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DIAGNOSTIC AND PREDICTIVE TOOLS IN LOCALIZED PROSTATE CANCER: BIOPSIES, MAGNETIC-RESONANCE IMAGING, AND TISSUE MARKERS

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ACADEMIC DISSERTATION

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The studies are referred to in the text by their Roman numerals. Study III has been included in an earlier compilation thesis (*Screening and active surveillance in prostate cancer: prognostic and short-term outcomes of active surveillance and quality of life aspects*) and is included here with permission from the first author.

CONTENTS

ABBREVIATIONS

ADC	Apparent-diffusion coefficient
AR	Androgen receptor
AS	Active surveillance
CI	Confidence interval
DRE	Digital rectal examination
DSS	Disease-specific survival
DWI	Diffusion-weighted imaging
EAU	European Association of Urology
ERG	*ETS transcription factor*
FDA	U.S. Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
FQ	Fluoroquinolone
FT	Focal therapy
GG	Grade group
GnRH	Gonadotropin-releasing hormone
GS	Gleason score
HR	Hazard ratio
IHC	Immunohistochemistry
LUTS	Lower urinary tract symptoms
mpMRI	Multiparametric MRI
MRI	Magnetic-resonance imaging
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
OR	Odds ratio
OS	Overall survival
PC	Prostate cancer
PI-RADS	Prostate Imaging - Reporting and Data System
PIVOT	Prostate Cancer Intervention versus Observation Trial
PPV	Positive predictive value
PRECISE	Prostate Cancer Radiological Estimation of Change in Sequential Evaluation
PRIAS	Prostate Cancer Research International Active Surveillance
PSA	Prostate-specific antigen
PTEN	*Phosphatase and tensin homolog*
RP	Radical prostatectomy
RT	Radiation therapy
SEER	Surveillance, Epidemiology, and End Results
SPCG	Scandinavian Prostate Cancer Group
TMA	Tissue microarray
TNM	Tumor-node-metastasis staging system
US	Ultrasound

ABSTRACT

Background: With 1.1 million new cases diagnosed annually worldwide and 4500 to 5000 in Finland, prostate cancer (PC) is, in developed countries, the most common non-cutaneous cancer in men. It is a highly heterogenous disease with great variability in its clinical course. Men diagnosed with PC are stratified into risk groups, reflecting how aggressive the disease is and how actively it should be treated and monitored. Low-risk PC is generally indolent and often requires no curative treatment. Active surveillance (AS) is its primary treatment option, whereas high-risk PC, at the opposite end of the disease spectrum, offers significant risk for local advance and metastasis; radical treatment is therefore necessary. Despite treatment, high-risk PC still, however, poses a risk for cancer recurrence and even risk of death. Intermediate- and high-risk PC are generally treated with radical prostatectomy (RP) or radiation therapy.

Accurate risk stratification is essential for choosing proper treatment. Currently, stratification is based on diagnostic prostate biopsies, the patient's prostate-specific antigen (PSA) level, and clinical stage. This current stratification system has well-established limitations. The biggest uncertainty stems from prostate biopsies. The biopsies are performed in a schematic manner with ultrasound guidance, which does not, however, distinguish possible tumors from surrounding benign tissue. Current risk stratification also ignores prostate magnetic-resonance imaging (MRI). Better strategies for the diagnosis and risk stratification of PC are thus necessary.

Study I: Prostate biopsy is one of the most common urological out-patient procedures. The procedure is carried out via the rectum and carries a substantial risk for complications, such as infection, bleeding, and pain. The most severe complications involve infections, an alarming rising trend in incidence of which has occurred globally in recent years. In Study I, we retrospectively evaluated the incidence of bacteremic post-biopsy complications in the Helsinki and Uusimaa hospital district during 2005-2013. Annual incidences were calculated by combining databases of all prostate biopsies and positive blood cultures during this period. Clinical data on the bacteremic patients allowed exploration of possible risk factors for infections.

Study II: The current standard prostate biopsy procedure involves taking 12 biopsy cores in a prespecified pattern, without knowledge of possible tumor location. Until the introduction of prostate MRI, biopsies were the only tool with which to plan curative therapies in detail. PC is often a multifocal disease, with several separate tumor foci in the prostate. In Study II we retrospectively investigated in RP specimens the performance of 12-core prostate biopsies in predicting tumor location and extent. We also analyzed tumor morphologies with emphasis on clinically significant PC and

the index tumors. This was achieved by charting all tumors in the RP specimens of 96 men treated with laparoscopic robot-assisted RP at our institution between 2009 and 2010. Detailed information on tumor locations and morphologies was compared with data from diagnostic biopsies.

Study III: AS entails close monitoring of patients and relies heavily on serial PSA measurements and repeat biopsies. This monitoring is increasingly complemented with prostate MRI. Study III was a prospective study investigating the value of prostate MRI in the follow-up of AS patients. In 2009-2011, 80 men underwent prostate MRI after being on AS for one year and before receiving their first follow-up biopsies. MRI findings were compared with clinical and pathological parameters to assess whether MRI added any value to the standard follow-up.

Study IV: Novel tools for better prediction of PC patients' outcomes are being actively explored, with much attention to PC tissue biomarkers. In Study IV, we retrospectively analyzed 358 men treated with RP between 1983 and 1998 at Helsinki University Hospital and 457 men operated on between 2000 and 2005 at Turku University Hospital. The expression of each of three PC tissue markers–ERG, PTEN, and AR–were analyzed by constructing tissue microarrays from the patients' RP samples. We explored the association of marker expression with clinical outcomes: requirement for secondary therapy after RP, disease-specific survival (DSS), and overall survival (OS).

Main results and conclusions: A 2.4-fold increase in the annual incidence of post-biopsy bacteremic complications emerged over the study period, with no clinical risk factor for developing bacteremic complications. Recent international travel was associated with development of an infectious complication by a fluoroquinolone-resistant organism. Strategies to avoid unnecessary biopsies and reduce biopsy-related infections call for development (**I**). Twelve-core prostate biopsies predicted location and extent of tumors in RP specimens unreliably, which makes them a poor tool for detailed planning of radical or focal therapies. Analysis of significant tumors and index tumors revealed that positive surgical margins and extraprostatic extension at RP were mostly caused by the index tumor. The index tumor can thus be chosen based on dedifferentiation instead of on tumor size (**II**). Prostate MRI added no value to the standard follow-up of AS patients. To perform reliably as a diagnostic and follow-up tool, prostate MRI should be performed and reported based on prespecified and standardized protocols (**III**). Loss of PTEN expression led to shorter DSS times and shorter secondary-therapy-free survival after RP. The poorest outcomes were for patients with PC samples negative for both ERG and PTEN expression and with strong AR expression. PTEN loss appears to be a strong driver for disease progression, and its performance as a prognostic tool should be further studied in prospective settings (**IV**).

1 INTRODUCTION

Prostate cancer (PC) is the most common cancer in men in the Western world (Torre et al. 2015), but is still, in many ways, a poorly characterized disease. The older the man, the more likely he is to be diagnosed with PC (Sakr et al. 1994), and men of African heritage are at higher risk (McGinley et al. 2016). Genetics also play a major role: roughly half of an individual's risk for PC is the result of advancing age and environmental factors, but the remaining half stems from genetic factors (Lichtenstein et al. 2000, Mucci et al. 2016). Despite this, no genetic tests can as yet aid in identifying at-risk men at population level. Age, race, and genetics are all unamenable factors, with no firmly-established environmental or life-style factors exist that men can avoid to lower their PC risk.

One unanswered question is how to properly screen for PC. PSA-based screening has been tested and studied in two large prospective trials in Europe and the USA (Schröder et al. 2014, Pinsky et al. 2017), but with conflicting results. PSA-based screening has been able to prevent deaths from PC (Schröder et al. 2014), but at such a high cost of over-detection and over-treatment that general screening for unselected men is not recommended. Unorganized or opportunistic PSA-based screening is, however, still widely prevalent in clinical practice, and the problem of over-detection and over-treatment of PC remains unsolved. In 2010-2014 in Nordic countries, the proportion of men dying from PC compared to men diagnosed with PC was 23% (NORDCAN 2017). This reflects the slow natural progression of PC and the relevance of competing causes of death for such men. Nevertheless, in 2014 in Finland, PC was still the second-most likely cancer to kill men (Finnish Cancer Registry 2016)

When a man presents with a PSA value higher than considered normal for his age, the next step is to decide whether to proceed with the diagnostic work-up. There are no safe cut-off values below which we can be sure that PC, even potentially lethal PC, does not occur (Thompson et al. 2007). The decision to proceed with further work-up such as prostate biopsies is therefore hardly ever straightforward. Besides the baseline PSA value, other factors need to be considered as well, such as patient age, comorbidities, assumed life expectancy, possible family history of PC, and personal preferences. A straightforward approach would be simply to take biopsies from all men who present with elevated PSA values, but that approach would not only be fraught with complications, but also expose men to an unnecessary risk of overdiagnosis. The biopsy procedure carries a risk for bleeding, pain, and most importantly, infectious complications that can be catastrophic (Borghesi et al. 2017). Traditional prostate biopsies have several limitations, of which the most important is their under-estimation of disease extent and grade (Epstein et al. 2012). Sampling all patients with elevated PSA in a non-organized setting

would also result in a substantial number of men overdiagnosed with low-grade, clinically insignificant PC with an inherent risk for overtreatment, causing an undue burden upon the patient and health-care system.

PC is a heterogenous disease. Most PCs progress slowly and most likely cause no harm during a patient's lifetime (Lu-Yao et al. 2009). Some PCs, on the other hand, are irrefutably aggressive, recur despite radical therapies (Stattin et al. 2016, Pompe et al. 2017), and progress to a metastatic and lethal stage. The challenge is in properly identifying which patients harbor "benevolent" and which patients aggressive disease. Current tools for characterizing PC are largely inadequate, especially regarding the proper assessment of disease aggressiveness. The current risk stratification is based on histopathological evaluation of PC needle biopsies, where a Gleason score (Gleason 1966) is assigned for the disease. This score is used in risk assessment along with PSA level at diagnosis, clinical disease stage, and, for low-grade disease, number of biopsies positive for PC (Mohler et al. 2016, Mottet et al. 2017). This risk stratification guides the choice of treatment, but the varying outcomes of patients within risk groups reflect how imperfectly these risk groups actually predict the course of the disease (Beauval et al. 2016a, 2016b, Carlsson et al. 2016). When assigning low-risk patients to AS, 50 to 70% of these patients will eventually end up having definitive therapies, such as radical prostatectomy (RP) or radiation therapy (RT) (Bokhorst et al. 2016b). After surgery or RT, 27 to 53% of patients will have disease recurrence (Mottet et al. 2017), and some will develop metastases and eventually die from PC.

Attempts are ongoing to overcome these shortcomings in risk stratification. Magnetic-resonance imaging (MRI) of the prostate holds great promise for improving the diagnostic process. Performance of prostate MRI before taking biopsies can potentially select the right patients for the procedure (Ahmed et al. 2017) and MRI-targeted biopsies appear to be more accurate in terms of determining disease location and aggressiveness (Siddiqui et al. 2015). A new prognostic grouping of histological cancer grades–grade grouping–aims to predict disease outcomes better than conventional Gleason scoring, mainly for the most frequent Gleason score 7 group (Epstein et al. 2016b). Research efforts in the field of PC biology have revealed some key genetic phenomena in disease progression that have given rise to potential biomarkers (Bostrom et al. 2015). Biomarkers would, ideally, reflect true disease aggressiveness and could be used in conjunction with conventional tools to estimate patients' risk for harboring a more aggressive disease than otherwise suspected.

This thesis focuses on the challenges and limitations of current diagnostic and predictive tools in assessing localized PC and aims to offer insight into areas with room for improvement.

2 REVIEW OF THE LITERATURE

2.1 EPIDEMIOLOGY OF PROSTATE CANCER

With 1.1 million new cases diagnosed in 2012, PC is the fourth most common cancer worldwide among both sexes, and the second-most common cancer in men. PC accounts for 8% of all new cancer cases globally and for 15% of new cancers in men. A marked difference occurs in PC incidence rates between developed and developing countries, with 68% of PC diagnoses in developed countries with only 17% of the world's male population. With an age-standardized rate (ASR) of 69.5 per 100 000, PC is, excluding skin cancers, the most common cancer of Western men (Torre et al. 2015). According to Cancer Research UK, about one man in eight in the UK and according to the American Cancer Society, one man in seven in the USA will be diagnosed with PC during their lifetime.

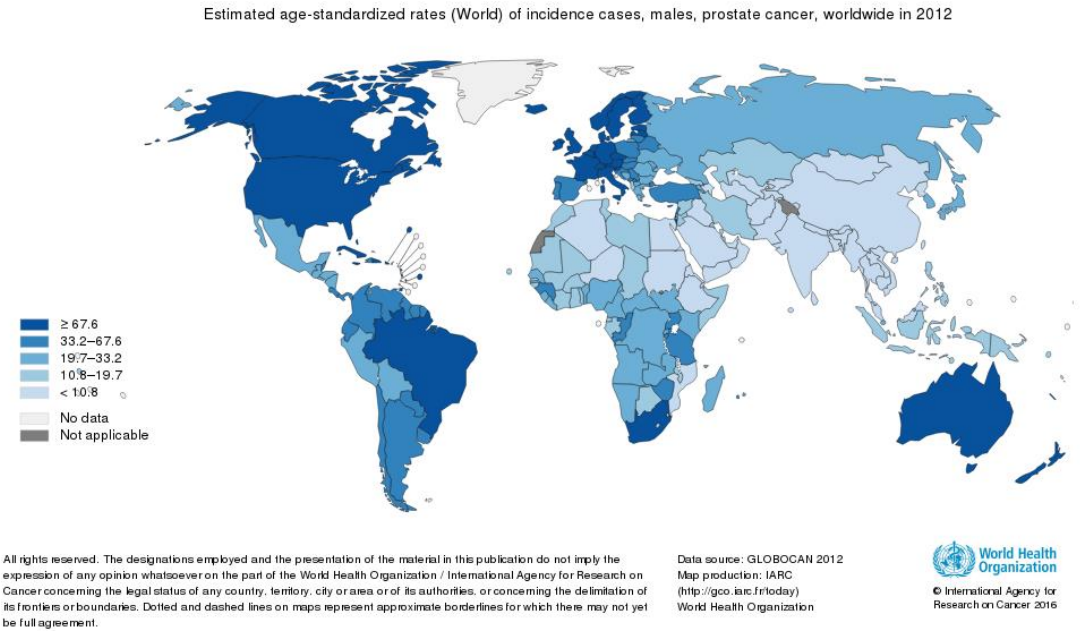


Figure 1 Estimated worldwide age-standardized incidence rates of prostate cancer in 2012. Reprinted with permission from the World Health Organization.

Globally improved standards of living and health awareness have led to an increased life expectancy associated with increasing PC incidence and prevalence. Improved health awareness has also led to unorganized screening for PC by PSA testing (Nordstrom et al. 2016). Historically, the Food and Drug Administration (FDA) approval of the PSA test in 1986 led to a sharp rise in PC diagnoses in the USA, reaching its peak five years later in 1992. This was succeeded by a steep decline, after which, incidence rates steadily started

increasing again. Similar trends have later been observable in many other countries where PSA-based detection has been extensive.

PC mortality rates and PC incidence rates differ markedly (Figure 2). Many countries have seen peak mortality rates in the 1990's, after which they have rapidly decreased. The diminishing mortality of PC is to some degree due to better therapies, but likely to a greater extent due to the extensive use of PSA, which leads to PC detection at earlier, asymptomatic, and localized stages. Most men diagnosed with PC will therefore survive despite their cancer, which is evident in the 10-fold incidence rates compared with mortality rates (Figure 2). This places great pressure on health-care systems to appropriately calibrate their diagnostic processes, in addition to adjusting their thresholds for radical therapies, to avoid overtreating and causing PC patients excessive harm.

2.2 ETIOLOGY AND RISK FACTORS FOR PROSTATE CANCER

2.2.1 ADVANCING AGE

Global PC incidence rates vary greatly (Figure 1), and PC is strongly associated with advancing age. It can, to some extent, be considered a natural occurrence in the aging process. In their seminal autopsy study from 1994, Sakr and co-workers found cancer foci in 2%, 29%, 32%, 55%, and 64% of prostates of men over 20, 30, 40, 50, and 60 years of age (1994). More-recent studies have shown that, at autopsy, 43.9% of men over age 70 harbored cancer foci in their prostates (Zlotta et al. 2013) and, in a review of 19 autopsy studies including over 6000 men, 22% of men aged 50-59, 29% aged 60-69, 34% aged 70-79, and 43% of men over 80 had undiagnosed PC at the time of death (Jahn et al. 2015). Advancing age is therefore a considerable risk factor for PC.

2.2.2 ETHNICITY

The highest PC rates are encountered in developed high-income regions with long life expectancies, such as Australia, New Zealand, North America, and Western and Northern Europe. Incidences are also relatively high in some less affluent regions such as the Caribbean, sub-Saharan Africa, and in South America. The lowest incidences are encountered in Eastern and South-Central Asia (Ferlay et al. 2015). This global variance in incidence may be explained by economic differences, varying practices of PSA testing and the accompanying biopsies, and by various PC risk factors.

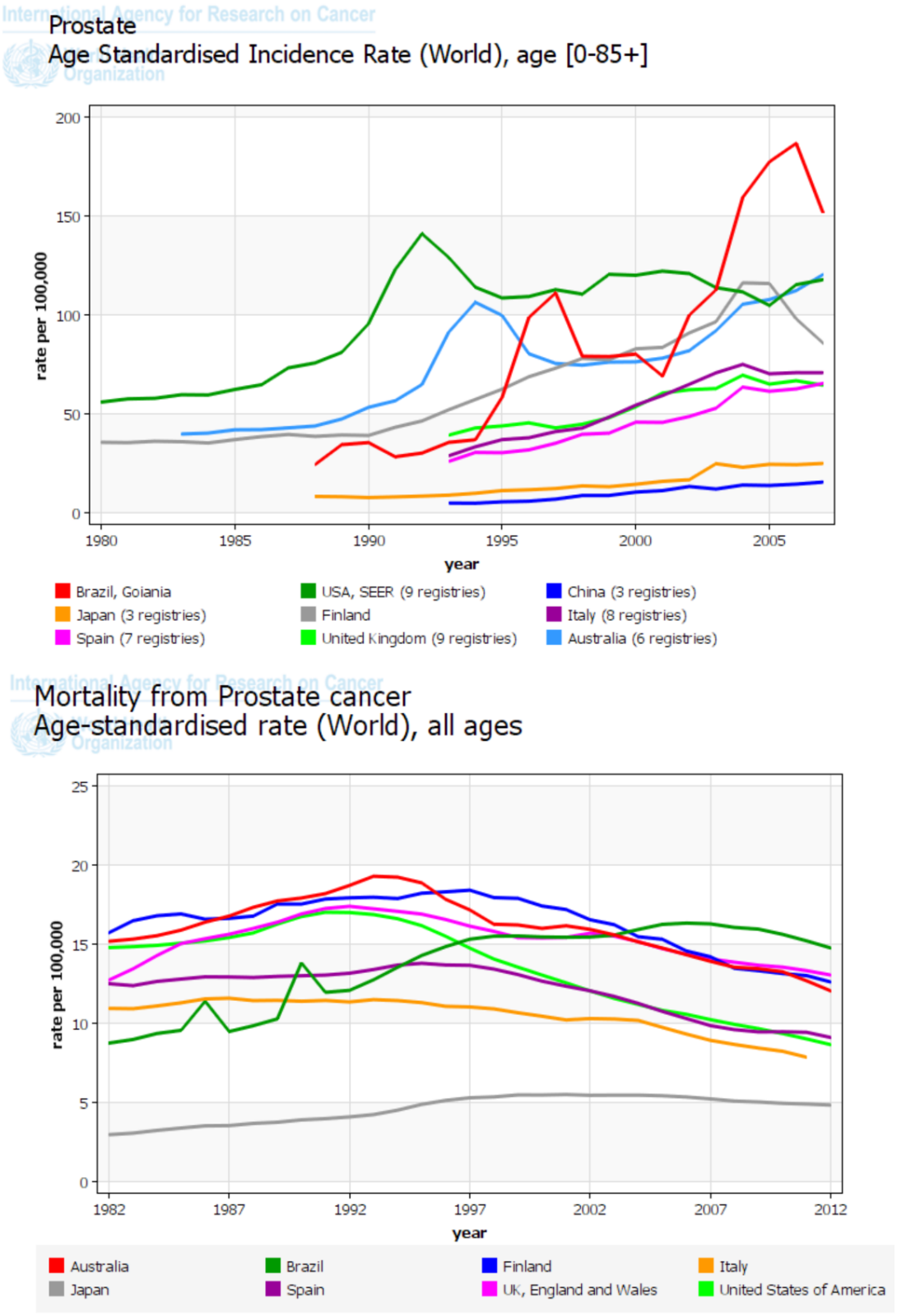


Figure 2 Age-standardized (world) prostate-cancer incidence (top) and mortality (bottom) trends. Mortality trends have been smoothed using three years' average. Source: International Agency for Research on Cancer (IARC). Website accessed on 11.7.2017. Reprinted with permission from the World Health Organization.

Race-associated differences occur in PC development, with men of African heritage being at highest risk. The world's highest incidences are on the Caribbean island of Martinique, with Trinidad and Tobago and Barbados also in the top five (Ferlay et al. 2015). Caribbean islands, along with Brazil and the USA, are the countries outside Africa with the highest proportions of African populations, as reflected in their corresponding high PC incidence rates (Figure 1). PC incidence is also highest among men of African heritage in the USA (McGinley et al. 2016). The lowest PC incidences are in Asian men (Center et al. 2012). This was also evident in the marked diferences between the prevalence of PC at time of death in men of different races: in the age group 70-79, African-American men had the highest prevalence of PC at 51%, Caucasian and European men were at 36%, and the lowest prevalence, 21%, was in Asian men (Jahn et al. 2015). Research into the genetic phenomena underlying these differences is ongoing.

2.2.3 GENETICS

Approximately 100 genes have been identified that raise an individual's risk for PC (Ciccarese et al. 2017), most importantly germline mutations in the tumor-suppressor breast cancer 1 and 2 genes, *BRCA1* and *BRCA2*. *BRCA2* mutations confer a 5-9-fold risk for developing PC, compared to that of men without the mutation, but the risk associated with *BRCA1* mutations, at approximately 4-fold, is less pronounced (Alanee et al. 2014, Eeles et al. 2014). Such mutations are also associated with worse PC outcomes (Alanee et al. 2014). The prevalence of *BRCA2* mutations in one general PC cohort was, however, only 1-2% (Kote-Jarai et al. 2011), so testing all PC patients for this mutation would be unlikely to prove beneficial.

A family history of PC may suggest an inherited risk. Having one affected first-degree relative raises the risk of PC 2.5-fold and having two or more affected first-degree relatives raises it 5- to 11-fold (Steinberg et al. 1990, Brandt et al. 2010). Moreover, having a father diagnosed with PC raises an individual patient's risk of PC by 2-fold, whereas a brother's PC raises the risk by 3-fold (Zeegers et al. 2003, Brandt et al. 2010). Carter and co-workers have suggested considering PC as hereditary, when there are either three or more affected members in a nuclear family, PC in three successive generations, or two or more individuals diagnosed with PC before the age of 55 (Carter et al. 1993). By this definition, 3-5% of PC cases could be classified as hereditary (Bratt 2000). A recent report from the Nordic Twin Study of Cancer group revealed significant excess familial risk for PC. The estimate of heritability, i.e. how much of an individual's risk for cancer results from genetic factors, has been as high as 57% (Mucci et al. 2016). An earlier study, also on a Nordic twin cohort, found the estimate to be 42% (Lichtenstein et al. 2000).

2.2.4 ENVIRONMENTAL AND LIFE-STYLE FACTORS

Age, ethnicity, and genetics–all nonmodifiable factors–are the only confirmed risk factors for PC. Myriads of environmental and life-style factors that may contribute to PC development under investigation, often with conflicting results (Giovannucci et al. 2007). This is presumably because of the disease's heterogeneous nature. Another speculation is that instead of being a precursor state, early-detectable indolent PC could possibly be a separate disease entity from lethal PC, with different etiologies and risk factors (Jahn et al. 2015).

The contemporary Western lifestyle, i.e. sedentary with a high-calorie diet, leading often to high cholesterol and diabetes, is speculated to play a role in PC development. Despite Japan's being a high-income country, PC is still far less prevalent in Japan than in Europe or North America. This fact is attributable to differing lifestyles, mainly dietary differences. The role of the environment has been highlighted in studies on Japanese immigrants in Hawaii which demonstrated that, because of a change in environment, PC incidence in first- and in second-generation immigrants have risen rapidly (Kolonel et al. 2004). Gradual adoption of the Western lifestyle is also suggested to explain the current steady rise in PC incidence in Japan, Singapore, and Thailand–countries where PSA testing is traditionally uncommon (Center et al. 2012).

High body-mass index seems to have a complex effect on risk for developing PC: it has been associated with increased risk for PC (Nunez et al. 2017) and with more advanced cancer (World Cancer Research Fund International: Continuous Update Project 2014), but on the other hand, associated with a reduction in risk for localized PC (Discacciati et al. 2012). Similarly, taller height has been clearly associated with development of lethal, but not of indolent, PC, suggesting that the two disease forms are distinct biological entities (Giovannucci et al. 2007).

