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HEALTH-RELATED QUALITY OF LIFE AND SURVIVAL OUTCOMES IN PROSTATE CANCER

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Susanne Bergius

DOCTORAL DISSERTATION

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To my family

”Minä kun kanssas kuuta katson
sinun kanssas kuuta katson
kultainen kuu luo
sydämiin siltaa”

- espoolainen tuutulaulu

Abstract

The aim of health care is to maximize health, and in practice, health must be produced in the context of scarce resources. In order to make wise resource allocations, health economic analyses are needed, often in the context of Health Technology Assessment (HTA), which is then used for informed decision-making. In addition to effectiveness, informed decision-making should also be based on other values, such as equity and equality. Health economic analyses concentrate on assessing the economic value of interventions, whereas full HTA also considers other aspects of decision-making.

In recent years, the concept of value-based health care (VBHC) has emerged on the side of traditional health economic analyses. They both try to answer questions concerning the value of interventions in health care - i.e., the relationship of outcomes and investments needed. The objective in VBHC is also to find such actions that can improve the cost-effectiveness of health care dynamically over time.

Health-related quality of life (HRQoL) is a patient-reported outcome measure which, in combination with survival data, can produce quality-adjusted life years (QALYs) gained needed as the outcome measure in cost-utility analyses (CUA). This thesis generates real-world data for the use of health economic analyses and compares outcomes of conventional treatment strategies in PC. According to the systematic literature review in this study, preference-based HRQoL data in PC patients are still scarce.

Prostate cancer (PC) is the second most common cancer among men, and its incidence rates have been rising especially in Western countries due to increased use of prostate-specific antigen (PSA) testing. However, due to improved diagnosis and advanced treatments, mortality rates are not increasing at the same rate, but in some countries, such as in Finland, there has even been a modest decline. As PC has become more prevalent, there is an increased burden to patients and society, demanding more understanding of real-world effectiveness and cost-effectiveness of interventions.

We measured the HRQoL of PC patients in different stages of the disease (Local, Locally Advanced and Metastatic) and in patients undergoing different treatments with two HRQoL instruments, namely the generic 15D and disease-specific EORTC QLQ-C30. HRQoL data were obtained from 1050 and clinical background data from 1024 patients. The mean age of the patients at baseline was 66.5 years, and most of the patients were in an early stage of the disease as only 59 (6%) of the patients were metastatic at the time of the diagnosis. Even though the mean 15D score of Local and Locally advanced patients did not differ from that of the age-standardized male population, there was a statistically significant difference on the dimensions of depression and distress among all patient groups, which indicates that there are psychological side effects from the awareness of cancer diagnosis. Out of the five functioning scales in the EORTC QLQ-C30 instrument, patients in the Local and Locally advanced groups scored the lowest in emotional function, which can indicate anxiety, worrying, irritation, and/or depression due to the awareness of the diagnosis.

The four major treatment strategies during the first year after diagnosis were active surveillance (n=226), radiation (n=280), radical surgery (n=299) and hormonal treatment (n=62). The mean follow-up time in the survival analysis was 77.7 months, and at the end of the follow-up, 84.4% of patients were alive. Median overall survival was 53.8 months (95% CI 44.5 – 63.2 months) in the hormonal group, and median survival for the other groups was not reached. Prostate cancer was a rare cause of death, especially in the active surveillance and surgery groups. The hormonal treatment group had the lowest HRQoL and survival among the studied treatment groups, and consequently, also experienced the least number of QALYs during the two-year follow-up. Outcomes of the three other treatment groups were similar in terms of HRQoL and overall survival, and thus also regarding the number of QALYs experienced. Our study provided evidence that baseline HRQoL, measured by 15D score or certain 15D dimensions, has prognostic value in assessing overall as well as PC-specific survival.

As shown by the literature review in this study, the use of generic preference-based instruments suitable for calculating QALYs among PC patients is scarce. Therefore, a regression model (mapping model) was built to predict the generic 15D score from disease-specific EORTC QLQ-C30 data. The explanatory power of the EORTC QLQ-C30 mapping model to the 15D score was as high as 79%, which indicates that EORTC scales explained well the variance of the 15D scores.

Tiivistelmä

Terveydenhuollon tavoite on maksimoida terveyttä, joka käytännössä tapahtuu niukkojen resurssien vallitessa. Jotta resurssien kohdentaminen olisi viisasta ja informoitua, laajemman terveydenhuollon menetelmien arvioinnin (engl. Health Technology Assessment, HTA) yhteydessä tarvitaan myös taloudellista arviointia. Taloudellisessa arvioinnissa tarkastellaan intervention taloudellista arvoa, kun taas menetelmäarviointi (HTA) käsittää myös muita viisaaseen päätöksentekoon tarvittavia elementtejä kuten tasapuolisuuden ja oikeudenmukaisuuden.

Viime vuosina perinteisen taloudellisen arvioinnin rinnalle on syntynyt käsite arvoon perustuvasta terveydenhuollosta (value-based health care, VBHC). Molemmat pyrkivät vastaamaan kysymykseen terveydenhuollon interventioiden arvosta eli vaikuttavuuden ja tarvittavien investointien suhteesta. VBHC:n tavoite on myös löytää sellaisia toimia, jotka voivat parantaa terveydenhuollon kustannusvaikuttavuutta.

Kun intervention aikaansaama, potilaan itse raportoima muutos terveyteen liittyvässä elämänlaadussa (health-related quality of life, HRQoL) yhdistetään tietoon elossaoloajan muutoksesta, voidaan laskea muutos laatupainotetuissa elinvuosissa (quality-adjusted life year, QALY), jota tarvitaan vaikuttavuusmittarina kustannusutiliteettianalyysissä (cost-utility analysis, CUA). Tämän väitöskirjatutkimuksen puitteissa tuotettiin tietoa eturauhassyöpäpotilaiden terveyteen liittyvästä elämänlaadusta terveydenhuollon arjen olosuhteissa ja verrattiin yleisimpien eturauhassyövän hoitolinjojen vaikuttavuutta. Tutkimuksessa tehdyn järjestelmällisen kirjallisuuskatsauksen perusteella preferenssipohjaisten elämänlaatumittareiden käyttö eturauhassyöpäpotilailla on harvinaista.

Eturauhassyöpä on toisiksi yleisin syöpä miehillä ja sen ilmaantuvuus on kasvanut länsimaissa etenkin lisääntyneen prostataspesifisen antigeenin (PSA) testauksen myötä. Kehittyneen diagnosoinnin ja tehokkaiden hoitojen ansioista eturauhassyöpäkuolleisuus ei ole lisääntynyt samassa suhteessa ilmaantuvuuden kanssa ja joissain maissa, kuten Suomessa, kuolleisuudessa on ollut pientä laskua. Koska eturauhassyöpä on tullut yhä yleisemmäksi, se muodostaa kasvavan tautitaakan potilaille ja yhteiskunnalle, mikä vaatii parempaa ymmärrystä hoitojen vaikuttavuudesta ja kustannusvaikuttavuudesta terveydenhuollon arjessa.

Tässä väitöskirjatutkimuksessa mitattiin eturauhassyöpäpotilaiden terveyteen liittyvää elämänlaatua taudin eri vaiheissa (paikallinen, paikallisesti edennyt ja metastaattinen tauti) ja eri hoidoissa kahdella eri elämänlaatumittarilla, jotka olivat geneerinen 15D ja sairaus-spesifi EORTC QLQ-C30. Elämänlaatutieto saatiin 1050 potilaalta ja kliiniset taustatiedot 1024 potilaalta. Potilaiden keski-ikä tutkimukseen tullessa oli 66,5 vuotta ja suurin osa heistä oli taudin varhaisessa vaiheessa. Metastaattisessa taudin vaiheessa oli tutkimuksen alussa 59 potilasta (6 %). Paikallisessa ja paikallisesti edenneessä taudissa 15D:n tuottaman keskimääräinen elämänlaatulukema ei eronnut ikävakioidun miesväestön lukemasta, mutta masennuksessa ja ahdistuneisuudessa havaittiin kaikissa taudin tiloissa tilastollisesti merkitsevä ero ikävakioituun miesväestöön verrattuna, mikä viittaa syöpädiagnoosin psyykkisiin vaikutuksiin. EORTC QLQ-C30:n viidestä toiminnallisesta ulottuvuudesta potilaat raportoivat alhaisimmat pisteet tunne-ulottuvuudessa, mikä voi viitata syöpädiagnoosiin liittyvään huoleen, pelkoon, hermostuneisuuteen ja/tai masennukseen.

Neljä merkittävintä hoitolinjaa ensimmäisen vuoden aikana diagnoosista olivat aktiivinen seuranta (n=226), sädehoito (n=280), radikaalileikkaus (n=299) ja hormonaalinen hoito (n=62). Keskimääräinen seuranta-aika elinaika-analyysissä oli 77,7 kuukautta ja seuranta-ajan lopussa 84,4 % potilaista oli elossa. Elossaoloajan mediaani hormonaalista hoitoa saaneilla potilailla oli 53,8 kuukautta (95 %:n luottamusväli 44,5 – 63,2 kuukautta). Muissa hoitoryhmissä mediaania ei saavutettu seuranta-aikana. Eturauhassyöpä oli harvinainen kuolinsyy etenkin aktiivisen seurannan ja leikkaushoidon ryhmissä. Hormonaalisen hoitoryhmän potilailla oli alhaisin elämänlaatu ja elossaoloaika, ja näin ollen myös alhaisin määrä saavutettuja QALY:ja kahden vuoden aikana tutkimuksen alusta. Kolmen muun hoitoryhmien erot elämänlaadussa, kokonaiselossaoloajassa ja näin ollen myös saavutetuissa QALY:issa olivat vähäisiä. Tutkimus myös osoitti, että hoidon alussa joko 15D-lukemalla tai eräillä 15D-dimensioilla mitatuilla terveyteen liittyvällä elämänlaadulla on ennustearvoa arvioitaessa potilaiden hengissäpysymistä.

Kuten kirjallisuuskatsauksessa havaittiin, geneeristen, preferenssipohjaisten elämänlaatumittareiden käyttö eturauhassyöpäpotilailla on melko harvinaista. Tästä syystä tutkimuksessa tehtiin regressiomalli geneerisen 15D-lukeman ennustamiseksi sairaus-spesifillä EORTC QLQ-C30-datalla. Tämän “mapping”-mallin selitysaste oli 79 %, joka kertoo, että EORTC-instrumentin muuttujat selittivät hyvin 15D-lukemien vaihtelua.

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List of original publications

The dissertation is based on the following articles, which are referred to by their Roman numerals I, II and III.

I Torvinen S*, Bergius S*, Roine R, Lodenius L, Sintonen H, Taari K. Use of patient assessed health-related quality of life instruments in prostate cancer research: a systematic review of the literature 2002-15. *International Journal of Technology Assessment in Health Care*. 2016 Jan;32(3):97-106.

II Bergius S, Torvinen S, Muhonen T, Roine R, Sintonen H, Taari K. Health-related quality of life among prostate cancer patients: real-life situation at the beginning of treatment, *Scandinavian Journal of Urology*, 2017;51(1):13-19.

III Bergius S, Roine R, Taari K, Sintonen H. Health-Related Quality of Life and Survival in Prostate Cancer Patients in a Real-World Setting. *Urologia Internationalis*, 2020, DOI: 10.1159/000510319

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Abbreviations

ADT	Androgen deprivation therapy
AQoL	Assessment of quality of life
ANOVA	Analysis of variance
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMA	Cost-minimization analysis
CRPC	Castrate resistant prostate cancer
CUA	Cost-utility analysis
EBM	Evidence-based medicine
EBRT	External beam radiation therapy
ECHOUTCOME	European consortium in healthcare outcomes and cost-benefit research
ECOG	Eastern Cooperative Oncology Group
eHR	Electronic health record
EMA	European medicines agency
EORTC	European Organization for Research and Treatment of Cancer
EPIC	Expanded prostate cancer index composite
FACT-G	Functional assessment of cancer therapy - general
FACT-P PCS	Functional assessment of cancer therapy - prostate cancer subscale
FDA	Food and Drug Administration
GDP	Gross domestic product
HAS	Haute Autorite´ de Santé
HYKS	Helsingin seudun yliopistollinen keskussairaala (Helsinki University Hospital)
HRQoL	Health-related quality of life
HTA	Health technology assessment
HTM	Health technology management
HUI	Health utilities index
HUS	Helsingin ja Uudenmaan sairaanhoitopiiri (Helsinki and Uusimaa hospital district)
ICD	International classification of diseases
ICER	Incremental cost-effectiveness ratio
ICHOM	International Consortium for Health Outcomes Measurement
ICUR	Incremental cost-utility ratio
INAHTA	International Network of Agencies for Health Technology Assessment
IQWiG	Institute for quality and efficacy in healthcare
LHRH	Luteinizing-hormone-releasing hormone agonists
LRP	Laparoscopic radical prostatectomy
MCDA	Multi criteria decision analysis
MeSH	Medical subject heading
mCRPC	Metastatic castrate resistant prostate cancer
NHP	Nottingham health profile
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OFT	Office of Fair Trading

OLS	Ordinary least squares
OS	Overall survival
PC	Prostate cancer
PFS	Progression free survival
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
PSA	Prostate-specific antigen
PC-QoL	Prostate Cancer – Quality of Life
PORPUS	Patient Oriented Prostate Utility Scale
QALY	Quality-adjusted life year
QoL	Quality of life
QWB	Quality of well-being scale
RARP	Robotic-assisted radical prostatectomy
RCT	Randomized controlled trial
RP	Radical prostatectomy
RWD	Real-world data
RWE	Real-world evidence
SD	Standard deviation
SF-36	Short form 36
SF-6D	Short form six dimension
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SRE	Skeletal-related event
TNM	Tumor Nodus Metastasis classification of malignant tumors
TTO	Time trade-off
UCLA-PCI	Expanded University of California Los Angeles prostate cancer index
VAS	Visual analogue scale
VBHC	Value-based health care
VBM	Value-based medicine
VBP	Value-based pricing
WHO	World Health Organization
WTP	Willingness-to-pay
ZIN	Zorginstituut Nederland

Appendices

Appendix 1: 15D and EORTC-QLQ-C30 questionnaires
Appendix 2: Published articles

CONTENTS

1. Introduction

The ultimate goal of health care is to maximize health with given resources. The quantity of health can be expressed as quality-adjusted life years (QALY), which is a concept that takes into consideration both the length and the health-related quality of life (HRQoL). As resources given to healthcare are limited, treatment decisions must be made in the context of scarce resources. This is the context in which the discipline of health economics operates.

Health economics tries to answer questions of equal, fair, and efficient allocation of resources in health care. The development of medicinal and pharmaceutical technology provides new, sometimes expensive, treatment options at the same time as the aging of the population is setting increasing pressure on the management of health care budgets. Thus, we need to make resource allocation decisions that are based on objective scientific evidence regarding the effectiveness and costs of various treatment alternatives. Cost-effectiveness analyses (CEA) are one element of informed decision-making. However, CEAs do not provide unambiguous answers for decision-making, as ethical and moral questions must also be considered.

Health-related quality of life (HRQoL) tries to capture patients' physical, mental, and social domains of health, and it has importance both clinically as well as in health economics. In health economics, it is essential to be able to compare generic HRQoL between diseases and therapy areas for the purposes of cost-utility analyses evaluating the value of different health care interventions.

This study is done in the setting of real-life clinical practice, which sets specific conditions for the study. Measuring outcomes in real-life circumstances will be enhanced in the future by digitalization and, subsequently, improved data availability. Real-world data (RWD) will help to understand the impact of healthcare interventions in clinical practice and it is assumed that increased usage of RWD will also impact the decision making of the health care authorities (Eichler 2018, FDA 2019).

Effectiveness of healthcare can be measured in various ways by measuring both patients' subjective outcomes such as HRQoL as well as objective clinical parameters. The usability and validity of different outcome measures during different stages of a patients' journey must be better understood to define their place in the overall assessment of the effectiveness of health care.

Generic HRQoL instruments may not be the most sensitive outcome measures in a given disease, but the importance of the utilization of these instruments arises from the need of a single and uniform outcome measure to appraise economic and clinical value of health care interventions across therapy areas. As QALY is chosen in some countries to be the uniform outcome measure used in cost-effectiveness analyses in Health Technology Assessments (HTA) of healthcare interventions and thus in prioritizing decisions (NICE 2013, Lääkkeiden hintalautakunta 2019), this creates also the framework for HRQoL measurement of prostate cancer (PC) patients in this study. As health economic evaluations based on QALY have health policy implications through prioritization decisions, the usability of QALYs in the context of economic evaluation and HTA is the focus of the background chapter of this study. In the background chapter I try to assess the place of QALYs in the overall value assessment framework of health care interventions. Considerations of the literature review about value assessment of interventions are not specifically linked to PC but are valid across disease areas.

