Tampere University

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Quality of Life in Prostate Cancer Patients after External Beam Radiotherapy, Docetaxel Chemotherapy and Combined Therapy

And the Impact of Comorbidity and Performance Status on the Survival after External Beam Radiotherapy

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the Auditorium F114
of the Arvo Building, Arvo Ylpön katu 34, Tampere,
on 29 September 2023, at 12 o'clock.

ACADEMIC DISSERTATION
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Finland

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-2927-3 (print)
ISBN 978-952-03-2928-0 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-2928-0

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2023

Dedicated to the loving memory of my grandfather Aapo and to the memory of my colleague Marie

ACKNOWLEDGEMENTS

This research work was carried out at twelve departments of oncology in three different countries: Tampere University Hospital, and Lahti and Seinäjoki Central Hospitals in Finland, Karolinska University Hospital, Uppsala University Hospital, Örebro University Hospital and Karlstad, Sundsvall, Eskiltuna, Vaxjö and Jönköping Hospitals in Sweden, and St Vincent's University Hospital in Dublin, Ireland.

This thesis would not have been possible without sufficient funding. I would like to thank Finnish Society for Oncology (Suomen Onkologiyhdistys) for providing me a personal grant which allowed me to work full-time on the dissertation and related studies for two months. I would like to acknowledge the role of other funders of professor Kellokumpu-Lehtinen that have supported the studies of the dissertation Competitive State Research Funding of the Expert Responsibility Area of Tampere University Hospital, Seppo Nieminen Foundation, Sanofi and Cancer Society of Finland.

I am deeply grateful to professor Pirkko-Liisa Kellokumpu-Lehtinen for her guidance and wisdom in the role of my principal supervisor, as well as agreeing to provide the role of custos. It is difficult to realise 10 years have passed since we began our collaboration in 2013, with my licentiate work that ultimately became Study I of this thesis.

My second supervisor, Jorma Sormunen, was also an important part of the group, providing the conclusive vote in the rare instances I and the professor did not agree on a particular detail. His more recent memories stemming from his own dissertation were valuable and gave motivation to carry out the project to this point.

I would like to thank my pre-examiners Sakari Karjalainen and Antti Rannikko for their much appreciated comments and words of wisdom that further improved this thesis. I thank Hanna Mäenpää for accepting the position of my opponent in my public defence.

The role of all authors in each study needs to be acknowledged, as well as the related primary endpoint publications. Special thanks to Petri Reinikainen, who was the first of author of Study II (while I was the second), and also participated in a significant role to Study I, attending our meetings with Pirkko, me and Lauri Heiskanen, and providing valuable practical knowledge there. Tiina Luukkaala had a

large role in the statistical analysis of Study IV, and also provided aid in the Study II, along with Harri Sintonen. Ilari Lehtinen had a significant part in the data collection, data management and statistical analysis in the studies II and IV.

This dissertation could not have been done without patients of course, and the support of their loved ones. Special credit for the participants of the prospective trials ESKO, SPCG-13 and PROSTY, who took part without certainty of a personal benefit for science and to provide valuable knowledge for the care of future patients. All research nurses and associated personnel deserve credit. My special thanks to Irja Kolehmainen in aiding with practical things, for example in matters related to my employment with the Science Centre and costs. I also thank Maarit Bärlund and Timo Joensuu for attending my follow-up group.

Leisure is as important as the work itself for a creative mind, and all of my friends (which luckily, I have so many) deserve credit, but I would like to especially mention Henri, Henrik, Mikko, Tatu, Topi and Ville. Finally, I would like to thank my family irreplaceable emotional support: my mother Jaana, my father Lasse, my sister Niina and her family, and my dear grandmother Liisa.

ABSTRACT

The evaluation of quality of life effects is a part of the process that new pharmaceuticals and medical devices should undergo before becoming part of clinical practice in prostate cancer treatment. In addition to the evaluation of quality-of-life effects, when choosing the optimal treatment modality for a patient, international guidelines also suggest assessment of the patient's life expectancy, which is in turn affected by the patient's comorbidity and performance status.

This dissertation addresses the effects of curative-intent external beam radiotherapy for prostate cancer on patient quality of life when given with docetaxel (Study III) or without it (Study II). The quality-of-life effects of different docetaxel regimens in metastatic, castration-resistant prostate cancer were studied in different docetaxel regimens (Study IV). The impact of comorbidity and performance status on survival outcomes was evaluated in patients treated with external beam radiotherapy given for local prostate cancer (Study I).

Study I was a retrospective study that consisted of patients of Tampere University Hospital treated with external beam radiotherapy between 2008 and 2013. Comorbidity was assessed by the Charlson Comorbidity Index (CCI) and performance status was assessed by the Zubrod Performance Status. The study showed, that high CCI scores (≥4 points) and Zubrod Performance Status values of one point or more are linked to higher all-cause mortality. Additionally, the general survival outcomes at Tampere University Hospital were determined.

Study II consisted of the participants of the ESKO-trial, whose quality-of-life results were compared with the general, age-standardised Finnish male population. In the ESKO trial, 73 patients with local, intermediate-risk prostate cancer were given external beam radiotherapy without androgen-deprivation therapy. Data collection was conducted prospectively, and the study was not randomized. Radiotherapy was either conventionally fractionated, moderately hypofractionated or stereotactic body radiation therapy. The quality-of-life results of ESKO participants were also compared to their pretreatment values. The results showed that the quality of life after treatment was similar to that of the general population and the pretreatment values. However, some aspects such as sexual activity were

worse after treatment and this particular facet remained poorer for a long period of time.

Study III consisted of patients who participated to SPCG-13 trial. In this prospective, randomized trial, 376 patients with local, intermediate- or high-risk prostate cancer were given radiation therapy (total dose of at least 74 grays) and androgen-deprivation therapy with LHRH-analogue for nine months. Furthermore, the intervention group was given 75 milligrams per square metre (mg/m^2) docetaxel every three weeks for six treatment cycles. The study reported decreased quality of life in the intervention arm in total quality-of-life score and in physical and functional well-being scores at six months, but the quality-of-life results in both arms were similar at one year and at four years.

Study IV investigated patients with metastatic, castration-resistant prostate cancer in the first-line treatment. It included participants from the prospective, randomized trial PROSTY. In the PROSTY trial, 361 participants were given docetaxel at a dosage of either 50 mg/m^2 every two weeks or docetaxel 75 mg/m^2 every three weeks. Additionally all patients were given prednisolone 10 milligrams a day. Neither treatment was superior in terms of quality of life. No large differences were found in quality-of-life subdomains, but the treatment given every two weeks may be superior to some extent in some aspects, such as emotional well-being.

In conclusion, the survival outcomes of external beam radiotherapy for local prostate cancer in Tampere University Hospital were good and equivalent to those in other high-income countries. The quality-of-life results were mainly comparable with those of the general population and the patient's pretreatment level. Conversely, docetaxel seems to affect quality of life negatively in patients with a local prostate cancer. In patients with a local disease, the need for such treatment should be carefully examined individually. In patients with metastatic, castration-resistant cancer, it is also important to find optimal dosing for patients to minimize harm and improve treatment outcomes.

TIIVISTELMÄ

Elämänlaatuvaikutusten arviointi on nykyään osa sitä prosessia, joka uusien lääkkeiden ja hoitolaitteiden tulisi käydä lävitse ennen päätymistään osaksi eturauhassyövän hoitokäytäntöjä. Elämänlaatuvaikutusten arvioimisen lisäksi hoitomuodon valinnassa tulisi ottaa kansainvälisten hoitosuositustenkin mukaan entistä enemmän huomioon potilaan elinajanodote, johon puolestaan vaikuttaa hänen muut sairautensa ja suorituskykynsä.

Tässä väitöskirjassa käsitellään paikallisen eturauhassyövään annetun parantamistavoitteisen ulkoisen sädehoidon vaikutuksia potilaan elämänlaatuun yhdistettynä doketakseliin (Osatyö III) tai ilman sitä (Osatyö II). Etäpesäkkeisen, kastraatioresistentin syövän osalta tarkastellaan erilaisten doketakseliannosteluiden vaikutusta elämänlaatuun (Osatyö IV). Monisairastavuutta ja suorituskykyä arvioitiin paikalliseen eturauhassyöpään potilaille annetun ulkoisen sädehoidon osalta tutkien, miten se vaikuttaa hoitotuloksiin (Osatyö I).

Osatyössä I tutkittiin retrospektiivisesti Tampereen yliopistollisen keskussairaalan vuosina 2008–2013 parantamistavoitteista sädehoitoa saaneet potilaat. Monisairastavuutta arvioitiin Charlsonin komorbiditeetti-indeksillä ja suorituskyvyn tilaa Zubrod-luokituksella. Osatyössä todettiin, että suuri Charlsonin komorbiditeetti-indeksin arvo (≥4 pistettä) ja Zubrod-luokituksen arvo yksi tai enemmän, ovat yhteydessä suurempaan kaikista syistä johtuvaan kuolleisuuteen. Lisäksi määritettiin Tampereen yliopistollisen sairaalan hoidon tuloksellisuus yleisellä tasolla tutkimuspopulaatiossa.

Osatyö II koostui ESKO-tutkimukseen osallistuneista potilaista, joiden elämänlaatua verrattiin yleiseen, suomalaiseen ikävakioituun miesväestöön. ESKO-tutkimuksessa 73 potilasta, joilla oli keskisuuren riskin paikallinen eturauhassyöpä, saivat ulkoisen sädehoidon ilman mieshormonin toimintaan vaikuttavaa hoitoa. Aineistonkeruu tehtiin prospektiivisesti, ja tutkimus oli satunnaistamaton. Sädehoito oli joko perinteiseen tapaan fraktioitua, kohtalaisesti hypofraktioitua tai stereotaktista sädehoitoa. ESKO-potilaiden elämänlaatua verrattiin myös heidän hoitoa edeltävään tasoonsa. Tulosten mukaan sädehoito ei heikentänyt potilaiden kokonaiselämänlaatua verrattuna yleiseen väestöön tai hoitoa edeltävään tasoon. Silti jotkin osa-alueet, kuten seksuaalinen aktiivisuus, heikkenivät hoidon jälkeen ja

verrattuna yleiseen väestöön, ja tämä nimenomainen osa-alue myös jäi vertailukohteita heikommaksi pitkäksi aikaa.

Osatyössä III tutkittiin SPCG-13 tutkimukseen osallistuneita potilaista. Tässä prospektiivisessa, satunnaistetussa tutkimuksessa kaikki 376 paikallista, suuren tai keskisuuren riskin eturauhassyöpää sairastavat potilasta saivat sädehoidon (kokonaisannos vähintään 74 grayta) ja yhdeksän kuukauden mieshormonin vaikutuksia vaimentavan hoidon LHRH-analogilla. Lisäksi interventioryhmä sai doketakselia 75 milligrammaa per neliömetri (mg/m^2) kolmen viikon välein yhteensä kuusi sykliä. Osatyössä todettiin interventioryhmän elämänlaadun heikenneen kokonaiselämänlaadun, fyysisen ja toiminnallisen hyvinvoinnin osalta kuuden kuukauden kohdalla verrokkeihin verrattuna, muttei enää vuoden tai neljän vuoden kohdalla.

Osatyössä IV tutkittiin levinnyttä, kastraatioresistenttiä eturauhassyöpää sairastavia potilaita ensilinjan hoidossa. Se koostui prospektiivisen, satunnaistetun PROSTY-tutkimuksen potilaista. PROSTY-tutkimuksessa, 361 osallistujaa sai doketakselia joko annoksella 50 mg/m^2 kahden viikon välein tai 75 mg/m^2 kolmen viikon välein. Lisäksi kaikki potilaat saivat prednisolonia 10 milligrammaa vuorokaudessa. Kokonaiselämänlaadun osalta tulokset olivat samankaltaisia molemmissa ryhmissä. Suuria eroja erilaisissa elämänlaadun osa-alueissakaan ei todettu, mutta kahden viikon välein annettava hoito saattaa olla tietyiltä osilta parempi esimerkiksi emotionaalisen hyvinvoinnin kannalta.

Kokonaisuutena paikallisen eturauhassyövän sädehoidon hoitotulokset todettiin Tampereen yliopistollisessa sairaalassa hyviksi ja korkean tuloluokan maita vastaaviksi sekä elossaoloon, leviämiseen että paikalliseen uusiutumaan liittyvien muuttujien osalta. Elämänlaatutulokset tässä hoidossa vastaavat pitkälti yleistä väestöä sekä potilaan hoitoa edeltävää tasoa. Doketakselihoitoon sen sijaan liittyy elämänlaatuhaittoja paikallisessa eturauhassyövässä. Paikallisessa syövässä sen tarvetta tulee yksilöllisesti tarkoin harkita, ja myös levinneessä, etäpesäkkeisessä syövässä optimaalisen annostelun löytäminen haittojen minimoiseksi ja hoitotuloksen parantamiseksi on tärkeää.

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ABBREVIATIONS

3-D = three-dimensional
ADT = androgen-deprivation therapy
AFU = Association Française d'Urologie (French Association of Urology)
AIDS = acquired immune deficiency syndrome
AJCC = American Joint Committee on Cancer
ALP = alkaline phosphatase
ALSYMPCA =Alpharadin in Symptomatic Prostate Cancer (trial)
ANCOVA = analysis of covariance
APCCC = Advanced Prostate Cancer Consensus Conference
AR = androgen receptor
AS = active surveillance
ASTRO = American Society for Radiation Oncology
ATM = Ataxia Telangiectasia Mutated gene
AUA = American Urological Association
BC = bladder cancer
BFI = Brief Fatigue Inventory
BPI-SF = Brief Pain Inventory Short Form
BR = biochemical recurrence
BRCA1 = Breast Cancer Susceptibility Gene type 1
BRCA2 = Breast Cancer Susceptibility Gene type 2
BRFS = biochemical recurrence free survival
BPH = Benign prostatic hyperplasia
BT = brachytherapy
CCI = Charlson Comorbidity Index
CI = confidence interval
CPG = Cambridge Prognostic Group
CRPC = castration-resistant prostate cancer
CRT = conformal radiotherapy
CT = computer tomography
CYP = cytochrome P450
DHT = dihydrotestosterone

DRE = digital rectal examination
EANM = European Association of Nuclear Medicine
EAU = European Association of Urology
EBRT = external beam radiotherapy
ECOG = Eastern Cooperative Oncology Group
ED = erectile dysfunction
EMA = European Medicines Agency
EORTC = European Organisation for Research and Treatment of Cancer
EPIC = Expanded prostate cancer index composite (questionnaire)
EPLND = extended pelvic lymph node dissection
EQ-5D = EuroQoL 5-dimension (questionnaire)
EQ-5D-3L = EuroQoL 5-dimension 3-level (questionnaire)
EQ-5D-5L = EuroQoL 5-dimension 5-level (questionnaire)
EPV = event per variable
ESMO = European Society of Medical Oncology
ESTRO = European Society of Radiation Oncology
ETS = Erythroblast Transformation Specific (proteins)
ESUR = European association of urology Section of Urological Research
EWB = emotional well-being (subscale in FACT-P questionnaire)
F-18 = fluorine-18
FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue (questionnaire)
FACT-G = Functional Assessment of Cancer Therapy – General (questionnaire)
FACT-P = Functional Assessment of Cancer Therapy – Prostate (questionnaire)
FACT-Taxane = Functional Assessment of Cancer Therapy – Taxane (questionnaire)
FAPSI-6 = Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 6 Item Version (questionnaire)
FAPSI-8 = Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 8 Item Version (questionnaire)
FDA = the United States Food and Drug Administration
FFS = failure-free survival (biochemical or clinical progression)
fr = fraction
frs = fractions
FSH = follicle-stimulating hormone
FWB = functional well-being (subscale in FACT-P questionnaire)
GETUG = Groupe d'Etude des Tumeurs Uro-Génitales

GI = gastrointestinal
GU = genitourinary
HADS = Hospital Anxiety and Depression Scale
HDR = high-dose rate
HGPIN = high-grade intraepithelial neoplasia
HMDP = hydroxymethylene diphosphonate
HR = hazard ratio
HRF = high risk feature
HRQoL = health-related quality of life
i.e. = id est, that is
ICIQ = International Consultation on Incontinence Questionnaire
ICSmaleSF = International Continence Society male Short-Form (questionnaire)
IGRT = image-guided radiotherapy
IIEF-5 = International Index of Erectile Function
IMRT = intensity-modulated radiation therapy
IPSS = International Prostatic Symptom Score
IRF = intermediate risk feature
ISOQOL = International Society for Quality of Life Research
ISUP = International Society of Urological Pathology
ISUP GG = International Society of Urological Pathology Grade Group
iv. = intravenous
KPS = Karnofsky Performance Status
LDR = low-dose rate
LE = life expectancy
LH = luteinizing hormone
LHRH = Luteinizing-Hormone Releasing Hormone
Lu-177 = lutenium-177
LUTS = lower urinary tract symptoms
MDP = methylene diphosphonate
MFS = metastasis-free survival
mCRPC = metastatic castration-resistant prostate cancer
mHSPC = metastatic hormone-sensitive prostate cancer
MID = minimum important difference
mPC = metastatic prostate cancer
MRI = magnetic resonance imaging
MSKCC = Memorial Sloan Kettering Cancer Centre
N = number (sample size)

NaF = sodium fluoride
NCCN = National Comprehensive Cancer Network®
NICE = National Institute for Health and Care Excellence
nmCRPC = non-metastatic castration-resistant prostate cancer
NNS = number needed to screen
NNT = number needed to treat
NZGG = New Zealand Guidelines Group
OCM = other-cause mortality
OM = overall mortality
OR = odds ratio
OS = overall survival
P = *P*-value
PAP = prostatic acid phosphatase
PARP = poly (ADP-ribose) polymerase
PC = prostate cancer
PCS = prostate cancer subscale (in FACT-P questionnaire)
PCSM = prostate cancer-specific mortality
PCSS = prostate cancer-specific survival
PEACE = Prostate Cancer Consortium in Europe
PET = Positron emission tomography
PFS = progression-free survival
PI-RADS® = Prostate Imaging - Reporting and Data System
PPI = Present Paint Intensity (item in the McGill-Melzack questionnaire)
PROs = patient-reported outcome measures
PSA = Prostate-specific antigen
PSA-dt = Prostate-specific antigen doubling time
PSAD = Prostate-specific antigen density
PSAV = Prostate-specific antigen velocity
PSMA = Prostate-specific membrane antigen
PTEN = Phosphatase and Tensin homolog gene
PWB = physical well-being (subscale in FACT-P questionnaire)
QALY = quality-adjusted life-year
QLQ = Quality of Life Questionnaire
QoL = Quality of Life
Ra-223 = radium-223
RC = rectal cancer
RCT = randomized controlled trial