Alcohol consumption is generally not considered to raise the risk for PC, although evidence to counter this is gradually accumulating (Rota et al. 2012, Dickerman et al. 2016). It is unclear whether cigarette smoking is a risk factor (Huncharek et al. 2008, Watters et al. 2009) as it has been related to a higher risk for lethal disease, but not indolent PC (Giovannucci et al. 2007) Long-standing inflammation may predispose to development of PC, and evidence exists from meta-analyses that suggests gonorrhea to be associated with increased risk for PC (Caini et al. 2014, Lian et al. 2015). The role of other sexually-transmitted diseases is less clear.

2.3 DIAGNOSING PROSTATE CANCER

2.3.1 PSA AND PSA-BASED SCREENING

PC rarely causes symptoms before it has progressed to an advanced stage. PC is, in fact, most often diagnosed at an earlier, asymptomatic stage solely by an

elevated PSA. A patient with advanced disease may suffer from lower urinary tract symptoms (LUTS): increased voiding frequency and urgency, nocturia, hematuria, and even urinary retention. Metastatic disease may present as skeletal pain, neurological symptoms, anemia, or general malaise. The process of diagnosing PC, initiated by either PSA screening or, rarely, PC symptoms, is presented in Figure 3.

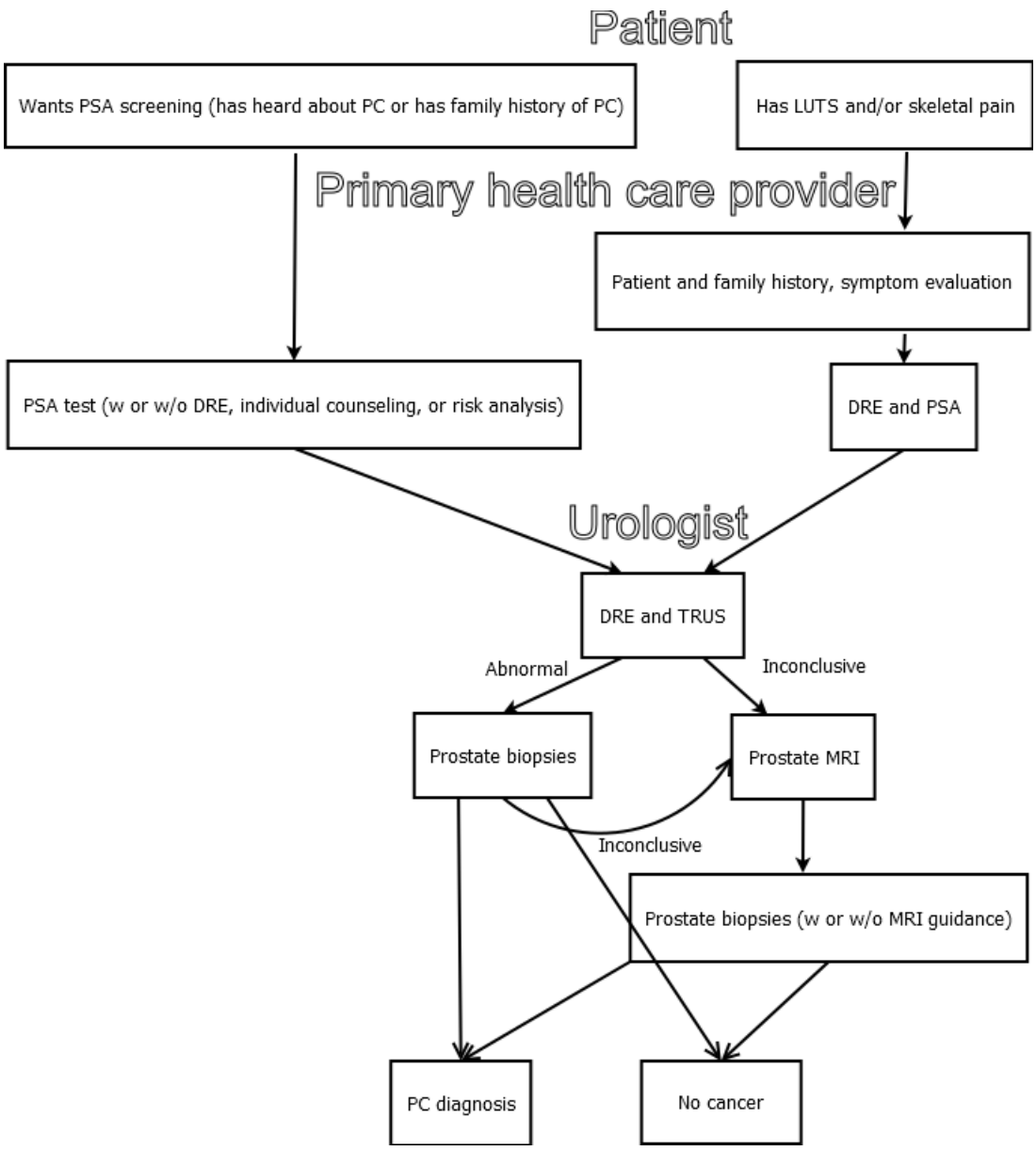


Figure 3 PSA-based and symptom-based detection of prostate cancer (PC). PSA=prostate-specific antigen, DRE=digital rectal examination, w=with, w/o=without, MRI=magnetic-resonance imaging, LUTS=lower urinary tract symptoms, TRUS=transrectal ultrasound

A first-line method of diagnosing PC is the PSA blood test. PSA is a kallikrein-like serine protease produced and excreted by the prostate. It is

reasonably specific to the prostate, and higher levels are associated with a greater likelihood of PC: at level < 1 ng/ml, the likelihood is 1%, at 2-4 ng/ml 15%, at 4-10 ng/ml 25%, and at > 10 ng/ml > 50% (The Finnish Medical Society Duodecim 2014). PSA's usefulness as a diagnostic test is, however, hampered by its susceptibility to increasing for benign reasons, such as benign prostatic hyperplasia, inflammation, ejaculation, and prostatic manipulations, among others. Elevated PSA is therefore not specific to PC. No safe cut-off values exist, below which no significant PC occurs. This fact was demonstrated in the Prostate Cancer Prevention Trial, where, in the control arm, even at a PSA level ≤ 0.5 ng/ml 6.6% of participants had PC, and 12.5% of those men had high-grade PC, defined as Gleason score ≥ 7 (Thompson et al. 2004). Reference PSA values are age-adjusted to account for the natural rise in PSA resulting from benign prostatic growth. Currently, the European Association of Urology (EAU) guidelines consider risk for PC to be elevated with a PSA > 1 ng/ml at age 40, and with a PSA > 2 ng/ml at 60 (Mottet et al. 2017).

Presently, no nation has a national screening program for PC, even though so-called opportunistic screening by PSA testing is quite prevalent in many Western countries. PSA testing appears, at first glance, to be an inexpensive and easy way to screen for PC, and the concept has therefore been tested globally in several large-scale studies. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial demonstrated no mortality benefit from organized PSA screening at 15 years (Pinsky et al. 2017), while the European Randomised study of Screening for Prostate Cancer found that, after 13 years, even though PSA screening reduces mortality from PC, the benefit comes at a cost of high over-detection and over-treatment (Schröder et al. 2014). PSA screening is thus not currently recommended at population level, although the synthesis of a 2014 Cochrane review and the American Urological Association guidelines state that PSA screening in men aged 55-69 may be considered after shared decision-making by the patient and doctor (Carter 2013, Hayes, Barry 2014). The EAU guidelines on PC also recommend an individualized risk-adapted strategy for early detection instead of systematic PSA-based screening. Early detection can be discussed with well-informed men who have a good performance status and at least 10-15 years' life expectancy, when they are considered as having elevated PC risk: age over 50, age over 45 with a family history of PC or African heritage, or a baseline PSA of > 1 ng/ml at 40 years or > 2 ng/ml at 60 (Mottet et al. 2017).

Because of PSA's poor specificity in predicting PC, several other blood and urine tests have been developed over the years with the aim of helping to select those men at increased risk for PC who thus are candidates for further diagnostic work-up. The ratio of free to total PSA (%fPSA) can be useful for men with a PSA between 4 and 10 ng/ml and negative digital rectal examination (DRE) (Mottet et al. 2017). PC was detected in 56% of such men at %fPSA < 0.10, but in only 8% with %fPSA > 0.25 (Catalona et al. 1998).

Reviews looking into the performance of urine-marker PCA3, a kallikrein panel called the 4K Score, and The Prostate Health Index, which incorporates

calculation of PSA, free PSA, and the [2]pro-PSA fraction, report that use of these tests would reduce unnecessary prostate biopsies and the diagnosis of insignificant PC (Bratt et al. 2015, Loeb et al. 2016). Currently, the widespread use of these tests is limited by their poor availability, high costs, and, in the case of the 4K Score, lack of FDA approval. The STHLM3 model, which includes a combination of plasma protein biomarkers and a panel of 232 single-nucleotide polymorphisms, combined with traditional PSA and clinical parameters, has been tested in a prospective setting in Sweden and seems to be a promising model for improving the specificity of PSA-based screening for PC (Grönberg et al. 2015). STHLM3, however, still lacks validation in non-Swedish populations.

2.3.2 PROSTATE BIOPSIES

2.3.2.1 Performing prostate biopsy

After DRE of the prostate and blood tests, the next step in the diagnostic work-up is taking prostate biopsies. Biopsies are essential for establishing cancer diagnosis and grade, but also aid in assessing the location and extent of the disease. Prostate biopsy is usually performed as an out-patient procedure, under local anesthesia, and most often via the transrectal route by a urologist. The procedure is performed with ultrasound (US) guidance, so in many countries the procedure may also be performed by a radiologist. US serves mainly for visualizing the prostate and its outlines and for guiding the biopsy needles. The resolution of US is rarely sufficient for visualizing PC, which means that standard prostate biopsies are obtained as systematic random biopsies. The most common biopsy scheme entails 12 cores from the peripheral prostate, from both sides: four from the bases, four from the mid-gland, and four from the prostatic apex (Gore et al. 2001) (Figure 4).

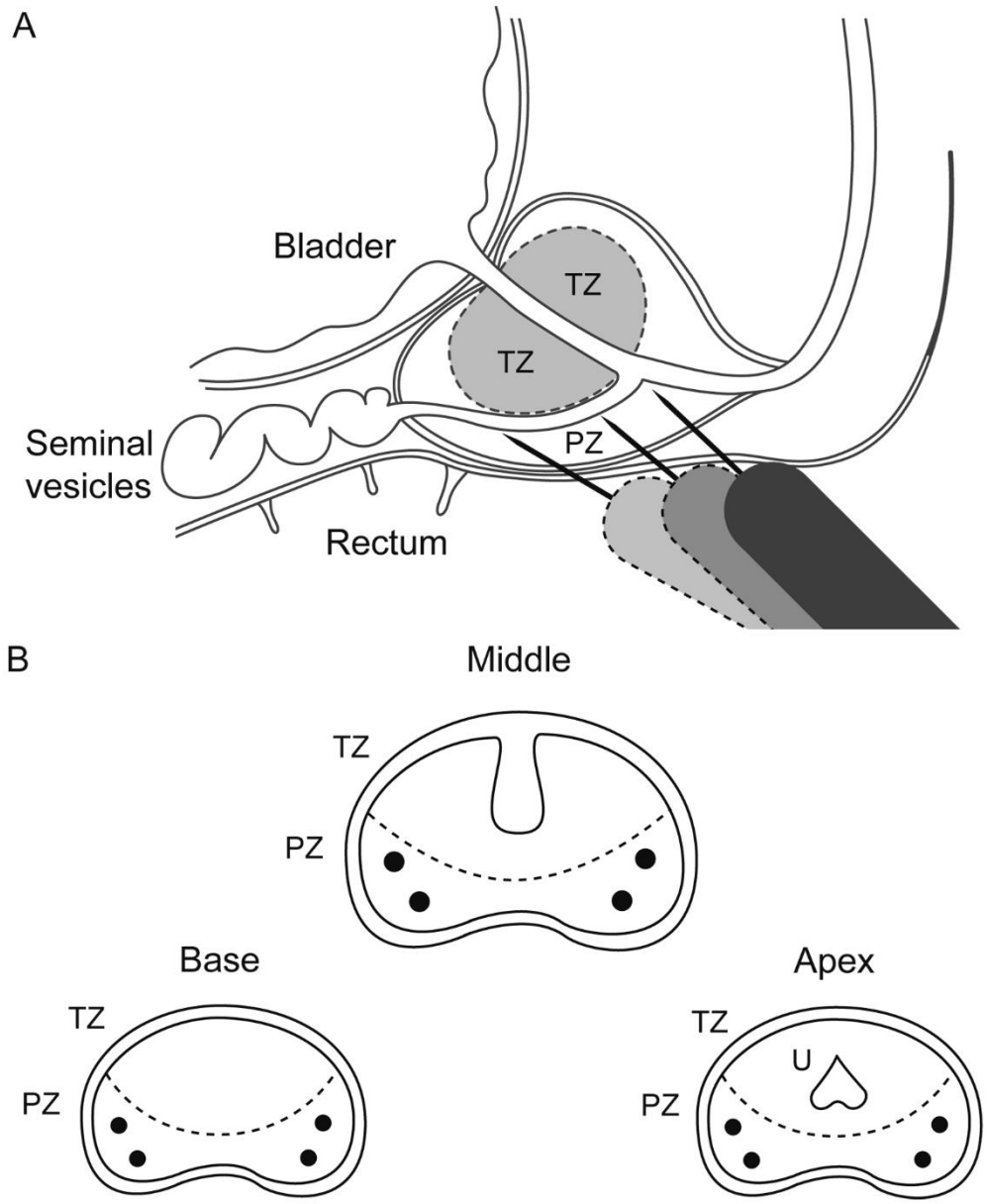


Figure 4 A. Taking prostate biopsies with transrectal ultrasound guidance. B. 12-core biopsy scheme, four biopsies each from the base, middle, and apex of the prostate. PZ=peripheral zone, TZ=transitional zone, U=urethra. (Illustration by Kristiina Tammisalo)

Sampling the prostate is an invasive procedure, with common side-effects. The most common adverse outcomes are hematuria, hematospermia, rectal bleeding, and pain, which are most often self-limiting and only rarely require further medical attention. The procedure can, however, also cause major harm to the patient, if he develops a major infectious complication, the most severe form of which is potentially life-threatening septicemia. The patient must be informed of the potential risks associated with the procedure before proceeding with prostate biopsies.

2.3.2.2 Gleason score and Grade grouping

Presently, the prevailing grading system is the tissue-architecture-based Gleason grading system (Gleason 1966) with major consensus modifications in 2005 (Epstein et al. 2005), 2010 (Epstein 2010), and 2014 (Epstein et al. 2016a). The modified grading system assigns the PC a Gleason score of 2 to 10, based on the prevalence of individual grade patterns. A new prognostic grade grouping system was launched in 2014 in a consensus meeting of the International Society of Urological Pathology. The new classification gives scores from 1-5, with Gleason patterns ≤ 3+3, 3+4, 4+3, 4+4/3+5/5+3, and 4+5/5+4/5+5 constituting grade groups 1, 2, 3, 4, and 5. This new grouping system aims to better reflect the different prognoses between the groups. It also aims to deemphasize the seriousness of Gleason score ≤ 6 cancers – grade group 1, on a scale of 1-5, as being easier for treating physicians and patients to accept as a low-risk disease, rather than Gleason score 6, on a scale of 2-10. Grade grouping also distinguishes subclasses in the most prevalent Gleason score 7 group, among other changes. This new grouping has been formally accepted by the World Health Organization in 2016 and for now, the Grade group should be reported in conjunction with the Gleason score (Epstein et al. 2016a).

2.3.2.3 Current 12-core biopsy technique

Before ultrasound (US) guidance became common, the first prostate biopsies were taken with only finger guidance, and with urologists taking as many cores as considered necessary. In their landmark study in 1989, Stamey and co-workers reported improved cancer detection rates by performing random systematic biopsies instead of biopsies exclusively directed at suspicious areas (Hodge et al. 1989). This approach, later dubbed the Stamey sextant protocol, involved sampling the prostate in a systematic fashion: one parasagittal core each from the base, middle, and apex of the prostate, from each lobe and with US guidance. The sextant protocol was later extended to include more laterally directed cores and gradually evolved into the current 12-core biopsy scheme that has been in use for practically the last two decades (Levine et al. 1998, Gore et al. 2001). The optimal number of cores needed to maximize cancer detection, with the procedure still being tolerable for the patient, has been studied extensively, with the 12-core scheme remaining an acceptable compromise (Eichler et al. 2006, De Laet et al. 2009, Ghafoori et al. 2013, Scattoni et al. 2014).

2.3.2.4 Detection of prostate cancer by random biopsies

Standard prostate biopsies have several well-known limitations (Figure 5).

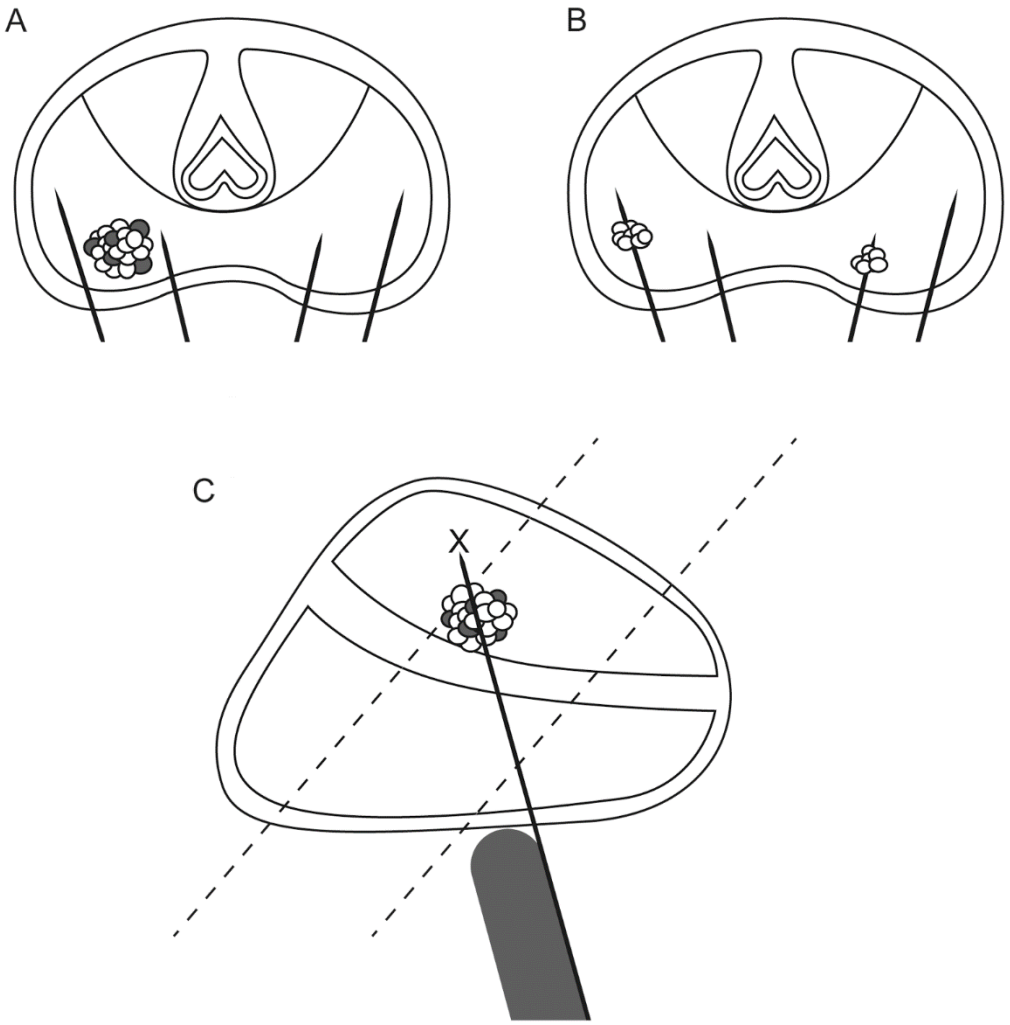


Figure 5 A. Random biopsies missing a significant tumor. B. Random biopsies detecting small, low-grade tumors. C. Inaccuracy in determining tumor location. Tumor assumed to be from the base of the prostate when in reality it is from the middle. (Illustrations by Kristiina Tammisalo)

As the biopsies randomly sample the entire prostate, the test may result in both underdiagnosis of clinically significant disease and overdiagnosis of indolent, clinically insignificant PC. Transrectal biopsies are also technically limited in estimating disease location. This has been demonstrated in many studies reporting the discordance in tumor location between biopsy and RP specimens (Schulte et al. 2008, De Laet et al. 2009, Iremashvili et al. 2012, Washington et al. 2012).

As a first-line test for detecting PC, transrectal random biopsies perform poorly. Initial biopsies may have detection rates of 28-70% (Meng et al. 2003, Presti Jr. 2003, de la Taille et al. 2003, Elabbady et al. 2006, Yuasa et al. 2008,

Serag et al. 2011, Zaytoun et al. 2011a, Aganovic et al. 2012). This wide range is due to heterogeneity in study cohorts and in biopsy indications. Consequently, after a first round of negative biopsies, if PC is still suspected, up to one-third of patients will have PC detected in repeat biopsies (Fleshner et al. 1997, Presti Jr. 2003, Scattoni et al. 2007, Yuasa et al. 2008, Campos-Fernandes et al. 2009, Zaytoun et al. 2011b). After a second round of biopsies, however, the detection rates, especially for clinically significant cancers, decrease markedly. If, after two rounds of negative biopsies, PC is still suspected, then a change in diagnostic strategy is therefore the general recommendation (Djavan et al. 2007, Zaytoun et al. 2011a).

In the situation of repeated negative prostate biopsies and persistent suspicion of PC, an intermediate step in the diagnostic work-up has traditionally been saturation biopsies, generally defined as obtaining > 20 cores. A transperineal approach to saturation biopsies is possible, but as it necessitates spinal anesthesia, it is thus more arduous. The advantage of the transperineal approach over the transrectal route, is, however, better access to the apex and anterior prostate. Saturation biopsies have become less popular with the advance of MRI targeting. Currently, the shift towards earlier incorporation of alternative diagnostic methods is strong, as an alternative to automatically repeating the biopsies. The EAU Prostate Cancer Guidelines recommend performing prostate MRI before repeat biopsies. The repeat biopsy procedure should then preferably include targeting of MRI-visible lesions in addition to systematic biopsies (Mottet et al. 2017).

Some limitations of traditional systematic prostate biopsies are inherent to the biopsy technique. The procedure's randomized nature and the inability to visualize tumors with US explain some of the sampling error. Large tumors, either exceptionally hypoechoic on US or palpable on DRE, can specifically be targeted, but otherwise the needles are placed in the tissue at random. The transrectal route also makes accessing the anterior prostate difficult (Bott et al. 2002). Sampling the prostatic apex requires angling the rectal probe and biopsy needle to a degree that is uncomfortable or even painful for the patient, leading to apical tumors' often being missed (Bolenz et al. 2009, Iremashvili et al. 2012). In primary biopsies, the peripheral zone, the area in which 68-85% of PC originates (McNeal et al. 1988, Stamey et al. 1998, Buyyounouski et al. 2017), should be targeted (Figure 6). This approach, however, frequently misses those tumors deriving from the transitional or central zones.

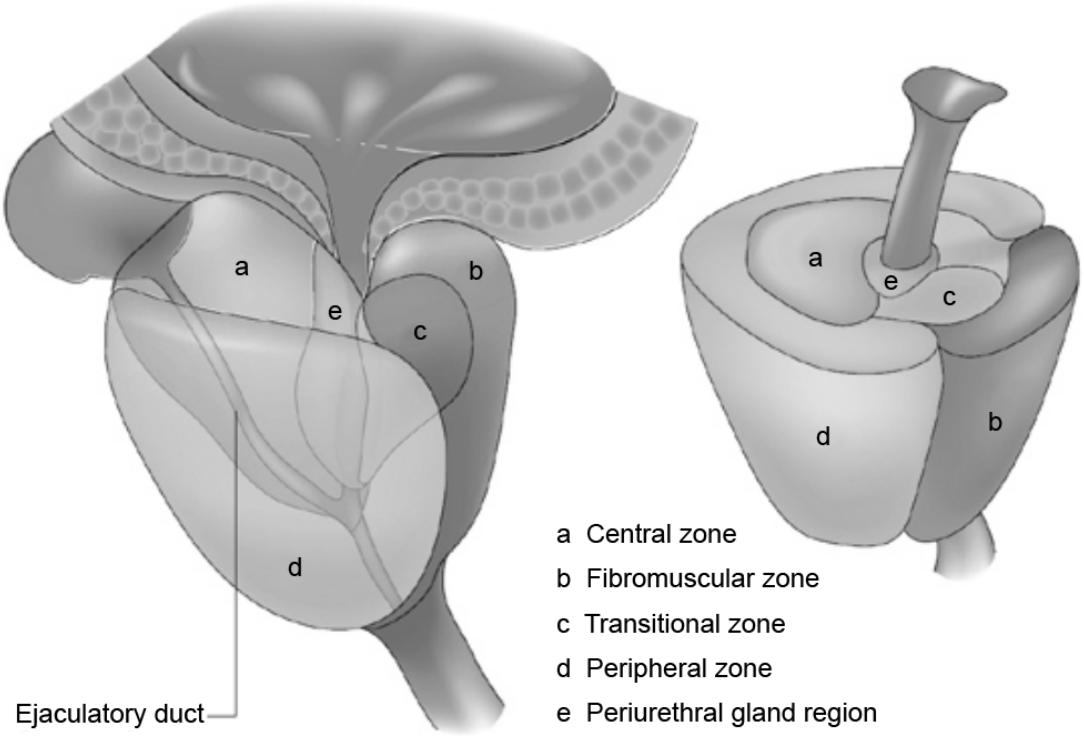


Figure 6 Zonal anatomy of the prostate. By some estimates, the peripheral zone harbors 80-85% of prostate cancer, the transitional zone 10-15%, and the central zone 5-10% (Buyyounouski et al. 2017). Figure reprinted with permission from Nature Publishing Group: *Nature Reviews Cancer*, 2007, Apr;7(4):256-69, De Marzo et al., "Inflammation in prostate cancer".