One of the aims of this study was to collect HRQoL data and thus to understand the validity of a generic HRQoL instrument, the 15D, among prostate cancer (PC) patients in supporting the decision-making of treatment choices in PC. Findings of the empirical part of this study are specific for PC and thus not transferrable to other disease areas. PC as an area of interest arises from the fact that PC is becoming an increasingly prevalent disease due to aging population and improved survival of PC patients in Finland. Therefore, PC poses a significant burden to public health in Finland and involves many lives making clinical and economic implications of treatment choices significant for the health care, the patients and thus for the society.

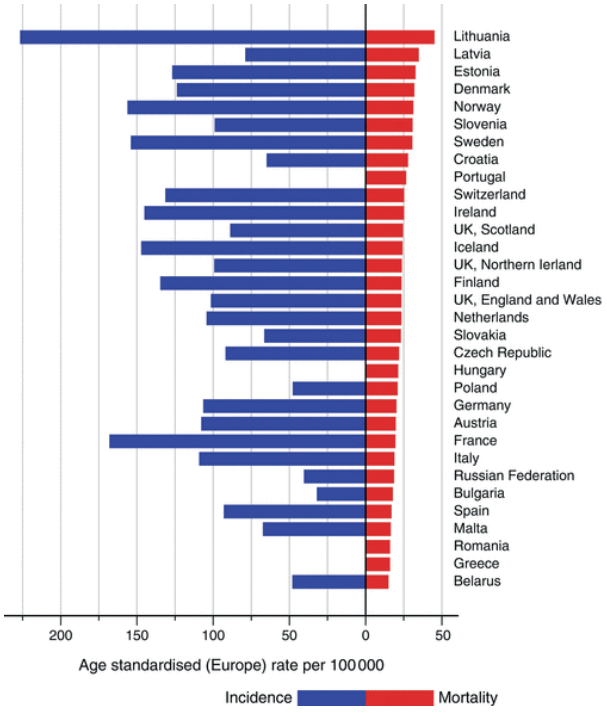
2. *Background and review of the literature*

2.1. Prostate cancer

Prostate cancer (PC) is a carcinoma that develops in the prostate, which is a walnut-sized gland in the male reproductive system. The prostate gland is located in the pelvis, between penis and rectum, and is responsible for producing seminal fluid to mix with sperm from the testis, and thus to help sperm to travel and survive.

PC is the second most common cancer among men with 1.3 million new cases of prostate cancer and 359,000 associated deaths worldwide in 2018 (Bray et al. 2018). PC incidence rates are highest in industrialized western countries such as the Nordic countries, Western Europe and Northem America, but mortality rates do not follow those of incidence in these countries (Bray et al. 2018). The introduction of prostate-specific antigen (PSA) testing for the detection of early-stage prostate cancers has been associated with a rapid increase in incidence rates, especially in higher-income western countries (Brawley 2012, Bray and Kiemeney 2017). There is variance in mortality rates at the global level (Bray et al. 2018), but in Europe and other Western countries, there has been a moderate decline in mortality rates (Bray and Kiemeney 2017). Figure 1 illustrates the incidence and mortality of PC in Europe.

Figure 1: PC incidence vs mortality in Europe based on age-standardized rates



Source: Bray and Kiemeney 2017

Relatively little is known about PC etiology, but age is the most important risk factor, and most of the cases are diagnosed in men over 70 years of age. Male hormones, ethnic and genetic background, and certain environmental factors are known risk factors. There is evidence that the importance of environmental factors is greater compared to inherited risk (Zaridze et al. 1984, Lichtenstein et al. 2000). Environmental risk factors include a diet containing high amounts of fat or meat and smoking (Hori et al. 2011, Zu and Giovannucci 2009). On the other hand, physical activity is known to reduce the risk of PC (Liu et al. 2011).

Early-stage PC usually does not cause symptoms, or they can be similar to those of benign prostatic hyperplasia. Early symptoms are mostly related to urinary dysfunction. Advanced prostate cancer can cause symptoms in sexual function, and metastatic disease that has spread to other parts of the body can cause additional symptoms such as bone pain.

2.1.1. Screening and diagnosis

PC mortality has decreased in the past decade, which is mainly attributed to the widespread use of PSA screening. While 1 in 7 men will be diagnosed with the disease during their lifetime, only one man in 30 with prostate cancer will die of the disease (Siegel et al. 2017). Still, PC remains the second leading cause of male cancer deaths. The dilemma in managing PC is the balance between the early detection of a potentially lethal disease that may benefit from treatment and the over-treating of low-risk (screening-detected) cancers that causes complications from the unnecessary treatment (Eastham 2017). This dilemma continues to be a controversy regarding prostate cancer screening and is one of the most debated topics in the urological literature (Loeb 2014).

Most of the PC cases are found through PSA testing. If PC is suspected, a tissue biopsy is needed for diagnosis. The Gleason grading is done using samples from the biopsy. Gleason grading is used for evaluating the prognosis of PC, and together with other parameters, it is used in PC disease staging, which helps to predict prognosis and guide therapy choices. The Gleason score is based on the microscopic appearance of PC cells. It ranges from 2 to 10, and PCs with a higher Gleason score are more aggressive and have a worse prognosis. The total Gleason score is a sum of two numbers. The first half of the score is based on the dominant cell morphology (scored 1—5), and the second half is based on the non-dominant cell pattern with the highest grade (scored 1—5). These two numbers are then combined to produce a total score of the PC (e.g. 3+3=6 for mild PC; 5+5=10 for very aggressive PC).

The identification and characterization of the disease have become increasingly precise in recent years. These advances are mainly due to the improved risk stratification, advances in magnetic resonance and functional imaging, as well as due to the emergence of several new biomarkers that can help to identify potential false-negative cases (Litwin & Tan 2017).

2.1.2. Treatments

There are multiple management options available for the treatment of PC and each treatment has its particular side effects. Most of the PC cases are detected at an early stage, and the treatment choice in localized PC is based on risk category (stage classification, histopathologic classification, and PSA), life expectancy of the patient (other morbidities, age, overall condition of the patient), expectations of the patient (adverse reactions from treatments, mental state, personality) and local

conditions (distances to treatments and treatment possibilities) (Prostate Cancer: Current Care Guidelines 2014). The treatment choice is made in discussion with the patient and possibly with his relatives so that the estimated life expectancy is put in proportion together with possible adverse reactions from treatments and risk of shorter life expectancy due to PC.

Active surveillance refers to a serial monitoring program for disease progression with the intent to take further action when needed. It appears to be a safe and more popular approach for men with less aggressive prostate cancer, particularly those with a PSA level of less than 10 ng/ml and tumors with Gleason score 3 + 3 (Litwin & Tan 2017). In active surveillance, the aim is to avoid unnecessary treatment in men with localized PC who do not require immediate treatment, but at the same time to monitor the patient and aim at the correct timing for curative treatment if needed (Bruinsma et al. 2017). Patients are under close surveillance through a structured surveillance program with regular follow-ups. The need for curative treatment is prompted by predefined thresholds that are indicative of potentially life-threatening disease, which is still potentially curable.

Watchful waiting and active surveillance are sometimes confused with being the same thing, which they are not. Watchful waiting refers to conservative management of patients that are considered unsuitable for curative treatment right from the beginning. Patients are "watched" for the development of either local or systemic progression and when progression is detected patients are treated with palliative intention according to their symptoms in order to maintain quality of life (Mottet et al. 2019)

Radical prostatectomy (RP) is a surgery that targets eradication of cancer, while whenever possible, preserving continence and potency. Radical prostatectomy can be performed in an open, laparoscopic, or robot-assisted approach. There are a number of studies comparing different approaches for radical prostatectomy (Coughlin et al. 2018, Allan & Ilic 2016; Yaxley et al. 2016). However, a Cochrane review comparing robotic-assisted radical prostatectomy (RARP) or laparoscopic radical prostatectomy (LRP) to open radical prostatectomy found no differences in oncological outcomes, urinary function or sexual function outcomes between the treatments. However, RARP and LRP both resulted in statistically significantly shorter hospital stays and reduced need for blood transfusions over open RP (Ilic et al. 2017). No surgical approach, however, has so far been recommended over another by the European Association of Urology (Mottet et al. 2019).

Incontinence and sexual dysfunction are the main adverse effects of RP and can have a significant impact on HRQoL (O'Connor & Fitzpatrick 2006).

Major categories of radiotherapy (RT) in PC are external beam radiotherapy (EBRT) and brachytherapy (BT), which is an internal radiation. In EBRT, which includes multiple techniques of radiation, beams of radiation are focused on the prostate gland from outside of the body. Brachytherapy uses small radioactive pellets, or "seeds," which are placed directly into the prostate. Brachytherapy alone is generally used only in men with early-stage PC. RT can result in early and late toxic effects. Additional side effects from radiotherapy can include bowel, urinary and erectile dysfunction. Modern radiation techniques have shown significant promise in delivering escalated doses to the prostate without seriously affecting the side-effect profile (O'Connor & Fitzpatrick 2006).

Hormonal therapy, also called androgen deprivation therapy (ADT), is a treatment that stops testosterone from being produced or reaching prostate cancer cells. As most PC cells need testosterone to grow, hormone therapy causes PC cells to die or grow more slowly. Testosterone-lowering therapy, i.e., castration, can be done by surgical or chemical castration. Long-acting luteinizing-hormone-releasing hormone agonists (LHRH) are currently the main form of ADT. Other traditional chemical ADTs are steroidal (such as. cyproterone acetate, megestrol acetate, and medroxyprogesterone acetate) or non-steroidal (such as nilutamide, flutamide, and bicalutamide) drugs. A problem with castration is that castration resistance (CRPC) will develop over time. This has led to the development of newer compounds for CRPC such as abiraterone acetate, enzalutamide, and apalutamide. Hormonal therapy is associated with a multitude of side effects that can impact HRQoL. Side effects from hormonal therapy can include osteoporosis, hot flushes, fatigue, loss of energy, emotional distress, sexual dysfunction and metabolic syndrome (O'Connor & Fitzpatrick 2006, Iversen et al. 2000, Patil & Bernard 2018). In addition, hormonal therapy has been associated with neurocognitive deficits, thromboembolic disease, and cardiovascular disease, although the data regarding the associations are mixed (Patil & Bernard 2018).

The choice of therapy ultimately depends on its effectiveness. However, if there are no clear advantages of one therapy over another, the side-effect profiles and their relative importance to the patient remains in a crucial role (O'Connor & Fitzpatrick 2006). Findings from direct comparisons

in randomized clinical trials among patients with localized PC suggest that EBRT, BT and RP are all effective treatments for localized prostate cancer and that post-operative EBRT is also effective but might be associated with additional toxicity (Wolff et al 2015). Studies have shown that treatment for localized prostate cancer involving either EBRT, BT or RP can result in long-term erectile dysfunction (ED) (Alemozaffar et al. 2011, Ferrer et al. 2008). Also urinary and bowel dysfunction are common side effects of treatments in localized PC (Donovan et al. 2016, Barocas et al. 2017). In a study of men with localized PC, RP was associated with clinically significant declines in sexual function compared to EBRT and AS, especially in men with excellent function at baseline. Urinary incontinence function also declined significantly after surgery compared to EBRT and AS, with 14% of RP patients reporting moderate or big problems with urinary leakage at 3 years, compared to 5% with EBRT and 6% with AS (Barocas et al. 2017).

Chemotherapy has a relatively new role in PC, and it was only established in 2004 after demonstrating a survival benefit with docetaxel in metastatic castrate-resistant prostate cancer (mCRPC) (Boulos & Mazhar 2017). Docetaxel has been the most used chemotherapy with cabazitaxel as second-line therapy (Nader et al. 2018). In addition, there are new evolving biological, molecular-targeted therapies and immunotherapies. Also, new vaccines, hormonal therapeutics, and bone-targeting agents have demonstrated efficacy in men with metastatic prostate cancer resistant to traditional hormonal therapy (Litwin & Tan 2017).

2.1.3. PC in Finland

In 2017 in Finland, 5446 new PC patients were diagnosed and there were 912 PC deaths (Finnish Cancer Registry 2017). The relative 1-year survival from diagnosis was 98 % and the 5-year relative survival 93 % (Prostate Cancer: Current Care Guidelines 2014). The incidence of PC is increasing due to early diagnosis and aging of the population, but luckily, mortality rates are not following incidence rates due to good surveillance of early disease and advanced treatment options.

2.2. Value in healthcare

Value plays a vital role in health care systems. In the concept of value, both outcomes and costs are essential, but the definition of value is not precise and can be differently interpreted depending on the perspective. Patients, physicians, policy- and decision-makers can all have a different definition of value. However, as we are facing increasing budget pressure from the aging population, it has

become pronounced in the past decades that clinical value is not enough and things also have to be evaluated in terms of economic value. On top of traditional Evidence-Based Medicine (EBM) (Guyatt et al. 1992), the concept of value-based-medicine (VBM) (Campolina 2018, Bae 2015) or value-based healthcare (VBHC) (Tsevat & Moriates 2018, Porter 2010) has emerged. Researchers are proposing that in the concept of VBM, also patient empowerment and patient-centricity are key aspects (Marzorati & Pravettoni 2017). Measurement of HRQoL and quality-adjusted life years (QALYs) is a key concept in economic evaluations, but also other concepts to capture value in healthcare exist. In the following chapters, I try to place the role of HRQoL into the perspective of overall value assessment in healthcare.

2.2.1. Outcome measures in PC

As PC is a heterogeneous disease, treatment options, and thus relevant outcome measures, vary depending on the disease stage. Some PC cases behave very aggressively, leading to metastases and eventually PC death, but most PCs, especially those detected early through PSA screening, have an indolent growth pattern. These PCs might never give rise to symptoms during a lifetime, even if left untreated. Radical treatment with surgery or radiotherapy of such cancers would thus result in undesirable side effects and deterioration of quality of life (Litwin & Tan 2017). The success of care in such cases is the combination of the absence of disease progression and good HRQoL. For localized PC, evolving patterns of care, including the increased use of active surveillance and the development of novel therapeutic options, are expected to have positive effects on HRQoL. Consequently, relevant outcome measures for follow-up require the use of patient-reported outcome measures (PROMs or PROs) such as HRQoL. Researchers point out that also in the assessment of long-term impacts of the disease, the use of PROs is required (Connell et al. 2019). It has been recommended already more than 20 years ago that to understand all aspects of outcomes in PC, both generic HRQoL and disease-specific measures must be used (Litwin et al. 1995).

In advanced PC, disease-progression is usually monitored more closely than in localized disease. In trials of advanced PC, the most common primary outcomes are overall survival (OS) and progression-free survival (PFS). A review assessing clinical trial endpoints in advanced PC did not find any trials using a QoL or pain outcome as a primary or co-primary endpoint (Fabricius et al. 2015). Another review found that in trials of metastatic castration-resistant PC patients, PROs were either not being measured routinely, or if used, were often not reported adequately (Fallowfield et

al. 2016). It has been emphasized that more focus should be placed on assessing PROs also in later stages of the disease (Morgans & Stockler 2019).

The International Consortium for Health Outcomes Measurement (ICHOM) has published guidelines about which patient-derived outcome measures would be useful to collect in different stages of PC. For men with early PC, ICHOM recommends that the disease-specific EPIC-26 and Utilization of Sexual Medications/Devices are collected as PROs. Other outcome measures to be collected are survival and disease progression parameters such as biochemical recurrence (ICHOM 2017). Moreover, for patients with advanced PC, Eastern Cooperative Oncology Group (ECOG) or WHO performance status, pain medication usage, EORTC QLQ-C30 questionnaire (for pain, fatigue, physical and emotional functioning) and additional parameters for disease progression such as symptoms from skeletal-related-event (SRE) are advised to be collected (ICHOM 2017).

2.2.2. Health-related Quality of Life

HRQoL is one type of PROMs. It is a broad concept reflecting a person's functioning in life and how a person perceives his/her health. The World Health Organization (WHO) defines health as a state of physical, mental, and social well-being, and HRQoL is functioning and well-being in relation to health. The history of measuring health status can be traced to the early 1970s, and measuring was motivated by a desire to measure outputs and performance of health care systems (Fanshel & Bush 1970).

There are both generic instruments that provide a summary of HRQoL, and disease-specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Disease-specific instruments are designed for assessing health in particular conditions, and they are not suited for comparison across interventions or populations. Therefore, to compare health between various diseases, interventions, or populations, generic HRQoL instruments should be used. Generic instruments can further be categorized into those providing health profiles and preference-based measures that generate health utilities, usually values between 0 and 1 (Guyatt et al. 1993), which allows comparison of cost-utility in health economic evaluations.

2.2.2.1. Prostate-specific HRQoL instruments

Common disease-specific PROs specifically used in PC are listed in table 1. The FACT-P PCS and EORTC QLQ-PR25 are PC-specific modules of the cancer-related QoL instruments FACT-G and EORTC QLQ-C30, respectively. The EORTC QLQ-PR25, FACT-P, and PORPUS are designed for all tumor stages, whereas EPIC, PC-QoL, and UCLA-PCI are specifically designed for patients at an early stage of the disease. Instruments are different with respect to health domains they include, and EORTC-QLQ-PR25 and EPIC are the only instruments that take into account the whole spectrum of symptoms in the urinary, bowel, sexual and hormonal domains (Schmidt et al. 2014).

