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To Jaana, Oosa and Iiris

ABSTRACT

Heikki Seikkula
Studies on prostate-specific antigen and prostate cancer epidemiology

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The prostate-specific antigen (PSA) is the main biomarker for diagnosis and treatment response monitoring in prostate cancer (PCa). In the first part of this thesis, we investigated the prognostic value of ultrasensitive PSAs (u-PSAs) in evaluating the risk of biochemical recurrence (BCR) and further progression after radical prostatectomy (RP). BCR after RP is defined by two consecutive PSA values greater or equal to 0.2 ng/ml. We found that u-PSA values above the threshold of 0.02-0.03 ng/ml predict progression to the BCR threshold (> 0.2 ng/ml). Furthermore, we demonstrated that the longitudinal modeling of u-PSA doubling time (uDT) could predict BCR after RP with very low PSA values. This can be beneficial in helping practitioners to avoid unnecessary adjuvant treatments or to start salvage treatments earlier for selected patients.

In the second part of this thesis, PCa survival and mortality was investigated in the pre- and post-PSA eras. One of the cohort studies evaluated the impact of socioeconomic status (SES) on the survival of PCa patients in the pre- and post-PSA eras. Our study showed that men with localized PCa are otherwise healthier than the general male population, and the increased difference between relative and cancer-specific survival reflects the most likely selection of men for opportunistic PSA-testing. Men in higher SES groups had significantly lower risks of dying from PCa than those in the lower SES groups, which was probably due to more intensive diagnostic/treatment strategies and the increased intensity of health conscious men seeking medical services such as PSA testing.

Keywords: prostate-specific antigen, ultrasensitive prostate-specific antigen, radical prostatectomy, prostate cancer epidemiology, prostate cancer specific survival, prostate cancer mortality

TIIVISTELMÄ

Heikki Seikkula
Tutkimuksia prostataspesifisestä antigeenista ja eturauhassyövän epidemiologiasta

Turun ylipisto, Lääketieteellinen tiedekunta, Kirurgia; Turun yliopiston kliininen tohtoriohjelma; Turun yliopistollinen keskussairaala, urologia

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Prostataspesifinen antigeeni (PSA) on tärkein eturauhassyövän verinäytetutkimus. Tämän tutkimuksen ensimmäisessä vaiheessa selvitimme ultrasensitiivisen PSA:n (u-PSA) merkitystä eturauhassyövän seurannassa radikaalin eturauhasen poistoleikkauksen jälkeen. Biokemiallinen relapsi (BCR) leikkauksen jälkeen tarkoittaa kahta peräkkäistä PSA-arvoa, jotka ylittävät arvon 0.2 ng/ml. Tutkimuksessamme osoitimme, että jos u-PSA nousee tasolle 0.02-0.03 ng/ml, PSA-pitoisuus nousee yli 90% potilaista myös BCR-tasolle. Lisäksi osoitimme, että u-PSA:n kahdentumisajan (uDT) longitudinaalinen mallintaminen auttaa BCR:n ennustamisessa jo hyvin pienillä u-PSA-arvoilla. Tämä on erityisen hyödyllistä, kun halutaan välttää turhia liitännäishoitoja ja toisaalta kohdentaa ne riittävän ajoissa oikeille potilaille.

Tutkimuksen toisessa vaiheessa eturauhassyöpäkuolleisuutta ja potilaiden elossaoloa (survival) tutkittiin ennen ja jälkeen PSA-testauksen yleistymistä. Tutkimus toteutettiin rekisteritutkimuksena Suomen Syöpärekisterin ja Tilastokeskuksen tiedoista. Tilastokeskuksen tiedoista selvitettiin vuosittainen eturauhassyöpäpotilaiden ikäryhmittäinen kuolleisuus suhteessa vertailuväestön kuolleisuuteen. Samoin potilaiden sosioekonomisen asema (SES) selvitettiin Tilastokeskuksesta. Tutkimus osoitti, että miehet joilla todettiin paikallinen eturauhassyöpä olivat muuten terveempiä kuin vertailuväestö. Eritoten PSA-testin käyttöönoton jälkeen eturauhassyöpäpotilaiden suhteellinen elossaololuku oli selvästi korkeampi kuin syöpäspesifinen elossaololuku potilailla, joilla oli paikallinen eturauhassyöpä. Tämä viittaa siihen, että nämä miehet valikoituivat useammin opportunistiseen PSA-seulontaan. Tutkimus osoitti myös, että korkeampi SES korreloi huomattavasti pienempään syöpäspesifiseen kuolleisuuteen. Tämä on oletettavasti selitettävissä, sillä että näille miehille tehtiin enemmän eturauhassyöpädiagnostiikkaa ja heitä hoidettiin intensiivisemmin kuin alhaisemmassa SES-asemassa olevia. Näille miehille myös ilmeisimmin tehtiin enemmän PSA-testausta. Yhteenvetona voidaan todeta, että u-PSA voi olla hyödyllinen taudin uusimisen arvioinnissa leikkauksen jälkeen, ja että PSA-testin käyttö pitäisi optimoida kaikille väestöryhmille, välttäen yli- ja alidiagnostiikkaa.

Avainsanat: prostata-spesifinen antigeeni, ultrasensitiivinen prostataspesifinen antigeeni, radikaali prostatektomia, eturauhassyövän epidemiologia, eturauhassyöpäkuolleisuus

TABLE OF CONTENTS

ABBREVIATIONS

4KRK	a panel of four kallikrein markers
5-ARI	5-alpha-reductase inhibitor
ADT	androgen deprivation therapy
AS	active surveillance
ASAP	atypical small acinar proliferation
ASR	age-standardized rate
AUC	area under the curve
BCR	biochemical recurrence
bpMRI	biparametric magnetic resonance imaging
BS	bone scan
CAB	complete androgen blockade
CHAARTED	Androgen Ablation Therapy with or without Chemotherapy in Treating Patients with Metastatic Prostate Cancer
CI	confidence interval
CR	cure rate
CRPC	castration resistant prostate cancer
CSS	cancer-specific survival
CT	computed tomography
cTNM	clinical Tumor, Node and Metastases classification
CVD	cardiovascular disease
CVM	cardiovascular mortality
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DRE	digital rectal examination
EBRT	external beam radiation therapy
ECLIA	electrochemiluminescence immunoassay
EPIC	European Prospective Investigation into Cancer and Nutrition
ePLND	extended pelvic lymph node dissection
ERSPC	European Randomized Study of Screening for Prostate Cancer
f/t PSA	a free/total prostate-specific antigen ratio
FCR	Finnish Cancer Registry
fPSA	free prostate-specific antigen
GUI	graphical user interface
Gy	Gray
HDL	high-density lipoprotein
HDR-BT	high-dose-rate brachytherapy
HGPIN	high-grade prostate intraepithelial neoplasia
hk2	human kallikrein 2
hk3	human kallikrein 3

IAD	intermittent androgen deprivation therapy
ICD-10	International Statistical Classification of Diseases and Related problems version 10
IGF-1	insulin-like growth factor-1
IGRT	image-guided radiotherapy
IMRT	intensity-modulated radiotherapy
iPSA	intact prostate-specific antigen
IRB	research ethical board
ISUP	International Society of Urologic Pathology
LHRH	luteinizing hormone releasing hormone
mCRPC	metastatic castration resistant prostate cancer
mpMRI	multiparametric magnetic resonance imaging
MSE	median squared error
NNT	number needed to treat
NSAA	nonsteroidal anti-androgen
NSAID	non-steroidal anti-inflammatory drug
OCS	other-cause survival
OS	overall survival
PCa	prostate cancer
PCA3	prostate cancer antigen 3
PCPT	prostate cancer prevention trial
PCSM	prostate cancer-specific mortality
PET	positron emission tomography
PFS	progression free survival
PHI	prostate health index
PI-RADS	prostate imaging-reporting and data system
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PLND	pelvic lymph node dissection
PRIAS	Prostate cancer Research International: Active Surveillance
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSAV	prostate-specific antigen velocity
PSMA	prostate-specific membrane antigen
pTNM	pathologic Tumor, Node and Metastases classification
PYs	person years
RALP	robot-assisted laparoscopic prostatectomy
RCT	randomized controlled trial
REDUCE	a clinical study to reduce the incidence of prostate cancer in men who are at increased risk

ROC	receiver-operative characteristics
RP	radical prostatectomy
RR	relative risk
RT	radiotherapy
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results program
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SES	sosioeconomic status
SM	surgical margins
SMR	standardized mortality ratio
SPCG-4	Scandinavian Prostate Cancer Group Study number 4
SPECT	single-photon emission computed tomography
SRE	skeletal-related event
STHLM3	the Stockholm 3 model
tDT	traditional PSA doubling time
t-PSA	total PSA
TNM	tumor, node and metastases
TRUS	transrectal ultrasound
uDT	ultrasensitive prostate-specific antigen doubling time
PSA	prostate-specific antigen
u-PSA	ultrasensitive prostate-specific antigen
u-PSAA	ultrasensitive prostate-specific antigen assay
WB-MRI	whole-body magnetic resonance imaging
WW	watchful waiting

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-IV.

I **Seikkula H, Syvänen KT, Kurki S, Mirtti T, Taimen P, Laato M, Boström PJ.** Role of ultrasensitive prostate-specific antigen in the follow-up of prostate cancer after radical prostatectomy. *Urol Oncol*. 2014 Nov 18. pii: S1078-1439(14)00353-6. doi: 10.1016/j.urolonc.2014.10.010. (Epub ahead of print)

II **Laajala TD¶, Seikkula H¶, Seyednasrollah F, Mirtti T, Boström PJ, Elo LL**. Longitudinal modeling of ultrasensitive and traditional prostate-specific antigen and prediction of biochemical recurrence after radical prostatectomy. ¶ These authors contributed equally. *Sci Rep*. 2016 Nov 2;6:36161.

III **Seikkula HA, Kaipia AJ, Rantanen ME, Pitkäniemi JM, Malila NK, Boström PJ.** Stage-specific mortality and survival trends of prostate cancer patients in Finland before and after introduction of PSA. *Acta Oncol.* 2017 Jul;56(7):971-977.

IV **Seikkula HA, Kaipia AJ, Ryynänen H, Seppä K, Pitkäniemi JM, Malila NK, Boström PJ.** The impact of socioeconomic status on stage specific prostate cancer survival and mortality before and after introduction of PSA test in Finland. *Int J Cancer (In Press). 2017. doi: 10.1002/ijc.31109*

1 INTRODUCTION

Prostate cancer (PCa) is the most common non-skin cancer in elderly males (> 70 years of age) in Europe. PCa is a major health concern, especially in developed countries with a greater population of elderly men in the general population (Mottet et al. 2016). PCa in developed countries is currently characterized by high incidence and low mortality. PCa is usually diagnosed at an advanced age, and disease progression is slow. In a Danish population-based study, the mean age of PCa diagnosis was 74.6 years, and the 5-year age-standardized relative survival of PCa patients between 1999 and 2007 was approximately 90% in Finland and 85% in Scandinavia (Ingimarsdottir et al. 2016, De Angelis et al. 2014).

The prostate-specific antigen (PSA) was established as a main biomarker of the disease with its discovery in 1979. Its use began in clinical applications in the late 1980s through 1990 (Sensabaugh 1978, Wang et al. 1979, Wang et al. 1981, Papsidero et al. 1980, Kuriyama et al. 1981). Today, PSA is widely used for the detection or screening of the disease and for monitoring patients after treatment. Some PSA assays are capable of detecting very low levels of PSA from human serum; these values are considered ultrasensitive PSA (u-PSA) values when they are detected at levels under 0.1 ng/ml (Ferguson et al. 1996). No studies, to the best of our knowledge, have demonstrated that uPSA-triggered therapy improves the prognosis or overall survival. However, u-PSA tests could potentially detect biochemical recurrence (BCR) after radical prostatectomy (RP) significantly earlier than traditional PSA (t-PSA) assays (Shen et al. 2005).

Since the onset of PSA testing, the incidence of localized PCa has increased rapidly (Neppl-Huber et al. 2012), and in Finland, it seems to have leveled off after 2008 (Fig. 1), according to the Finnish Cancer Registry (Finnish Cancer Registry). PCa mortality has sharply declined during the recent decades in Finland (Fig. 1). Also in the United States the mortality rate of PCa has declined since early 1990 (Tarone, Chu and Brawley 2000). Still, the observed decline in mortality since 1991 is unlikely to be explained by PSA screening alone (Etzioni et al. 1999). However, opportunistic and organized PSA screening policy alone explains part of the decline of PCa-specific mortality in recent decades (Siegel et al. 2014, Stattin et al. 2014, Welch and Albertsen 2009, Schroder et al. 2014). One hypothesis about the decline in mortality is that it is partly due to more aggressive treatment of PCa since the 1980s, whereas the rates of both RP and radiotherapy (RT) have risen steadily (Welch and Albertsen 2009). Radical treatment may even explain one-third of the decline in PCa mortality (Kvåle et al. 2007).

One important mediating factor for PCa mortality is socioeconomic status (SES). Patients with lower SES have lower incidence and higher mortality from PCa than

those in higher SES, which is widely explained by higher tumor aggressiveness, comorbidity, treatment, and metabolic indicators (Larsen et al. 2016). However, despite of accumulating evidence about the risk factors and mediating indicators for the risk of PCa progression and mortality, the individual contributions of the different factors to the observed changes in PCa outcomes remain uncertain.

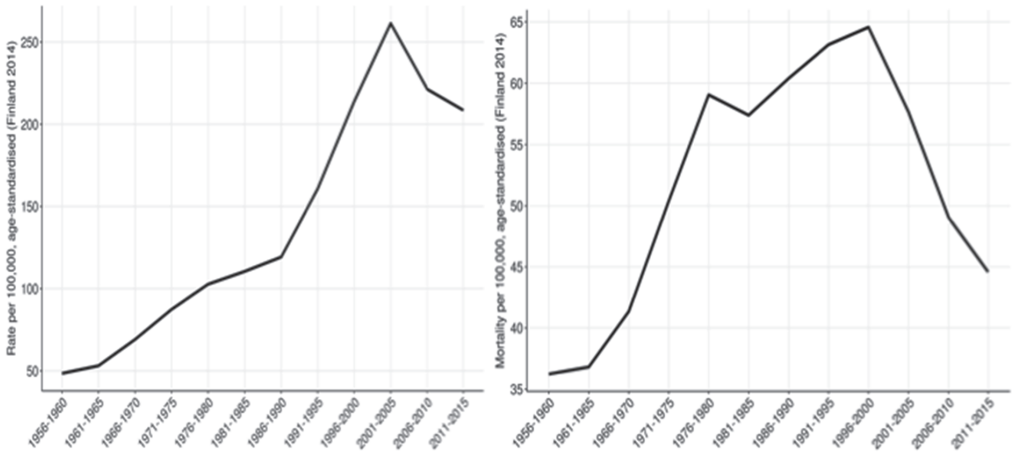

Figure 1: Age standardized 5-year periodal prostate cancer incidence (left) and mortality (right) in Finland between 1956-2015 (Modified from Finnish Cancer Registry).

2 REVIEW OF LITERATURE

2.1 Prostate cancer definition and epidemiology

2.1.1 Definition

Adenocarcinoma of the prostate is the most predominant malignant lesion of the prostate gland, comprising more than 95% of prostate malignancies. Other malignancies, such as sarcomas, lymphomas, and transitional and squamous cell carcinomas, are rare. Adenocarcinoma of the prostate is characterized by a transformed epithelial cell population in the prostate gland. This current study's focus is only on adenocarcinoma of the prostate. The majority of the adenocarcinomas are in the peripheral zone of the prostate gland (Epstein et al. 1994). The remaining proportions of tumors are predominantly in the transition zone (i.e., periurethrally or anteriorly). Adenocarcinoma of the prostate is multifocal in more than 85% of cases (Byar and Mostofi 1972). The most frequent sites of metastatic PCas are the lymph nodes and bone; 90% of patients with distant non-nodal metastases have bone metastases, and 26% have lung metastases (Bubendorf et al. 2000). Almost all cases with lung metastases have bone involvement as well (Varkarakis et al. 1974). The clinical progression of PCa is slow, and estimates from autopsy studies indicate that approximately 50% of men older than 50 years of age have PCa (Franks 1973, Hølund 1980, Zlotta et al. 2013). In the United States, men have a lifetime risk of 17% to have PCa and a 2.6% risk of dying from PCa (American Cancer Society 2008), whereas 35% of Swedish men and 16% of US men diagnosed with PCA die from this disease (Epstein et al. 2012). On average 4827 new PCa cases were detected and 873 men died from PCa yearly during the time period 2011-2015 in Finland (Finnish Cancer Registry).

2.1.2 Incidence and prevalence

PCa is major health concern in developed countries with a greater population of elderly males in the general population. The onset of the disease usually occurs rather late in life, and most patients are > 70 year of age (Mottet et al. 2016). In less developed areas, the disease is less frequently diagnosed. The age-standardized rate (ASR) of PCa incidence was 77.62/100,000 person years (PYs) in 2014 in Finland (Finnish Cancer Registry 2014).

There were approximately 1.1 million new cases of PCa worldwide in 2012, and the ASR was 69.5/100,000 PYs in developed areas and 14.5/100,000 PYs in less developed areas. The highest estimated PCa incidence rates (age-standardized rate per 100,000, in 2012) are observed in the highest resourced areas of the world, in

North America (97.6), Australia/New Zealand (111.6), Western Europe (94.9), and Northern Europe (85.0), and the lowest rates are in South-Central Asia (4.5) (Torre et al. 2015).

During the last few decades, the incidence of clinically localized PCa, in particular, has increased in Finland. However, the incidence rate has stabilized during recent years (Fig. 2). A total of 47,361 men had PCa diagnosis at the end of 2014, and the prevalence was 1759.4/100,000 PYs in Finland (Finnish Cancer Registry 2014).

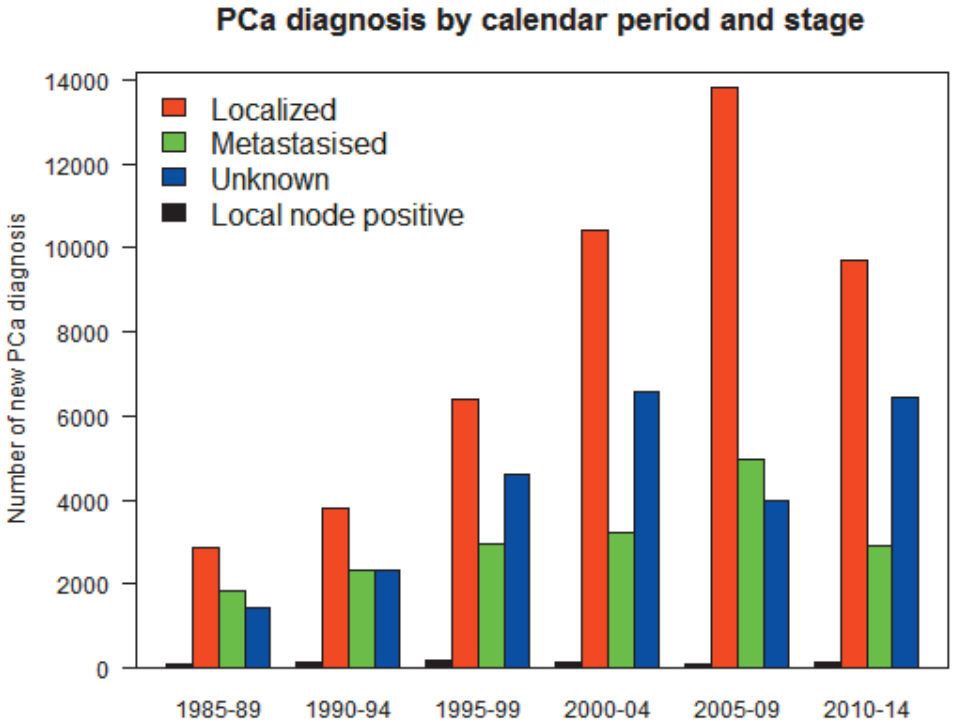

Figure 2: Newly diagnosed prostate cancers by stage from 1985 until the end of 2014 (Modified from Finnish Cancer Registry).

2.1.3 The natural course of clinically localized prostate cancer

High-grade prostate intraepithelial neoplasia (HGPIN) is a known precursor of PCa. An increase in the size and number of high-grade PIN foci can be observed in prostates with cancer compared with prostates without carcinoma; with increasing amounts of high-grade PIN, a greater number of multifocal carcinomas are seen. Both high-grade PIN and carcinoma preferentially involve the peripheral zone, and biomarkers and molecular changes show a similarity between high-grade PIN and carcinoma (Bostwick, Pacelli and Lopez-Beltran 1996, Haggman et al. 1997).

Most localized PCas are believed to have an indolent course. In an era when PCa is typically diagnosed by PSA testing, and the detected tumors are most often localized, clinically unapparent cancers with a well-differentiated cancer grade (a low Gleason score). Approximately 6-20% of patients diagnosed with cancer at an early stage progress to metastatic disease and die from PCa within 10 to 15 years (Chodak et al. 1994, Johansson et al. 2004). However, cancer-specific survival (CSS) for men with well-differentiated, nonpalpable tumors was shown to have declined slowly for 20 years and more rapidly between 20 and 25 years (from 75.2% 95% confidence interval (CI), 48.4-89.3 to 25% 95% CI, 22.0–72.5) (Popiolek et al. 2013). This estimation was done with patients for whom PCa detection was made prior to the introduction of PSA testing, and it is unclear how the results are relevant with tumors detected by elevated PSA levels (Popiolek et al. 2013). Thus, the natural progression of early-stage PCa is very slow, but it still may cause death to patients in the long term.

2.1.4 Mortality and prognosis

PCa has been the second common cause of cancer deaths after lung cancer in Finland in recent years. Thus, 856 men succumbed from PCa in 2014, and the mortality rate was 12.67/100,000 PYs during the 5-year period (2010–2014) in Finland. With an estimated 307,000 deaths worldwide in 2012, prostate cancer was the fifth leading cause of death from cancer in men (6.6% of the total men deaths) (Globocan 2012 prostate cancer fact sheets 2012).