2.3.2.5 Treatment planning based on biopsies

Despite their known limitations, and outside of clinical study settings, transrectal systematic biopsies are still the first-line test by which most PC is diagnosed. Before prostate MRI and MRI-targeting, prostate biopsies were essential in planning the treatment of PC patients. The histopathological assessment of disease grade is essential in appropriately assessing the patient's risk group (Table 2).

Prostate biopsies may, however, perform less than ideally in evaluating the Gleason score. Accounts of mostly upgrading and also of downgrading of the Gleason score in comparisons between biopsies and RP specimens are numerous. Rates of upgrading of Gleason score at RP range from 14.8-46.6% (Elabbady et al. 2006, Reis et al. 2013, Dinh et al. 2015, Khoddami et al. 2016, Winters et al. 2016, Herlemann et al. 2017), with downgrading less frequent at 8.5-19.5% (Reis et al. 2013, Khoddami et al. 2016, Herlemann et al. 2017). This problem is in part due to differences in assigning the Gleason score for biopsies and RP specimens (Epstein et al. 2012) and in part to the biopsies' random and imperfect discovery of tumors.

Prostate biopsies may also underestimate tumor size and extent. This has mostly emerged from a situation of minimal cancer core involvement at diagnosis and subsequent faulty classification of patients as "low-risk"

(Johnstone et al. 2007). Biopsies have indicated the location and laterality of the disease inaccurately (Schulte et al. 2008, Abdollah et al. 2011, Pereira et al. 2014). Possible explanations are inaccurate needle placement by the urologist or errors in processing of the biopsy samples. A 12-core biopsy also yields approximately 0.1 g of prostatic tissue for analysis, which would amount to less than 1% of, for example, a moderate-size 50-gram prostate. Undersampling and missing of tumors is therefore unsurprising. These errors may lead to misinformed decisions in treatment planning, such as to perform a nerve-sparing RP on the side of the prostate harboring the significant and extensive disease.

Such inaccuracies involving prostate biopsies in determinination of disease grade, extent, and location can currently be somewhat remedied by prostate MRI. MRI can either confirm the findings or reveal significant tumors perhaps missed by biopsy.

2.3.2.6 The index tumor and focal therapy (FT)

Precise and accurate knowledge of tumor characteristics, based on biopsies and on MRI applications, is essential in considering FT of PC (Lecornet et al. 2010, Abdollah et al. 2011, Tseng et al. 2011, Gallina et al. 2012, Washington et al. 2012, Kanthabalan, Emberton & Ahmed 2014). FT aims to target all clinically significant tumors in the prostate while leaving the rest of the gland intact. Among various ways to define PC as "clinically significant," the prevailing definition is a tumor at least 0.5 ml in volume, a Gleason 4 pattern, or non-organ-confined disease at RP (Stamey et al. 1993, Kanthabalan, Emberton & Ahmed 2014, Kryvenko, Epstein 2016). In 1994, Epstein and co-workers proposed pretreatment criteria predictive of significant disease: a PSA density of ≥ 0.15 ng/ml/g, Gleason grade 4 in biopsies, ≥ 3 biopsy cores showing cancer, and ≥ 50% of any biopsy core length with cancer (Epstein et al. 1994). These Epstein criteria became widely validated and are still in use (Ploussard et al. 2011).

The concept of an index tumor often arises regarding FT feasibility. Autopsy studies and analyses of RP specimens have revealed that PC is most often a multifocal disease, which is the rationale supporting whole-gland radical therapies. The tumors can also be heterogenous in their degree of dedifferentiation, and one hypothesis is that there always exists one primary tumor carrying the highest potential for spread and metastasis (Liu et al. 2009, Karavitakis et al. 2011, Boyd et al. 2012, Karavitakis et al. 2012, Singh et al. 2013), the index tumor. Currently, the prevailing practice is to designate the largest tumor as the index tumor (Bott et al. 2010, Mouraviev et al. 2011, Kozminski et al. 2014), although the index tumor may in fact be the most dedifferentiated one or the one causing extraprostatic extension. Most often the largest tumor is the one that also exhibits these unfavorable characteristics (Karavitakis et al. 2011, Huang et al. 2014a).

2.3.3 PROSTATE MRI

2.3.3.1 Performing and reporting of prostate MRI

MRI has recently gained substantial attention in the diagnostic work-up of PC. Although first developed in the 1980's, prostate MRI became a routine practice only when functional imaging was developed, offering information on prostate tissue physiology as well as anatomy. The current gold standard in prostate imaging is multiparametric MRI (mpMRI). The European Society of Urogenital Radiology published guidelines in 2011 regarding the technical performance of mpMRI and proposed a structured reporting system to help minimize variation in interpreting the images and reporting the findings (Barentsz et al. 2011). This Prostate Imaging - Reporting and Data System (PI-RADS) was updated in 2015 into the current reporting system: PI-RADS version 2 (Weinreb et al. 2016).

In mpMRI, traditional T1- and T2-imaging sequences are complemented with dynamic contrast enhancement and diffusion-weighted imaging (DWI), obtained at different diffusion values, i.e. b values. DW images are further processed to create apparent-diffusion coefficient (ADC) maps which reveal the tissue enhancement of suspicious foci. MRI thus offers good soft-tissue resolution without harmful radiation to the patient. Highly aggressive PC is densely packed with cells, which restricts the movement of water molecules at cellular level. This gives the tissue a distinct bright appearance on DWI. Conversely, low-grade cancer may resemble the surrounding benign tissue, making it more challenging to detect. ADC maps, derived from DWI, show malignant lesions as dark areas. As ADC is a mathematical parameter, it has a numeric value. Lower values have been shown to correlate with higher-grade cancer and, conversely, higher values with more benign tissue (Woodfield et al. 2010). This information can even serve, in highly specialized PC-MRI centers, to estimate possible Gleason grades of visualized tumors, but thus far no generally accepted cut-off values allow differentiation between tumor grades in ADC maps (deSouza et al. 2008, Kim et al. 2016, Shaish et al. 2017, Tamada et al. 2017, Wu et al. 2017).

The popularity of prostate MRI can be explained by its ability especially to detect clinically significant PC. A 2015 review of 12 studies reported a fairly large range in the positive and negative predictive values (PPV and NPV) of mpMRI for this purpose: 34-93% and 63-98% (Fütterer et al. 2015). A more extensive and recent review appearing in 2017 covered 48 studies, including a meta-analysis of 8; it reported a median NPV of 88.1% for clinically significant PC at a prevalence of 30%, although when prevalence rose to 60%, NPV decreased to 67% (Moldovan et al. 2017). A recent prospective study found MRI to have a PPV of 65% for detection of any Gleason score 3+4 PC, at a prevalence of 53%, and an NPV of 76% (Ahmed et al. 2017). In sum, the NPV of MRI is consistently higher than the PPV, making MRI a good potential tool for ruling out clinically significant disease.

2.3.3.2 MRI-targeted biopsy

Due to MRI's ability to locate suspicious areas in the prostate, and its higher sensitivity in detecting high-grade versus low-grade cancers (Delongchamps et al. 2013, Pokorny et al. 2014, Schoots et al. 2015b, Siddiqui et al. 2016), MRI-guided biopsies are becoming exceedingly popular. MRI guidance or -targeting refers to the practice of using MRI-provided information as to the location of a suspicious area, in order subsequently to target that specific area. MRI guidance can be implemented in the biopsy procedure in three ways: 1) directly by the urologist by what is called cognitive fusion, 2) by performing the biopsy procedure with simultaneous MR imaging, an "in-bore" procedure, or 3) by specific software that fuses the information from the MRI with real-time US imaging. MRI targeting generally entails taking fewer biopsies than in the 12-core standard procedure. This is expected to reduce biopsy-related adverse effects, although evidence to support this is as yet limited (Overduin et al. 2013, Egbers et al. 2014).

Prostate MRI can aid in decision-making in the case of negative prostate biopsies but persistant suspicion of PC. Performing MRI in this setting would possibly reveal tumors missed by random biopsies, often anteriorly located tumors, and aid in targeting in subsequent biopsy settings. A negative MRI could also help in the decision not to proceed to repeat biopsies (Hansen et al. 2016, Thompson et al. 2016, De Visschere et al. 2016). Cancer-detection rates have been 22-52% as a result of MRI-targeted biopsies in this setting (Sonn et al. 2014, Mendhiratta et al. 2015, Salami et al. 2015). The National Comprehensive Cancer Network (NCCN) and EAU both recommend in their clinical guidelines considering mpMRI in men with previously negative biopsies and persistent suspicion of PC (Mohler et al. 2016, Mottet et al. 2017).

2.3.3.3 Prebiopsy MRI

One promising approach to improving diagnostic accuracy is to precede prostate biopsies with first-line MR imaging, in which the decision to advance to prostate biopsies is based on MRI results. If no tumors are visible, then biopsies may be unnecessary, but if a suspicious lesion is evident, then the biopsy procedure may, if desired, be performed with MRI guidance. Recent reports from prospective studies find that MRI, used as a triage test before the first prostate biopsy, can reduce unnecessary biopsies by 24-27% (Ahmed et al. 2017, Jambor et al. 2017). A prebiopsy MRI, followed by targeted biopsies, was also performed as a substudy of the Göteborg Randomised Screening Trial, with promising results (Grenabo Bergdahl et al. 2016). This has prompted a new prospective trial, the Göteborg-2, which will explore the role of MRI in screening for PC. Preceding the biopsies with MRI–outside of study settings–is currently rare in clinical practice, but is slowly becoming more common. For now, this practice is restricted by the additional costs and limited

availability of both MRI and radiological expertise in interpreting prostate MRI outside of PC-referral centers.

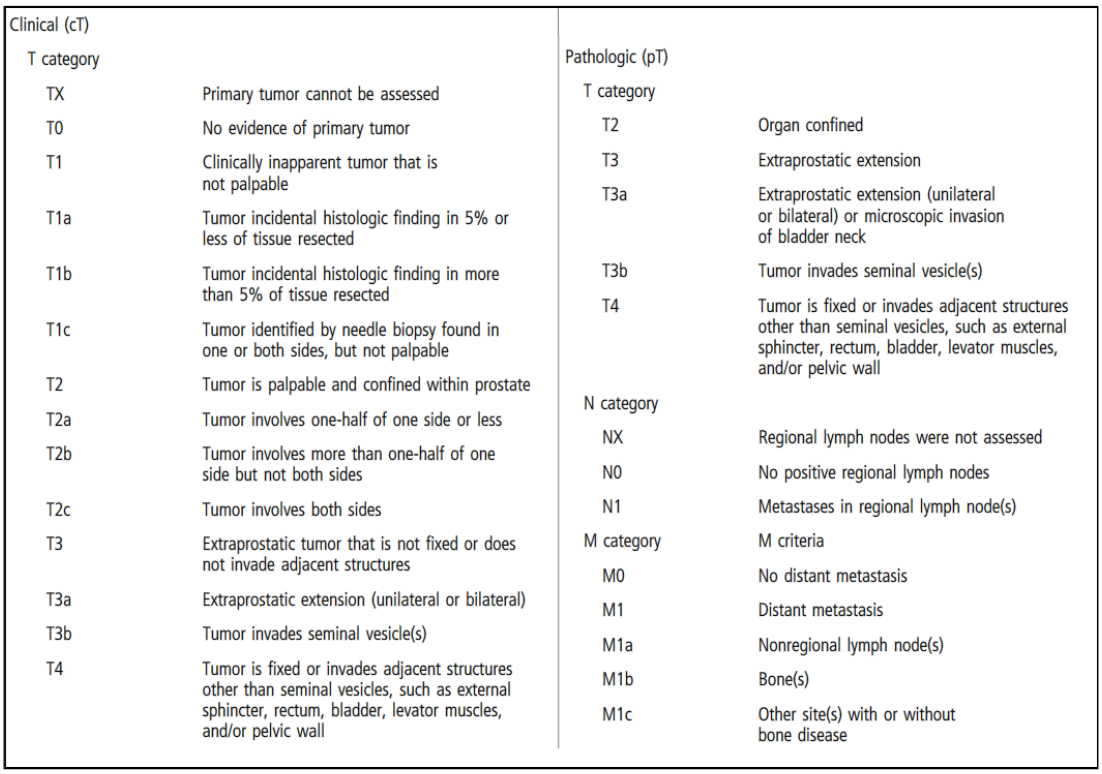
There exist, however, some studies suggesting a limited benefit from this approach specifically in cohorts of men with no prior biopsies (Siddiqui et al. 2015, Baco et al. 2016, Tonttila et al. 2016), in which cancer detection rates between targeted biopsies and systematic random biopsies were comparable. This is presumably because the prevalence of previously undetected cancers in this population is higher than in previously biopsied men. This is also highlighted by the lower median NPV of MRI and higher prevalence of PC in patients with no previous biopsies—69.9% with a prevalence of 51.4%—versus an NPV of 82.6% with a PC prevalence of 42% for men who have previously had a negative biopsy (Moldovan et al. 2017). These findings, considered together, suggest that performing MRI when suspecting PC may be more beneficial only after the first round of negative random biopsies, as the EAU and NCCN guidelines on PC currently recommend (Mohler et al. 2016, Mottet et al. 2017).

Implementing prebiopsy MRI in the diagnostic pathway of PC seems, however, promising, with several trials underway and many reports sure to be forthcoming in the following years. Reports increasingly suggest it also to be a cost-effective strategy (de Rooij et al. 2014, Cerantola et al. 2016, Pahwa et al. 2017, Venderink et al. 2017).

2.4 PROSTATE CANCER TREATMENT

2.4.1 STAGING AND RISK STRATIFICATION

PC staging is based on the Tumour Node Metastasis (TNM) Classification (Figure 7, Table 1).



Clinical (cT)	
T category	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Pathologic (pT)	
T category	
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
N category	
NX	Regional lymph nodes were not assessed
N0	No positive regional lymph nodes
N1	Metastases in regional lymph node(s)
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Figure 7 The American Joint Committee on Cancer Tumour Node Metastasis criteria for prostate cancer. Reprinted by permission from John Wiley and Sons: *CA: Cancer Journal for Clinicians*, Feb 21, 2017, Buyyounouski *et al.*, "Prostate cancer – major changes in the American Joint Committee on Cancer eight edition cancer staging manual".

Table 1. Staging of prostate cancer based on Tumour (T) Node (N) Metastasis (M) classification (Data from Brierley et al. 2016).

Stage I	T1-T2a	N0	M0
Stage II	T2b-T2c	N0	M0
Stage III	T3-T4	N0	M0
Stage IV	Any T	N1	M0
	Any T	Any N	M1

PC is a very heterogenous disease with great variation in its clinical course between the opposite ends of the disease spectrum (Lu-Yao et al. 2009, Rider et al. 2013). To better characterize PC and to guide the treatment planning, PC is divided into differing risk groups. Several risk stratifications have been created, but the most commonly used–the D'Amico classification–hails from 1998 (D'Amico et al. 1998). It has since been validated in prospective cohorts

and serves, essentially unchanged, as a basis for contemporary risk group classifications (Mohler et al. 2016, Mottet et al. 2017) (Table 2).

Table 2. Risk stratifications in prostate cancer (Data from D'Amico et al. 1998, Mohler et al. 2016, and Mottet et al. 2017)

Risk group	D'Amico Classification (1998)	NCCN Clinical Practice Guidelines in Oncology (2016)	EAU Clinical Guidelines (2017)
Very low		cT1, N0, M0 **and** GS ≤ 6 **and** PSA < 10 ng/ml **and** cancer in < 3 biopsy cores **and** ≤ 50% cancer in any biopsy core **and** PSA-density < 0.15 ng/ml/g	
Low	cT1-T2a, N0, M0 **and** GS ≤ 6 **and** PSA ≤ 10 ng/ml	cT1-T2a, N0, M0 **and** GS ≤ 6 **and** PSA < 10 ng/ml	cT1-T2a, N0, M0 **and** GS ≤ 6 **or** GG = 1 **and** PSA < 10 ng/ml
Intermediate	cT2b **or** GS=7 **or** PSA 10-20 ng/ml	cT2b-T2c **or** GS = 7 **or** PSA 10-20 ng/ml	cT2b **or** GS = 7 **or** GG 2 or 3 **or** PSA 10-20 ng/ml
High	cT2c or higher **or** GS ≥ 8 **or** PSA > 20 ng/ml	cT3a **or** GS 8-10 **or** PSA > 20 ng/ml	cT2c or higher **or** GS ≥ 8 **or** GG 4 or 5 **or** PSA > 20 ng/ml
Very high		cT3b-T4 **or** GS 5+4, 5+5 **or** > 4 biopsy cores with GS 8-10	
NCCN=National Comprehensive Cancer Network, EAU=European Association of Urology, cT=clinical tumor stage, N=node, M=metastasis, GS=Gleason score, PSA=prostate-specific antigen, GG=grade group			

The risk groups reflect an individual patient's probability of biochemical disease recurrence, meaning detectable and rising post-treatment PSA levels, after radical therapies for PC and, as such, can serve as a guide in choosing appropriately effective treatments. The available treatment options for PC also depend on disease stage (Table 1).

Stages I-III, i.e. localized and locally advanced diseases without nodal or distant metastases, are generally treated actively. The appropriate treatment choice is based on the risk group, i.e. low, intermediate, or high (Table 2).

2.4.2 ACTIVE SURVEILLANCE (AS)

Recent decades have seen a shift towards PC's being diagnosed at progressively earlier stages. Treating all asymptomatic early-stage cancers aggressively with radical therapies would constitute overtreatment, because only some cancers would ever progress to cause harm during an individual

patient's lifetime. This overtreatment would also lead to excessive harm since curative cancer therapies inherently carry a risk for adverse side-effects. It is these two factors–potential overtreatment and unnecessary harmful effects–that led to the introduction of AS in the 1990's (Epstein et al. 1994), and its adoption as the primary treatment for low-risk PC (Cooperberg et al. 2011). Immediate curative treatment has also failed to offer overall or disease-specific mortality benefits in low-risk PC (Wilt et al. 2012, Hamdy et al. 2016).

AS aims at surveillance without the chance of missing the window of curability. Eligibility criteria for AS differ slightly between guidelines, but are most often essentially the Epstein criteria for insignificant disease: PSA-density of < 0.15 ng/ml/g, Gleason score ≤ 6 in biopsies, a maximum of 2 biopsy cores involving cancer, and < 50% of any biopsy core involving cancer (Epstein et al. 1994). Patients must also be sufficiently young and fit to be eligible for possible curative treatment if their disease progresses. In an autopsy study by Zlotta and co-workers (2013), 320 prostates were evaluated from men aged 20-89 who died without any history of PC. A significant proportion of all of these men (35.6%) had malignant lesions in their prostates, and although the majority of these cancers were Gleason score 6 (55.6%), another 25.6% harbored Gleason score 7 disease. This finding supports the notion that some men with low-volume Gleason 3+4 PC might be candidates for AS. However, one must bear in mind that Gleason pattern 4 clearly indicates increased risk for progression, also in an AS setting (Dall'Era et al. 2017).

2.4.2.1 Monitoring during AS

Patients on AS are carefully monitored, usually by a predetermined surveillance protocol. Serial PSA measurements are integral to all forms of PC treatments and monitoring, most crucially in AS. Whereas a rising PSA level is indicative of tumor growth, such a rise can also result from benign causes such as prostate enlargement and inflammation, making it a somewhat unreliable and unspecific PC-monitoring tool on its own. Other markers, ones based on PSA measurements, have been developed: free PSA, meaning the amount of noncomplexed PSA in the bloodstream (Lilja 1993); %fPSA, the percentage of total PSA levels amounting to free PSA (Catalona et al. 1995); PSA density, the ratio of PSA level to estimated prostate volume (Benson et al. 1992); and PSA and %fPSA kinetics, the rates at which PSA and %fPSA change in serial measurements (Carter et al. 1992). All these PSA-derived parameters have been utilized in the decision whether to continue AS or offer curative treatment, although with conflicting findings (Ross et al. 2010, Iremashvili et al. 2013, Vasarainen et al. 2015, Iremashvili et al. 2016). PSA-doubling time and PSA density are, however, still integral elements of the Prostate Cancer Research International Active Surveillance (PRIAS) protocol (Bokhorst et al. 2016b).

Repeat prostate biopsies are also an integral part of AS regimens. Some AS programs mandate immediate confirmatory biopsies to ensure the diagnosis of low-grade and low-volume disease before initiation of AS, whereas many require repeat biopsies after one year of AS. Thereafter, biopsies are generally repeated at predetermined time-points, usually at 2- to 4-year intervals. The findings of repeat biopsies guide the decision to either continue with AS or progress to definitive treatment. All AS protocols have specified criteria on what findings should trigger curative treatment (Bruinsma et al. 2016). Compared to PSA measurements, DRE, and prostate MRI, biopsies are invasive procedures, and as such, are uncomfortable. If patients refuse to take part in recommended repeat biopsies, the patency and safety of AS may be compromised (Bokhorst et al. 2015, 2016a), unless the lack of histological confirmation is compensated for by other means of follow-up, for example by prostate MRI or biomarkers.

Some patients become anxious over knowing that they are living with a malignant disease and opt for immediate radical treatment, either RP or RT, even in the absence of signs of progression. Many patients, however, manage to continue AS for many years without its markedly affecting their quality of life (Vasarainen et al. 2012, Pham et al. 2016, Venderbos et al. 2017).

2.4.2.2 Prospective AS studies

AS is extensively studied in several high-volume cancer centers (Adamy et al. 2011, Bul et al. 2013, Selvadurai et al. 2013, Klotz et al. 2015, Tosoian et al. 2015, Welty et al. 2015, Godtman et al. 2016). One multi-center prospective study is the PRIAS trial, launched in 2006 at the Erasmus University Medical Center in Rotterdam, Netherlands (van den Bergh et al. 2007). It has evolved into the largest prospective AS trial, with over 150 participating centers from 18 countries (Bokhorst et al. 2016b). The latter study was initially launched at eight centers, one of which being Helsinki University Hospital, which is the second largest participating center to date. Figure 8 presents the follow-up criteria for the PRIAS study, updated in 2015 (Bokhorst et al. 2015).

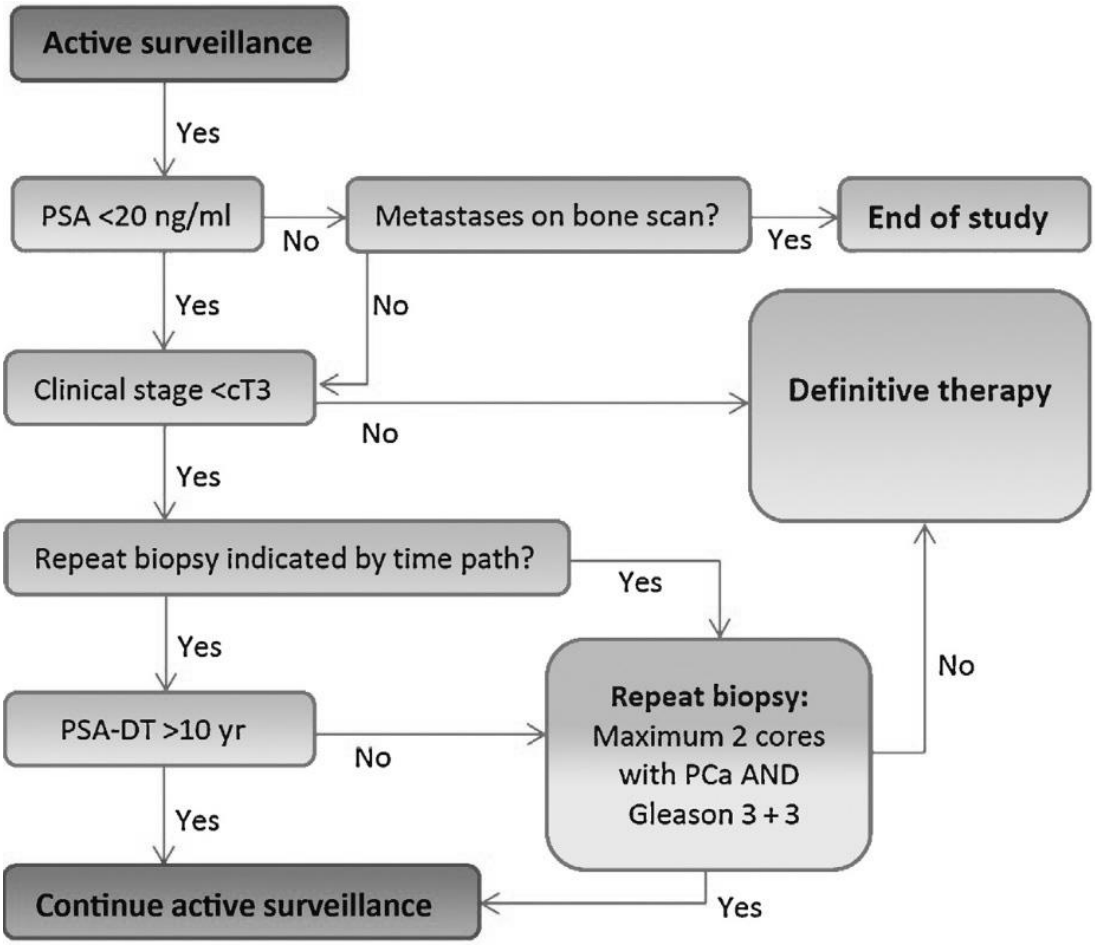


Figure 8 Outline of the follow-up in the Prostate Cancer Research International Active Surveillance study. PSA=prostate-specific antigen, PSA-DT=PSA-doubling tiome, PCa=prostate cancer. Figure reprinted by permission from Elsevier: *European Urology*, 2015 Nov;68(5):814-21, Bokhorst et al., "Compliance Rates with the Prostate Cancer Research International Active Surveillance (PRIAS) Protocol and Disease Reclassification in Noncompliers".