Table 1: Prostate-specific HRQoL instruments

Disease-specific instrument	**Abbreviation**	**Tumor stage***	**Source**
Expanded Prostate Cancer Index Composite-26	EPIC	early stage	Wei et al. 2000
Expanded University of California-Los Angeles Prostate Cancer Index	UCLA-PCI	early stage	Litwin et al. 1998
Functional Assessment of Cancer Therapy - Prostate Cancer Subscale	FACT-P PCS	all	Cella et al. 1993
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire prostate specific	EORTC QLQ-PR25	all	van Andel et al. 2008
Prostate Cancer – Quality of Life	PC-QoL	early stage	Giesler et al. 2000
Patient Oriented Prostate Utility Scale	PORPUS	all	Krahn et al. 2000

*recommended tumor stage

Many of the prostate cancer-specific PROs claim that the instruments measure HRQoL or overall QoL, but their dimensions focus on urinary, sexual and bowel symptoms, and functioning. Their main focus is thus on the physical impact of the disease, and less attention is paid to the mental or social dimensions. A review assessing the usefulness of PROs among PC patients undergoing radical surgery concluded that there are gaps in their content and inadequate evidence of reliability, validity, and responsiveness, as well as their suitability for use in clinical practice with individual patients (Protopapa et al. 2017). Nevertheless, researchers recommend that HRQoL should be used more widely both in clinical trials as well as to inform patients and regulatory agencies on HRQoL aspects of therapies (Morgans & Stockler 2019).

Enhanced tumor detection with PSA testing has moved PC diagnoses to younger patients at earlier stages, and men are living longer with the knowledge of the disease and possible side effects of treatments. Disease-specific instruments have an important role in the evaluation of benefits and harms to PC patients. The responsiveness, i.e., ability to detect the change when it has occurred, may be better in some disease-specific instruments than generic HRQoL instruments, and the PORPUS questionnaire was found to be more sensitive than certain generic instruments (Krahn et al. 2007). The most obvious explanation for this is that the health domains of greatest importance in HRQoL following prostate cancer diagnosis and early treatments are often sexual, urinary, and bowel function. None of the generic instruments in the study by Krahn et al. (2007) included any items related to sexual function.

2.2.2.2. Generic HRQoL instruments

An advantage of generic HRQoL instruments is that they are applicable across a wide range of populations and thus allow comparison of HRQoL between different diseases and therapy areas. Generic health profile instruments include the widely used SF-36 (Stewart et al. 1992, McEwen & McKenna 1996) and the Nottingham Health Profile (NHP). Health profile instruments provide multiple outcome scores that can be useful to clinicians and/or researchers when attempting to measure differential effects of conditions or treatments on various HRQoL domains. However, they do not produce a single index score needed for cost-utility analyses. Consequently, the SF-36 has been revised into a six-dimensional health state classification called the SF-6D, which is a preference-based measure providing a single index score for economic evaluations (Brazier et al. 2002).

Similarly, also other preference-based HRQoL measures provide a single number, usually between the continuum from perfect health (1) to death (0), although other scales also exist. The health index score represents the respondent's subjective health status and incorporates a preference value (utility) for that overall health state. Utilities can be elicited in two different ways: either by direct or indirect valuation methods (Brazier et al. 1999).

Valuation methods include such approaches as the Standard Gamble (SG) (Torrence 1976), the Time-Trade-Off (TTO) (Dolan et al. 1996), the Rating Scale (RS) (Rosser and Kind 1978), and the Visual Analogue Scale (VAS) (Gudex et al. 1996). In the TTO method, respondents' preferences are

examined by asking what they value equally - living in a given health state for a certain period of time, or a shorter time in full health. In the SG method, respondents are choosing between a certain outcome in a given health state or a gamble with a probability (p) for the best possible outcome and a probability (1-p) for the worst possible outcome, usually dying. In the VAS method, respondents are asked to rate their health state on a continuous rating scale e.g., from 0 (worst possible health, dead) to 100 (perfect health). An advantage of the VAS method is its simplicity (Brazier et al. 1999).

In the direct valuation people either value their own health or the health states to be valued are described in a written form in their entirety to those, from whom the valuations are elicited (usually members of the general public), and they must imagine themselves in these hypothetical states even if different valuation methods are used. In the indirect approach, a small set of health states is valued directly and using these data, values for a wider set of health states are predicted by regression techniques. Or health states are split into parts and these parts are then valued separately and finally aggregated to values of different health states. Then, different health states defined by generic HRQoL questionnaires are weighted with these values or preferences to represent the values of the community regarding the appreciation of different health states (Brazier et al. 1999). The most commonly used multi-attribute utility instruments are introduced in table 2. These instruments provide a framework for respondents to describe their health states, to which preference values are then applied from population-based preference functions to calculate a single index utility score.

Table 2: Generic multi-attribute, single index HRQoL instruments

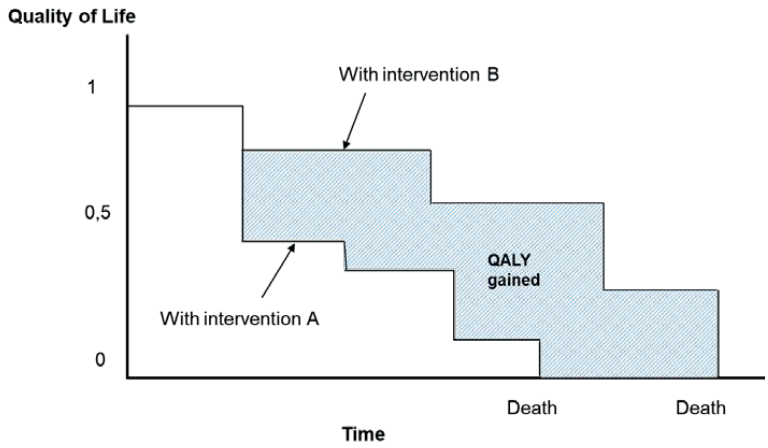
Generic instrument	**Abbreviation**	**Source**
EuroQol	EQ-5D	Brooks 1996
Health Utilities Index, Mark II/Mark III	HUI	Torrance et al. 1982
Short Form 6D	SF-6D	Brazier et al. 2002
Assessment of Quality-of-Life	AQoL	Hawthorne and Richardson 2001
15D	15D	Sintonen 1981

2.2.2.3. Quality-adjusted life years

A commonly used application of utility is quality-adjusted life years (QALY), which combines both the quality and length of life. The idea of calculating QALYs is straightforward - the amount of time

spent in a given health state is weighted by the utility score given to that health state. Thus, one year of perfect health (utility score of 1) generates one QALY, and two years in a health state valued with 0.5 is also worth one QALY. As utilities, the number of QALY gained provides a common currency to assess the extent of benefit gained by different healthcare interventions in terms of HRQoL and survival and also allows comparisons between interventions. When the number of QALYs gained is combined with the costs associated with interventions, they provide an assessment of the relative value of the intervention, i.e., the worth of the intervention from an economic perspective. The number of QALYs gained combined with costs incurred generates a comparable cost-utility ratio. Figure 2 illustrates a situation in which intervention B provides a better utility compared to intervention A through the time. The difference in QALYs can be calculated as the difference in the areas under the curves for interventions A and B (Drummond et al. 2005).

Figure 2. QALYs gained between intervention A and B



The concept of QALYs is not without critique. The QALY approach has been criticized on technical and ethical grounds (Prieto & Sacristán 2003, Sanders et al. 2016). One of the technical issues has to do with the choice of utility instruments, which are known to provide different results and thus impact the cost per QALY comparison (Whitehurst et al. 2014). There is no consensus of a gold standard regarding the most appropriate generic preference-based measure of utility. Other areas of controversy include the limitation of the QALY approach in terms of the health benefits it can capture, its blindness towards equity concerns, and the underlying theoretical assumptions. A growing debate is related to whether a QALY is the same regardless of to whom it accrues and also

to the issue as to who should value health states (Whitehead & Ali 2010). The European Commission project "European Consortium in Healthcare Outcomes and Cost-Benefit Research (ECHOUTCOME)" was studying how 27 European health system organizations use health outcomes in the frame of Health Technology Assessments (HTA) and the robustness of the QALY as an indicator of health. The recommendation of the project was that QALY assessment for health decision-making should be abandoned due to limitations and controversies of the QALY approach and cost-effectiveness analyses should rather be expressed as costs per relevant clinical outcome (Beresniak et al. 2015). However, QALY assessments are still central in decision-making in Europe, and no other approach has so far proved to be more robust. Germany adopted an "efficiency frontier" approach to compare the efficiency of new technologies to existing ones within disease classes using disease-specific metrics, rather than cost per QALYs approach for cross-disease comparisons (Caro et al. 2010). This approach could result in inequities, and political tension as different cost-effectiveness thresholds might be used for different therapeutic areas. On the other hand, the same issue can still exist in the cost per QALY approach as the pure cost/QALY ratio is usually not, and also should not be, the only criterion for decision-making.

The use of QALYs in cost-utility analyses has been the approach in HTAs in Europe but not traditionally in the United States (Neumann & Greenberg 2009). The need to deliver health care efficiently, and the importance of using analytical techniques to understand the clinical and economic consequence of interventions, has increased and also in the US there is a relatively recent recommendation to use the cost/QALY approach in HTAs with the understanding that it cannot be the mere basis for decision-making (Carias et al. 2018, Sanders et al. 2016).

2.2.3. Health economic evaluation

Health economic evaluations are needed to understand the relationship between health outcomes and investment needed, i.e., what is the worth of a health care intervention. Economic evaluation requires systematic identification, measurement, and valuation of inputs and outcomes of comparative technologies at issue (Drummond et al. 2005). Economic evaluations are most commonly employed in the context of health technology assessment (HTA) when new medicines and other technologies are introduced to healthcare systems. In Finland, there are guidelines on how to perform health economic evaluation for medicines (Lääkkeiden hintalautakunta 2019), but similar guidelines for other technologies do not exist. In the UK, there are guidelines to do

appraisals, not just for medicines, but also for medical devices, diagnostic techniques, surgical procedures, and health promotion activities (NICE 2013).

The most commonly used methods for health economic evaluation are cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). CMA assumes equal effectiveness of comparative technologies, which then allows a simple comparison of costs, and the logical decision is to choose the least expensive option. In CBA, also outcomes are expressed in monetary terms in order to calculate a net benefit. In CEA, outcomes are measured using "natural units", such as events avoided, change in cholesterol level, or hospital days avoided. CUA is a specific case of CEA in which outcomes are expressed as QALYs gained (Drummond et al. 2005).

Table 3: Types of economic evaluation methods

Method	**Cost**	**Outcome**	**Expression of cost per outcome**
Cost-minimization analysis (CMA)	Monetary	Equivalence of outcomes in comparative treatments	Difference in costs of comparative treatments
Cost-benefit analysis (CBA)	Monetary	Monetary	Net benefit = outcomes - costs
Cost-effectiveness analysis (CEA)	Monetary	Single "natural" unit	cost per outcome measure e.g. cost/avoided event
Cost-utility analysis (CUA)	Monetary	QALY	cost/QALY gained

Adopted from Drummond et al. (2005).

2.2.3.1. Incremental cost-effectiveness

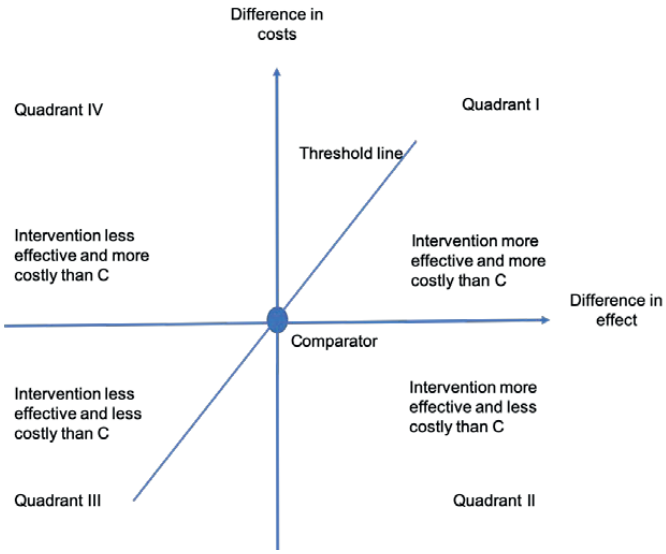
Decision-making about health care resource allocation can be complex, often requiring decision-makers to consider trade-offs, values of the patients and the society, and other types of evidence in the face of uncertainty and affordability. However, decision-making based purely on cost-effectiveness is fairly simple, and one needs only to decide which treatment is the better option. A cost-effectiveness plane was introduced to health care as an aid for decision-making in different situations (Black 1990) (Figure 3). If treatment is both less costly, and it provides better outcomes, it is a strongly dominant option (quadrant II in Figure 3) and should be chosen. The decision in quadrant IV is also clear and should not be chosen as it is both more expensive and less effective.

Decisions in quadrant I and III should be made based on incremental cost-effectiveness, i.e., the comparison of the difference in costs over the difference in outcomes to derive incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{Cost\ (A) - Cost\ (B)}{Outcome\ (A) - Outcome\ (B)}$$

In the case of extended (weak) dominance, there is a combination of two treatments that shows greater cost-effectiveness than a third one. Thus, in extended dominance, an intervention that has an incremental cost-effectiveness ratio that is greater than that of a more effective intervention is ruled out (Drummond et al. 2005).

Figure 3: Incremental cost-effectiveness plane, intervention vs. comparator (C)



Source: Adapted from Drummond et al. 2005

2.2.3.2. Willingness-to-pay

In practice, the situation is often as illustrated in quadrant I in figure 3, in which a new treatment is both more costly and more effective than the comparative treatment. In those cases, decisions must be made based on willingness-to-pay (WTP) for additional effectiveness. WTP is thus a maximum price at or below which the society (or a consumer) will buy a product or service (Varian 1992), or

in the case of CUA one QALY. The WTP threshold eventually defines if an intervention is cost-effective or not. Visual interpretation of the WTP threshold line in figure 3 is that treatments below the threshold line are considered cost-effective and those above not.

Not many countries have an explicit threshold for maximum WTP for a QALY, but those countries that do, mainly fall within the WHO's recommended range of one-to-three times gross-domestic-product (GDP) per capita (Cameron et al. 2018). For example, in Finland, politicians or health authorities have not explicitly stated any range of an acceptable cost/QALY ratio. A traditionally referenced value in American health economic literature is the value of 50 000$ USD per QALY, which may arise from the cost of dialysis in the 1980s but lacks any scientific justification (Neumann et al. 2014). In the US, interventions in the cost/QALY range of $50 000-$100 000 are often reported to be cost-effective (Shiroiwa et al. 2010). In the UK, the National Institute for Health and Care Excellence (NICE) recommends a value of 20 000 - 30 000 UK pounds per QALY, which represents an informed estimate of the health forgone, based on the evidence that is available about the productivity of other NHS activities (Culyer et al. 2007).

2.2.3.3. Perspective

The perspective of an economic evaluation depicts the point of view that is adopted when deciding which types of costs and health benefits are to be included in an economic evaluation. The perspective taken is an important element and has an impact on the analysis. Typical viewpoints are those of the patient, hospital/clinic, other providers, healthcare system, or society. The broadest perspective is societal, which reflects a full range of social opportunity costs. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force defines the full societal perspective to include three conditions: 1) the inclusion of time costs, 2) the use of opportunity costs, and 3) the use of community preferences, which in practice very rarely takes place (Garrison et al. 2010). A typical approach is to include productivity losses arising from patients' inability to work but the full societal perspective includes also relevant non–health-related impacts in other sectors such as in education and legal aspects, thus it is understandable that the full societal perspective is rarely taken (Garrison et al. 2018, Drost et al. 2017). It has been proposed that the terms "restricted" or "limited" societal perspective, defined as analyses including indirect costs and using community preferences, should be used as other types of analyses are often too theoretical.

It has also been emphasized that one should be explicit when using the healthcare system perspective or the payer perspective compared to a true societal perspective (Garrison et al. 2018).

A typical perspective adopted by HTA agencies, e.g., by the NICE in the UK, is the perspective of a healthcare system or provider, recognizing that the societal perspective may bias against those not working, such as retired persons or those not able to work due to health reasons. Thus, costs not to be included are patients' costs of obtaining care such as transportation, over-the-counter purchases, co-payments, or time off work (NICE 2013).

The use of the term "societal perspective" is often adopted merely based on the choice of including productivity costs. In a systematic review assessing which costs were included in economic evaluations that were said to adopt the societal perspective, only a few studies included in addition to productivity costs also other costs such as informal or social care costs (Drost et al. 2017).