Mortality rates of PCa have declined substantially since 1985 in many parts of the world (Center et al. 2012). Because PSA testing has a much greater effect on incidence than on mortality, worldwide mortality rates vary less (10-fold from approximately 3 to 30 per 100,000) than the observed incidence rates, with the number of deaths from prostate cancer higher in less developed than in more developed regions (165,000 and 142,000, respectively). Mortality rates are generally high in predominantly black populations (Caribbean, 29 per 100,000; sub-Saharan Africa, 19–24 per 100,000), very low in Asia (e.g., 2.9 per 100,000 in South-Central Asia), and intermediate in the Americas and Oceania (Globocan 2012 prostate cancer fact sheets 2012). Albeit, the incidence of PCa has remained stable in Finland during the most recent years, but mortality has decreased by 3.1% per year since 2000 (Center et al. 2012), and the mortality rate of PCa declined 2.9% in Finland between 1998 and 2007 (Bray et al. 2010).

2.2 Risk factors for prostate carcinogenesis

The only well-established risk factors for PCa are older age, black race/ethnicity, and a family history of the disease (Platz and Giovannucci 2006). A study of age-specific incidence from autopsy data revealed that PCa risk begins to rise sharply after the age of 55 years and peaks in the 70–74 age range, declining slightly thereafter. By the age of 70, a histological PCa was identified in 60% of men, and this rose to 80% for those who had some form of PCa by the age of 80 (Sakr et al. 1994). On the other hand, results from the Prostate Cancer Prevention Trial (PCPT) have showed that after 18 years of follow-up, PCa was diagnosed on 1412 of 9457 (14.9%) the men in the placebo group (Thompson et al. 2013). This finding probably correlates with men`s lifelong risk of PCa in PSA era.

Autopsy studies have confirmed that PCa has a long induction period and that many men have incipient lesions in their 20s and 30s (Yatani et al. 1982). The frequency of incidental and autopsy-detected cancers is roughly the same in different parts of the world (Haas et al. 2008). Furthermore, an incidental Gleason score ≥ 7 PCa was often detected from Japanese men, according to recent autopsy study (Zlotta et al. 2013). This evidence is in sharp contrast to the incidence of clinical PCa, which varies widely between different areas; incidence is high in the United States and Northern Europe and low in Southeast Asia (Torre et al. 2015). Studies on native Japanese men have revealed that after they move to the United States, their risk of PCa increases substantially, approaching that of American men (Breslow et al. 1977). These findings indicate that exogenous factors affect the risk of progression from latent, unapparent PCa to clinical PCa. Several explanatory factors for this have been suggested, such as diet, sexual behavior, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation, and occupational exposure (Nelson, De Marzo and Isaacs 2003, Leitzmann and Rohrmann 2012). Still, no evidence currently suggests that dietary interventions can reduce the risk of PCa. The European Prospective Investigation into Cancer and Nutrition (EPIC) showed a weak correlation between insulin-like growth factor (IGF-1) levels, a high intake of protein-form dairy products, and an increased risk of PCa. The potential protective role of selenium and vitamin E have also been studied in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), where the outcome was negative and the supplements were not recommend for the prevention of PCa (Lippman et al. 2009). Lycopene is a member of the carotenoid family and is found in high quantities in tomatoes and tomato-rich products. Lycopene's strong antioxidant properties have been hypothesized to decrease PCa risk (Clinton 1998). However, a meta-analysis of eight randomized controlled trials (RCTs) comparing lycopene to a placebo did not find a significant difference in the incidence of PCa (Ilic and Misso 2012).

Metabolic syndrome (diabetes, abdominal obesity, high cholesterol and high blood pressure) is weakly associated with the risk of PCa; however, the associations vary with geography. According to a meta-analysis of 14 studies with 4,728 PCa cases, metabolic syndrome was associated with a 12% increase in PCa risk ($p = 0.231$), which was lower in the cohort studies (7 studies, RR = 1.04, $p = 0.791$) than other studies (RR = 1.23, $p = 0.125$). Among the single components of metabolic syndrome (e.g., body mass index, dysglycemia or dyslipidemia, high triglycerides, and low high-density lipoprotein (HDL) cholesterol), only hypertension and waist circumference > 102 cm were associated with a significantly greater risk of PCa (Esposito et al. 2013). Currently, no evidence indicates that medical therapy for metabolic syndrome or its components would effectively reduce the progression of PCa, with possible exception of statins and metformin (Preston et al. 2014, Yu et al. 2014).

The role of medication in the development of PCa has been investigated in several subgroups. The role of testosterone replacement therapy and the possible increased risk of PCa have been suggested. Although no evidence shows that testosterone therapy increases the risk of PCa, there is a paucity of long-term data. Testosterone therapy in hypogonadal men does not increase the risk of PCa (Haider et al. 2015). If guidelines for testosterone therapy are properly applied, testosterone treatment is safe in hypogonadal men (Haider et al. 2015). Several epidemiologic studies have been performed to clarify the protective effect of regular aspirin use on PCa risk; however, the results remain controversial. One recent meta-analysis of a total of 24 observational studies, including 14 case-control studies and 10 cohort studies, found a correlation between long-time regular aspirin use and the reduced risk of PCa (Huang et al. 2014). According to another retrospective study of prospectively collected data from an academic institution's prostate biopsy database, the use of aspirin and other NSAIDs were associated with the increased probability of detecting PCa, whereas the association with aspirin use and risk was clinically significant (Gleason score 7) (Bhindi et al. 2014).

Several 5-alpha-reductase inhibitors (5-ARIs) have been studied to assess their effect on reducing the risk of developing PCa. A systematic review of 15 RCTs stated that symptomatic men with a PSA ≤3.0 ng/ml, who were regularly screened with PSA or were anticipating undergoing annual PSA screenings for early detection of PCa, may benefit from a discussion of both the benefits of 5-ARIs for 7 years for the prevention of PCa and the potential risks (including the possibility of high-grade PCa) (Kramer et al. 2009). Although it seems that 5-ARIs have a potential benefit in preventing or delaying the development of PCa (~25%, for Gleason 6 cancer only), this must be weighed against the treatment-related side effects and the potential increased risk of high-grade PCa. However, there was no significant between-group difference in the rates of overall survival or survival

after the diagnosis of PCa after 18 years of follow-up (Thompson et al. 2013). None of the available 5-ARIs have been approved for this indication (Andriole et al. 2010, Thompson et al. 2003).

Multiple prospective cohort studies have examined the association between statins and risk of being diagnosed with PCa. A decreased risk of advanced PCa has been reported among men using statins. However, the evidence on overall PCa risk is conflicting. A previous Finnish population-based case-control study showed no evidence for reduced overall PCa risk among users of cholesterol-lowering drugs, whereas the risk of advanced cancer was decreased among statin users (Murtola et al. 2007). Another study from Finland compared he relative risk between current users and nonusers of statins or other cholesterol-lowering medications in a population undergoing systematical PCa screening from the Finnish prostate cancer screening trial. The results from that particular study found a correlation in a lowered overall incidence of PCa among statin users when bias due to differential PSA testing between medication users and nonusers was eliminated by systematical PCa screening (Murtola et al. 2010). A recent meta-analysis and the results from the REDUCE study did not confirm the possible preventive effect of statin use in relation to the risk of PCa (Esposito et al. 2013, Freedland et al. 2013). However, others have reported that use of statins may reduce the risk of lethal PCa (Yu et al. 2014).

2.3 Classification of prostate cancer

2.3.1 Histology

The vast majority of PCa (more than 90%) cases are adenocarcinomas of the prostate (Grignon 2004). Sarcomas of the prostate account for 0.1% to 0.2% of all malignant prostatic tumors, and leiomyosarcomas are the most common sarcomas involving the prostate in adults (Sexton et al. 2001, Cheville et al. 1995). Primary urothelial carcinoma of the prostate without bladder involvement accounts for 1% to 4% of all prostate carcinomas (Sawczuk et al. 1985). Furthermore, in some cases, lymphomas can invade the prostate, and the awareness of this is important in patients who have history of lymphoma disease since primary prostatic lymphoma without lymph node involvement appears to be much less common than secondary infiltration of the prostate (Bostwick and Mann 1985). Adenocarcinoma of the prostate also has a few more uncommon subtypes. Mucinous adenocarcinoma of the prostate gland is one of the least common morphologic variants. They behave like nonmucinous prostate carcinomas, having a propensity to develop bone metastases with advanced disease (Epstein and Lieberman 1985). A remarkable proportion of adenocarcinomas of the prostate have neuroendocrine

differentiation: Even in ordinary PCa without light microscopic evidence of neuroendocrine differentiation, almost half show neuroendocrine differentiation on evaluation with immunohistochemistry for multiple neuroendocrine markers (di Sant'Agnese 1992, Fine 2012). Small cell carcinomas of the prostate are identical to small cell carcinomas of the lung, and they carry a very poor prognosis (Tetu et al. 1987, Tetu et al. 1989). Between 0.4% and 0.8% of prostatic adenocarcinomas arise from prostatic ducts, and most of these cancers, defined as intraductal adenocarcinomas, are in an advanced stage at presentation and have an aggressive clinical course (Epstein and Woodruff 1986, Brinker, Potter and Epstein 1999).

2.3.2 Grading

The most widely used histological grading system is named after Donald Gleason, a pathologist at the Minneapolis Veterans Affairs Hospital, who developed it with colleagues at that facility in the 1960s. He reported nine patterns of prostate gland formation, ranging from organized and uniform to disordered and infiltrative. The consolidation was made into five distinct patterns based on different clinical outcomes of patients (Gleason 1966). The original Gleason score is attained by adding the Gleason grade or pattern of the most extensive (primary) pattern and the second most common pattern (secondary pattern), if two are present. If one pattern is present, the Gleason score is obtained by doubling the single score. When three grades are present, the Gleason score comprises the most common grade plus the highest grade, irrespective of its extent.

The Gleason grading system for prostate adenocarcinoma has evolved from its original scheme, established in the 1960s and 1970s, to a significantly modified system after two major consensus meetings conducted by the International Society of Urologic Pathology (ISUP) in 2005 and 2014, respectively (Epstein et al. 2005, Epstein et al. 2016). The 2005 ISUP consensus meeting introduced many changes to Gleason grading: The existence of Gleason grade 1 in any specimen was questioned, Gleason grades 1 and 2 should never be diagnosed in needle biopsies, and Grade 4 criteria were changed. It was also recommend for needle biopsies that the secondary pattern, if of a higher grade, be included in the score even if this was < 5% of the tumor volume. Conversely, the consensus was that if the secondary pattern was of a lower grade and < 5% of the tumor volume, it should not be included in the modified Gleason score, and higher tertiary grade patterns in needle biopsies should be treated as the secondary pattern (Epstein et al. 2005).

The 2014 ISUP Gleason grading conference of prostatic carcinoma introduced the concept of the grade groups of PCa to align their grading with other carcinomas, to emphasize the fact that the most well-differentiated cancers have a Gleason score of 6, and to further codify the highly significant clinical distinction between

Gleason score 7 (3 + 4) and 7 (4 + 3) PCa. A new 5-portal Gleason grade group classification was introduced (Table 1). The active use of this new grading system has recently been endorsed by several editors in chief of journals in the field of urology (Zietman et al. 2016).

Table 1. International Society of Urological Pathology 2014 grade groups (Modified from Epstein JI et al. Am J Surg Pathol 2016)

Gleason score	Grade group	10 year biochemical recurrence -free progression after RP
2-6	1	95%
3+4	2	80%
4+3	3	50%
8 (4+4 or 3+5 or 5+3)	4	37.5%
9-10	5	17%

RP=radical prostatectomy

2.3.3 Staging

The staging of the PCa is based on the traditional WHO TNM staging system, consisting of three components: T = the extent of the primary tumor, N = the absence or presence of the lymph node metastases, and M = the absence or presence of distant metastases (Table 2) (Sobin and Wittekind 2009). The objective of a tumor classification system is to combine patients with similar clinical outcomes. This allows for the design of clinical trials on relatively homogeneous patient populations and comparisons of clinical and pathological data obtained from different hospitals across the world so that recommendations on treatment can be made (Mottet et al. 2016). The TNM classification is divided into two categories on PCa staging: clinical TNM (cTNM) and pathologic TNM (pTNM). The cTNM is based on a digital rectal examination (DRE), transrectal ultrasound (TRUS), multiparametric magnetic resonance imaging (mpMRI), computed tomography (CT) and/or a bone scan (BS), depending on the risk stratification by the EAU guidelines described in Table 3. For instance, in a low-grade diseases, no additional imaging for nodal or metastasis staging is needed; however, in the case of intermediate risk diseases and primary Gleason pattern 4/Gleason grade group 3 or high-risk diseases, further abdominal and pelvic CTs and BSs are prompted and mpMRI is encouraged for local staging (Mottet et al. 2016). The Pathological TNM (pTNM) is evaluated after the removal of the prostate and seminal vesicles in a radical prostatectomy (RP) operation. The specimen is further studied to describe the pTNM, histopathological type, grade, and surgical margins. Often, pelvic lymph nodes are also removed from certain areas to evaluate local nodal spreading (Mottet et al. 2016).

Table 2. TNM classification (Modified from: Sobin et al. 2009, UICC International Union Against Cancer 2009)

T – Primary Tumor
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically inapparent tumor not palpable or visible by imaging
T1a Tumor incidental histological finding in 5% or less of the resected tissue
T1b Tumor incidental histological finding in more than 5% of the resected tissue
T1c Tumor identified by needle biopsy (e.g., because of elevated PSA level)
T2 Tumor confined within the prostate
T2a Tumor involves one half of one lobe or less
T2b Tumor involves more than half of one lobe, but not both lobes
T2c Tumor involves both lobes
T3 Tumor extends through the prostatic capsule
T3a Extracapsular extension (unilateral or bilateral), including microscopic bladder neck involvement
T3b Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N – Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M – Distant metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)

Table 3. EAU risk groups for biochemical recurrence of localized and locally advanced prostate cancer (modified from Mottet et al. 2016, www.uroweb.org)

	Low risk	**Intermediate risk**	**High risk**	
Definition	PSA < 10 ng / ml and GS < 7 and cT1-2a	PSA 10-20 ng /ml or GS 7 or cT2b	PSA > 20 ng / ml or GS > 7 or cT2c	Any PSA Any GS cT3-4 or cN+
	Localized		**Locally advanced**	

GS= Gleason Score, EAU = European Association of Urology

2.4 Diagnosis

2.4.1 Prostate-specific antigen

The discovery and use of tumor markers have positively affected early detection, diagnosis, and staging for many malignancies. When early detection of cancers is improved by tumor markers, better curative success rates of the cancers are usually also seen. Thereby, the discovery of clinically relevant tumor markers has been greatly beneficial for detection and curative treatment for PCa. The earliest investigations of tissue-specific antigens in the human prostate were conducted in 1970 (Ablin et al. 1970a, Ablin et al. 1970b). Others later reported the discovery of prostate antigens in seminal plasma (Hara et al. 1971, Li and Beling 1973). Subsequently, researchers found a potential forensic tool for detecting semen that could be used in the investigation of rape crimes (Sensabaugh 1978). Since the discovery of the PSA, a further clinical application for detecting, staging, and monitoring PCa in men was introduced (Wang et al. 1979, Papsidero et al. 1980, Wang et al. 1981).

PSA is a member of the human kallikrein family and is also known as human kallikrein 3 (hk3). The function of the PSA is in the liquefaction of the seminal coagulum to allow the release of spermatozoa (Lilja 1985). PSA is organ specific and primarily produced by the prostatic luminal epithelial cells, although small amounts of ectopic expression have been reported, for example, from malignant breast cancer and normal breast tissues and adrenal and renal carcinomas (Levesque et al. 1995, Yu and Diamandis 1995b, Diamandis et al. 2000). The widespread use of PSA as a PCa marker started in the mid-1980s, mostly in North America (Hernandez and Thompson 2004). However, PSA became rapidly available and was also a widely used diagnostic test in the early 1990s in Nordic countries (Kvåle et al. 2007). The first clinical observations were mostly that PSA values decreased after treatment and appeared to rise preceding disease recurrence (Hernandez and Thompson 2004). Furthermore, it became apparent that after RP, PSAs should be undetectable; if not, disease recurrence was likely (Stamey et al. 1987, Oesterling et al. 1988).

The use of the PSA as a serum marker has revolutionized PCa diagnosis by allowing earlier diagnosis and better chance to have curative treatment. Despite being organ specific it is not cancer specific; therefore, PSA values may also increase in benign prostate hypertrophy (BPH), prostatitis, and other nonmalignant conditions. Thus, further diagnostics of PCa, when the trigger to proceed to prostate biopsies is the PSA value, should be based on consequent PSA level elevation rather than a single measurement (Eastham et al. 2003). No agreed-upon standards are defined for measuring PSAs in the detection of possible PCa (Semjonow et al.

1996). Previously, a PSA increase above 4 ng/ml was considered abnormal (Catalona et al. 1993). Later, age-adjusted PSA levels were encouraged because the number of PSAs increases with age, mainly due to increase of prostate volume by age. The lower upper limit of normal should be used for younger men. For a healthy 60-year-old man with no evidence of PCa, the serum PSA concentration increases by approximately 3.2% per year (0.04 ng/ml per year). A former landmark study of age-specific reference rates of PSA recommended a reference range for serum PSA (95th percentile) for men aged 40 to 49 years of 0.0 to 2.5 ng/ml; for 50 to 59 years, 0.0 to 3.5 ng/ml; 60 to 69 years, 0.0 to 4.5 ng/ml; and 70 to 79 years, 0.0 to 6.5 ng/ml (Oesterling et al. 1993). Nevertheless, later studies have prevailed in establishing that even with low PSA values, many men can harbor significant PCa (Table 4). However, very low baseline PSA level (<1.0 ng/ml) at the age of 45-55 years correlates with very low risk for PCa death in later life (Vickers et al. 2013).

Table 4. Risk of PCa in relation to low PSA values (modified from Mottet et al. 2016, www.uroweb.org)

PSA level (ng/ml)	Risk of PCa (%)	Risk of significant PCa, (Gleason ≥ 7) (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

Based on the findings from the placebo arm of the Prostate Cancer Prevention Trial, it became apparent that as many as 15% of men with a "normal" (< 4.0 ng/ml) PSA level had PCa, including high-grade cancers (Thompson et al. 2004). Lately, many different nomograms have been developed for clinical use to help in predicting indolent versus significant PCa (Dong et al. 2008).

An increasing PSA level is often observed in men who are later diagnosed with PCa. PSA velocity (PSAV) is defined as the absolute annual increase in serum PSA over time (ng/ml/year). An annual increase of 0.75 ng/ml/year is considered significant for the risk of PCa, and thus further diagnostics are recommended (Carter et al. 1992). However, one recent Danish study found 3.4 times increased risk in age-adjusted PCa mortality in men whose PSAV was more than 0.35 ng/ml/year (Orsted et al. 2013). The role of PSAV, however, has been questioned in several systematic review studies. Hence, the specificity of PSAV has deemed to be low or very low (Loughlin 2014, Vickers et al. 2009, Vickers et al. 2014). Furthermore, doubling of the PSA per year (PSADT) is also not clearly associated with an adverse clinical course of PCa when adjusted prior to any PCa treatment

(Vickers et al. 2014). At this time, a current Finnish PCa guideline still considers PSAV important in evaluating the risk of PCa (Aaltomaa et al. 2014). The PCa guideline of the European Association of Urology states that these measurements (PSAV and PSADT) do not provide additional information compared with PSA alone (Mottet et al. 2016).

PSA predominantly occurs in a complex with proteins of human plasma, mostly with alpha 1-antichymotrypsin (Lilja et al. 1991). Still, the proportion of free PSA (fPSA) is usually between 5% and 40% in serum. A free/total (f/t) PSA ratio can be used to differentiate BPH from PCa, and it might be useful when PSA level is between 4 ng/ml and 10 ng/ml and the DRE is negative. PCa was detected by biopsy in 56% of men with f/t PSA < 0.10, but in only 8% with f/t PSA > 0.25 ng /ml (Catalona et al. 1998). However, f/t PSA must be used cautiously because it may be adversely affected by several preanalytical and clinical factors (Stephan et al. 1997). Currently, the use of f/t PSA is promoted in the Finnish PCa guideline, and it is widely used to evaluate the risk of PCa and the need for prostate biopsies (Aaltomaa et al. 2014).

2.4.2 Other kallikreins and biomarkers

The Prostate Health Index (PHI) combines total PSA, fPSA, and (−2)proPSA. According to a meta-analysis of eight studies, comprising 2,969 men, PHI is superior to fPSA alone for PCa detection at the first biopsy in men with total PSA values of 2–10 ng/ml (Bruzzese et al. 2014). According to a large prospective study from the United States, the PHI was clearly higher in men who had significant (Gleason score 7) PCa. PHI also significantly reduced the amount of unnecessary biopsies and reduced the possible risk of overdiagnosis (Loeb et al. 2014). A panel of four kallikrein markers (4KRK) in blood helps to identify patients who are eligible for biopsy based on the probability of having aggressive PCa and helps to avoid unnecessary biopsies in low-risk patients. The 4KRK markers in blood consist of free PSAs (fPSAs), single-chain intact PSAs (iPSAs), total PSAs (tPSA), and human kallikrein 2 (hK2). A few prospective multicenter studies have demonstrated that both the PHI and 4KRK tests outperformed f/t PSA PCa detection, with an improved prediction of clinically significant PCas in men with a PSA value between 2 ng/ml and 10 ng/ml (Loeb and Catalona 2014, Bryant et al. 2015).

Prostate cancer antigen 3 (PCA3, also referred to as DD3) is a prostate cancer-specific antigen that is encoded by a gene on chromosome 9q21-22. PCA3 is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The PCA3 score, along with the PSA count and other risk factors, could be incorporated into a nomogram for improved risk stratification. The most widely

studied utility of the PCA3 score has been its ability to predict malignancy in men with an elevated PSA score and a prior negative biopsy (Saini 2016).