RNA = Ribonucleic acid

RP = radical prostatectomy

rPFS = radiographic progression-free survival

RT = radiation therapy

RTOG = Radiation Therapy Oncology Group

SBRT = stereotactic body radiation therapy

SD = standard deviation

SEM = standard error of measurement

SF-12 = Medical Outcomes Study 12-Item Short-Form General Health Survey

SF-8 = Medical Outcomes Study 8-Item Short-Form General Health Survey

SF-MPQ = Short-Form McGill Pain Questionnaire

SIOG = International Society of Geriatric Oncology/Société Internationale d'Oncologie Gériatrique

SOC = standard of care

SPCG = Scandinavian Prostate Cancer Group

SPECT = single photon emission computed tomography

SRT = salvage radiotherapy

SWB = social/family well-being (subscale in FACT-P questionnaire)

SWOG = Southwest Oncology Group

Tc = technetium

Tc-99m = metastable technetium-99

TF = treatment failure

TOI = Functional Assessment of Cancer Therapy – Prostate Trial Outcome Index

TS = total score (in FACT-P questionnaire)

TURP = transurethral resection of the prostate

UCLA PCI = University of California, Los Angeles Prostate Cancer Index

UI = urinary incontinence

UK = the United Kingdom

US = the United States (of America)

USPSTF = the United States Preventive Services Task Force

VAS = visual analogue scale

VHRF = very high-risk feature

VMAT = volumetric arc radiation therapy

vs. = versus

WHO = World Health Organization

Z = Zubrod score

Trial acronyms and full titles

AFFIRM = A multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in patients with progressive castration-resistant prostate cancer previously treated with docetaxel based chemotherapy

ARAMIS = Androgen Receptor Antagonizing Agent for Metastasis-free Survival

ARASENS = Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer

ARCHES = A phase III, randomized, double-blind, placebo-controlled study of enzalutamide + androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer

ASCENDE-RT = Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy

CARD = Cabazitaxel versus abiraterone or enzalutamide

CHAARTED = Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer

CHHiP = Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer

COU-AA = Cougar (biotechnology) Abiraterone Acetate (study)

DETECTIVE = Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative

ENZAMET = Enzalutamide in the First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer

ERSPC = European Randomized Study of Screening for Prostate Cancer

FIRSTANA = Randomized, open label, multi-centre study comparing cabazitaxel at 25 mg/m^2 and at 20 mg/m^2 in combination with prednisone every 3 weeks to docetaxel in combination with prednisone in patients with metastatic castration resistant prostate cancer not pre-treated with chemotherapy

HYPO-RT-PC = a phase III study of HYPOfractionated RadioTherapy of intermediate risk localised Prostate Cancer

HYPRO = Hypofractionated versus conventionally fractionated radiotherapy for patient with prostate cancer

IMPACT = Identification of Men with a genetic predisposition to Prostate Cancer/Immunotherapy for Prostate Adenocarcinoma Treatment

LATITUDE = Long-acting therapy to improve treatment success in daily life

NHS 2011 = National Health Survey 2011

PACE-B = Prostate Advances in Comparative Evidence B

PCOS = Prostate Cancer Care and Outcomes Study

PREVAIL = A multinational phase 3, randomized, double-blind, placebo controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy

PROfound = A study of olaparib versus enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer

PROSELICA = Randomized, open label multi-centre study comparing cabazitaxel at 20 mg/m^2 and at 25 mg/m^2 every three weeks in combination with prednisone for the treatment of metastatic castration resistant prostate cancer previously treated with a docetaxel-containing regimen

PROSTY = A Phase III Trial comparing docetaxel every third week to biweekly docetaxel monotherapy in metastatic hormone refractory prostate cancer patients

ProtecT = Prostate Testing for Cancer and Treatment

STAMPEDE = Systematic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

ORIGINAL PUBLICATIONS

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

Publication I **Lehtonen M**, Heiskanen L, Reinikainen P, Kellokumpu-Lehtinen PL. Both comorbidity and worse performance status are associated with poorer overall survival after external beam radiotherapy for prostate cancer. BMC Cancer. 2020 Apr 15;20(1):324.

Publication II Reinikainen P, **Lehtonen M**, Lehtinen I, Luukkaala T, Sintonen H, Kellokumpu-Lehtinen PL. Health-related Quality of Life of Patients Treated With Different Fractionation Schedules for Early Prostate Cancer Compared to the Age-standardized General Male Population. Clin Genitourin Cancer. 2022 Aug 3:S1558-7673(22)00168-9.

Publication III **Lehtonen M**, Sormunen J, Hjälm-Eriksson M, Thellenberg-Karlsson C, Huttunen T, Ginman C, Kellokumpu-Lehtinen PL; Investigators of the Scandinavian Prostate Cancer Group Study No 13. Health-related Quality of Life in Intermediate- or High-risk Patients Treated With Radical External Radiotherapy and Adjuvant Docetaxel for Localized Prostate Cancer: A Randomized, Phase III SPCG-13 Study. Anticancer Res. 2022 Jan;42(1):87–92.

Publication IV **Lehtonen M**, Sormunen J, Luukkaala T, Marttila T, McDermott R, Joensuu T, Lehtinen I, Ginman C, Kellokumpu-Lehtinen PL. 2-weekly versus 3-weekly docetaxel for metastatic castration-resistant prostate cancer: complete quality of life results from the randomised, phase-III PROSTY trial. Acta Oncol. 2022 Aug;61(8):963–971.

AUTHOR'S CONTRIBUTION

Publication I	Writing of the original draft and revisions according to the peer-review, statistical analysis, visualization, data collection, conceptualization.
Publication II	Writing of the original draft with the first author of the article. Miikka Lehtonen's remit included the sections Introduction, Discussion and Limitations. Abstract was produced jointly with the first author. Revisions according to the peer-review with the first author. Visualization (reference management in particular). M.L. also provided his expertise on conceptualization (including participation in meetings) and methodology/validation (statistical advice and scientific views based on the previous experience from other works to be considered for the first author).
Publication III	Writing of the original draft and revisions according to the peer-review, conceptualization, interpretation of statistical analyses, visualization (with the team statistician).
Publication IV	Writing of the original draft and revisions according to the peer-review, conceptualization, statistical analysis (with the team statistician), visualization (with the team statistician), data curation.

Publication II is used with the first author's permit in the dissertation.

1 INTRODUCTION

Prostate cancer (PC) is the most common cancer in Finland by incidence and the fourth most common cancer globally [1,2]; therefore, the importance of PC research is easy to understand. However, despite its malignant nature, PC is not a particularly deadly disease. In Finland, only approximately 28% of men diagnosed with PC die because of it, and the five-year cancer-specific survival rate was 94% in 2020 [1]. Nevertheless, metastatic prostate cancer (mPC) remains incurable [3], motivating drug research to find even more efficient pharmaceuticals to prevent local PC from progressing to a metastatic stage and prolong the life expectancy (LE) of those who already have metastatic disease.

A proportion of PC cases are discovered by using prostate-specific antigen (PSA) in the very early phases of the disease, and the median age of those diagnosed is over 70 years [4], which sets a special challenge for a physician in balancing the benefits and harms of treatment. While the harms of the treatment may show instantaneously, the benefit of treating a low-risk local disease may not show until after 5−10 years [5]. Reporting quality-of-life (QoL) results was not customary in clinical trials until the 1990s [6]. Since the 2010s, reporting QoL results has been considered a standard for a well-designed randomized controlled trial (RCT) [7]. However, unfortunately, there are still agents introduced in the market with limited or unpublished QoL data. In addition, most clinical trials include only patients who are either very or quite fit, and many elderly men with common diseases, such as renal failure or heart disease, are prevented from entering these trials. This leaves oncologists, urologists or consulting geriatricians wondering whether a particular patient would benefit from curative or life-prolonging treatment or if it would be best to just watchfully wait and treat the symptoms if needed.

This work adds to the knowledge of certain particulars of the PC treatment pathway, namely, the effect of comorbidities and patient performance scores in the treatment of local PC with radical external beam radiotherapy (EBRT), QoL effects of EBRT treatment with or without adjuvant docetaxel treatment for local PC, and the QoL effects of biweekly dosing of docetaxel 50 milligrams per square metre (mg/m^2) compared to the standard triweekly 75 mg/m^2 dosage in metastatic castration-resistant prostate cancer (mCRPC). Hopefully, these results can be used

to improve the principles of personalized and patient-shared decision-making in clinical practice.

2 REVIEW OF THE LITERATURE

2.1 Prostate anatomy

The prostate is a part of the male urogenital system. It is located in the true pelvis, posterior to the pubic symphysis, inferior to the urinary bladder and anterior to the rectum [8,9]. The prostatic part of the urethra pierces the prostate, easily causing urinary obstruction in cases of prostate hyperplasia [10,11]. Posterior to the prostate lie paired seminal vesicles [12]. Their ducts combine with the vasa deferentia to form the ejaculatory ducts, which then penetrate the prostate and open into the urethra inside the prostate [9,12]. The regional anatomy is depicted in Figure 1.

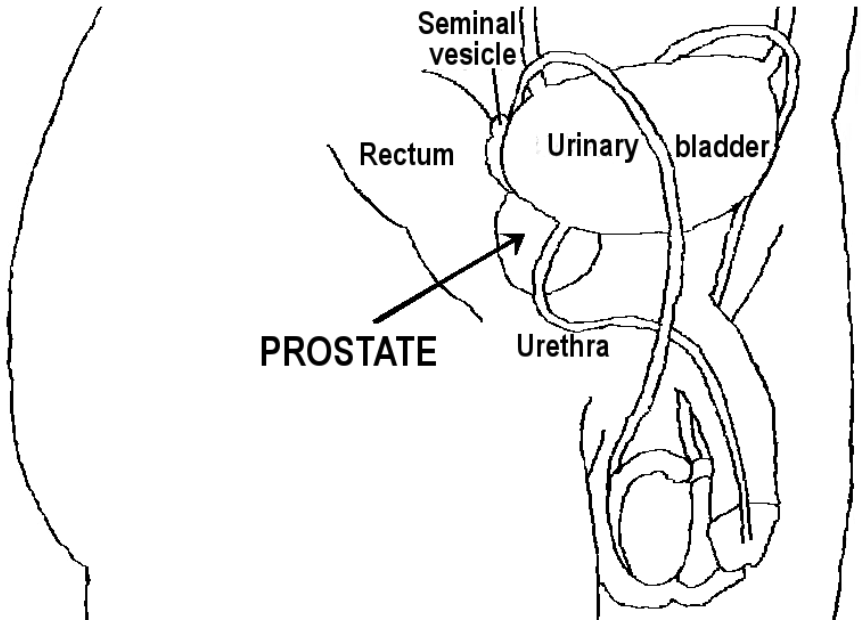

Figure 1. The macroscopic anatomy of the prostate and the surrounding organs. The paired seminal vesicles lie posteriorly and superiorly to the prostate and posterior to the urinary bladder.

The prostate is supplied by paired prostatic arteries, usually one on each side [13]. Veins circumventing the prostate form a plexus that eventually drains to the internal iliac veins [10]. Lymphatic drainage occurs in the internal iliac and sacral lymph nodes [10].

The prostate is innervated by the prostatic nerve plexus [9]. This plexus originates from paired inferior hypogastric plexuses [9]. The inferior hypogastric plexus includes sympathetic fibres from hypogastric nerves and parasympathetic fibres from pelvic splanchnic nerves [9]. Pelvic splanchnic nerves originate from nerve roots S2 to S4 [9].

The prostate is divided into four zones: central, peripheral, transitional and periurethral [12]. The prostate is largely covered by a thin fibromuscular band, which may be clinically referred to as a 'capsule' [14].

2.2 Histology of the prostate

The prostate consists of 30–50 tubuloalveolar glands, which are positioned in three layers [12]. The innermost layer is the mucosal layer, where the glands secrete directly into the urethra [12]. The outermost layer is the peripheral layer, which contains the main prostatic ducts, and the intermediate layer lies between the two [12]. The peripheral and intermediate layers have ducts that lead into the prostatic sinuses located on the posterior wall of the urethra [12]. The glands comprise mainly simple columnar epithelium [12].

The central zone is located around the ejaculatory ducts and comprises approximately one-quarter of the glandular tissue [12]. The peripheral zone forms the bulk of the prostate (approximately 70% of the glandular tissue) and encircles the other zones from all directions, except anterosuperiorly where the anterior fibromuscular stroma is located [12].

2.3 Physiology of the prostate

The prostate is a male accessory sex organ along with the bulbourethral, urethral and preputial glands, seminal vesicles and ampullae of the vasa deferentia [15]. These glands produce approximately 95% of seminal fluid and contribute to male fertility by secreting various substances that protect the viability and fertilization capability

of the sperm and mucus to prevent entrapment of sperm in the walls of the urethra [16–18].

Male sex hormones, such as testosterone and adrenal androgens, are needed for prostate growth and homeostasis [12,19]. Prostatic glandular epithelium converts testosterone to dihydrotestosterone (DHT), which is approximately 50 times more potent than testosterone, through the enzyme 5α-reductase [12]. DHT stimulates the growth and proliferation of prostatic glandular cells [12]. Growth is downregulated by prostatic acid phosphatase (PAP) [20].

2.4 Pathology of prostate cancer

Similar to cancers in general, PC occurs when either acquired or germline mutations in genes promoting cell growth (proto-oncogenes), inhibiting cell growth (tumour suppressors), regulating apoptosis, or involving DNA repair cause a cell to divide uncontrollably, heedless of external impulses, in a process called carcinogenesis [21]. Usually, more than one mutation in one gene is needed to cause cancer [22]. Over a variable amount of time, dysplastic cells acquire the ability to invade surrounding tissues and metastasize to distant organs [23]. Cancerous cells move towards dedifferentiation, which means that they resemble the tissue of origin less and become more similar to embryonic stem cells [24]. Anaplastic tumours have a higher rate of metastases and mortality than well-differentiated tumours [25].

Approximately 98% of PCs are adenocarcinomas [4]. Types of prostate cancer based on the 2016 World Health Organization (WHO) classification and their relative incidence are shown in Table 1.

Table 1. Primary prostatic malignancies and their proportional incidence. Adapted from [26]

Cancer subtype	Relative incidence
Adenocarcinoma	Approximately 98% [4], over 95% [27]
Ductal adenocarcinoma	<1% [28]
Urothelial carcinoma	0.7−3.8% [28]
Squamous cell carcinoma	0.5−1.0% [29]
Intraductal carcinoma	0.26% [30]
Adenoid cystic/basal cell carcinoma	Very rare [31]
Adenosquamous carcinoma	Very rare [32]
Neuroendocrine tumour	Approximately 1% [33]
Mesenchymal tumour (incl. sarcoma)	<1% [34]
Lymphoma	0.09% [35]
Other miscellaneous tumours	Very rare [36–40]

2.5 Gleason classification and International Society of Urological Pathology grading

Histopathologically, adenocarcinomas of the prostate are graded by the Gleason system developed by pathologist Donald F. Gleason in 1966 [41–43]. In the WHO Classification of Tumours, it has been the sole classification system for prostate adenocarcinomas since 2004, replacing the previous Mostofi grading [43]. The classification system underwent a major revision at the International Society of Urological Pathology (ISUP) Consensus Conference in 2005 and some minor changes again at the 2014 and 2019 ISUP conferences [44–46]. Atypic structures are graded between I and V, where grade I is the most well-differentiated pattern and grade V is the most anaplastic [47]. The pathologist then identifies the two most frequent patterns in the tumour and sums the numerical values of the corresponding grades to obtain the Gleason score (GS) [47]. If there is only one pattern present, the numerical value of the pattern is multiplied by two [47]. Gleason patterns I and II are no longer used in clinical practice due to poor reproducibility and poor correlation between biopsy samples and samples obtained during the surgical removal of the prostate [48]. A more detailed description of grading is shown in Table 2.

At the 2014 Conference, the ISUP released a competing model for pathological grading [45,49]. The grades are directly derived from Gleason scores [49]. ISUP grade group (ISUP GG) 1 corresponds to GS ≤6, ISUP GG 2 corresponds to GS 3+4, ISUP GG 3 corresponds to GS 4+3, ISUP GG 4 corresponds to GS 8 and ISUP GG 5 corresponds to GS 9−10 [49].

Table 2. Description of Gleason patterns. Gleason score = the most frequent pattern + the second most frequent pattern. Adapted from [48]

Gleason pattern	Description
I	Not used, corresponds to benign adenosis
II	Not used, samples previously considered pattern II are now usually classified as pattern III
III	Well-formed discrete glands that may vary in size, including branching glands
IV	Poorly formed, fused, cribriform or glomeruloid glands
V	Barely glandular structures. Cancerous cells form sheets, cords, or solid nests or are unorganized. If comedonecrosis is present within solid nests or cribriform glands, the pattern is also considered type V.

2.6 Aetiology and epidemiology of prostate cancer

PC had the highest incidence and second-highest prevalence of all malignant tumours in Finland in 2020 [1]. It caused the fourth most cancer-related deaths in Finland in 2020 according to the GLOBOCAN 2020 database [2]. Globally, it was the fourth most diagnosed cancer in 2020 and caused the ninth most cancer-related deaths [2]. The incidence of PC varies greatly in different parts of the world [2]. The age-adjusted incidence was the highest in western and northern Europe, North America and the Caribbean, and the highest estimated age-adjusted incidence in 2020 was in Ireland, with 110.7 new cases per 100 000 men [2]. The age-adjusted incidence was lowest in the Middle East and in East Asia [2]. The lowest estimated age-adjusted incidence was in Bhutan, with only 0.9 cases per 100 000 men in 2020 [2].