Measuring and interpretation of QALYs have been argued to be problematic depending on the perspective that economic evaluation adopts. It has been argued that including indirect costs to the perspective of analysis involves double counting if those effects are considered in the QALY measure. However, there is evidence indicating that productivity costs due to morbidity are not captured within individuals' health state valuations (Davidson & Levin 2008). These findings, therefore, suggest that productivity costs due to morbidity should be included as a cost in cost-effectiveness analyses. For QALYs to be interpreted as only a measure of health benefit, productivity effects need to be explicitly excluded when the value of a health state is assessed (Jönsson 2009). However, as QALYs are often based on the general population's valuation of health outcomes, in that sense the QALY is capturing a societal perspective.

2.2.4. Health Technology Assessment

Health Technology Assessment (HTA) is originally defined by the International Network of Agencies for Health Technology Assessment (INAHTA) as "a multidisciplinary field of policy analysis, studying the medical, economic, social and ethical implications of development, diffusion and use of health technology" (Luce et al. 2010). HTA is used to assist decisions about reimbursement and funding of new technologies. Economic evaluation forms a core element of an HTA assessment guiding decisions on resource allocation. However, the ICER approach lacks the elements needed for

decision-making, such as ethics and equity (Saarni et al. 2008). In addition, it lacks elements such as affordability, budget impact, or feasibility of implementation of an intervention, which are also crucial elements needed for decision-making. Criteria related to the disease (such as severity of disease, capacity to benefit, and past health loss), criteria related to characteristics of social groups an intervention targets (socioeconomic status, area of living, gender, race, ethnicity, religion and sexual orientation), and non-health consequences of an intervention (financial protection, economic productivity, and care for others) have been proposed to be included in the decision-making (Norheim et al. 2014). While HTA, in general, has a societal policy perspective, many agencies in practice take a narrower healthcare or provider budget perspective when performing economic evaluations (Jönsson 2009).

Even though other criteria, such as severity and equity, can be assessed along with ICERs in a full spectrum HTA, there are concerns that such approaches may fail to capture other important sources of value if they are not quantifiable in cost-effectiveness analysis. Baeten and colleagues (2010) have tried to capture equity into a quantifiable element to be included in cost-effectiveness analysis (Baeten et al. 2010), but these types of analyses are scarce.

Value dimensions often outside the scope of an ICER can include the value of innovation to the society, unmet need, disease severity, reduced caregiver burden and patient compliance (Goldman et al. 2010). Some of these dimensions could be quantifiable in ICER assessment, but some elements are in practice difficult to capture in a reliable and systematic way. If value dimensions are not quantifiable in an ICER, Goldman and colleagues (2010) suggest a two-part protocol in which technologies are scored along key dimensions of value neglected by most current HTA approaches. Value dimensions would be scored publicly and transparently, and a composite 'value score' would be constructed. The composite value score could be considered jointly with the ICER (Goldman et al. 2010).

2.2.4.1. Multi-criteria Decision Analysis

The approach Goldman et al. (2010) proposes is similar to the Multi-criteria Decision Analysis (MCDA) approach that has also been suggested as a method to capture the benefits beyond QALYs in a transparent and consistent manner (Thokala & Duenas 2012). Multi-criteria decision analysis

frameworks have been suggested to offer a more holistic perspective to value assessment compared to traditional HTA (Angelis & Kanavos 2016).

MCDA has been defined as "an extension of decision theory that covers any decision with multiple objectives. It has been characterized as a methodology for appraising alternatives on individual, often conflicting criteria, and combining them into one overall appraisal..." (Keeney & Raiffa 1993). Another definition by Belton and Stewart is that MCDA is "an umbrella term to describe a collection of formal approaches, which seek to take explicit account of multiple criteria in helping individuals or groups explore decisions that matter" (Belton & Stewart 2002).

There are areas of uncertainty involved with using MCDA in the HTA process, such as uncertainty of problem structuring, evidence, and variation in preferences (i.e., uncertainty in performance scores, criteria weights, thresholds, etc.) (Thokala & Duenas 2012). These uncertainties are similar to those related to traditional cost-effectiveness modelling. A systematic review reported that there is currently interest in MCDA in healthcare, which is mirrored in an increase in the application of MCDA to evaluate healthcare interventions. However, there are many MCDA methods available, which can be challenging (Marsh et al. 2014). The ISPOR task force has established a common definition for MCDA in health care decision making and developed good practice guidelines for conducting MCDA to aid health care decision making (Thokala et al. 2016). The use of MCDA in health care is in early stages; thus, good practice guidelines can only be considered "emerging" (Marsh et al. 2016).

2.2.5. Value-based healthcare

Value-based healthcare (VBHC) is a broad concept without just one unambiguous definition. An expert group set up by the European Commission defined VBHC in a recent opinion paper as actions needed to ensure the financial sustainability of universal healthcare and a reallocation of resources from low to high-value care. The same expert group stated, that as consistent and common language or practices about VBHC are not yet in place, much work and investments are needed in piloting, monitoring, and evaluating the reallocation and shifting of resources (EXPH 2019). Another definition of value-based healthcare is that by Porter and Teisberg (2006), who define value in health care as health outcome per money expended. This is similar concept to ICER, but outcomes obtained are divided by the costs. What Porter brings on top of traditional health economic theory are the elements of competition and dynamic improvement of effectiveness in health care. Porter

proposes that value should be created around patient by focusing on analyzing the entire health care delivery value chain and incentivizing on value created on the patient. In some economic markets, competition drives continuous improvements in quality and costs. However, especially in publicly funded (Nordic) health care systems, health care competition based on competing on value has not been a traditional way of functioning, and there are multiple reasons related to uncertainties and risks of demand, supply and the product (health) causing health care market to operate differently from normal competitive market (Arrow 1963).

2.2.5.1. Value-based pricing

Value-based pricing (VBP) is a way of incentivizing based on value delivered. In the UK, the English National Health Service (NHS) defines VBP as the price that ensures that the expected health benefits of a new technology exceed opportunity cost of the health to be displaced elsewhere in the NHS, due to the additional cost invested in the technology (Claxton 2007). Thus, the value assessment relies on cost-effectiveness analysis and the setting of an ICER threshold beyond which a new technology is not funded. In Sweden, VBP is defined more broadly, and the decision-making of new technologies is adopting the human value principle to guard against discrimination of individuals, the need and solidarity principle that gives priority to those in greatest need, and the cost-effectiveness principle (Persson et al. 2012). In other words, Swedish VBP relies on a broad societal perspective compared to the UK approach, but in both definitions, ICER assessment is in a key role.

In the UK, the Office of Fair Trading (OFT) recommended more than ten years ago a pharmaceutical price regulation scheme (PPRS) to make a reform where the price is based on the health benefit offered by a pharmaceutical over a combination of profit and price controls (Claxton 2007). This value-based pricing (VBP) enables flexible pricing and negotiation and involves price setting based on a cost-per-QALY threshold plus periodic ex-post reviews (Towse 2007) with a possibility to conduct additional evaluative research. Since then, decision-makers in England and Wales have considered the negotiation process to include broader and more transparent assessment methodology (Department of Health 2011) in the context of value-based-pricing.

The concept of VBP is not fully established and can be interpreted differently depending on the health care environment also in terms of a single buyer vs. a multiple buyer context (Pauly 2017).

Particularly in the US, the VBP concept has taken several modified forms related to the price setting of a product (ICER 2015, Toth et al. 2017). In the broader sense, VBP means that activities should be oriented, organized, or funded to maximize health benefits for patients and societies. Thus, it proposes to link payments to health services. It also means evidence-based assessments of value for patients, their relatives and the society as a whole (Vogler et al. 2017) and could include a need for further evaluative research e.g., in real-life clinical practice to demonstrate real-world outcomes.

2.2.5.2. Real-world data

Real-world data (RWD) in healthcare mean data that can be derived from multiple sources that are associated with outcomes in the real-world, as opposed to data traditionally gathered in medicine in experimental settings such as randomized controlled trials (RCTs). In a real-world setting, circumstances or populations are not controlled, and the populations may be heterogeneous, as is usual in everyday clinical practice (Makady et al. 2017a). RWD can consist of e.g. electronic health records (eHR), hospital discharge data, prescription data, claims and billing data, and (disease-specific) quality registries. Knowledge gained through RWD is called real-world evidence (RWE).

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) both recognize that RWD and RWE are playing an increasingly important role in health care decisions (Eichler 2018, FDA 2019). Especially HTA agencies are in search of robust methods to assess real-world effectiveness, rather than efficacy, in routine clinical practice. The use of RWD among different HTA agencies in Europe was recently assessed in a review, reporting that the practices varies among countries. The review concludes that in order to facilitate the use of RWD for HTA across Europe, more alignment of policies seems necessary as methods vary (Makady et al. 2017b). RWD can be used in HTA e.g. to assess relative effectiveness (relative effectiveness assessment, REA) or in CEAs. A review of five European HTA agencies in England (National Institute of Clinical Excellence, NICE), Scotland (Scottish Medicines Consortium, SMC), France (Haute Autorite´ de Santé, HAS), Germany (Institute for Quality and Efficacy in Healthcare, IQWiG) and The Netherlands (Zorginstituut Nederland, ZIN) found that RWD inclusion was higher in CEAs than REAs, and RWD was mostly used to estimate prevalence and incidence, to predict long-term effectiveness for CEAs and to identify drug-related costs (Makady et al. 2018).

Countries vary in their readiness of eHR systems and possibilities to contribute to (inter)national health information and research. Countries like Finland and Sweden are forerunners in the use of eHR and have a possibility of piloting of RWD usage for different purposes (Parikka et al. 2019, Jormanainen et al. 2019). One example of real-world data collection in routine clinical practice is the HRQoL data collected in this study. Incorporating this type of data in value assessments of treatments can facilitate informed decision-making both at the clinical and the policy level.

Increasing usage of digital tools and applications for patients is also increasing PROM data, such as HRQoL, collected in clinical settings. Questionnaires in an electronic format can make the data collection less burdensome, but not all patients are used to fill in questionnaires through applications or digital tools.

3. Structure and aim of the thesis

Healthcare systems are struggling with the sustainability of funding as the aging of the population and diminishing birth rates result in a deteriorating dependency ratio between working-aged and others. In addition, while new technologies emerge, focus on how resources are allocated is needed even more than before. As PC incidence is increasing, more information is needed to understand the optimal patient journey, which should produce value for the patients, and thus, value also for the society. Only through knowledge, it is possible to understand cost-effective ways of working in healthcare to be able to create a sustainable healthcare environment that is equitable and just.

The purpose of this thesis is to generate data and knowledge on how PC patients perform in real-life clinical practice and to understand what kind of patient value is being created by the current healthcare system. As a comparison between therapy areas is needed, the focus of this study was on generic utility measurement and its usability in practice. The data gathered in this research can be utilized in future cost-effectiveness analyses. The motivation for this thesis emerges from the fact that through the understanding of the real-world impacts of different treatments, value assessments are possible and, consequently, the healthcare system can be led with knowledge on how to work efficiently to maximize health outcomes to the patients and the society.

Particular goals of the empirical part of the study were:

1. To systematically review evidence and literature on the usage of validated, generic HRQoL instruments allowing the calculation of QALYs and which are thus directly usable for economic evaluations (Study I);

2. To measure HRQoL of PC patients in different stages of the disease and in patients undergoing different treatments (Studies II and III), to compare HRQoL with that of the general male population and to assess whether the EORTC-QLQ30 and 15D instruments are interchangeable in PC (Study II);

3. To assess if HRQoL can serve in predicting overall or PC-specific survival (Study III) and to assess QALYs experienced by different treatment lines to estimate their overall value for the patients (Study III).

4. Materials and methods

4.1. Patient population and clinical data (II and III)

The study was conducted in the Helsinki University Hospital (HYKS) that provides specialized medical care for the cities of Helsinki, Espoo, Vantaa, Kerava, Kirkkonummi, and Kauniainen covering approximately 1,2 million inhabitants. The study is part of a larger observational survey, approved by the Ethics Committee of the Helsinki and Uusimaa Hospital Group (registration number 207/13/03/2008), investigating HRQoL, effectiveness, and cost-effectiveness of PC and breast cancer patients and their treatments. Patients were invited to participate in the study during 2008-2013.

PC patients were invited to participate by the research nurse at the time of the diagnosis. Unfortunately, no records were kept about non-respondents. The estimated response rate to the questionnaire based on annual new PC patients in the HYKS area and subjects in the study sample was 15%. Clinical background data were collected retrospectively from the hospital patient records by the study nurse. Clinical data consisted of TNM classification (classification of malignant tumors), Gleason score, the planned treatment at baseline, and the actual treatment given during the first year after diagnosis.

To assess the baseline HRQoL by disease stage, patients were categorized, based on the TNM classification at baseline, into three mutually exclusive disease groups: Local disease group included patients with tumor classification T1 or T2 with no distant metastases (M0), no regional lymph node metastases (N0) or regional lymph nodes were not assessed (NX). Locally advanced disease group included patients with tumor class T3 or T4, and metastases classification M0, N0, and NX. Metastatic disease group included patients with any tumor classification with distant metastases (M1) or metastases in regional lymph nodes (N1).

To assess HRQoL by given treatment during the first year after diagnosis, patients were categorized into four treatment groups of major conventional treatment strategies: active surveillance group included patients following the Prostate Cancer Research International: Active Surveillance protocol (PRIAS) (van den Bergh et al. 2007) or a lighter surveillance protocol, radiation therapy, radical surgery, or hormonal treatment. The radiation therapy group consisted of patients having been

treated with external beam radiation, brachytherapy, neoadjuvant hormonal treatment + radiation, or neoadjuvant hormonal treatment + radiation + adjuvant hormonal treatment. The radical surgery group consisted of patients having undergone robotic-assisted laparoscopic surgery (RALP), open surgery, or surgery + adjuvant radiation. The hormonal treatment group included patients having been prescribed antiandrogen medication, luteinizing hormone-releasing hormone (LHRH) treatment, or a combination of them.

The date and causes of death were obtained from Statistics Finland until the end of 2017. Thus, the maximum follow-up time for the patients recruited at the start of the project in 2008 was 10 years. In addition to overall survival, PC-specific survival was assessed using both the primary and contributory causes of deaths based on the International Classification of Diseases (ICD-10 coding) to identify deaths directly associated with PC.

An age-standardized male population from the Helsinki and Uusimaa Hospital District (HUS) area was used as a comparison population. The data for the general population came from the National Health 2011 Survey representing the Finnish population aged 18 and over (Koskinen et al. 2012). The multi-stage, complicated sampling procedure for the survey has been described in detail elsewhere (Lundqvist & Mäki-Opas 2016). For the comparative analysis with patients those male individuals were selected from the total population sample, who were in the age range of the patients (n=465). This subsample was weighted to reflect the age distribution of the patients.

Study set-up with sources of data is illustrated in figure 4.

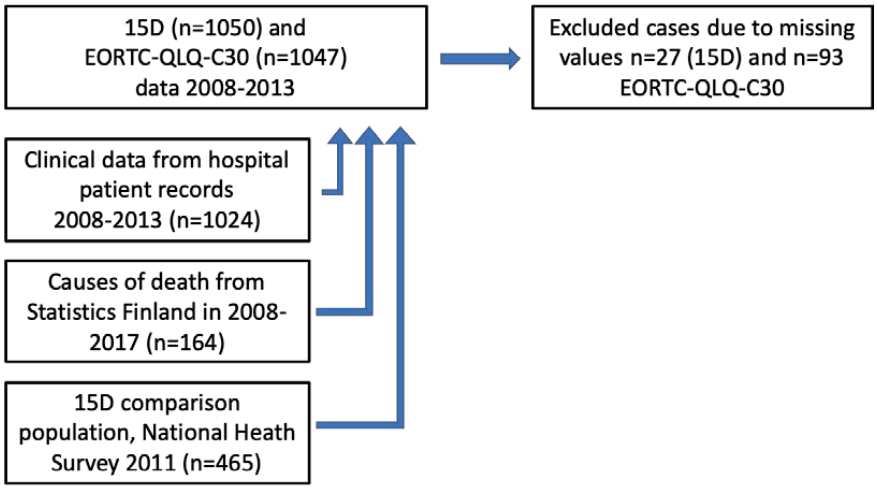


Figure 4: Study cohort and sources of data

4.2. HRQoL data (II and III)

Both one generic HRQoL instrument, the 15D, and one cancer-specific HRQoL instrument, the EORTC QLQ-C30, were used in the study. HRQoL was measured by the generic 15D at baseline and 3, 6, 12, and 24 months after diagnosis. The 15D questionnaire is composed of the dimensions of mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity, with five ordinal levels on each. The overall HRQoL is expressed in a single index score (15D score) on a 0-1 scale. The dimension level values, reflecting the goodness of the levels relative to no problems on the dimension (=1) and to being dead (=0), are calculated from the questionnaire by using a set of population-based preference or utility weights. Mean dimension level values are used to draw 15D profiles for groups (Sintonen 2001).