2.4.3 CURATIVE THERAPIES

2.4.3.1 Radical prostatectomy (RP)

RP is a first-line treatment option in intermediate- or high-risk localized PC (Bill-Axelson et al. 2014). RP entails the surgical removal of the entire prostate gland and seminal vesicles. This procedure can be complemented with a lymphadenectomy when more accurate staging is deemed necessary or when a suspicion exists of lymph node involvement (Gandaglia et al. 2017, Nguyen et al. 2017). The operation can be performed either as a conventional open procedure or laparoscopically, with or without 3D technique or robot assistance. RP requires the patient to be sufficiently fit for general anesthesia and major surgery. In high-risk disease, RP with lymphadenectomy is the first-line choice, but the more aggressive the disease, the more likely it is that RP

needs later to be complemented with adjuvant radiotherapy, leading to a so-called multimodal treatment approach (Daly et al. 2011, Mottet et al. 2017). Reported rates of biochemical disease recurrence after RP range from 20 to 50% (Novara et al. 2012, Meurs et al. 2013, Lee et al. 2015).

In intermediate- and high-risk PC, RP is beneficial in that it reduces disease-specific mortality and development of metastases (Wilt et al. 2012, Bill-Axelson et al. 2014), even offering overall-survival benefit (Bill-Axelson et al. 2014) compared to no intervention. These reductions have been demonstrated in two large prospective trials where patients with localized, clinically T1-T2, disease were randomized to either RP or to observation: the Scandinavian Prostate Cancer Group (SPCG)-4 trial (Bill-Axelson 2014) and the Prostate Cancer Intervention versus Observation Trial (PIVOT) (Wilt et al. 2012).

The SPCG-4 trial recruited patients between 1989 and 1999 in Sweden, Finland, and Iceland. During its recruitment period, in Nordic countries, PSA testing was less prevalent than it is today. A large proportion of patients were therefore diagnosed with PC on clinical grounds, with 40% of patients being diagnosed with symptomatic disease. The SPCG-4 study revealed RP as offering significant reductions—compared to those from solely observation—in overall mortality, disease-specific mortality, and development of metastases when all patients were pooled. This included an especially pronounced benefit for patients under 65 and for those with intermediate-risk disease (Bill-Axelson et al. 2014).

Findings from the PIVOT were more modest (Wilt et al. 2012). The patient cohorts in PIVOT and SPCG-4 were similar in many respects: PSA levels were < 10 ng/ml for 65% vs. 50% of patients, and biopsy Gleason scores were ≤ 6 for 70% vs. 60%. The PIVOT patients were, however, recruited in the USA between 1994 and 2002, after PSA testing had become common and after the peak years of PC diagnoses in the USA. Of these patients, 50% had non-palpable disease at diagnosis, compared to only 12% of SPCG-4 patients. This demonstrates how patients in the PSA era are diagnosed with PC at an earlier stage than before PSA testing, exemplifying lead-time bias. The PIVOT trial detected the potential benefit of RP versus observation only in subgroups of patients with PSA > 10 ng/ml and intermediate- to high-risk disease based on a post-hoc analysis (Wilt et al. 2012).

More recently, the Prostate Testing for Cancer and Treatment (ProtecT) trial from the UK—a trial comparing AS, RP, and RT for screen-detected localized PC—demonstrated no survival benefit from radical therapies compared to that of AS (Hamdy et al. 2016). Development of metastases was, however, rarer for patients receiving radical therapies; RP and RT, than for those on AS. This highlights the importance of proper patient selection for radical therapies: considering that these patients were aged 50-69 at recruitment, this reduction in disease progression will, during prolonged follow-up, likely translate into improved survival.

2.4.3.2 Predicting outcomes after RP

Assessing the long-term outcomes of RP objectively can be difficult because of variations between studies in reporting their results. Outcomes most often reported are biochemical recurrence, disease-specific mortality, or overall mortality, or, conversely, survival without these events. Need for secondary therapies, or disease progression or metastases after RP are also possible study endpoints. Depending on the endpoint of interest, outcomes also vary greatly between patient subgroups, with some groups reporting on said clinical outcomes for only low-risk or high-risk PC, for patients younger or older than 65, for different clinical or pathological disease stages, or for such variables as positive or negative surgical margins. Obtaining tangible estimates of the results of RP for general patient populations is therefore challenging.

Currently, patients are stratified into risk groups by their TNM stage, PSA, and Gleason scores (Table 2). Although intended for estimating the risk for disease recurrence after radical therapies, this risk stratification falls short. This holds especially true for the former Gleason-score 7 population, where patients' outcomes have varied markedly. The new grade group system aims to improve risk stratification especially for this population (Epstein et al. 2016a). The predictive performance of the new grade groups lacks validation from prospective contemporary cohorts but has been validated in retrospective studies (Epstein et al. 2016b, Spratt et al. 2016). The new grade grouping demonstrated, among other findings, marked differences in biochemical-recurrence-free survival rates between Gleason score 3+4 and 4+3 cancers, especially after RP, differences evident with stratifications made from both pre-RP biopsies and RP specimens (Epstein et al. 2016b) (Figure 9). This five-tier stratification correlated with cancer-specific mortality, not just with biochemical recurrence, in contemporary SEER registry data from 2006-2012 (He et al. 2017). The new grade grouping–however promising–is only part of the solution, as many parameters other than biopsy Gleason scores must be considered prior to decisions on appropriate treatment.

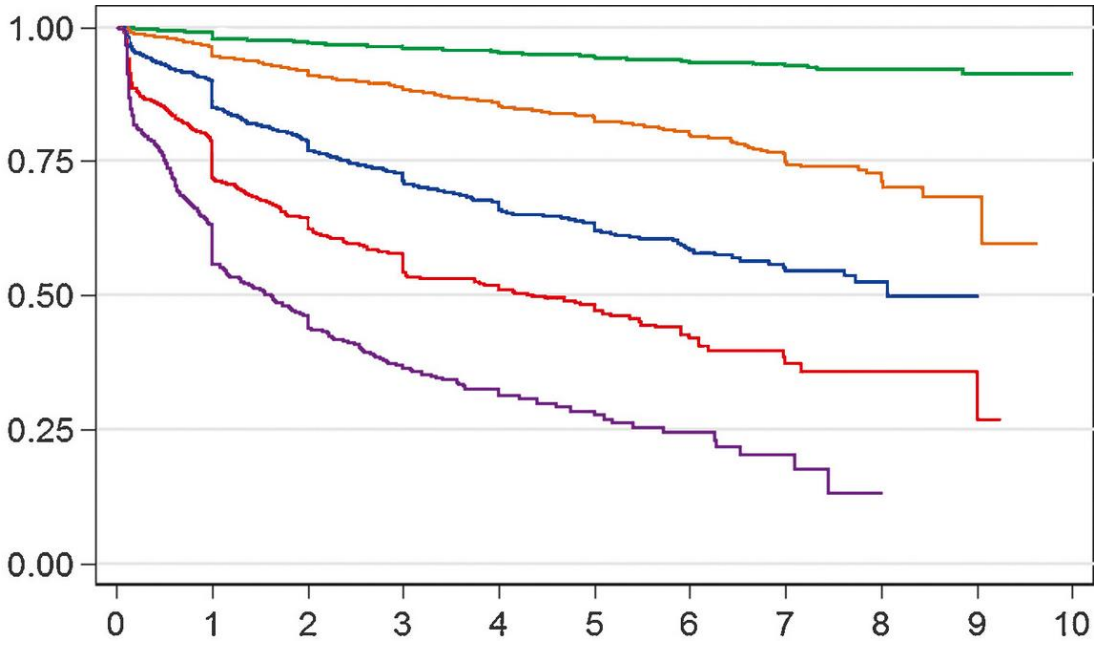


Figure 9 Probability of survival without biochemical disease recurrence in the years following radical prostatectomy (RP), stratified by Grade groups (GG) from pre-RP biopsies. Green: Gleason score (GS) ≤6/GG1. Orange: GS 3+4/GG 2. Blue: GS 4+3/GG 3. Red: GS 8/GG 4. Purple: GS ≥9/GG 5. Figure reprinted by permission from Elsevier: *European Urology*, 2016 Mar;69(3):428-35, Epstein et al., "A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score".

Several nomograms and risk-assesment tools for predicting the clinical outcome of PC patients after radical therapies have emerged. A literature search in 2008 discovered over 100 prediction tools (Shariat et al. 2008), and many more have since been developed. Some tools are designed for the pre-treatment setting (Kattan et al. 1998, D'Amico et al. 1999, Cooperberg et al. 2005, Stephenson et al. 2006), and some are intended for estimating outcomes after radical therapies (D'Amico et al. 1998, Moul et al. 2001, Roberts et al. 2001, Stephenson et al. 2005, Schroeck et al. 2008, Cooperberg, Hilton & Carroll 2011). Nomograms have also been designed for use upon the event of any biochemical recurrence after radical therapies (Abdollah et al. 2013, Brockman et al. 2015, Dell'Oglio et al. 2016). For nomograms to be of definitive value in the clinical setting requires their being externally validated in the separate patient cohorts from which they were developed, with sufficiently long follow-up, to accurately predict meaningful clinical end-points such as PC mortality. They also must be easy to use and interpret (Nguyen et al. 2009, Lughezzani et al. 2010, Teeter et al. 2013, Boehm et al. 2016, Jaderling et al. 2016).

For the postoperative prediction of PC-specific mortality, the CAPRA-S nomogram (Cooperberg, Hilton & Carroll 2011) appears to be the most robust, with its prognostic performance having been externally validated in several RP cohorts on several continents (Seong et al. 2013, Punnen et al. 2014, Seo et al.

2014, Tilki et al. 2015) and even in one radiation-therapy cohort (Zimmermann et al. 2016). Recently, MRI-derived parameters have been added to existing nomograms in an attempt to increase their predictive power (Morlacco et al. 2017, Zhang et al. 2017).

2.4.3.3 Radiation therapy (RT)

RT, also a treatment option with curative intent for intermediate- or high-risk PC, entails radiating the entire prostate gland, effectively killing the cancer but leaving the prostate in situ. RT is the preferred treatment in intermediate- or high-risk clinically T3 PC, because no data exist from randomized phase III trials for surgery in T3 disease, whereas several trials for RT, when supplemented with hormonal therapy, have been published in this setting (Widmark et al. 2009, Mottet et al. 2012). Analysis of data provided by the Surveillance, Epidemiology, and End Results (SEER) registry—a cancer registry of the National Cancer Institute in the USA, which covers approximately 28% of the US population—revealed that for 42 403 men diagnosed with localized PC in 2010, the proportion receiving RT as a form of local treatment rose along with ascending NCCN risk group. Of men with high-risk disease, 43% were treated with RT and 31% with RP, and the corresponding figures were 38% and 45% for men with intermediate-risk disease (Mahmood et al. 2014). A study from 2015, looking at 13 803 men who received either RP, RT, or brachytherapy at two American institutes, 1995-2008, also observed that men receiving RT had more adverse disease characteristics, such as higher PSA, higher-grade cancers, and more advanced clinical stage than did those receiving RP (Lee et al. 2015).

RT can be performed either as external-beam radiotherapy, with daily administration spanning several weeks, or as high-dose-rate brachytherapy delivered directly into the prostatic tissue generally in one to four sessions. Low-dose-rate brachytherapy—also a form of RT—is recommended mainly for "low- and favorable intermediate-risk PC" (Mottet et al. 2017), where radical therapies are generally not encouraged. Low-dose-rate brachytherapy is therefore not commonly practiced.

External-beam radiotherapy and high-dose-rate brachytherapy both customarily require neoadjuvant hormonal therapy in the 3 to 6 preceding months. In the case of high-risk PC the hormonal therapy is typically continued for 2 to 3 years post-treatment, to lower risk for disease recurrence (Bolla et al. 2009, 2010, Mottet et al. 2012). Biochemical-disease-recurrence rates after RT have generally been reported to be 20-30% (Kupelian et al. 2002, Lee et al. 2015).

A 2016 meta-analysis of 19 observational studies comparing RT and RP for treating localized PC found RT to associate with an increased risk of overall and PC-specific mortality (Wallis et al. 2016). This should, however, be interpreted with consideration for potential bias arising from: 1) residual confounding, which stems from RT's being, compared to RP, more often

offered to older patients with more co-morbidities, and 2) different rates of salvage therapies, because RP is often followed by RT after disease recurrence, whereas if PC recurs after RT, surgery is seldom performed. The long-awaited 10-year results of the ProtecT trial revealed no survival differences when patients were randomized to receive either RT or RP (Hamdy et al. 2016).

2.4.4 OTHER THERAPIES

2.4.4.1 Focal therapies

The increasing detection of PC cases around the world, more often at earlier stages, has given rise to a novel treatment form, focal therapy (FT). FT entails treating only the malignant lesion in the prostate while leaving the rest of the gland intact. This approach aims to confer less treatment-related harm than do whole-gland therapies while providing acceptable cancer control. The energy that destroys the cancer can be delivered into the prostate focally by a wide selection of techniques: high-intensity focused ultrasound, radiofrequency ablation, and cryotherapy, among others. The targeting of the tumor is most often carried out with MRI. FT is advertised as a middle-ground therapy in situations in whiche AS might be deemed an unsafe option and whole-gland radical therapies would be too aggressive. FT is already being carried out in prospective clinical trials with promising preliminary results (Ahmed et al. 2015, Feijoo et al. 2016), but long-term safety and disease-control results can be properly evaluated only after many years. FT also lacks any comparison with other curative therapies, namely RP and RT, most likely because these treatment forms are intended for distinctly different patients.

2.4.4.2 Therapies for metastatic prostate cancer

In disseminated stage IV disease, or if the patient is elderly or unfit or both, radical therapies such as RP and RT may be inappropriate. For an asymptomatic elderly or unfit patient, generally with less than 10-15 years' life-expectancy, one who hasn't developed distant metastases, one treatment option is watchful waiting. This treatment option is not strictly outlined (Mottet et al. 2017), but can entail repeated PSA measurements and clinical check-ups to assess disease stage and general well-being. Interventions may become necessary when the patient develops symptoms, such as pain from skeletal metastases or LUTS.

In metastatic PC, the primary treatment option is castration therapy because, until near the patient's death, PC cells generally maintain their dependency on circulating testosterone. This dependency was discovered in 1941 by two doctors, Huggins and Hodges, leading to Huggins's later receiving the Nobel prize in medicine in 1966. Castration can be achieved either

surgically or by continuous administration of luteinizing hormone-releasing hormone (LHRH) agonists or antagonists. It can be complemented with early chemotherapy in select patients (Sweeney et al. 2015, James et al. 2016).

Such hormonal therapy has, however, a limited effective period of 2-3 years before the disease eventually progresses, despite castration levels of testosterone, i.e. it becomes castration-resistant (Pienta et al. 2006). At this point, the next treatment option has conventionally been to advance to cytotoxic chemotherapy, mainly docetaxel, but recent years have seen the advance of an abundance of novel therapies for castration-resistant PC. These include a novel antiandrogen, enzalutamide (Scher et al. 2012), an androgen-synthesis inhibitor, abiraterone (de Bono et al. 2011), an alpha-emitting radiopharmaceutical, radium-223 (Parker et al. 2013), and a novel cytotoxic drug, cabazitaxel (de Bono et al. 2010). Sipuleucel-T is the first FDA-approved immunological therapy for PC, although it is unavailable in Europe. Other immunological therapies are in development, but none have thus far demonstrated overall-survival benefit in phase III trials (Slovin 2016). Optimal patient selection, timing, and treatment sequences of these novel therapies are thus far unknown, but are the focus of intense research (Sweeney et al. 2015, James et al. 2016, Ritch et al. 2016).

2.5 INFECTIOUS COMPLICATIONS OF PROSTATE BIOPSIES

2.5.1 BIOPSY-RELATED COMPLICATIONS

Transrectal biopsies can cause many complications for patients (Borghesi et al. 2017), among which are pain, hematuria, hematospermia, rectal bleeding, and infection. Prostate biopsy may also cause temporary impairment to erectile function, which usually returns to baseline by 1-6 months after the procedure (Borghesi et al. 2017). Non-infectious complications are most often mild and self-limiting, only rarely requiring hospitalization (Borghesi et al. 2017), whereas infectious complications can be more severe.

During the biopsy procedure, the needles pass through the rectal wall repeatedly. Although the procedure occurs in conjunction with antibiotic prophylaxis, it is nearly impossible to completely avoid all infections when operating in a region contaminated with fecal bacteria. Transrectal biopsies therefore inherently carry a risk for infectious complications, occurring in up to 7% of procedures (Eichler et al. 2006). These complications range in severity from the mildest forms' being asymptomatic bacteriuria or symptomatic lower urinary tract infections to more severe forms including febrile urinary tract infections, with their reported incidence of 2.2-4.2% (Loeb et al. 2012, Batura et al. 2013), and in the worst cases, septic infections, the incidence of which ranges from 0.6 to 3.1% (Carmignani et al. 2012, Hayatzaki et al. 2014, Bruyere et al. 2015, Bulut et al. 2015, Liss et al. 2015b). The latter

manifestations are the most feared, since they may lead to patients' requiring intensive care, can cause abscesses and other secondary complications, and may even prove fatal. Mortality rates at 30 days have been reported at 0.09-0.3% (Loeb et al. 2011, Nam et al. 2013), but the rates increase with longer observation periods, with a 90-day-mortality rate of 1% reported from Sweden (Lundström et al. 2014) and a 120-day-rate of 1.3% from Canada (Gallina et al. 2008). Mortality is associated with septic complications, advanced age, and worsening of co-morbid conditions.

2.5.2 FLUOROQUINOLONE RESISTANCE

The last 15-20 years have seen an alarming rise in the incidence of post-biopsy infections (Nam et al. 2013, Anastasiadis et al. 2015). One explanatory factor is the number of biopsy procedures increasing as a result of widespread PSA testing, the aging populations in developed countries, and the emergence of AS as a treatment strategy for low-risk PC. Another contributory factor is the increasing resistance of enteric bacteria, typically *Escherichia coli*, to fluoroquinolone (FQ) antibiotics (Zowawi et al. 2015) (Figures 10 and 11).

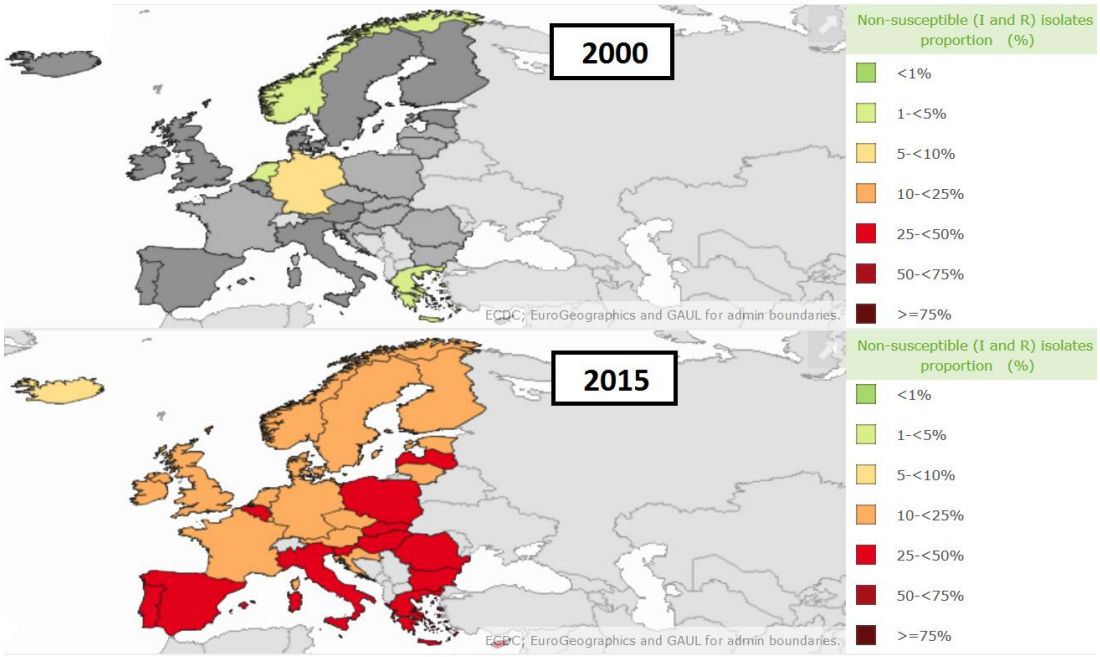


Figure 10 Increasing proportions of non-fluoroquinolone-susceptible *Escherichia coli* in European countries, from 2000 to 2015. Gray indicates no calculated data. (Source: European Centre for Disease Prevention and Control, website accessed 16 Feb 2017, reprinted here with permission.)

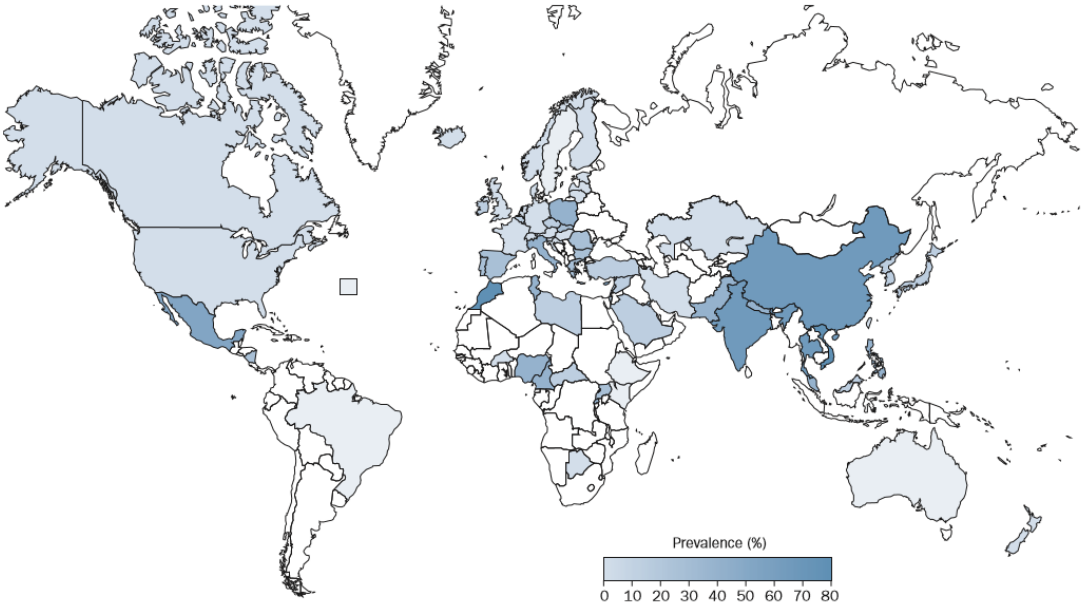


Figure 11 Global prevalences of fluoroquinolone resistance in Gram negative uropathogens. Figures from studies published in 2009-2014. Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Urology*, 2015(12), 570–584, Zowawi et al., "The emerging threat of multidrug-resistant Gram-negative bacteria in urology", copyright 2015.

FQs are the prophylactic antibiotics most commonly used for the prostate biopsy procedure (Mottet et al. 2017), due to their easy oral administration, generally good coverage against enteric bacteria, and favorable drug penetration of prostatic tissue (Dan et al. 1986). The cause of biopsy-related infections is therefore often FQ-resistant bacteria residing in the patients' rectal flora which are translocated by the penetrating biopsy needles (Carmignani et al. 2012, Williamson et al. 2012, Taylor et al. 2013, Ehdaie et al. 2014, Hayatzaki et al. 2014, Rudzinski et al. 2014, Song et al. 2014, Liss et al. 2015a, 2015b, Marino et al. 2015).

Rising global levels of FQ resistance result from the liberal administration of FQs to treat community-acquired urinary tract infections (Fasugba et al. 2015), from the use of antibiotics in agriculture in developed countries (Oliver et al. 2011), and from easy over-the-counter access to antibiotics in developing countries.

A risk factor clearly associated with developing post-biopsy infections is recent international travel (Patel et al. 2012, Anderson et al. 2015). The mechanism underlying this association is temporary colonization of the patient's intestinal flora by FQ-resistant bacteria (Kantele et al. 2014) picked up when traveling to an area that exhibits marked FQ resistance. The recent use of antibiotics–FQs or some other–may also raise the risk for post-biopsy infections (Patel et al. 2012, AbuGhosh et al. 2013, Loeb et al. 2013, Anderson et al. 2015, Bruyere et al. 2015). Speculation is that the mechanism is antibiotics' temporary disturbance of the balance in rectal bacterial flora, again allowing for temporary colonization by more virulent, often FQ-resistant

strains. Many studies have demonstrated FQ-resistant bacteria in the rectal flora to be a strong risk factor for development of post-biopsy infections. This has prompted the introduction of prebiopsy rectal swabs that allow the tailoring of antibiotic prophylaxis instead of administration of possibly ineffective FQs. This strategy has been effective in reducing post-biopsy infections (Duplessis et al. 2012, Taylor et al. 2012, Suwantarat et al. 2013, Roberts et al. 2014, Li et al. 2016), and it is suggested to be cost-effective (Duplessis et al. 2012, Taylor et al. 2012, Li et al. 2016).

