velocity \((p=0.001)\) (Fig.10).

**Table 20.** Baseline %fPSA and after 12 months of AS, stratified into subgroups on the basis of treatment change (study V).

<table>
<thead>
<tr>
<th>AS continue/ discontinue (n=438)</th>
<th>AS continued (n=324)</th>
<th>AS discontinued due to protocol-based reasons (n=114)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%fPSA at dg, median (25-75p)</td>
<td>14.4 (8.9-18.5)</td>
<td>13.0 (8.7-17.9)</td>
<td>0.602</td>
</tr>
<tr>
<td>%fPSA after 12 months, median (25-75p)</td>
<td>16.6 (10.7-20.9)</td>
<td>13.1 (10.0-18.5)</td>
<td>0.031*</td>
</tr>
</tbody>
</table>

*Significant result \((p<0.05)\)

dg = diagnosis; 25-75p = 25th and 75th percentiles
Figure 10. Treatment-free survival of study patients stratified into subgroups based on %fPSA characteristics (study V).

1) %fPSA ≥15 and %fPSA velocity positive
2) %fPSA ≥15 and %fPSA velocity negative
3) %fPSA <15 and %fPSA velocity positive
4) %fPSA <15 and %fPSA velocity negative

Statistical differences between groups: 
- p <0.05; 1 vs. 4
- p ≥0.05; all other comparisons

Cox regression analysis demonstrated an association between PSAD and treatment change, as well as an association between the number of PC positive cores at the diagnostic biopsy and treatment change due to protocol-based reasons (Table 21). Cox regression analysis also revealed that PSAD was the only baseline variable predictive for unfavourable RP findings (T3 and/or Gleason score of >6) (Table 22).

Table 21. Association of baseline characteristics with treatment change (protocol-based) over time (study V).

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Treatment change (n=181)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age at dg</td>
<td>1.0 (0.97-1.02)</td>
<td>0.81</td>
</tr>
<tr>
<td>PSA</td>
<td>1.0 (0.94-1.14)</td>
<td>0.48</td>
</tr>
<tr>
<td>%fPSA</td>
<td>0.99 (0.88-1.20)</td>
<td>0.74</td>
</tr>
<tr>
<td>PSAD</td>
<td>1.1 (1.01-1.11)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>T1c</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1.3 (0.74-2.18)</td>
<td></td>
</tr>
<tr>
<td>Total Bx cores</td>
<td>1.0 (0.92-1.08)</td>
<td>0.92</td>
</tr>
<tr>
<td>Positive Bx cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.5 (1.07-2.01)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant result (p<0.05)

PSA = prostate-specific antigen; %fPSA% = free/total PSA ratio (%); PSAD = prostate-specific antigen density; HR = hazard ratio
Table 22. Association of baseline characteristics and PSA-DT with unfavourable radical prostatectomy findings (Cox regression) (study V).

<table>
<thead>
<tr>
<th>Baseline characteristics and PSA-DT</th>
<th>Radical prostatectomy (n=53) HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.0 (0.97-1.01)</td>
<td>0.43</td>
</tr>
<tr>
<td>PSA</td>
<td>0.9 (0.74-1.06)</td>
<td>0.18</td>
</tr>
<tr>
<td>%fPSA</td>
<td>1.0 (0.98-1.06)</td>
<td>0.43</td>
</tr>
<tr>
<td>PSAD</td>
<td>3.5 (1.14-5.09)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>T1c</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>0.76 (0.21-2.73)</td>
<td></td>
</tr>
<tr>
<td>Total biopsy cores</td>
<td>1.1 (0.72-1.68)</td>
<td>0.84</td>
</tr>
<tr>
<td>Positive biopsy cores</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>1</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.1 (0.63-2.12)</td>
<td></td>
</tr>
<tr>
<td>PSADT</td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>Negative or &gt;10 yrs</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>3 to 10 yrs</td>
<td>1.0 (0.48-2.11)</td>
<td></td>
</tr>
<tr>
<td>&lt;3 yrs</td>
<td>0.6 (0.25-1.43)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant result (p<0.05)

HR = hazard ratio; PSA = prostate-specific antigen; %fPSA = free/total PSA ratio (%); PSAD = prostate-specific antigen density; PSADT = PSA doubling time
9. DISCUSSION

9.1 Short-term outcomes of the PRIAS study (study I)

AS has been proposed to alleviate the problem of overdiagnosis and overtreatment of low-risk PCs. Special interest in AS was shown when the ERSPC data on decreasing mortality were published (Schröder et al. 2009; Schröder et al. 2012) in tandem with the notion of overdiagnosis.

The study I presents interim data from the largest prospective AS cohort, with a good protocol compliance, based on the first 500 PRIAS study inclusions. The main outcome parameter was ATFS. The results showed that one out of every four patients following a strict surveillance protocol discontinued AS, the ATFS value was 73% after 2 years. In the majority of cases, AS was discontinued for protocol-based reasons (83%). Adverse rebiopsy findings were an important reason for discontinuation of AS, since every fifth patient had adverse characteristics in the standard 1-year rebiopsy. PSADT, which was calculated after a year of surveillance, was not significantly associated with favourable or unfavourable rebiopsy outcomes. The short-term results of this prospective study are valuable in assessing the utility of this AS protocol in men with early PC.

Recently published results from more mature PRIAS data demonstrated a slightly higher ATFS rate of approximately 77% at two years (Bul et al. 2013b). In general, results of this study are in accordance with the other AS studies, which have reported ATFS rates between 67-86% (van As et al. 2008; Dall'Era et al. 2008; Klotz et al. 2010b; Soloway et al. 2010; Tosoian et al. 2011), though this depends on patient selection and median follow-up periods. During AS, approximately every third PC will be reclassified and such patients have higher risk for disease progression. The proportion of men discontinuing surveillance, mainly depends on how stringent the inclusion criteria for AS are and how rapidly the clinician is willing to initiate active treatment. The more stringent criteria for AS, i.e. biopsies with only one or two positive cores with minimal PC will be, the more likely to comprise a cohort that remain untreated. Based on the interim results of PRIAS trial (I) and other AS studies, it seems obvious, that a considerable number of patients discontinue AS during follow-up and this emphasizes the importance of accurate staging and grading at diagnosis. If patient selection could be improved, perhaps AS follow-up strategies could be simplified. Avoiding or delaying radical treatments is a fundamental goal of AS. Therefore, the switching to deferred active treatment during surveillance when reclassification or progression of disease occurs, is a relevant part of this strategy.