It is important to distinguish clinically significant PCs from those that are indolent in nature and would unlikely affect the health or LE of the patient if left untreated [50]. However, there is no clear consensus on the definition of clinically significant PC [51]. Based on autopsy studies, the prevalence of latent PC seems to mirror the prevalence of clinically significant disease [52].

Advanced age is the main risk factor for PC [53,54]. The crude incidence of new PC diagnoses by age group in Finland in 2020 is shown in Table 3. Incidence increases rapidly after the age of 50 years, and the mean age at the time of diagnosis of PC in Finland was approximately 69 years in 2019 [55].

Table 3. The crude incidence of prostate cancer by age group in Finland. Adapted from [2,56]

Age (years)	Estimated incidence per 100 000 men in 2020	Proportion of cases between 2015 and 2019 (%)
0–39	<0.01	0
40–44	4.0	0.11
45–49	8.1	0.68
50–54	73.2	2.7
55–59	191.9	6.8
60–64	380.3	12.6
65–69	617.4	21.3
Over 70	917.8	55.6

2.6.1 Family history and risk of prostate cancer, genetic predisposition and ethnic background

PC has the highest level of genetic transmission of all malignancies [57]. Having a first-degree relative diagnosed with PC increases the PC risk approximately 2.5-fold [58]. The familial form has been estimated to account for 10−20% of PC incidence [59]. In the Nordic Twin Study (NorTwinCan), which studied 48,734 monozygotic and dizygotic twins, the heritability index was approximately 58%, with a 95% confidence interval (CI) of 0.52−0.63 [60]. In another twin study by Lichtenstein et al. with 44,788 pairs of twins, heritable factors explained 42% of the PC risk (95% CI: 29−50%) [61].

Ethnic background is known to correlate with the risk of PC [62]. African Americans have a 60% increased risk compared to Caucasians [63], while men of Asian background may have a reduced risk compared to Caucasians [64]. In the United Kingdom (UK), men with African Caribbean backgrounds had the highest risk of PC [65].

Many known germline gene mutations predisposing to malignant diseases are overrepresented in men with PC, the most important being breast cancer susceptibility genes type 1 and 2 (*BRCA1* and *BRCA2*), prevalent in 1.1% and 4.5% of cases, respectively; pathogenic variants of the tumour suppressor gene checkpoint kinase 2 (*CHEK2*, prevalence 2.2%); and carcinogenic mutants of the ataxia telangiectasia, mutated gene (*ATM*, prevalence 1.8%) [66]. The prospective evidence in two studies is strongest for *BRCA2* mutations [67,68]. *BRCA1* mutations increased the incidence in an Israeli study by Mano et al. but not in the interim analysis of the multinational Identification of Men with a genetic predisposition to Prostate Cancer (IMPACT) study [67,68].

2.6.2 Environmental factors and the risk of prostate cancer

Japanese emigration to Western countries has been shown to increase the relative incidence of PC among emigrants in several studies, thus demonstrating the role of environmental factors in the pathogenesis of clinically significant PC [69–71]. A Western dietary pattern seems to increase the risk [72]. The known culprits are alcohol consumption, dairy products and fried foods [49,73–75]. Meat consumption, obesity and smoking do not seem to be significant in the incidence of PC [76–78]. Diabetes patients have a reduced risk of PC [79–81], which might be due to medications such as sulfonylureas and insulin [49,82–85].

The consumption of soy foods and tomatoes seems to reduce the risk of PC [86,87]. Both vitamin D deficiency and excess amounts of vitamin D in blood seem to predispose patients to PC [88]. Vitamin E supplements seem to increase the risk of PC [89].

Inflammatory bowel disease is associated with an increased risk of PC [90]. Physical activity does not seem to increase or reduce the risk of PC, although it might reduce PC mortality [91].

Exposure to Agent Orange, an herbicide used in the Vietnam War, has been shown to increase the incidence of PC in Vietnam veterans [92,93].

2.6.3 Androgens and the risk of prostate cancer

In 1941, Charles Huggins and Clarence V. Hodges demonstrated that oestrogen injections delay the progression of mPC, while testosterone injections accelerate it [94]. They postulated that androgens influence prostate cancer growth [94]. This hypothesis led to the development of the first antiandrogens in the late 1960s and luteinizing hormone-releasing hormone (LHRH) agonists in the 1980s, and Huggins and Hodges were awarded the Nobel Prize in Medicine for their work in 1966 [95,96].

In the 1980s, Pollard et al. demonstrated that exogenous testosterone induces prostate carcinomas in a rat model, a result that has been replicated several times [97–99]. Pollard's model resulted in hypotheses that testosterone is needed for the initiation of PC, endogenous testosterone levels correlate with the risk of PC and exogenous testosterone treatment increases the risk of PC [97,100,101]. There is no consensus concerning the role of testosterone in the initiation of prostate cancer [100].

In 1986, Vladimir Petrow showed that PC growth is dependent on DHT, not testosterone [102]. Two 5α-reductase inhibitors on the market, finasteride and dutasteride, have been shown to decrease the incidence of PC [103,104]. However, they may also increase the risk of poorly differentiated cancers and thus are not approved by the European Medicines Agency (EMA) for chemoprevention [49,103,104].

2.7 Natural history of prostate cancer

After the age of 50, men have an approximately one in three chance of having incidental PC on their autopsy [105,106]. The only lesion that is widely accepted as a precursor of PC is high-grade intraepithelial neoplasia (HGPIN) [107]. The cancer risk after solitary HGPIN is approximately 25% three years after the initial biopsy [108]. The transition of normal prostate tissue to HGPIN and well-differentiated cancer is characterized by genetic and epigenetic changes, including decreased expression of glutathione-S-transferase P1, decreased expression of homeobox transcription factor Nkx3.1, increased lipid metabolism and recurrent chromosomal rearrangements and overexpression of erythroblast transformation-specific (ETS) proteins [109]. Many genes that encode ETS proteins are upregulated by androgen signalling [109].

The progression to poorly differentiated carcinoma is characterized by the loss of the phosphatase and tensin homologue gene (*PTEN*); amplification and overexpression of the transcription factor c-MYC; overexpression of hepsin, ephrin type-b receptor 2 (EPHB2) and enhancer of zester homologue 2 (EZH2); and loss of microribonucleic acid (microRNA) 101 [109]. Cancerous cells typically escape the prostate in early stages, with 70% of patients having cancerous cells in their bone marrow at the time of radical prostatectomy (RP) [109,110]. However, at this point, the disseminated cells seem to be in a dormant state, although their presence predicts biochemical recurrence (BR) [110]. In the castration-resistant stage, more androgen-dependent mechanisms occur, including overexpression of androgen receptor (AR) and AR variants, that bind with lower androgen concentrations than normal [109].

Approximately 70% of cancerous tumours arise from the peripheral zone [111,112]. The proportion of PC cases in each zone is illustrated in Figure 2. The first symptoms typically resemble those found in benign prostate hyperplasia (BPH), including lower urinary tract symptoms (LUTSs) [113]. LUTSs are further divided into 1) voiding/obstructive symptoms, including urinary hesitancy, weak and/or intermittent urinary stream, straining, prolonged miction, feeling of incomplete emptying of the bladder, dribbling, and others and 2) storage/irritative symptoms, including urinary frequency, nocturia, urgency and urge incontinence [114]. Other possible symptoms include haematuria, sexual symptoms (erectile dysfunction, haematospermia, other alterations of ejaculatory functions), weight loss and perineal and back pain [115–118]. Fatigue is rarer than in other cancers [119]. Prostate cancer typically spreads first to the lymph nodes and bones [120,121].

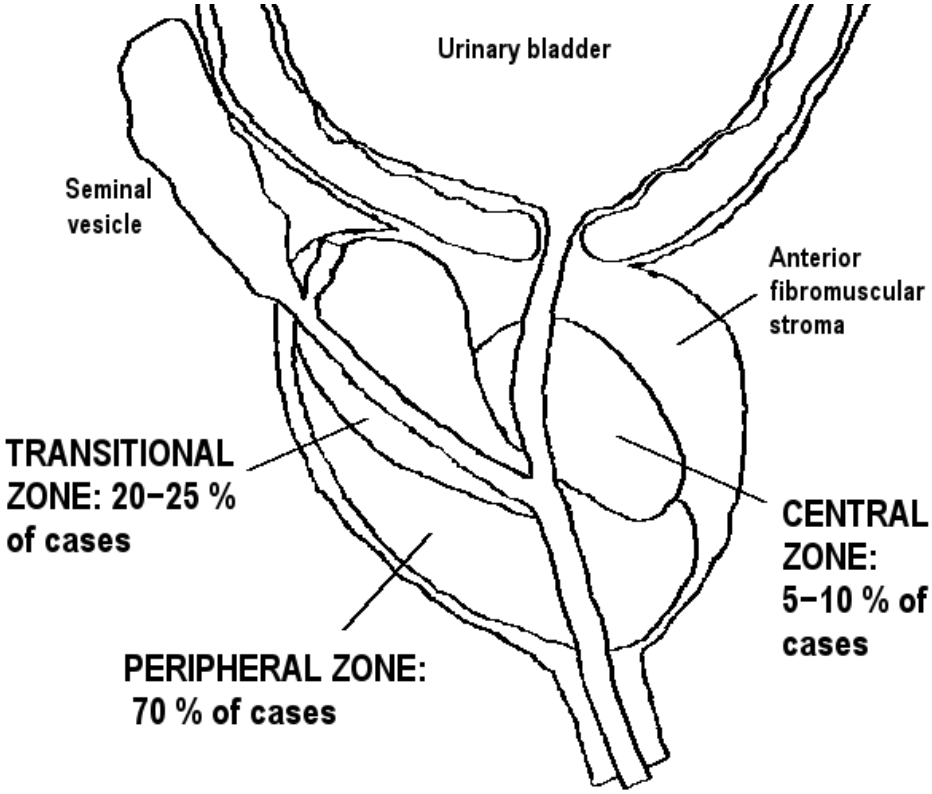

Figure 2. The three prostatic anatomical zones and the proportion of prostate cancer tumours in each zone by point of origin. Sources: [111,112,122]

2.8 Prostate cancer diagnostics

According to the British National Institute for Health and Care Excellence (NICE) guidelines, a physician should consider the PSA test and digital rectal examination in patients with any LUTSs, erectile dysfunction (ED) or visible haematuria [115]. Normally, the amount of PSA in the blood is low; typically, the barriers preventing PSA from escaping into the circulation are disrupted in prostate cancer, making serum PSA measurement useful in cancer diagnostics [123]. However, elevated PSA values are not specific to cancer, as PSA values are often elevated in nonmalignant diseases such as BPH, prostatitis and trauma [123]. PSA values can also rise due to biopsy or manipulation, such as DRE, bicycle riding, strenuous physical activity and ejaculation [123]. The reference PSA values vary for different age groups due to the

increased incidence of BPH in ageing men [115,123]. It should also be noted that 5α-reductase treatment for BPH lowers PSA values, affecting diagnostics [123].

NICE recommends referral to the urologist if PSA is elevated above the age-specific reference or the prostate feels malignant on DRE [115], while the New Zealand Guideline Group (NZGG) recommends referral if a man has both LUTSs and an abnormal prostate on DRE, LUTSs and a PSA value above 10 nanograms per millilitre (ng/ml) or LUTSs and a PSA value above the age-specific reference value or rising PSA [124]. The Canadian guideline is similar to the NZGG guideline, but discussion with the patient about the benefits and risks of PSA testing is recommended for patients with symptoms suggestive only of local disease (LUTS) [125]. The Finnish Current Care guideline recommends DRE if the patient has symptoms that could indicate PC, such as LUTSs or bone pain [126]. A confirmed measurement in cases of elevated PSA is recommended [126].

In addition to total plasma or serum PSA, certain related measures exist. Free PSA is a PSA molecule that is not bound to other plasma proteins [127]. PSA velocity (PSAV) refers to the expected growth of PSA concentrations over a year [128]. At least three blood samples taken within a year are recommended for the calculation of PSAV [129].

2.8.1 Imaging and biopsies in the primary setting

Based on recent science, magnetic resonance imaging (MRI) is now recommended for all biopsy-naïve patients prior to biopsy and patients with a previous negative biopsy in both the European Association of Urology (EAU) and American National Comprehensive Cancer Network® (NCCN) guidelines [49,92]. The EAU guidelines are also supported by the European Association of Nuclear Medicine (EANM), European Association of Radiation Oncology (ESTRO), European Association of Urology Section of Urological Research (ESUR) and International Society of Geriatric Oncology (SIOG, Société Internationale d'Oncologie Gériatrique) [49] but will be referred to as EAU guidelines for clarity. The Finnish guideline enforces the EAU guideline with regard to imaging [126]. The benefits of MRI have been demonstrated in multiple trials and a Cochrane review by Drost et al., where the MRI pathway detected 12% more clinically significant cancers (ISUP GG 2 or higher) and 37–38% fewer ISUP GG 1 cancers considered clinically insignificant (the former number is for biopsy-naïve patients, the latter for patients with a previous negative biopsy) and reduced one-third of biopsies in MRI-negative men

[130–136]. Biopsy may be performed with direct MRI guidance using ultrasound/MRI fusion software or cognitive techniques based on visual memorization since the results from different trials and reviews have been contradictory [49,137–140]. According to the EAU guidelines, systematic biopsy may still be used if MRI is not available [49].

The decision whether to perform a biopsy is made using the Prostate Imaging – Reporting and Data System (PI-RADS®) [49,92,141]. PI-RADS® is a 5-point Likert-type scale, where each lesion is given a score depicting the risk of clinically significant cancer (ISUP GG 2 or higher) [141]. Biopsy is recommended for patients with a PI-RADS® score of 3 or higher (intermediate to very high risk), since 44% of patients in this group have ISUP GG ≥ 2 cancer compared to 8% with a PI-RADS® score of 1−2 [49,92,142]. If systematic biopsy is performed, 8−12 transperineal or transrectal biopsies are recommended depending on prostate volume [49]. The biopsy may be performed transperineally or transrectally [49,92].

In biopsy-naïve patients, a combination of targeted and systematic biopsy is recommended [49,92,136]. Omitting systematic biopsy would reduce the detection of ISUP GG ≥ 2 tumours by 16% [136]. In systematic biopsy, biopsies are taken from predefined areas regardless of imaging results, while targeted biopsies are taken from abnormal areas identified either by DRE or imaging [143,144].

2.8.2 TNM classification of prostate cancer

T class describes the extent to which the primary tumour has spread locally [145]. N class describes whether the cancer has spread to the regional lymph nodes [42]. M class describes whether the cancer has spread to distant organs [145]. T class has values of T0-T4 [145]. T class for carcinoma in situ is Tis [145]. N class has values of N0-3 [145]. However, N2 and N3 are not used for prostate cancer [145]. M class has values of M0 and M1, the former assigned to patients with no spreading to distant organs and the latter for the presence of distant metastasis or metastases [145]. Whether T and N classes were determined based on clinical or pathological examination can be described using a prefix (c for clinical and p for pathological). Detailed TNM classification for prostate cancer is shown in Table 4.

Table 4. TNM classification for prostate cancer. Source: TNM Classification of Malignant Tumours, 2017 [145]

T class for primary tumour	
TX	T class cannot be determined.
T0	No proof of primary tumour.
T1 • T1a • T1b • T1c	Tumour not palpable or apparent clinically • Carcinoma present in ≤ 5% of tissue resected during transurethral resection for benign prostatic hyperplasia • Carcinoma present in > 5% of tissue resected during transurethral resection for benign prostatic hyperplasia • Carcinoma identified using needle biopsy
T2 • T2a • T2b • T2c	Tumour is palpable but confined to the prostate • Tumour involves ≤ 50% of one side • Tumour involves > 50% of one side but not both sides • Tumours extends to both sides
T3 • T3a • T3b	Invasion outside the prostatic capsule (but not into structures other than seminal vesicles) • Extraprostatic extension excluding seminal vesicles (for example bladder neck involvement) • Tumour extends to seminal vesicles
T4	Tumour is adhered to or grows into the external sphincter, rectum, levator muscles or pelvic wall.
N class for regional lymph node involvement	
NX	N class cannot be determined.
N0	No regional lymph node involvement.
N1	Regional lymph node metastasis or metastases.
M class for distant metastases	
M0	No distant metastases
M1 • M1a • M1b • M1c	Distant metastasis or metastases • Metastases involve only nonregional lymph nodes • Metastases involve bone • Metastases involve other sites

2.8.3 Prostate cancer staging

Union for International Cancer Control (UICC) staging for PC is based solely on TNM classification [145]. T1−T2aN0M0 tumours are classified as stage I, T2b−T2cN0M0 tumours as stage II and T3−T4N0M0 tumours as stage III [145]. If the disease has spread to regional lymph nodes or distant organs, it is considered stage IV regardless of T grade [145]. The American Joint Committee on Cancer

(AJCC) publishes another staging system that also accounts for histopathological grade and serum PSA level [146,147]. It is represented in Table 5.

Table 5. AJCC staging system for prostate cancer. Adapted from [146,147]

Stage I	• cT1a–cT2aN0M0 or pT2N0M0 • PSA < 10 • ISUP GG 1
Stage IIA	ISUP GG 1 T1–T2N0M0 tumours with PSA values between 10−20
Stage IIB	• ISUP GG 2 • T1–T2N0M0 • PSA < 20
Stage IIC	• ISUP GG 3 or 4 • T1–T2N0M0 • PSA < 20
Stage IIIA	• ISUP GG 1−4 • T1–T2N0M0 • PSA ≥ 20
Stage IIIB	• ISUP GG 1−4 • T3–T4N0M0
Stage IIIC	ISUP GG 5 tumours that have not spread to regional lymph nodes or distant organs (N0M0)
Stage IVA	Any N1M0 disease
Stage IVB	Any M1 disease

Abbreviations: ISUP GG = International Society of Urological Pathology Grade Group, PSA = prostate-specific antigen

2.8.4 Evaluating the risk of metastatic disease using risk stratification systems

Most guidelines divide the malignancy into low-, intermediate- and high-risk groups based on the T-stage, PSA value and GS/ISUP GG [148]. The EAU and European Society of Medical Oncology (ESMO) guidelines use the D'Amico classification system [49,148–150]. The D'Amico classification is also called the Harvard classification system [148]. In this classification, prostate malignancies with PSA values under 10 ng/ml, GS 6 and T grade ≤ T2a are considered low risk [49,148,149]. If the PSA value is over 20, GS is 8 or higher or T grade ≥ T2c, the disease is considered high risk [49,148,149]. Cases in between are considered intermediate-risk [49,148,149]. The EAU guidelines further classify any T3–T4 or N1 disease as locally advanced [49].