The cancer-specific EORTC-QLQ-C30 was used in the baseline HRQoL assessment. EORTC-QLQ-C30 produces a global health status, five functional scales (physical, role, emotional, cognitive, social) and nine symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). The scales of the scores range from 0 to 100; for the global health status and functional scales, a higher value indicates better functioning, and for the symptom scales, a higher value indicates more symptoms (Aaronson et al. 1993, Fayers et al. 2001).

4.3. Review of the HRQoL literature (I)

A systematic literature review was done in order to assess PC studies in which HRQoL was collected using generic, validated instruments. The purpose of the literature review was to assess how broadly generic HRQoL instruments are used in PC and to establish the extent of the evidence base for utilities in PC that can be used to calculate QALYs in health economic evaluations.

A professional information specialist performed systematic literature searches without language restrictions using prostate cancer and quality-of-life as keywords according to Medical Subject Heading (MeSH) terminology. The systematic literature searches were conducted on two occasions - in March 2013 for the years 2002–13 and in June 2015 for the years 2013–15 - from the Medline, Cochrane Library, PsycINFO, and CINAHL databases. The most recent publications that had not yet been indexed were searched manually from the Pubmed in Process references. The searches were restricted to meta-analyses, systematic reviews, randomized controlled trials, and observational studies. Congress abstracts were not included. The results obtained from Medline were filtered with the filters developed by SIGN (Scottish Intercollegiate Guidelines Network) (Harbour & Miller 2001). Bibliographies of potential articles that, e.g., included HRQoL or utility data as inputs of cost-effectiveness analyses were reviewed manually by the authors. Initial screening was based on the abstracts, which were reviewed independently by at least two of the authors, and the selection of relevant articles was agreed in discussion between the reviewers. Full-text articles that were obtained for closer evaluation were again read independently by at least two of the authors.

Inclusion criteria were RCTs or observational studies, in which 1) HRQoL data were collected from prostate cancer patients, 2) the results were reported as single index utility scores, and 3) validated HRQoL instruments were used (either direct valuation using TTO, SG, VAS, or RS or indirect valuation using 15D, EQ-5D, SF-6D, HUI, AQoL, QWB, or Rosser-Kind).

4.4. Statistical methods (II and III)

Clinical demographics and descriptive statistics of the study population were in general summarized by disease or treatment group. Means and standard deviations of the HRQoL scores were reported. The 15D dimension level values and the total utility score were compared with those of the age-standardized general male population from the same hospital district where the patients were from, but EORTC QLQ-C30 population comparison data are not available in Finland. Differences in means

compared to the population were analyzed using Student's independent-samples t-test. Patient subgroups were compared to each other using one-way analysis of variance (ANOVA) to test the differences in means between groups. The 15D dimension level values and changes of the 15D scores over time were graphically presented in figures.

To examine how the variance in the 15D scores can be explained by the clinical background information of the subjects, a multilinear regression model was built. A mapping model to predict the 15D score by the EORTC-QLQ-C30 domains was also built. In a random sample of 50% of the patients, an ordinary least squares (OLS) regression model was built using EORTC QLQ-C30 domains as predictor variables, and the constructed model was tested in the remaining 50% of the patients. Correlations between EORTC-QLQ-C30 domains were assessed by Pearson's bivariate correlation coefficient. If very high correlations between predictor variables were present, some of the predictor variables were removed to avoid multicollinearity. Both stepwise and backward methods were used as the selection processes of variables to test the robustness of the model. Model fit was examined by the adjusted R^2 and by the root mean square error (RMSE).

The study patients' overall survival (OS) and PC-specific survival (PC-S) were calculated as the time between the date of the first visit to the hospital at the time of the diagnosis and date of death from any cause (OS) or PC-specific death (PC-S), or the last date the patient was known to be alive. The follow-up ended on 31st Dec 2017, resulting in a maximum follow-up time of 10 years. OS and PC-S were calculated using the Kaplan-Meier method. Multivariate Cox proportional hazard models were built separately for OS and PC-S to find out if the treatment given and the 15D data were predictors of survival. As the given treatment is to a large extent based on the patient's TNM classification and Gleason score, those variables were left out as covariates from the Cox regression model due to issues with multicollinearity. Models were built in two blocks of covariates to test if HRQoL brought additional value for the prediction of survival. The likelihood ratio test was used to assess if adding a block statistically significantly improved the model precision.

The number of QALYs experienced was calculated with the area-under-the-curve method. Missing HRQoL scores were imputed with the last observation carried forward method. If the HRQoL score was missing due to death, a value of 0 was imputed. HRQoL was assumed to develop linearly

between measurement points. Associations of age, baseline HRQoL and treatment group to QALYs experienced were analyzed in a linear regression model.

The statistical analyses were performed using SPSS versions 22 and 25 (Released 2013 and 2017. Armonk, NY: IBM Corp.). P-values ≤ 0.05 were considered statistically significant.

5. Results

5.1. Use of generic, single index HRQoL instruments in PC (I)

In the literature search, a total of 2.171 references were identified, of which 190 were duplicates and thus were eliminated. Based on the abstracts, 237 studies were obtained for full-text review, and after the assessment of the full-text articles, 33 studies fulfilling the inclusion criteria were included in the systematic review.

Of the total of 33 articles, 24 (73%) used an indirect valuation, and 16 (48%) a direct valuation method (adds up to more than 100% as some of the studies included instruments using both approaches). The most commonly used instrument was the EQ-5D, which was used in 21 (64%) studies. The VAS was also common as it was used in ten (30%) studies. Geographically, the EQ-5D and the VAS were used all over the world, which was not the case in the TTO as all of the studies using it originated from the United States (Table 4). The 15D was used in five studies (15%), of which three were carried out in Finland, one in Norway and one in Turkey. The Health Utilities Index (HUI) and the Quality of Well-Being scale (QWB) were used in two Canadian studies. SG was used in two U.S. studies, and SF-6D was used in one study conducted in Finland. There were no studies that reported HRQoL being measured by the Assessment of Quality-of-Life, Rosser-Kind, or Rating Scale instruments.

HRQoL values varied in localized and early-stage disease from 0.63 to 0.91, in patients having undergone radical prostatectomy between 0.68 and 0.91 and in advanced/metastatic stage disease between 0.50 and 0.87. The large variance in HRQoL scores in all disease stages is probably a consequence of the variation of different HRQoL instruments and variation in the study settings and methods (Table 4)

Most of the studies (64%) were done in the setting of clinical practice or were observational by nature. A clinical trial setting was found in approximately one-third of the studies. HRQoL data from real-life clinical practice seemed to be the most popular form of study design. A vast majority of studies (94%) elicited the patient's current health state, and only a few studies elicited preferences for hypothetical health states predefined by investigators.

Table 4: Summary of characteristics of publications included

Disease stage	First author, publication year, country, reference	Population	Number of patients	HRQoL instrument or valuation method	Follow-up period (months*)
Early/localised					
	Knight 2004, USA	Newly diagnosed localized PC	95	TTO	0, 3, 12
	Elstein 2005, USA	Localized PC	127	TTO	0, 3-6 months later
	Korfage 2005, Netherlands	Localized PC	314	EQ-5D, VAS	-1, 6, 12, 52
	Sommers 2008, USA	Localized PC	167	TTO	0
	Soyupek 2008, Turkey	Locally advanced PC	20	15D	0
	Fernández-Arjona 2012, Spain	Locally advanced or disseminated PC	561	EQ-5D, VAS	0
Advanced/metastatic					
	Saad 2002, multinational	Hormone-refractory metastatic PC patients	643	EQ-5D	0, 15
	Reed 2004, USA	Advanced PC (treatment of SRE)	1469	EQ-5D	0, every 3 months
	Weinfurt 2005, multinational	Metastatic PC with sign of SRE	248	EQ-5D, VAS	0, 3 month up to 24 months
	Sullivan 2007, multinational	Metastatic hormone-refractory PC patients	280	EQ-5D	0, 3, 6, 9
	Namiki 2008, Japan	Advanced or metastatic PC	23	EQ-5D	0, 3, 6, 9 and 12 months
	Wu 2008, USA	Metastic hormone refractory PC	280	EQ-5D	0, 3, 6, 9
	Färkkilä 2013, Finland	Palliative PC, BrC, CRC	30	15D, EQ-5D, VAS	0
	Skaltsa 2014, multinational	Metastatic castration-resistant PC	209	EQ-5D	0, 13 and every subsequent 12 week
	Diels 2015, multinational	Metastatic castration-resistant PC	602	EQ-5D	0
	Loriot 2015, multinational	Asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-	1717	EQ-5D	0, weeks 5, 13, 25, 37, 49, 61
Screening					
	Booth 2012, Finland	PC screening	5516	15D, EQ-5D, SF-6D	surveys in 1998, 2000, 2004 and
Prostatectomy					
	Smith 2002, USA	After radical prostatectomy	209	TTO, SG	0
	Glazener 2011, UK	Radical prostatectomy or TURP	853	EQ-5D	3, 6, 9, 12
	Wang 2014, Sweden	PC patients at least 10 years after laparoscopic radical prostatectomy	49	EQ-5D	0
Mixed/other					
	Krahn 2003, Canada	PC	141	HUI, QWB	0
	Stewart 2005, USA	PC, older than 60	162	SG	0
	Volk 2004, USA	PC screening and metastatic PC	168	TTO	0
	Krahn 2007, Canada	Three cohorts: newly diagnosed, metastatic and other	248	HUI 2/3, EQ-5D, QWB	0, 2, 12
	Pearcy 2008, UK, Ireland	PC	25	VAS	0
	Shimizu 2008, Japan	Localised PC and hormone refratory PC	323	EQ-5D	0
	Meghani 2009, USA	PC or men at risk	188	TTO/VAS	single time-point
	Pickard 2009, USA	PC	87	EQ-5D, VAS	0
	Cameron 2012, Canada'	PC patients after radiotherapy	73	EQ-5D, VAS	0, 1
	Ruland 2013, Norway	PC and BrCa patients	325	15D	0, 3, 6, 12
	Mickeviciene 2013, Lithuania	PC	501	VAS	0
	Torvinen 2013, Finland	PC patients (different states)	630	15D, EQ-5D, VAS	0
	Freytag 2014, USA	Intermediate-risk PC	44	EQ-5D	0, 6, 12, 24, 36

EQ-5D; EuroQoL,HUI; Health Utilities Index, QWB; Quality of Well being, SF-6D; Short Form 6D, 4026
TTO; Time-Trade-off, SG; Standard Gamble, VAS; Visual Analog Scale

PCa; Prostate Cancer, BrCa; Breast Cancer, CRC; colorectal cancer
* Months if not otherwise mentioned in the text

5.2. Demographics of the population (II and III)

The mean age of the patients at baseline was 66.5 years and varied between 40 and 90 years. According to the TNM classification, most of the patients were in the early stage of the disease, and there were 540, 262, 162 and 16 patients in T-classes 1, 2, 3 and 4, respectively. The mean Gleason score was seven, and it ranged from 4 to 10. Clinical demographics of the study population at baseline are presented in table 5. Only 59 (6%) of the patients were metastatic at the time of the diagnosis. Of all metastatic patients, 41 had bone metastases, 11 metastases in distant lymph nodes, 25 in regional lymph nodes, and five in other locations (some patients had metastases in several of the above-mentioned locations).

Clinical background data were obtained for 1024 subjects. At baseline, there were 811 patients in Local disease stage, 143 in Locally advanced and 59 in Metastatic disease stage at the time of the diagnosis. The patients in the Local stage (mean age 66.0 ± standard deviation 0.8) were two years younger than patients in the Locally advanced (68.3±8.9) or Metastatic group (68.3±8.7). The Gleason score was also lower in the Local stage (6.7±0.8) compared to Locally advanced (7.6±1.0) and Metastatic (8.2±1.0) patient groups.

Table 5: Clinical demographics

Disease group	n	Age		Gleason score	
		Mean	SD	Mean	SD
Local	811	66.0	8.3	6.7	0.8
T1	546				
T2	265				
Locally advanced	143	68.3	8.9	7.6	1.0
T3	135				
T4	8				
Metastatic	59	68.3	8.7	8.2	1.0
T1	10				
T2	6				
T3	31				
T4	12				
All	**1013**	**66.5**	**8.4**	**6.9**	**0.9**

5.3. Treatment (III)

Categorized into treatment groups by the treatment received during the first year after diagnosis, there were 226 patients in active surveillance, 280 patients in radiation, 299 in radical surgery, and 62 patients in hormonal treatment groups, respectively (Table 6). These were the four major treatment strategies. In addition, there were some patients undergoing watchful waiting (n=13), receiving some other treatment (n=11), or sent for treatment into occupational health service, primary care, or mobile surveillance (n=241). These patients were excluded from analyses as the treatment they had received could not be checked from the hospital records.

Table 6: Patient characteristics at baseline categorized by treatment line during first year after diagnosis

Treatment line	N	Age		Gleason		T-classification			
		Mean	SD	Mean	SD	1	2	3	4
Active surveillance	226	65.4	7.74	6.11	0.367	213	13	0	0
Radiation	280	70.3	6.59	7.13	0.900	186	44	45	5
Radical surgery	299	62.7	6.92	6.78	0.658	69	177	53	0
Hormonal	62	77.0	10.00	8.02	1.048	19	8	25	10
Total	**867**	**66.9**	**8.42**	**6.81**	**0.89**	**487**	**242**	**123**	**15**

Patients in the hormonal treatment group were the oldest (mean age 77.0 years), and patients in the surgery group the youngest (62.7 years).

5.4. HRQoL (II and III)

5.4.1. 15D

The total sample of the 15D responses was 1050. Due to the missing answers on individual dimensions, the 15D score could not be calculated for 27 patients.

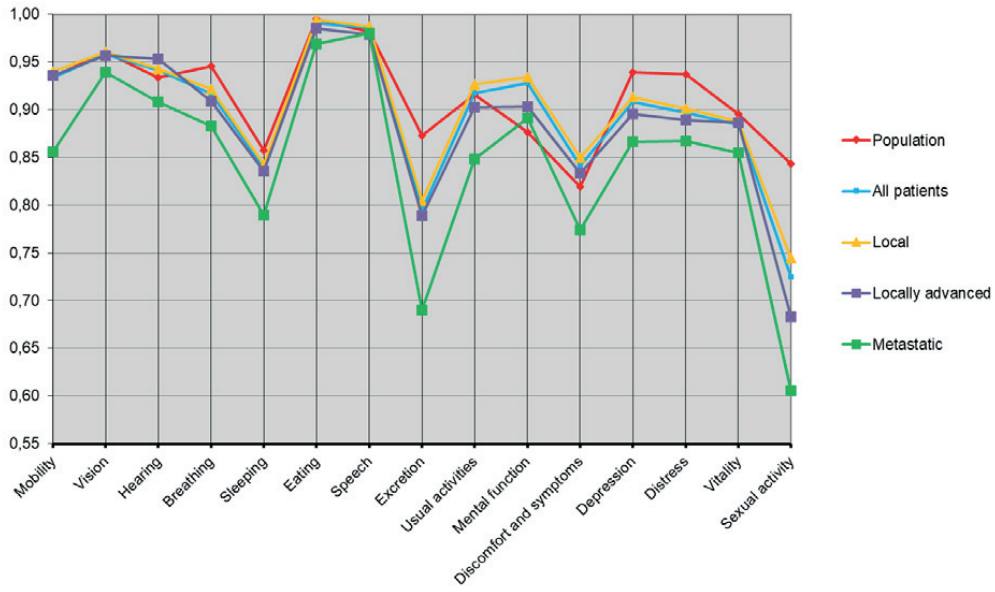
At baseline, the mean 15D score of newly diagnosed PC patients was lower than that of the age-standardized general male population, but the difference was not statistically significant or clinically important (0.905±0.089 vs. 0.915±0.082, p=0.057). PC patients were statistically significantly worse off on the dimensions of breathing, excretion, depression, distress, and sexual activity and better off on the dimensions of mental function and discomfort and symptoms (Table 7; Figure 5). Metastatic patients had a significantly ($p<0.001$) lower mean 15D score than the population, and the absolute score on each dimension was lower on all other dimensions except for mental function. The mean 15D scores of Local and Locally advanced patients were similar to those of the population. Regardless of the disease group, the most impaired dimensions of HRQoL were excretion and sexual activity. Ten percent of the patients obtained a maximum 15D score of 1. Of those patients, 84 were in the Local, 13 in Locally advanced, and two in the Metastatic groups.