Many additional biomarkers have been developed and used in the diagnosis and risk stratification of PCa. The *TMPRSS2-ERG* gene fusion test relies on recurrent gene fusion involving the ETS transcription factor family member genes (usually *ERG,* a v-ets erythroblastosis virus E26 oncogene homolog) and the androgen-regulated gene *TMPRSS2* (transmembrane serine protease isoform 2), which are frequently encountered in prostate tumors (~50% of tumors). *TMPRSS2-ERG* fusions in urinary sediments have been associated with high specificity (93%) and positive predictive value (94%), although its sensitivity has been reported to be low (37%). Additionally, combined *TMPRSS2-ERG* and PCA3 scores have been reported to improve the performance of serum PSAs for predicting PCa and high-grade PCa at biopsy (Saini 2016). Other available tests include the Mi-Prostate score test (incorporates blood PSA levels and urinary levels of *TMPRSS2-ERG* and PCA3 for PCa risk assessment), Oncotype DX test (multi-gene expression assay), ProMark test (measures protein expressions in biopsy tissue sections employing an automated immunofluorescence method), ConfirmMDx test (detects an epigenetic field effect associated with a cancerization process at the DNA methylation level in cells adjacent to cancer foci), Prolaris test (a genomic test for predicting prostate cancer aggressiveness), Prostate Core Mitomic test (is based on mitochondrial DNA alterations in prostate cancer biopsies), Prostarix test (test is based on a panel of four metabolites excreted into urine), and Decipher test (is a genomic test hat assesses the disease progression risk after RP) (Saini 2016). One new potential tool for detection of clinically significant PCa (Gleason score ≥ 7) is also the Stockholm 3 model (STHLM3). This model combines plasma protein biomarkers, genetic polymorphisms and clinical variables. The STHLM3 model could reduce unnecessary biopsies without compromising the ability to diagnose prostate cancer with a Gleason score of ≥ 7 (Gronberg et al. 2015). These tests are commercially available, but not officially approved for clinical use. Promising alternatives that are still under further development and research involve circulating tumor cells, microRNA biomarkers, and exosomal biomarkers (Bostrom et al. 2015).

2.4.3 Digital rectal examination and transrectal ultrasound and prostate biopsies

Before the introduction of PSA testing, PCa was mostly diagnosed by digital rectal examination (DRE). Most PCa cases are in the peripheral zone of the prostate and thus can possibly be detected by DRE when the tumor volume is more than 0.2 ml. In approximately one-fifth of cases, PCa is detected by DRE alone, irrespective of PSA level (Richie et al. 1993). Positive (abnormal) DRE is associated with

unfavorable cancer histology and is an indication for prostate biopsy (Okotie et al. 2007).

Transrectal ultrasounds of the prostate (TRUS) are done on a daily basis in urological outpatient clinics. With TRUS visualization of the zonal anatomy, the prostate size and periprostatic structures can be identified. Furthermore, TRUS is a needle track tool and enables multiple prostate biopsies. However, a normal grayscale TRUS does not detect areas of PCa with adequate reliability (Lee et al. 2006). New sonographic modalities, such as sonoelastography and contrast-enhanced ultrasound, are being investigated. Currently, there is not enough evidence for their routine use (van Hove et al. 2014). The need for prostate biopsies is evaluated based on PSA-level and DRE findings. At the baseline biopsy setting, risk stratification for the risk of PCa and comorbidity adjustment is useful to avoid unnecessary biopsies and possible overdiagnoses. TRUS-guided biopsies are the standard of care in most places; however, transperineal biopsies are optional, providing similar detection rates of PCa (Takenaka et al. 2008). Usually, for a prostate volume of 30–40 ml, more than eight cores should be sampled. Further, 10 to 12 core biopsies are recommended, with more than 12 cores not being significantly more conclusive (Eichler et al. 2006). An antibiotic prophylaxis should be given prior to the prostate biopsies. Usually, quinolones are the drugs of choice; however, recently increased resistance against quinolones has been seen (Aron, Rajeev and Gupta 2000, Cuevas et al. 2011). Rectal-cleansing enemas are usually not used in Finland. A TRUS-guided periprostatic block is recommended, and data suggest that infiltration anesthesia around the nerve bundles with a local anesthetic provides excellent pain control, which is increasingly important when using extended biopsy techniques (Trucchi et al. 2005). If the baseline biopsies are negative, additional biopsies might be indicated in some cases. The EAU PCa guidelines recommend considering a new set of biopsies, with or without additional tests, with rising/persistently elevated PSA, suspicious DRE, atypical small acinar proliferation (ASAP), extensive multiple biopsy sites (i.e., > 3), high-grade prostatic intraepithelial neoplasia (HGPIN), a few atypical glands immediately adjacent to HGPIN, intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade PCa, and a positive mpMRI finding. Additional information may be gained by a urine test for PCA3, 4KRK and PHI test, or a tissue-based epigenetic test (ConfirmMDx). Also, saturation biopsy techniques (> 20 cores) by TRUS or a perineal approach can be considered (Mottet et al. 2016).

2.4.4 Imaging

The conventional diagnostic pathway in men with elevated serum PSA levels and/or abnormal DRE consists of a random systematic TRUS-guided prostate biopsy. Nevertheless, 20–30% of clinically significant cancers, mainly in the anterior

and apical part of the prostate, are missed using this method (Mottet et al. 2016). The detection of clinically significant PCa is a major challenge. It has been shown that mpMRI facilitates the localization of PCa and can help in targeting prostate biopsy. Owing to its high soft-tissue contrast, high resolution, and ability to simultaneously image functional parameters, MRI provides the best visualization of the prostate compared to other imaging methods. For standardization and diminished variation in the acquisition, interpretation, and reporting of prostate mpMRI, the Prostate Imaging – Reporting and Data System (PI-RADS) has been developed, and version 2 is currently used (PI-RADSv2) (Weinreb et al. 2016, Barrett, Turkbey and Choyke 2015).

Based on studies in which the pathological findings of an RP specimen have been compared to the features of the mpMRI, mpMRI has excellent sensitivity for the detection and localization of Gleason score 7 cancers (Turkbey et al. 2011). Furthermore, mpMRI has shown that it can reliably detect significant PCa prior to any prostate biopsies (Jambor et al. 2015). However, mpMRI also has its flaws. Evidence suggests that mpMRI can yield false negative results in 20–30% of patients harboring clinically significant PCa (Pokorny et al. 2014, Meng et al. 2016). Recently, a Finnish randomized RCT compared traditional TRUS guided biopsies and mpMRI targeted fusion biopsies. According to the results from the study, a targeted biopsy did not improve the PCa detection rate compared with a TRUS-guided biopsy alone in patients with suspicion of PCa based on PSA values (Tonttila et al. 2016). Nevertheless, evidence suggests that an MRI-targeted biopsy detects more high-grade cancers than a systematic biopsy and that an MRI performed before a biopsy can predict the risk of high-grade cancer (Meng et al. 2016). Recently, new, less time-consuming modalities to enhance prostate MRI studies have also been studied. A recent Finnish trial introduced a new approach for prostate MRI: 3T biparametric magnetic resonance imaging (bpMRI) including T2-weighted imaging and three separate diffusion-weighted imaging acquisitions and targeted biopsies. According to the results from the study, this approach may significantly reduce unnecessary biopsies and misses only a few (2%) significant PCa cases (Jambor et al. 2017). Furthermore, mpMRI has also been studied in active surveillance of PCa. Although mpMRI and targeted biopsies may improve the detection of high-grade cancers when compared to systematic biopsy, mpMRI and targeted biopsies cannot currently replace systematic biopsies in active surveillance settings (Ma et al. 2017). In current clinical practice, mpMRI and targeted biopsies are most often used in repeat biopsy settings after initial negative biopsies and the sufficient suspicion of PCa. One recent meta-analysis confirmed that MRI and targeted biopsies markedly improved the detection of significant PCa in a repeat biopsy setting (relative sensitivity 1.62, 95% CI 1.02–2.57), but not in men with an initial biopsy (relative sensitivity 0.97, 95% CI 0.94–1.01) (Schoots et al. 2015). In summary, an MRI of the prostate is a useful tool in local staging

and in the diagnosis of PCa. However, despite the fact that mpMRI has a relatively good spesificity to detect clinically significant PCa it suffers a quite low sensitivity for detecting small extraprostatic extension (cT3). Additionally, the current EAU PCa guidelines mainly recommend the use of mpMRI in local staging of the PCa and in prior repeat biopsy settings (Mottet et al. 2016).

Other imaging modalities are mostly used for the staging (TNM classification) of PCa after an initial diagnosis. To evaluate the possible local and nodal spreading of the PCa, mpMRI, and CT are the most used imaging modalities. Their sensitivity is low, and microscopic invasion cannot be detected. An abdominal CT and prostate/pelvic mpMRI should mainly be used for nodal staging in high-risk PCa and should be avoided in low-risk diseases (Mottet et al. 2016). In the staging of possible metastasis of PCa, the BS has been the most widely used method. However, the specificity of a BS is rather low, and nowadays, the addition of single-photon emission computed tomography (SPECT) to the BS is used and has markedly improved the diagnostic benefit (Langsteger et al. 2012). Thus, suspicious lesions from BSs often need to be verified with another imaging modality, such as SPECT or conventional CT. The use of a BS is not beneficial for low-risk diseases, but it is promoted for high-risk diseases, with a rather high rate of positive results (Mottet et al. 2016).

Positron emission tomography (PET), a modality with higher spatial resolution than that of SPECT, can be particularly helpful in detecting small lesions. Moreover, PET imaging using various specific radiotracers has the advantage of detecting malignant diseases in both bone and soft tissues (Langsteger et al. 2012). Mostly, PET is done with PET/CT settings. The most useful tracer for PET/CT is ^{11}C-choline (Choline-PET/CT), which is more sensitive than a conventional BS, but it has higher specificity, with fewer indeterminate bone lesions (Picchio et al. 2012). Furthermore, a whole-body-MRI (WB-MRI) has good sensitivity for bone metastasis and can be conducted without radiation. However, small (<1 cm) nodal and lung metastasis are not identified, and it is also rather time consuming and expensive. The information from a WB-MRI is also widely radiologist dependent, and acquisition is difficult for radiologists with less experience (Padhani et al. 2017). The use of molecular imaging of glutamate carboxypeptidase II, also called the prostate-specific membrane antigen (PSMA), with its clinical amplification called PSMA-PET/CT, has become widely available in recent years. This tracer has potential to completely replace the radiolabeled Choline-PET/CT in the imaging of recurrent PCas (Mottaghy, Heinzel and Verburg 2016). Still, according to a recent prospective RCT, PSMA-PET/CT has low sensitivity (64%) but high specificity (95%) in detecting pelvic lymph node metastasis. The lack of sensitivity may limit the clinical use of the PSMA. Furthermore, the use of PSMA-PET/CT is still experimental in staging and disease recurrence settings, and there is not

enough evidence to date to recommend it for standard clinical use (Cornford et al. 2016). Altogether, evidence shows that Choline-PET/CTs and mpMRIs are more accurate than BSs; nevertheless, these techniques are currently limited by their lack of availability.

2.5 Screening

2.5.1 Organized prostate-specific antigen screening

After the advent of PSA-testing, it soon became widely available and could provide rather specific tumor markers for PCa detection. Thus, the use of PSAs in organized population-based screening setting has been widely studied. The objective of screening is to reduce overall and PCa-specific mortality (PCSM) by increasing the detection of high-risk disease in curable phase, and to improve overall health outcomes by reducing locally advanced disease and metastasis. The goal is also to identify and treat the disease at an early stage. Currently, screening for PCa is one of the most controversial topics in the urological literature (Barry 2009). In the worst scenario there is little effect on mortality but it merely results in overdiagnosis. The main evidence on population-level screening on healthy men is based on two large RCTs: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and European Randomized Study of Screening for Prostate Cancer (ERSPC) trial. ERSPC is actually a collection of trials in different countries with different eligibility criteria, randomization schemes, and strategies for screening and follow-up. After 13 years of follow-up, the ERPSC trial showed a significant reduction of PCSM, with a relative risk (RR) of 0.79 (95% CI 0.69–0.91), but no difference in all-cause mortality (Schroder et al. 2014), whilst the PLCO study concluded that there was no significant benefit after 15 years of follow-up, with an RR of 1.04 (95% CI, 0.87–1.24). The RR for all-cause mortality was 0.977 (95% CI, 0.950–1.004) in the PLCO trial (Pinsky et al. 2017). A major shortcoming in the PLCO trial is the substantial frequency of PSA testing before randomization, which was done in 44% of men in both arms and during follow-up in the control arm with 40% to 52% of controls screened each year (Pinsky et al. 2010). A recent report showed that in fact as many as 90% of men in the control arm underwent PSA testing before or during the trial (Shoag, Mittal and Hu 2016). A Cochrane database systematic review and meta-analysis concluded that PCa screening did not significantly decrease PCSM in a combined meta-analysis of five RCTs (Ilic et al. 2013). Currently, organized PSA screening is not recommend by the EAU guidelines or Finnish Prostate Cancer guidelines (Mottet et al. 2016, Aaltomaa et al. 2014). However, the EAU recommended obtaining a baseline PSA measurement at age 40–45 years, as this measurement predicts the risk of future life-threatening disease. Moreover, they recommended that the baseline PSA measurement

should be used to inform the screening interval. For example, they suggested a screening interval of 2–4 years if the baseline level is > 1 ng/ml, whereas a longer interval up to 8 years could be used for men with a lower baseline PSA level (Mottet et al. 2016).

2.5.2 Opportunistic prostate-specific antigen screening

In contrast to an organized PSA screening policy, early detection or opportunistic (ad-hoc) testing consists of individual case findings, which are initiated by the man being tested (patient) and/or his physician. According to a Swedish study that studied PSA-based screening, the cumulated uptake of PSA testing in men aged 55–69 years in Sweden increased from zero in 1997 to 56% in 2007 (Jonsson et al. 2011). Recently Kilpeläinen et al. reported 63% PSA contamination at 12 years in the control arm of ERSPC Finland. The relative mortality reduction in the screening arm has been less pronounced in the Finnish trial than at the Swedish and Dutch ERSPC centers. Contamination in the control arm is likely a reason for this result (Kilpelainen et al. 2017). Furthermore, evidence from the Göteborg screening study claims that opportunistic PSA testing had little if any effect on PCa mortality and resulted in more overdiagnosis, with almost twice the number of men needed to be diagnosed to save one man from dying from PCa compared to men offered an organized biennial screening program (Arnsrud Godtman et al. 2015). However, owing to the lack of reliable data on opportunistic screening, the reduction of the PCSM rate can be partly explained by an ad-hoc screening effect (Welch and Albertsen 2009, Stattin et al. 2014).

2.6 Treatment

2.6.1 Active surveillance

Many PCa cases are indolent and with low-risk of progression; thus, a conservative approach for treatment is a feasible choice in many cases. However, active surveillance (AS) is a concept of deferred treatment strategy, where a patient with reasonable good life expectancy (> 10 years) is monitored regularly and definitive treatment is given in the case of disease progression. It should be divided from another deferred treatment strategy (watchful waiting), which can be offered for men with comorbidities, life expectancy < 10 years, and in more advanced stages of the disease. PRIAS (Prostate cancer Research International: Active Surveillance) protocol is currently the most used AS program in Finland. Inclusion criteria for PRIAS are: men fit for curative therapy, PSA at diagnosis less than 10 ng/ml, PSA density (PSA/prostatic volume) less than 0.20, one or two biopsy cores bearing prostate cancer (using a fixed volume-dependent number of cores), Gleason

score 3+3 and digital rectal examination T1c or T2. Follow-up program in PRIAS includes regular PSA testing, DRE and control biopsies. Results from all PRIAS centers showed that after 5 and 10 yr of follow-up, respectively, 48% and 27% of men were still on AS, 34% and 41% discontinued because of protocol-based reclassification, 5% and 5% discontinued due to anxiety/patient request (without having reclassification, anxiety and patient request were equally distributed), 5% and 15% switched to WW or died of another cause (without having reclassification), and 8% and 12% discontinued for other reasons (without having reclassification) (Bokhorst et al. 2016). At present, there are no results from high-level RCTs concerning AS. Thus, the results have been mainly attributed to ongoing prospective or retrospective cohorts. AS may be offered for the patient with a good life expectancy and cT1-T2, Gleason score 6, with a maximum of two positive biopsy cores, unilateral disease, and no more than 50% cancer involvement in each biopsy (Mottet et al. 2016). However, good results have also been obtained with selected Gleason 7 PCa in men over 70 years of age (Klotz et al. 2015).

2.6.2 Radical prostatectomy

There is probably no better choice to cure cancer that is confined to the prostate than total surgical removal of the organ. Radical prostatectomy (RP) is also the only treatment for localized PCa and has been shown in an RCT to reduce progression to metastases and death from the disease (Bill-Axelson et al. 2014). RP involves the removal of the entire prostate gland and both seminal vesicles, along with enough surrounding tissue to obtain negative surgical margins (SMs). Mostly for staging purposes, bilateral pelvic lymphadenectomy is also often carried out. The goal of RP is to eradicate the disease, with negative SMs, while preserving continence and, whenever possible, potency (Bianco, Scardino and Eastham 2005). These outcomes are also defined as the “trifecta” (cancer control, continence, and potency).

Between 1989 and 1999, the Scandinavian Prostate Cancer Group study number 4 (SPCG-4) randomly assigned 695 men with early PCa to watchful waiting (WW) or RP. During 23.2 years of follow-up, 200 of 347 men in the RP group and 247 of the 348 men in the WW group died. The study showed a reduction of all-cause mortality with a relative risk (RR) of 0.71 (95% CI 0.59-0.86). The number needed to treat (NNT) to prevent one death at 18 years follow-up was 8, but NNT was 4 in men younger than 65 years of age. RP showed a declined PCSM (RR 0.56; 95% CI 0.41–0.77). The greatest benefit was for men younger than 65 years (RR 0.45; 95% CI 0.29–0.69). Furthermore, risk reductions for different risk groups were RR 0.54 (95% CI, 0.26–1.13) at low risk, RR 0.38 (95% CI 0.23-0.62) at intermediate risk, and 0.87 (95% CI 0.52–1.46) at high risk, respectively. Thus, the only statistically significant benefit was for men in the intermediate risk group. However, RP

also showed a reduced risk of metastases among older men (RR 0.68; 95% CI 0.46–1.00) (Bill-Axelson et al. 2014). This landmark study provided the highest evidence to promote RP for the treatment of localized PCa. At present, no high-level RCT concerning external beam radiation therapy (EBRT) versus WW has been done. Another RCT, the Prostate Cancer Intervention versus Observation Trial (PIVOT), was carried out in the United States to compare RP and WW. The study showed no overall survival (OS) or CSS benefit for RP. In the study, conducted from November 1994 through January 2002, 731 men (mean age, 67 years; median PSA value, 7.8 ng/ml) with localized PCa were treated with RP or WW. However, more patients were in the low-risk group compared to SPCG-4. Of note, the study population included more patients with comorbid conditions than SPCG-4. After a median of 10 years of follow-up, 354 men (48.4%) had died. Among the men in the RP group, 171 (47.0%) died, as compared with 183 (49.9%) in the WW group. However, RP was associated with reduced all-cause mortality among the men with a PSA value greater than 10 ng/ml (P = 0.04 for interaction) and possibly among those with intermediate-risk or high-risk tumors (P = 0.07 for interaction) (Wilt et al. 2012). It should be also noted that while PIVOT included patients in the era of PSA testing (1994-2002), whilst SPCG-4 included patients before the era of PSA testing (1989-1999). This different time period may explain some of the difference between results of these two studies. At present only one high-level RCT has compared RP to EBRT and AS. Prostate cancer Testing for Cancer and Treatment (ProtecT) trial randomized 1643 men to undergo randomization to AS (545 men), RP (553), or EBRT (545). The primary outcome was prostate-cancer mortality at a median of 10 years of follow-up. Secondary outcomes included the rates of disease progression, metastases, and all-cause deaths. At a median of 10 years there was no significant difference in PCSM between groups. RP and EBRT were associated with lower incidences of disease progression and metastases than was AS (Hamdy et al. 2016). The shortcoming of that particular study is high proportion of low-risk patients.

Although RP is most feasible for low- to intermediate-risk tumors, it may also have a role in more advanced disease. The incidence of organ-confined disease is 26–31% in Gleason 8–10 lesions. Patients with organ-confined disease and high-grade tumors still have a good prognosis after RP. However, a multimodal treatment approach is often needed with adjuvant or salvage RT sometimes combined with androgen-deprivation therapy (ADT) (Walz et al. 2011). Patients with high PSAs (> 20 ng/ml) have varying risk levels of disease progression and PCSM, after RP. Decisions about operations should be made in concurrence with other risk factors, especially with low-grade biopsies (Gleason 6) and intermediate-grade biopsies (Gleason 7) RP provides a good treatment option for men with high preoperative PSAs (Spahn et al. 2010).

The treatment of locally advanced disease varies between countries. The surgical treatment has traditionally been sparse. Indeed, RP for cT3-T4/cN+ disease is associated with an increased risk of positive SMs, lymph node metastasis, and disease recurrence/distant progression (Boccon-Gibod et al. 2003). The use of nomograms in evaluating the pathological stage of disease (pTNM) is encouraged at patient counseling for treatment decisions. Only one non-randomized prospective study, EORTC 30001, has compared the outcome of RP for cT3-patients. The aim of the study was to determine whether RP was safe and could provide a cure for good prognosis patients with clinical T3 prostate cancer in a multicenter setting. This study still lacked power due to the low number of patients (40) enrolled for the study. The study was also discontinued due to a low cure rate (CR), possibly explained by the high number of positive SMs (Van Poppel et al. 2006). However, many retrospective cohorts have reported good results and CRs of RP in cT3 PCa (Freedland et al. 2013, Xylinas et al. 2009). As evidence for an oncological benefit so far, is mainly drawn from retrospective data it is difficult to draw conclusion what is the real benefit of RP in locally advanced disease. Ongoing RCTs as Scandinavian Prostate Cancer Group study number 15 (SPCG-15), that seeks to study whether RP (with or without the combination of external radiation) improves PCa specific survival in comparison with primary radiation treatment and hormonal treatment among patients diagnosed with locally advanced (T3) prostate cancer, will hopefully solve this problem (Scandinavian Prostate Cancer Group 2017). The role of RP in oligometastatic PCa (only few bone metastases +/- node metastases) is still investigational. While some retrospective evidence suggest OS and CSS benefit after surgery, we are still waiting evindence from prospective RCTs (Mandel, Steuber and Graefen 2017).