In most cases tumour upgrading is probably caused by undersampling at diagnostic biopsy, thus subsequently leading to tumour reclassification at rebiopsy (Bul et al. 2012a), although true biological progression of PC may also occur. 22% of our patients had adverse rebiopsy findings in the 1-year rebiopsy. Results for PRIAS data with longer follow-up and larger patient cohort are similar, as 27% of men experienced PC reclassification at rebiopsy during surveillance. Other studies have reported reclassification rates between 18-55% of cases (Al Otaibi et al. 2008; Ross et al. 2010; Adamy et al. 2011; Isharwal et al. 2011; Kotb et al. 2011). In our analysis the number of positive biopsy cores at diagnostic biopsy was the only parameter that showed a positive association to unfavourable rebiopsy result. The
most recent analyses from PRIAS data have demonstrated, that the strongest predictor for reclassification is PSAD, in addition to the number of positive biopsy cores (Bul et al. 2012a; Bul et al. 2013b). One of the main aims of AS studies is an attempt to find those factors that could predict and identify higher risk PCs in AS cohorts. With more precise predictors and patient selection it would be possible to reduce the number of patients who undergo reclassification of PC and treatment change. At present, MRI and novel biomarkers such as isoforms of PSA are under very active research in their potential roles as tools in AS protocols.

The number of RP specimens in the present study (I) is too low to draw any definite conclusions. However, the results of our cohort of deferred RPs are in line with those of previously published studies that have evaluated RP outcomes of men who would have been eligible for AS (Conti et al. 2009; Kane et al. 2010; Thaxton et al. 2010; Drouin et al. 2012;). The rate of tumour upgrading in these studies varied between 21-36%, positive surgical margin rates ranged between 14-35% and the extracapsular extension rates were between 5-19%. One of the main issues related to the AS is the concern of ‘missing the window’ of curability. In comparison to immediately treated patients, it would be logical that larger PCs and more extracapsular extension could appear in RP specimens after surveillance. Patients were directed for deferred active treatment mainly because of increasing PSA values or because of an upgrading at rebiopsy. This would make the patient cohort more selected than those in a retrospective series, which evaluate RP outcomes of patients who would otherwise have been eligible for AS. Several studies have already evaluated the oncological outcomes of the RP series compared to immediate treatment in men with low-risk PC and in most series no significant differences between outcomes have been observed (Warlick et al. 2006; van den Bergh et al. 2010b; Holmstrom et al. 2010; Dall’Era et al. 2011; Bul et al. 2012c). Recently, RP outcomes from the more mature PRIAS data have been published. Those authors found that in the majority of cases pathology results of deferred RPs had organ-confined PC and favourable Gleason gradings.

The strengths of this study (I) are its prospective nature and the large patient cohort. The PRIAS study has already included more patients than any other prospective AS trial. This study also has robust protocol compliance with PRIAS and adherence, which is probably due to web-based inclusion and follow-up. The limitations of this study are the lack of a randomized control group, which received immediate radical treatment after PC diagnosis and a short follow-up period. Based on the current analysis, I conclude that no new indications could be found that would tighten the existing PRIAS criteria and thereby improve the safety of the AS strategy. Moreover, the data of study I emphasizes the importance of prostate rebiopsy during AS.

9.2 QOL during the continuum of PC: the effect of the screening process and AS (studies II and III)

Studies II and III both show that short-term changes in health-related QOL appear non-substantial during the screening process or during AS, as measured by the RAND-36 instrument. In addition, both studies show that the mean HRQL scores are comparable to those of the general Finnish population; in patients on AS perhaps
even better. This is likely a consequence of selecting those patients for AS who, according to a treating clinician, can psychologically cope with it.

9.2.1 Short-term effects of PC screening on HRQL (study III)

Although reduction in mortality from PC is the principal endpoint in the screening trials, the effects on QOL are also important. Some concern has been raised about the possible negative effects on psychological health and QOL that relate to screening process. Our results suggest that population-based PC screening does not seem to provoke major effects on participants’ short-term HRQL, as assessed by the structured and validated RAND-36 instrument (III). The minor differences in HRQL observed between the five phases of PC screening were not significant. The changes in HRQL seem to have been temporary as they occurred only at one time point and did not persist throughout the screening process. Our results are supported by the outcomes of previous studies that concluded PC screening has only little if any impact on the psychological health of the participants (Brindle et al. 2006; Awsare et al. 2008). Negative emotional impacts may arise, but these do not seem to persist in the long-term (Collins et al. 2011). Increased cancer-related anxiety in the short-term has been reported, but again, no severe or long-term effects were observed (Wardle et al. 1993). One exception may be those screening participants who have pre-existing anxiety, as they also tend to remain anxious (Essink-Bot et al. 1998). In concordance with our results, the Rotterdam section of the ERSPC trial also reported minor effects of PC screening on QOL or health-status in the short-term. An exception were short-lasting side effects that were related to the prostate biopsy (Essink-Bot et al. 1998). This is logical, since TRUS-guided prostate biopsy has been associated with discomfort, anxiety and substantial pain in a proportion of men (Peyromaure et al. 2002), even to the extent, that some men refused rebiopsy. TRUS and biopsy could be considered as a threshold for screening participants as they are the most invasive part of PC screening process. However, only a minority of men experience elevated distress levels at the time of prostate biopsy or after receiving negative results (Macefield et al. 2010). Similarly, a higher serum PSA value, older age or a PC positive family history did not predict anxiety in men during a testing process for PC (Macefield et al. 2009). Even men with false-positive screening results have been reported to view their screening experience as positive (Essink-Bot et al. 2003). In contrast, a later study revealed that a proportion of men with a benign prostate biopsy result were concerned about PC (Katz et al. 2007). Overall it seems that the most significant adverse psychological and QOL effects occur mainly after PC diagnosis during the period of different treatments or surveillance strategies.

Overall, only a few statistically significant differences were observed between different phases of the screening process in this study. The emotional-role subscale score decreased following DRE, but it is unclear, if this is the effect of the examination itself or if it relates to the awareness of further diagnostic examinations. Study participants were aware of their abnormal screening results, but at the time their HRQLs were evaluated, they were not aware of the findings of the current screening phase. Therefore, these screening phases were thought to be the most stressful, but surprisingly HRQL scores turned out to be better in men with an abnormal screening finding (PSA≥3), compared to participants with normal PSA value. One explanation for this can be, that men with an abnormal PSA result felt
relieved by the fact that they were being further examined by the clinician. The ordinal regression analysis indicated that a higher PSA was associated with a better HRQL except at the DRE phase. However, some studies have shown, that men with an elevated PSA value are not able to assess the risk for false-negative or false-positive results, or risk for PC, as both over- and underestimations are common (Frosch et al. 2001; Chan et al. 2003; Katz et al. 2007).