Another strategy to reduce post-biopsy infectious complications is to circumvent the contaminated transrectal route and perform transperineal biopsies instead. Sepsis rates have generally been lower following transperineal procedures, although such procedures are associated with higher rates of urinary retention (Bennett et al. 2016). This procedure, however, requires spinal anesthesia, making it more demanding than transrectal biopsy, which can be performed with local anesthesia as an outpatient procedure.

2.5.3 OTHER RISK FACTORS FOR POST-BIOPSY INFECTIONS

Effort has gone into identifying other factors possibly raising the risk for post-biopsy infections. Some report an increased risk as being associated with repeated biopsies (Ehdaie et al. 2014). This is worrisome because repeat prostate biopsies are an integral part of the AS protocols (Bruinsma et al. 2016), but patients who develop post-biopsy complications may be reluctant to comply with programed repeat biopsies (Bokhorst et al. 2015, 2016a). Having undergone prostate biopsies typically means having recently taken FQs as a prophylactic antibiotic. This predisposes the patient to harboring FQ-resistant bacteria, placing the patient more at risk for post-biopsy infection (Roberts et al. 2014). Currently no consensus exists as to whether repeat biopsies raise the risk for infections, although large-scale studies (Loeb et al. 2013a, Aly et al. 2015, Bokhorst et al. 2016a, Halpern et al. 2017) and one meta-analysis (Roberts et al. 2014) suggest no connection.

Any factors weakening a host's ability to fight bacterial infection can naturally be considered risky. Regarding biopsy-related infections, these factors may include diabetes (Simsir et al. 2010, Loeb et al. 2012, Halpern et al. 2017), other comorbidities (Aly et al. 2015, Anastasiadis et al. 2015, Shahait et al. 2016), old age (Anastasiadis et al. 2015, Shahait et al. 2016), and urinary-catheter use (Simsir et al. 2010, Eruz et al. 2017).

2.6 MRI IN THE AS OF PROSTATE CANCER

2.6.1 MRI IN SELECTING PATIENTS FOR AS

No clinical guidelines on AS currently recommend the routine use of MRI (Bruinsma et al. 2016). It is, however, increasingly employed, and several AS guidelines recommend it in situations when any discrepancy emerges between biopsy findings and clinical parameters, such as PSA levels or DRE or transrectal ultrasound findings. The two most common indications to perform prostate MRI for low-risk-PC patients are: 1) to confirm the diagnosis of low-grade, low-volume disease and to determine whether no significant lesion may have been missed by random biopsies, and 2) to monitor disease progression during AS (Schoots et al. 2015a).

Roughly one-third of men on AS will have their disease reclassified as worsening in their first confirmatory or follow-up biopsies (Dall'Era et al. 2012) and will therefore no longer be eligible for AS. This largely fails to reflect the true clinical progression of their disease, but rather reflects undersampling in their diagnostic biopsies. This inaccuracy has prompted the use of prostate MRI with the goal of better identifying those men for whom AS is the proper treatment option. In their 2015 review, Schoots and-co-workers (2015a) concluded that prostate MRI in men eligible for AS, if based on biopsy data, reveals a positive lesion in 70%. When these men receive repeat biopsies, with or without MRI targeting, 47% will be reclassified as having worse disease than at inclusion for AS. In short, this would imply that if MRI were routinely performed for all men before initiation of AS, one-third would evidently have a poorer prognosis than predicted and would no longer be suitable candidates for AS.

There exist, however, caveats in interpretation of these results. First, studies reporting on reclassification rates of MRI-positive men cannot always report on corresponding rates for those men without an MRI-positive lesion, because such men will not necessarily undergo repeat biopsies. Second, when performing repeat biopsies with MRI targeting, the cancer yield tends to be higher than for random biopsies, leading automatically to higher reclassification rates. The PRIAS protocol was accordingly modified in 2015 so that if the diagnostic biopsies were performed with MRI guidance, the protocol would allow a higher number of positive cores at inclusion. Consequently, the number of positive cores permitted during repeat biopsies was adapted based on the number at baseline (Bokhorst et al. 2016b). Despite these caveats, prostate MRI shows promise as a tool for better risk stratification at AS inclusion.

2.6.2 MRI AS A FOLLOW-UP TOOL IN AS

Another indication for prostate MRI during AS is to monitor possible disease progression. Since AS is a treatment option reserved solely for low-volume,

low-grade PC, employing MRI as a follow-up tool for AS patients is somewhat challenging (Schoots et al. 2015a). Low-grade PC is hard to differentiate from benign tissue, making tumor monitoring difficult. The goal of MRI in AS is to detect those lesions prompting active therapies, i.e. clinically significant disease. MRI is well suited to this purpose because of its NPV for Gleason 4 or higher grades (Moldovan et al. 2017).

Before adopting MRI into AS protocols, what should, however, be decided, is what constitutes radiological progression and how MRI findings dictate further action. The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) panel of 19 experts in the fields of urology, radiology, and radiation oncology has recently released its recommendations for documenting changes in MRI findings during AS (Moore et al. 2017). Serial MRIs may monitor the size of tumors or, alternately, other radiologic parameters such as decrease in ADC values (van As et al. 2009, Morgan et al. 2011) or other adverse features. Standardized structured reporting systems for MRI such as PI-RADS (Weinreb et al. 2016) are essential in properly comparing serial images, and ideally the same versions of the reporting systems should be the choice. Another issue is how great a change between images should trigger further action or whether absolute lower limits are necessary, such as a certain tumor diameter or a prespecified PI-RADS score (Moore et al. 2017).

When performing MRI to monitor AS patients, it is natural to utilize MRI data to aid in guiding repeat biopsies. Performing MRI-guided biopsies in addition to standard biopsies during AS follow-up has allowed detection of more Gleason-grade upgrades than by standard biopsies alone (Hoeks et al. 2014, Walton Diaz et al. 2015, Ma et al. 2017). This approach is, however, impractical, because the goal of MRI-guided biopsies is to achieve accurate results with fewer cores than standard biopsies require, instead of with more cores. The as-yet-limited added value of MRI-guided biopsies in the AS setting may be explained by the patient population: MRI-guided procedures perform best when targeting high-grade lesions, and AS patients by definition harbor only low-volume, low-grade PC.

Since prostate biopsy is an invasive and often problematic procedure, one speculation is that in AS, prostate MRI could someday replace repeat biopsies. This would entail continuing surveillance as long as PSA and MRI findings remain stable, showing no disease progression, but otherwise advancing to active treatment. This may already be practiced in real-life, but accurate knowledge of the NPV of MRI still needs confirmation from biopsies performed on men with negative MRI findings. Thus far, the NPV for detecting Gleason score ≥ 7 PC after a negative MRI in AS patients is reported to be as high as 93.1-100% (Wysock et al. 2016, Lu et al. 2017). The PRIAS study group has launched an MRI sidestudy with the hopes of further clarifying this issue among others (Hoeks et al. 2014). For prostate MRI to trigger active therapies by itself would require a strict definition of radiological disease progression and firm knowledge of the correlation between adverse radiologic features and

with histopathological findings. MRI can result in false-positive results, so the decision to advance to active therapies is hardly ever made without histopathological confirmation from biopsy. Prostate MRI cannot as yet replace repeat biopsy in AS.

2.7 BIOMARKERS IN PROSTATE CANCER

2.7.1 MULTIPLE-GENE ASSAYS

Novel tools for better prediction of patient outcomes are constantly appearing. Today, great emphasis is upon finding biomarkers that will aid in outlining a PC-patient's outcome. Biomarkers can range from genes, gene products, or cancer-metabolism products to radiological findings that have, in some circumstances, been associated with either aggressive PC, risk for expansion, or the risk for developing metastases. The presence of such single or multiple biomarkers in a patient's blood or urine sample, prostate biopsy, RP specimen, or MR image would theoretically indicate the patient's having worse disease than the standard prediction tools would indicate.

The first commercially available gene-expression application was the Prolaris® test introduced in 2010, which measures the expression of 46 genes found to correlate with PC cell proliferation, producing a cell-cycle progression score. This score, combined with the PSA and the Gleason score, aims to predict the 10-year risk for PC progression and risk of death. Other genetic panels have since entered the market, namely the Oncotype DX® that tests for 17 genes, and the 22-gene Decipher® test. These commercial genetic panels are marketed as additional predictive tools to aid physicians and patients in making treatment decisions. Oncotype DX®, a prognostic tool also for breast cancer, aids in deciding whether a patient with low-risk PC can safely choose AS instead of immediate radical therapy (Klein et al. 2014, Cullen et al. 2015), whereas Decipher® aims to help in deciding on possible adjuvant therapies after RP (Den et al. 2015, Klein et al. 2015). The Prolaris® test, according to its manufacturer, is suited for both scenarios (Freedland et al. 2013, Cuzick et al. 2015, Koch et al. 2016).

Being laboratory-developed tests, these commercial panels lack approval by the FDA (Office of Public Health Strategy and Analysis, Office of the Commissioner, Food and Drug Administration 2015), but are covered by some insurance policies and advocated in the USA by NCCN clinical guidelines on PC (Mohler et al. 2016). These tests have shown promising results in prospective validation studies, as reviewed by Boström and co-workers (2015), but are currently expensive, with their cost-effectiveness unestablished. There is, interestingly, also no overlap between genes for which these assays test. Performances of these panels have yet to be compared with each other in head-to-head analyses (Moschini et al. 2016).

2.7.2 SINGLE BIOMARKERS, FISH, IHC, AND TMA

Single biomarkers are most often single genes or gene products detectable in blood, urine, or tissue samples. One detection method is fluorescence in situ hybridization (FISH), which finds DNA sequences or RNA targets in cancer cells. FISH can be performed on fresh or formalin-fixed paraffin-embedded tissue samples, but requires fluorescence microscopy and is a somewhat cumbersome technique. An alternate easier and less-costly method is immunohistochemistry (IHC), which detects protein products of relevant genes in malignant tissues. Compared to RNA sequencing of multiple genes, the study of single biomarkers by IHC is easy and inexpensive. If desired, it can be implemented in diagnostic processes in clinical practice, for example in the histopathologic analysis of diagnostic biopsies or RP specimens.

A method for analyzing samples from hundreds of patients is to construct a tissue microarray (TMA). TMAs are paraffin blocks that contain tissue sample cores from dozens of patients. These blocks are sectioned to produce thin (5-µm) sections for study by FISH or IHC techniques (Figure 12), allowing for rapid analyses of large patient series. As such, TMAs of large historic patient cohorts are a practical means to study expression levels of promising biomarkers.

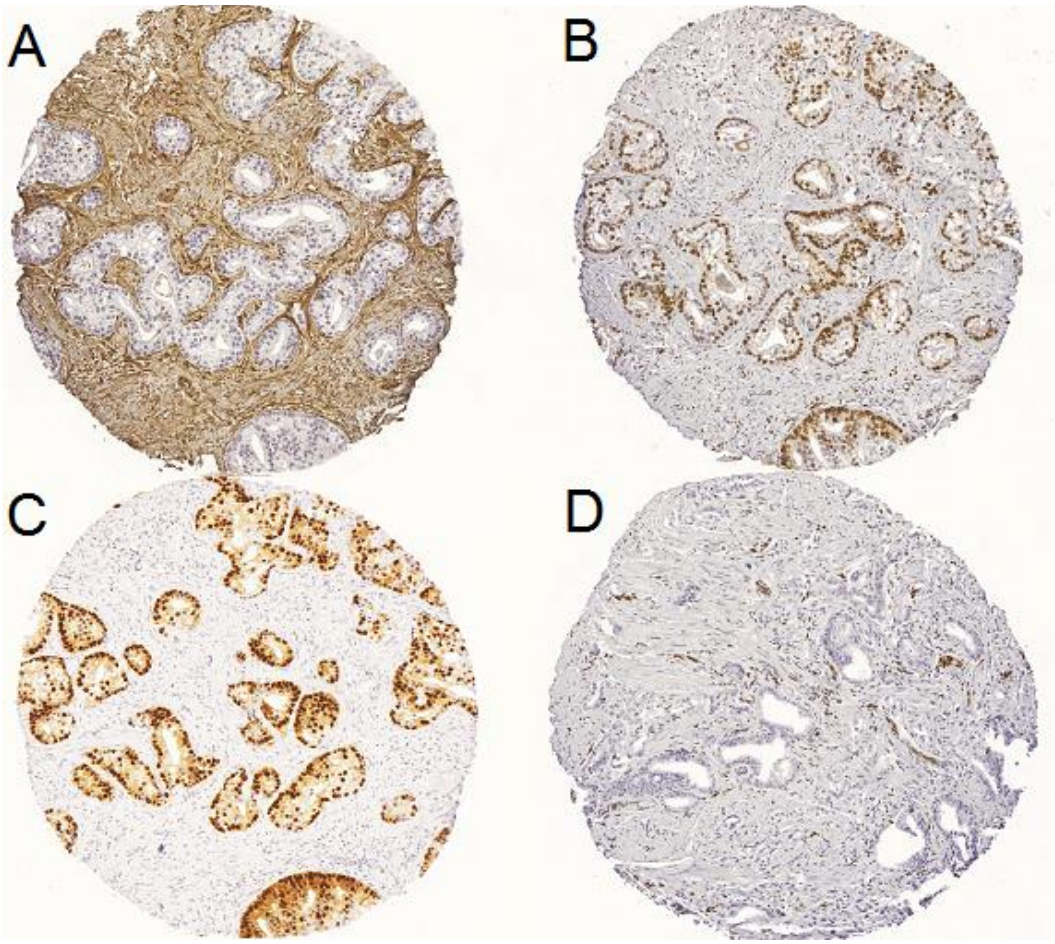


Figure 12 Immunohistochemical stainings of tissue microarray (TMA) cores with prostate cancer (PC). A. PC demonstrating cytoplasmic loss of PTEN expression (=pale gray cytoplasm). B. Sequential section of the same TMA spot as in A, but demonstrating positive nuclear ERG expression (=brown nuclei). C. Sequential section of same TMA spot as in A and B, but demonstrating high nuclear AR expression (=dark brown nuclei). D. A separate core demonstrating negative nuclear ERG expression (=gray nuclei). Modified from a figure published in *Modern Pathology*, 29(12):1565-74 (2016), Lahdensuo et al., "Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy" and reprinted here by permission from Macmillan Publishers Ltd.

2.7.3 *TMPRSS2:ERG* FUSION

An interesting and widely studied PC biomarker is the fusion of *TMPRSS2*, a serine protease gene, with *ERG*, an *ETS* family transcription factor oncogene. Among the functions of *ERG* and the other 27 members of the *ETS* family of transcription activators and repressors is regulation of gene expression in cancers of the breast, reproductive organs, and prostate (Gutierrez-Hartmann et al. 2007). *TMPRSS2:ERG* fusion is detectable in prostatic tissue by either FISH or IHC methods, of which the latter involves detecting the expression of the protein ERG. Such fusion is considered the most prevalent genetic alteration in PC development, present in 40-80% of PC samples (Tomlins et al. 2005, Yoshimoto et al. 2008, Hoogland et al. 2011, Minner et al. 2011, Pettersson et al. 2012, Attard et al. 2015). It is also evident in premalignant tissues, indicating this alteration to be an early occurrence in carcinogenesis. This fusion is therefore not unique to malignant tissues, but it is detectable in increasing numbers with rising degrees of disease aggressiveness and stage (Pettersson et al. 2012, Attard et al. 2015). This has been the premise for use of *TMPRSS2:ERG* fusion status to gauge an individual patient's poorer prognosis. One hypothesis, however, is that *TMPRSS2:ERG* fusion is necessary in early PC development, but less functionally relevant in later disease stages (Baena et al. 2013). Positive ERG status has conversely also correlated in RP specimens with less aggressive histology (Kimura et al. 2012, Suh et al. 2012). This would explain why positive *TMPRSS2:ERG* fusion status appears to lack prognostic power in terms of mortality (Pettersson et al. 2012, Fleischmann et al. 2014).

2.7.4 *PTEN* LOSS

Another common genetic phenomenon is loss of function of the tumor suppressor gene *PTEN*, also detectable with either FISH or IHC techniques (Lotan et al. 2011, Picanco-Albuquerque et al. 2016). Original exploratory studies have detected, in PC samples, heterozygous *PTEN* loss in 29-55% (Cairns et al. 1997, Feilotter et al. 1998, Pesche et al. 1998) and homozygous *PTEN* loss in 10-15% (Cairns et al. 1997, Wang, Parsons & Ittmann 1998, Whang et al. 1998).

PTEN loss activates the *PI3K/Akt* signaling pathway driving anabolic metabolism in cancer cells (Ward et al. 2012), which consequently activates the *mTOR* pathway, which promotes cell division (Hahn-Windgassen et al. 2005). *PTEN* loss thus occurs in many cancers other than PC. Its prognostic value has been under study in breast cancer (Wang et al. 2013, Beg et al. 2015), colorectal cancer (Atreya et al. 2013, Lin et al. 2015), endometrial cancer (Westin et al. 2015), and ovarian cancer (Martins et al. 2014), among others, and it is associated with a worse prognosis in many other cancers (Qiu et al. 2015). As a driver of disease progression, *PTEN* loss, however, seems to be of more importance in PC than in other cancer types, often correlating with more aggressive disease and, consequently, poorer outcomes, such as unfavorable findings at RP (Lotan et al. 2014, Guedes et al. 2016), biochemical-disease recurrence (Chaux et al. 2012, Krohn et al. 2012, Barnett et al. 2014, Lotan et al. 2016, Murphy et al. 2016), PC metastasis, and death (Lotan et al. 2011, Cuzick et al. 2013, Mithal et al. 2014, Ahearn et al. 2015).

For a single prognostic biomarker to be of value in improving risk stratification of PC it would ideally be implemented at the diagnostic stage to aid in treatment planning. *PTEN* loss detected in pre-treatment biopsy specimens has predicted disease upgrading or non-organ confined disease at RP (Lotan et al. 2014, Guedes et al. 2016, Lokman et al. 2017), shorter time to biochemical recurrence after brachytherapy (Fontugne et al. 2014), and even increased PC mortality after RP (Mithal et al. 2014). Given the promising prognostic power of *PTEN* loss, determining PTEN expression status from diagnostic biopsies or RP specimens could probably aid in treatment planning. This may prove most beneficial for patients assumed to be at low risk who are deciding between either AS or radical therapies.

2.7.5 *TMPRSS2:ERG* FUSION AND *PTEN* LOSS TOGETHER

Since *TMPRSS2:ERG* fusion can be evident in benign tissue as well, the fusion alone fails to predict an aggressive disease course (Hoogland et al. 2011, Minner et al. 2011, Pettersson et al. 2012, Leinonen et al. 2013, Xu et al. 2014), but it may be an indicator of other cancer-promoting mechanisms at play. *TMPRSS2:ERG* fusion and loss of *PTEN* are often detected together (Attard et al. 2009, Carver et al. 2009, Han et al. 2009, Gumuskaya et al. 2013, Shah et al. 2015, Lotan et al. 2016), suggesting a causal link between the two genetic transformations, with *PTEN* loss assumed to be a later-occurring phenomenon (Krohn et al. 2014). Their joint occurrence has, in some studies, reflected an even worse clinical presentation than does either genetic transformation alone (Yoshimoto et al. 2008, Leinonen et al. 2013, Fontugne et al. 2014). The prognostic significance of *PTEN* loss is, however, probably so strong that it can predict a poorer outcome also in the absence of *TMPRSS2:ERG* fusion (Reid et al. 2010, Ahearn et al. 2015, Qu et al. 2016).

Interestingly, the commercially available genetic panels—Prolaris®, Oncotype DX®, and Decipher®–do not test for *ERG* fusions or loss of *PTEN*,

but instead for wholly different genes mostly associated with cell-cycle progression, cell profileration, and androgen signaling. This reflects the speed at which novel biomarkers associated with poorer PC prognosis are constantly being discovered.

2.7.6 ASSOCIATIONS OF *ERG* AND *PTEN* WITH THE ANDROGEN-RECEPTOR PATHWAY

TMPRSS2 is an androgen-regulated gene, and *TMPRSS2:ERG* fusion is generally thought to occur in the presence of, and through the influence of circulating androgens such as testosterone (Tomlins et al. 2005). Until the castration-resistant stage, depriving PC of androgens halts its progress. The effects of androgens in PC cells are mediated via the androgen receptor (AR). Elevated levels of AR expression in PC appear to correlate with more aggressive disease (Donovan et al. 2010, Sahu et al. 2011, Qu et al. 2016). In the current era of rapid development of novel drugs aimed at treating PC in its castration-resistant stage, much interest focuses on elucidating the mechanisms by which castration-resistant PC progresses despite androgen deprivation (Hoang et al. 2017).

The relationship between AR activity and *TMPRSS2:ERG* fusion apperars to be reciprocal (Hoogland et al. 2011, Minner et al. 2011, Huang et al. 2014b). One murine study has shown fusion of *TMPRSS2* with *ETS* transcription factors–*ERG* and *ETV1*–to upregulate *AR*, even predisposing PC tissue to loss of *PTEN* function (Chen et al. 2013). Other groups, however, have found this to be true only for *ETV1,* and found that *TMPRSS2* fusion with *ERG* may actually down-regulate *AR* (Shin et al. 2009, Yu et al. 2010, Baena et al. 2013), which may then promote loss of *PTEN*. This would suggest that high *AR* activity may be promoted by agents other than *TMPRSS2* fusion with *ERG*, for example, by *ETV1, IGF-1* (Culig et al. 1994), or *FOXA1* (Sahu et al. 2011), among many others (Hoang et al. 2017).

Complicating the issue further, loss of *PTEN* has also been found to downregulate *AR*, promoting androgen-independent progression of PC by activated compensatory signaling pathways (Kaarbo et al. 2010, Carver et al. 2011, Mulholland et al. 2011). Findings are, however, conflicting, with one group reporting that the direction of this interaction is dependent on stage of PC. Loss of *PTEN* and consequent activation of the *PI3K/Akt/mTOR* pathway suppresses *AR* activity in androgen-dependent LNCaP cells, whereas conversely, this pathway enhances *AR* activity in LNCaP cells with high passage numbers (Lin et al. 2003, 2004). This finding suggests that high *AR* activity, when in the setting of *PTEN* loss, would reflect a more advanced disease stage. Figure 13 outlines some of the crosstalk between *TMPRSS2* fusions and other pathways.

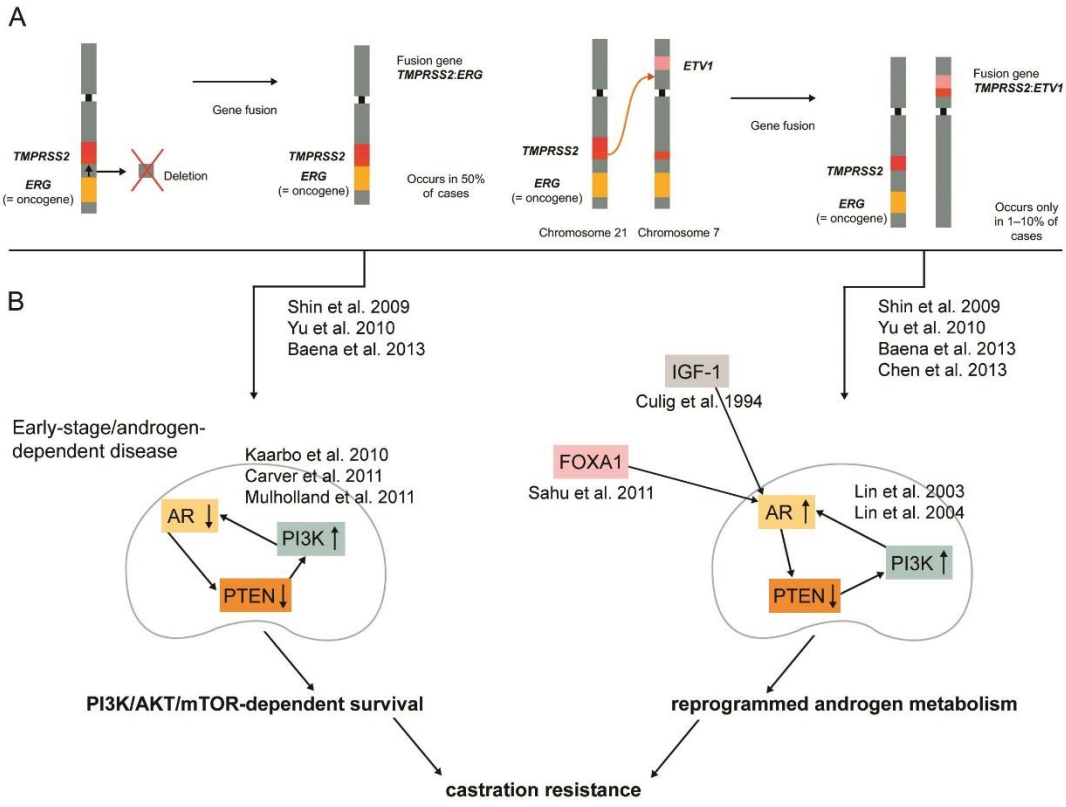


Figure 13 A. Fusion of *TMPRSS2* and *ERG* through chromosomal deletion and *TMPRSS2* with *ETV1* by translocation. Figure reprinted by permission from Elsevier: *European Urology Supplements*, 2010 Dec;9(11):794-99, Martinez-Pineiro, "Personalised Patient Diagnosis and Prognosis in Prostate Cancer: What Are the Future Perspectives?" B. Consequent interactions with *AR* signaling and loss of *PTEN* (Illustration by Kristiina Tammisalo)

These findings may have clinical significance regarding androgen-deprivation therapy in advanced PC. A poorer response to androgen deprivation has been reported both for patients with a negative *TMPRSS2:ERG* fusion status (Attard et al. 2009, 2015, Graff et al. 2015) and for those with loss of *PTEN* (Ham et al. 2009, Mulholland et al. 2011, Mithal et al. 2014, Ferraldeschi et al. 2015). In sum, this would suggest that patients with negative *TMPRSS2:ERG* fusion status and loss of *PTEN* would represent a sub-population of PC patients with shorter survival after development of metastases. Results from preclinical studies suggest that patients with loss of *PTEN* and with activated *PI3K/Akt/mTOR* signaling may benefit from therapy involving androgen-deprivation coupled with *PI3K/Akt/mTOR*-targeting agents (Kaarbo et al. 2010, Carver et al. 2011, Mulholland et al. 2011, Yadav et al. 2016). This strategy has been tested in phase I-II trials with varying results (Meulenbeld et al. 2013, Chow et al. 2016), and several trials are currently ongoing (Statz et al. 2017).