Table 7: The mean 15D scores and dimension level values by disease group and the difference (delta) compared to the age-standardized population from the same geographic region

	Local		Locally advanced		Metastatic		All patients	
	mean	delta	mean	delta	mean	delta	mean	delta
15D score	**0.912**	**-0.003**	**0.897**	**-0.018**	**0.855**	**-0.060 ****	**0.905**	**-0.009**
Mobility	0.940	0.006	0.935	0.001	0.856	-0.079 *	0.934	-0.001
Vision	0.960	0.000	0.957	-0.003	0.939	-0.021	0.959	-0.002
Hearing	0.943	0.010	0.953	0.020	0.908	-0.025	0.941	0.008
Breathing	0.922	-0.023 *	0.909	-0.037 *	0.883	-0.062 *	0.917	-0.029 **
Sleeping	0.843	-0.015	0.836	-0.022	0.790	-0.068 *	0.839	-0.019
Eating	0.994	-0.001	0.985	-0.010	0.969	-0.026	0.991	-0.004
Speech	0.987	0.005	0.979	-0.003	0.980	-0.002	0.986	0.004
Excretion	0.805	-0.068 **	0.789	-0.084 **	0.690	-0.183 **	0.795	-0.078 **
Usual activities	0.926	0.011	0.903	-0.013	0.848	-0.067 *	0.917	0.002
Mental function	0.935	0.058 **	0.903	0.027	0.891	0.015	0.928	0.052 **
Discomfort and symptoms	0.850	0.031 *	0.834	0.014	0.774	-0.045	0.841	0.022 *
Depression	0.913	-0.026 *	0.895	-0.043 *	0.866	-0.073 *	0.908	-0.031 **
Distress	0.901	-0.036 **	0.889	-0.048 *	0.867	-0.070 *	0.897	-0.041 **
Vitality	0.888	-0.008	0.886	-0.009	0.854	-0.041 *	0.884	-0.012
Sexual activity	0.744	-0.099 **	0.683	-0.160 **	0.606	-0.237 **	0.725	-0.118 **

* <0.05 compared to the age-standardized general male population from the same region
** <0.001 compared to the age-standardized general male population from the same region

Figure 5: The mean 15D profiles and scores in different disease groups compared to those of an age-standardized sample of general male population.



The mean 15D score was highest among the Local disease group patients (0.912±0.084) and lowest among the Metastatic patients (0.855±0.109). Metastatic patients had the lowest absolute scores on all dimensions of the 15D instrument between disease stages. The differences between Local and Locally advanced groups were minor, and a statistically significant difference was found only in mental function and sexual activity.

The progress of age-standardized total 15D scores by treatment line is presented in figure 6 for two years after diagnosis (0, 3, 6, 12, and 24 months). HRQoL in the active surveillance and surgery groups was very similar, but the decrease in HRQoL was greater in the active surveillance group than in the surgery group during the second follow-up year. Patients in the hormonal group had the worst baseline HRQoL which started to deteriorate six months after the diagnosis. Compared to baseline, there was a clinically important decrease in the mean 15D score at 24 months in all other treatment groups except in the surgery group.

Sexual activity was the most impaired HRQoL dimension in all treatment groups but remained best in active surveillance among all treatment groups (Figure 7). The largest decrease in sexual activity was found in the surgery group, in which also excretion deteriorated immediately after operation but recovered during follow-up. Also in the hormonal treatment group, sexual activity deteriorated stedily during the follow-up period. There was a significant decline on the dimension of excretion in the surgery group at 3 months, but later the excretion function recovered even to a level above the baseline situation. Also in the radiation group excretion was impaired (largest decrease at 6 months), but had recovered at 2 years. Dimensions reflecting psychological health - depression and distress - were not significantly affected in any of the treatment groups.

Figure 6: Age-standardized 15D scores during two-year follow-up

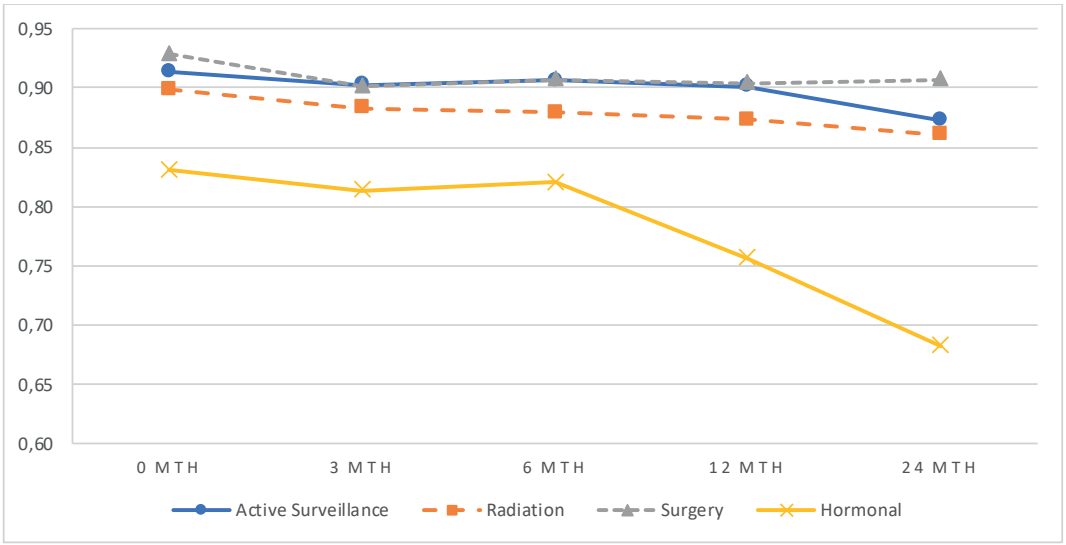
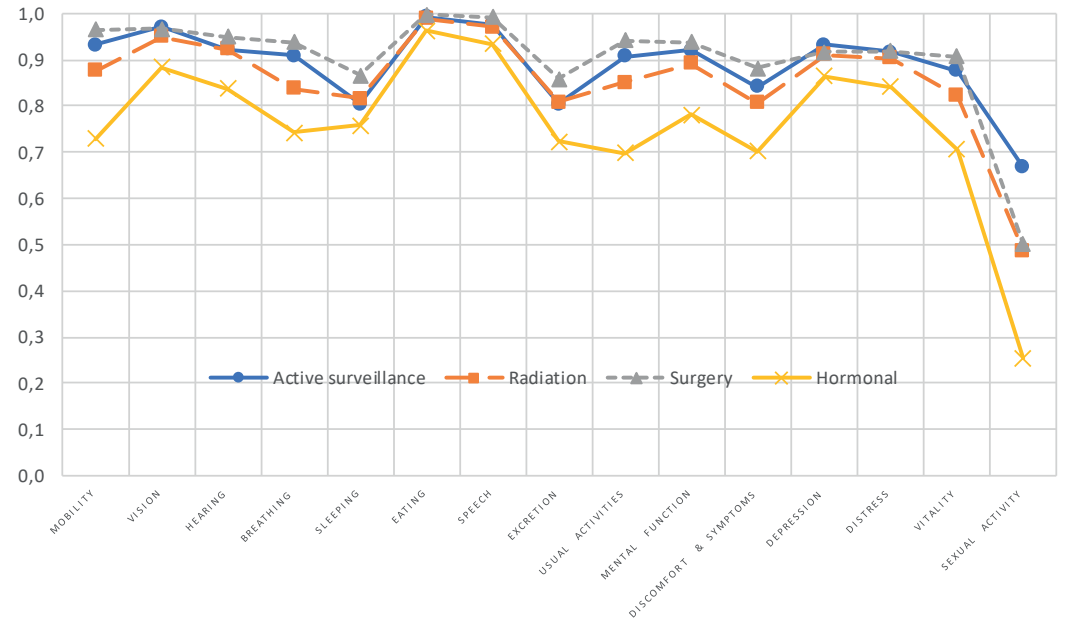


Figure 7: The mean 15D profiles by treatment lines at 2-year follow-up



In the regression model, the clinical factors associated with impaired HRQoL were age, bone metastases, and Gleason score, and the adjusted R2 of this model was 0.051. The basic assumption for the OLS regression of normally distributed residuals was satisfied sufficiently, and multicollinearity was not an issue in this model examined by standard collinearity indicators. The clinical background information collected in this study did not explain well the variance in the 15D scores, and there is evidence that socioeconomic factors such as education, income, financial difficulties, and marital status may be correlated with HRQoL (Pappa et al. 2009, Torvinen et al. 2013, Koskinen et al. 2019). Therefore, the obvious weakness of this study was that socioeconomic background information of the subjects was limited.

5.4.2. EORTC QLQ-C30

The total sample of EORTC QLQ-C30 responses was 1047, and full EORTC data were available for 954 patients. The mean (SD) Global Health Status (QoL) scores were 76.8 (20); 77.3 (19.5); 78.0 (21.3) and 68.3 (22.0) for all patients, Local, Locally advanced and Metastatic groups, respectively. There were statistically significant differences between disease groups in QoL, physical, role and social functioning and in pain. Comparison to the population of the same age and location could not be performed as general population EORTC data have not been collected in Finland. Of the five functioning scales, patients in Local and Locally advanced groups scored the lowest in emotional function, which can indicate anxiety, worrying, irritation, and/or depression due to the awareness of the diagnosis.

Metastatic patients scored the lowest in QoL and all functioning scales and had the most symptoms in all other symptom scales except for dyspnoea. Especially metastatic patients had more pain compared to the Local and Locally advanced patients. The differences between Local and Locally advanced patients were minor and not statistically significant.

The EORTC research group has very recently published thresholds for the instrument's clinical importance (TCI) levels to facilitate the interpretation of scores at a single point of time (Giesinger et al. 2019). TCIs can be useful e.g., for symptom screening in daily practice or for calculating symptom prevalence rates from EORTC QLQ-C30. Comparing the results of this study to published TCI scores, the only dimension that was clinically relevantly impaired in the light of TCI scores was the physical function in the Metastatic patient group. Comparison at a group level is probably not

the best use of TCIs as TCIs are not stratified by age, gender, or region, and the comparison should be considered only indicative. The most relevant comparison would most likely be the changes over time compared to the baseline score of the patient himself.

5.4.3. Mapping of EORTC QLQ-C30 to 15D

The mapping model to predict 15D scores with EORTC QLQ-C30 dimensions explained approximately 79% of the variance of the 15D scores. All other EORTC QLQ-C30 domains except social functioning, nausea/vomiting, diarrhea, and financial difficulties were identified as predictors in the mapping model (Table 8). A stepwise entering method for explanatory variables was used, but the results were robust for backward and enter methods as well. Among all sub-groups, the predicted 15D values, based on the mapping algorithm, were within the confidence intervals of the observed 15D values (Table 9).

Table 8: The results of the EORTC QLQ-C30 mapping model to the 15D

Variables	**B**	**adjusted R^2**	**p-value**
Constant	0.5599		<0.001
Physical Function	0.0014	0.577	<0.001
Cognitive Function	0.0011	0.681	<0.001
Global health status/QoL	0.0007	0.736	<0.001
Insomnia	-0.0005	0.760	<0.001
Dyspnoea	-0.0007	0.772	<0.001
Fatigue	-0.0006	0.779	0.004
Pain	-0.0004	0.783	0.008
Constipation	-0.0004	0.787	0.004
Role Function	0.0005	0.790	0.004
Emotional Function	0.0005	0.792	0.002
Appetite loss	0.0004	0.794	0.027

** The minus-sign indicates decrement in the 15D score*

*** P-value of the predictor variable*

Table 9: Mean observed and predicted 15D scores in different disease groups based on the mapping model.

		Observed 15D score		Predicted 15D score	
Disease group	**n**	**Mean**	**95% CI**	**Mean**	**95% CI**
Local	363	0.908	0.899-0.917	0.902	0.894-0.910
Locally advanced	59	0.931	0.916-0.946	0.922	0.907-0.936
Metastatic	25	0.877	0.841-0.913	0.882	0.847-0.917
All patients	447	0.909	0.901-0.917	0.904	0.897-0.911

5.5. Survival (III)

The mean follow-up time in the survival analysis was 77.7 months. At the end of the follow-up, 84.4% of patients were alive. OS in the hormonal treatment group was worse than in the other groups, as 50% of patients had died by 53.8 months (95% CI 44.5 – 63.2 months) (Figure 8). Median survival for the other groups was not reached. Prostate cancer was a rare cause of death in the active surveillance and surgery groups (Figure 9). Again, the only treatment group in which 50% of patients had died during the follow-up was the hormonal group (median PC-specific survival 78.5 months; 95% CI 53,4 – 103.5 months).

Covariates that were analyzed in the Cox proportional hazards model in relation to OS and PC-S were treatment line, age, and either the 15D score (in model 1) or the 15D dimensions (in model 2). The 15D score or 15D dimensions were added as a block 2 into the model to estimate how much additional power in explaining the difference in variation in survival the total 15D score and the 15 dimensions brought.

Compared to the reference treatment line, active surveillance, the hormonal treatment line was consistently and statistically significantly associated with lower overall survival and PC-specific survival. Hormonal treatment was associated with 5.1 ($p<0.001$; model 1) and 6.1 ($p<0.001$; model 2) times higher risk of death from any cause, and 49.3 ($p<0.001$; model 1) and 78.0 ($p<0.001$; model 2) times higher risk of PC-related death compared to active surveillance. Radiation was associated with 6.5 ($p=0.013$) and 7.7 ($p=0.007$) higher risk for PC death compared to active surveillance group. The difference in OS of surgery or radiation group compared to the active surveillance was not

statistically significant. There was no difference in OS or PC survival between active surveillance and surgery.

Figure 8: Kaplan-Meier curves of overall survival

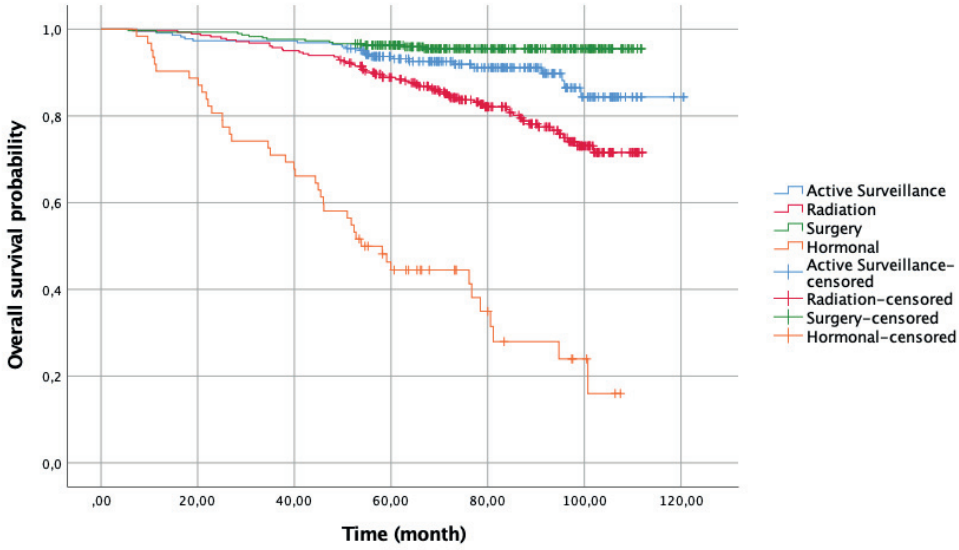
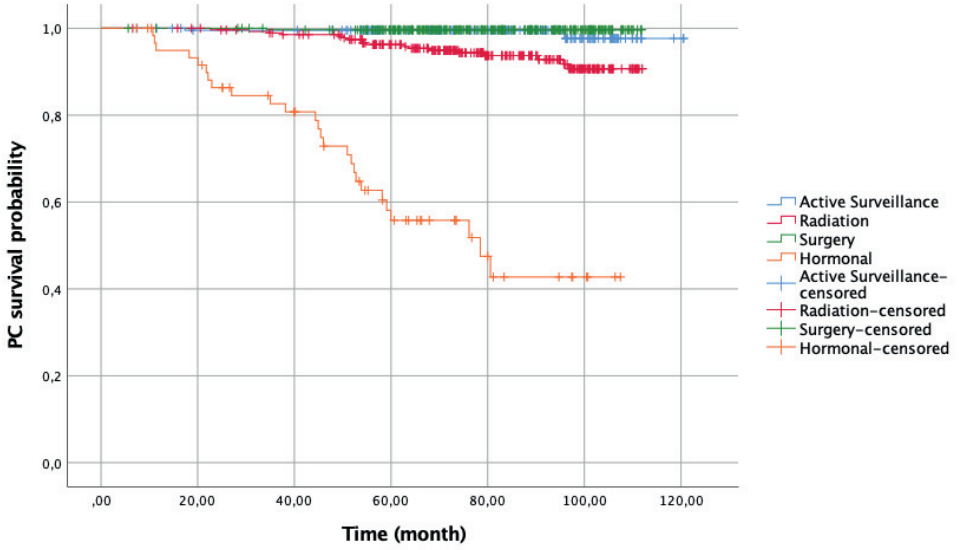


Figure 9: Kaplan-Meier curves of PC-specific survival



5.6. Association of HRQoL and survival (III)

Adding the total 15D score to the models for both overall survival and PC-specific survival improved the performance of the models in explaining the variance in survival. The estimated overall survival and PC-specific survival curves based on the Cox regression model 1 are presented in figures 10 and 11, respectively. A one-point increase in the 15D score (multiplied by 100) decreased the probability of death during the follow-up period by about 3.8 percentage points which, other things equal, is reflected in a hazard ratio of 0.962. Adding all 15D dimensions instead of the total 15D score to the models improved model performance even slightly more. However, the models became more complex without changing the overall picture compared to adding the 15D score alone. Besides, due to the high intercorrelations between many dimensions, it is not possible to estimate the contribution of separate dimensions. It seems though that usual activities, depression and sexual activity might be the most influential dimensions, which was the result when adding 15D dimensions using the stepwise enter method.