Studying five different cohorts at different phases of screening instead of a longitudinal cohort moving along each of five phases may be considered as a shortcoming of this study. However, this study design was originally chosen to avoid bias arising from loss during follow-up, which would likely have occurred, if the same study group had been asked to fill in the same questionnaire for up to four times at consecutive phases of the screening process. In addition, a large number of participants would have been needed, to ensure that a sufficient cohort of study participants would have been available in the final phase, due to incomplete participation and the relatively low number of men that would be referred and have to undergo prostate biopsy. A potential bias could also have resulted from participants responding to the questions in the same way out of habit. Our study design may increase sampling error, but we found no indication of such as judged by the sociodemographic and lifestyle factors of three study samples. A potential bias that should be taken into account when interpreting our study results, is the lack of comparisons between groups of respondents and non-respondents.

9.2.2 Short-term changes in HRQL during AS (study II)

Some concern has been raised about AS causing a psychological burden on patients as they live with untreated PC. Our results (II) contradict this and show that men with low-risk PC manage AS well, i.e. AS does not seem to provoke adverse HRQL changes in the short-term. The only statistically significant finding was the improvement in physical role functioning, but that change was not considered to be clinically significant (II). In our study cohort, none of the patients discontinued AS due to non-protocol based reasons such as anxiety or distress. In the majority of men, the reason for discontinuation was reclassification of PC in the first prostate rebiopsy a year after follow-up. These results are in line with the findings of recent studies showing that QOL is relatively good in most men on AS, with low levels of anxiety and distress, and good psychological and physical wellbeing (van den Bergh et al. 2009a; van den Bergh et al. 2010a).

Psychological factors, such as increased anxiety or distress, may lead to discontinuation of AS. In the public mind the term ‘cancer’ is generally conflated with a dreaded disease, and a diagnosis of cancer is strongly associated with a distressing experience. The diagnosis of PC is also likely to cause many psychosocial responses in patients and their family members. Men who consider low-risk cancer as a dreaded and life-threatening disease, are probably more suitable candidates for immediate curative treatment, as a conservative management option such as AS may be difficult for them to accept thus causing more anxiety, distress and perhaps reduces their general QOL. Awareness of the untreated cancer may also cause undue anxiety during follow-up, resulting in discontinuation of surveillance in the absence of objective signs of disease reclassification or progression. Some studies have reported nonmedical reasons to be a significant factor, which
contributes to discontinuing AS (Choo et al. 2002). In our study cohort of 500 patients (I), only a minority (17%) of men stopped AS due to psychological factors (i.e. increased anxiety/distress) or on request. In a recent update of the PRIAS trial, the proportion of patients who switched from AS to deferred treatment because of anxiety was 9% (Bul et al. 2013b). Interestingly, none of the patients in the Finnish arm of the trial discontinued AS due to anxiety (II). It is remarkable that these studies are nonrandomized and participants comprise a highly self-selected cohort. This may explain to large extent the low impact of AS on HRQL (II). After PC diagnosis, patients are comprehensively informed about the different treatment options in the discussions with a clinician and with a specialized PC nurse. Our patients (II) also completed their first HRQL questionnaire only after choosing AS as their treatment option and thus they were already aware of the good prognosis of their disease. This may have further alleviated the anxiety and psychological stress.

After discussions with the treating urologist and in the opinion of that urologist’s, only patients considered able to be able to cope well mentally with the idea of ‘possibly insignificant PC’ and ‘living with untreated PC’, were actually offered AS as their primary treatment choice, making the study cohort highly selected. Thus, it may be possible that only those patients with favourable psychological characteristics and who are likely to adhere to study protocol are eventually included. Perhaps as a result of the multidisciplinary teamwork (a clinician and a PC nurse) described in this study and the highly selected group of patients, none of the patients in our cohort discontinued due to anxiety (II).

When properly selecting patients for AS, it is important for a clinician to be aware of the possible risk of psychological morbidity in men during AS, as psychological symptoms may influence patient’s likelihood to discontinue surveillance. The personality of the patients and their behavioural characteristics should be considered within a broader perspective, because these may have a considerable effect on the psychological burden in the long-term (Blank and Bellizzi 2006). On some occasions, uncertainty and awareness of the existence of an untreated cancer may become too much for a patient to bear, leading to immediate radical treatment instead of AS, to prevent continuing or increasing concerns about the disease (Patel et al. 2004). The Dutch PRIAS investigators reported that during a nine-month period of AS, anxiety and distress levels remain relatively low, but patients with a more neurotic personality and lower physical health scores had higher anxiety and distress levels (van den Bergh et al. 2009a; van den Bergh et al. 2010a). Impaired mental health has also shown to be a predictive factor for poor QOL in men on AS (Bellardita et al. 2013).

Although AS as a management option for low-risk PC is gaining popularity currently, only a limited proportion of men who were suitable for this strategy eventually choose AS (10-57%) (Cooperberg et al. 2007; Miocinovic et al. 2011). The main reason for choosing AS, is the wish to delay the possible physical side effects of radical treatments (van Vugt et al. 2012). However, uncertainty related to untreated PC and the fear of cancer progression are the main reasons to abandon AS as an option (Steginga et al. 2008; Xu et al. 2011). Experiences of friends and family members have a significant influence on a patient when he is considering the choice of treatment options (Xu et al. 2011). Demographic factors and the extent of knowledge about PC may influence and also contribute to the treatment choice (van den Bergh et al. 2012). The clinician has a key role in the choice made as the patients are strongly influenced by their treating clinicians with regard to selecting
A previous study suggested that men diagnosed with low-risk PC should obtain improved support and patients and their partners should be more involved in the decision-making process (Steginga et al. 2008). The active participation of the patient in the treatment decision may have a positive effect on that patient’s sense of control. A common phenomenon is that patients have difficulties in decision-making and thus decision-related distress may persist over time. Cancer-specific psychological distress (such as fear of recurrence, but not overall anxiety) appears to be related to elevations of PSA levels; and this distress also influences treatment pathways. Decision support interventions are known to be acceptable to men, they improve patients’ knowledge and may reduce decision- and cancer-related distress (Steginga et al. 2008). Every person is unique and there is a wide variation in the amount of psychological care and support an individual needs (Lintz et al. 2003). It is probable that the importance of multidisciplinary teams will be emphasized in supporting men during AS, such as when guiding how to cope with higher levels of anxiety and distress. Increased education, communication and peer-support groups may also alleviate and improve the sense of patient’s control of the situation during AS (Pickles et al. 2007).