The role of pelvic lymph node dissection (PLND) is controversial. For staging purposes (to detect the possible spread of disease to lymph nodes), PLND has evidently an important role. However, no data is available that would indicate that PLND would improve oncological or survival outcomes in terms of CSS or OS. Nevertheless, the data supports higher rates of complications in regard to PLND and especially for more extended PLND. A very recent systematic review of 63 studies, recruiting a total of 275,269 patients, addressed the outcomes of PLND in patients undergoing RP. The oncological outcomes were addressed by 29 studies, one of which was a RCT. Non-oncological outcomes were addressed by 43 studies, three of which were RCTs. High risks of bias and confounding factors were found in most studies. Conflicting results emerged when comparing biochemical and clinical recurrence, while no significant differences were observed among groups for survival. Conversely, the majority of studies showed that the more extensive the PLND, the greater the adverse outcomes in terms of operating time, blood loss, length of stay, and postoperative complications. No significant differences were observed in terms of urinary continence and erectile function recovery (Fossati et

al. 2017). Furthermore, EAU guidelines recommend performing an extended LND (eLND), including nodes overlying the external iliac artery and vein, the nodes within obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery (Mottet et al. 2016). Joniau et al. stated in 2013 that although performing ePLND would correctly stage 94% of patients, it would remove all positive lymph nodes in only 76% of patients, thus, possibly achieving suboptimal long-term results (Joniau et al. 2013). Thus, to detect enough nodes, a very extensive PLND should be done, and yet no evidence for survival benefit exists. This dilemma is waiting for a high-level RCT to solve the problem.

The main surgical approach for RP has changed over the years. Currently, a majority of RPs are done with robot-assisted laparoscopic prostatectomy (RALP). In Finland, 68% of operations were RALPs in 2012 (Riikonen et al. 2016). RALP provides a smoother learning curve for the surgeon and offers probably shorter hospital stays and less intraoperative bleeding for patients (Zargar-Shoshtari, Murphy and Zargar 2017). However, in terms of functional or oncological outcomes, no clear evidence promoting RALP over open RP has been established yet (Yaxley et al. 2016). An operation can also be done with a pure laparoscopic approach. This surgical modality became more popular in Finland again after the introduction of new three-dimensional endoscopic cameras. Laparoscopic prostatectomy offers similar advantages to RALP, and good overall results can be achieved (Stolzenburg et al. 2009).

2.6.3 External beam radiation therapy

External beam radiation therapy (EBRT) with intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard of radiation therapy (RT) for localized PCa. A dose escalation to 74–80 grays (Gy) should be carried out to provide better 5-year survival outcomes without BCR compared to lower-dose RT (Mottet et al. 2016). The role of neoadjuvant and adjuvant ADT depends on the risk stratification of the disease. For low-risk disease, it is not needed; for high-risk disease EBRT, a longer ADT (2 to 3 years) is mandatory (Bolla et al. 2010, Pilepich et al. 2005). EBRT is rarely a good treatment choice for low-risk PCa due to possible less adverse effects with other options, mainly AS and brachytherapy. In the case of low-risk disease with unfavorable tumor characteristics (many positive biopsy scores), RP may also offer a better option for men with life expectancy > 10 years, providing pathological staging and possible future multimodality treatment options (Mottet et al. 2016). For intermediate-risk disease, combined IMRT with short-term ADT (4–6 months) should be given (D'Amico et al. 2008, Jones et al. 2011). The duration of adjuvant ADT in different PCa risk groups is defined in Table 5. For high-risk and locally advanced

PCa, IMRT for prostate and pelvic lymph nodes is encouraged, and long-term ADT should be added to the treatment (Mottet et al. 2016). The role of RT for pelvic lymph node metastasis (cN+/pN+) is questionable, as no clear oncological outcome benefits have been shown (Leibel et al. 1994). Furthermore, PLND may be indicated to detect right patients to postoperative irradiation; thus, some patients may benefit pelvic irradiation (Mottet et al. 2016).

Table 5. Duration of adjuvant ADT in radiation therapy of prostate cancer (Modified from Mottet et al. 2016, www.uroweb.org)

EAU PCa risk group	Definition	Duration of ADT
Low-risk PCa	PSA<10ng/ml and PSA<10 ng/ml and GS<7 and cT1-2a	0 months
Intermediate-risk PCa	PSA 10-20 ng/ml or GS 7 or cT2b	4-6 months
High-risk PCa	PSA >20 ng/ml or GS >7 or cT2c	24-36 months
Locally advanced PCa	Any PSA, Any GS and cT3-4 or cN+	24-36 months

ADT=androgen deprivation therapy, GS= Gleason score, PCa=prostate cancer, EAU= European Urology Association

High-dose-rate brachytherapy (HDR-BT) provides a treatment option for RT of PCa. When administrated, HDR-BT is often combined with IMRT. This provides the ability to escalate the dosage for the prostate and to avoid radiation injury of surrounding tissues. For example, combined HDR-BT and IMRT can substitute a short-term ADT for intermediate-risk disease (Mottet et al. 2016).

After RP multimodality treatment, RT is often follows RP, either based on the risk stratification for progression after RP (adjuvant RT) or for detected biochemical or local disease progression (salvage RT). Three prospective trials have assessed the role of adjuvant RT after RP. The baseline study criteria involved pT3 disease and/or positive SMs and Gleason score greater than or equal to 7; one study recruited only patients with pT3. Adjuvant RT clearly seems to improve progression-free survival (PFS), and some evidence suggests better OS (Bolla et al. 2012, Wiegel et al. 2014, Thompson et al. 2009). However, in terms of CSS and OS benefits, it is also feasible to give RT in a salvage RT setting when BCR or clinical local recurrence is detected. Salvage RT should be given before the PSA value exceeds 0.5 ng/ml (Stephenson et al. 2007). Recent results from a double-blind, placebo-controlled RCT showed that salvage RT combined with daily 24-month bicalutamid 150 mg treatment resulted in significantly higher rates of long-term OS and lower incidences of metastatic PCa and PCSM than RT plus placebo (Shipley et al. 2017). As adjuvant RT is associated with the risk of impaired quality of life (e.g., the risk of incontinence) (Ficarra et al. 2009), salvage RT is a tempting

option. In this approach, RT is recommended if BCR is documented after RP, thus avoiding RT in men who are cured with RP. However, to date, we lack studies comparing adjuvant to salvage RT.

2.6.4 Focal therapies

Cryosurgery/cryotherapy (CSAP) refers to a therapy that involves freezing the prostate through TRUS-guidance with cryoneedles. The aim of the treatment is to obtain cell death by freezing. Another focal therapy option is a high-intensity-focused ultrasound of the prostate (HIFU). Currently, the role of CSAP for localized PCa is questionable. Research in terms of CSS and OS outcomes with CSAP has indicated a lot of bias across studies. Thus, results are inconclusive. No high-level data supports the use of CSAP. HIFU consists of ultrasound waves that obtain tissue damage by mechanical and thermal effects and cavitation. At present, the use of HIFU for localized PCa is investigational. The current guideline recommendation is to use local therapies only in clinical trial settings (Mottet et al. 2016).

2.6.5 Androgen deprivation therapy

Hormonal therapy or ADT offers many different options: surgical castration, luteinizing hormone-releasing hormone agonists/antagonists (LHRH-agonist/antagonist), estrogens, and oral anti-androgens. Surgical castration is the oldest and fastest method to achieve low testosterone levels (called “castration level”). The current castration level is 1.7 nmol/l; however, it is based on very old data. The median value of the testosterone level after surgical castration is < 0.5 nmol/l, and thus a testosterone level < 1 nmol/l would be a more appropriate “castration level” nowadays (Oefelein et al. 2000). The response of PCa to ADT is among the most reproducible, durable, and profound of any systemic therapy for a solid tumor. ADT has been the cornerstone treatment for men with locally advanced or metastatic prostate cancer (PCa) since the 1940s (Huggins, Stevens and Hodges 1941).

Immediate ADT is the treatment of choice in M+ prostate cancer (Cornford et al. 2016). Although only < 5% of patients with newly diagnosed PCa have distant metastases at first presentation, compared with 20–25% > 20 years ago, the use of ADT increased sharply between 1989 and 2001 (Ryan and Small 2005, Cooperberg et al. 2003). Most, but not all, population-based analyses have suggested that LHRH-agonists are associated with a greater risk of incident coronary artery disease, myocardial infarction, and diabetes (DM) in men with PCa (Keating, O'Malley and Smith 2006, Keating et al. 2010, D'Amico et al. 2007). Subsequent reports have suggested that men with comorbidities or prior cardiovascular disease (CVD) treated with LHRH agonists might have an increased risk of cardiovascular mortality (CVM) (Saigal et al. 2007, Nanda et al. 2009). Based on these observations, a science advisory consensus statement on LHRH-agonist therapy and

cardiovascular risk was issued, and a US Food and Drug Administration safety warning addressing the concern of increased risk of myocardial infarction, stroke, sudden cardiac death, and DM was released (Levine et al. 2010). However, compelling results have also been reported. According to the recent meta-analysis of a pooled analysis of RCTs in unfavorable-risk PCa, ADT use was not associated with an increased risk of CVM, but was associated with a lower risk of PCSM and all-cause mortality (Nguyen et al. 2011). A large population-based study utilizing the SEER database resulted in lower OS rates of men treated with primary ADT with localized disease (Wong et al. 2009). On the contrary, other evidence suggests that ADT may even reduce cardiovascular mortality for localized PCa when started immediately after diagnosis as opposed to deferred treatment (Studer et al. 2006). The use of LHRH agonists is also associated with a known "flare-up" phenomenon, which can have serious consequences for patients with high-volume metastatic disease, spinal cord compression, obstructive renal failure, urinary obstruction, or even cardiovascular death (Bubley 2001). Concomitant use of anti-androgens with LHRH agonists reduces the risk, but does not completely remove it.

LHRH antagonists may provide treatment resulting in fewer CVD and metabolic side effects (Albertsen et al. 2014). Currently, degarelix is the only available LHRH antagonist. It should be administrated with monthly subcutaneous injections, although some LHRH agonists have longer-acting formulas requiring injections every 3 or 6 months. The castration level is obtained at day three; hence, degarelix provides faster ADT without the risk of clinical flare-ups (Crawford et al. 2011).

Anti-androgens can also be used for ADT. A nonsteroidal anti-androgen (NSAA), bicalutamide, is used in Finland. It may be used as a monotherapy or with LHRH agonists/antagonists; the combination is called a complete androgen blockade (CAB). Bicalutamide (150 mg), either as a monotherapy or adjuvant to standard care, improves PFS in patients with locally advanced PCa. However, for patients with localized PCa, bicalutamide does not improve PFS (Iversen et al. 2010). For M1 disease, NSAAs are not as effective as other ADTs, and reduced PFS and OS have been reported (Kunath et al. 2014). Bicalutamide monotherapy is more likely to be used as a bone-protective treatment compared to other ADTs, because bicalutamide as other NSAAs are not reducing serum testosterone levels (Wadhwa et al. 2009). Also, markedly less sexual dysfunction (erection dysfunction and loss of libido) is reported with NSAAs (Iversen, Melezinek and Schmidt 2001).

ADT can be offered as intermittent ADT (IAD) for some locally advanced and M1a-b patients. In terms of quality of life issues, metabolic/CVD side effects, and bone protection, IAD may provide a better option. In the case of IAD, ADT is stopped when clear clinical and PSA responses have been observed, usually with

PSAs < 4 ng/ml. Treatment is resumed when clinical progression or rising PSAs above a predetermined (empirically set usually at 10–20 ng/ml) threshold is captured in metastatic patients. The same treatment is used for at least 3 to 6 months (Cornford et al. 2016).

2.6.6 Treatment of metastatic disease

The definition of castration resistant prostate cancer (CRPC) is castration level serum testosterone and either biochemical progression (three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir; and s PSA > 2ng/ml) or clear radiological progression (Cornford et al. 2016). Docetaxel chemotherapy for CRPC was introduced in 2004 (Tannock et al. 2004). After the introduction of an efficient chemotherapy for CRPC, the whole treatment of CRPC and metastatic CRPC (mCRPC) PCa was revolutionized (Crawford et al. 2015). New therapies that become available are studied only with mCRPC patients. It remains uncertain how we should treat patients with CRPC without metastases. Two new hormonal agents for mCRPC that are now available are abiraterone acetate and enzalutamide. Abiraterone blocks cytochrome P450 17, inhibiting androgen synthesis, whereas enzalutamide inhibits the androgen receptor, reducing nuclear translocation of the androgen receptor complex and subsequent DNA binding (Crawford et al. 2015). In Finland, the costs for both drugs are reimbursed only after previous docetaxel treatment. However, both drugs have shown increased OS and PFS rates over a placebo either after docetaxel chemotherapy or in chemotherapy naive patients (Cornford et al. 2016). When applied after an earlier phase of doxetacel therapy, cabazitaxel chemotherapy has also shown efficiency in terms of OS and PFS compared to conventional mitoxantrone therapy (Cornford et al. 2016).

Recent findings have shown that docetaxel-based chemotherapy is efficient when combined with ADT as the first line (early chemohormonal treatment) in the castration-sensitive phase when metastatic PCa is diagnosed. Recent data from the CHAARTED (Androgen Ablation Therapy with or without Chemotherapy in Treating Patients with Metastatic Prostate Cancer) trials showed a significant advance for initial docetaxel treatment. A total of 790 patients were randomized to receive ADT plus docetaxel (75 mg/m2 every 3 weeks for 6 cycles) or ADT alone. Median OS was significantly longer for ADT plus docetaxel compared with ADT in the overall intent to treat the population (57.6 vs. 44.0 months, $p = 0.0006$) and in the subgroup of patients with high-volume disease (49.2 vs. 32.2 months, $p = 0.0012$) (Sweeney et al. 2015). Recent RCTs have showed a clear benefit of upfront docetaxel for patients with M1-disease as well, regardless of disease volume (James et al. 2015). Reflecting on these reports, upfront docetaxel combined with ADT should be considered as a new standard in men presenting with metastases at

first presentation, provided that they are fit enough to receive the drug (Vale et al. 2016). Furthermore, results from two different RCTs: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) and A Study of Abiraterone Acetate plus Low-Dose Prednisone Plus ADT versus ADT Alone in Newly diagnosed Participants With High-Risk Metastatic Hormone-Naive Prostate Cancer (LATITUDE) have showed OS and PFS benefit from combination therapy of ADT plus docetaxel or abiraterone acetate in first-line treatment of hormone-naive metastatic PCa (James et al. 2016, Fizazi et al. 2017). In STAMPEDE trial`s abiraterone comparison study, ADT plus abiraterone and prednisolone was associated with significantly higher rates of OS and failure-free survival than ADT alone also among men with locally advanced but not metastatic disease (James et al. 2017).

Most patients with mCRPC have painful bone metastases. Good treatment option for such patients is radium-223, an α-emitter which is the only bone-specific drug that is associated with a survival benefit in the treatment of CRPC. Biphophonates are used in mCRPC to reduce skeletal-related events (SRE). Zoledronic acid was used mostly when no other anticancer treatments than docetaxel was available for mCRPC. Later Denosumab has shown to be superior compared to zoledronic acid in delaying or preventing SREs in mCRPC. Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB ligand), a key mediator of osteoclast formation, function, and survival. The toxicity of biphosphonates, the risk of jaw necrosis in particular, must always be kept in mind. Patients should have a dental examination before starting biphosphonate therapy (Cornford et al. 2016).

2.7 Follow-up after radical prostatectomy

2.7.1 Definition of biochemical and clinical progression

The standard monitoring of patients after RP includes regular PSA-testing and imaging, whenever needed. The European consensus on the biochemical recurrence (BCR) after prostatectomy is defined by two consecutive PSA values greater or equal to 0.2 ng/ml (Boccon-Gibod et al. 2004). Approximately one out of five patients will experience BCR after a radical operation (Freedland et al. 2013). Less than a third of these patients will ultimately develop a clinical progression. The median time to develop metastasis is 8 years after BCR, and death occurs 5 years after the first metastasis on average (Pound et al. 1999). The early and reliable detection of BCR is important because postoperative RT is most effective when administered in an adjuvant setting or as a salvage RT when serum PSA first attains a detectable level (Eggener et al. 2011).

2.7.2 Ultrasensitive PSA

PSA detection methods with detection levels under 0.1 ng/ml are considered ultrasensitive, and some assays are capable of detecting levels approaching 0.001 ng/ml (Ferguson et al. 1996). The use of ultrasensitive PSA assays (u-PSAAs) remains controversial due to questions regarding the reliability and usefulness of u-PSAAs (Cornford et al. 2016). However, u-PSAAs could potentially detect BCR after RP significantly earlier than traditional PSA (t-PSA) assays (Shen et al. 2005). One definition for a u-PSA relapse is three rising u-PSA values after nadir (Shimizu et al. 2007). Detectable u-PSA levels after RP can predict PCa recurrence (Eisenberg et al. 2010). Patients with undetectable u-PSAs 2 years after surgery are unlikely to develop rapid clinical progression of PCa (PSADT < 9 months) if experiencing BCR later (Chang et al. 2010). Moreover, recent long-term review indicates that if patients have continuously undetectable u-PSA levels by an u-PSAA for 5 years, PSA monitoring can be stopped with an extremely low risk of subsequent BCR (Matsumoto et al. 2017). Based on the current literature, the correlation between the general PSADT and ultrasensitive doubling times (uDT) is poor (Reese et al. 2011). False positive findings from u-PSAAs may also originate from laboratory measurement errors (Ellis et al. 1997, Yu and Diamandis 1995a). Albeit, some authors claim that u-PSA measurements are helpful in determining early BCR after RP (Doherty et al. 2000, Haese et al. 1999, Shen et al. 2005), but others have claimed that it offers no benefit and mainly causes unnecessary anxiety for patients (Taylor et al. 2006).

2.8 Socioeconomic status and prostate cancer

2.8.1 Definition of socioeconomic factors

Although the survival rates of PCa have improved in recent decades, survival analyses regarding socioeconomic status (SES) suggest inequalities, indicating worse prognosis for lower SES groups. Information about underlying causes that explain socioeconomic differences in PCa survival and mortality is sparse. Evidently, SES also has an impact for PCa treatment. SES is defined as the differences in education level, income, occupation, unemployment, home ownership status, and other similar factors (Klein and von dem Knesebeck 2015).

2.8.2 Association with incidence and mortality

A higher incidence of PCa is reported in men who are in higher SES positions after the advent of PSA testing (Clegg et al. 2009). The increasing incidence of PCa has been reported in most Western countries during the latest two decades (Bray et al. 2010). SES differences are also reflected among different areas over the world.

Thus, incidence has increased most in areas with higher socioeconomic levels. However, men in lower SES positions have a greater likelihood to die from PCa (Rapiti et al. 2009). Low SES is also associated with more advanced cancer stage and higher age at diagnosis (Aarts et al. 2013).

Factors that may contribute to social variations in mortality may depend not only on tumor and host-related factors. These factors can also be related to unequal access and provision to health care (Lyratzopoulos et al. 2010). If the causality between lower SES position and mortality inequality is modeled by adjusting the effect of comorbidity and higher cancer stage at diagnosis, the difference diminishes (Byers et al. 2008).

The racial disparities in PCa incidence are also well documented: for example, African-Americans have very high incidence and mortality rates, whereas incidence is low in many parts of Asia. However, while African-American men have higher incidence and mortality rates from PCa, this cannot only be explained by SES factors (Cheng et al. 2009). Thus, while a greater proportion of African-Americans are in lower SES groups compared for instance to non-Hispanic whites in the United States, they still carry a higher incidence of PCa.

2.8.3 Diagnosis and treatment differences

Men with lower SES have a lower probability of being screened and receiving curative treatment for PCa and are more likely to receive ADT treatment for PCa than those in higher SES groups. Men with lower SES have a higher disease stage at diagnosis and are less likely to be treated with RP or RT and more likely to be treated with WW (Rapiti et al. 2009, Lyratzopoulos et al. 2010). Also, men with higher education are probably more health conscious and more likely to seek medical and health care services, such as PSA testing (Bowen et al. 2011, Weber et al. 2013). Therefore, persons who attend medical trials are apparently healthier than the general population. This phenomenon is known as the healthy volunteer effect (Pinsky et al. 2007). Men with low SES may have lower health literacy and awareness, and they may perceive cancer screening tests as more threatening, more difficult to accomplish, and less beneficial (von Wagner et al. 2011, Robb et al. 2009).

Furthermore, the inequality in treatment of PCa between the different SES positions may not only be related to treatment decisions (e.g., more conservative treatment approach for lower SES males), but it may also be a result of treatment delays, which may refer to patient, doctor, or system delays (Hansen et al. 2008). On the one hand, the treatment delays may be due to worse awareness and appraisals of cancer symptoms; on the other hand, the delay may be due to barriers regarding access to screening programs and health care in general, which in turn leads to small chances of incidental findings (Klein and von dem Knesebeck 2015).

2.8.4 Mediating factors

As mentioned earlier, information about the underlying causes that explain the socioeconomic differences in PCa survival and case fatality is sparse (Klein and von dem Knesebeck 2015). The increased mortality of men with lower SES could be largely explained by lifestyle and clinical parameters. Low SES is associated with increased PCa-specific and all-cause death. The mediating factors for increased mortality are tumor aggressiveness, comorbidity, treatment, and metabolic indicators (Larsen et al. 2016). Comorbidity differences are often associated with a higher prevalence of obesity, type 2 diabetes, and metabolic syndrome in lower SES groups, especially for persons with low education levels (Sacerdote et al. 2012). Furthermore, these comorbidity factors are shown to correlate with a higher cancer stage and delayed diagnosis of PCa (Cao and Ma 2011). Recent studies have not shown any decrease in the inequality gap between high versus low SES in terms of outcome of PCa (Shafique and Morrison 2013, Woods, Rachet and Coleman 2006).