In conclusion, *AR* signaling with associated *TMPRSS2:ERG* fusions and the *PI3K/Akt/mTOR* pathway–two of the most important pathways in PC–cooperate in the development of androgen-independent and eventually fatal

PC. Their interactions are, however, complex and need clarification from further research with contemporary patient cohorts.

3 AIMS OF THE STUDY

The true clinical outcome for an individual patient diagnosed with PC is inaccurately predicted with currently available diagnostic tools. The need is ongoing for better strategies in the diagnosis and treatment-planning of PC. The aims of this thesis study were to evaluate safety for the patient and the performance of conventional prostate biopsies, the utility of MRI in the AS of PC, and the value of putative prognostic PC tissue biomarkers.

The specific aims were to discover and establish:

1) incidences and possible risk factors for bacteremic infectious complications following transrectal biopsies (Study I).
2) ability of transrectal biopsies to estimate tumor size and location in RP specimens. Morphologies of significant and index tumors were also a subject of study (Study II).
3) suitability of prostate MRI in the AS of PC (Study III).
4) effects of *TMPRSS2:ERG* fusion and *PTEN* loss in clinical outcomes of surgically-treated PC (Study IV).

4 PATIENTS AND METHODS

4.1 STUDY COHORTS AND TIMELINES

Study I

The laboratory archives of the entire Helsinki and Uusimaa Hospital District (HUSLAB Laboratory Services), covering a population of 1.62 million people, provided the study population. The study analyzed 17 183 biopsy procedures, performed at 11 urological centres, on 13 303 men during the period 1 January 2005 to 31 December 2013.

The annual incidence of post-biopsy bacteremias were determined by means of data searches in the centralized laboratory archives of the hospital district (HUSLAB), housing data both on all biopsies and all blood cultures. First, a list of all biopsy procedures was extracted with the procedure code for transrectal biopsies. A list of all positive blood cultures of male patients over age 20 during the same time period also came from the same records. Patients who had both undergone a biopsy procedure and had a positive blood culture were then detectable by matching with patients' social security numbers. Blood cultures positive within 30 days of the biopsy we considered relevant. These men were confirmed by review of their medical records to have suffered a post-biopsy complication. Patients who had other causes of bacteremic infections were excluded from analysis, leaving 111 men as the bacteremic cohort. More detailed information regarding possible risk factors was available from the medical records of 107 patients from the bacteremic cohort.

Study II

Study II was retrospectively conducted on 96 patients treated with RP between February 2009 and April 2010 at Helsinki University Hospital. These study patients were selected from among the first 162 patients treated with laparoscopic robot-assisted RP at our clinic who had had their diagnostic biopsies taken at our institution. The 96 study patients also had to have histological slides of RP specimens available for re-evaluation. Main presurgery characteristics and surgical findings are summarized in Table 3.

Study II tested the performance of the standard 12-core transrectal biopsy in detecting tumors and predicting tumor location and size. Detection of significant tumors and index tumors were the emphasis.

Table 3. Characteristics of the 96 patients in Study II. Modified from two tables published as "Performance of transrectal prostate biopsies in detecting tumours and implications for focal therapy," Lahdensuo et al., in the *Scandinavian Journal of Urology*,© Acta Chirurgica Scandinavica Society, reprinted by permission of Taylor & Francis Ltd, on behalf of the Acta Chirurgica Scandinavica Society.

Median age, years (range)	61.7 (45-74)
Median preoperative PSA, ng/ml (range)	7.2 (1.5-28.0)
Preoperative PSA, ng/ml, *n* (%)	
0-4.0	13 (13.5)
4.1-10.0	67 (69.8)
>10.0	16 (16.7)
Biopsy Gleason score, *n* (%)	
6	39 (40.6)
3+4	36 (37.5)
4+3	15 (15.6)
≥8	6 (6.2)
Median combined biopsy cancer percentage, % (range)	5.4 (0.5-100)
Median combined biopsy cancer length, mm (range)	8.0 (0.5-97.0)
Positive surgical margins at RP	26 (27.1)
Extraprostatic extension at RP	16 (16.7)
RP Gleason score, n (%)	
6	15 (15.6)
3+4	55 (57.3)
4+3	17 (17.7)
≥8	9 (9.4)

PSA=prostate-specific antigen

RP=radical prostatectomy

These purposes required re-evaluation of study patients' archived RP slides. The prostates had been dissected in their entirety and mounted serially from apex to base to create the slides. During re-evaluation, tumor location, Gleason score, and size were recorded and charted by prostate sextant. The same sextant division was utilized as in prostate biopsy sampling, making comparisons between preoperative diagnostic biopsies and RP specimens possible. The total number of cancer foci was charted as well as whether the RP specimen contained significant PC, defined as the presence of Gleason grade 4 or 5 patterns. An index tumor was identified for all patients: either the most dedifferentiated tumor or the largest tumor in the absence of Gleason patterns 4 or 5. The largest tumor was designated based on the total continuous tumor area in consecutive histological sections. If extraprostatic extension or positive surgical margins were present—categorized simply as positive or negative—their location was charted and also whether they were the result of the index tumor or of a secondary lesion.

Study III

The study population comprised 80 men who took part in the Finnish arm of the PRIAS trial and who, after being on surveillance for one year, underwent prostate MRI between February 2009 and May 2011 (Table 4).

Table 4. Disease characteristics of 80 study patients in Study III. Table modified from one published as "Diffusion-weighted magnetic resonance imaging in prostate cancer patients on active surveillance one year after diagnosis and before repeat biopsy." Vasarainen et al., in the *Scandinavian Journal of Urology*,© Acta Chirurgica Scandinavica Society, reprinted by permission of Taylor & Francis Ltd, on behalf of the Acta Chirurgica Scandinavica Society.

Age at diagnosis, median (range)	64 (50-77)
PSA at diagnosis (ng/ml), median (range)	5.7 (1.4-10.0)
Prostate volume (ml), median (range)	44 (16-100)
Diagnostic biopsy findings	
Cancer in biopsies (mean), mm (%)	2.1 (1.2)
GS 6, n (%)	78 (97.5)
GS 7, n (%)	2 (2.5)
MRI findings	
Tumor visible on T2 images, n (%)	40 (50.0)
Tumor visible in ADC maps, n (%)	30 (37.5)
Repeat biopsy findings	
Cancer in biopsies (mean), mm (%)	5.0 (2.6)
No repeat biopsies, n (%)	2 (2.5)
No cancer, n (%)	30 (37.5)
GS 6, n (%)	37 (46.3)
GS 7, n (%)	10 (12.5)
GS 9, n (%)	1 (1.3)

PSA=prostate-specific antigen

GS=Gleason score

MRI=magnetic-resonance imaging

ADC=apparent-diffusion coefficient

Study III looked at the performance of prostate MRI in detecting tumors of AS patients and predicting treatment change. Study patients, at the time of undergoing MRI, had all been on AS for one year and had repeat biopsies taken after the MRI, as required by the PRIAS surveillance protocol.

MRI studies were performed with a 3 Tesla body-array scanner from Philips Medical Systems by use of a pelvic coil. In addition to T2-weighted images, echo-planar DW images and ADC maps were obtained. The prostate, for interpreting the images, was divided into seven regions: anterior part, left apex, middle, and base and right apex, middle, and base. The T2-weighted images were first interpreted, and if any suspicious area was detectable, then the same region was further assessed in the corresponding DW images and ADC maps. Images were ranked as either positive or negative regarding suspicion of tumor. The patients subsequently underwent their repeat

biopsies, and correlations between MRI findings and repeat biopsy findings and MRI findings and possible discontinuation of AS were compared.

Study IV

Study IV utilized the two clinical databases for all patients treated with RP between 1983 and 1998 at Helsinki University Hospital and between 2000 and 2005 at Turku University Hospital. The Helsinki cohort originally comprised 478 patients, of whom 358 were included in analyses. Turku University Hospital provided 532 patients, of whom 457 were included. These two cohorts were combined to form the final study cohort of 815 patients. Figure 14 presents the selection process and Table 5 the patient characteristics.

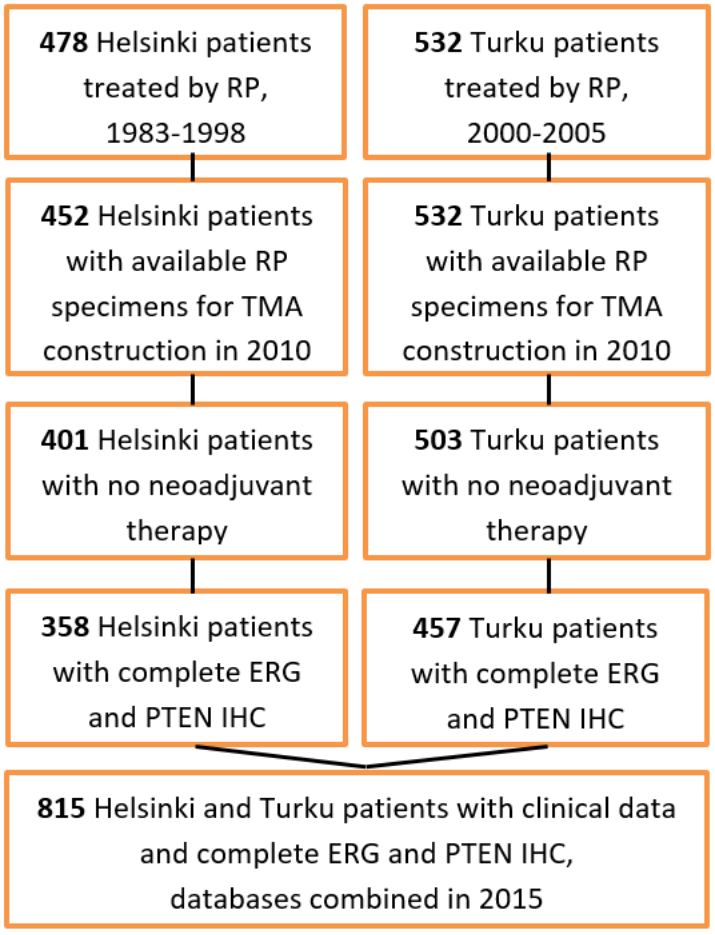


Figure 14 Forming the study cohort for Study IV. RP=radical prostatectomy, TMA=tissue microarray, ERG= *ETS transcription factor,* PTEN=*Phosphatase and tensin homolog*, IHC=immunohistochemistry.

Table 5. Characteristics of 815 patients in Study IV treated with radical prostatectomy between 1983 and 2005. Table modified from one published in *Modern Pathology*, 29(12):1565-74 (2016), Lahdensuo et al., as ”Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy”, by permission from Macmillan Publishers Ltd.

	Helsinki patients (1983-1998) (n=358)	**Turku patients (2000-2005) (n=457)**	**Total**
Age at RP, years (mean, SD) (*N* = 815)	63.4 (5.9)	61.6 (5.8)	62.4 (5.9)
Preoperative PSA, ng/ml (n, %) (*n* = 708)			
≤10.0	143 (50.5)	294 (69.2)	437 (61.7)
10.1-20.0	89 (31.4)	96 (22.6)	185 (26.1)
>20.0	51 (18.0)	35 (8.2)	86 (12.2)
Gleason score at RP (n, %) (*N* = 815)			
≤6	93 (26.0)	168 (36.8)	261 (32.0)
7	207 (57.8)	197 (43.1)	404 (49.6)
8-10	58 (16.2)	92 (20.1)	150 (18.4)
Grade group at RP (n, %) (*N* = 815)			
1	93 (26.0)	168 (36.8)	261 (32.0)
2	93 (26.0)	134 (29.3)	227 (27.9)
3	114 (31.8)	63 (13.8)	177 (21.7)
4	45 (12.6)	70 (15.3)	115 (14.1)
5	13 (3.6)	22 (4.8)	35 (4.3)
Pathological tumor stage (n, %) (*n* = 774)			
2	202 (60.5)	233 (53.0)	435 (56.2)
3 (including three patients with T4)	122 (39.5)	207 (47.0)	339 (43.8)
Lymph node status (n, %) (*n* = 806)			
Negative	342 (97.2)	434 (95.6)	776 (96.3)
Positive	10 (2.8)	20 (4.4)	30 (3.7)
ERG status in TMA (n, %) (*N* = 815)			
Any core positive	181 (50.6)	228 (49.9)	406 (49.8)
Negative	177 (49.6)	229 (50.1)	409 (50.2)
PTEN status in TMA (n, %) (*N* = 815)			
Intact	164 (45.8)	338 (74.0)	502 (61.6)
Any loss	194 (54.2)	119 (26.0)	313 (38.4)
Complete loss	77 (21.5)	58 (12.7)	135 (16.6)
AR status in TMA (n, %) (*n* = 358)			
Low	127 (35.5)	n.a.	
High	231 (64.5)	n.a.	
Follow-up time after RP, years (median, range) (*N*=815)	15.7 (0.7-28.6)	9.5 (0.2-14.0)	11.9 (0.2-28.6)
Death from any cause (n, %) (*N* = 815)	172 (48.0)	73 (16.0)	245 (30.0)
Death from prostate cancer (n, %) (*N* = 815)	33 (9.2)	19 (4.2)	52 (6.4)
Patients receiving secondary therapy after RP (n, %) (*n* = 796)	124 (34.6)	136 (31.1)	260 (32.7)

RP=radical prostatectomy

SD=standard deviation

PSA=prostate-specific antigen
ERG=*ETS transcription factor*
TMA=tissue microarray
PTEN=*Phosphatase and tensin homolog*
AR=*Androgen receptor*
n.a.=not available

Study IV looked into the value of tissue markers ERG, PTEN, and AR in predicting outcomes of patients after RP, utilizing two clinical databases with extensive preoperative and follow-up information and corresponding TMAs. These TMAs had been constructed between 2005 and 2010 at both clinics and later combined as part of a national PC-TMA-study initiative (FinnProstata IX). The TMAs had been constructed in slightly differing fashions: in Helsinki, two cores were obtained from the dominant Gleason pattern and one from the secondary pattern, whereas in Turku, a median of three cores were obtained from the index tumor, assigned primarily on the basis of degree of dedifferentiation. The Helsinki TMA slides had been stained and analyzed for AR expression and were further stained for ERG and for PTEN expression for the purposes of this study. The Turku TMA slides were stained for ERG and PTEN expression with the same antibodies and dilutions as in Helsinki, enabling combination of the cohorts. ERG and PTEN expression was, in each tissue core, evaluated by investigators blinded to the clinical and other pathological data. If PTEN loss was detectable, it was determined as either complete (=all patient's cores negative) or partial (=any of a patient's cores negative).

For this study, the two clinical databases were combined and updated in 2015 by the Finnish Cancer Registry's data on patients' all-cause and disease-specific mortality. Information on possible secondary therapies after RP came from patient records. The decision to administer secondary therapies after RP was that of the treating urologists, according to current clinical practices. The association of marker expression status with clinical variables and survival was then analyzed.

4.2 STATISTICAL ANALYSES

All statistical analyses were performed with IBM SPSS Statistics versions 17-23 (IBM, Chicago, IL, USA) and Stata/SE 12.0 (StataCorp LP, College Station, TX, USA) (Study I). Statistical significance was set at $P<0.05$ in two-sided tests.

Study I

Annual bacteremia incidences came from dividing the number of bacteremic complications annually by the number of biopsy procedures performed in the same year. Confidence intervals of 95% (95% CI) for annual bacteremia rates were calculated by Wilson score. Calendar year of biopsy, patient age at biopsy, and serial number of the biopsy session were included as independent variables in a multiple regression analysis of all biopsies to discover possible risk factors for developing any bacteremia or bacteremia caused by a FQ-resistant bacterium in the entire biopsy cohort. Possible risk factors for bacteremia with FQ-resistant bacteria in the bacteremic cohort were studied, for the 107 patients with available medical records, by means of Pearson's and Fisher's chi-squared tests (univariate analysis) and exact logistic regression (multivariate analysis).

Study II

Pearson's chi-squared test was employed to evaluate the performance of biopsies in predicting tumor location in RP specimens. The correlation between extent of cancer in biopsies and RP specimens was studied with the aid of Spearman's rank order correlation and linear regression analysis. In linear regression analysis, the dependent variable was the squared percentage of cancer in the RP sextant. The square root of the dependent variable served to correct for the moderately positively skewed distribution of the variable.

Study III

Spearman's rank order correlation and Pearson's chi-squared test were employed to study whether any clinical variable correlated with the tumor's being visible on MRI. The association of tumor location sextant-wise between MRI and repeat biopsies was also tested with Pearson's chi-squared test. Visualizations of tumors on either standard T2 images or ADC maps were included in a multivariate logistic regression model predicting deferred radical treatment, along with patient age, PSA level at diagnosis, PSA density at diagnosis, percentage of cancer in diagnostic biopsies, PSA doubling time, and PSA level at the time of radical treatment.

Study IV

The correlation between ERG and PTEN expression status and clinical variables was explored with Pearson's and Fisher's chi-squared tests. Kaplan-Meier survival analyses with Mantel-Cox log rank statistics and uni- and multivariate Cox regression analyses compared various marker expressions for their effects on disease-specific survival (DSS), overall survival (OS); and, for the Helsinki cohort, secondary-therapy-free survival. Standard variables–

age at surgery, preoperative PSA, pathological tumor stage, Gleason score, and lymph node status–were also included in the Cox regression models.

4.3 ETHICS

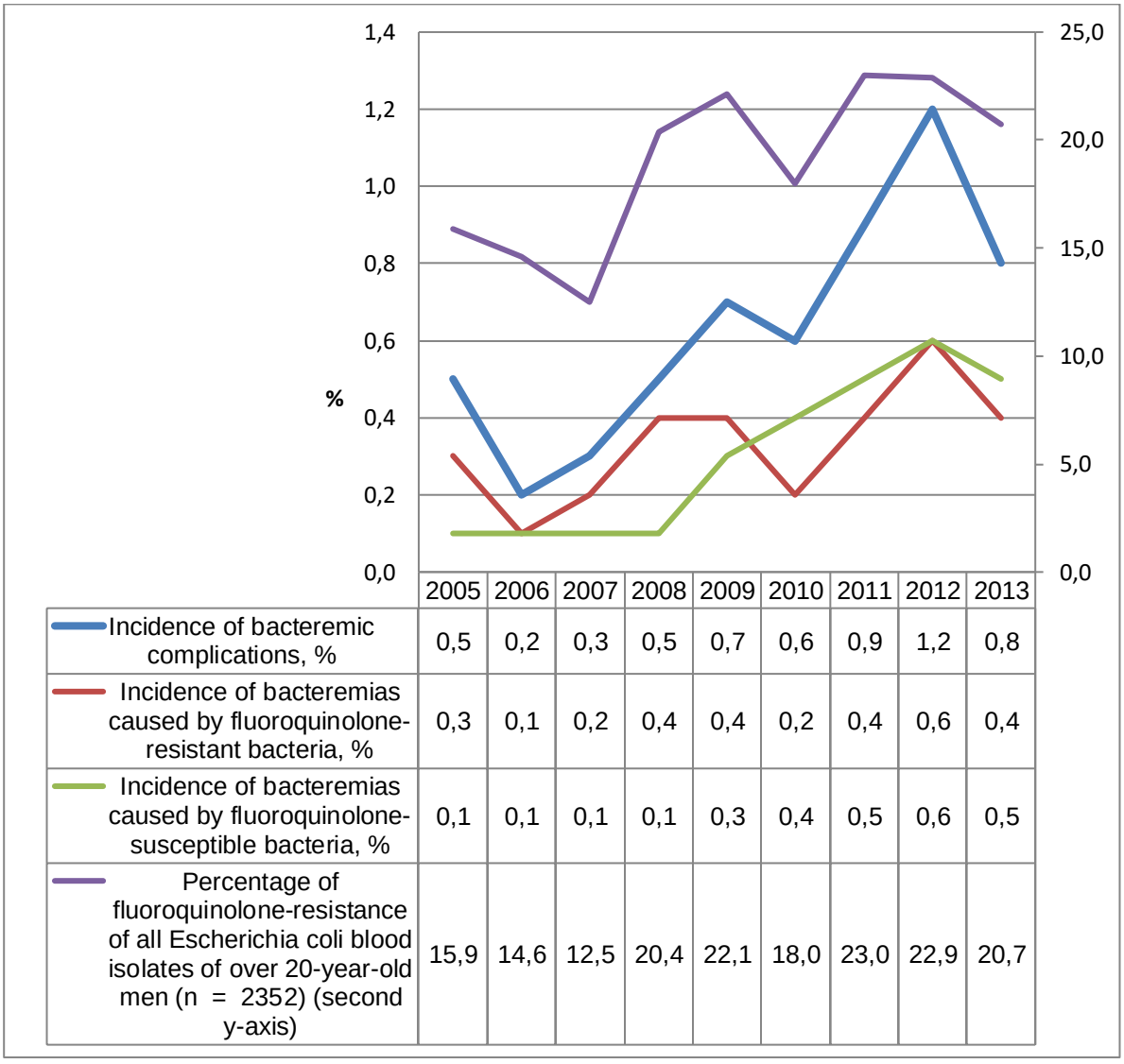
Data for Studies I, II, and IV were gathered retrospectively from patient records, laboratory archives, and from the Finnish Cancer Registry (Study IV), before anonymization, without requiring informed consent from patients. Study III was conducted as part of the prospective PRIAS trial, in which patients had given informed consent at enrollment.

All studies were approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District. In addition, the inclusion of patients from Turku University Hospital in Study IV was approved by the Ethics Committee of the Hospital District of Southwest Finland. For Study IV, use of tissue materials was approved by the National Supervisory Authority for Welfare and Health (Valvira), and the Cancer Registry's data by the National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos).

5 RESULTS

5.1 STUDY I

The average incidence of post-biopsy bacteremias in our hospital district between 2005 and 2013 was 0.7% (111 of 17 183 biopsies, or 7 bacteremic complications per 1000 biopsies). The incidence increased from 0.5%, or 5 bacteremic complications per 1000 biopsies, in 2005 (95% CI 0.3-0.9) to 1.2%, or 12 bacteremic complications per 1000 biopsies, in 2012 (95% CI 0.8-1.8). Concurrently, the percentages of FQ-resistant *Escherichia coli* blood isolates of adult male patients over the same period rose from 15.9% to 22.9% (Figure 15).



	2005	2006	2007	2008	2009	2010	2011	2012	2013
Incidence of bacteremic complications, %	0,5	0,2	0,3	0,5	0,7	0,6	0,9	1,2	0,8
Incidence of bacteremias caused by fluoroquinolone-resistant bacteria, %	0,3	0,1	0,2	0,4	0,4	0,2	0,4	0,6	0,4
Incidence of bacteremias caused by fluoroquinolone-susceptible bacteria, %	0,1	0,1	0,1	0,1	0,3	0,4	0,5	0,6	0,5
Percentage of fluoroquinolone-resistance of all Escherichia coli blood isolates of over 20-year-old men (n = 2352) (second y-axis)	15,9	14,6	12,5	20,4	22,1	18,0	23,0	22,9	20,7

Figure 15 Increasing rates of bacteremias after transrectal prostate biopsies and fluoroquinolone(FQ)-resistance of *Escherichia coli* blood isolates of over 20-year-old men in the Helsinki and Uusimaa hospital district during 2005–2013. Figure published in *Prostate Cancer and Prostatic Diseases*, 19, 417-422 (2016), Lahdensuo et al., "Increase of prostate biopsy-related bacteremic complications in southern Finland, 2005–2013: a population-based analysis", by permission from Macmillan Publishers Ltd.

In examination of risk factors for developing post-biopsy bacteremia in the biopsy cohort, a previous biopsy session and later calendar year of biopsy significantly raised the risk, according to univariate logistic regression analysis. Only later calendar year of biopsy, however, remained statistically significant in multivariate analysis (Table 6).

Table 6. Logistic regression analyses for risk of developing post-biopsy bacteremia in the biopsy cohort (17183 biopsies during 2005–2013). Table modified from one published in *Prostate Cancer and Prostatic Diseases*, 19, 417-422 (2016), Lahdensuo et al., "Increase of prostate biopsy-related bacteremic complications in southern Finland, 2005–2013: a population-based analysis", by permission from Macmillan Publishers Ltd.

	Univariate				**Multivariate**			
	OR	**95% CI**		***P***	**OR**	**95% CI**		***P***
Calendar year of biopsy	1.164	1.079	1.255	<0.000	1.155	1.070	1.247	<0.000
Increasing serial number of biopsy session	1.232	1.020	1.488	0.030	1.174	0.969	1.423	0.101
Patient age at biopsy	1.006	0.985	1.027	0.575	1.004	0.982	1.025	0.746

OR=odds ratio

CI=confidence interval

These regression analyses were repeated for those patients who had bacteremia caused by FQ-resistant bacteria, but none of these variables was statistically significant.