The results of study II indicate that AS does not seem to provoke significant short-term QOL disturbances in respect of urinary or erectile function, as assessed by the standardized IPSS and IIEF-5 questionnaires. A minor, but statistically nonsignificant, increase was noted in the IPSS total score. Urinary, sexual and bowel function scores have been shown to decrease due to aging alone during WW and the same is expected to occur during AS (Arredondo et al. 2008). Side effects of radical treatments may improve even for a long time after treatment, whereas urinary, bowel and sexual functions may worsen during AS. A previous retrospective study has demonstrated the preferable side effect profile of AS (urinary, bowel or sexual function scores) compared with the side effects of radical treatments (Thong et al. 2010). However, prospective and randomized trials with longer follow-up are needed to clarify the true longitudinal changes associated with AS.

The strengths of study II are its prospective nature and the use of standardized, validated questionnaires. Its limitations include the lack of randomization and a highly selected patient cohort. A longer follow-up period is needed to have longitudinal evidence regarding to HRQL in patients on AS. The effects of different treatments for low-risk PC on HRQL should also be compared more comprehensively in randomized trials, such as the ProtecT study (Lane et al. 2010).

### 9.2.3 Challenges in measuring QOL (studies II and III)

In both of the QOL studies (II and III), the same generic HRQL instrument, RAND-36 was used. This questionnaire is extensively validated and has been used earlier. A challenge in measuring HRQL is in its multidimensional nature, which includes physical, mental and social components. Generic, domain- or disease-specific questionnaires can be used for QOL studies. The advantage of using generic questionnaires, such as RAND-36, is the possibility for comparison across diseases, disease stages, treatments and between individuals with and without the condition. A drawback of generic questionnaires is the lack of sensitivity and specificity for the detection of minor subtle changes in a person’s mental or physical health, which are
induced by inter alia PC screening or the AS protocol. Baseline psychological factors can continue to be predictive of anxiety and distress long after the screening process and during AS. These psychological phenomena may not be measurable by using only general HRQL questionnaires. In addition, measuring generic HRQL is merely an indirect way of studying possible coincidental emotional reactions that have arisen during screening process or during AS. In this study, we did not have information on the men’s personality traits such as their predisposition to anxiety, or their coping strategies. In order to detect possible subtle changes in men’s psychological function during the screening process or in AS, more sensitive measures that focus on specific symptoms such as anxiety or distress might be useful (Avery et al. 2008; Macefield et al. 2010). In addition, another challenge to QOL based-studies is the timing of when the questionnaires were given as it has been observed that QOL can vary rather rapidly, even while waiting for a PSA result (Dale et al. 2005).

9.3 Possible diagnostic and prognostic tools for AS (studies IV and V)

9.3.1 DW-MRI in AS (study IV)

One objective of study IV was to evaluate, if DW-MRI interpreted in a routine clinical setting by a general uroradiologist, could be used as a diagnostic or prognostic tool in AS. A specific aim of the study was to clarify, whether DW-MRI findings would correlate with rebiopsy findings and whether treatment change could be predicted. Study data revealed only a poor correlation between tumour location on MRI and prostate biopsies, and also tumour appearance on MRI could not predict either treatment change or rebiopsy findings.

DW-MRI has been shown to be more sensitive and specific in detecting malignant tumours than conventional T2-W MRI (Kim et al. 2007; Afaq et al. 2011; Miao et al. 2007). DW-MRI also offers additional information and value in the form of ADC maps (Vargas et al. 2011). Only a few studies have shown MRI and ADC mapping to be a valuable tool in PC imaging on AS. One of those studies showed that ADC values for both benign and cancerous tissue decreased over time in men with PC progression in AS, whereas the changes in ADC values were not significant in non-progressors (Morgan et al. 2011). Other studies showed that tumour ADC values can be potentially differentiated between high-risk and low-risk PC (deSouza et al. 2008) and predicted deferred radical treatment (van As et al. 2009). Multiparametric MRI i.e. the combination of different MRI modalities (T2 weighted imaging combined DW-MRI and/or DCE-MRI and/or MR spectroscopy) may further improve the performance of MRI (Turkbey et al. 2011a). The usefulness of MRI in patients on AS is currently under active research, and some studies have already supported the incorporation of MRI into surveillance protocols (van As et al. 2009; Fradet et al. 2010; Vargas et al. 2011; Margel et al. 2012).

Results of the present MRI-study (IV) showed a poor correlation between biopsy and MRI findings, especially in the apex. One explanation for this result may be, that the biopsies themselves correlated poorly with the respective RP specimen
Moreover, most of the study patients in our PRIAS AS programme (IV) were likely to have a minimal low-grade PC. We found that one out of three patients had no cancer on rebiopsy and the majority of men with cancer on rebiopsy had small Gleason score 6 PC foci. This finding is in line with the results of previous studies, which found that low-grade PCs are a challenge to visualize on MRI (Vargas et al. 2011; Guzzo et al. 2012). Although encouraging results have been published for the use of MRI during AS (van As et al. 2009; Fradet et al. 2010; Vargas et al. 2011; Margel et al. 2012), some studies have failed to show such a benefit (Cabrera et al. 2008; Ploussard et al. 2011c; Shukla-Dave et al. 2012). Clearly, our results are hampered by the fact that MRIs were evaluated by a general radiologist, instead of uroradiologist with a special expertise in interpreting prostate MRI findings. It has been shown that the experience of radiologists has a significant influence on diagnostic accuracy in interpreting MR images. The number of false reports is dependent on the observer and the rate of misinterpretations has been found to be significantly higher in a less experienced group of radiologists (Krampla et al. 2009). In the present study (IV), the small number of RPs was such that the correlation analysis between MRI and RP findings lacked statistical-power.