While mediating factors to this are related to comorbidity, treatment, health care, and symptom awareness-related issues, it is also important to interpret the differences in PCa outcome between high versus low SES with caution. Men with high SES are probably more prone to undergo PSA testing. In this context, such artificial effects as the lead time bias should be taken into account (Auvinen and Karjalainen 1997, Dickman and Adami 2006). Lead time bias increases the survival of a PCa patient due to earlier detection of cancer, but it does not delay the death of the patient. Thus, screening by PSA just seems to increase survival time without altering the natural course of the disease (Draisma et al. 2009). PSA screening also often leads to prostate biopsies and to treatment of PCa, and thereby screening increases the risk of overtreatment. Hence, as the uptake of screening programs among PCa patients differs by SES, inequalities could be overestimated (Klein and von dem Knesebeck 2015).

3 AIMS OF THE STUDY

The aims of the study were:

1. To evaluate the PSA threshold in the ultrasensitive range predicting biochemical recurrence (BCR) after radical prostatectomy (RP) and to evaluate the relation of ultrasensitive PSA doubling time (uDT) and traditional PSA doubling time (tDT).

2. To develop novel tools that reduce the unreliability related to ultrasensitive PSA assays (u-PSAAs), to assess the potential prognostic significance of uDT for predicting BCR after RP, and to apply comprehensive mathematical modeling of u-PSAs and traditional PSAs (t-PSA) to establish an accurate predictive link between early measurements of PSAs and the risk of BCR.

3. To assess the excess risk of death among men with various stages of prostate cancer according to pre- and post-PSA periods.

    3.1 To estimate cancer-specific survival (CSS) to assess whether the decrease in excess risk is related to the selection of men due to opportunistic PSA testing.

4. To assess the possible inequality of different socioeconomic status (SES) groups in terms of CSS and other-cause survival (OCS) before and after the advent of PSA testing.

4 MATERIALS AND METHODS

4.1 Data sources

4.1.1 Turku University Hospital medical records

For studies I-II data was collected retrospectively from Turku University Hospital's medical records and PSA data was obtained from Turku University Hospital laboratory data sources. The collected data included all essential clinic-pathological variables (PSA values, Gleason scores, c/pTNM classification and SMs), neoadjuvant and adjuvant therapies, and follow-up information. Basic patient characteristics and clinic-pathological variables were available for all patients.

4.1.2 The Finnish Cancer Registry

The FCR is a nationwide database on cancer cases in Finland since 1953. It covers more than 99% of all solid cancers in Finland. The registry is maintained by the Finnish Cancer Organizations, and data are collected by mandatory notifications of cancer diagnoses made by all Finnish health care units, including public and private facilities. The reported information includes primary site and date of cancer, basis of diagnosis, TNM stage, histology/cell type, and information on treatment. The registry file is annually matched through computerized record linkage with the Cause of Death Register (Statistics Finland). The registry file is also regularly linked with the Central Population Register, where the correctness of the personal identifier digit is checked, and the complete name, vital status, possible date of death, emigration status, and the official place of residence prior to the date of diagnosis are obtained. The FCR has been internationally recognized for its high levels of data quality and completeness (Teppo, Pukkala and Lehtonen 1994).

4.1.3 Statistics Finland

Founded in 1865, Statistics Finland is the only Finnish public authority specifically established for statistics. It produces the vast majority of Finnish official data and is a significant international actor in the field of statistics. The data is derived from existing registers of the general government and from inquiries and interviews when the necessary data cannot be obtained elsewhere (Statistics Finland). In this study, the information on socioeconomic status, such as the level of education and occupation information, was obtained from the Statistics Finland longitudinal census data. The statistics on the causes of death cover persons who have died in Finland or abroad during the calendar year and who were domiciled in Finland at the time of death. The data is gathered from death certificates, which are supplemented

with data from the population information system of the Population Register Centre (Statistics Finland). Death certificate information includes primary, immediate, and contributory causes of death, coded according to the international ICD-10 classification (International Statistical Classification of Diseases and Related Health Problems).

In Finland, cause-of-death determination and death certification are of high quality because of high autopsy rates. Also, cause-of-death determination and death certification practices are directed, supervised, and partly carried out by medical examiners. The Finnish death certificate form, death certification practices, and the cause of death validation procedures enable the appropriate coding of causes of death for mortality statistics and form a relevant reference background for the evaluation of epidemiological studies on mortality (Lahti and Penttila 2001, Lahti and Penttila 2003).

4.1.4 Population Register Centre

The Population Register Centre contains information, such as the date of birth, residence area, and date and cause of death, for all Finnish citizens (Population Register Centre: Population information system). The data on the area of residence is collected by mandatory notification from citizens and public authorities. Other information, such as dates of birth, death, and causes of death, are provided by different health care institutions.

4.2 Study settings

4.2.1 Retrospective studies I–II

The prognostic significance of rising u-PSA levels was studied in retrospective study I.

A total of 604 consecutive patients undergoing open RP and limited PLND at Turku University Hospital during 2004–2008 were included. The current u-PSAA has been used in Turku University Hospital since January 1, 2004. This new study was initialized in 2013, and a minimum 5-year follow-up period was chosen. Patients who received neoadjuvant or adjuvant androgen deprivation were excluded, no exclusion was done on adjuvant RT and data from a total of 548 patients were analyzed. Data was also tested with exclusion of adjuvant RT patients, but this had no effect to results. Patient's u-PSA values were monitored every 3 months for the first year after the surgery and then semiannually, although the follow-up protocol was not standardized. All the PSA-analyses were done with an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics GmbH), which has a

detection threshold of 0.003 ng/ml. To calculate the PSADT at ultrasensitive and traditional ranges, the cut-off value was set to 0.2 ng/ml, which is considered the threshold of BCR after RP (Boccon-Gibod et al. 2004). The aim of the study was first to assess the u-PSA threshold that following the u-PSA levels probably continues to rise to the traditional BCR threshold (> 0.2 ng/ml). Furthermore, we questioned how high the u-PSA levels might rise because of biological variation or laboratory-technical issues without a true detection of later BCR. Secondly, we wanted to estimate the correlation of uDT and tDT. The uDT time was calculated using the values < 0.2 ng/ml, and tDT was measured using the values ≥ 0.2 ng/ml. The PSA nadir was defined as the lowest PSA measurement < 0.2 ng/ml or as the lowest value after which the PSA level started to rise. The study's end point was either the initiation of salvage therapy or the last follow-up. The patients who received salvage treatment with PSA values < 0.2 ng/ml were excluded from the DT analysis.

In the second study, we wanted to evaluate the u-PSAA's predictive value in terms of BCR. Also, the aim of this study was to develop novel tools that reduce the unreliability related to u-PSAAs. Furthermore, we assessed the potential prognostic significance of uDT for predicting BCR after RP and applied comprehensive mathematical modeling of u-PSAs and t-PSAs to establish an accurate predictive link between the early measurements of PSA and the risk of BCR. Patients undergoing open RP and limited PLND at Turku University Hospital during 2004–2008 were included (n = 604). The follow-up period was a minimum of 6 years. The patients who received neoadjuvant or adjuvant ADT were excluded; this also meant the exclusion of node-positive patients, resulting in 555 patients. For practical reasons, all types of ADT during the follow-up period were called adjuvant ADT, resulting in the population including no patients with hormonal treatment. From the 555 patients, full follow-up information was unavailable for 33 patients, and 19 patients died of causes unrelated to PCa, resulting in a final set of 503 patients. The PSA measurements with non-detected quantities were imputed using the smallest non-zero measurement. Of all the eligible post-surgery measurements, 4,502 (79.6%) were u-PSAs (≤ 0.1 ng/ml) and 1,151 (20.4%) were t-PSAs (> 0.1 ng/ml). The post-surgery PSA nadir was defined as the lowest PSA measurement within a 3-month window after surgery.

4.2.2 Population-based studies III–IV

In the third study, we wanted to assess whether the initiation of opportunistic and controlled PSA screening affects PCa survival and the standardized mortality ratio (SMR) of the PCa patients at a population level. A study cohort was chosen to cover the decade before the PSA era and the years after the introduction of PSA testing. The PCa cases that had been diagnosed from 1985 until December 31,

2013, were retrieved from the FCR. In all, 91,329 PCa cases were identified. They were defined as localized, local node positive, and metastasized at diagnosis based on the FCR data. However, cancer stage information was missing for 27.8% of the patients. PYs were calculated from the date of the PCa diagnosis to death, emigration, or December 31, 2013, whichever occurred first. The age group (1-year) and calendar year-specific mortality rates for the Finnish male population were obtained from Statistics Finland. In our study, the years between 1985 and 1994 are defined as the pre-PSA period, and the years after 1995 represent the post-PSA period.

In the fourth study, we aimed to evaluate the impact of SES on CSS and OCS for the PCa population. The study idea was also to determine the impact of PSA testing in terms of SES and the outcomes of PCa. All PCa cases diagnosed from 1985 until December 31, 2014, were retrieved from the FCR. The study cohort was chosen from 1985 to cover cases diagnosed before and after the introduction of PSA testing. PSA testing became more popular in Nordic countries in the late 1990s (Jonsson et al. 2011), and thus, the years after 1995 can be described as the post-PSA period and the years before 1995 as the pre-PSA period. In all, 95,076 PCa cases were identified. They were defined as localized or metastatic at diagnosis based on the FCR data. The assessment of metastases was most commonly done with a BS examination, traditionally being the most used staging method (Mottet et al. 2016). SES groups were also identified from Statistics Finland. The divisions between SES groups were based on education level, using the most recent antecedent information from census data. The educational levels were divided into three categories according to the highest attained educational degree or certificate as follows: basic (lasting typically < 10 years), upper secondary (10–12 years), and higher education (13 years or more). Occupational information was used for men on the basic education level to evaluate their more specified SES since the proportion of men with basic education levels was high compared to other education groups. Men whose occupation prior to retirement was unknown were excluded from these analyses. Among the men on the upper secondary and higher education level, the occupational SES information was not used.

4.3 Statistics

4.3.1 Retrospective studies (I–II)

In the first study, a statistical analysis was carried out first to compare the uDT with tDT. The doubling times were cross-tabulated, and the sensitivity and specificity measurements for the uDT to estimate the tDT were calculated. The PSADTs were obtained by fitting a linear model for the logarithm of PSA values and then

dividing the log 2-adjusted values by the slope of the regression line. Secondly, to compare ultrasensitive and traditional PSADTs, a weighted Cohen`s kappa statistic was applied to test for agreement across the categories. For cross-tabulation, we used PSADT ordinal categories of 0 to 3 months, 3 to 9 months, 9 to 15 months, and greater than 15 months. To evaluate the specificity of the analysis more closely, we compared the doubling times between categories. The correlation between the uDT and tDT using a single DT cut-off (9 months) period was studied in detail. Thirdly, the correlation between the uDT and tDT was also tested with receiver-operative characteristics (ROC) curve analysis. Fourth, we also made multivariate Spearman`s correlation analyses of the standard primary disease characteristics pT classification, Gleason score, preoperative PSA, and the variables describing PSA kinetics, such as BCR and PSADT. We also repeated all analyses after the exclusion of adjuvant RT therapies. We also adjusted the model in terms of how high u-PSA levels might rise without further progression to BCR with a scatter plot diagram.

In the second u-PSA study, the PSA measurements with non-detected quantities were imputed using the smallest non-zero measurement. Of all the eligible post-surgery measurements, 4,502 (79.6%) were u-PSAs (≤0.1 ng/ml) and 1,151 (20.4%) were t-PSAs (> 0.1 ng/ml). The post-surgery PSA nadir was defined as the lowest PSA measurement within a 3-month window after surgery. The 3-month period was chosen because 8 weeks is ample time to allow PSA levels to clear after RP, and detectable u-PSA values within 1–3 months after RP are suggested as a marker for BCR progression (Oesterling 1991, Eisenberg et al. 2010). The mathematical modeling was based only on the post-nadir measurements prior to possible salvage treatments. To evaluate the generalization ability of the modeling, the data was randomized into three subgroups of subjects prior to model development, where factors such as age, BCR status, and Gleason score were balanced. Two of the subgroups were randomly chosen to generate the exploratory data and were fully utilized in the model development. Within this exploratory data, generalization ability was maintained through cross-validation. The remaining third of the data was utilized as a validation set to retain an objective view of the robustness of the final model. For mathematical modeling, cubic penalized splines were used in the exploratory set with a wide range of values for the spline-smoothing parameter λ. The optimal smoothing parameter was identified by minimizing the cross-validation median squared error (MSE) of the spline fits. Penalized splines provided a flexible approach to explore whether the log_2-transformed PSA would display complex nonlinear patterns (low λ) or linear patterns (high λ). Based on the highly linear patterns of the log_2-transformed PSA that were observed, a linear mixed-effects model was built. The parameter estimates of the model for the log_2-PSA nadir and PSADT were used for detecting the differences between the BCR and non-BCR patients. A clinical risk assessment tool was

further derived using generalized linear models as binary classifiers for BCR, using parameter derivatives from the patient-wise nadir and PSADT. The mathematical modeling was conducted using the R statistical software (version 3.2) (R-Foundation 2015), along with the R-packages *psplines* (Ripley 2013) and *lme4* (Bates D et al. 2014) for the penalized cubic splines and linear mixed-effects models, respectively.

4.3.2 Population-based studies III–IV

In the third study, the standardized mortality ratio (SMR) was used to compare the mortality rates of PCa patients to those of the Finnish male population. The SMR is estimated as the ratio of observed and expected number of deaths standardized indirectly with age and calendar year. The observed number is the number deaths from any cause in the PCa cohort. The expected number for each standard variable stratum is derived by multiplying the population mortality rates by the PYs of the cohort (Breslow and Day 1987). The patients were censored after 10 years of follow-up to allow comparisons of the mortality of patients diagnosed in different calendar periods. The 95% confidence intervals (CIs) were calculated assuming a Poisson distribution for observed deaths.

The relative survival ratio is defined as the ratio between the observed survival of the PCa patients and their expected survival. The expected survival was derived from the Finnish male population mortality rates stratified by age and calendar time by using the Ederer II method (Seppa et al. 2015). The CSS with respect to deaths from PCa was estimated using a life table method in which the deaths due causes other than PCa (or the deaths due to PCa when CSS is estimated with respect to other causes) were considered censored events. Traditional direct-age standardization was used to compare the survival estimates between different groups. In each comparison, the age distribution of the patients diagnosed in the pre-PSA era (1985–1994) was used as the standard (four age groups: 0–59, 60–69, 70–79, and 80 years old and older).

In the fourth study, CSS with respect to deaths from PCa and from causes other than PCa, respectively, were estimated using a life table method (Cutler and Ederer 1958). Traditional direct-age standardization was used for survival comparisons between the educational groups and between the groups of SES (among patients with basic education), as the groups differed in age structures (Pokhrel and Hakulinen 2008). In each comparison, the age distribution of the patients diagnosed in the whole study period (1985–2014) by tumor stage was used as the standard (five age groups: 0–54, 55–64, 65–74, 75–84, and 85 years old and older). The CSS proportion was estimated separately for patients diagnosed during the periods

1985–1994, 1995–2004, and 2005–2014 by tumor stage (three categories: localized, metastatic, and unknown).

A Poisson regression model was used to quantify the differences in PCa mortality between the patient groups. The model results are reported as relative risk (RR) of death from PCa. The models included six follow-up time intervals (annual intervals from 0 to 5 years and a 5-year interval at 5–10 years), age at diagnosis (the same categories as in the age standardization), and the level of education or SES. The models were fitted separately for each period and stage. Interactions between age and follow-up time were included to allow for nonproportional cancer mortality by age at diagnosis (Dickman et al. 2004). The first 10 years of follow-up was considered, and longer survival times were censored at 10 years. Analyses were also tested with longer (15 year) follow-up time. This assesment with longer follow-up did not change study findings. We also wanted to evaluate homogenous 10 year periodal cohorts.

4.4 Ethics

The research Ethics board (IRB) of the Hospital District of Southwestern Finland approved the study protocols of the retrospective studies (I–II). For the population-based studies (III–IV), the study protocol was also approved by the IRB of the Hospital District of Southwestern Finland, and the Finnish National Institute of Health and Welfare approved access to registry data (study number 182/5.05.00/2015). For study IV, Statistics Finland approved access to cause of death and SES data (study number TK-53-86-17).

5 RESULTS

5.1 Ultrasensitive PSA after radical prostatectomy (Studies I–II)

In the first study, the median age at the time of RP was 61.8 years, with a standard deviation (SD) of 5.7 years. The median follow-up time was 5.6 years (SD 2.4 years). Half (50%) of the patients had Gleason ≤ 6 disease in the RP specimen. The proportion of high grade (Gleason 8–10) PCa was 9% of the study population. However, 44% of the patients had pT3 disease, but only 0.4% of patients had node-positive disease. SMs were positive for 38% of patients. Still, PSA failure occurred only for 13% of patients during the follow-up time. Only one patient died from PCa during the follow-up time, when patients who received neoadjuvant or adjuvant ADT were excluded. Adjuvant RT was given for 11% of the patients, and salvage RT was given for 16% of patients. A total of 71 (13%, out of 548) patients had BCR (in t-PSA area) and did not receive any adjuvant treatment.

There were 229 non-relapsed patients who did not have three consecutive rising PSA values after nadir. Their highest PSA value was between 0.003 ng/ml and 0.1 ng/ml. To assess the PSA threshold for BCR in the ultrasensitive range from these 229 patients, we created a scatter plot of PSA values, including all PSA measurements after nadir (Fig. 3).

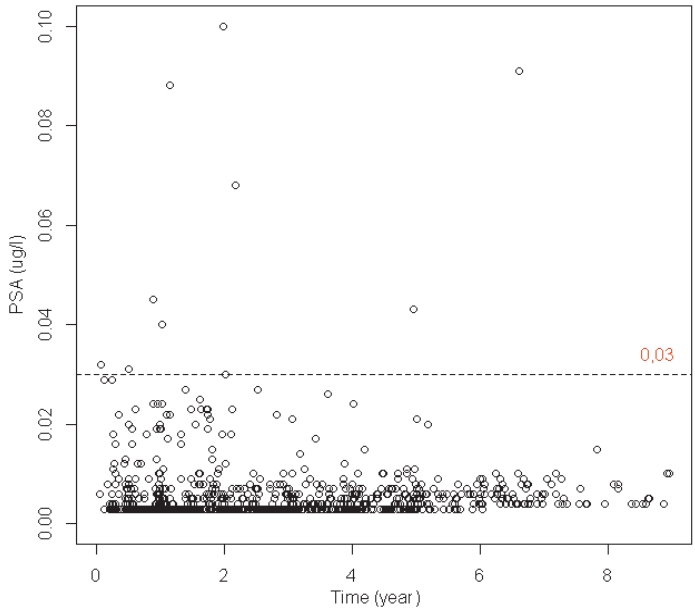

Figure 3: A scatterplot of PSA measurements in patients without three rising post-nadir PSA measurements. The minimum follow-up time was 2 years (n = 229**).** Modified from Seikkula et al. Urologic Oncology 2014.

In 97.4% of patients, the highest PSA value was below 0.03, and in 89% of patients, it was below 0.02. The values could be considered as clinically nonsignificant and normal variation without the risk of BCR and higher values are associated with the progression to BCR.

The agreement of uDT with tDT afterwards showed a poor agreement across the categories. The weighted Cohen´s kappa statistic between these two groups was 0.30 (95% CI 0.09–0.50). The correlation of tDT < 9 months with uDT was tested with an ROC-curve with an AUC value 0.737 (95% CI 0.577–0.897). This showed a fair agreement across uDT and tDT (Fig. 4). Spearman`s correlations of the traditional clinical and pathological features of the study population with uDT and tDT, with and without adjuvant RT, are described in Tables 6 and 7. Similar results were found for patients with or without adjuvant RT.

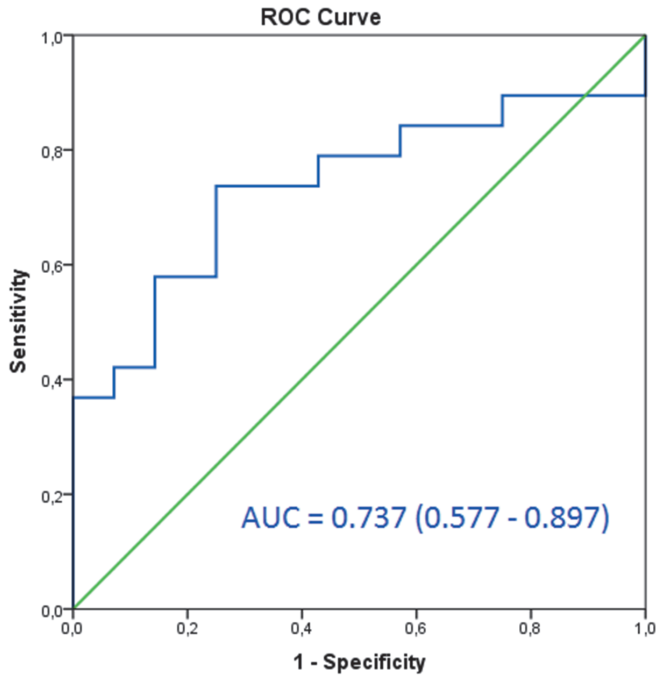

Figure 4: ROC (receiver-operating characteristic) curve. The effectiveness of uDT as a classifier, if the gold standard for a poor prognosis is defined to be tDT < 9 months. AUC = area under the curve. Modified from Seikkula et al. Urologic Oncology 2014.