The American Urology Association (AUA)/American Society for Radiation Oncology (ASTRO) guidelines classify malignancies with PSA ≥ 20 ng/ml, GS 8 or higher or T grade T3–T4 as a high-risk disease [151]. The criteria for low-risk disease

are identical to those of the D'Amico classification [151]. The intermediate-risk group in the AUA/ASTRO classification is further classified into favourable and unfavourable risk groups [151]. Favourable intermediate-risk malignancies are T2b–c Gleason 3+3 tumours with PSA values of 10–20 ng/ml and <50% of positive biopsy cores [151]. All other malignancies are classified as unfavourable intermediate risk [151].

The NCCN guidelines use their own risk stratification system, which is the most complex of those presented and is depicted in Table 6 [152]. The NCCN risk stratification system defines three classes of risk factors, namely, intermediate-risk factors (IRFs), high-risk factors (HRFs) and very high-risk factors (VHRFs) [152]. IRFs include T grade T2b–T2c, ISUP GG 2–3 and PSA 10–20 ng/ml [152]. HRFs include T grade T3a, ISUP GG 4–5, and PSA>20 ng/ml [152]. VHRFs include T grade T3b–T4, primary Gleason pattern 5 and >4 cores with ISUP GG 4–5 [152]. The NCCN guideline is also the only risk stratification system of those presented to include prostate-specific antigen density (PSAD) [152]. PSAD is defined as total PSA divided by prostate volume (or mass) [153,154].

Table 6. NCCN risk stratification system for prostate cancer. Source: NCCN guideline on prostate cancer [152]

Risk group	Description
Very low	• T1c • ISUP GG 1 • PSA < 10 ng/ml • PSAD < 0.15 ng/ml/g
Low	• T1–T2a • ISUP GG 1 • PSA < 10 ng/ml • Do not qualify as a very low risk
Favourable intermediate	• ISUP GG 1–2 and < 50% positive biopsy cores • At least one IRF • No HRFs • No VHRFs
Unfavourable intermediate	• ISUP GG 3 or ≥ 50% positive biopsy cores • At least one IRF • No HRFs • No VHRFs
High	• Exactly one HRF • No VHRFs
Very high	• At least one VHRF or two HRFs

Abbreviations: HRF = high-risk factor; IRF = intermediate-risk factor; ISUP GG = International Society of Urological Pathology Grade Group; VHRF = very high-risk factor.

Finally, the English/Welsh NICE guideline uses the Cambridge Prognostic Group (CPG) classification, which divides prostatic malignancies into five groups (CPG 1–5), for which only numerical depictions are given [155,156]. CPG 1 consists of tumours with ISUP GG 1, PSA <10 μg/l and T grade T1–T2. CPG 2 tumours also have a T grade of T1–T2, but either ISUP GG is 2 or the PSA value is 10–20 μg/l [155]. CPG 3 is similar, but all three conditions (not just two) listed for CPG 2 must be met [155]. CPG 3 also includes ISUP GG 3 T1–T2 tumours regardless of PSA value [155]. CPG 4 tumours meet one of the following criteria: ISUP GG 4, PSA >20 μg/l or T grade T3 [155]. CPG 5 meets two or more of the risk factors listed for CPG 4, or the tumour is T4 or ISUP GG 5 [155].

2.8.4.1 Imaging based on risk stratification in the primary setting

The EAU guidelines recommend both soft tissue and bone scans for patients with D'Amico high-risk (or any N1) disease, as well as for those who have ISUP GG 3 intermediate-risk disease [49]. The minimum recommended imaging modality is abdominopelvic computed tomography (CT) or MRI combined with bone scintigraphy [49]. The ESMO guidelines recommend technetium (Tc)-based bone scintigraphy and thoracoabdominal CT, whole-body MRI or prostate-specific membrane antigen (PSMA)-labelled positron emission tomography (PET) for all (D'Amico) intermediate- and high-risk patients [149]. AUA/ASTRO recommends bone scintigraphy and pelvic MRI or CT routinely only for high-risk patients (according to their criteria) [151]. The Finnish guideline recommends whole-body CT and bone scintigraphy for ISUP GG > 3 and high-risk patients [126]. The NICE guidelines do not recommend routine scintigraphy for CPG 1-2 patients but otherwise do not comment on the topic [155]. The NCCN guidelines recommend bone and soft tissue imaging for all unfavourable intermediate-risk, high-risk and very high-risk patients, as well as bone imaging for any patient showing symptoms that are consistent with bone metastases [152]. Tc-based scintigraphy, plain films, MRI, and CT, along with PET-CT and PET-MRI with PSMA labelling or more conventional molecules, can all be used for screening bone metastases [152]. Thoracic CT and abdominopelvic CT/MRI are recommended for the exclusion of soft tissue metastases [152]. If PSMA PET/CT is used, separate soft tissue imaging is considered unnecessary [152].

It should be noted that even though PET/CT, PSMA-PET and whole-body MRI have superior sensitivity and specificity compared to scintigraphy and CT, the outcome data using these imaging modalities are few, and most of the clinical trials

on which the current guidelines are based were performed using more conventional imaging [49].

2.8.4.2 Basics of isotope imaging used in prostate cancer diagnostics

Nuclear imaging has substantially developed in prostate cancer diagnostics over the past decade, and various new modalities have emerged [157]. All nuclear imaging uses tracers labelled with radioactive nuclides, which are ingested, inhaled or injected [158]. In bone scintigraphy for prostate cancer, metastable technetium-99 (Tc-99m)-labelled methylene diphosphonate (MDP) or hydroxymethylene diphosphonate (HMDP) is used [152,159]. After intravenous (iv.) administration, Tc-99m-MDP/HMDP accumulates in the target tissue, bone, with the highest affinity for sites with the most active metabolism, such as bone metastases [159,160]. Tc-99m decays due to its metastable nature into stable technetium-99 and gamma radiation with a half-life of approximately six hours [159]. The resulting gamma radiation emission is then detected by a gamma camera, usually 3–4 hours after the iv. administration [159]. The principle of using radionuclides to detect bone metastases was presented in the 1960s, and the current method still in use to produce plain images based on Tc-99m was proposed by Subramanian and McAfee in 1971 [161,162].

While the traditional method produces plain two-dimensional images, a regular gamma camera can be replaced with a rotating detector to produce three-dimensional (3-D) images [159]. This is called single photon emission computed tomography (SPECT) [159]. Since the early 2000s, SPECT cameras have been combined with regular CT (SPECT/CT) [159].

In PET imaging, radionuclides decay in a manner that produces positrons [163]. These positrons then react with electrodes in the circulation in electron-positron annihilation, resulting in gamma radiation, which is then registered by PET detectors [163]. Similar to SPECT, PET can be combined with regular CT (PET/CT) but also with MRI (PET/MRI) [163,164]. Fluorine-18 (F-18)-labelled sodium fluoride (NaF) is one of the most researched tracers in the diagnosis of PC and has shown increased sensitivity compared to scintigraphy [165,166]. However, compared to scintigraphy, it has cost-effectiveness issues with questionable added value [165,167]. Choline-based tracers with different F-18 or carbon-11 (C-11) labelling have increased specificity but worse sensitivity compared to scintigraphy and F-18 sodium fluoride PET [168]. Thus, choline PET can be considered only in special scenarios [168].

Due to the low added clinical value of F-18 NaF PET/CT compared with scintigraphy, the need for alternative, more accurate tracers has emerged [169]. Currently, PET/CT that uses PSMA tracers is becoming increasingly common, despite the limited outcome data [49,169]. PSMA is a transmembrane carboxylase that has folate hydrolase activity [170]. It is normally expressed in the prostate, kidneys, jejunum and glial cells in the nervous system [171]. It is highly overexpressed in PC cells in all stages of the disease [172]. However, the overexpression is further intensified after the development of androgen resistance [172]. PSMA PET/CT can be performed using either F-18 or gallium-68 (Ga-68) labelling [169]. Both methods have both superior sensitivity and specificity compared to scintigraphy [49,169].

2.8.4.3 Evaluating the risk of local lymph node metastases

On CT or MRI, a lymph node over 8 millimetres (mm) by its minor axis is generally considered malignant in the pelvis, whereas outside the pelvis, the limit is 10 mm [49]. In PSMA PET/CT, the suspicion of malignancy is determined by tracer uptake [49]. However, currently, even PSMA PET/CT cannot replace the diagnostic accuracy of surgical dissection of pelvic lymph nodes, which may be performed simultaneously with radical surgery for PC [173].

There are several nomograms that combine MRI and clinical data to evaluate the risk of local lymph node metastases [49]. The Memorial Sloan Kettering Cancer Centre (MSKCC) nomogram is one of the most researched and used in clinical practice [174]. It includes data on prior hormone therapy or chemotherapy, radiation therapy (RT), age, PSA level, primary and secondary Gleason grades, T stage and, optionally, the percentage of positive biopsy cores to calculate the risk of local lymph node metastases [175]. The Briganti nomogram is one alternative to the MSKCC nomogram [49]. It includes data on the percentage of positive cores, PSA level, T stage and primary and secondary Gleason grade [176]. The nomogram was developed by Alberto Briganti at Vita-Salute University in Milan, and its first version was published in 2006 [177]. Both nomograms have been externally validated [174]. In 2021, Meijer et al. were the first to modify and validate these nomograms for PET PSMA data [178].

2.8.5 Screening for prostate cancer

There have been at least five RCTs that have investigated PSA-based screening programs to detect asymptomatic PC: the European Randomized Study of Screening for Prostate Cancer (ERSPC), Norrköping trial, Quebec trial, Stockholm trial and Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial [179–184]. Of these, only the ERSPC reported a significant reduction in prostate cancer-specific mortality (PCSM), and a combined meta-analysis conducted by the Cochrane collaboration showed no benefit in PCSM or overall mortality (OM) [179]. Screening also causes harm, including overtreatment, overdiagnosis and adverse effects such as biopsy-related infection and bleeding [185]. A Cochrane review concluded that PSA screening is unlikely to be beneficial [179].

The ERSPC is a very large trial that takes place in eight European countries (the Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, and France) and includes over 180,000 patients [186]. From Finland, 80,000 patients from the Helsinki and Tampere regions are included [129]. Long-term follow-up is still ongoing, and the 16-year follow-up data were published in 2019 [187]. After nine years, the number needed to screen (NNS) was 1,410, and the number needed to treat (NNT) was 48 [49,187]. However, the results have improved in long-term follow-up, and at 16 years, the NNS was 570, while the NNT was 18 [49,187]. The 16-year results for NNS now surpass the results reported for breast cancer screening [49,187]. In this context, NNS and NNT mean the number needed to screen/treat patients to prevent one PC death [188].

There are currently several trials investigating the utility of MRI for PC screening, either alone or in combination with PSA [189].

2.8.5.1 Quality-of-life aspects of screening and the concept of quality-adjusted life-years

Regarding QoL, based on a simulation model by Heijnskdik et al., PSA screening of all men aged 55–69 years would gain 56 quality-adjusted life-years (QALY) per 1,000 men and 82 life-years in total at 11 years [190]. QALY is a quantitative variable that can have values ranging from 0 to 1 [191]. One QALY equals one year in full health [191].

Based on the Finnish sample from the ERSPC, there were no differences in health-related quality of life (HRQoL) at any point between screened men and men in the control arm [192]. However, these results are limited by a low response rate

(33% for the screening arm and 22% in the control arm) and low sample sizes related to the response rate and data collection problems [192].

2.8.5.2 Guideline recommendations for PSA screening

The EAU guidelines recommend early PSA testing for informed men with risk factors for PC [49]. These include age above 50 years, age above 45 years and a family history of PC or African genealogy, and age above 40 years and being a *BRCA2* mutation carrier [49]. Early PSA testing is also recommended for all men who have been properly informed and have a life expectancy of at least 10–15 years [49]. If the PSA value is > 1 ng/ml for men over 40 years or > 2 ng/ml for men over 60 years, follow-up every two years is recommended [49]. If the PSA level is below these values, the follow-up can be postponed to eight years [49]. The Finnish guideline enforces the EAU guideline on screening [126]. The ESMO guideline criteria for early PSA testing do not differ from the EAU criteria [49,149].

The United States Preventive Services Task Force (USPSTF) recommends PSA screening for informed men aged 50–69 years who request it [193,194]. Screening of men over 70 years is not recommended [193,194]. The NCCN guidelines recommend PSA testing for informed men aged 45–75 years or 40–75 years with risk factors (African American men, genetic risk for PC, family history) [92]. If the PSA level is < 1 ng/ml, follow-up testing is recommended with 2–4-year intervals [92]. If the PSA level is between 1 and 3 ng/ml, follow-up testing is recommended at 1–2-year intervals [92]. PSA testing is also possible for informed men over 75 years if they are in good health and have few comorbidities [92]. Then, repeat testing is recommended with 1–4-year intervals if the PSA level is < 4 ng/ml and DRE is normal [92].

The AUA recommends against PSA testing for PC in men under 40 years of age [151]. Routine PSA testing is not recommended for men between 40 and 54 years or over 70 years [151]. For 40- to 54-year-old men with risk factors, shared decision-making between the physician and the informed patient is recommended [151]. For men aged 55–69 years with an LE over 10 years, similar shared decision-making is recommended [151]. PSA screening every other year is preferred over an annual schedule [151].

2.9 Treatment of localized and locally advanced prostate cancer

Currently approved treatments for localized and locally advanced PC include radical prostatectomy, EBRT, androgen-deprivation therapy (ADT) as monotherapy or combined with other treatments, brachytherapy (BT), active surveillance (AS) and observation/watchful waiting [49,149,151,152,155]. The choice of treatment modality depends on the patient's life expectancy (LE) and tumour characteristics (PSA, T grade, ISUP GG) measured by risk stratification systems [49,149,151,152,155]. Of these, RP, EBRT and BT are curative-intent treatment options, while AS was developed to avoid overtreatment of tumours whose treatment would harm the patient more than the cancer itself [195,196]. ADT monotherapy is a life-extending treatment [197]. In general, patients with a shorter LE and more well-differentiated disease should be offered less invasive and less harm-causing treatments [49,151,152].

2.9.1 Active surveillance

Active surveillance means an active follow-up program for the patient, without initiating treatment or postponing it until deemed necessary. The EAU recommends AS for low-risk and intermediate patients with LE > 10 years [49]. Based on a European consensus meeting, the Deferred Treatment with Curative Intent for Localized Prostate Cancer from an International Collaborative (DETECTIVE) study, endorsed by the EAU, ESUR, ESTRO, EANM and SIOG, the following exclusion criteria should be used for AS: high-stage disease on MRI, ISUP GG 3 or higher, T grade T2c or higher, and intraductal or cribriform histology on biopsies [198]. ISUP GG 2 (intermediate-risk) patients are only suitable for AS if the PSA level is ≤ 10 ng/ml, T stage is T2a or better and the percentage of positive cores is low [198].

NICE recommends AS for CPG 1−2 tumours, and it can also be considered for CPG 3 if the patient decides against immediate curative-intent treatment [155]. MRI should be offered to the patient if not previously performed [155]. The ESMO and AUA guidelines both recommend AS for low-risk disease [149,151]. It is also an option for patients with intermediate-risk disease, although only for the favourable intermediate-risk group in the AUA guidelines [149,151].

The NCCN prefers AS for very low-risk disease (if LE is below 10 years, patients should only be observed) and for most patients in the low-risk group with an LE ≥

10 years (such as patients with no increased genomic risk, low percentage of positive cores, and low PSAD) [152]. AS is also possible for the favourable intermediate-risk group with an LE > 10 years [152].

2.9.1.1 Advantages and disadvantages of active surveillance

The benefits of AS include avoiding and delaying the harms of the treatment in a safe manner [152]. However, in 32−50% of patients, AS will lead to radical treatment within ten years [152]. The risk of progressing to locally advanced or M1 disease seems to be very low, under 0.5% [152].

It has been speculated that AS could cause psychological distress due to fear of cancer progression. However, based on the current (limited) evidence, the mental QoL of AS patients does not seem to differ considerably from that of patients treated curatively [199]. Repeat biopsies and MRI in the long term may be undesirable to some patients. Regular check-ups and repeat PSA testing are also recommended after active treatment [49,152].

2.9.1.2 Active surveillance protocols

The DETECTIVE protocol includes PSA control every six months and DRE every year [198]. Repeat biopsy criteria are worsening of PI-RADS® score, increase in tumour volume or radiological T stage or disease progression as determined by PSA or DRE [198]. Repeat biopsy should be targeted [198]. AS should not be continued if the patient's LE worsens below 10 years [198]. Depression and anxiety symptoms related to PC are indications for ending the active follow-up (i.e., moving to watchful waiting or active treatment), as is the patient's desire not to undergo repeat biopsies or imaging [198].

The NICE protocol includes PSA testing every 3−4 months in the first year and then every six months [155]. DRE should be performed yearly, and MRI should be performed every 12−18 months [155]. Additionally, PSAD and PSAV should be monitored [155]. Disease progression or a change in patient wishes (based on a shared decision-making process) should warrant considering reclassification [155].

The AUA recommends repeat PSA testing and prostate biopsies [200]. PSA should be measured every six months and should be accompanied by physical examination (including DRE) every 1−2 years [200]. Follow-up MRI is encouraged [200]. Rising PSA levels based on several samples, abnormal DRE or other

(unspecified) concerns are causes for MRI and repeat biopsy, if needed [200]. Increases in tumour volume or T grade are causes for considering reclassification [200].

The NCCN protocol recommends confirmatory biopsy 1−2 years after the diagnostic biopsy [152]. PSA should not be measured more often than six months [152]. DRE, repeat MRI and repeat biopsy should not be performed more often than yearly [152]. Clinical causes may justify deviation from recommendations [152]. If the patient's LE changes to below ten years, the patient should be moved to observation [152]. Reclassification can be caused by worsening of tumour grade, increase in tumour volume, PSAD increase or patient anxiety [152].