Guidelines have recently been introduced for prostate MRI imaging including a structured reporting protocol (Barentsz et al. 2012), to improve the reproducibility and reliability of MRI. The published guidelines indicate, that the current minimal requirements for DW-MRI are b-values of 0, 100, and 800-1000 s/mm² (Barentsz et al. 2012). When study (IV) was originally designed, no standard technique for performing prostate DW-MRI existed, nor was there any recommendation for a structured reporting protocol. The b-values used (300-600 s/mm²) in study (IV) may not have been optimal, as clearly higher b-values are currently recommended for PC detection (Hoeks et al. 2011). It may be that the tumours are probably not visible with b-values under 600 s/mm² (Afaq et al. 2011). Another limitation of this study is the use of qualitative (rated as either positive or negative) instead of quantitative analysis. Dichotomizing continuous variable (ADC-values) may have resulted in a loss of power of the analysis, despite the fact that currently there is no consensus of the cut-off ADC values for malignant findings for the prostate (Kim et al. 2007; Gibbs et al. 2009; Woodfield et al. 2010; Vargas et al. 2011). Patients in our study had MRI only after one year of follow-up, but not at the diagnosis. This can cause some bias in the assessment of MRI as changes during surveillance cannot be analysed. However, the rationale to conduct MRI before standard 1-year rebiopsy was based on the fact that transrectal prostate biopsy may miss a considerable number of tumors, especially tumours that are located apically. Another aim of the study was to rule out these tumours during AS (Vis et al. 2000; Mazal et al. 2001; Iremashvili et al. 2012). In addition, multiparametric MRI was not available in our institution at the time and this may also have contributed to the results (Turkbey et al. 2011a). Multiparametric imaging in PC diagnosis would also require a specially trained uroradiologist to interpret the MRI images. Such uroradiologists will probably not be available in many small-volume centres. The absence of endorectal coil and the use of a pelvic coil instead, may be considered as a relative shortcoming of the study, although no consensus exists about the use of coil type (Dickinson et al. 2011).

The strengths of this study are the use of modern imaging technology (3T MRI), timing of the rebiopsies and the prospective nature of the study. A recent
European consensus meeting concluded that 3T MRI is an optimal imaging technique (Dickinson et al. 2011) for PC.

The present study (IV) results indicate that DW-MRI as performed here, did not provide any additional prognostic benefit or reliable information to guide the treatment of PC patients on AS. Further evaluations by a well-trained uroradiologists are essential to assess whether multiparametric MRI prostate imaging will add sufficiently to prognostic tools to justify its routine use in a clinical setting.

9.3.2 %fPSA ratio as a prognostic tool on AS (study V)

Although AS is a widely accepted management option for PC, more accurate staging and grading at an early stage of PC could further increase the acceptance and uptake of this strategy. Although there are a lot of expectations for the utility of MRI as a tool in AS programs, novel biomarkers are also needed and they are under ongoing urologic research. In the present study (V) we aimed at evaluating if free/total %fPSA could serve as a prognostic tool in the AS protocol. The specific aim of the study V was to address, whether a %fPSA evaluation at diagnosis and during follow-up would associate with rebiopsy or RP findings or whether the discontinuation of AS could be predicted. Although median %fPSA values were statistically significantly different between those men still on AS compared to those who had discontinued, the results showed no clinically relevant associations of diagnostic %fPSA to guide clinical practice. However, the probability of continuing AS was the highest in men with favourable %fPSA characteristics at diagnosis and also during surveillance.

The %fPSA as a marker in predicting the probability of PC diagnosis is widely evaluated (Partin et al. 1996; Catalona et al. 1998). The association between a low %fPSA and a clinically significant PC has been demonstrated (Nam et al. 2007), in addition to the association between a low %fPSA and a higher grade PC with aggressive characteristics (Southwick et al. 1999; Catalona et al. 2000). Only a few studies have clarified the role of %fPSA as a prognostic tool in the AS setting. In contrast to our results, a few previous studies demonstrated that %fPSA may predict adverse histology in rebiopsy (Selvadurai et al. 2013) and the time to deferred radical treatment (van As et al. 2008; Selvadurai et al. 2013) in men with low-risk PC on AS. In contrast to the PRIAS protocol used in studies (I, II, IV and V), the other patient cohorts also included higher risk cancers, i.e. Gleason score 7 (3+4), which is likely to increase the statistical power of the analyses for the end-points used. The PRIAS patient population represents a rather homogenous cohort, as only minimal findings of low-risk PC and maximum Gleason score of 6 are accepted criteria. In addition, the definitions for adverse rebiopsy findings and also %fPSA cut-off used at follow-up, were all different making it difficult to compare the results between studies. Only the 1-year rebiopsy results were predominantly used for the analysis in our study due to the limited number of patients available with both %fPSA and first rebiopsy results. It is probable that first rebiopsies after the year of surveillance are likely to have a high preponderance of misclassification of PC at diagnosis instead of true cancer progression. Longer follow-up is, therefore, needed to further assess the role of diagnostic %fPSA in this PRIAS patient cohort. The multivariate analysis indicated that baseline characteristics that were associated with
treatment change due to protocol-based reasons, were PSAD and the number of PC positive cores at diagnostic biopsy (study V). This is in line with results from other AS cohorts (Kotb et al. 2011; San Francisco et al. 2011) and with the data from a recent PRIAS analysis (Bul et al. 2013b), which also support the validity of the present analysis.

Although baseline %fPSA could not predict the treatment change, the median %fPSA value after one year of surveillance was significantly higher in men continuing AS compared to men who discontinued AS due to protocol-based reasons. The difference was particularly significant when %fPSA and %fPSA-velocity were used as a joined categorical variable in the analysis. The probability to continue AS was highest in those patients with a favourable %fPSA at diagnosis and during surveillance, i.e. an initial %fPSA of over 15 and a positive %fPSA velocity. At present, the literature on the utility of %fPSA-velocity as a prognostic tool in AS strategies is scarce. Although the role of PSA-kinetics in general is still unclear and its utility in AS strategy has raised some doubts (Iremashvili et al. 2013), to our knowledge %fPSA-velocity has not been studied as a predictor of AS outcomes before. It may be that longitudinal biomarker measurements have a better predictive accuracy than a single baseline value in AS programmes (Ng et al. 2009) and serial measurements over time may provide the potential to characterize the tumour more accurately than on the basis of a single baseline measurement. Interestingly, recently published data suggests that PSA-velocity risk count is independently associated with adverse histology in rebiopsy in an AS cohort (Patel et al. 2013). The multivariate analysis of our study (V) determined that the baseline variables predictive of adverse histology in rebiopsy were the number of PC positive cores at diagnostic biopsy and age. Reclassification of disease was more likely to occur in men with two cancer positive cores at diagnostic biopsy compared to men who had only one positive biopsy core. This finding concords with those data of the recent PRIAS interim study (Bul et al. 2013b), and also with the results from other AS series (van As et al. 2008; Dall’Era et al. 2008; Klotz et al. 2010b; Tosoian et al. 2011).