Table 6. Correlations of preoperative PSA, Gleason score, positive surgical margins, pT-classification, and biochemical recurrence with ultrasensitive PSA doubling time and traditional PSA doubling time.

		prePSA	**Gleason**	**PM**	**pT**	**BCR**	**uDT**	**tDT**
PrePSA	ρ	1.000	0.154	0.104	0.146	0.101	−0.120	0.028
	p-value		0.001	0.021	0.001	0.025	0.478	0.869
	N	489	489	489	489	489	37	37
Gleason	ρ	0.154	1.000	0.125	0.190	0.259	−0.037	−0.108
	p-value	0.001		0.006	<0.001	<0.001	0.826	0.526
	N	489	489	489	489	489	37	37
PM	ρ	0.104	0.125	1.000	0.791	0.108	0.056	0.360
	p-value	0.021	0.006		<0.001	0.017	0.743	0.029
	N	489	489	489	489	489	37	37
pT	ρ	0.146	0.190	0.791	1.000	0.161	0.064	0.196
	p-value	0.001	<0.001	<0.001		<0.001	0.708	0.244
	N	489	489	489	489	489	37	37
BCR	ρ	0.101	0.259	0.108	0.161	1.000	NA*	NA*
	p-value	0.025	<0.001	0.017	<0.001		NA*	NA*
	N	489	489	489	489	489	37	37
uDT	ρ	−0.120	−0.037	0.056	0.064		1.000	**0.495**
	p-value	0.478	0.826	0.743	0.708			**0.002**
	N	37	37	37	37	37	37	37
tDT	ρ	0.028	−0.108	0.360	0.196		**0.495**	1.000
	p-value	0.869	0.526	0.029	0.244		**0.002**	
	N	37	37	37	37	37	37	37

Patients with adjuvant radiation therapy were excluded. ρ = Spearman`s correlation coefficient, N = number, prePSA = preoperative PSA, PM = positive surgical margins, pT = pathological tumor classification, BCR = biochemical recurrence, uDT = ultrasensitive PSA doubling time, and tDT = traditional PSA doubling time. NA= not applicable, *Not enough events

Table 7. Correlations of patients with adjuvant radiation therapy

		prePSA	**Gleason**	**PM**	**pT**	**BCR**	**uDT**	**tDT**
PrePSA	ρ	1.000	0.163	0.131	0.163	0.094	−0.178	−0.002
	p-value		<0.001	0.002	<0.001	0.028	0.231	0.991
	N	548	548	548	548	548	47	47
Gleason	ρ	0.163	1.000	0.182	0.235	0.261	−0.004	−0.105
	p-value	<0.001		<0.001	<0.001	<0.001	0.976	0.482
	N	548	548	548	548	548	47	47
PM	ρ	0.131	0.182	1.000	0.805	0.125	0.069	0.316
	p-value	0.002	<0.001		<0.001	0.003	0.643	0.030
	N	548	548	548	548	548	47	47
pT	ρ	0.163	0.235	0.805	1.000	0.158	0.069	0.158
	p-value	<0.001	<0.001	<0.001		<0.001	0.647	0.289
	N	548	548	548	548	548	47	47
BCR	ρ	0.094	0.261	0.125	0.158	1.000	NA*	NA*
	p-value	0.028	<0.001	0.003	<0.001		NA*	NA*
	N	548	548	548	548	548	47	47
uDT	ρ	−0.178	−0.004	0.069	0.069		1.000	**0.428**
	p-value	0.231	0.976	0.643	0.647			**0.003**
	N	47	47	47	47	47	47	47
tDT	ρ	−0.002	−0.105	0.316	0.158		**0.428**	1.000
	p-value	0.991	0.482	0.030	0.289		**0.003**	
	N	47	47	47	47	47	47	47

ρ = Spearman`s correlation coefficient, N = number, prePSA = preoperative PSA, PM = positive surgical margins, pT = pathological tumor classification, BCR = biochemical recurrence, uDT = ultrasensitive PSA doubling time, and tDT = traditional PSA doubling time, NA= not appicable, * Not enough events

In the second study, the population was similar to first study. However, more follow-up time resulted in a slightly different study setup. The patient characteristics of the study are reported in Table 8. The major PSA trends were effectively captured readily by linear components in the model based on the optimality of the high values of the smoothing parameter λ (Fig. 5c), as well as upon visual inspection (Fig. 5d–f; Fig. 6a–b). The first order derivatives that capture longitudinal changes in PSADT clearly distinguished between the BCR and non-BCR, suggesting that a longitudinal follow-up of PSADT could provide an accurate predictor of BCR (Fig. 6c). The u-PSAs and t-PSAs did not exhibit markedly different patterns in the splines (Fig. 6b–c). Since splines suggested that linear model families were suitable for modeling the log_2-PSA patterns, we fitted linear regression models to perform parametric inference for the population effects. The focus was on the log_2-PSA nadir and PSADT. Patient-wise estimates for these coefficients are shown in Fig. 7a–b with 1- or 3-year follow-up, respectively. Finally, generalized linear

Table 8. Patient characteristics of study II

Variable	*Instance*	*Exploratory 2/3*		*Validation 1/3*	
pT	**2**	180 (53.3%)		92 (55.8%)	
	3	156 (46.2%)		73 (44.2%)	
	4	1 (0.3%)			
	Missing	1 (0.3%)			
Gleason score (GS)	**≤ 6**	157 (46.4%)		80 (49.1%)	
	7 (3+4)	101 (29.9%)		49 (30.1%)	
	7 (4+3)	50 (14.8%)		18 (11.0%)	
	≥ 8	28 (8.3%)		16 (9.8%)	
Margins	**Missing**	2 (0.6%)			
	Negative	200 (59.2%)		100 (60.6%)	
	Positive	137 (40.5%)		65 (39.4%)	
	Missing	1 (0.3%)			
Adjuvant RT	**No**	295 (87.3%)		147 (89.1%)	
	Yes	42 (12.4%)		18 (10.9%)	
	Missing	1 (0.3%)			
Salvage RT	**No**	275 (81.4%)		136 (82.4%)	
	Yes	63 (18.6%)		29 (17.6%)	
PSA at surgery	**< 10**	251 (74.3%)		121 (73.3%)	
	10–20	67 (19.8%)		36 (21.8%)	
	≥ 20	19 (5.6%)		8 (4.8%)	
	Missing	1 (0.3%)			
Age	**< 60**	123 (36.4%)		61 (37.0%)	
	60–70	193 (57.1%)		96 (58.2%)	
	70	21 (6.2%)		8 (4.8%)	
	Missing	1 (0.3%)			
Total counts of PSA measurements in different time windows	**Time post-surgery**	*t-PSA*	*u-PSA*	*t-PSA*	*u-PSA*
	< 1y	166	875	161	466
	1y–3y	120	788	78	413
	> 3y	236	1000	164	649
Patient status	**No recurrence**	279 (82.5%)		140 (84.8%)	
	Recurrence (BCR)	52 (15.4%)		22 (13.3%)	
	Metastasis/other	7 (2.1%)		3 (1.8%)	

models were used as binary classifiers to connect the patient-wise characteristics from Fig. 7a–b to the known BCR statuses. The prediction accuracy using 1-year or 3-year post-nadir follow-up was 85.3% or 88.8%, respectively, using the prediction surfaces provided in Fig. 7c–d. Overall, only minor variations were detected between the u-PSA and t-PSA assays in terms of model diagnostics, exemplified by the slight decrease of heteroscedasticity over the threshold for the model residuals (Fig. 7e). Our results indicate that u-PSAAs provide useful information for predicting BCR after RP. We provide a practical computational example for the validated generalized linear models for predicting the BCR risk of a patient and an easy-to-use graphical user interface that is freely available (http://compbiomed.shinyapps.io/u-pa). Our easily accessible mathematical pipeline established a novel baseline for future validation studies of the importance of the u-PSAA and further method development.

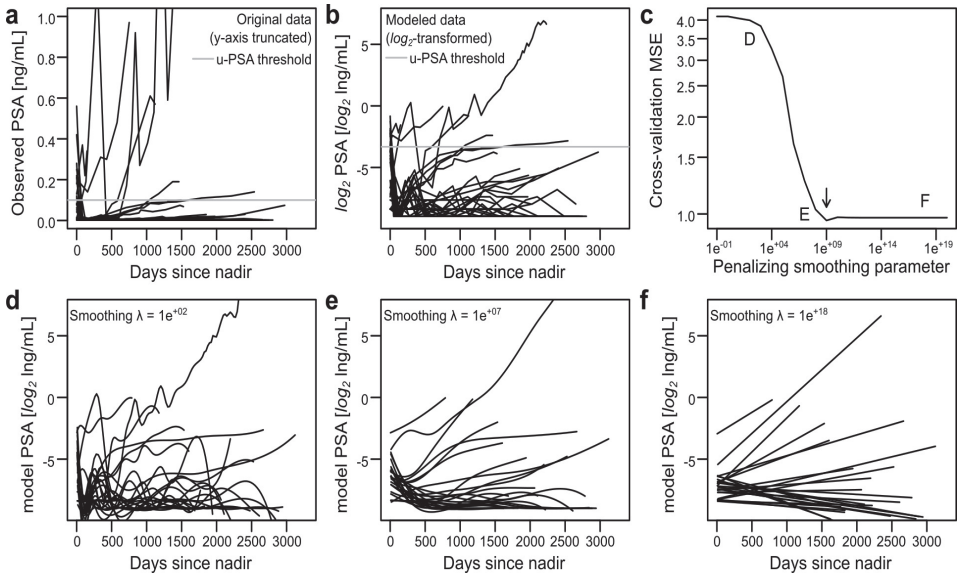

Figure 5: Longitudinal PSA profiles for 30 randomly chosen patients using penalized cubic splines. (a) The raw PSA profiles exhibited varying patterns as a function of time since the post-surgery nadir. (b) After log_2-transformation, the unit increase in the response corresponds to doubling in the original scale. (c) Model complexity was chosen according to cross-validation (CV) median squared error (MSE). Three example models are visualized in panels d–f. The optimal model ($\lambda = 10^9$) is indicated with the arrow. (d–f) Example model fits for varying λ are shown for the log_2-scale data from panel b. Modified from Laajala TD, Seikkula H et al. Scientific Reports 2016.

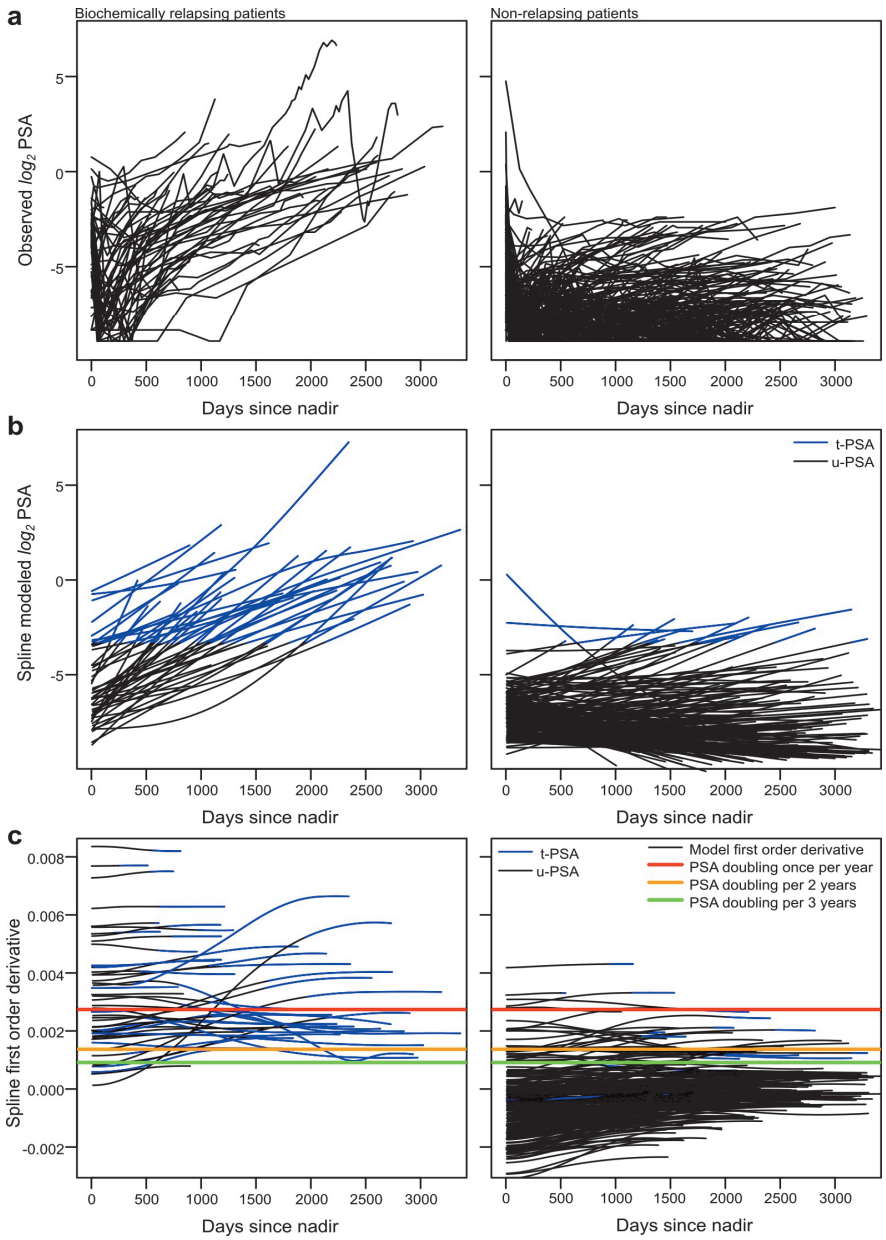

Figure 6: All the modeled exploratory data, model fits, and the first order derivatives of the penalized splines for the relapsing (left column; $N = 52$) and non-relapsing patients (right column; $N = 279$). (a) Modeled log_2-transformed data. (b) Corresponding penalized cubic spline fits. (c) The first order derivatives (few exceptions, the derivatives maintained relatively constant levels over the follow-up period). **Once per year or once per 2 years, the PSA doubling criteria were good indicators of relapse or non-relapse of patients.** Noticeable differences between u-PSA (black) and t-PSA (blue) were not present. Modified from Laajala TD, Seikkula H et al Scientific Reports 2016.

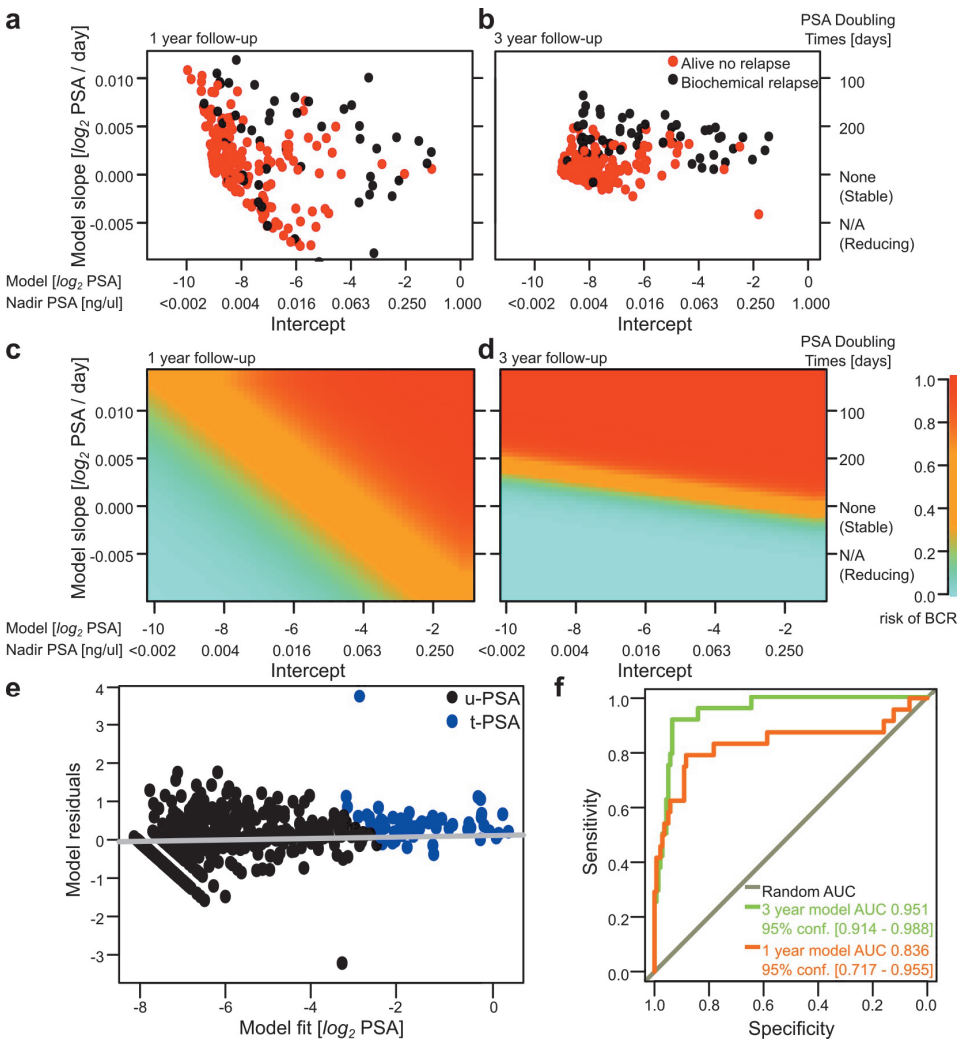

Figure 7: (**a**–**b**): Linear mixed-effects yielded estimates for the patient-specific nadir intercept and doubling coefficient using a 1-year (panel **a**) or a 3-year post-nadir window (panel **b**). (**c**–**d**): Using generalized regression, we identified the prediction surfaces for the risk of BCR using a 1-year (panel **c**) or a 3-year post-nadir time window (panel **d**). The probability annotations for the generalized linear models were annotated using the color key on the right. (**e**): The regression residuals for the 1-year post-nadir window using linear-mixed effects models display a slight decrease in the residual variance as a function of u-PSAs versus t-PSAs, though no systematic increasing or decreasing trends were detected. (**f**): The validation dataset suggested high predictive accuracy for BCR using the fitted models from the exploratory portion of data. Modified from Laajala TD, Seikkula H et al Scientific Reports 2016.

5.2 Pre- and post-PSA period survival and mortality trends (Study III)

The number of all PCa diagnoses increased almost fourfold from 1985 to 1989 (N = 6227) and to 2005–2009 (N = 22868) and mostly of a localized stage. Most cases

were of high age at diagnosis: 55.7% were aged 70 years or more. The majority of men with localized PCa died from other causes (N = 11 228) than PCa (N = 4058) during the first 10 years of follow-up, while the majority of men with metastatic disease died from PCa during the same period. During the first 10 years of follow-up, the absolute number of deaths in localized PCa has been essentially the same from the pre-PSA testing era (1730) to the post-PSA testing era (1722). However, the number of deaths due to other causes has increased (from 2,973 to 5,320). Among the metastasized PCa patients, the absolute number of deaths due to PCa did not change significantly from the pre-PSA period (3,121) to the post-PSA period (3,455), but increased due to other causes of death (from 759 to 1,542 deaths) (Table 9).

The declining trend in SMRs was seen for the whole study population: SMR 2.08 (95% CI 2.02–2.14) during 1985–1985 to 1.35 (95%CI 1.32–1.38) during 2000–2004. The SMR for the overall period (1985–2009) was 1.55 (95% CI 1.54–1.57) (Table 10). The SMR for localized PCa decreased significantly over time ($p < 0.001$) from 1.50 (95% CI 1.44–1.57) during 1985–1989 to 0.98 (95%CI 0.95–1.01) during 2000–2004. Since the early 2000s, the SMR among men diagnosed with localized PCa has been lower compared to the SMR in the Finnish male population. In metastatic PCa, a similar declining trend ($p < 0.001$) was seen: The SMR was 4.51 (95% CI 4.30–4.72) during 1985–1989 and 3.01 (95%CI 2.89–3.12) during 2000–2004 (Table 10). In the unknown stage group, the SMR also decreased over the time period, similarly to all PCa patients (Table 10). The SMRs for localized, unknown, and metastasized disease are illustrated using SMR splines (Fig. 8). The mortality from localized PCa was only slightly elevated during the 29-year study period. Also, the risk of death from metastasized PCa declined over time, and mortality from PCa stabilized 5 years after diagnosis (Fig. 8).

In metastasized PCa, the estimates of relative and CSS were similar in both the pre- and post-PSA eras. In the post-PSA era, the 10-year relative survival was 34.7%, and the cause-specific survival was 34.1% (Table 11). In the pre-PSA period, the respective numbers were 16.9% and 14.1%. Also, in localized PCa cases diagnosed in the pre-PSA era, the 10-year relative and CSS estimates were similar: 66.1% and 63.6%, respectively. However, in the post-PSA era, the difference between the 10-year relative (94.6%) and cause-specific (84.2%) survival was 10.4 percentage points. Between the pre- and post-PSA eras, the CSS with respect to the causes of death other than PCa increased 12.7 percentage points in localized PCA but only 1.7 percent points in metastasized (Table 11). The results on SMR and survival did not change substantially when extending follow-up time up to 15 years.

Table 9. Basic characteristics of the study population

		PCa diagnosis		Deaths in 5-year follow-up		Deaths in 10-year follow-up	
		N	Percent	PCa deaths	Other deaths	PCa deaths	Other deaths
Total		91,329	100.0	13,051	14,552	17,244	22,460
Stage	Localized	47,001	51.5	2,379	6,735	4,058	11,228
	Unknown	25,391	27.8	2,992	5,206	4,207	7,653
	Metastasized	18,153	19.9	7,505	2,527	8,714	3,448
	Local node positive	784	0.8	175	84	265	131
Year of diagnosis	1985–89	6,227	6.8	2,222	1,457	2,853	2,276
	1990–94	8,579	9.4	2,665	2,054	3,506	3,192
	1995–99	14,130	15.5	2,817	3,052	3,944	5,037
	2000–04	20,365	22.3	2,420	3,515	3,596	6,360
	2005–09	22,868	25.0	2,117	3,394	2,535*	4,515*
	2010–13	19,160	21.0	810*	1,080*		
Age at diagnosis (Median 71.3 y, IQR = (64.7–77.8)	> 80	16,178	17.7	3,816	5,514	4,480	7,445
	70–79	34,683	38.0	5,189	6,333	7,090	10,339
	60–69	29,613	32.4	3,073	2,308	4,370	3,987
	50–59	10,063	11.0	863	380	1,171	664
	< 50	792	0.9	110	17	133	25
Pre PSA (1985–1994)	Localized	6,637	61.4	1,066	1,767	1,722	2,973
	Metastasized	4,172	38.6	2,773	576	3,121	759
Post-PSA (1995–2004)	Localized	16,831	73.3	891	2,745	1,730	5,320
	Metastasized	6,137	26.7	2,754	950	3,455	1,542

* Not all patients had complete follow-ups.