Figure 10: Overall survival curves based on Cox regression model

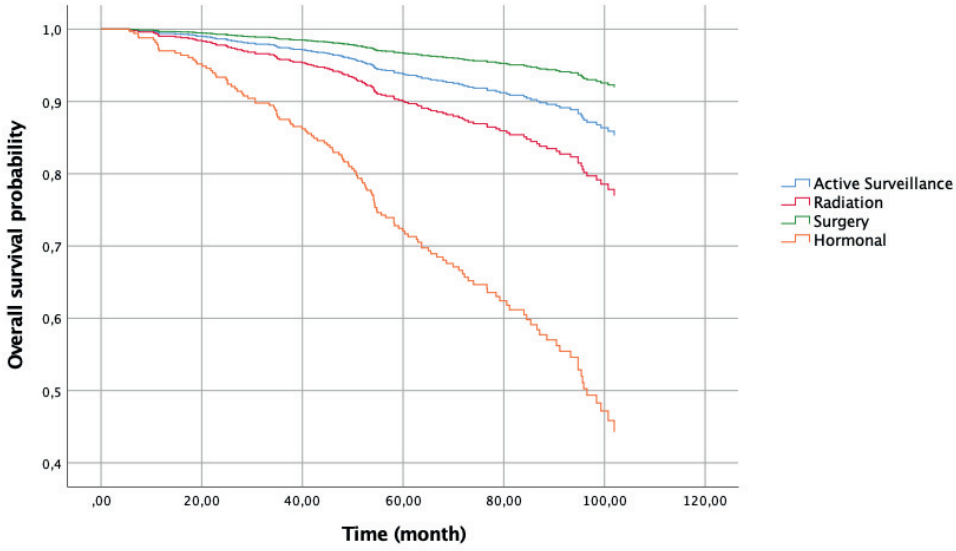
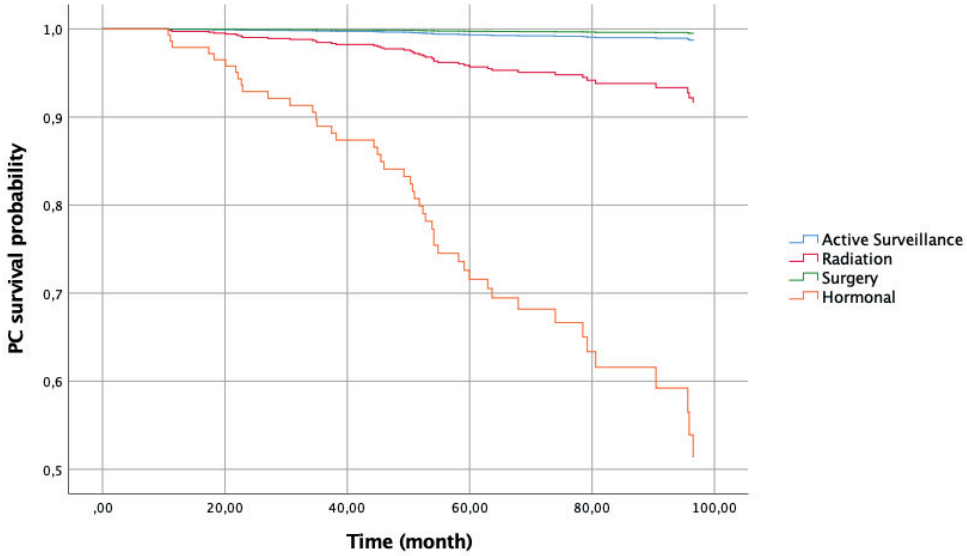


Figure 11: PC-specific survival curves based on Cox regression model



5.7. Quality-Adjusted Life Years (III)

The mean number of QALYs experienced by all PC patients during the two-year follow-up was 1.753 (Table 10). Without controlling for age and baseline 15D score, patients having undergone surgery experienced the highest number of QALYs (1.813). When controlling for age and baseline 15D, patients in the surgery group experienced 0.006 less QALYs compared to active surveillance (p=0.673). Patients in the hormonal treatment line experienced the lowest number of QALYs (1.452) with the difference being statistically significant compared to all other treatment lines. In the linear regression model age (p=0.027) and baseline 15D score (p<0.001) were statistically significant factors associated with the number of QALYs experienced.

Table 10: The number of QALYs experienced by treatment line for first two years after diagnosis

Treatment	Without controlling for age and baseline 15D			Controlled for age and baseline 15D			N
	Mean	95% CI	p-value*	Mean	95% CI	p-value*	
Active Surveillance	1.790	1.760 - 1.820		1.790	1.645 - 1.877		221
Radiation	1.723	1.653 - 1.793	0,001	1.767	1.602 - 1.883	0.115	269
Surgery	1.813	1.744 - 1.883	0.252	1.784	1.621 - 1899	0.673	294
Hormonal	1.452	1.357 - 1.547	<0.001	1.665	1.480 - 1.801	<0.001	59
Total	**1.753**						**843**

6. Discussion

6.1. Use of generic, single index HRQoL instruments in PC

In the systematic review, only 33 (1.5%) out of 2,171 abstracts fulfilled inclusion criteria in the reviewed period from 2002 to 2015. It was evident that, although we did not record the number of disease-specific HRQoL instruments, there is more research on the symptoms of the disease evaluated by using disease-specific instruments compared to generic HRQoL instruments. One of the main reasons for assessing HRQoL and QALYs is their usability in health economic analysis and policy decisions. Lack of published evidence on HRQoL in different stages of the disease and on the number of QALYs gained by different interventions may jeopardize a reliable health economic assessment.

In localized disease, disease-specific domains like urinary, sexual, and bowel function are the most profoundly affected domains, whereas, with some exceptions, general HRQoL usually remains mostly unaffected (Torvinen et al. 2013, Eton & Lepore 2002). The substantial disutility of asymptomatic disease was thought to reflect the anxiety caused by the uncertainty of not knowing whether the cancer would spread, rather than the current actual state of health (Stewart et al. 2005), highlighting the importance of psychological aspects in disease management. Longitudinal follow-up studies on HRQoL are needed to draw more accurate conclusions on the HRQoL impact of the side effects of the treatments in localized and early PC (Korfage et al. 2005).

In the advanced or metastatic disease stage, many reviewed articles focused on the HRQoL effects of skeletal-related events (SREs). Significant impacts on HRQoL were related to SREs (Reed et al. 2004, Weinfurt et al. 2005, Sullivan et al. 2007), although in one study, HRQoL decrements due to SREs were not statistically significant (Saad et al. 2002). This could have resulted from the insensitivity of the generic EQ-5D instrument that was used, although Weinfurt et al. (2005) and Sullivan et al. (2007) did find significant changes in HRQoL due to SREs using the same instrument. General population participants also rated significant disutility related to SREs when the TTO method was used (Matza et al. 2014).

Pain is a frequent symptom associated with SREs, and many HRQoL studies, therefore, incorporate disease-specific instruments such as the Brief Pain Inventory or the EORTC QLQ-C30, which includes

a pain domain. Only one of the studies covering the advanced/metastatic stage disease specifically focused on the HRQoL impact of palliative care (Färkkilä et al. 2014).

The overall limitation of direct valuation is that the utility theory suggests that utility assessment should be done in the general population who pay for health care (Torrance et al. 1972, Gold et al. 1996). It has also been suggested that population-based preferences are used in economic analyses. However, another view supported by some clinicians and researchers is that patients who have undergone the experience of a specific health condition are the best evaluators of the value of health states (experience-based valuations) (Gold et al. 1996). In instruments using indirect valuations, where weights from population-based preferences are used, this issue does not exist in the same sense.

Few of the articles examined how well the HRQoL results reported by PC patients and by care-givers/significant others are correlated (proxy approach). One of the reviewed articles concluded that utility scores derived from the patients' own health were higher than community-derived utilities (Krahn et al. 2003). Also, Stewart et al. (2005) found that men who had experienced impotence or urinary incontinence rated these conditions with higher utility scores than men who had not experienced these symptoms. In addition, Pearcy et al. (2008) found that patients' estimates of their HRQoL were higher than the estimates of their spouses or clinicians. These findings support the thinking that adaptation to a current health condition means that patients report higher utilities in comparison to the population. A common approach is that the patients themselves assess their own current state of health, which was also supported by the findings of this review.

6.2. HRQoL at time of the diagnosis

The mean 15D score of our patients did not differ from that of the age-standardized general male population, which is logical since most of the patients entering treatment were in the early phase of the disease. However, the baseline measurement was done with patients being aware of the diagnosis, which can impact especially psychological dimensions of HRQoL. The mean total 15D score of Local or Locally advanced patient groups was not different from that of the population, but

there was a statistically significant difference in depression and distress among all groups compared to the age-standardized population.

Although the mean 15D score in our total sample of patients did not differ from that of the age-standardized general male population, there was a statistically significant difference on seven dimensions; two in favor of the patients and five in favor of the population. One has to bear in mind though that with large sample sizes, like ours, even small differences can become statistically significant without necessarily reaching the level of clinical importance.

Six percent of the patients in this study were metastatic when they entered treatment, which is in line with what has been reported at the national level in Finland during 2013-2017, which was also 6% (Finnish Cancer Registry 2017). Metastatic patients suffered from impaired HRQoL, especially on the dimensions of excretion, sexual activity, and discomfort and symptoms. The Metastatic patients were, based on results obtained by both the 15D and the EORTC QLQ-C30 instruments, distinctly worse off than the localized PC patients. By contrast, the differences between Local and Locally advanced groups were, according to both instruments, small. When EORTC-QLQ-C30 and 15D were compared by their ability to detect differences between patient groups, no large discrepancy in HRQoL outcomes based on the different instruments was seen. The apparent differences in the contents of the two instruments are the lack of sexual and bladder functions in EORTC-QLQ-C30 and the lack of financial and social dimensions in the 15D. Sexual activity and excretion were found to be impaired already at baseline, which supports the usefulness of the 15D among PC patients.

A comparison of the HRQoL values to those reported in the literature is challenging as patient populations and HRQoL instruments used vary, as was seen in the literature review of this study. Torvinen et al. (2013) used the 15D to measure HRQoL and obtained similar values to ours. However, their study was cross-sectional, whereas the present study was longitudinal, which limits the direct comparison of the results. The most insightful comparisons in this study are thus changes over time in the same study group and the comparison to the age-standardized general male population from the same region.

6.3. Mapping of the EORTC QLQ-C30 to 15D

As was shown by the literature review in this study, the use of generic preference-based instruments that would allow the calculation of utilities suitable for calculating QALYs is scarce. Given the extensive use of EORTC QLQ-C30 also among PC patients, several mapping exercises have been performed to generate utility values from EORTC QLQ-C30 data. Mapping tools from EORTC QLQ-C30 exist mostly for the EQ-5D and mostly across all tumor types and not specifically for prostate cancer patients (Crott & Briggs 2010, Crott 2018, Woodcock et al. 2018, Doble & Lorgelly 2016, Kim et al. 2012). To my knowledge, only two other mapping studies besides the one done in this study have been done from EORTC QLQ-C30 into 15D values (Kontodimopoulos et al. 2009, Bastani & Kiadaliri 2012).

The explanatory power of the EORTC QLQ-C30 mapping model to the 15D score was as high as 79%, which indicates that EORTC scales explained well the variance of the 15D scores. The mean observed and predicted 15D scores were very close to each other in all disease groups. The RMSE, which indicates how close the predicted values were on average to the observed ones, was 0.042, which is a small number indicating the closeness of true and predicted values. Previous research on the mapping of the EORTC QLQ-C30 to the 15D is limited, but similar levels of model fitness indicators were reported by Kontodimopoulos et al. (2009), who reported an R2 of 0.909 and RMSE of 0.050 among gastric cancer patients (Kontodimopoulos et al. 2009). In addition, Bastani & Kiadaliri (2012) did a mapping of EORTC QLQ-C30 values to 15D, but similar model fitness parameters were not reported. Our results from the mapping exercise indicate that the 15D utility score aggregates quite accurately the information of the EORTC QLQ-C30 and the 15D is sensitive and usable also among PC patients. In the test of the internal validity of the mapping algorithm to the other half of the sample, predicted values were within the 95% confidence intervals of the observed values demonstrating the validity of the mapping algorithm. In addition, the test of external validity of the mapping algorithm, assessment to other populations, is strongly recommended as the generalizability of the mapping algorithm has not yet been tested. One should also be cautious when interpreting the results of the mapping as the sample in this study might not be representative.

The mapping algorithm was suitable for all disease stages in this study. The sample size that was used to build the model in metastatic patients was small (n=25), and especially among this patient group, caution should be used if the algorithm were to be applied to other populations. Disease

severity is known to be a factor when selecting the most suitable mapping algorithm to apply in practice (Woodcock et al. 2018), and utility values of all disease stages were at a relatively high level in this study. The OLS method was used as a regression method, which seems to be the most often used method in mappings done from EORTC QLQ-C30 to EQ-5D (Crott 2018, Doble & Lorgelly 2016, Crott & Briggs 2010). Although other regression models have also been widely tested, they do not seem to have performed superiorly over the regular OLS method (Doble & Lorgelly 2016, Woodcock et al. 2018).

6.4. Real-world outcomes of conventional treatment strategies in PC

The hormonal treatment group had the lowest HRQoL and survival among the studied treatment groups, and, consequently, also experienced the lowest number of QALYs during the two-year follow-up. Patients in the hormonal group were on average 10 years older than the rest of the patients, which is reflected on the survival and HRQoL outcomes of this group, and thus on overall number of QALYs experienced. Outcomes of the three other treatment groups were similar in terms of overall HRQoL and overall survival, and thus also regarding the number of QALYs experienced. However, in the radiation group, there were more PC-related deaths compared to the active surveillance and surgery groups. Unfortunately, data on length of radiation treatment were not available. Patients in the radiation group were on average 3 years older than the mean age of the study sample.

Our observation that patients in early stages of the disease and treated with active surveillance or surgery, are more likely to die from other causes than prostate cancer, is in line with earlier findings (Lloyd et al. 2015). Even though surgery is an invasive treatment, it did not differ from active surveillance in terms of QALYs experienced. Active surveillance retained the sexual function statistically significantly better than surgery. However, in the active surveillance group, HRQoL deteriorated during the second follow-up year, which may be explained by changed treatment strategies during the second year as a transition from active surveillance to surgery was relatively common. At baseline, average Gleason score of patients in the active surveillance group was 6.11. Many of the patients had a latent disease with a Gleason score of 3+3 at baseline, which is unlikely to impact HRQoL and survival.

Alanne et al. (2015) have assessed the clinical importance of changes in 15D scores. The changes in 15D scores between baseline and 24 months were -0.041; -0.039; -0.022; -0.149 for active surveillance, radiation, surgery, and hormonal treatments, respectively. When comparing these changes to the classification into global assessment scale categories suggested by Alanne et al. the change between 2 years and baseline measurement corresponded to the category of "much worse" for all treatment groups besides surgery, for which the change according to the categorization suggested by Alanne et al. is "slightly worse". It is to be noted though that these deteriorations cannot be attributed to PC and its treatments alone, as mere aging by two years in the age groups of PC patients reduces the mean 15D score by about 0.005 in the general male population.

Depression is a known response to a diagnosis of cancer unrelated to disease stage or severity at the time of the diagnosis (Korfage et al. 2006). In our study, baseline measurement was done when the patients were aware of the cancer diagnosis, and thus baseline score without the knowledge of the cancer diagnosis is not known. In the active surveillance group, there were slightly better scores on the depression dimension at the end of the follow-up compared to baseline (0.917, 0.914; 0.917; 0.930; 0.932 at baseline, 3, 6, 12 and 24 months, respectively.) There was a similar pattern of slight improvement at 24 months also in the radiation and surgery groups (radiation group 0.914; 0.900; 0.918; 0.911; 0.911 and surgery group 0.908; 0.896; 0.907; 0.908; 0.918), indicating that treatment did not have clinically significant impact on psychological dimensions of health. The depression dimension in the hormonal group remained most stable of all four groups, even though it was at the lowest level among all groups. HRQoL changes on psychological dimensions were overall minor. A similar finding was observed in a prospective study of 1643 localized prostate cancer patients for whom no significant differences were observed among the treatment groups of active surveillance, radical prostatectomy and radiotherapy in measures of anxiety or depression (Donovan et al 2016). There are studies investigating HRQoL impact of active surveillance vs. active treatment on psychological health domains and in many studies psychological domains have not been affected by active surveillance (Donovan et al. 2016, Bellardita et al. 2015, Carter et al. 2015), although also contradictory evidence exists (Ruane-McAteer et al. 2019, Watts et al. 2015).