Study (V) data could not show any association between %fPSA and RP findings and the only predicting variable identified by the multivariate analysis was PSAD, which has also been demonstrated previously (Vellekoop et al. 2014). In contrast to study V data, few previous studies have shown the association between low %fPSA values and significant upgrading of low-grade PC after RP (Visapaa et al. 2010). However, the capability of %fPSA in predicting higher stage PC in RP (Southwick et al. 1999; Elabbady and Khedr 2006) and also further adverse pathology following surgery have been reported (Steuber et al. 2007). The small number of RPs done in our series is insufficient to provide the statistical power needed for meaningful analysis and therefore results of study V do not allow drawing of definite conclusions. Furthermore, a larger AS cohort and longer follow-up time is needed to clarify this issue more precisely.

9.4 Future perspectives

Several prospective AS studies have been initiated within the past decade to increase our knowledge on AS as a management option for low-risk PC. Unfortunately, follow-up periods in the majority of AS cohorts are still too short and longer follow-
up is needed to evaluate proper long-term outcomes and resolve the optimal eligibility criteria, the follow-up protocol and any triggers for intervention in AS. At present, the PRIAS study is the largest prospective AS trial. However, a lack of randomization must be considered as a study weakness. There are a few challenges in AS study design regarding the randomization, as the patient cohort needed would be very large and would need to have a long follow-up time. It is also probable that eventually the differences in survival benefits of radical treatments appear minor (Bill-Axelson et al. 2008). In the near future, the results from a randomized ProtecT-trial are awaited. That study aims to evaluate the differences between radical treatments and AS in low-risk PC, and hopefully it will clarify the assessment of mortality and morbidity associated with AS and radical treatment approaches (Lane et al. 2010).

Unless there is a new strategy to prevent the overdiagnosis of low-risk PCs implemented, AS is likely to remain as a major management option for insignificant PC. The rationale for the AS strategy is obvious, but there are still challenges to resolve, e.g. how to distinguish reliably insignificant PCs from aggressive PCs, so that the curability of the disease is not missed due to misclassification or true progression or a combination of both. A more accurate staging and grading of PC is thus needed and research on new biomarkers and imaging techniques, such as multiparametric MRI, is essential and will hopefully improve the usefulness of AS in routine clinical practice. Targeted biopsies that use MRI have raised interest in focal ablation. Treating the dominant PC lesion instead of the whole prostate gland may result in sufficient PC control while avoiding the side effects of radical treatments (Hou et al. 2009).

Retrospective studies with longer follow-up have provided evidence that AS is a safe management option in men with low-risk PC (Bul et al. 2012b; Godtman et al. 2013), but prospective longitudinal series with longer follow-up are warranted to validate the accuracy of this interpretation. Currently the inclusion criteria, surveillance protocols and the triggers for intervention vary between AS trials. Therefore, detailed reporting of the data from these trials is essential as they mature, which is the aim of the ongoing PRIAS study. A global AS database with data from all the major AS series is currently under consideration to overcome inherent challenges in randomized trials on low-risk prostate cancer. Creation of biobanks, e.g. the Prostate Active Surveillance Study (PASS), will allow research on the genetic and molecular profile of low-risk PC and changes of these characteristics during AS (Newcomb et al. 2010). Patients on AS also represent a cohort that enables research on secondary prevention strategies (Parsons et al. 2009). Finally, QOL is a subject for further analysis and requires long-term data to clarify the possible long-term effects of AS on anxiety, distress and QOL in general. The importance of options and capabilities of multidisciplinary teams in supporting men during AS especially needs further evaluation.
10. SUMMARY AND CONCLUSIONS

The objectives of the present study were to analyse the feasibility of AS strategy and outcomes in the short-term after PC diagnosis. The QOL of men during the first steps of the continuum of PC disease, i.e. during the screening and AS was also studied. The utility of DW-MRI and free/total PSA ratio, as additional prognostic tools in AS were investigated.

The following conclusions of the five studies can be drawn:

I. AS appears to be a feasible strategy to avoid overtreatment in the short-term in selected men diagnosed with low-risk PC. Active monitoring and applying strict criteria of the PRIAS protocol in study I resulted in a quarter of the patients discontinuing surveillance after two years. The main reason for stopping AS was the adverse findings in the standard 1-year rebiopsy and biopsy results, and were independent of the PSADT. The present short-term analysis, indicated the mortality outcomes remain unknown, but the PRIAS-based protocol used in study I seems not to have comprised curability.

II. The standardized QOL questionnaires revealed that AS does not seem to cause short-term QOL disturbances, when the questionnaires were administered to patients after entering AS and who were receiving specialized support for their management choice. During the short follow-up none of the study patients discontinued due to anxiety or distress. The HRQL of patients on AS was significantly better than for the general age-stratified Finnish male population.

III. HRQL effects of PC screening, as carried out in the Finnish arm of the ERSPC study and assessed by standardized HRQL-questionnaire, appear minor and transient in the short-term. The screened participants were also found to be comparable to the general population as HRQL scores were similar to those of the age-stratified general Finnish male population.

IV. DW-MRI data, as interpreted in a routine clinical setting and performed in study IV, did not provide additional prognostic benefit in comparison with the PSA measurement or with prostate rebiopsies. Localized low-grade PC is challenging to visualize by DW-MRI and it should be further studied. It remains to be seen, if the multiparametric approach of prostate MRI and well-trained uroradiologists will add sufficiently to pre-existing prognostic tools of AS and induce the routine use of MRI in a clinical setting.