2.9.2 Radical prostatectomy

Radical prostatectomy is the oldest curative treatment used for PC [201]. Currently, RP may be performed using robot-assisted, laparoscopic or conventional open surgery techniques [49]. Robotic-assisted radical prostatectomy may have less acute bleeding and reduced hospital admission times, but long-term outcome results do not differ from those of open surgery [202,203]. Depending on the risk stratification, extended pelvic lymph node dissection (EPLND) may be performed, which consists of dissecting lymph nodes near the external and internal iliac artery and obturator nerve [49].

The EAU guidelines consider RP as a viable option for patients with low-risk tumours who decline AS and patients with intermediate-risk tumours with an LE over 10 years [49]. For high-risk patients, it may be offered as a part of multimodal treatment that may include salvage radiotherapy (SRT) or adjuvant ADT [49]. EPLND should be performed for intermediate- and high-risk patients [49]. In locally advanced disease, EPLND should be performed before RP [49]. NICE recommends it as an alternative for CPG 2-3 patients and CPG 1 patients who decline AS [155]. The ESMO guidelines recommend EPLND as an alternative for all risk groups, but EPLND should be performed for high-risk/locally advanced patients [149]. The AUA recommends it as an option for intermediate- and high-risk patients [151]. The NCCN guidelines recommend RP as an alternative for patients with very low-risk disease and an expected survival over 20 years, low- and intermediate-risk disease and an expected survival over 10 years, and high- and very high-risk disease and an expected survival over five years or if the patient is symptomatic [152].

Thirty-day mortality after RP is approximately 0.11-0.13% [204]. The most common side effects of the treatment include ED, urinary incontinence (UI), vesicourethral anastomotic stricture and inguinal hernia [205]. In a study by Korfage et al., the prevalence of ED was 88%, and the prevalence of UI was 31% at 52 months [206]. Erectile function may improve from the immediate postoperational state up to two years of follow-up [205]. The incidence of vesicourethral anastomotic stricture was 5.5% at 52 months in a single-centre study (N=2048) by Gillitzer et al. [207]. In the Scandinavian Prostate Cancer Group (SPCG)-4 study, 9.3% of RP patients had developed inguinal hernia at 48 months compared to 2.4% in the watchful waiting group [208]. The P value (P) for statistical significance was 0.001 [208].

2.9.3 Brachytherapy

In brachytherapy (BT), radioactive material is implanted internally directly into the prostate [209]. Two different types of BT are in use in clinical practice [49]. One is low-dose rate (LDR) BT, where radioactive seeds are permanently implanted into the prostate [49]. The seeds can consist of iodine-125 (I-125), palladium-103 (Pd-103) or caesium-131 (Cs-131) isotopes [49]. The seeds emit radiation for weeks or months until the desired total radiation dose is delivered [49]. Acute side effects, mainly consisting of urinary complaints (in almost all patients) and gastrointestinal issues, typically last for months [49,210]. A review by Stone and Stock reported that the incidence of acute urinary retention was 1.5-22% [211]. There is a European consensus statement that LDR BT should be used only for patients who have good urinary function, measured as an International Prostatic Symptom Score (IPSS) ≤ 12 and a maximum flow rate > 15 millilitres per minute (ml/min) on a urinary flow test [49,212]. LDR BT can be combined with EBRT in selected patients [49]. In the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial, this led to increased biochemical recurrence-free survival (BRFS), but severe genitourinary (GU) toxicity was also much higher: 18.4% in the combination treatment groups versus (vs.) 5.2% in the monotherapy group at five years (P<0.001) [213]. In the ASCENDE-RT trial, patients belonged to the NCCN intermediate- or high-risk group and received ADT [213].

The other type of BT is high-dose rate (HDR) BT, where the desired radiation dosage is achieved in minutes and the implantation is temporary in nature [49].

Radiation is delivered through needles or catheters, and iridium-192 (Ir-192) is used as a radioactive isotope [49]. Acute side effects typically last for weeks [49]. HDR BT can be given as a single dose or in a fractionated manner, where the desired total radiation dosage is achieved through multiple treatment sessions [49]. HDR BT is usually combined with EBRT with a total dose of 45 Gy or more [49]. When given in combination with EBRT, ADT should also be used, since it has been shown to improve metastasis-free survival (MFS) and overall survival (OS) [49,214,215]. It is also possible to administer it as a monotherapy, but in those cases, a fractionated treatment plan should be used, since it seems to improve BRFS results [49,216].

2.9.3.1 Long-term tolerability of brachytherapy

In the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA), 37% of patients who had adequate pretreatment erectile function reported ED two years after BT, which was superior to RP [217,218]. In another study, the cumulative incidence of late urinary complications (a year or later after BT) was 8.6% for mild complications, 6.5% for moderate-severe complications, 1.7% for severe complications and 0.5% for very severe complications [219]. In a review by Phan et al., the cumulative incidence of late rectal complications was 4−10% at five years in patients who had not received EBRT [220]. Combined HRT BT and EBRT treatment seems to increase the incidence of late grade 2−4 (moderate, severe or very severe) gastrointestinal (GI) complications but not GU complications compared to BT alone [221].

Since BT is a form of RT, secondary cancers are also possible. In a study by Nieder et al., the risk of bladder cancer (BC) was 1.52 times higher in men treated with BT monotherapy than in men who underwent RP (95% CI = [1.24−1.87]) [222]. For men treated with BT + EBRT, BC risk was 1.85 times the risk in men treated with RP (95% CI = [1.22−2.67]) [222]. The risk for rectal cancer (RC) was not increased in this study [222].

2.9.3.2 Patient selection for brachytherapy

The EAU recommends LDR BT monotherapy as an option for patients who have good urinary function and low- or intermediate-risk disease and whose disease is ISUP GG 2 and involves under 33% of biopsy cores [49]. LDR BT + EBRT or HDR BT + EBRT may also be offered to patients with good urinary function and

whose disease is ISUP GG 3, PSA level is between 10 and 20 ng/ml or both, even though the evidence for this patient group is weak [49]. Similarly, LDR BT + EBRT or HDR BT + EBRT may be considered for patients with good urinary function and high-risk or locally advanced disease [49]. For HDR BT, the EAU also enforces Groupe Europeen de Curietherapie (GEC)/ESTRO guidelines, which recommend HDR BT + EBRT to patients who have T1b-T3b disease; have not received transurethral resection of the prostate (TURP) within 3−6 months; and do not have rectal fistulae, pubic arch interference or contraindications to the lithotomy position or to anaesthesia [49,223]. The IPSS should also be over 20, and the maximum urinary flow rate should be under 10 millilitres per second (ml/s) [223].

In the ESMO guidelines, BT is an option for patients with low- or intermediate-risk disease [149]. The AUA guidelines consider LDR BT and HDR BT monotherapy as equal options compared to EBRT in patients with low- or favourable intermediate-risk disease [224]. LDR BT + EBRT + ADT and HDR BT + EBRT + ADT are acceptable options for patients with unfavourable intermediate- and high-risk disease [224]. NICE recommends BT + EBRT as an alternative in CPG 2−5 localized or locally advanced PC [155]. NICE does not recommend BT monotherapy for patients with CPG 4−5 disease [155].

The NCCN recommends BT monotherapy as an alternative for patients with very low-risk PC and LE > 20 years (AS is preferred), low-risk PC and LE ≥ 10 years and favourable intermediate risk-disease and LE > 5 years (observation is preferred if LE is between five and ten years) [152]. The NCCN guidelines recommend combination therapy with EBRT, BT and ADT as an alternative for patients with unfavourable intermediate-risk disease and LE over five years and for patients with high- or very high-risk PC and LE over five years or who are symptomatic [152]. In combination treatment, the duration of ADT should be four to six months in the unfavourable intermediate-risk group and 1.5−3 years in the high- or very high-risk group [152].

2.9.4 External beam radiotherapy

The recommended techniques for EBRT are either intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) [49]. Image guidance is recommended in both techniques [49]. IMRT replaced the previous 3-D conformal radiotherapy (CRT) in the 2000s [225]. IMRT allows more precise dose delivery compared to the 3-D CRT box [225]. This more precise technique allows a

higher dose per fraction (fr) and reduced toxicity [225]. VMAT was introduced in 2007 [226]. Compared to IMRT, it uses rotating gantries, allowing a reduced monitor unit (machine output) and delivery time [225,226]. VMAT seems to spare more rectal tissues from harmful radiation compared to IMRT, but it does not seem to reduce acute toxicity [227,228].

In conventional fractionation, the dose per fraction is 1.8-2 Gy, and the total dose is 72-78 Gy [4,49]. If the risk of invasion to seminal vesicles or metastasis of regional lymph nodes is over 15%, seminal vesicles and/or regional lymph nodes are recommended to be irradiated as well [4]. The recommended dose is 50-56 Gy for seminal vesicles and 45-50 Gy for pelvic lymph nodes [4]. Conventional fractionation results in 36-43 fractions, which also means 36-43 hospital visits for the patient.

Theoretically, since PC is generally a slow-growing tumour, it would benefit from an increased dose per fraction [229]. This claim was supported by a meta-analysis by Dasu and Toma-Dasu based on real-life biochemical data from 14,168 patients [230]. In the 2010s, four RCTs investigated moderated hypofractionation (fraction size 2.5−3.4 Gy and total radiation dose 60−70 Gy) [49,231–236]. BRFS and OS were not inferior to CRT in any of the trials, nor were there significant differences in the rate of treatment failures (TFs) [231,233,235,236]. One trial also reported prostate cancer-specific survival (PCSS) with no significant differences [236]. The Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP) and Ontario Clinical Oncology Group (OCOG) trials reported no differences in toxicity [232,233,236]. The NRG Oncology Radiation Therapy Oncology Group (RTOG) 0415 trial reported increased late GI and GU grade 2 and 3 adverse effects [231]. The HYpofractionated irradiation for PROstate cancer (HYPRO) trial could not prove noninferiority for cumulative late GU and GI toxicity [234]. The Cochrane meta-analysis concluded that there are no differences in acute or late toxicity between moderately hypofractionated RT and CRT [237]. However, more long-term follow-up data (10-15 years after the treatment) are needed to confirm the long-term safety [237]. Since moderately hypofractionated RT is more cost-effective than CRT with no worse outcome results, it is now recommended by both the EAU/ESTRO and AUA/ASTRO [49,238,239].

In ultrahypofractionated RT, the dose per fraction was increased to 3.5 Gy or more [49]. High fraction size requires the use of image-guided RT (IGRT) as well as stereotactic body radiation therapy (SBRT) [49]. SBRT is characterized by the use of equipment that requires reliable immobilization of the patient [240]. Two phase III RCTs have reported results for ultrahypofractionation thus far: the HYPOfractionated RadioTherapy of intermediate risk localized Prostate Cancer

(HYPO-RT-PC) trial and the Prostate Advances in Comparative Evidence B (PACE-B) trial [241–244]. HYPO-RT-PC reported ultrafractionation (42 Gy in 7 Gy/fr) to be noninferior to CRT (78 Gy in 2 Gy/fr) in terms of failure-free survival (FFS, biochemical or clinical progression) [242]. However, acute GI toxicity (but not GU toxicity or erectile function) was worse compared to CRT [242]. PACE-B reported no statistically significant differences in either GI or GU toxicity (grade 2 or worse) between men receiving either 78 Gy in 39 fractions (frs), 62 Gy in 20 frs or 36.25 Gy in five frs [244]. Since long-term data on ultrahypofractionation are lacking, it is still considered experimental [49].

2.9.4.1 Long-term tolerability of external beam radiotherapy

At five years, the cumulative incidence of grade ≥ 2 (moderate or worse) GU toxicity is 17−33% based on a review by David et al. [245]. The cumulative incidence of any GI toxicity is approximately 4% at five years [246]. Recent studies have reported that 30-40% of patients develop ED after EBRT, which is substantially better than was previously thought [247]. Compared to RP, ED occurs with a latency period of one year or later after treatment and generally worsens over time [247].

In a study by Nieder et al., the risks for both BC and RC were increased in men treated with EBRT compared to men treated with RP [222]. The hazard ratio (HR) for BC was 1.88 (95% CI = [1.70−2.08]), and for RC, it was 1.26 (95% CI = [1.08−1.47]) [222]. The subjects consisted of men treated between 1988 and 2003; most were treated with CRT, which means that the results may be different for IMRT and VMAT [222].

2.9.4.2 Patient selection for external beam radiotherapy

The EAU guidelines consider EBRT as an alternative treatment in all risk groups [49]. For low-risk patients, it is an option for informed patients who decline AS and accept the toxicity related to EBRT [49]. There have not been RCTs that directly compared EBRT and AS specifically in low-risk groups [49]. For intermediate-risk patients, either conventionally fractionated or moderately hypofractionated RT with ADT for four to six months is a recommended option in addition to RP and BT [49]. If the patients decline ADT, standard or moderately hypofractionated RT is still an option, but the evidence for this is cited as weak [49]. For high-risk patients or patients who have locally advanced disease, conventional or moderately

hypofractionated RT combined with ADT for 2−3 years is the treatment option best supported by evidence [49]. Triple treatment with EBRT, long-term ADT and abiraterone acetate for two years may be considered for selected patients with locally advanced disease [49]. For selected high-risk patients, RP is also a possibility, but the patient should be aware that SRT and ADT may still be required [49].

In the ESMO guidelines, EBRT is an alternative treatment for all patients with local and locally advanced disease [149]. For patients with intermediate-risk disease, EBRT should be combined with neoadjuvant ADT for four to six months [149]. For high-risk localized and locally advanced disease, ADT should be given as a neoadjuvant treatment before EBRT for 4−6 months and then continued for two years after EBRT [149]. Triple treatment with EBRT, long-term ADT and neoadjuvant docetaxel can be considered for patients with high-risk or locally advanced disease [149].

The NICE guidelines recommend EBRT for patients with CPG 2-5 PC and for CPG 1 patients who decline AS [155]. RP is always considered an equivocal alternative for EBRT and AS for CPG 2 patients [155]. If EBRT is chosen, 60 Gy in 20 frs is the preferable treatment course [155]. If hypofractionated treatment is not suitable, 74 Gy in 37 frs is recommended [155]. For CPG 2-5 patients, neoadjuvant or adjuvant (given during/after the treatment) ADT for six months is recommended [155]. For CPG 4-5 patients, continuing ADT for up to three years should be considered [155].

The AUA guidelines consider EBRT as an alternative treatment for intermediate-risk and high-risk patients [151]. In patients with unfavourable intermediate- or high-risk PC and LE over 10 years, EBRT should be combined with ADT [151]. In selected high-risk patients, triple treatment with EBRT, ADT and abiraterone acetate (and prednisone) may be considered [151]. Offering moderately hypofractionated RT is recommended [224]. The duration of ADT should be 4-6 weeks in patients with unfavourable intermediate-risk PC and 1.5-3 years in patients with high-risk PC [224]. Radiating pelvic lymph nodes with 45-52 Gy may be offered to high-risk patients [224].

In the NCCN guidelines, EBRT is one possible treatment modality for very low-risk patients with an LE > 20 years (AS is preferred), low-risk patients with an LE ≥ 10 years (AS is preferred), favourable intermediate-risk patients with an LE > 5 years (observation is preferred if LE is 5-10 years), unfavourable intermediate-risk patients with an LE > 5 years and high- or very high-risk patients with an LE > 5 years or who are symptomatic [152]. In unfavourable intermediate-, high- and very high-risk PC, ADT should be used [152]. The recommended duration for ADT is 4-6 months

in unfavourable intermediate-risk patients and 1.5-3 years in high- and very high-risk patients [152]. In very high-risk patients, combining EBRT + ADT treatment with either docetaxel or abiraterone is a possibility [152]. EBRT + ADT or EBRT + ADT + abiraterone acetate are also possibilities in N1 disease in patients with an LE > 5 years or who are symptomatic [152].

2.9.5 Androgen deprivation therapy

Successful castration is currently defined by the EAU as testosterone levels below one nanomole per litre (nmol/l), even though historically, a level below 1.7 nmol/l has been used, and most trials still use this limit [49]. Testosterone suppression can be achieved either by blocking the production of androgens (LHRH antagonists, LHRH agonists and surgical castration) or by blocking their action at the cellular level (antiandrogens, oestrogens) [49]. Bilateral orchiectomy (surgical castration) is very rarely used in the treatment of M0 PC due to its irreversible nature.

Most guidelines do not comment directly on which type of treatment should be used in the first line [49,149,151,155]. An exception is the NCCN guidelines, which recommend LHRH agonists (goserelin, histrelin, leuprolelin, triptorelin), LHRH antagonists (degarelix, relugolix) or combined LHRH agonist and antiandrogen treatment (with nilutamide, flutamide or bicalutamide) [152]. LHRH antagonists bind to LHRH receptors directly, blocking their action [248]. This subsequently leads to the suppression of androgen production, since their production is upregulated by LHRH [248]. LHRH agonists stimulate the release of LHRH from the hypothalamus at the beginning of treatment [248]. This can lead to worsening of PC symptoms in a process called the flare that may warrant preventive antiandrogen treatment [49,129]. However, given time, the number of LHRH receptors in the pituitary is downregulated, and thus, the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) is downregulated as well, leading to castration [49,248].

The most notable side effects of ADT include osteoporosis, metabolic syndrome (including type II diabetes), sexual dysfunction (in over 90% of patients), gynaecomastia (especially in men receiving antiandrogens), fatigue, hot flashes and anaemia [249]. Osteoporosis may be prevented with osteoporosis medication [249]. The diabetes risk is elevated by approximately 16−44% [249]. Gynaecomastia may be prevented using tamoxifen or preventive radiotherapy of mamillas, but it occurs in only 10−15% of patients receiving LHRH antagonist monotherapy [249,250]. Hot

flashes occur in up to 80% of patients [250]. Treatment options include gabapentin, venlafaxine, medroxyprogesterone and cyproterone [249].