For the bacteremic cohort of 107 patients whose medical records provided possible clinical risk factors, Pearson's and Fisher's chi-squared tests revealed that foreign travel within the three preceding months was statistically significantly associated with development of bacteremia caused by FQ-resistant bacteria. This was also a statistically significant risk factor in exact logistic regression (Table 7). The 95% CI started from above one and extended to infinity, most likely because of the lack of patients with a history of recent travel in the group with FQ-susceptible bacteremia.

Table 7. Univariate and multivariate analyses of risk factors for developing bacteremia with fluoroquinolone(FQ)-resistant bacteria in the bacteremic cohort. Table modified from one published in *Prostate Cancer and Prostatic Diseases*, 19, 417-422 (2016), Lahdensuo et al., "Increase of prostate biopsy-related bacteremic complications in southern Finland, 2005–2013: a population-based analysis", by permission from Macmillan Publishers Ltd.

	Univariate			Multivariate[a]		
Risk factors (107 patients)	**FQ-resistant bacteraemia (*n* = 52)**	**FQ-susceptible bacteraemia (*n* = 55)**	***P***	**OR**	**95% CI**	***P***
Repeat biopsy	18 (34.6%)	16 (29.1%)	0.678[b]	1.355	0.521–3.569	0.638
Antibiotic treatment within three months	8 (15.4%)	4 (7.3%)	0.228[b]	3.485	0.702–23.695	0.154
Foreign travel within three months	6 (11.5%)	0 (0%)	0.011[c]	9.144	1.238–infinite	0.028
Diabetes	7 (13.5%)	16 (29.1%)	0.061[b]	0.330	0.091–1.041	0.060
Immunosuppressive medication	3 (5.8%)	1 (1.8%)	0.354[c]	4.371	0.331–238.21	0.395
Indwelling or suprapubic catheter	1 (1.9%)	3 (5.5%)	0.618[c]	0.242	0.003–4.332	0.557
[a]Exact logistic regression, [b]Pearson's chi-squared test, [c]Fisher's exact test, because of expected cell frequencies of less than five						

FQ=fluoroquinolone

OR=odds ratio

CI=confidence interval

5.2 STUDY II

Standard 12-core biopsies performed poorly in predicting tumor location. When analyzed by prostate sextant, the concordance of cancer locations between biopsies and RP specimens was modest (Table 8).

Table 8. Sextant distributions of cancer in diagnostic biopsies and radical prostatectomy (RP) specimens of 96 patients. Percentages in Biopsy and RP columns exceed 100% in total, because patients harbored cancer in multiple sextants. Table modified from one published in "Performance of transrectal prostate biopsies in detecting tumours and implications for focal therapy", Lahdensuo et al., *Scandinavian Journal of Urology*,© Acta Chirurgica Scandinavica Society, reprinted by permission of Taylor & Francis Ltd, on behalf of the Acta Chirurgica Scandinavica Society.

Tumor location by sextant		**Biopsy *n* (%)**	**RP *n* (%)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
Base	**Left**	41 (42.7)	29 (30.2)	48.3	59.7	34.1	72.7
	Right	48 (50.0)	41 (42.7)	58.5	56.4	50.0	64.6
Middle	**Left**	41 (42.7)	74 (77.1)	48.6	77.3	87.8	30.9
	Right	50 (52.1)	78 (81.3)	57.7	72.2	90.0	28.3
Apex	**Left**	40 (41.7)	73 (76.0)	46.6	73.9	85.0	30.4
	Right	55 (57.3)	80 (83.3)	62.5	68.8	90.9	26.8

RP=radical prostatectomy
NPV=negative predictive value
PPV=positive predictive value

Sensitivities and specificities of diagnostic biopsy were also unsatisfactory. Disease locations predicted by biopsy appeared to be evenly distributed between the sextants, but analysis of RP specimens revealed tumors to be dominantly in the middle and apex. A positive needle biopsy from the base overestimated the prevalence of disease, i.e. this region yielded the greatest number of false-positive results, and conversely, a biopsy from the apex underestimated the prevalence. The PPV and NPV of a test are dependent on the true prevalence; consequently, the low true prevalence—based on RP findings—of tumors in the base of the prostate led to a low PPV and a fairly high NPV for positive biopsies from the base. The opposite applied to apical tumors, which were prevalent in RP specimens, but went underdetected by biopsy. This improved the PPV and impaired the NPV of a positive biopsy finding from the apex of the prostate.

Standard 12-core biopsies were also inaccurate in predicting unilateral disease. Of the 47 cases, only 11 (23.4%) that were presumed on biopsy to be unilateral, were, in analysis of RP specimens, actually unilateral. More puzzlingly, biopsies predicted bilateral disease for the 7 patients who in reality had cancer confined to only one lobe. This is most likely explained by the biopsy needle's inadvertently crossing the midline of the prostate.

In comparisons of the extent of cancer sextant-wise between biopsies and RP specimens by Spearman's rank order analysis, both the length and percentage of cancer in biopsy cores correlated positively with the percentage of cancer in the RP specimen. This correlation was statistically significant in the apex and middle of the prostate, but not in the base, probably because of the low prevalence of cancer there. The positive correlation of cancer extent between biopsies and RP specimens was also corroborated in linear regression analysis (Table 9).

Table 9. Correlations of extent of cancer between biopsies and radical prostatectomy specimens per sextant with linear regression analysis. Analyses performed separately with cancer length (mm) in biopsies and cancer percentage (%) in biopsies as independent variables. Table modified from one published in "Performance of transrectal prostate biopsies in detecting tumours and implications for focal therapy", Lahdensuo et al., *Scandinavian Journal of Urology*,© Acta Chirurgica Scandinavica Society, reprinted by permission of Taylor & Francis Ltd, on behalf of the Acta Chirurgica Scandinavica Society.

		Constant coefficient	**95% CI**	**Slope coefficient**	**95% CI**	***p***
Correlations using length of cancer (mm) in biopsy cores						
Base	**Left**	0.74	0.33-1.15	0.11	0.00-0.22	0.043
	Right	0.92	0.55-1.29	0.08	0.00-0.15	0.033
Middle	**Left**	1.94	1.50-2.37	0.25	0.14-0.36	<0.001

	Right	2.39	1.91-2.86	0.19	0.09-0.28	<0.001
Apex	**Left**	2.45	1.95-2.95	0.16	0.05-0.27	0.005
	Right	2.55	2.05-3.06	0.26	0.14-0.37	<0.001
Correlations using percentage of cancer (%) in biopsy cores						
Base	**Left**	0.77	0.35-1.18	0.16	-0.02-0.33	0.073
	Right	0.93	0.56-1.30	0.13	0.00-0.25	0.043
Middle	**Left**	1.98	1.54-2.41	0.36	0.19-0.53	<0.001
	Right	2.38	1.91-2.86	0.31	0.15-0.47	<0.001
Apex	**Left**	2.48	1.99-2.97	0.24	0.07-0.41	0.007
	Right	2.53	2.04-3.02	0.43	0.25-0.61	<0.001

CI=confidence interval

The higher constant coefficients for tumors in the middle and apex of the prostate further highlighted their higher prevalence.

In further analysis of RP specimens, the majority of the 96 patients, 74 (77.1%) had multifocal disease, i.e. two or more tumor foci. Cancer foci were considered as being significant PC in the presence of a Gleason grade 4 or 5 pattern, resulting in 81 patients (84.4%) with significant tumors. In examining the prevalence and distribution of significant PC, of the 81 patients, 36 (44.4%) had significant PC confined to one side of the prostate; 39 (48.1%) had solitary significant tumors, i.e. these patients' other cancer foci exhibited solely a Gleason grade 3 pattern.

Index tumors chosen from each RP specimen had their morphologies studied separately. The index tumors were mostly unilateral (81 of 96, 84.4%), i.e. confined to one side of the prostate. Sizewise, these index tumors presented in one sextant in 45 (46.9%) specimens, with 51 (53.1%) extending to two or more adjacent sextants (Table 10).

Table 10. Detailed pathological findings of 96 patients at radical prostatectomy. Table modified from one published in "Performance of transrectal prostate biopsies in detecting tumours and implications for focal therapy", Lahdensuo et al., *Scandinavian Journal of Urology,*© Acta Chirurgica Scandinavica Society, reprinted by permission of Taylor & Francis Ltd, on behalf of the Acta Chirurgica Scandinavica Society.

	n	**(%, of 96, unless stated otherwise)**
Tumor foci per patient		
1	22	22.9
2	21	21.9
3	34	35.4
≥ 4	19	19.8
Significant disease (presence of Gleason grade 4 or 5)	81	84.4

Only one significant tumor, *n* (% of 81 cases)	39	48.1
Tumor laterality		
Unilateral any PC	18	18.8
Bilateral any PC	78	81.3
Unilateral significant disease, *n* (% of 81 cases)	36	44.4
Unilateral index tumor	81	84.4
Index tumor extending over midline	15	15.6
Index tumor characteristics		
GS 3+3	15	15.6
GS 3+4	55	57.3
GS 4+3	17	17.7
GS ≥ 8	9	9.4
Extraprostatic extension, *n* (% of 16 cases)	14	87.5
Positive surgical margins, *n* (% of 26 cases)	23	88.5

PC=prostate cancer

GS=Gleason score

5.3 STUDY III

Of the 80 patients who underwent prostate MRI after one year on surveillance, only 50% had MRI-visible tumors. No clinical variable: patient age, prostate volume, diagnostic PSA, percentage of cancer at diagnostic biopsy, PSA doubling time, or PSA at discontinuation, correlated with MRI visibility in Spearman's rank order correlation. This was also explored with Pearson's chi-squared test with slightly different clinical variables: Gleason score at diagnostic or repeat biopsy, number of positive cores at diagnostic or repeat biopsies, or discontinuation of AS, with no statistically significant findings. This analysis was also repeated for the subgroup of 23 patients who had disease progression in repeat biopsy or who discontinued AS, but this, again, revealed no statistically significant associations.

When comparing cancer locations sextant-wise between MR images and subsequent repeat biopsies, Pearson's chi-squared test revealed a statistically significant association only for tumor location between right mid-gland in MRI and right base in repeat biopsy (Table 11).

Table 11. P-values for associations of sextant-wise cancer locations between magnetic-resonance imaging (MRI) (vertical) and repeat biopsy (horizontal) findings with Pearson's chi-squared test. Table modified from one published in "Diffusion-weighted magnetic resonance imaging in prostate cancer patients on active surveillance one year after diagnosis and before repeat biopsy", Vasarainen et al., *Scandinavian Journal of Urology*,© Acta Chirurgica Scandinavica Society, reprinted by permission of Taylor & Francis Ltd, on behalf of the Acta Chirurgica Scandinavica Society.

MRI	Repeat biopsies	Left base	Left middle	Left apex	Right base	Right middle	Right apex
Left base		0.409					
Left middle		0.545	0.059				
Left apex				0.584			
Right base					0.977		
Right middle					0.004	0.430	
Right apex							0.307

MRI=magnetic-resonance imaging

At the time of analysis, 23 patients had discontinued AS, 19 due to progression on repeat biopsies and 4 to decreasing PSA-doubling time. In logistic regression analysis, which included tumor visibility on T2-images or ADC maps, the only variable statistically significant for predicting treatment change was PSA at the time of discontinuation (Table 12).

Table 12. Logistic regression analysis of variables predicting discontinuation of active surveillance. Table modified from one published in "Diffusion-weighted magnetic resonance imaging in prostate cancer patients on active surveillance one year after diagnosis and before repeat biopsy", Vasarainen et al., *Scandinavian Journal of Urology*,© Acta Chirurgica Scandinavica Society, reprinted by permission of Taylor & Francis Ltd, on behalf of the Acta Chirurgica Scandinavica Society.

	p	OR (95% CI)
Patient age	0.057	0.9 (0.7-1.0)
PSA at diagnosis	0.371	0.8 (0.4-1.4)
PSA density at diagnosis	0.921	1.0 (1.0-1.0)
Percentage of cancer at diagnostic biopsy	0.199	1.8 (0.7-4.3)
PSA-doubling time	0.921	1.0 (1.0-1.0)
PSA at time of discontinuation	0.002	1.8 (1.2-2.6)
Tumor visible on T2 images	0.273	3.4 (0.4-30.1)
Tumor visible in ADC maps	0.691	0.6 (0.1-5.9)

OR=odds ratio

CI=confidence interval

PSA=prostate-specific antigen

ADC=apparent-diffusion coefficient

5.4 STUDY IV

Crosstab analyses revealed that complete loss of PTEN expression was significantly associated with several clinical variables that indicate more

aggressive PC, such as higher Gleason score, higher pathological tumor stage, and positive lymph nodes. It was also associated with poorer OS and DSS and increased likelihood of receiving secondary treatment after RP. Positive ERG status, however, correlated only with lower preoperative PSA and increased likelihood of receiving secondary therapy but not with DSS or OS (Table 13).

Table 13. Correlations of ERG and PTEN expressions with clinical variables by Pearson's and Fisher's chi-squared tests for 815 patients treated with radical prostatectomy. Table modified from one published as electronic supplementary material to accompany "Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy", Lahdensuo et al., *Modem Pathology,* 29(12):1565-74 (2016), by permission from Macmillan Publishers Ltd.

	PTEN			ERG		
	Intact (n, %)	**Complete loss (n, %)**	**P**	**Positive (n, %)**	**Negative (n, %)**	**P**
All patients (N = 815)	680 (83.4)	135 (16.6)	–	409 (50.2)	406 (49.8)	–
Preoperative PSA (n = 708)			0.363[a]			0.042[a]
≤ 10.0 ng/ml	372 (85.1)	65 (14.9)		237 (54.2)	200 (45.8)	
10.1-20.0 ng/ml	157 (84.9)	28 (15.1)		88 (47.6)	97 (52.4)	
> 20.0 ng/ml	68 (79.1)	18 (20.9)		35 (40.7)	51 (59.3)	
Gleason score (N = 815)			0.000[a]			0.102[a]
≤ 6	243 (93.1)	18 (6.9)		117 (44.8)	144 (55.2)	
7	337 (83.4)	67 (16.6)		215 (53.2)	189 (46.8)	
≥ 8	100 (66.7)	50 (33.3)		77 (51.3)	73 (48.7)	
Pathological tumor stage (n = 774)			0.000[a]			0.070[a]
2	392 (90.1)	43 (9.9)		203 (46.7)	232 (53.3)	
3	254 (75.6)	82 (24.4)		184 (54.8)	152 (45.2)	
4	1 (33.3)	2 (66.7)		1 (33.3)	2 (66.7)	
Lymph node involvement (n = 806)			0.000[b]			0.353[b]
Yes	15 (50.0)	15 (50.0)		18 (60.0)	12 (40.0)	
No	659 (84.9)	117 (15.1)		387 (49.9)	389 (50.1)	
Secondary therapy after RP (n = 796)			0.000[b]			0.019[b]
Yes	177 (68.1)	83 (31.9)		146 (56.2)	114 (43.8)	
No	484 (90.3)	52 (9.7)		252 (47)	284 (53)	
Overall survival (N = 815)			0.001[b]			0.446[b]
All-cause death	188 (76.7)	57 (23.3)		128 (52.2)	117 (47.8)	
Alive	492 (86.3)	78 (13.7)		281 (49.3)	289 (50.7)	
Disease-specific survival (N = 815)			0.004[b]			1.000[b]
Death due to prostate cancer	36 (69.2)	16 (30.8)		26 (50.0)	26 (50.0)	
Alive or all-cause death	644 (84.4)	119 (15.6)		380 (49.8)	383 (50.2)	

[a] Pearson Chi-squared test, [b] Fishers-exact test

PTEN=*Phosphatase and tensin homolog*
ERG=*ETS transcription factor*
PSA=prostate-specific antigen
RP=radical prostatectomy

Performing Kaplan-Meier analyses with ERG status alone revealed no associations with OS, DSS, or time until the patient received secondary therapy. PTEN expression status was unable to predict OS, but both partial and complete PTEN loss was statistically significantly associated with shorter DSS time (Figure 16).

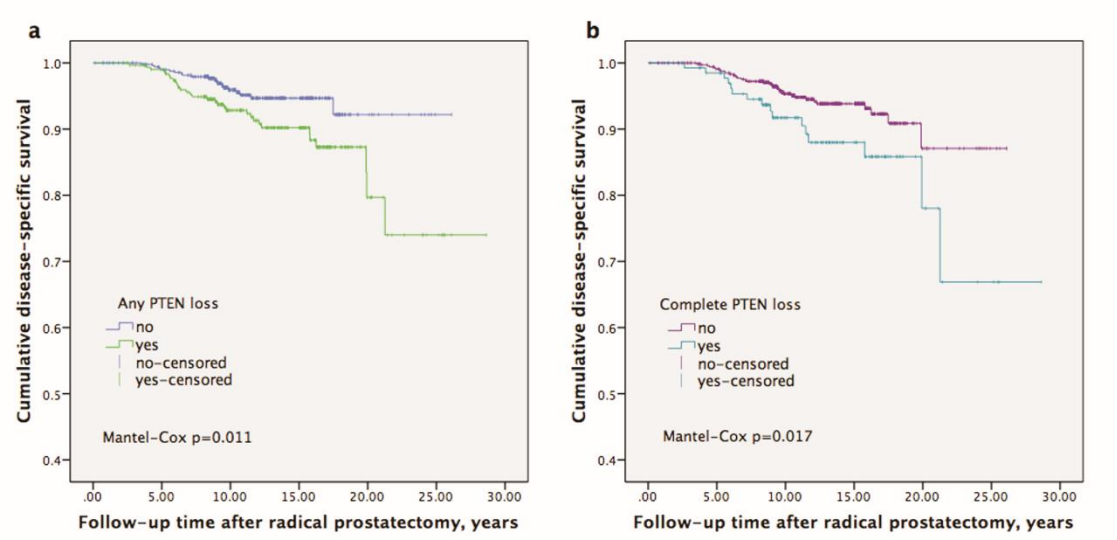


Figure 16 Both partial (A) and complete (B) loss of PTEN expression led to shortened disease-specific survival times. Figure previously published in *Modern Pathology*, 29(12):1565-74 (2016), Lahdensuo et al., "Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy", by permission from Macmillan Publishers Ltd.

Complete loss of PTEN expression, when compared with intact or partially lost PTEN, raised the risk of PC death with a hazard ratio (HR) of 2.16 (95% CI 1.17-3.98, P=0.014) in univariate Cox regression analysis, although not in multivariate analysis. In the multivariate analysis, only positive lymph nodes or pathological tumor stage >2 statistically significantly raised the risk of PC death. Risk of PC death was also raised for patients with high AR expression status, but only in univariate analysis (HR 2.38, 95% CI 1.01-5.60, P=0.048). Marker expression status failed to associate with increased risk of death from any cause in uni- or multivariate analysis. Complete PTEN loss raised the risk for receiving secondary therapies after RP in both uni- and multivariate analysis (HR 2.78, 95% CI 1.85-4.19, P<0.001 and HR 2.29, 95% CI 1.31-3.99, P=0.003, respectively).

The association of combined ERG/PTEN expression status with the likelihood of receiving secondary treatment after RP was explored with Kaplan-Meier analyses. Complete loss of PTEN expression was associated with

shorter secondary-therapy-free survival in both ERG-positive and ERG-negative patients. Complete PTEN loss in ERG-negative patients was significantly associated with shorter DSS time when compared to ERG-positive patients with PTEN intact or only partially lost (Figure 17).

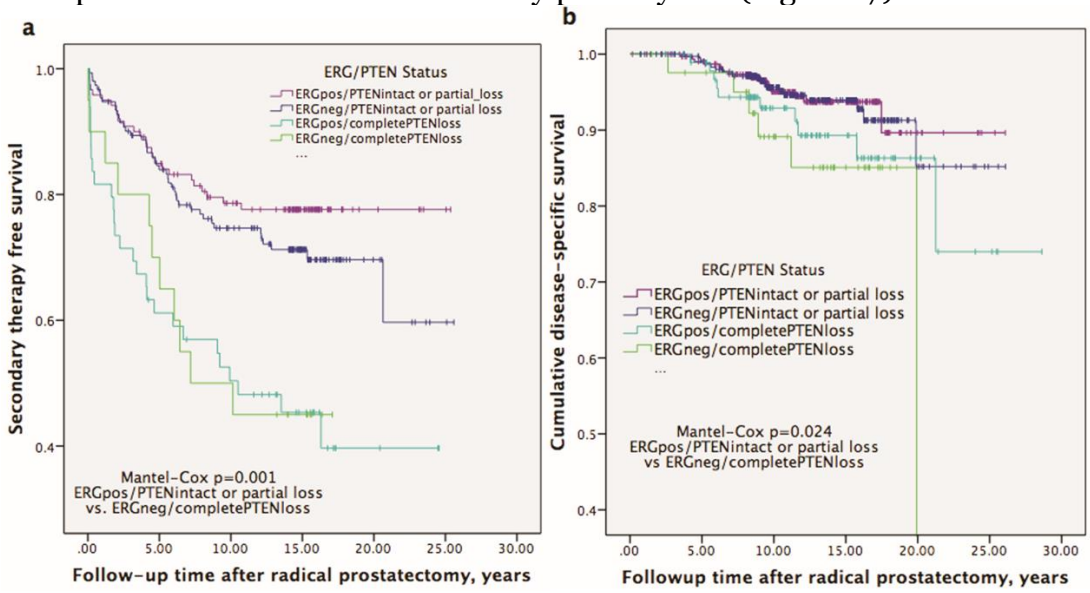


Figure 17 Association of combined ERG and PTEN expression status with (A) survival until seconday therapies and (B) disease-specific survival. Figure previously published in *Modern Pathology*, 29(12):1565-74 (2016), Lahdensuo et al., "Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy", by permission from Macmillan Publishers Ltd.

The utility of combined ERG/PTEN status in stratifying patients with intermediate-grade PC (Gleason score 7 or Grade group 3) was also assessed with Kaplan-Meier analysis. For these subgroups–similar to findings for the entire cohort–negative ERG expression coupled with complete PTEN loss led to the shortest DSS times (Figure 18).

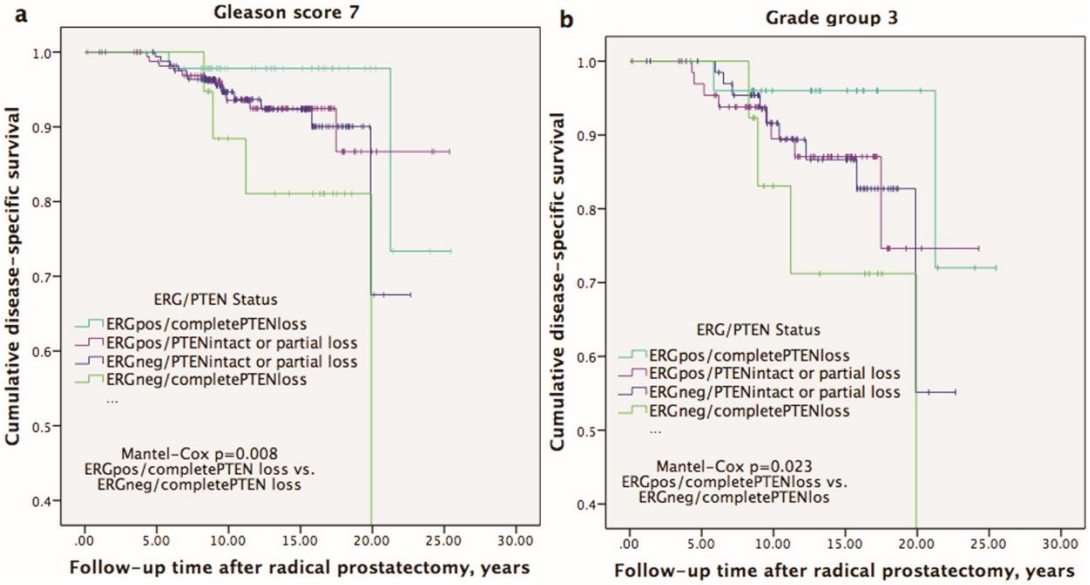


Figure 18 Association of combined ERG and PTEN expression status with disease-specific survival times in (A) Gleason score 7 subgroup and (B) Grade group 3. Figure previously published in *Modern Pathology*, 29(12):1565-74 (2016), Lahdensuo et al., ”Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy”, by permission from Macmillan Publishers Ltd.

The effect of AR expression status in ERG-positive and ERG-negative cancers with PTEN loss was also tested. Of the ERG-negative patients, 52% (92 of 177) showed high AR expression, compared to 76.8% (139 of 181) of the ERG-positive patients. In Kaplan-Meier analysis, ERG-negative patients with high AR expression had a significantly shorter DSS time than did ERG-negative patients with low AR expression. This shorter DSS time among ERG-negative patients with high AR was further accentuated by their complete loss of PTEN, and a similar effect occurred in analysis of the subgroup of Gleason score 7 patients (Figure 19). For ERG-positive patients, AR status failed to determine survival differences, nor did differences emerge among patients with complete PTEN loss in terms of AR-status-determined disease-specific survival.