V. Diagnostic %fPSA alone could not provide any detectable additional prognostic benefit when compared to other predictors already used in AS protocols, such as PSA-kinetics. However, %fPSA coupled to %fPSA-
velocity during AS may aid in predicting the probability for discontinuation of AS due to protocol-based reasons and future treatment change.
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Helsinki, May 2014

Hanna Vasarainen
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13. APPENDICES

The FinnProstate XI Co-ordinators and Trial Centers

Etelä- Pohjanmaa Central Hospital, Seinäjoki: Markku Leskinen
Etelä-Savo Central Hospital, Mikkeli: Niilo Hendolin, Tapani Liukkonen
Helsinki University Hospital: Antti Rannikko
Kuopio University Hospital: Sirpa Aaltomaa
Kuusankoski District Hospital: Markku Multanen, Markku Onali
Oulu University Hospital: Pekka Hellström, Erkki Ollikkala
Päijät-Häme Central Hospital, Lahti: Taina Isotalo
Tampere University Hospital: Andres Kotsar, Teuvo Tammela
Rand-36 health-related quality of life questionnaire

1. Onko terveyttenne yleisesti ottaen ...
   (ympyröikää yksi numero)
   1 erinomainen
   2 varsin hyvä
   3 hyvä
   4 tyydyttävä
   5 huono

2. Jos vertaatte nykyistä terveydentilaanne vuoden takaiseen, onko terveyttenne yleisesti ottaen ...
   (ympyröikää yksi numero)
   1 tällä hetkellä paljon parempi kuin vuosi sitten
   2 tällä hetkellä jonkin verran parempi kuin vuosi sitten
   3 sumpnelleen samanlainen
   4 tällä hetkellä jonkin verran huonompi kuin vuosi sitten
   5 tällä hetkellä paljon huonompi kuin vuosi sitten

Seuraavassa luettelaa erilaisia päivittäisiä toimintoja. Rajoitettaessa terveydentilaanne nykyisin suoriuttumistaan seuraavista päivittäisiä toimintoista? Jos rajoittaa, kuinka paljon?
   (ympyröikää yksi numero joka riviä)

<table>
<thead>
<tr>
<th></th>
<th>kyllä, rajoittaa paljon</th>
<th>kyllä, rajoittaa hiukan</th>
<th>ei rajoita lainkaan</th>
</tr>
</thead>
</table>
3. | .......................................................... | 1 | 2 | 3 |
4. | kohdallisia panostusvapaata toimintaa, kuten pöydän siirtäminen, insurointi, keilailu | 1 | 2 | 3 |
5. | ruokakassien nostaminen tai kantaminen | 1 | 2 | 3 |
6. | nouseminen portaista useita kerroksia | 1 | 2 | 3 |
7. | nouseminen portaista yhden kerroksen | 1 | 2 | 3 |
8. | vartalon taivuttaminen, polvistuminen, kumartuminen | 1 | 2 | 3 |
9. | noin kahden kilometrin matkan kävely | 1 | 2 | 3 |
10. | noin puolen kilometrin matkan kävely | 1 | 2 | 3 |
11. | noin 100 metrin matkan kävely | 1 | 2 | 3 |
12. | kylpeminen tai puuteutuminen | 1 | 2 | 3 |
Onko teillä viimeisen 4 viikon aikana ollut RUUMILLISEN TERVEYDEN-
TILANNE TAKIA alla mainittuja ongelmia työssänne tai muissa tavanomais-
sissa päivittäisissä tehtävissänne?
(ympyröikää yksi numero joka riviltä)

kyllä  ei

13. Vähensit työhön tai muuhin tehtävän käytämisän aikaa ............ 1 .......... 2

14. Saitte aikaiseksi vähemmän kuin halusitte ........................................ 1 .......... 2

15. Terveydentilanne asetti teille rajoittuksia joissakin
    työ- tai muissa tehtävissä ................................................................. 1 .......... 2

16. Töistäsi tai tehtävistäsi suoristumisen tuotti
    vaikeuksia (olette joutunut esim. pommittelemaan
    tavallista enemmän) ................................................................. 1 .......... 2

Onko teillä viimeisen 4 viikon aikana ollut TUNNE-ELÄMÄÄN LIITTYVIEN
vaikeuksien (esim. masentuneisuus tai ahdistuneisuus) takia alla mainittuja
ongelmia työssänne tai muissa tavanomaisissa päivittäisissä tehtävissänne?
(ympyröikää yksi numero joka riviltä)

Kyllä  ei

17. Vähensit työhön tai muuhin tehtävän käytämisän
    aikaa ..................................................................................... 1 .......... 2

18. Saitte aikaiseksi vähemmän kuin halusitte ........................................ 1 .......... 2

19. Eette suorittautut töistäsi tai muita tehtäviä yhtä
    hmoilelaisesti kuin tavallisesti .................................................. 1 .......... 2

20. MISSÄ MÄÄRIN ruumiillinen terveydentilanne tai tunne-elämän vaikeudet
    ovat viimeisen 4 viikon aikana häirinneet tavanomaista (sosiaalista)
    toimintaanne perheen, ystävien, naapureiden tai muiden ihmisten parissa?
(ympyröikää yksi numero)

1  ei lainkaan
2  hieman
3  kohtalaisesti
4  melko paljon
5  erittäin paljon
1. ei lainkaan
2. hyvin lieviä
3. lieviä
4. kohtalaisia
5. voimakkaita
6. entistä voimakkaita

22. Kuinka paljon kipu on häirinnyt tavanomaista työtä (kotena tai kodin ulkopuolella) viimeisen 4 viikon aikana? (ylpeydykkää yksi numero)
1. ei lainkaan
2. hieman
3. kohtalaisesti
4. melko paljon
5. entistä paljon

Seuraavat kysymykset koskevat sitä, mitä teistä on tuntunut viimeisen 4 viikon aikana. Merkitä kunon kysymyksen kohdalla se numero, joka parhaiten kuvaa tunteamukianne. (ylpeydykkää yksi numero joka riviltä)

<table>
<thead>
<tr>
<th>Kuinka suuren osan ajasta olette viimeisen 4 viikon aikana</th>
<th>koeko</th>
<th>suurin</th>
<th>liheinestä</th>
<th>jonkin</th>
<th>vähän</th>
<th>en lainkaan</th>
</tr>
</thead>
<tbody>
<tr>
<td>oman ajan osan</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

23. Tunteet olevanne täynnä elinvoimaa
24. Ollut hyvin hermoostunut
25. Tunteet nielat Anne niin matalaksi, ettei päästä ole voidut teitä puristaa
26. Tunteet itseen tyyneksi ja ruhalaiseksi
27. Ollut täynnä tavoaa
28. Tunteet itseen alakuliseksi ja apeeksi
29. Tunteet itseen "loppumukuisaksi"
30. Ollut onnellinen
31. Tunteet itseen väsyneeksi
32. Kuinka suuren osan ajasta ruumiillinen terveydentilaanne tai tunne-elämän vaikeudet ovat viimeisen 4 viikon aikana häirinneet tavanomaista sosiaalista toimintaaanne (ystävien, sukulaisten, muiden ihmisten tapaaminen)?
(ympyröikää yksi numero)
- 1 koko ajan
- 2 suurimman osan aikaa
- 3 jonkin aikaa
- 4 vähän aikaa
- 5 ei lainkaan

Kuinka hyvin seuraavat väärtömät pitävät paikkansa teidän kohdallanne?
(ympyröikää yksi numero joka riviltä)