The use of ADT as a neoadjuvant/adjuvant treatment is covered in the previous sections. The EAU does not recommend ADT monotherapy for asymptomatic patients [49]. High-risk patients with prostate-specific antigen doubling time (PSA-dt) under a year and a PSA level > 50 ng/ml or poorly differentiated tumours may be treated with ADT monotherapy if their decline is not fit for radical treatment [49]. This is based on Early Prostate Cancer (EPC) trial findings, where 8113 men were treated with either antiandrogen bicalutamide monotherapy or placebo [251]. Bicalutamide provided no benefit to progression-free survival (PFS) or OS [251]. PSA-dt is the calculated time at which PSA values double, based on at least three measurements each at least four weeks apart [49].

The AUA guidelines state that ADT monotherapy is a possible palliative option for high-risk symptomatic PC patients with limited LE [224]. The NCCN guidelines consider ADT as an alternative for high- and very high-risk patients (including N1 cases) with an LE ≤ 5 years [152]. NICE does not recommend ADT monotherapy for local PC [155].

2.9.6 Docetaxel and abiraterone acetate for local prostate cancer

As discussed previously, two alternatives to conventional androgen-suppressing agents are approved by the NCCN to be used for very high-risk disease: docetaxel and abiraterone acetate [152]. Both have been studied as an adjuvant therapy with EBRT and ADT [152]. According to the NCCN, abiraterone acetate can also be used for N1 disease adjuvant to EBRT + ADT or with AFT after TF following EBRT [152]. The ESMO guidelines mention only docetaxel as an option for high-risk and locally advanced disease [149]. The NICE guidelines also mention docetaxel, but not abiraterone acetate, as an option for men who have high-risk disease and no major comorbidity who are beginning ADT [155]. On the other hand, the AUA guidelines only mention abiraterone acetate + ADT + EBRT as an option for high-risk patients with an LE over 10 years [151]. The EAU does not recommend either treatment, not commenting on the use of docetaxel or abiraterone acetate for N0 high-risk PC or citing insufficient evidence considering N1 disease [49].

The evidence regarding the use of docetaxel for very high-risk disease stems from the NRG Oncology RTOG 0521 trial [252]. In this trial, EBRT + ADT + docetaxel improved 6-year BRFS (P=0.043), 6-year MFS (P=0.044) and 4-year OS (P=0.034)

compared to EBRT + ADT [252]. Inclusion criteria were the following: NCCN high-risk disease, GS 9−10 disease or GS 7−8 disease with PSA ≥ 20 ng/ml or GS 8 with PSA <20 ng/ml and T grade ≥ T2 and self-caring performance status [252]. Exclusion criteria included laboratory abnormalities (not fully specified in the article), N1 or M1 disease or PSA > 150 ng/ml [252]. The median age was 66 years in both arms [252]. In the NRG Oncology RTOG 0501 trial, six courses of docetaxel 75 mg/m^2 were given with prednisone every three weeks in the treatment arm [252].

Three other RCTs investigated adjuvant docetaxel with EBRT and ADT. The SPCG-13 trial included NCCN intermediate- and high-risk patients and found no benefit in using docetaxel 75 mg/m^2 without prednisone for six cycles in relation to BRFS [253]. In the Groupe d'Etude des Tumeurs Uro-Génitales (GETUG)-12 trial, EBRT + ADT + docetaxel + estramustine increased BRFS (P=0.017) compared to EBRT + ADT [254]. The patient population consisted of high-risk patients (the criteria were equivocal to AUA risk stratification) [254]. Docetaxel was given with prednisone at a dose of 70 mg/m^2 for four cycles with 3-week intervals [254]. Estramustine (an oestrogenic agent with cytotoxic properties) was given at the beginning of every docetaxel cycle for five days at 10 milligrams per kilogram (mg/kg) [254,255]. The updated 12-year study showed no differences in MFS, with a 95% confidence interval for the HR of [0.60−1.09] [256]. The Systematic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial showed similarly improved BRFS (P=0.002) but no benefit in MFS (P=0.43) or OS (P=0.44) [257]. The chemotherapy plan was identical to that of the NRG Oncology RTOG 0521 trial. The STAMPEDE trial design was rather complicated, consisting of four arms (EBRT + ADT, EBRT + ADT + docetaxel, EBRT + ADT + zoledronic acid, and EBRT + ADT + docetaxel + zoledronic acid) and including men in all stages of the disease (including N1 and M1) [258]. Thus, the report by James et al. should be considered a subgroup analysis.

In another STAMPEDE group analysis published recently in January 2022, combination therapy with abiraterone acetate and prednisolone with EBRT and ADT increased 6-year MFS and OS (P<0.001) in high-risk patients [259]. The results reported consist of two separate trials; in one, the intervention group received EBRT + ADT + abiraterone acetate + prednisolone (N=459) and in the other, the intervention group received EBRT + ADT + abiraterone acetate + prednisolone + enzalutamide (N=527) [259]. The control group in both trials received EBRT + ADT (Ns 455 and 527 for each trial, respectively) [259]. The main problem with this analysis was that it also included patients with relapsed PC analysed together with hormone-sensitive disease, although there were relatively few (2.8% in the control

group, 4.0% in the treatment group) [259]. Another issue is that another treatment group included patients receiving enzalutamide, and the results for patients receiving only abiraterone acetate + prednisolone are not numerically reported [259]. N1 status was allowed (39.2% in the combined control groups, 38.9% in treatment groups) [259].

Docetaxel is a semisynthetic analogue of paclitaxel, which is naturally occurring and extracted from the bark of the Pacific yew tree [260,261]. Docetaxel was developed by the drug company Sanofi-Avantis, and its patent expired in Europe in 2010 [262]. Docetaxel acts by stabilizing cellular microtubules, thus leading to cellular apoptosis [260]. Abiraterone acetate is a prodrug that converts to its active metabolite, abiraterone, by the hydrolysis of the acetyl group [263]. Abiraterone acts in the liver by inhibiting cytochrome P450 (CYP) 17, thus hindering the synthesis of androgens [264]. Despite this, it is not truly an antiandrogen that targets AR but is an androgen biosynthesis inhibitor [265]. It must be taken with prednisone or prednisolone due to corticosteroid suppressive activity [266]. The patent holder is Janssen [266]. The structural formulae for both substances are shown in Figure 3.

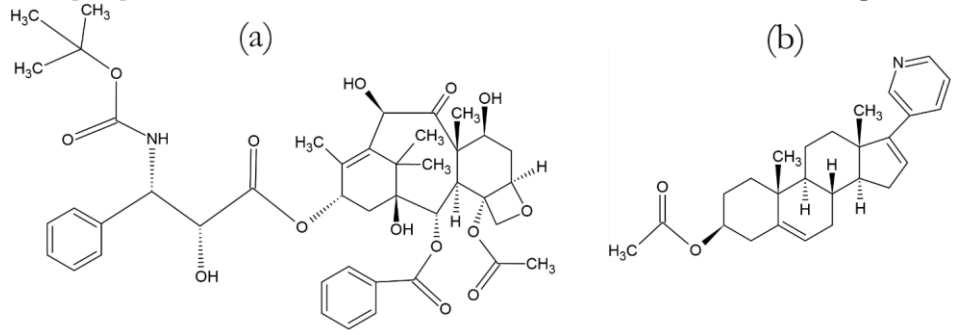

Figure 3. Structural formulae for a) docetaxel and b) abiraterone acetate

Serious side effects for docetaxel include neutropenia (including neutropenic infections and febrile neutropenia), neuropathy (motor and sensory), anaemia, thrombocytopenia, thromboembolic events, diarrhoea, nausea, vomiting, fatigue, stomatitis, anaphylaxis and sudden death [267,268]. Neutropenia is quite common, occurring in 12−32% of patients, and febrile neutropenia occurs in 6−15% [268]. Other complications are more rare, with grade ≥ 3 adverse effects occurring in ≤ 6% of patients [268]. Notably, only 39% of patients were nonmetastatic in the STAMPEDE trial, which reported the highest toxicity rates (except for simple neutropenia) among the trials included in the review by Puente et al. [268], and two other trials included only metastatic patients [268]. In the Prostate Cancer Consortium in Europe (PEACE)-1 trial, which consisted of patients with metastatic

disease, the most common grade ≥ 3 side effects of abiraterone acetate were hypertension (29% vs. 16% in the control arm) and hepatotoxicity (6% vs. 1%) [269]. Otherwise, it seems to be quite well tolerated.

2.9.7 Watchful waiting and observation

If the patient is too ill due to comorbidities to benefit from curative-intent treatment or AS programs, watchful waiting is often the best solution. Watchful waiting has no follow-up program: patients may contact health care services when needed, or there may be seldom regular check-ups [49]. The need for PSA control tests should mainly be determined by clinical decision-making (whether the patient has new symptoms or if the old symptoms have worsened) [49]. ADT may be initiated during the follow-up if the patient progresses symptomatically [149].

The EAU guidelines consider watchful waiting as an option for patients with an LE < 10 years, and it can be used for all patients regardless of risk stratification [49]. The ESMO and NICE guidelines consider it an option for patients who are unsuitable for or unwilling to undergo curative-intent treatment [149,155]. The AUA recommends watchful waiting for asymptomatic patients with a limited LE [151]. An exact LE cut-point is not given, but the guideline states that people with an LE ≤ 5 years do not benefit from treatment [151].

The NCCN guidelines recommend observation instead of watchful waiting [152]. Observation involves a doctor's appointment with a physical exam once a year or less often [152]. It is advised for asymptomatic patients with very low- and low-risk PC and an LE ≤ 10 years, as well as for patients with intermediate-risk PC with an LE ≤ 5 years [152]. It is also a possibility for patients with intermediate-risk PC and an LE between five and ten years and any asymptomatic PC patient regardless of risk stratification status when LE is ≤ 5 years [152]. If the patient becomes symptomatic during observation, both active treatment and palliation may be considered [152].

2.10 Follow-up of local prostate cancer after radical treatment

After radical treatment, patients should be routinely followed up [49]. The EAU recommends PSA testing, anamnesis and DRE every six months and then every year [49]. In men receiving ADT, the follow-up visits should be in 3−6 month intervals

and include liver and renal function laboratory testing, as well as serum testosterone and metabolic parameters [49]. Bone density and vitamin D and calcium level measurements are also encouraged [49]. ESMO also recommends actions to prevent bone loss in ADT patients (lifestyle modifications, regular bone density measurements or osteoporosis medication) [149]. The ESMO recommends genetic testing for patients with a familial history of PC [149].

NICE recommends PSA measurements six weeks after the treatment, every half a year up to two years, and then yearly [155]. NICE does not recommend routine DREs [155]. The NCCN recommends PSA measurement every 6−12 months for five years and then yearly [152]. DRE is recommended for patients who are suspected for recurrence [152]. In N1 patients, follow-up programs should be more frequent, including PSA measurement and physical examination every 3−6 months [152]. Genetic testing is recommended for those belonging to higher risk groups with a family history of PC, genetic predisposition or prior male breast cancer [152].

The AUA recommends PSA measurement and symptom evaluation every 3−6 months up to two years, then every half year up to 10 years, and then on a shared decision-making basis (if PSA stays low) [200].

2.11 Failure after local treatment

Since extraprostatic tissues produce undetectable amounts of PSA in the bloodstream [270], ideally, the serum PSA levels after RP should also be undetectable. However, there is no universal consensus for the PSA threshold for defining biochemical recurrence (BR, PSA relapse) after RP [49]. PSA failure can be defined as PSA levels that are elevated in subsequent testing above 0.4 ng/ml, since this level predicts the most accurate incidence of metastases [49]. The AUA defines BR after RP as a confirmed PSA level ≥ 0.2 ng/ml [271]. However, it is clarified that this is not necessarily the threshold for treatment [271]. The NCCN defines PSA failure after RP as detectable PSA after RP (PSA persistence) or PSA that is initially undetectable and then increases in two subsequent tests or elevates above 0.1 ng/ml (PSA recurrence) [152].

The RTOG-ASTRO Phoenix Consensus Conference defined BR after RT as an elevation of PSA concentration by 2 ng/ml or more from the nadir value (the lowest measured value after treatment) [272]. There are no separate definitions for BT [49,152,271].

After curative-intent treatment, patients have an approximately 10−20% probability of biochemical failure within five years [273]. The probability of BR seems to be smaller in men treated with BT or RP compared to EBRT, probably due to differences in patient selection (BT and RP have lower risk profile tumours) [273].

Even in the absence of BR, surgery may fail due to positive margins, invasion to seminal vesicles, extracapsular carcinomatous extension or postoperative detectable PSA [152]. The NCCN still recommends considering adjuvant RT or ADT for these patients [152]. The EAU, ESMO or AUA guidelines do not encourage adjuvant RT, citing overtreatment of patients compared to early SRT [49,149,200]. However, the EAU suggests considering it for patients with the following HRFs (at least two required): ISUP GG ≥ 4, T3 or positive surgical margins [49]. The Advanced Prostate Cancer Consensus Conference (APCCC) 2022 recommended RT + ADT following RP in patients with PSA persistence (1−2 months post-operatively) and N0 disease and at least two of the following: ISUP GG ≥ 4, T3 or microscopic residual disease [274]. The EAU recommends against ADT for N0 patients [49]. However, offering it as an option is recommended for N1 patients after EPLND by both the EAU and AUA [49,200]. NICE recommends both adjuvant RT and ADT outside clinical trials, even if the margins are positive [155].

2.11.1 Imaging and biopsies after biochemical recurrence without adjuvant deprivation therapy

The evidence for the benefits of imaging after PSA relapse or persistence in asymptomatic patients is very limited [49]. Clinical metastases typically occur 7−8 years after BR [49]. Regarding PSMA PET/CT, a meta-analysis based on retrospective studies showed 64% PSMA positivity (95% CI = 38−87%) for patients with a long PSA-dt and 92% PSMA positivity (95% CI = 87−96%) for patients with a short PSA-dt [275]. The clinical importance of this is uncertain, since PSMA PET/CT has not yet been studied enough in prospective clinical trials to affect treatment decisions [49]. PSMA positivity may mean residual cancer or N1 or M1 positivity [276]. In a retrospective study by Verburg et al. (N = 155), the presence of distant metastases was 15% in patients with PSA < 1 ng/ml, 37% for patients with PSA between 1 and 2 ng/ml and 41% in men with PSA ≥ 2 ng/ml [276]. However, APCCC 2022 recommended PSMA PET to all patients with PSA persistence 1−2 months after RP [274].

The EAU recommends imaging only when it affects treatment decisions [49]. Examples include patients considered for local salvage prostatectomy after RT (PSMA PET/CT, MRI) [49]. Guided biopsies are also recommended if salvage prostatectomy is considered [49]. For BR following RP, the NCCN recommends considering imaging of both bone and soft tissues, as well as prostate bed biopsy for patients with an LE > 5 years [152]. For BR following RT and patients with an LE > 5 years, the NCCN recommends bone and soft tissue imaging, risk assessment using PSA-dt and consideration of biopsy for imaging-negative patients [152]. NICE recommends against routine MRI before SRT [155]. NICE also recommends PSMA PET/CT for symptomatic patients or those with rising PSA levels if SRT is considered [155]. Biopsies are recommended only for patients enrolling in a trial [155]. The ESMO guidelines recommend PET CT if salvage RT is considered [149]. APCCC 2022 recommended PSMA PET for the majority of patients (not further elaborated) with rising PSA levels ≥ 0.2 ng/ml following RP and PSA-dt under one year or ISUP GG ≥ 4 [274]. Similarly, the conference recommended PSMA PET following BR after EBRT, regardless of PSAV [274].

2.11.2 Treatment of biochemical recurrence

BR does not necessarily require any treatment: continued monitoring is therefore an acceptable option in most guidelines [49,152,155,271]. The ESMO guidelines are an exception, recommending early SRT after PSA failure following RP [149]. The NCCN does not recommend monitoring if the patient is N1 based on imaging [152]. Monitoring does not differ from the principles of follow-up described previously in the EAU or NCCN guidelines [49,152].

SRT is the preferred active treatment in the guidelines after BR following RP [49,149,152,155]. In SRT, early initiation of the treatment is preferred [49,149]. PSA levels should be preferably still < 0.5 ng/ml [149]. Simultaneous irradiation of pelvic nymph nodes is a possibility [149]. Combining SRT with ADT is also possible but not mandatory [49,149,277]. Two years of SRT + bicalutamide 150 mg/day improved 12-year OS compared to SRT + placebo in the RTOG 9601 trial [278]. The EAU recommends a total dose of at least 64 Gy to the prostate bed [49]. The EAU cites the Swiss Group for Clinical Cancer Research (SAKK) 09/10 trial, where 64/2 Gy was better tolerated than 70/2 Gy [279]. The NCCN guidelines consider that a combination of SRT, ADT and abiraterone acetate may be used [152]. This is apparently based upon the STAMPEDE trial described previously, where a minority

of participants had prior BR (2.8% in the control group, 4.0% in the treatment group) [259].

ADT monotherapy may be used after BR for both post-RP and post-RT patients [152]. The EAU, however, recommends it only for patients with PSA-dt under 6−12 months, GS ≥ 8 and long LE [49], citing the review conducted by the EAU panel itself published in 2016 [280]. The ESMO recommends early ADT monotherapy only for patients with short PSA-dt or symptomatic progression [149]. NICE does not recommend ADT (with or without SRT) unless the patient is symptomatic or has a PSA-dt under three months [155]. The AUA does not recommend ADT to be habitually used, suggesting that the patient be enrolled in a clinical trial instead if monitoring is unacceptable [271].

Salvage prostatectomy (outside the clinical trial setting) is not generally recommended after RT failure [49,149]. However, the NCCN guidelines mention it as a possibility for patients with an LE > 5 years and biopsy-confirmed recurrence following RT [152]. BT, cryotherapy and high-intensity ultrasound are also mentioned [152]. Based on a review, these options seem to suffer from questionable efficacy with increased toxicity [281]. EPLND or pelvic nodes may be considered if the imaging suggests regional metastases [152].

2.12 The concept of castration-resistant prostate cancer

Disease progression either biochemically or radiologically during ADT indicates transition to the castration-resistant stage [49]. Castration-resistant prostate cancer (CRPC) is defined either as three successive elevations in PSA measured at least a week apart that surpass the nadir value by 50% at least twice (biochemical progression) or two or more bone lesions or one soft tissue lesion in imaging (radiological progression) [49]. Testosterone must be at castration levels (below 1.7 nmol/l) when CRPC is diagnosed [49,149]. Radiological lesions should be classified according to Response Evaluation Criteria in Solid Tumours (RECIST) [49]. Diagnosing progression based only on symptoms is not recommended by the EAU [49]. In the TAP 32 trial, only 23% of patients with T3−T4 tumours progressed biochemically during long-term ADT after EBRT, compared to 37% with ADT monotherapy [282].