Health dimensions of sexual activity and excretion were found to be affected by PC as was also found in earlier studies (Torvinen et al. 2013, Donovan et al. 2016, Barocas et al. 2017). Surgical treatment was associated with the largest decrease on the dimensions of sexual activity and

excretion immediately after treatment initiation, which is in line with previous findings (Donovan et al. 2016). In another cohort of men with localized prostate cancer, RP was associated with a larger decline in sexual function and urinary incontinence than radiotherapy (Barocas et al. 2017), which is also in line with the findings of this study and support usefulness of 15D in PC. The impairment of sexual activity in the hormonal group in our study may also be a consequence of the higher mean age in this treatment group.

Many studies investigating HRQoL outcomes of treatment strategies have utilized disease- or cancer-specific HRQoL instruments and focused on urinary, sexual and bowel functions, making direct comparisons to the results of our study difficult (Barocas et al. 2017, Donovan et al. 2016, Potosky et al 2004). A systematic review of disease-specific HRQoL instruments suggested that for a period of up to 6 years after treatment, men with localized prostate cancer who were managed with active surveillance reported good HRQoL. Men treated with surgery reported mainly urinary and sexual problems, while those treated with external beam radiotherapy reported mainly bowel problems. Men eligible for brachytherapy reported urinary problems for up to a year after therapy, but their HRQoL returned gradually to the level it was before treatment (Lardas et al. 2017). Findings regarding active surveillance and surgery were thus similar as in our study.

None of the HRQoL instruments has earlier been demonstrated to be better over another. As there is no "gold standard" HRQoL instrument, further work in HRQoL instruments' usability in different therapy areas is needed even though both the 15D and the EORTC QLQ-C30 were useful in this study among PC patients in various stages of the disease. The generic HRQoL instrument, 15D, provided a holistic view on patients' wellbeing and was sensitive to PC-specific morbidities. A benefit of using a generic HRQoL instrument is the possibility to compare utilities or incremental cost-effectiveness ratios between therapy areas in health economic analyses which allows prioritization of resources and subsequent health policies. However, it was not possible to draw clear conclusions about causalities between treatment and HRQoL as we were not able to stratify analyses with possible covariates including patients' societal and economic background factors. Since HRQoL is affected also by other parameters outside the scope of health care (Romero et al. 2013), more specific outcome parameters in addition to HRQoL could be useful in value assessments and for value-based pricing of health care interventions.

6.5. Association between HRQoL and survival

The results indicate that the total 15D score or certain HRQoL dimensions could provide added value in predicting patient survival. Earlier studies have shown that fatigue, pain, constipation, dyspnea, and cognitive function are associated with survival in patients with advanced PC (Braun et al. 2012, Halabi et al. 2008, Sullivan et al. 2006, Gupta et al. 2013). Thus, associations between advanced-stage PC survival and HRQoL may be stronger, but the sample size of advanced-stage patients in our study was too limited for analyzing this more thoroughly. The estimation of the impact of different 15D dimensions on survival is also complicated by the intercorrelations between some dimensions. However, our results seem to suggest that usual activities, depression, and sexual activity may be influential dimensions in overall survival. A larger number of later stage PC patients could have revealed associations of different dimensions better.

The prediction of PC progression is based on objective clinical parameters such as prostate-specific antigen (PSA) values and tumor progression. Several other prognostic factors have been identified related to demographic, genetic, physiological, comorbidity, lifestyle, biochemical, and medical factors (Merriel et al. 2018). It is clear that objective clinical parameters, such as PSA or Gleason score, cannot be bypassed in assessing the progression of the disease, but our study suggests that assessment of HRQoL could provide additional information for the prognosis of survival among many other factors. HRQoL may capture certain psychological or social elements contributing to overall health that might not be otherwise measurable in healthcare. HRQoL questionnaires provide a validated and standardized tool to formally capture those, otherwise perhaps less obvious, dimensions of health that could contribute even to survival.

Gotay et al. (2008) suggested that there are several possible explanations for the association between HRQoL and survival duration in cancer outcome studies, which were summarized into four categories 1) HRQoL measures reflect distinct aspects of well-being and may reflect biologic parameters not picked up by other prognostic indicators; 2) HRQoL data, especially those collected at baseline before disease progression, could pick up relevant information earlier than established clinical prognostic factors; 3) HRQoL data are markers of patients' health behavior that affect survival e.g., through medical adherence; and (4) HRQoL scores reflect individual characteristics such as personality style and adapting and coping strategies, which affect the disease process and outcomes in cancer patients. However, the impact of coping strategies on survival is not clear, and

no evidence was found in a systematic review about the influence of psychological coping on survival and recurrence in cancer patients (Petticrew et al. 2002).

6.6. Strengths and weaknesses of the study

The strengths of our study were relatively large sample of PC patients in Finland and relevant real-world outcomes of both HRQoL and survival of these patients. The medical era is moving towards personalized medicine, in which optimal treatment for each individual patient is carefully planned. In this context, emphasis is also placed on patients' own preferences. Our study contributes to the local real-world evidence, which can be helpful to patients and clinicians when matching optimal treatment lines to patients' personal preferences. In addition, the landscape of PC management will become more complex when new treatment strategies and pharmacotherapies emerge. Consequently, HRQoL and survival data from this study may be useful in future health economic evaluations of interventions to assess cost-effectiveness of treatments. There are also limitations to our study. These include the fact that due to the retrospective nature of the clinical background data, we were not able to control for additional factors such as socioeconomic background, income, education, marital status, or medical comorbidities. Since the survival of PC patients is good, a longer HRQoL follow-up period and/or a larger sample of advanced stage PC patients would have been needed to analyze associations between HRQoL dimensions and survival more thoroughly. Further analysis of HRQoL changes over time could also help to understand whether dynamic changes in HRQoL can predict survival better than the baseline information.

As is often the case with RWD, there is no randomized control group, and the only comparator group that was available for these data is the age-standardized male population living in the HUS area in 2011. Thus, it was not possible to draw conclusions about the incremental effectiveness of treatments, which is undoubtedly most convincingly done in an RCT setting. Most of the analyses of this study are descriptive and not comparative. As T-classification and Gleason score were not used as covariates in the survival models due to issues with multicollinearity, results about survival must be interpreted as descriptive rather than comparative between treatment lines. In addition, the unsystematic HRQoL data collection is clearly a limitation in this study and a possible source of bias. Data collection was concentrated on certain time periods as the collection was driven by few active study nurses at specific time periods. Still, the distribution of patients between study years was relatively even. The share of metastatic patients at the time of diagnosis is the same (6%) in this

study to what has been reported in Finland overall (Finnish Cancer Registry 2017). In Finnish Cancer Registry approximately 2/3 of the patients between 2013-2017 did not have information about the disease stage at the time of the diagnosis, which makes comparison of the share of local and locally advanced patients cumbersome, as one could assume that information at earlier stages of the disease is more likely recorded less accurately compared to those cases in which metastases are found.

6.7. Future research

This study was observational and did not aim to try to detect the relative effectiveness of various treatments. However, there has been an increase in the use of HRQoL and other PROs in medical research, and the use of these measures has become more common also in phase III RCT settings. However, their sensitivity to show differences between therapies in RCTs has been criticized, claiming that they may not be sensitive enough to capture subtle differences between therapies (Adamowicz 2017, Van Steen et al. 2002). If there are challenges in demonstrating HRQoL differences of treatments in RCTs, one might wonder, how can it be possible in a real-life situation where confounding factors are plenty. However, in RWD setting, sample sizes can be far greater compared to RCTs when, e.g. data are collected routinely in clinical practice, which helps to overcome some of the challenges. Still, careful consideration of the study setting, and design and analytical methods is needed to be able to conclude relative differences of interventions in a real-life setting and to avoid conclusion biases such as due to reverse causation (Franklin & Schneeweiss 2017). With more sophisticated data collection and quality registries, there are possibilities to generate information about relative effectiveness and cost-effectiveness of treatments more reliably and efficiently.

In addition to assessing the cost-effectiveness of healthcare, these data could be used to identify differences in care compared to other regions in Finland, offering the potential for improvements in health care systems and showing the differences in outcomes and quality of care. All healthcare districts are encouraged to collect and publish HRQoL data to be benchmarked to other districts. The 15D provides a useful preference-based HRQoL tool to be used among PC patients, but also other HRQoL instruments could be used to facilitate international comparisons. Especially in patients with later-stage disease, disease-specific instruments, such as the EORTC QLQ-C30 or its prostate-specific questionnaire EORTC QLQ-PR25 could be used. To reduce the patient burden of

answering multiple HRQoL questionnaires, wearable technologies and mobile applications can offer granularity over traditional sources of RWD, but their validity and applicability remain yet largely unknown (Booth et al. 2019).

RWD brings new possibilities to understand in more detail the true outcomes in healthcare. One of the goals in values assessments should also be to find parameters that will be actionable in terms of improvements needed in healthcare. In essence, this could mean that we shift from one-off HTAs into more dynamic Health Technology Management (HTM) in which continuous changes (e.g. in data, patient groups, treatment pathways) can be considered more flexibly, optimally resulting in producing more health with the same resources. One dimension which then comes essential is the time perspective in which HRQoL and other real-world outcomes are measured. Ideally, measures would be such that they provide fact access to steer healthcare to a new direction if outcomes and resource usage are not optimal. This also calls for automation and electronic collection of RWD measures so that data are readily available to patients, physicians, healthcare providers, and decision-makers. Also, if financial incentives are to be incorporated to support performance-based payments, the outcome measures linked to these payments need to be timely, measurable, and clinically relevant. HRQoL is a patient-centered outcome consisting of dimensions that could be linked to performance-based agreements between the healthcare provider and payer, but since there are many factors influencing HRQoL, careful planning is needed.

7. Conclusions and implications

The main conclusions from this study are:

HRQoL assessment in PC is an evolving field, but especially in the context of generic, preference-based, single index measures that can be used directly for QALY estimations, the literature is scarce. Given the fact that PC is one of the most common solid tumors with increasing incidence, it is important to focus on the treatment options and on their unique effects on the quantity and quality of life which is essential for a patient-centric and personalized health care.

The HRQoL of PC patients entering treatment was similar to that of the age-standardized general male population. HRQoL was most impaired among patients with metastatic disease, whereas the difference between patients with localized PC and the general population was minor. Psychological HRQoL dimensions in local stage PC were impaired at baseline compared to the population, but dimension level values of depression and distress recovered during follow-up.

Both HRQoL instruments, the 15D and the EORTC QLQ-C30, served well in providing HRQoL data of PC patients. Mapping indicated that the 15D score aggregates accurately the information from the EORTC QLQ-C30. The 15D dimensions of sexual activity and excretion showed similar responses as expected based on earlier research, validating the usefulness of the generic 15D instrument in PC.

Prostate cancer-specific survival of patients in the active surveillance and surgery groups was high. In the short-term, patients in the active surveillance, surgery, and radiation groups experienced a similar number of QALYs. By contrast, patients in the hormonal treatment group had significantly impaired HRQoL and survival compared to other treatments. Sexual activity and excretion were most affected health dimensions by PC.

Our study provides evidence that baseline HRQoL has prognostic value in assessing overall as well as PC-specific survival. Both total 15D score and certain 15D dimensions have prognostic value in predicting the survival of PC patients. To assess in more detail if HRQoL can help in predicting survival, dynamic changes over time and focus on advanced or metastatic stage patients is needed in further research.

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Appendices

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä terveydentilaanne. On tärkeää, että vastaatte kaikkiin 15 kysymykseen rastittamalla kustakin yhden vaihtoehdon.

1. Liikuntakyky

1 ☐ Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2 ☐ Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3 ☐ Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4 ☐ Pystyn kävelemään sisälläkin vain toisen avustamana.
5 ☐ Olen täysin liikuntakyvytön ja vuoteenoma.

2. <u>Näkö</u>

1 ☐ Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ☐ Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ☐ Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4 ☐ En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ☐ En näe kulkea oppaatta eli olen lähes tai täysin sokea.

3. <u>Kuulo</u>

1 ☐ Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
2 ☐ Kuulen normaalia puheääntä pienin vaikeuksin.
3 ☐ Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
4 ☐ Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ☐ Olen täysin kuuro.

4. <u>Hengitys</u>

1 ☐ Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ☐ Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
3 ☐ Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4 ☐ Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5 ☐ Minulla on hengenahdistusta lähes koko ajan, myös levossa.

5. Nukkuminen

1 ☐ Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.

2 ☐ Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.

3 ☐ Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.

4 ☐ Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.

5 ☐ Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

6. Syöminen

1 ☐ Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.

2 ☐ Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).

3 ☐ Tarvitsen hieman toisen apua syömisessä.

4 ☐ En pysty syömään itse lainkaan, vaan minua pitää syöttää.

5 ☐ En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

7. Puhuminen

1 ☐ Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.

2 ☐ Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.

3 ☐ Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.

4 ☐ Muilla on vaikeuksia ymmärtää puhettani.

5 ☐ Pystyn ilmaisemaan itseäni vain elein.

8. Eritystoiminta

1 ☐ Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.

2 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa.

3 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.

4 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.

5 ☐ En hallitse lainkaan virtsaamista ja/tai ulostamista.

9. Tavanomaiset toiminnot

1 ☐ Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).

2 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.

3 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.

4 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.

5 ☐ En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

10. Henkinen toiminta

1 ☐ Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.
2 ☐ Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti.
3 ☐ Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä.
4 ☐ Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä.
5 ☐ Olen koko ajan sekaisin ja vailla ajan tai paikan tajua.

11. Vaivat ja oireet

1 ☐ Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.
2 ☐ Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.
3 ☐ Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.
4 ☐ Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.
5 ☐ Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

12. Masentuneisuus

1 ☐ En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.
2 ☐ Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.
3 ☐ Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.
4 ☐ Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.
5 ☐ Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

13. Ahdistuneisuus

1 ☐ En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
2 ☐ Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
3 ☐ Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
4 ☐ Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.
5 ☐ Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

14. Energisyys

1 ☐ Tunnen itseni terveeksi ja elinvoimaiseksi.
2 ☐ Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.
3 ☐ Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.
4 ☐ Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".
5 ☐ Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

15. Sukupuolielämä

1 ☐ Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.
2 ☐ Terveydentilani vaikeuttaa hieman sukupuolielämääni.
3 ☐ Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.
4 ☐ Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.
5 ☐ Terveydentilani tekee sukupuolielämäni mahdottomaksi.

EORTC QLQ-C30 (VERSION 3.0.)

Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympyröimällä parhaiten sopiva numero. Tässä kyselyssä ei ole "oikeita" eikä "vääriä" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
Tuntuvatko rasittavat työt kuten painavan ostoskassin tai matkalaukun kantaminen teistä työläältä?	1	2	3	4
Tuntuvatko pitkät kävelymatkat työläiltä?	1	2	3	4
Tuntuvatko lyhyet kävelymatkat kotinne ulkopuolella työläiltä?	1	2	3	4
Pitääkö teidän pysytellä levolla tai istumassa päivän mittaan?	1	2	3	4
Tarvitsetteko apua ruokaillessanne, pukeutuessanne, peseytyessänne tai WC:n käytössä?	1	2	3	4

Kuluneella viikolla:	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
Oliko teillä vaikeuksia suoriutua työstänne tai muista päivittäisistä toimistanne?	1	2	3	4
Oliko teillä rajoituksia harrastus- tai muissa vapaa-ajan toiminnoissanne?	1	2	3	4
Oliko teillä hengenahdistusta?	1	2	3	4
Oliko kipuja?	1	2	3	4
Tunsitteko levontarvetta?	1	2	3	4
Oliko unettomuutta?	1	2	3	4
Tunsitteko heikotusta?	1	2	3	4
Oliko ruokahaluttomuutta?	1	2	3	4
Oliko pahoinvointia?	1	2	3	4
Oksensitteko?	1	2	3	4

Kuluneella viikolla:	**Ei lainkaan**	**Vähän**	**Melko paljon**	**Hyvin paljon**
Oliko ummetusta?	1	2	3	4
Oliko ripulia?	1	2	3	4
Olitteko väsynyt?	1	2	3	4
Häiritsikö kipu päivittäisiä toimianne?	1	2	3	4
Oliko teillä keskittymisvaikeuksia esim. sanomalehteä lukiessanne tai televisiota katsellessanne?	1	2	3	4
Olitteko jännittynyt?	1	2	3	4
Olitteko huolestunut?	1	2	3	4
Olitteko ärtynyt?	1	2	3	4
Olitteko masentunut?	1	2	3	4
Oliko teidän vaikea muistaa asioita?	1	2	3	4
Häiritsikö hoito tai fyysinen kuntonne perhe-elämäänne?	1	2	3	4
Häiritsikö hoito tai fyysinen kuntonne sosiaalista kanssakäymistä?	1	2	3	4
Aiheuttaako fyysinen kuntonne tai hoito taloudellisia vaikeuksia?	1	2	3	4

Vastatkaa seuraaviin kysymyksiin ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto

Millainen yleinen terveydentilanne oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono						Erinomainen

Millainen yleinen elämänne laatu oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono						Erinomainen

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