<table>
<thead>
<tr>
<th>pitää</th>
<th>pitää en</th>
<th>enimmäk-</th>
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<tbody>
<tr>
<td>ehdottu-</td>
<td>sein ei</td>
<td>sein</td>
<td>ehdot-</td>
</tr>
<tr>
<td>masti</td>
<td>maan</td>
<td>sanoo</td>
<td>masti</td>
</tr>
<tr>
<td>paikkansa</td>
<td>paikkansa</td>
<td>sanoa</td>
<td>paikkansa</td>
</tr>
</tbody>
</table>

33. Minusta tuntuu, että sairastun
jonkin verran helpommin kun
muut ihmiset ................................................. 1 .............. 2 .............. 3 .............. 4 .............. 5

34. Olen vähintään yhtä terve
kuin kaikki muutkin
tuntemani ihmiset ................................................. 1 .............. 2 .............. 3 .............. 4 .............. 5

35. Uskon, että terveyteni
tulee heikkenemään ............................................. 1 .............. 2 .............. 3 .............. 4 .............. 5

36. Terveyteni on erinomainen ............................................. 1 .............. 2 .............. 3 .............. 4 .............. 5
IPSS questionnaire

1. Kuinka usein teillä on ollut tunne, että rakko ei ole tyhjentynyt täysin virtsaamisen jälkeen?
   - Ei koskaan
   - Noin joka 5. kerta
   - Noin joka 3. kerta
   - Noin joka 2. kerta
   - Noin kahtena kertana kolmesta
   - Melkein aina

2. Kuinka usein teidän on täytynyt virtsata uudelleen ennen kuin edellisestä virtsaamisesta on kulunut kaksi tuntia?
   - Ei koskaan
   - Noin joka 5. kerta
   - Noin joka 3. kerta
   - Noin joka 2. kerta
   - Noin kahtena kertana kolmesta
   - Melkein aina

3. Kuinka usein olette huomannut, että virtsasuihku on katkeillut virtsaamisen aikana?
   - Ei koskaan
   - Noin joka 5. kerta
   - Noin joka 3. kerta
   - Noin joka 2. kerta
   - Noin kahtena kertana kolmesta
   - Melkein aina

4. Kuinka usein teillä on ollut vaikeuksia pidättää virtsa virtsaamistarpeen ilmaannuttua?
   - Ei koskaan
   - Noin joka 5. kerta
   - Noin joka 3. kerta
   - Noin joka 2. kerta
   - Noin kahtena kertana kolmesta
   - Melkein aina
5. Kuinka usein olette huomannut, että virtsasuihku on heikentynyt?

- Ei koskaan
- Noin joka 5. kerta
- Noin joka 3. kerta
- Noin joka 2. kerta
- Noin kahtena kertana kolmesta
- Melkein aina

6. Kuinka usein olette joutunut ponnistelemaan saadakseen virtsamisen käyntiin?

- Ei koskaan
- Noin joka 5. kerta
- Noin joka 3. kerta
- Noin joka 2. kerta
- Noin kahtena kertana kolmesta
- Melkein aina

7. Kuinka monta kertaa yön aikana olette tavallisimmin joutunut nousemaan virtsalle mentyänne illalta nukkumaan ja ennen kuin nousitte aamulla ylös?

- En kertaakaan
- Kerran
- 2 kertaa
- 3 kertaa
- 4 kertaa
- 5 kertaa tai useammin
IIEF-5 questionnaire

Sukupuolieläintä häiriöiden kyselykaavake miehille (IIEF-5)

Tämä kyselykaavake on suunniteltu helpottamaan Sinun ja lääkärisi välistä keskustelua erektiohäiriösi selvittelyssä ja hoidon suunnitteluessa. Valitse ja ympyröi kunkin kysymyksen vastausvaihtoehtoista se, joka parhaiten kuvaav Sinun tilannettasi viimeisen 6 kuukauden aikana. Valitse jokaiseen kysymykseen ainoastaan yksi vastaus!

Viimeisen 6 kuukauden aikana:
1. Millaiseksi arvioitte luottamuksenne siihen, että voitte saavuttaa erektion ja säilyttää sen yhdyynnän ajan
   1 = Hyvin vähäiseksi
   2 = Vähäiseksi
   3 = Kohtalaiseksi
   4 = Suureksi
   5 = Hyvin suureksi

2. Kun Teillä oli seksuaalisen kiihottumisen aikana erektioita, kuinka usein ne olivat tarpeeksi kovia yhdyntään?
   0 = Ei seksuaalista toimintaa
   1 = Ei koskaan tai ei juuri koskaan
   2 = Muutaman kerran (harvemmin kuin joka toisella kerralla)
   3 = Joskus (noin joka toisella kerralla)
   4 = Useimmien (useammin kuin joka toisella kerralla)
   5 = Melkein aina tai aina

3. Kuinka usein pystytte yhdymnässä ylläpitämään erektion sisään työntymisen jälkeen?
   0 = En yrittänyt yhdyntää
   1 = En koskaan tai en juuri koskaan
   2 = Muutaman kerran (harvemmin kuin joka toisella kerralla)
   3 = Joskus (noin joka toisella kerralla)
   4 = Useimmien (useammin kuin joka toisella kerralla)
   5 = Melkein aina tai aina

4. Kuinka vaikeaa Teidän oli säilyttää erektonne yhdynnän loppuun saakka?
   0 = En yrittänyt yhdyntää
   1 = Äärimmäisen vaikeaa
   2 = Hyvin vaikeaa
   3 = Vaikeaa
   4 = Hieman vaikeaa
   5 = Ei lainkaan vaikeaa

5. Kun yrititte sukupuoliyhdyntää, kuinka usein saitte siitä tyydyttystä?
   0 = En yrittänyt yhdyntää
   1 = En koskaan tai en juuri koskaan
   2 = Muutaman kerran (harvemmin kuin joka toisella kerralla)
   3 = Joskus (noin joka toisella kerralla)
   4 = Useimmien (useammin kuin joka toisella kerralla)
   5 = Melkein aina tai aina

Yhteispistemääri:
Alle 22 pistettää viittaa erektiohäiriön olemassaoloon. Keskustelkaa tilanteesta lääkärinne kanssa, jos haluatte hoitoa erektiohäiriön hoitamiseksi.

Nimi ____________________________________________

Sosiaaliturvatunnus ________________________________

Päivämäärä __________________________
14. ORIGINAL PUBLICATIONS