While radiological progression certainly indicates mPC, biochemical progression does not necessarily indicate it. Symptoms suggestive of bone metastases and

biochemical progression are both causes for imaging (scintigraphy, CT, PSMA PET CT/MRI) in patients receiving ADT [49,152].

2.13 Treatment and follow-up of local castration-resistant prostate cancer

In the 2010s, three novel antiandrogens were approved for the treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC): enzalutamide, apalutamide and darolutamide [265]. These drugs all work by preventing the nuclear translocation of AR [265]. All three have demonstrated OS benefits in nmCRPC in clinical trials [49] and are recommended by the EAU, ESMO, NCCN and AUA [49,149,152,283]. However, these second-generation antiandrogens are indicated only if the PSA-dt is ≤ 10 months [49,152]. They are used with continued ADT [149,152]. If the PSA-dt is > 10 months, the NCCN recommends monitoring or substituting conventional ADT with another treatment [152].

The most common side effects of second-generation antiandrogens are hypertension (20% in a cohort by Hussain et al.), eczema (13%), arthralgia (12%), peripheral oedema (8%) and diarrhoea (8%) [284]. There are no statistically significant differences between serious adverse effects between the three drugs [285].

The general principles of follow-up during ADT apply to men with nmCRPC [49,152]. Further biochemical progression or symptoms suggestive of metastases should lead to prompt consideration of restaging through imaging [49,152].

The mechanism of action of second-generation antiandrogens is further explained in Figure 4, along with other ADT treatments.

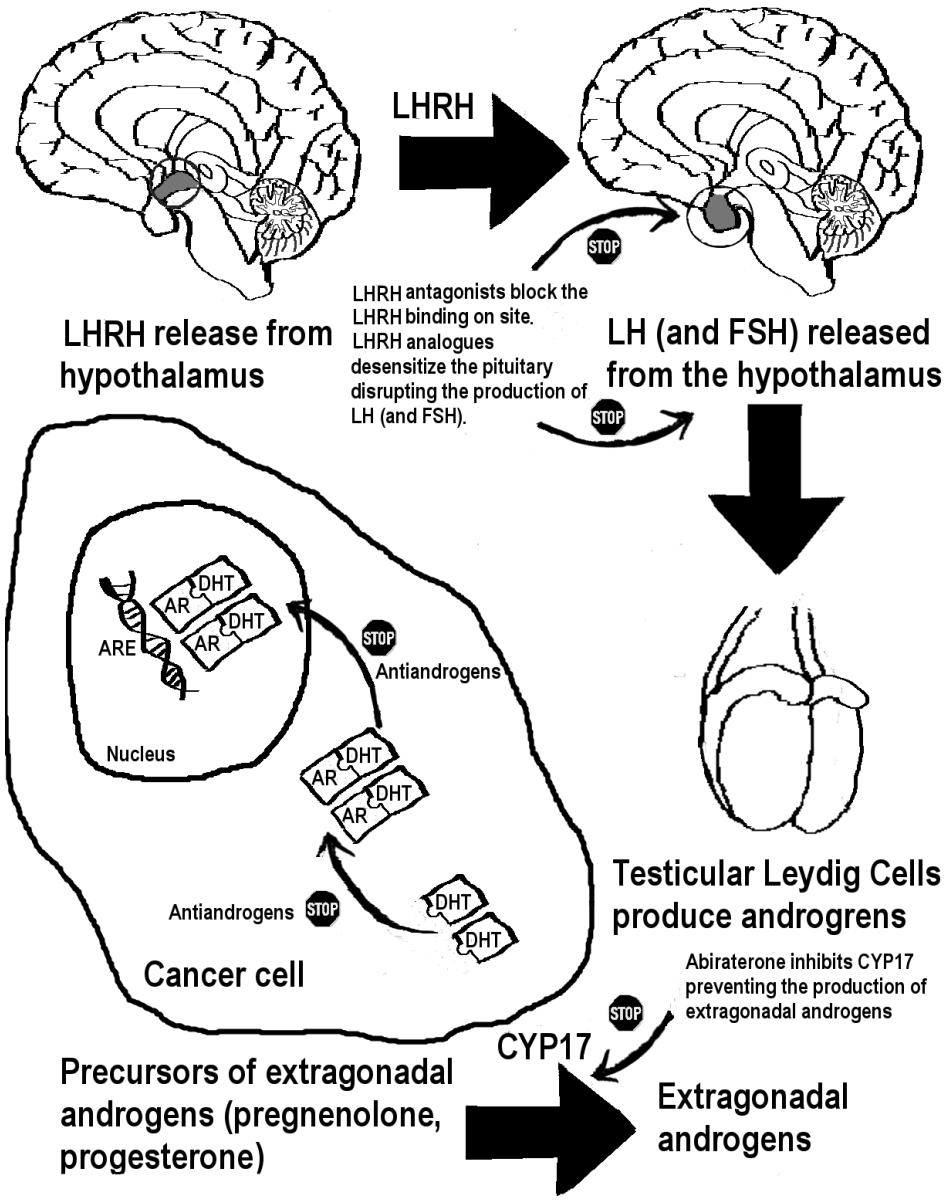

Figure 4. An illustration representing the mechanism of action of current androgen-suppressing and antiandrogen therapies. Antiandrogens block the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). With the second-generation antiandrogens (enzalutamide, apalutamide, darolutamide), the inhibition is irreversible. Antiandrogens also prevent DHT-AR complex translocation into the nucleus and the activation of androgen response element (ARE). CYP17 = cytochrome P450 17; FSH: follicle-stimulating hormone; LH: luteinizing hormone; LHRH = luteinizing hormone-releasing hormone. Sources: [12,286–288]

2.14 Metastatic M1 prostate cancer

Approximately one in five men diagnosed with PC progress to the M1 stage within seven years [289]. Additionally, 5% of NCCN high-risk and 22% of very high-risk tumours are M1 when diagnosed, while the risk is ≤ 0.5% for the remaining risk groups [290]. When PC is already in the M1 stage when first diagnosed, it is referred to as synchronous (de novo) mPC [49]. PC progressing to M1 during follow-up is referred to as metachronous mPC [49].

Furthermore, mPC can also be classified as metastatic hormone-sensitive prostate cancer (mHSPC) or mCRPC [49]. In the United States (US), Surveillance, Epidemiology, and End Results Program (SEER) registry data from 2000−2016 showed that approximately 2 in 3 men died within five years after the cancer progressed to stage IVB [291]. Seventy-eight percent of decedents died of PC, and the majority (two out of three) died within two years after progressing to the final stage [291].

Finally, mPC can be classified as low-burden or high-burden disease with varying criteria depending on the number of metastases and their sites (no consensus on the definition currently exists) [292].

2.14.1 Treatment of metastatic hormone-sensitive prostate cancer

ADT monotherapy is not generally recommended in the treatment of mHSPC unless the patient cannot tolerate any other treatments [149,293]. The primary treatment alternatives according to various guidelines (EAU, AUA, ESMO) are either combination therapy with conventional ADT and a newer androgen-suppressive agent (enzalutamide, apalutamide or abiraterone acetate + prednisone) or conventional ADT and chemotherapy with docetaxel [49,149,271]. However, NICE recommends only docetaxel + ADT as the first-line treatment in mHSPC [155].

In March 2022, the Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer (ARASENS) trial reported a 32.5% risk reduction of death from any cause with darolutamide combination therapy compared to standard ADT + docetaxel + placebo ($P<0.001$) at 40 months without notable differences in serious adverse effects [294]. Similarly, the PEACE-1 trial reported a benefit in OS ($P = 0.03$) with combination therapy with standard of care (SOC) + abiraterone acetate + prednisone with or without radiation therapy compared to SOC alone with or without radiation therapy [269]. Grade ≥ 3 side

effects were more frequent in the abiraterone acetate group (63% vs. 52%) [269]. It should also be noted that PEACE-1 included only de novo mHSPC patients [269].

The NCCN guidelines have already adopted combination therapy with conventional ADT, docetaxel and either darolutamide or abiraterone acetate + prednisone in its recommendations instead of ADT + docetaxel [293]. The guideline also acknowledges standard ADT with either enzalutamide, apalutamide or abiraterone acetate + prednisone (without docetaxel) [293]. Finally, for low-burden disease only, EBRT of the primary tumour combined with conventional ADT may be used [293], which is also supported by the ESMO, AUA and EAU [49,149,271], but the latter supports it only for de novo patients [49]. The EAU recommends that Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial criteria be used for tumour burden [49], which were a) no presence of visceral metastases and b) ≤ 3 bone metastases for low-volume disease [295]. It should be noted that neither of the two trials that investigated RT of the primary tumour found an OS benefit, only a benefit in FFS [149].

2.14.2 Treatment of metastatic castration-resistant prostate cancer

Until the mid-1990s, mCRPC was viewed as chemotherapy resistant [296]. In 1996, a Canadian RCT investigating mitoxantrone 12 mg/m^2 every three weeks and prednisone 5 mg twice a day demonstrated a benefit in symptom palliation and QoL (but not OS) compared to prednisone alone [297]. In 2004, two trials investigating docetaxel for mCRPC published results showing improvement in OS: the Southwest Oncology Group (SWOG) 99-16 trial and the TAX 327 trial [298,299]. In SWOG 99-16, patients received either docetaxel 60 mg/m^2 every three weeks combined with estramustine 280 mg three times a day for five days in every cycle starting a day before each docetaxel infusion and dexamethasone 20 mg three times a day every evening before docetaxel infusion or mitoxantrone + prednisone as in the Canadian trial mentioned previously [297,298]. OS in the docetaxel group was 17.5 months compared with 15.6 months in the mitoxantrone group (P=0.02) [298]. In the TAX 327 trial, docetaxel 75 mg/m^2 every three weeks + prednisone 5 mg twice a day was superior to mitoxantrone (as in the Canadian trial) (OS 18.9 vs. 16.3 months, P=0.009), while docetaxel 30 mg/m^2 every week plus prednisone 5 mg twice a day was not superior to mitoxantrone (P=0.36) [296]. In 2013, a phase III trial conducted in Finland, Sweden and Ireland comparing docetaxel every third week to biweekly

docetaxel monotherapy in metastatic hormone refractory prostate cancer patients (PROSTY) showed that biweekly docetaxel 50 mg/m^2 compared to docetaxel 75 mg/m^2 every three weeks improved OS and reduced toxicity (OS 19.2 months vs. 17.8 months, P=0.021) [300]. Prednisolone 10 mg/day was given in both arms [300]. The toxicity result was supported by a recent Spanish retrospective study (N=200) [301].

Furthermore, both abiraterone acetate and enzalutamide have indications for mCRPC in docetaxel-naïve patients [49]. In the Cougar-Abiraterone Acetate (COU-AA)-302 study, docetaxel-naïve patients received either abiraterone acetate 1 gram (g) daily plus prednisone 5 mg twice a day or placebo plus prednisone. Both OS (34.7 vs. 30.3 months, P=0.003) and radiographic progression-free survival (rPFS) were improved in the abiraterone acetate + prednisone arm [49,302]. Enzalutamide was examined in an RCT in which docetaxel-naïve patients received enzalutamide 160 mg a day or placebo (OS 32.4 vs. 30.2 months, P<0.001) [303]. Sipuleucel-T, which is an immunotherapeutic agent manufactured from the patient's own white cells collected through leukapheresis and then incubated with PAP, also has indications for mCRPC [49,304]. In the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial (not to be confused with the trial of the same name investigating PC genetics described in Section 2.6.1), three infusions of sipuleucel-T every two weeks improved OS by approximately four months (P=0.03) compared to placebo [305]. The majority of patients (57.2% in the treatment arm, 50.3% in the control arm) had received prior docetaxel [306].

In the Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, patients with symptomatic bone metastases, either unfit for or declined docetaxel (43%) or after TF with docetaxel (57%) received six infusions of radium-223 (Ra-223) dichloride or placebo [307]. Both OS (P=0.02) and QoL (P=0.006) were better in the treatment arm [307]. In RCTs, both abiraterone acetate and enzalutamide have shown OS benefits compared to placebo after TF with docetaxel [49]. Cabazitaxel, which is a taxane and a chemotherapeutic agent similar to docetaxel, has also shown OS benefits when used with prednisone and compared to mitoxantrone + prednisone [49]. In the Cabazitaxel versus abiraterone or enzalutamide (CARD) trial, cabazitaxel 25 mg/m^2 every three weeks + prednisone 10 mg/day + granulocyte colony-stimulating factor (GCSF) had superior OS compared to abiraterone 1 g/day + prednisone 5 mg twice a day or enzalutamide 160 mg/day (P=0.008) in patients who had failed prior novel hormone therapy [308]. In the third and fourth line of treatment (with docetaxel and/or cabazitaxel and novel hormone therapy), lutetium-177 (Lu-177)-labelled PSMA-617 has been shown to increase OS compared to SOC

(15.3 vs. 11.3 months, P<0.001) in an RCT setting [309]. A summary of the different lines of treatment of mCRPC is presented in Table 7.

In the field of precision medicine, the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib has been proven to increase OS (19.1 vs. 14.7 months, P<0.001) in men who have germline or somatic mutations in the *BRCA1*, *BRCA2* or *ATM* genes compared to novel hormone therapy with abiraterone acetate + prednisone or enzalutamide [310]. In this trial, patients received olaparib as a second-line treatment after TF with novel hormone therapy (no prior docetaxel) [310]. A similar agent, rucaparib, has been approved for the treatment of mCRPC by the United States Food and Drug Administration (FDA) but not by the EMA [49]. Ipatasertib, an experimental protein kinase B inhibitor, has shown improvement in rPFS in mCRPC patients with *PTEN* loss mutation, but OS results have not yet been published [49].

Table 7. Drugs used to treat mCRPC in different lines of treatment with guideline recommendations. Sources: [49,149,155,283,293]

Drug	First line	Second line	Third/fourth line	Guideline recommendations
Docetaxel (D)	Yes			NCCN*, NICE, EAU*, ESMO, AUA
		Yes		NCCN*, EAU, ESMO, AUA
			Yes (D rechallenge after prior D and novel HT)	NCCN*
Abiraterone acetate (AA) + prednisone (P) or enzalutamide (E)	Yes			NCCN*, EAU, AUA ESMO: asymptomatic or mild symptoms only NICE: recommends against
		Yes		EAU, ESMO*, AUA NCCN*: dexamethasone may be used instead of P with AA
			Yes	NCCN** EAU: after two lines of CTx
Sipuleucel-T	Yes, in every line if not previously treated with sipuleucel-T			EAU AUA**: no or mild symptoms NCCN: no or mild symptoms, no LMets, LE > 6 months, good PS
Radium-223 dichloride	Yes (unfit for D)			EAU NCCN: only if symptomatic BMets ESMO: only if symptomatic BMets and no VMets AUA: only if symptomatic BMets and no VMets or LAD > 3 cm

		Yes		EAU NCCN: only if symptomatic BMets ESMO: only if symptomatic BMets and no VMets AUA: only if symptomatic BMets, no VMets or LAD > 3 cm
Cabazitaxel	No			
		Yes		EAU*, ESMO*: following D NCCN*: may be combined with carboplatin in selected patients
			Yes	ESMO EAU*, AUA**: following D and E or AA + P NCCN*: may be combined with carboplatin in selected patients
Mitoxantrone	No			
		Yes, for SP in patients unfit for other therapies		NCCN
Olaparib	Yes: *BRCA* and *ATM* mutation carriers			EAU ESMO**: *BRCA* mutation carriers
		Yes: *BRCA* and *ATM* mutation carriers		EAU, NCCN, AUA ESMO**: *BRCA* mutation carriers
Rucaparib	No			
		Yes: *BRCA* mutation carriers		NCCN, AUA
Lutetium-177-PSMA-617	No			
		Yes		EAU: only if PSMA-positive metastases
			Yes	EAU, NCCN: only if PSMA-positive metastases
Other HT***	Yes			NCCN
Platinum-based CTx	No			
		Yes, if HRR gene mutations and unfit for PARP-inhibitor		AUA**

*) preferred treatment **) clinicians may offer the treatment ***) not further elaborated. Abbreviations: AA = abiraterone acetate; *ATM* = ataxia telangiectasia mutated (gene); AUA = American Urological Association; *BRCA* = breast cancer susceptibility gene; BMets = bone metastases; CTx = chemotherapy; EAU = European Association of Urology; ESMO = European Society of Medical Oncology; HRR = homologous recombination repair; HT = hormonal therapy; LAD = lymphadenopathy; LE = life expectancy; LMets = liver metastases; NCCN = National Comprehensive Cancer Network®; NICE = National Institute for Health and Care Excellence; PARP = poly (ADP-ribose) polymerase; PS = performance status; PSMA = prostate-specific membrane antigen; SP = symptom palliation; VMets = visceral metastases.

The NCCN and AUA guidelines have also recommended pembrolizumab for patients with mCRPC and mutations with high microsatellite instability and mismatch repair deficiency, and pembrolizumab was approved by the FDA for this purpose [283,293]. However, in August 2022, Merck released a statement that the results regarding OS and rPFS had remained negative in the first phase III study, where pembrolizumab was used adjuvantly with docetaxel [311]. There are still two ongoing phase III trials [312], which have not yet published even preliminary results.

2.14.3 Follow-up of metastatic prostate cancer

The EAU guideline follow-up principles resemble those for local PC with hormonal treatment [49]. However, follow-up visits should be organized with 3−6 month intervals [49]. The physician should look for and ask about signs of spinal cord compression and urinary tract obstruction [49]. Restaging (i.e., imaging) is recommended if mHSPC is suspected to have progressed to mCRPC based on PSA values if it affects the treatment decisions [49].

The AUA recommends PSA measurements every 3−6 months [271]. In mCRPC patients, alkaline phosphatase (ALP), haemoglobin, lactate dehydrogenase and testosterone should routinely be measured, as well as symptom and performance status assessment [283]. Radiological follow-up programs (based on conventional methods) can be considered [271].