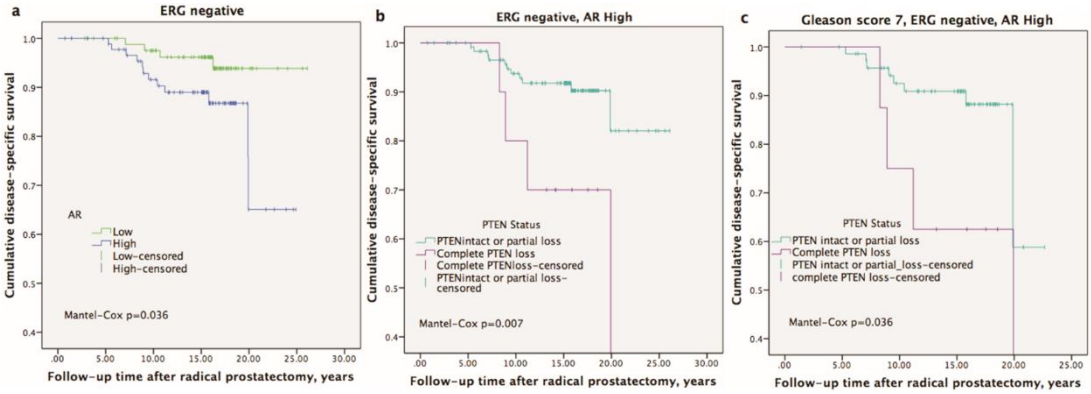


Figure 19 Association of combined marker statuses with disease-specific survival (DSS) time. (A) AR status stratified patients regarding DSS time for ERG-negative cases. (B) Complete PTEN loss was associated with shorter DSS time for ERG-negative patients with high AR expression. (C) Same analysis as in figure B, but for Gleason score 7 patients. Figure published in *Modern Pathology*, 29(12):1565-74 (2016), Lahdensuo et al., ”Loss of PTEN expression in ERG-negative prostate cancer predicts secondary therapies and leads to shorter disease-specific survival time after radical prostatectomy”, by permission from Macmillan Publishers Ltd.

6 DISCUSSION

6.1 MAIN FINDINGS AND DISCUSSION OF SUBSTUDIES

Study I

The rise in the incidence of post-biopsy bacteremias over the 9-year study period was 2.4-fold, which may be explained by several factors. Similar rising trends have been noted in other countries as well and have been linked to the concomitant rise in FQ resistance of enteric bacteria. Interestingly, half the causative organisms responsible for bacteremias in our material were FQ resistant, and the rest were FQ susceptible. This finding has brought to our attention shortcomings in implementing proper antibiotic prophylaxis for the biopsy procedure. The evident rising incidence of bacteremias may be in part a result of the evolving clinical practice of ordering blood cultures more actively for febrile patients now that urologists' awareness of serious post-biopsy complications has improved.

One important finding is that, in multivariate analysis, repeat biopsies did not elevate the risk for bacteremic infections. Repeat biopsies may predispose the patient to an increased risk for infectious complications, but evidence is already robust to counter this (Loeb et al. 2013a, Aly et al. 2015, Bokhorst et al. 2016a, Halpern et al. 2017). This is reassuring, considering that AS protocols rely heavily on repeat biopsies (Bruinsma et al. 2016) with the protocols at Johns Hopkins and the University of Miami even mandating biopsies annually.

Urologists need to be aware of the rising incidence of post-biopsy infectious complications. The possibility of developing an infectious complication requiring hospitalization–and hospital admission rates have been as high as 6.9% (Loeb et al. 2013b, Borghesi et al. 2017)–should be mentioned when discussing prostate biopsies with a patient. Prior to the procedure, the patient's possible predisposing risk factors for infections, especially diabetes (Simsir et al. 2010, Loeb et al. 2012, Halpern et al. 2017) and urinary catheters (Simsir et al. 2010, Eruz et al. 2017), need assessment. If the patient has recently traveled abroad (Patel et al. 2012), he should not receive the standard FQ prophylaxis but instead an alternative antibiotic or should be considered for targeted prophylaxis based on a pre-biopsy rectal swab (Duplessis et al. 2012, Taylor et al. 2012, Roberts et al. 2014, Cussans et al. 2016, Li et al. 2016). Having previously undergone a biopsy procedure need not be considered a risk factor for post-biopsy infections.

Limitations of this study include its retrospective design and its including information on only blood-culture-positive post-biopsy infections. Collecting data prospectively, ideally with patient-reported outcomes, would have provided a more comprehensive view of the occurrence of infectious

complications, not just blood-culture-positive infections. Lack of data on the number of negative blood cultures also prevents us from drawing definitive conclusions regarding our region's rising bacteremia-incidence trend and its underlying causes. Because the annual numbers of all blood cultures—positive and negative—were unknown, we are unable to rule out of the increasing incidence figures the role of urologists' ordering blood cultures more actively. This limitation was acknowledged during data acquisition, but extracting data on all blood cultures—positive and negative—during the observation period proved technically too challenging and had to be abandoned. The study's strengths derive from the comprehensive patient registries, which have covered the 9-year observation period for the entire hospital district and allowed collection of detailed clinical data on the bacteremic cohort.

Study II

The study confirmed that random biopsies are unreliable in predicting sextant-wise prostate tumor location and unilateral disease. These shortcomings make random biopsies a poor tool for detailed planning of radical therapies such as RP or RT. Not only did biopsies accurately predict unilateral disease in only one-fourth of the patients with unilateral disease at RP, but, puzzlingly, for 7% of patients, the biopsies predicted bilateral disease when it was actually unilateral. Similarly discouraging findings had occurred earlier, before our own data gathering (Schulte et al. 2008, De Laet et al. 2009, Gallina et al. 2012, Iremashvili et al. 2012, Washington et al. 2012), so we were interested in whether this held true for us. That our results are in line with those of other institutions indicates that our practices do not markedly differ from theirs.

The poor performance of 12-core biopsies is disheartening, but instead of abandoning the procedure, efforts should focus on improving it. Young doctors need proper training, with sufficient biopsy procedures performed under supervision to ensure that systematic errors do not occur. Active communication between the person taking the biopsies and the one placing the cores in specimen jars is key to ensuring correct sorting and labeling. The incorporation of a check list–similar to ones already in routine use in operating rooms—which ensures that all personnel involved with taking the biopsy know the required equipment and procedure stages, could also help to minimize errors in sampling and specimen handling. Finally, the placement of needles in the prostate could be routinely documented by registering devices such as those for fusion of US and MR images.

The sextant-wise analysis of RP specimens revealed that PC is rarely found in the base of the prostate and is more prevalent in the middle and apex. Although this is not widely studied, similar findings have emerged (Mai et al. 2002, Takashima et al. 2002, Ishii et al. 2007). Biopsies overestimated the prevalence of cancer in the base of the prostate, leading to low PPVs for positive biopsy from the base. This is most likely due to a systematic error in

the biopsy procedure, where the needle fails to be inserted adequately deeply in the prostate due to the aim of avoiding unnecessarily sampling the seminal vesicles or puncturing the bladder neck and causing bleeding (Figure 5C).

Our statistical analyses indicate that the extent of cancer in biopsy cores correlates positively with extent of cancer in the corresponding RP-specimen sextant, but the clinical significance of our finding is less clear. It is possible that the strengthening of the positive correlation as we move from the base to the apex is more indicative of the concurrent increasing prevalence of tumors in the craniocaudal direction. The lower prevalence of tumors in the base is possibly explained by the zonal anatomy of the prostate. The peripheral zone, where most PC arises, extends to the base only in the posterior part of the prostate (Figure 6). Likewise, the transitional zone, the second-most common origin zone for PC, does not reach the base. The base is therefore mostly comprised of the central zone and fibromuscular stroma. This could explain the low prevalence of PC in the base.

In further assessment of tumor morphology, half the patients with significant PC had only one significant lesion, which would hypothetically make these patients candidates for focal therapies of such lesions. Around 40% of our patients with significant PC had their significant disease confined to one side, making them candidates for possible hemiablative techniques. Random 12-core biopsies are, however, not nearly reliable enough for planning of such tissue-sparing techniques.

Most cases of extraprostatic extension and positive surgical margins at RP were extensions of the index tumor. Choice of index tumors was based on degree of dedifferentiation as opposed to the more common criterion of tumor volume (van der Kwast et al. 2011). With these criteria, we were able to pinpoint those tumors that had caused unfavorable outcomes at RP. This should encourage the practice of assigning the index tumor based primarily on degree of dedifferentiation, and only secondarily on tumor size.

The limited performance of biopsies in our study raises the question of the role of random biopsies in the diagnosis and treatment planning of PC patients today. Urologists should be aware of shortcomings in predicting tumor location and extent and avoid relying too heavily on biopsies in the risk stratification of patients. It is this uncertainty that has made urologists ready to adopt prostate MRI in the diagnosing and staging of localized PC, because MRI appears to be more reliable in estimating disease location and even its aggressiveness. For the time being, however, random biopsies are the first-line tool for diagnosing PC until prostate MRI becomes more readily accessible and affordable. Prostate MRI may someday make random biopsies redundant, because possible MRI-visible lesions can consequently be sampled with MRI-targeting techniques. The objective of this approach would be the accurate detection of clinically significant disease while leaving apparently low-grade tumors undiagnosed. If radical therapies are later planned, the patients will then already have undergone prostate MRI, useful in planning of nerve-sparing RP or treatment fields for RT with greater reliability than with current

random biopsies. MRI is, however, also an imperfect tool for this purpose. A 2016 meta-analysis has shown the sensitivity and specificity of overall detection of T3 disease—pooling results from 38 studies—to be 61% and 88% (de Rooij et al. 2016).

Our findings came from a fairly small number of patients, which may limit generalizability. A potential source of bias in comparing tumor locations sextant-wise is the assignment of sextant divisions differing between the persons taking the biopsies. Our analysis also did not take prostate volume into account, although sampling very small and very large prostates have their own challenges. The study's strengths are in the reliability of the data because of standardized biopsy protocols and specimen-handling procedures as well as reanalysis of all RP specimens by one experienced uropathologist.

Study III

Study III can be viewed as a report of our early experiences with prostate MRI. We were interested in evaluating how prostate MRI would perform as a follow-up tool for patients on AS at our institution and whether it would bring additional value.

PC was visible on MRI for only half these patients. This is in line with the fact that these patients all harbored low-risk PC. Tumor MRI visibility showed no positive correlation with any clinical or pathological finding that could possibly indicate greater tumor burden, nor did it correlate with discontinuation of AS; the latter was somewhat surprising. MRI reports were available to the treating urologists when the patients came in for their repeat biopsies. What could therefore have been expected is that an MRI-visible tumor would affect decision-making towards discontinuation of AS, but this again reflects how unacquainted urologists were with prostate MRI and its significance at the time. Today we know that the PPV of an MRI-visible lesion for accurately detecting clinically significant PC is modest. The PROMIS study has found the PPV to be 65%, while a 2015 review has reported it to range between 34 and 93% (Fütterer et al. 2015). The decision to discontinue AS and advance to radical therapy should therefore not be made solely because of an MRI-visible tumor; histological confirmation with biopsy of higher-grade disease is, for the time being, mandatory.

When a tumor was visible on MRI, its location correlated poorly with the tumor location estimated by prostate biopsies. This is more likely a reflection of the inaccuracy of prostate biopsies than of MRI shortcomings.

In our study, MRI lacked value as a follow-up tool for AS patients, and the information it offered failed to influence clinical treatment choices. Based on the study findings, prostate MRIs were not ordered for AS patients at our clinic for some years. The study taught us that even though the patient population was homogenous, and the question regarding MRI–"Is the cancer visible on MRI or not?"–was well defined, performing MRIs with suboptimal techniques and inadequate standardization would likely be of limited value. Prostate MRI

has since developed enormously, however. The uroradiologists at our institution now show a great deal of interest in prostate MRI, and both versions of the PI-RADS system have been adopted into clinical practice: version 1 in 2012 and version 2 in 2015. This means that prostate MRI is currently performed with multiparametric techniques and has been reported in a standardized and structured format since 2012. As a result, prostate MRI is now more informative and is readily ordered for AS patients. At our institution, its timing is most commonly immediately after diagnosis of PC either to exclude the presence of significant PC or in the same setting as in our study, meaning before repeat or confirmatory biopsies. For PRIAS patients it is also employed when the surveillance protocol mandates extra measures because of decreased PSA-doubling time. Patients who take part in the PRIAS study and who have prostate MRI as part of their follow-up are currently included in the ongoing prospective PRIAS-MRI side-study (Hoeks et al. 2014). It will be interesting to see how the implementation of PRECISE guidelines for reporting of MRI for patients on AS (Moore et al. 2017) will affect radiological practices and AS-patient treatment.

An obvious limitation to the validity of our findings stems from the methods by which prostate MRIs were conducted and assessed. The MRIs were performed without much previous experience and before local standardization of imaging techniques. Compared to imaging standards today, the DWI was then performed with inadequately low b values and with no dynamic-contrast enhancement–a requirement for mpMRI. The radiological assessment of images also lacked current standardization, but at least all of the images were viewed by the same uroradiologist. One strength of our study is that the MRIs were performed on a homogenous patient population: patients with only low-volume, low-grade PC, all studied after one year on surveillance and before their repeat biopsies; this eliminated any possible effects on the images of biopsy artefacts.

Study IV

The main finding was that complete loss of PTEN expression raised the risk of PC death and the risk for receiving secondary therapies after RP. As a single biomarker, complete loss of PTEN expression appears the most promising indicator of disease progression for clinical use, because of its strong association with required secondary therapies after RP and shortened DSS time. Another finding was that, in regard to DSS, ERG-negative-PTEN-negative patients with high AR expression had the poorest outcomes. We can only speculate on the underlying mechanisms: based on other reports, it appears that in the absence of *TMPRSS2:ERG* fusion, some as-yet poorly defined factors contribute to activating AR-signaling and promote PC progression (Culig et al. 1994, Sahu et al. 2011, Hoang et al. 2017). This may be the reason why *TMPRSS2:ERG*-fusion-negative patients have poorer

treatment responses to androgen-deprivation therapy (Attard et al. 2009, 2015, Graff et al. 2015).

Marker-expression status did not stratify patients in regard to OS, which could be viewed as a shortcoming. OS can to some degree be considered an even more meaningful and significant endpoint than DSS. This is because OS is not susceptible to interpretation bias, whereas with DSS what is not always obvious is whether or not PC was the definite cause of death. When studying the effects of cancer treatment, OS should ideally be the end-point, because the aim of treatment is prolongation of life expectancy. Our study was, however, not an intervention trial; it was instead an observational study of the effects of marker expression on outcome after RP. In this setting, OS is therefore less relevant than DSS.

Findings from our observational retrospective study on heterogenous patient cohorts can be considered hypothesis-generating only, because of its retrospective design and because marker expression status had no influence on treatment choice. Properly exploring the prognostic performance of these biomarkers would require prospective study settings; ideally, marker expression status would be determined from diagnostic biopsy.

Based on our results, what can be speculated is that patients with unfavorable marker combinations may be unsuitable candidates for AS and should possibly opt for immediate radical therapy instead. When opting for immediate RT, perhaps those patients would benefit from a higher radiation dose, larger treatment fields, or longer adjuvant hormonal therapy after RT or even high-dose brachytherapy in addition to conventional RT. If unfavorable markers were encountered in an RP specimen, perhaps that patient would benefit from more intense PSA follow-up, or even immediate adjuvant RT, instead of salvage RT at a later stage.

Because ERG-negative-PTEN-negative patients may have a poorer reponse to treatment with either conventional androgen-deprivation therapy or abiraterone, they may be good candidates for early administration of cytotoxic therapies at their hormone-naïve but metastatic stage. Furthermore, in the castration-resistant stage, they may possibly benefit from sequential cytotoxic treatments instead of novel antiandrogens. Because *PTEN* loss activates the *PI3K/Akt/mTOR* pathway, patients demonstrating loss of PTEN expression may possibly benefit from mTOR-targeted therapies–a concept currently studied in patients with castration-resistant PC (Statz et al. 2017).

The main limitation of this study is its retrospective design: the fact that the patients' operations took place between 1983 and 2005. It can also be argued that the Helsinki patient cohort was historical, as those patients treated in the 1980's were diagnosed in the pre-PSA era. Because of slow disease progression, very long follow-up times are, however, necessary when studying survival outcomes of PC, especially if the outcome is DSS. The study's strengths include our fairly large patient cohort and comprehensive mortality data. Our findings were achieved by means of IHC methods for determining marker expression status instead of more cumbersome techniques. This is

encouraging when considering assessment of marker expression status in the clinical practice of PC diagnosis and treatment.

6.2 THE CHANGING NATURE OF LOCALIZED PROSTATE CANCER

When deciding on appropriate treatments for localized PC today, it is virtually impossible to find studies of similar patients with reliable data on long-term outcomes. Ten to fifteen years is generally considered the minimum follow-up time before achievement of any meaningful conclusions about PC outcomes. This makes study patients inherently very different from today's newly-diagnosed patients, because the clinical practice in diagnosing and treating patients is constantly evolving. The greatest shift occurred with introduction of the PSA test in the 1980's. The European Randomised Study of Screening for Prostate Cancer revealed that PSA screening led to PC's being detected almost seven years earlier than it would have been otherwise (Finne et al. 2010). Study cohorts of men from the pre-PSA era differ markedly from later ones, a fact well-known and actively mentioned especially in discussing results of the SPCG-4 trial (Bill-Axelson et al. 2014).

Since the 1980's, other modifications have occurred in the diagnostic process of PC, but none with such major effects as the PSA test. As one example, 12-core biopsies are currently standard practice, unlike 15 years ago. Twelve-core biopsies detect more low-volume tumors than do sextant biopsies, making sextant biopsies now obsolete. Strategies for sampling the prostate have also evolved. Instead of repeating random biopsies multiple times, the strategy is now actively changed even after the first round of negative biopsies–either to more anteriorly directed biopsies or to MRI-targeted approaches. These biopsy practices lead to high detection rates of early-stage, low-volume PC, some of which will eventually receive radical therapies. The increasing incorporation of prostate MRI at the diagnostic stage concurrently leads to more MRI targeting of prostate biopsies. Because MRI has a high sensitivity for Gleason grade 4 and higher disease, such lesions are frequently targeted. This results in the overdetection of low-volume Gleason score 3+4 cancers that may have previously been diagnosed as Gleason score 3+3 based on biopsies and could have been managed with AS instead of with radical therapies.

The Gleason grading system has also undergone modifications that affect the comparability of historical patient cohorts with contemporary ones. In 2005, the decision was that instead of reporting the most and second-most prevalent Gleason grade patterns in biopsy samples, the report should state the most common and the most dedifferentiated pattern (Epstein et al. 2005). Another modification entailed assigning distinct histological patterns as Gleason grade 4 rather than grade 3 (Epstein et al. 2005). This resulted in both Gleason score 6 and 7 PC constituting less aggressive disease today than prior

to 2005. It also remains to be seen how the most-recently introduced Grade grouping (Epstein et al. 2016b) will affect treatment planning.

These changes in biopsy sampling and pathological practice have resulted in contemporary RP and RT cohorts representing less aggressive disease than did historical cohorts, even when stratifying patients by PSA level or Gleason score—evident in the differences between SPCG-4 and PIVOT study patients (Wilt et al. 2012, Bill-Axelson et al. 2014). Results from studies on historical cohorts must therefore be interpreted while remaining mindful of these differences. One way to counteract this phenomenon of RP and RT cohorts' now comprising patients with less aggressive disease would be to update contemporary guidelines on risk stratification and AS. Allowing AS protocols to include a higher number of positive cores and—to a certain extent—including Gleason grade 4 as a secondary pattern would make more patients eligible for AS and, consequently, reserve RP and RT as treatment choices for truly higher-risk disease. MRI and MRI-targeted biopsy are increasingly employed for AS patients. Possible undetected anterior tumors and higher-grade tumors are therefore increasingly ruled out at the commencement of AS, which makes AS safer for patients compared to the situation in the pre-MRI era. Risk stratification could, all things considered, also include MRI findings, because MRI is currently routinely used in disease staging and in checking for clinically significant disease.

On the other hand, so-called inverse stage migration has already been noticed in contemporary RP cohorts (Budaus et al. 2011, Silberstein et al. 2011, Bernie et al. 2014). This is a consequence of RP's currently being offered less often for patients with low-risk PC, following accumulated evidence of limited benefit for such patients (Wilt et al. 2012, Hamdy et al. 2016). Low-risk patients are therefore most often offered AS. RP is also increasingly offered to patients with locally advanced disease as part of a multimodal-treatment approach (Mottet et al. 2017).

6.3 IMPLICATIONS AND FUTURE PERSPECTIVES

Over the period during which this thesis study took place, the diagnostic workup of PC has changed substantially, mainly due to the introduction of contemporary mpMRI and PI-RADS. The shortcomings of random biopsies in detecting PC, especially clinically significant cancer, and predicting disease location and extent are well-established. Prostate MRI has a high sensitivity and NPV for clinically significant PC (Moldovan et al. 2017), making it a promising tool for prebiopsy screening. This has now in part led to the clinical practice of unorganized "two-tier" screening: first, PSA screening by primary-care doctors, and then MRI screening at the urological clinic, only after which may patients be invited for prostate biopsies: either conventional or most often MRI-targeted.

Evidence is already robust that MRI targeting detects more cases of clinically significant PC than does a standard prostate biopsy. Due to the poor performance of random prostate biopsies, the need is ongoing to explore their replacement with MRI and MRI-targeted biopsies. This has already been investigated in randomized trials, but thus far with conflicting results (Panebianco et al. 2015, Baco et al. 2016, Porpiglia et al. 2016, Taverna et al. 2016, Tonttila et al. 2016).

Among the goals of such a radical shift in clinical practice would be to lessen harm to patients by reducing unnecessary biopsies and biopsy-related complications. An interesting secondary end-point—besides accuracy–in comparing these diagnostic strategies would be the revelation of whether differences exist in the occurence of post-biopsy events like infection, pain, and hemorrhagic complications. These should ideally be assessed by means of patient-reported outcome and evaluation of quality of life. The total cost of both diagnostic pathways, including the cost of post-biopsy complications, also requires calculation. The seemingly higher initial cost of the prebiopsy-MRI approach may later balance out, because the current standard of care for patients with PC detected by random biopsy is to undergo prostate MRI before initiation of radical therapy.

Some pathological considerations regarding the replacement of random biopsies with prebiopsy MRI and MRI-targeted biopsies are as yet unanswered. In a hypothetical trial comparing the two strategies, many patients with significant PC in either arm would advance to RP, which would then offer the opportunity to compare the performance of random versus MRI-targeted biopsy in predicting disease location and aggressiveness. Presumably there would be less upgrading and downgrading of disease in the prebiopsy-MRI arm, but there exists as yet scant evidence to support this hypothesis. MRI targeting would most likely also perform better than random biopsy in detecting the index tumor in the prostate, the index tumor's being the most dedifferentiated and often the largest.

Incorporating the study of tissue markers would be an additional interesting aspect. Prospective assessment of marker expression, such as for ERG and PTEN, both from diagnostic biopsies and from RP specimens, would allow comparison of the ability of MRI-targeted and random biopsies to detect unfavorable marker expression in PC foci. Tissue marker expression in MRI-targeted biopsies has thus far lacked much intensive study.

To assess whether the diagnostic approach of prebiopsy MRI followed by MRI-targeted biopsies results in improved risk stratification, the clinical outcomes of treated patients would also require analysis. An immediate end-point would be, for those patients undergoing RP, unfavorable pathological outcomes such as seminal-vesicle invasion, extraprostatic extension, and positive surgical margin; these could be compared between trial arms. Intermediate end-points could be discontinuation of AS, biochemical recurrence, and requirement of secondary therapy after RP and RT, plus clinical disease progression such as metastases. Long-term results like OS and

DSS would likely require very extensive follow-up, 10 years at a minimum, to show differences between trial arms.

Total incidence rates of PC in developed countries are currently not rising (Finnish Cancer Registry 2016, Hoffman et al. 2016). This is likely due to the substantial number of cases already diagnosed during the "heydays" of organized and unorganized PSA screenings and due to doctors' improved awareness of the adverse effects of screening today. The PSA test is, nonetheless, here to stay. Doubtlessly, the prevailing clinical practice, in which, without recommendations for PC screening, PSA screening is arbitrarily offered to unselected men, is unsatisfactory for precise detection of clinically significant PC.

As screening is now less frequent, PC incidence, diagnosed at the metastatic stage, has started rising again, at least in 50- to 69-year-old US men based on SEER registry data (Hoffman et al. 2016). It is therefore possible that screening for PC, perhaps with a combination of PSA and genetic markers, will someday make a comeback. In light of this, it is especially important to optimize diagnostic processes and risk stratification in order to avoid overdetection and overtreatment of low-risk PC and to detect in time significant PC and offer patients necessary curative treatment appropriately.

7 CONCLUSIONS

1) The average annual incidence of bacteremic complications following transrectal biopsies was 0.7%, with a trend toward a rising incidence observable. No clinical risk factor for bacteremias was identifiable. Recent international travel significantly raised the risk for developing bacteremia from an FQ-resistant organism. Patients with recent travel abroad should be candidates for alternative antibiotic prophylaxis or, following rectal swabs and fecal cultures, for tailored prophylaxis. Reduction in unnecessary biopsies and in biopsy-related infections calls for development of new strategies.
2) Twelve-core transrectal biopsies predicted the locations and extent of PC tumors in RP specimens unreliably and would have performed poorly in planning of focal therapies. Planning of radical therapies is currently based on findings from prostate MRI. Positive surgical margins and extraprostatic extension at RP mostly resulted from the index tumor, supporting the rationale of designating the index tumor based primarily on its degree of dedifferentiation instead of on tumor size.
3) Prostate MRI had limitations when serving as a follow-up tool in the AS of PC. Low-volume, low-grade PC was visible on MRI for only half the patients. Without standardized imaging and reporting protocols such as PI-RADS, prostate MRI does not add value to the diagnosis and follow-up of PC patients.
4) Loss of PTEN expression appeared to be a strong driver of disease progression, leading to shorter DSS times and after RP, shorter survival time free of secondary therapy. The subpopulation of patients with the poorest outcomes had cancers that were ERG-fusion negative and PTEN negative with high levels of AR expression. The prognostic performance of PTEN loss should be investigated further in prospective-study settings.

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