Table 10. SMR by stage and year of diagnosis

Stage	Year of diagnosis	Observed number of deaths	Expected number of deaths	Person-years	SMR (CI: 95%)
	All	39,599	25,526.5	465,436	1.55 (1.54–1.57)
All stages combined	1985–89	5,120	2,460.8	29070.6	2.08 (2.02–2.14)
	1990–94	6,687	3,444.6	43051.2	1.94 (1.90–1.99)
	1995–99	8,951	5,590.9	87213.5	1.60 (1.57–1.63)
	2000–04	9,912	7,340.4	145907.0	1.35 (1.32–1.38)
	2005–09	7,040	5,354.5	124777.0	**1.31 (1.28–1.35)
				*p-value <0.001	
Localized	1985–89	2,103	1,399.1	16562.2	1.50 (1.44–1.57)
	1990–94	2,580	1,825.2	23535.8	1.41 (1.36–1.47)
	1995–99	3,285	2,818.7	46753.2	1.17 (1.13–1.21)
	2000–04	3,729	3,813.9	84809.9	0.98 (0.95–1.01)
	2005–09	2,986	3,171.6	81512.7	**0.94 (0.91–0.98)
				*p-value <0.001	
Metastasized	1985–89	1,759	390.3	4971.2	4.51 (4.30–4.72)
	1990–94	2,118	555.8	7375.7	3.81 (3.65–3.98)
	1995–99	2,374	816.8	12661.0	2.91 (2.79–3.03)
	2000–04	2,610	868.2	15091.6	3.01 (2.89–3.12)
	2005–09	2,512	1,054.0	21546.1	**2.38 (2.29–2.48)
				*p-value <0.001	
Unknown	1985–89	1,182	639.0	7048.0	1.85 (1.75–1.96)
	1990–94	1,888	1,023.2	11398.2	1.85 (1.76–1.93)
	1995–99	3,182	1,916.1	26715.3	1.66 (1.60–1.72)
	2000–04	3,500	2,624.8	44932.4	1.33 (1.29–1.38)
	2005–09	1,513	1,106.7	21146.2	**1.37 (1.30–1.44)
				*p-value <0.001	

The period 1985–94 represents the pre-PSA era, and the period 1995–2004 is the post-PSA era. Follow-up is limited to 10 years. *P-value tests for significance of the calendar trend. **Not all patients had completed follow-up.

Table 11. Survival estimates for localized and metastasized prostate cancer

Stage	Survival type	PSA era	5-year survival %	10-year survival %
Localized	Relative	Pre	84.7 (81.6–88.0)	66.1 (61.3–71.2)
		Post	99.5 (97.8–101)	94.6 (91.4–97.8)
	Cancer	Pre	81.4 (79.5–83.4)	63.6 (60.8–66.5)
		Post	93.1 (92.3–93.9)	84.2 (82.9–85.5)
	Other causes	Pre	72.6 (70.7–74.6)	47.6 (45.3–49.9)
		Post	80.5 (79.4–81.6)	60.3 (59.0–61.6)
Metastasized	Relative	Pre	29.5 (26.3–33.0)	16.9 (13.6–21.1)
		Post	53.9 (50.9–57.1)	34.7 (31.1–38.7)
	Cancer	Pre	27.5 (24.9–30.3)	14.1 (12.0–16.7)
		Post	51.8 (49.4–54.3)	34.1 (31.5–36.8)
	Other causes	Pre	74.7 (71.2–78.3)	51.8 (46.4–57.7)
		Post	77.8 (75.6–80.1)	53.5 (50.3–56.8)

Relative survival (Relative) and cause-specific survival with respect to PCa (Cancer) and causes other than PCa (Other causes) of localized and metastasized prostate cancers in the pre- (1985–94) and post-PSA testing eras (1995–2004).

Figure 8. Standardized mortality ratios (SMRs) of the prostate cancer patients by stage in Finland (N=91,329).

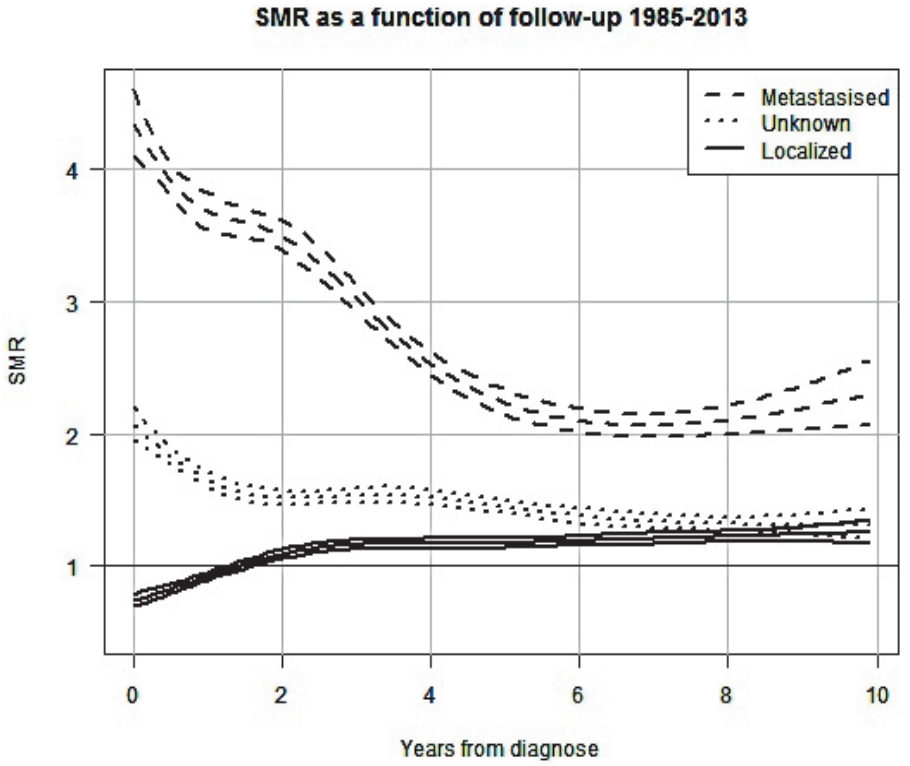

Figure 8: Curves illustrate the trends of prostate cancer patients SMRs by stage during a 29 years period with 10 year follow-up time. N=number.

5.3 Socioeconomic status and prostate cancer survival in the pre-and post-PSA periods (Study IV)

Half of the identified PCa patients (N = 95076) had localized disease (N = 49047, 51.6%), and one-fifth had metastatic disease (N = 18325, 19.3%). The vast majority (66%) of the whole study population were old (> 70 years) at diagnosis. The stage remained unknown in close to one-third of patients (N = 27704, 29.1%) overall, and the missing stage increased over time (Table 12). There were over seven times more localized PCa cases in men with a higher education level during 2005-2014 (N = 6,943) compared to the 1985–1994 period (N = 937). Meanwhile, the number of new localized PCa cases only doubled in men with a basic education level: N = 5,016 between 1985 and 1994, and N = 11,794 between 2005 and 2014, respectively. The proportion of men with a higher education level increased substantially in the metastatic disease category: 12% during 1985–1994 compared to 19% during 2005–2014, while the proportion of men with a basic education level with metastatic disease decreased from 77% (1985–1994) to 57% (2005–2014), respectively (Table 12).

Cancer-specific 10-year survival rates were 64% (1985–1994) and 86% (1995–2004) for men with localized disease and a basic education level. In the first period of observation, patients in the upper secondary and higher education level had distinctly better 10-year CSS rates than men at the basic education level. In recent years, this difference has not been that evident (Table 13 and Fig. 9). Men with a higher education level with metastatic disease had better 10-year CSS rates than men on the basic education level during the study period. From 1985 through 1994, 13% (basic level), 14% (upper secondary level), and 17% (higher level) survived 10 years. Between 1995 and 2004, the 10-year CSS rates were 33% (basic level), 35% (upper secondary level), and 41% (higher level), respectively (Table 13 and Fig. 10). An improving survival rate was clearly seen in the post-PSA period compared to the pre-PSA period in all SES groups. Among men with an unknown PCa stage, 10-year CSS was better at the higher education level than at lower levels, as well as in the pre-PSA period (Table 13 and Fig. 11). OCS was better with men with a higher education level compared to others in all study periods and for all stage groups (Table 13).

A Poisson regression coefficient for PCSM showed substantially reduced RR for PCa death for men with a higher education level, as well as for those in the pre-PSA period as opposed to the post-PSA period. In the 1985–1994 period, the RR for PCa death was 0.76 (95%CI 0.66–0.88) compared to basic education level and 0.61 (95%CI 0.53–0.67) for 1995–2004. The risk of dying was also lower in metastatic disease, with an RR of 0.85 (95%CI 0.76–0.95) during 1985–1994 and 0.78 (95% CI 0.71–0.86) during 1995–2004, respectively. In men with an unknown disease

stage, there was no statistically significant difference in the pre-PSA period; still, the difference was evident in the post-PSA period, with an RR of 0.68 (95%CI 0.60–0.77) during 1995–2004 and 0.61 (95%CI 0.49–0.75) during 2005–2014 for men on the higher education level compared to the basic education level (Table 13).

A subgroup analysis of men on the basic education level with occupational information showed that many of these men were manual workers. The proportion of self-employed persons was rather high, especially in first two periods of observation. There were more self-employed persons in the older (> 70 years of age) men category (Table 14). CSS of the basic education population was not clearly different between occupation groups during the period of observation, although self-employed persons and manual workers had better 10-year survival rates in metastatic disease from 1985 to 1994 (Table 15). However, the number of survivors was low (Table 15).

The only significant difference in the risk of PCSM between the occupation groups in terms of basic education level with localized disease was in the post-PSA period (1995–2004), when manual workers (RR 0.75; 95% CI 0.62–0.92) had a significantly increased risk for PCSM than self-employed persons (reference group). For employees RR was 1.12 (95% CI 0.97–1.29) and for others RR was 1.03 (95% CI 0.82–1.29) compared to self-employed persons. In metastatic and unknown stage groups, no significant difference was seen (Table 15).

Table 12. Basic characteristics of the study population (Study IV)

EL	Stage	Period		Period		Period	
		1985-1994		1995-2004		2005-2014	
		N (%)					
		All ages	< 70 yr	All ages	< 70 yr	All ages	< 70 yr
Basic	**Localized**	5,016 (76%)	1,564 (72%)	10,017(59%)	4,151 (49%)	11,794(46%)	4,888 (34%)
Upper sec.		690 (10%)	265 (12%)	3,027 (18%)	1,954 (23%)	6,793 (27%)	4,799 (34%)
Higher		937 (14%)	353 (16%)	3,830 (23%)	2,379 (28%)	6,943 (27%)	4,593 (32%)
All		6,643(100%)	2,182 (100%)	16,874 (100%)	8,484 (100%)	25,530 (100%)	14,270 (100%)
Basic	**Unknown**	2,883 (77%)	665 (72%)	7,470 (67%)	2,095 (54%)	6,544 (51%)	1,899 (36%)
Upper sec.		390 (10%)	109 (12%)	1,668 (15%)	860 (22%)	3,150 (25%)	1,782 (34%)
Higher		491 (13%)	144 (16%)	2,042 (18%)	910 (24%)	3,066 (24%)	1,559 (30%)
All		3,764(100%)	918 (100%)	11,180 (100%)	3,865 (100%)	12,760 (100%)	5,240 (100%)
Basic	**Metastatic**	3,202 (77%)	1,086 (73%)	4,227 (69%)	1,417 (61%)	4,566 (57%)	1,421 (47%)
Upper sec.		452 (11%)	193 (13%)	911 (15 %)	463 (20%)	1,892 (24%)	755 (25%)
Higher		526 (12%)	206 (14%)	991 (16%)	452 (19%)	1,568 (19%)	854 (28%)
All		4,170(100%)	1,485(100%)	6,129 (100%)	2,332 (100%)	8,026 (100%)	3,030 (100%)

EL = education level, Basic = basic education, Upper sec. = upper secondary education, Higher = higher education

Table 13. Risk ratio of death from PCa and CSS and OCS by period and education level

EL	**Period/Stage**											
	Localized 1985–1994				**Localized 1995–2004**				**Localized 2005–2014**			
	RR (95%CI)	**p**	**CSS, 10yr**	**OCS, 10yr**	**RR (95%CI)**	**p**	**CSS, 10yr**	**OCS, 10yr**	**RR (95%CI)**	**p**	**CSS, 10yr**	**OCS, 10yr**
BE	ref	**<0.001**	64%	54%	ref	**<0.001**	86%	66%	ref	0.293	90%	67%
US	0.81 (0.69–0.95)		69%	58%	0.84 (0.73–0.96)		88%	70%	0.94 (0.78–1.14)		90%	69%
HL	0.76 (0.66–0.88)		70%	64%	0.61 (0.53–0.70)		91%	74%	0.87 (0.72–1.04)		91%	78%
	Unknown 1985–1994				**Unknown 1995–2004**				**Unknown 2005–2014**			
BE	ref	**p**	47%	44%	ref	**p**	72%	54%	ref	**p**	NA	NA
US	1.01 (0.85–1.20)	0.132	46%	49%	0.82 (0.72–0.93)	**< 0.001**	76%	60%	0.74 (0.61–0.91)	**< 0.001**	NA	NA
HL	0.85 (0.73–1.00)		51%	49%	0.68 (0.60–0.77)		80%	62%	0.61 (0.49–0.75)		NA	NA
	Metastatic 1985–1994				**Metastatic 1995–2004**				**Metastatic 2005–2014**			
BE	ref	**p**	13%	51%	ref	**p**	33%	54%	ref	**p**	NA	NA
US	0.95 (0.94–1.06)	**0.009**	14%	58%	0.90 (0.82–0.99)	**<0.001**	35%	60%	0.82 (0.74–0.91)	**<0.001**	NA	NA
HL	0.85 (0.76–0.95)		17%	68%	0.78 (0.71–0.86)		41%	62%	0.76 (0.68–0.85)		NA	NA

EL = education level, BE = basic education, US= upper secondary education, HL= higher education, RR = relative risk, CSS = cancer-specific survival, OCS = other cause survival, ref = reference, CI = confidence interval, NA = not applicable*, and p = test for period and education interaction all/basic. *Not enough follow-up information

Table 14. Basic characteristics of the basic education population divided to occupation groups

Stage	Occupation	Period 1985–1994		Period 1995–2004		Period 2005–2014	
		N (%)					
		All ages	< 70 yr	All ages	< 70 yr	All ages	< 70 yr
Localized	Self-empl.	1,123 (38%)	401 (30%)	2,500 (28%)	867 (21%)	2,604 (23%)	884 (18%)
	Employees	385 (13%)	180 (13%)	1,314 (15%)	615 (15%)	1,646 (14%)	699 (15%)
	Manual worker	1,301 (44%)	661 (49%)	4,252 (47%)	1,884 (47%)	4,984 (44%)	1,945 (40%)
	Others	161 (5%)	108 (8%)	937 (10%)	669 (17%)	2,208 (19%)	1,288 (27%)
	All together	2,970 (100%)	1,350 (100%)	9,003 (100%)	4,035 (100%)	11,442 (100%)	4,816 (100%)
Unknown	Self-empl.	633 (40%)	174 (30%)	1,989 (31%)	477 (24%)	1,500 (24%)	316 (17%)
	Employees	192 (12%)	71 (13%)	894 (14%)	305 (15%)	907 (14%)	276 (15%)
	Manual worker	660 (42%)	286 (50%)	2,948 (46%)	908 (45%)	2,789 (44%)	746 (40%)
	Others	84 (6%)	41 (7%)	553 (9%)	326 (16%)	1,133(18%)	533 (28%)
	All together	1,569(100%)	572(100%)	6,384(100%)	2,016(100%)	6,329(100%)	1,871(100%)
Metastatic	Self-empl.	742 (39%)	270 (28%)	1,084 (29%)	321 (23%)	1,110 (25%)	255 (18%)
	Employees	224 (12%)	111 (12%)	469 (13%)	174 (13%)	508 (12%)	160 (12%)
	Manual worker	825 (43%)	476 (50%)	1,751 (48%)	625 (46%)	1,969 (45%)	576 (41%)
	Others	129 (6%)	97 (10%)	380 (10%)	248 (18%)	767 (18%)	401 (29%)
	All together	1,920 (100%)	954 (100%)	3,684 (100%)	1368 (100%)	4,354 (100%)	1,392 (100%)

Men whose occupations prior to retirement were unknown were excluded from the data. N = number, and Self-empl. = self-employed person.

Table 15. Risk ratio of death from PCa and CSS and OCS by period and occupation of the basic education population

Occupation	Period/Stage											
	Localized 1985–1994				**Localized 1995–2004**				**Localized 2005–2014**			
	RR (95% CI)	**p**	**CSS, 10 yr**	**OCS, 10 yr**	**RR (95% CI)**	**p**	**CSS, 10yr**	**OCS, 10 yr**	**RR (95% CI)**	**p**	**CSS, 10 yr**	**OCS, 10 yr**
Self-empl.	ref	0.851	65%	55%	ref	**0.002**	84%	67%	ref	0.956	NA	NA
Employees	0.97(0.83–1.14)		64%	62%	1.12(0.97–1.29)		88%	70%	0.96(0.76–1.22)		NA	NA
Manual workers	0.94(0.76–1.18)		63%	54%	0.75(0.62–0.92)		86%	63%	0.93(0.69–1.24)		NA	NA
Others	1.10(0.80–1.50)		61%	51%	1.03(0.82–1.29)		85%	62%	0.95(0.70–1.29)		NA	NA
	Unknown 1985–1994				**Unknown 1995–2004**				**Unknown 2005–2014**			
Self–empl.	ref	**p**	NA	NA	ref	**p**	71%	55%	ref	**p**	NA	NA
Employees	1.10(0.92–1.32)	0.676	NA	NA	1.13(1.00–1.28)	0.083	75%	56%	0.91(0.72–1.13)	0.075	NA	NA
Manual workers	1.02(0.78–1.32)		NA	NA	0.92(0.78–1.10)		74%	52%	0.84(0.64–1.12)		NA	NA
Others	1.16(0.83–1.63)		NA	NA	1.11(0.90–1.36)		71%	54%	1.28(0.98–1.68)		NA	NA
	Metastatic 1985–1994				**Metastatic 1995–2004**				**Metastatic 2005–2014**			
Self-empl.	ref	**p**	16%	52%	ref	**p**	34%	55%	ref	**p**	NA	NA
Employees	0.99(0.88–1.11)	0.304	8%	44%	0.96(0.87–1.06)	0.393	36%	56%	0.95(0.84–1.08)	0.06	NA	NA
Manual workers	1.08(0.92–1.28)		17%	56%	0.90(0.78–1.03)		32%	55%	0.88(0.74–1.05)		NA	NA
Others	1.19(0.96–1.47)		9%	24%	1.02(0.88–1.19)		32%	54%	1.15(0.99–1.33)		NA	NA

Men whose occupations prior to retirement were unknown were excluded from the data. RR = relative risk, CSS = cancer-specific survival, OCS = other cause survival, Self-empl. = self-employed persons, ref. = reference, CI = confidence interval, NA = not applicable*, and p = test for the period and education interaction for all/self-employed persons. *Not enough follow-up information

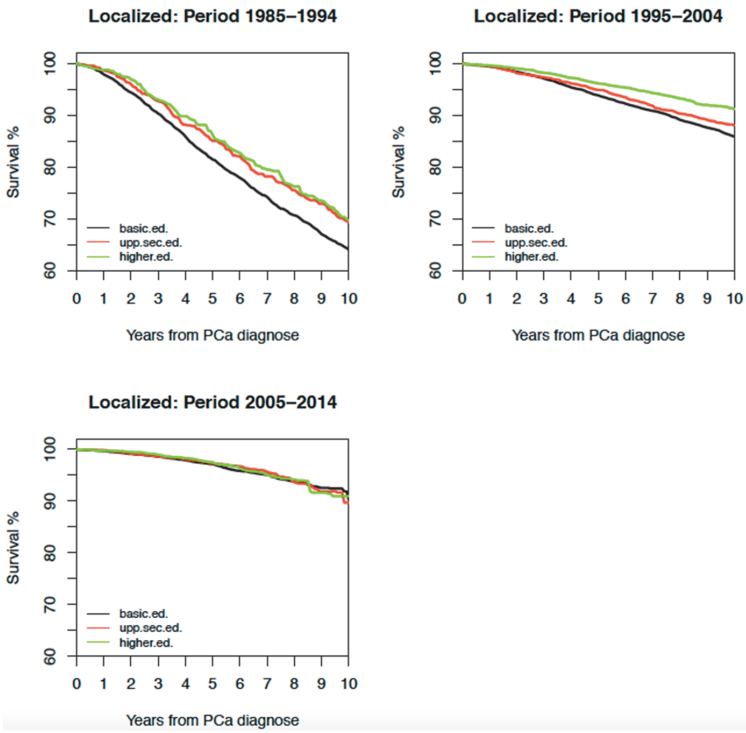

Figure 9. Cancer-specific survival by education level with localized prostate cancer

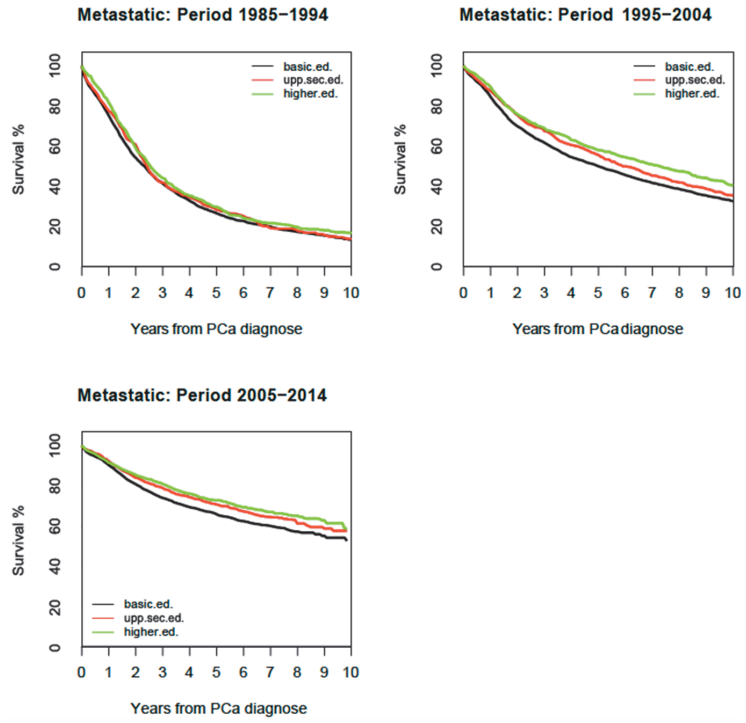

Figure 10. Cancer-specific survival by education level with metastatic prostate cancer

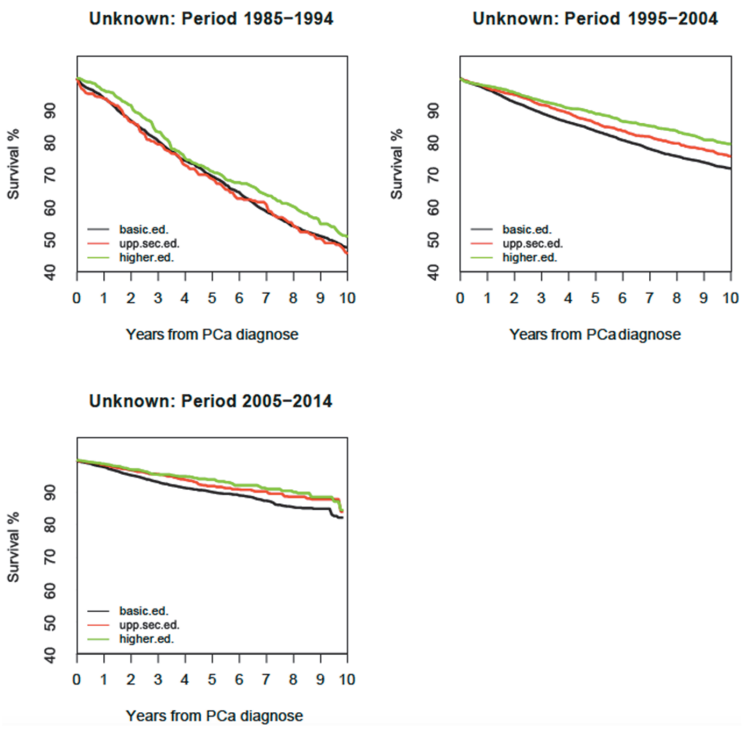

Figure 11. Cancer-specific survivals by education level with unknown prostate cancer stage group

6 DISCUSSION

Our studies on u-PSA showed that it is useful markers in defining the risk of disease progression after RP and in optimizing salvage treatments after RP. The u-PSA levels may increase up to 0.02–0.03 ng/ml after RP without the risk of further progression of PSA values. However, u-PSA progression is significant after these thresholds and helps to determine the right timing for salvage treatments. The longitudinal modeling of u-PSA values helped us to develop a practical computational example for the validated generalized linear models for predicting the BCR risk of a patient and an easy-to-use graphical user interface that is freely available (http://compbiomed.shinyapps.io/u-pa). Our easily accessible mathematical pipeline established a novel baseline for future validation studies of the importance of u-PSAs and further method development.

In another phase of the thesis, we evaluated the impact of PSA testing and screening on PCa survival on the population-based national level. Due to the influence of opportunistic and controlled PSA screenings, the number of especially localized PCa diagnoses has increased dramatically. Furthermore, the relative survival of men with localized PCa was clearly better compared to CSS in the post-PSA era. This and their decreased other-cause mortality indicate that men diagnosed with localized PCa are on average healthier than the Finnish male population. The prognosis of PCa, on average, in all disease stages has improved over 30 years of time. When the effect of PSA testing and screening was indirectly estimated between different SES groups, it was evident that male populations with a higher education level are more likely to test for the PSA; thus, their CSS was better than those with less education. The clear impact of higher education for improved CSS and OCS was also seen in the pre-PSA period. This result reflects the probable better health and literacy awareness of an educated population. Thus, the diseases of better educated men were diagnosed earlier and treated more actively in the pre-PSA period as well. When OCS at the population level was compared between different SES groups, the results showed that men with higher education levels were otherwise clearly healthier than men with lower levels of education.

6.1 Methodological considerations

The major limitation of the u-PSA studies is the relatively low number of patients and the low number of disease progression events, such as detected metastasis or deaths from PCa. Thus, we could not assess the possible impact of u-PSAs in the progression of PCa in terms of “real” disease outcomes. When considering the slow disease progression of PCa and the long natural course of the disease, slightly

elevated PSA—especially u-PSA—values after RP can often only cause the patient anxiety and excessive fear without a real thread of disease progression. Our findings and novel tools should be validated with a larger number of patients and with significantly longer follow-up times to discern the u-PSA thresholds that should be considered significant or nonsignificant. However, low u-PSA values after RP may help us to save patients from further PSA follow-up and relieve resources for more effective clinical work, from a health care service perspective (Matsumoto et al. 2017). Our u-PSA studies also suffered methodological problems due to the retrospective nature of the studies. If the follow-up protocol would have been standardized and the data prospectively collected, the interpretation of the findings could have been different. In a prospective study setting, different PCa risk groups and other disease characteristics could have been better compared with u-PSA results upon evaluating the results from the study. Furthermore, in terms of uDT and tDT calculations, more measurement points (u-PSA values) from each patient would have been needed; thus, higher specificity of the study findings could have been achieved. This estimation reflects the need for a longer follow-up time.

In our population-based studies, the major limitations were the lack of cancer-specific and patient-related data. We chose to use 10 year follow-up time periods to compare patient cohorts with similar follow-up time. Longer follow-up time for each period may have been more definitive due to slow natural progression of PCa. With more detailed data on cancer histology, laboratory parameters, cancer treatments, and comorbidities, our results would have been more definitive. Hence, these results on nearly 100,000 men with PCa would have revealed more specified information for clinical physicians to determine the right treatment and follow-up protocol for each patient. Furthermore, survival and SMR estimates for the PCa population are biased because of lead time issues in the post-PSA period. The outcomes from attempting to detect a cancer case years before it would have become clinically evident in survival estimates cannot be reliably compared to results from an era when PSA testing was not available. Our study on SES and PCa also lacked data on patient's comorbidities. Health-related inequality is related to the different prevalence levels of adult type 2 diabetes, metabolic syndrome, cardiovascular diseases, and other maladies between higher versus lower SES groups (Sacerdote et al. 2012). Thus, regarding these considerations, more specified data on comorbidity factors would have been needed to accurately evaluate the study population. Also, when the effect of PSA screening was estimated from the SES/education level-based data, the lack of information about PSA testing and screening rates of the study population may have introduced bias to the data.

In our study population, we do not know how many PSA tests these men had undergone before the cancer was detected. We also lacked SES information from the

control population. Thus, we were not capable of assessing the incidence of PCas between different SES groups.

This study still has several strengths. The u-PSA values were collected from a institute, and all the measurements were done with the same electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics GmbH) in the same laboratory unit. Another strength of the u-PSA studies was the extensive mathematical modeling of both the u-PSA and t-PSA measurements, which was offered as an easy-to-use web-based graphical user interface (GUI) platform. In our population-based study I, the study's strength is that it covers a national (close to 100%) cohort of all PCa cases, more than 90,000 patients, from a country with a high PCa survival rate. We demonstrated that the PSA-based detection of PCa has an impact on survival and the downgrade stage migration of PCa. In addition, we have completed 10-year follow-up information on all cases in both the pre- and post-PSA eras. The Finnish Cancer Registry has extensive cause-of-death information for all cancer patients obtained from Statistics Finland. Similar population-based coverage of follow-up information is not available in many of the other European countries, except for the Nordic regions. Although randomized controlled studies provide the highest level of evidence, analyses of data from population-based registries yield important information for the management of the effects of diagnosis and treatment practices at the population level. Also, in our population-based study on SES and PCa survival in Finland over 30 years of time, the data covers nearly 100% of patients affected. Furthermore, information about SES also contains 100% of the study population. The data also covers the specific cause of death information of all individuals. Therefore, the difference in CSS and OCS describes the real relation between SES groups in Finland.

6.2 Ultrasensitive PSAs in the follow-up after radical prostatectomy

Our studies suggest that the u-PSAA is a helpful tool in determining the risk of disease progression after RP. In the current guideline, the use of u-PSAAs remains controversial due to questions regarding the reliability and usefulness of u-PSAAs (Mottet et al. 2016). However, u-PSAAs could potentially detect BCR after RP significantly earlier than t-PSA assays (Shen et al. 2005). A recent study stated that in patients with undetectable u-PSA levels (< 0.01 ng/ml) five year after RP, the 10- and 15-year BCR-free survival rates were both 100%, and the PSA monitoring could be discontinued after 5 years for these individuals (Matsumoto et al. 2017). Another previous study from Malik et al. showed that the 7-year cumulative BCR-free survival rate for patients with u-PSAs ≤ 0.04 ng/ml was 0.957 (95% CI 0.920–0.978) 3 years after RP (Malik et al. 2011). These findings confirmed the

statements of Matsumoto et al., which took the higher threshold (0.04 vs. 0.01 ng/ml) into account. However, according to the literature, the specificity of the u-PSA is relatively poor, and to date, the evidence that earlier detection of recurrence translates into prolonged time to metastasis is lacking. Integrating u-PSAs with other clinicopathological factors can help determine the optimal adjuvant and salvage therapy (Tilki et al. 2015). Our findings support the current evidence suggesting that patients with low u-PSA values several years after RP seldom develop recurrence. Also, when utilizing sophisticated mathematical modeling over time, we identified no major discrepancies between the u-PSA and t-PSA assays. In our analyses, the ability to distinguish between the non-BCR and BCR patients was only marginally improved when 3 years of post-nadir follow-up was allowed instead of 1 year. Hence, the prognostic implications of u-PSAs might be assessed in a 1-year window after RP when longitudinal modeling and our graphical user interface are used. Even though some claim that u-PSAs offer no benefit and mainly cause unnecessary anxiety for patients (Taylor et al. 2006), they still improve the time to detection of PSA relapse by months to years (Tilki et al. 2015). This lead time to relapse would seem to improve the patient chance of durable progression-free survival, with salvage therapy given at a lower cancer burden and a wider window for cure (Stephenson et al. 2007). When reviewing the current literature in relation to our findings, it seems obvious that the benefit of u-PSA monitoring is the optimal timing of salvage treatments after RP.

6.3 Stage specific mortality and survival trends of prostate cancer patients in Finland before and after the introduction of PSAs

The number of new PCa diagnoses substantially increased in Finland after the introduction of PSA testing. Since the late 1990s, active use of PSA testing has doubled the incidence of PCa in developed countries (Welch and Albertsen 2009, Siegel et al. 2014), and in Finland, it seems to have leveled off after 2008 (Finnish Cancer Registry 2014). Our study on PCa survival and the SMRs of men with PCa showed a deep decline of SMRs over the study period. In our cohort, which covered nearly 100% of men who were diagnosed with PCa during a nearly 30-year period, the SMR of all PCa patients declined from 2.08 (95% CI 2.02–2.14) during 1985–1989 to 1.35 (95%CI 1.32–1.38) during 2000–2004. Moreover, the SMR for localized PCas decreased significantly over time ($p < 0.001$) from 1.50 (95% CI 1.44–1.57) during 1985–1989 to 0.98 (95%CI 0.95–1.01) during 2000–2004. Also, a decreasing trend in the SMR of patients with metastatic PCa was seen during the study period. Similar declining mortality rates of PCa have been seen since 1985 in many parts of the world (Center et al. 2012). The inclining trend of relative survival of PCa patients was seen especially in localized PCa, whereas the

difference between relative survival and CSS notably increased in the post-PSA period in men with localized PCa, reflecting smaller other-cause mortality of these individuals in recent years. In localized PCa, a favorable prognosis is likely to be due to the common use of PSA testing (Kilpelainen et al. 2013) and the active utilization of curative treatment. In addition to overdiagnosis and lead-time bias, opportunistic PSA testing has resulted in men with a low risk of death from other causes (e.g., from CVD) being overrepresented in localized PCa patients. Also, in general, volunteers for prevention or screening trials tend to be healthier or more health conscious than the overall population; this has been denoted the "healthy volunteer effect," which is well described in the literature (Pinsky et al. 2007). It is presumable that these men usually seek preventive services and attend screening programs. The test may also be more often available for men with higher SES (e.g., offered by occupational health services). This kind of selection can be seen from the increased difference between relative and CSS estimates and from the mortality ratios below 1. Therefore, the SMRs and relative survival do not describe the excess mortality caused by the localized PCa itself, and the trend in the SMR reflects the effects of the selection and earlier diagnosis due to PSA testing and advanced treatments.

In metastasized PCa, the estimates of relative survival and CSS were similar in both the pre- and post-PSA eras. In the post-PSA era, the 10-year relative survival was 34.7% and the CSS was 34.1%. In the pre-PSA period, the respective numbers were 16.9% and 14.1%. Hence, the increased mortality of men with metastatic PCa is mainly caused by cancer itself, and such an increasing difference during the post-PSA period between relative and CSS was not seen. The improving survival rate of advanced and metastatic PCa is mainly explained by more extensive diagnostic workups and cancer treatments. Awareness of the benefits of chemotherapy and novel hormonal agents in the treatment of mCRPC has, indeed, improved the survival of metastatic PCa. Furthermore, modern imaging and active monitoring of PCa patients with rising PSA values or with symptom complaints have also played a notable role in terms of the OS and CSS of PCa patients (Cornford et al. 2016).

6.4 The impact of socioeconomic status on stage-specific prostate cancer and overall survival before and after the introduction of the PSA test in Finland

In our population-based study on PCa patients in Finland, we found that CSS was lower in men with lower SES (defined as education level) compared to men with high SES. The same result was also found among men with metastatic disease.

Furthermore, in the post-PSA period (1995–2004), men with a higher education level had 39 percentage points lower PCSM than those with a basic education level, while in the pre-PSA period (1985–1994), the same difference was 24 percentage points for localized PCa. The lower PCSM among men with localized disease and high SES was evident in the diagnostic periods of 1985–1994 and 1995–2004 (both $p < 0.001$), but not during 2005–2014 ($p = 0.293$). The risk of death from PCa has also been lower among men with high SES in metastatic disease during the past 30 years. The risk for other-cause mortality was considerably lower for men with high SES during the whole study period in all disease stage groups (all $p < 0.005$).

In survival estimates of CSS and OCS, the better survival of men with a higher SES position was clearly seen. This trend was seen as well in localized PCa as in metastatic PCa. Also, in men with an unknown PCa stage, similar results were apparent. The same trend was also seen in OCS, where the impact of death from PCa was eliminated. However, the difference for favorable CSS in men with higher SES was more pronounced during 1995–2004 (after the advent of PSA testing) than in 1985–1994 for men with localized PCa. This also reflects the lead time bias that alters the survival rate for men who had more PSA testing. Nonetheless, we showed that even before PSA testing, patients at the upper secondary and higher education level carried better survival rates for localized disease than those at a basic education level. In the post-PSA period, it was evident that CSS of men with a higher education level increased substantially even for those in the upper secondary level with localized PCa and metastatic PCa. In metastatic PCa, the difference in survival estimates is likely prone to more intensive diagnostic, screening, and treatment procedures of these individuals. A threefold increase (from earliest cohort to latest) of metastatic PCa was found in men with a higher education compared to only a 1.5-fold increase for those at the basic education level. Thus, all oligometastatic/low metastatic tumor burden cases are discovered earlier in educated men than those in men with less education. Such a "stage migration" may thuse appear due to more advanced imaging modalities, which have been used in recent years. This is called "Will Rodgers" phenomenon, which is recognized as one of the most important biases limiting the use of historical controls groups in trials (Sormani 2009). In the unknown disease stage group, CSS of the population yielded pronounced survival of men in the higher education group in the post-PSA period: the RR for cancer death was 0.68 (95% CI 0.60–0.77) compared to the basic education group during 1995–2004 and 0.61 (95% CI 0.49–0.75) during 2005–2014. This reflects the unfortunate fact that a high proportion of men with PCa lacked information about their cancer stage, when most of these individuals were in a localized stage. Thus, the survival trends follow the trends in localized PCa, and furthermore, most of the diagnosed cancers are in localized stage groups in general. Between 2005 and 2014, 25,530, 12,760 and 8,026 new PCa diagnoses

were made in the localized, unknown, and metastatic stage groups, while the same numbers during 1985–1994 were 6,643, 3,764, and 4,170 in localized, unknown, and metastatic stage groups, respectively. The number of new localized PCa cases increased dramatically during the post-PSA period, especially among men with higher education levels. In the pre-PSA period, most of the men (76%) were at the basic education level in the localized PCa group, but during 2005–2014, no more than 46% of men were at the basic education level in the localized PCa group. For metastatic PCa, most of the men were at a basic education level during 1985–1994 (77%), 1995–2004 (67%), and 2005–2014 (57%). Most of men who were diagnosed with PCa in the pre-PSA period and in the early post-PSA period were born in the 1910s and 1920s, in an era when the opportunity to get higher education was limited. Therefore, we assessed the survival of these men with respect to different occupation groups. Our results showed no clear trend for favorable survival (CSS or OCS) of any occupation group. However, it should be noted that when SES is defined by education level, older time cohorts are not similar than more recent ones. This reflects to changes happened in our society during the last decades when substantial socioeconomic development has happened.

Our findings from the FCR cohort showed clear PCa survival discrepancies between different educational SES groups in Finland, and the significant differences were seen in all cancer stages. Several previous reports have shown similar results (Rapiti et al. 2009, Berglund et al. 2012, Hussain et al. 2008). An earlier Finnish report stated that 20–25% of the deaths from PCa between 1996 and 2005 could have been avoided if the impairing survival impact of limited education had been taken into account (Pokhrel et al. 2010). The increased mortality is largely attributable to delayed diagnoses, suboptimal diagnostic workups, and less-invasive treatments among these individuals (Rapiti et al. 2009). Similar results have also been established with other malignancies, such as colon and breast cancers (Carsin et al. 2008, Bouchardy, Verkooijen and Fioretta 2006). A large Swedish population-based study on high-risk PCA patients showed that men in blue-collar positions were less likely to be treated with RP than patients in white-collar positions (Berglund et al. 2012). An earlier English study showed that patients with lower SES were rarely treated with radical surgery or radiotherapy but more commonly with WW (Lyratzopoulos et al. 2010). Furthermore, these men with lower SES are more often treated with observation or hormonal therapy than those with higher SES (Klein and von dem Knesebeck 2015). The reason to offer less-intensive treatments for men with lower SES is probably due to comorbid conditions. Men with lower SES have a higher risk of dying from CVDs than those with higher SES (Woodward et al. 2015). Still, the associations among the potential mediating factors are unclear. A recent Danish cohort study of PCa patients showed that men with lower SES status are often overweight and obese at the baseline, and increased

cancer-specific and all-cause mortality can also be explained by lifestyle and comorbidity factors (Larsen et al. 2016).

When PSA testing is common, highly educated men are likely overrepresented in the screening population. The possible benefits of testing and screening would only be gained if PSA screening would be provided for all citizens in an organized manner. However, the current dilemma of overdiagnosis and overtreatment of PCa remains to be unsolved.

6.5 Implications and future prospects

The prognostic value of u-PSAs in the estimation of disease progression after RP has been questioned. However, no studies that report the survival benefit of u-PSA calculation after RP currently exist. Our novel tool and modeling of u-PSAs need external validation with more patients and a longer follow-up time. Owing to the slow progression of PCa, especially after radical treatment, a follow-up time of 15 or more years would be needed to show the possible difference in disease progression in terms of PFS or OS. However, it seems that if a u-PSA calculation were done with a method that is comparable between patients, it might be quite specific in showing the risk of disease progression even beyond BCR. Thus, a new multi-institutional validation study will hopefully be launched in the near future.

When we evaluate prognostic markers and more specified diagnostic procedures in our clinical work on a daily basis, it is very important to know who dies from PCa. Therefore, in another phase of the study, we concentrated on PCa epidemiology and survival before and after the introduction of PSA testing. This quite mundane information about PCa epidemiology is not well described for the Finnish population. Although randomized controlled studies provide the highest level of evidence, analyses of data from population-based registries yield important information for the management of the effects of diagnosis and treatment practices at the population level. Future prospects on the national level would be to collect more sophisticated information about cancer treatments, comorbidities, medications, and so on to evaluate the state of affairs on PCa survival and mortality in Finland over a long period of time. These prospects include information from the Social Insurance Institution of Finland Prescription Register and from the registries of the National Institute of Health and Welfare concerning hospitalization and treatments (the HILMO registry). With more specified data, it would be possible to evaluate the effect of ADT and other cancer treatments in terms of OS and CSS, as well as comorbid conditions and OCS.

7 CONCLUSIONS

1. Testing for u-PSAs helps to determine the risk of BCR after RP. The use of u-PSAA helps in evaluating the need for further follow-up after RP, and for patients who have low u-PSA values a few years after RP; the follow-up can probably be discontinued.

2. With novel longitudinal modeling of u-PSAs, the risk of BCR can be predicted even with small u-PSA progression.

3. It was evident that survival of PCa in all disease stages improved for several decades in Finland after the introduction of PSA testing. This and the increased difference between relative and cancer-specific survival reflects most likely opportunistic PSA-testing among health conscious male population. This highlights the importance for better diagnostics tools for localized prostate cancers.

4. Opportunistic PSA testing appears to be popular in men with a higher education background. Men with higher SES also likely receive radical treatments such as RP more often. The use of PSAs in the screening, detection, and monitoring of patients should be balanced with other risk factors and should be equally offered for individuals with different backgrounds (e.g., diverse SES groups).

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