The NCCN recommends physical examination, PSA measurements and conventional imaging with 3−6-month intervals for mHSPC patients [293]. For mCRPC patients, imaging (CT, bone scans) can be performed as often as every 2−3 months [293]. Physical exams and PSA measurements should be continued as long as the patient is in life-prolonging treatment [293].

2.14.3.1 Bone health in metastatic prostate cancer

The EAU recommends denosumab or zoledronic acid for mCRPC patients with bony metastases and offering vitamin D and calcium supplements simultaneously [49]. The ESMO also recommends denosumab or zoledronic acid if the patient has mCRPC or bone metastases and is at increased risk for skeletal complications [149]. Actions to prevent bone loss are also encouraged for patients with local PC on long-term ADT [149]. Lifestyle modification can include smoking cessation, exercise,

reduction of alcohol consumption and ensuring sufficient calcium and vitamin D intake [149].

The AUA recommends vitamin D and calcium supplements for all men with advanced PC [283]. Physical exercise and smoking cessation are also encouraged for reasons related to bone health [283]. Preventive osteoporosis medication can be considered for those estimated to be at increased bone fracture risk [283]. Denosumab or zoledronic acid are recommended for mCRPC patients with bone metastases [283]. The NCCN likewise recommends denosumab (preferred) or zoledronic acid for mCRPC metastatic to the bone [293].

The NICE recommends considering bisphosphonates for mPC after initial hormonal failure [155].

2.14.3.2 Genetic testing in metastatic prostate cancer

The EAU recommends offering broad genetic testing (somatic mutations, germline mutations, mismatch repair deficiency/microsatellite instability) for mCRPC patients [49]. The ESMO recommends germline testing for all mPC patients [149]. Mismatch repair deficiency/microsatellite instability testing is recommended for mCRPC patients [149].

The AUA recommends offering genetic testing for patients with mHSPC rather than mCRPC [271,283]. The NCCN recommends germline testing for all mPC patients [293].

Germline mutations of anoctamin 7 (*ANO7*) have been studied in the PROSTY population, and one variant was identified to have a superior treatment response to docetaxel [313].

2.15 Performance status and its importance in evaluating cancer therapy fitness

In 1948, Karnofsky et al. published the first scale to describe a patient's performance in activities of daily living and symptomaticity [314,315]. Their original intent was to use it in the evaluation of treatment response in their study on palliative treatment of lung cancer [314]. The Karnofsky performance status (KPS) can obtain values from 0% to 100% in ten percent intervals, where 0% corresponds to death and 100% corresponds to normal performance and being asymptomatic [314]. In 1960, Zubrod

et al. from the Eastern Cooperative Oncology Group (ECOG) introduced a simpler scale focusing only on performance [316]. The Zubrod score (Z) is currently 6 points, with 0 corresponding to normal activity and 5 indicating death (originally deceased persons were not classified) [316,317]. The Zubrod score is also known as the ECOG performance score or the WHO score [315]. It was similar to the KPS developed to evaluate treatment response in clinical trials [317]. Since the 1970s, performance status has been used more as an eligibility criterion in the trial setting (for example, patients with Z≥3 are ineligible) since accepting patients in all conditions in trials was shown to lead to heterogeneity bias [317]. Both the EAU and AUA guidelines recommend taking the patient's performance status into account when selecting treatment for mCRPC [49,283]. The principles of the Zubrod and Karnofsky classifications are shown in Table 8.

Table 8. General principles for Zubrod and Karnofsky performance status scores. Sources: [314,315,318]

Description for Z score	Z	Corresponding Karnofsky score
Fully active	0	100%: asymptomatic, normal activity
Restricted in strenuous physical activity but ambulatory, capable of light work	1	90%: minimally symptomatic, normal activity
		80%: moderately symptomatic, normal activity with effort
Self-caring, unable to work, ambulatory > 50% of waking hours	2	70%: self-caring, unable for work or normal activity
		60%: requires occasional assistance, mostly self-caring
Ambulatory < 50% of waking hours, capable of limited self-care	3	50%: needs considerable assistance and frequent medical care
		40%: disabled, requires special care
Bedridden, not able to carry out any self-care	4	30%: severe disability, hospitalization (or equivalent care) recommended, death not imminent
		20%: requires hospitalization/active supportive care
		10%: moribund
Dead	5	0%: dead

2.15.1 Performance status and the prognosis of metastatic prostate cancer

A recent meta-analysis by Chen et al. that included 34 studies concluded that CRPC patients with a performance status of Z≥2 have increased OM compared to those with Z<2 (HR=2.10, 95% CI = [1.68−2.62], P<0.001) [319]. Approximately 98.6% of the patients included in the analysis were M1 [319]. The meta-analysis was

stratified for Gleason score [319]. The results for taxane chemotherapy (docetaxel or cabazitaxel) and androgen-targeting therapy (abiraterone acetate or enzalutamide) were similar: the HR was 2.21 [1.58−3.10] for the taxane subgroup and 1.97 [1.56−2.47] for the androgen-targeting therapy subgroup [319]. A Zubrod score ≤ 1 has also been found to be an independent predictor of OS after palliative RT for mPC with bone metastases [320]. KPS≤70% seems to be linked to worse OS after RT for cerebral metastases in mPC [321].

In a small (N=237) Japanese single-centre study with a follow-up period up to fifteen years, a Z score ≥ 1 was also associated with poorer OS (P<0.05) in patients with mHSPC in a multivariate model [322]. Ninety-four deaths occurred during the follow-up period, and the study model included 16 variables [322]. This yields an event per variable (EPV) ratio of approximately 6:1, which may be too small to draw reliable conclusions [323]. In 1985, Emrich et al. showed that patients with advanced PC and performance status Z≤1 had better OS than patients with Z≥2 [324]. Performance status does not seem to have an effect on PFS in mPC patients [325].

2.15.2 Performance status and the prognosis of local prostate cancer

Considering local PC, in a Norwegian study by Fosså et al., performance status Z≥1 was associated with increased OM in those who received local treatment (N=2234, HR=2.03, [1.67−2.48]) and PCSM (HR=1.45, [1.02−2.05]) [326]. The local treatment was either RP (N=895) or EBRT with or without ADT (N=1339) [326]. The results were similar for those who received no local treatment: HR=1.93 [1.53−2.44] for OM and HR=1.46 [1.00−2.14] for PCSMS [326]. Aas et al. reported similar results with HR=1.4 ([1.12−1.86], P=0.006) for OS in Z≥1 and HR=2.0 ([1.23−3.20], P=0.008) for PCSM; this study was also from Norway and had a 10-year follow-up [327]. Performance status, unlike age, does not seem to impact referrals considering curative treatment for PC, at least in Belgium [328].

2.15.3 Performance status as an eligibility criterion

As discussed previously, many novel drugs have not been studied in patients who have worse performance scores, since performance status is usually an eligibility criterion. In other instances, the drug may be studied, but the results are different in the worse performance status subgroup. An example of this is abiraterone acetate + prednisone in the treatment of mHSPC in the Long-Acting Therapy to Improve

Treatment Success in Daily Life (LATITUDE) trial, which did not demonstrate an OS benefit in the Z=2 group in the subgroup analysis [329]. The novel drugs are classified according to their licenced performance statuses in Table 9.

Table 9. Novel pharmaceuticals according to the performance statuses studied

Drug	Patient group studied	Drug	Patient group studied
Abiraterone acetate + prednisone/prednisolone (PO, ARPI)	Z ≤ 2 for mCRPC after docetaxel [330], Z ≤ 1 for mCRPC in docetaxel-naïve patients [330], Z ≤ 2 for mHSPC* [329]	Apalutamide (PO, ARPI)	Z ≤ 2 for mHSPC [330], Z ≤ 1 for nmCRPC [331]
Cabazitaxel (IV, CTx)	Z ≤ 1 [330]	Darolutamide (PO, ARPI)	Z ≤ 1 for nmCRPC and mHSPC [294,332]
Docetaxel (IV, CTx)	KPS ≥ 60% for mCRPC [155,299], Z ≤ 2 for mHSPC [295]	Enzalutamide (PO, ARPI)	Z ≤ 2 for mCRPC after docetaxel [333], Z ≤ 1 for mCRPC in docetaxel-naïve patients [303], Z ≤ 1 for mHSPC and nmCRPC [334,335]
Lu-177-PSMA-617 (IV, RAD)	Z ≤ 2 [309]	Mitoxantrone (IV, CTx)	Z ≤ 3 [297]
Olaparib (PO, PARPI)	Z ≤ 2 [310]	Ra-223 dichloride (IV, RAD)	Z ≤ 2 [307]
Rucaparib (PO, PARPI)	Z ≤ 1 [336]	Sipuleucel-T (IV, CIT)	Z ≤ 1 [293]

*) the OS benefit was not proven for the Z = 2 subgroup. ARPI = androgen receptor pathway inhibitor; CIT = cellular immunotherapy; CTx = chemotherapy; IV = intravenous administration; PARPI = poly (ADP-ribose) polymerase inhibitor; PO = peroral administration; RAD = radioactive drug.

2.16 Comorbidities and prostate cancer

As many guidelines base their recommendations on life expectancy, comorbidity is another important issue for a clinician to consider along with performance score and tumour-specific characteristics [126]. Comorbidity burden can be assessed in cancer patients using comorbidity indices [337]. The two comorbidity indices most studied in cancer patients are the Charlson Comorbidity Index (CCI) and the Elixhauser Index [337]. The CCI was created specifically to predict mortality in cancer patients (originally in breast cancer), whereas the Elixhauser Index was developed to predict

in-hospital mortality in patients admitted to the hospital for any cause [337]. The CCI score is defined by 19 conditions, whereas the Elixhauser Index contains 30 conditions [337]. Despite being simpler, the CCI has outperformed the Elixhauser Index in certain cancer patients [337]. The CCI has been validated for PC [337]. Since the CCI was published in 1987, several modified versions have been published attempting to reflect the improved treatment and prognosis of certain conditions, but none of the modified versions has outrightly supplanted the original [337]. The original version can still be considered an accurate predictor of mortality [337].

In the CCI, each of the 19 items is given a weight [337]. The CCI score is calculated by adding the weight of each Charlson comorbidity to the patient [337]. The higher the weight of a comorbidity is, the more it has a statistically significant impact on the affected patient's survival [338]. For example, 'mild liver disease' has a weight of 1, whereas 'severe or moderate liver disease' has a weight of 3 [338]. The CCI reflects the patient's total comorbidity burden (higher scores are linked to higher all-cause mortality) [338]. A list of CCI comorbidities and their weights is presented in Table 10.

Table 10. The original CCI comorbidities and their weights. Sources: [337,338]

Comorbidity	Weight
Cerebrovascular disease, without any or minor residual symptoms	1
Chronic pulmonary disease	1
Congestive heart failure	1
Connective tissue disease	1
Dementia	1
Diabetes, without end-organ damage (nephropathy, neuropathy, retinopathy)	1
Liver disease, mild	1
Myocardial infarction	1
Peptic ulcer disease	1
Peripheral vascular disease (intermittent claudication)	1
Any solid tumour, initially treated within five years	2
Diabetes, with end-organ damage (nephropathy, neuropathy, retinopathy)	2
Hemiplegia, paraplegia	2
Leukaemia	2
Lymphoma	2
Renal disease, moderate or severe (including renal transplant patients)	2
Liver disease, moderate or severe (cirrhosis)	3
Acquired immune deficiency syndrome (AIDS)	6
Metastatic solid tumour	6

2.16.1 Comorbidities and local or locally advanced prostate cancer

The CCI score has been shown to be prognostic on survival and mortality after PC diagnosis in several large good-quality studies [339–342]. In 2017, Rajan et al. published results from a large prospective Swedish sample (N=118,543) [339]. After adjustment for patient and tumour characteristics, 16-year other-cause mortality (OCM) was consistently affected by CCI score. When CCI=0 was used as a reference, CCI=1 had an HR of 2.43 ([2.35−2.50], P<0.001) for OCM, CCI=2 had an HR of 2.06 ([1.97−2.16], P<0.001) and CCI≥3 had an HR of 3.33 ([3.14−3.54), P<0.001) [339]. Rajan et al. also performed subgroup analyses for RP, RT, ADT and WW patients for which the results for HR for other-cause mortality were consistent (HR>1 and P<0.001 for CCI=1, CCI=2 and CCI≥3 vs. CCI=0 in all treatment modalities) [339]. Rajan et al. also investigated PCSM for which, after adjustments, the CCI score had an impact only in the CCI≥3 group vs. CCI=0 (HR=1.15, [1.06−1.25], P<0.001) [339]. In the RP, RT and WW subgroups, CCI scores had no effect on PCSM after adjustments [339].

In another Swedish registry sample (N=77,536), CCI score also had an effect on 10-year OM and OCM [340]. CCI=1 had an HR of 1.45 for OM ([1.41−1.50]) vs. CCI=0, whereas CCI≥2 had an HR of 1.99 ([1.93−2.05]) [340]. In OCM, CCI=1 had an HR of 1.75 ([1.67−1.83)], and CCI≥2 had an HR of 2.66 ([2.56−2.78]) [340]. The result was consistent for all risk groups (low, intermediate and high) and for the N1 group [340]. There was no difference in PCM [340]. A study based on a Swiss registry sample of local PC patients (N=1,527) also reported increased 10-year OCM in CCI=1 (HR=2.07, [1.51−2.85]) and CCI≥2 (HR=2.34, [1.59−3.44]) patients compared to men with CCI=0 [341]. There was no difference in PCSM [341]. The study also reported OM results, which were significant: for CCI=1, the HR was 1.59 ([1.27−2.00]), and for CCI≥2, the HR was 2.11 ([1.62-2.73]) compared to CCI=0 [341]. The model was adjusted for age, treatment, stage and grade [341]. CCI=1 and CCI≥2 patients were also more likely to receive AS or WW than CCI=0 patients: the odds ratio (OR) for CCI=1 was 1.44 ([1.00−2.06]), and the OR for CCI≥2 was 1.74 ([1.13−2.69]) [341]. In an American retrospective sample (N=14,052) consisting only of RP patients, after adjustment for age, CCI=1 and CCI≥2 scores were similarly associated with higher OM and OCM rates compared to CCI=0 but not with PCSM rates [342].

The CCI score seems to be associated with poorer OS in BT, at least in HDR BT + EBRT treatment [343]. The investigators also found an association between CCI score and FFS in this Swedish study [343]. Other studies have reported contradictory

results regarding BRFS and MFS [344]. Based on preliminary evidence, CCI scores do not seem to have an effect on the decision to initiate deferred treatment in AS [345].

2.16.2 Comorbidities and metastatic M1 prostate cancer

A registry study by Berglund et al. also reported results for M1 patients (N=13,611) for which CCI=1 and CCI≥2 patients had an increased OM compared to CCI=0 patients [340]. The HR for CCI=1 was 1.25 [1.49−1.65], and the HR for CCI≥2 was 1.57 ([1.49−1.65]) [340]. The results were similar for OCM: CCI=1 had an HR of 1.50 ([1.37−1.65]), and CCI≥2 had an HR of 2.10 ([1.92−2.92]) [340]. There was no difference in PCM [340].

In an American study (N=15,501), the modified CCI (according to Deyo et al.) had an effect on 3-year OS in men with mPC who did not receive chemotherapy as a primary therapy [346,347]. A total of 9.5% of patients received local therapy for the primary tumour [346]. Modified CCI=1 had an HR of 1.27 ([1.20−1.35], P=0.03), and modified CCI≥2 had an HR of 1.56 ([1.42−1.70], P<0.001) compared with modified CCI=0 [346]. In the subgroup analysis, the result was similar for those who did not receive local therapy for the primary tumour (N=14,031) [346]. The model was adjusted for age, GS, TNM stage and PSA level [346].

Similarly, the CCI score has also been shown to have an effect on OS in men with mHSPC receiving chemotherapy in another American cohort [348]. The HR for CCI=1 was 1.15 ([1.00−1.32], P=0.056), which was not statistically significant, but the HR for CCI≥2 was 1.46 and statistically significant ([1.21−1.77], P<0.001) [348]. The median follow-up time in this study was 22.6 months, and the sample size was 3737, of which 1033 (27.6%) received chemotherapy [348]. The result was similar in a smaller Danish study (N=207), which consisted of de novo mPC patients [349]. Here, the HR for OS was 1.20 ([0.95−1.52], P=0.13) for CCI=1 patients vs. CCI=0, and the HR for CCI≥2 was 1.45 ([1.10−1.93], P=0.009) [349]. A total of 16.5% of this cohort received docetaxel, and 6.3% received cabazitaxel [349].

The CCI score does not seem to have an effect on OS in mCRPC patients receiving docetaxel based on a Slovenian sample (N=208) [350].

The EAU, AUA and NICE guidelines recommend taking comorbidities into consideration when selecting the best treatment for mPC patients [49,155,271].

2.17 General principles of patient-reported outcome measures and quality-of-life research

The EMA has defined HRQoL as "the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being" [351]. A related term is "health status", which depicts the actual perceived health [352].

HRQoL questionnaires in adult oncology are considered patient-reported outcome measures (PROs) [351], although HRQoL can also be estimated indirectly without PROs, such as in QALYs [353]. In general, PROs are multidimensional, meaning that outcome data are formed from multiple questions ("domains") [353,354]. Exceptions include the visual analogue scale (VAS) for pain when used on its own [354,355]. In addition to HRQoL as an entirety, PROs can assess individual aspects, such as fatigue or pain alone [351]. Multidimensional HRQoL outcome measures can be further divided into index and profile measures, of which index measures form a single output ("index") from multiple domains, and profile measures form multiple outputs ("profiles") [353,356].

Statistically significant differences (i.e., $P \leq 0.05$) in HRQoL may not reflect truly clinically significant differences in HRQoL [357]. The minimum important difference (MID) is used to reflect the clinically significant difference relevant to the patient [357]. There is no single definition for MID [357,358]. It can be defined through distribution-based methods, anchor-based methods and the Delphi method [357,358]. Distribution-based methods can be based on, for example, standard error of measurement (SEM), standard deviation (SD), effect size, standardized response mean, minimal detectable change or reliable change index [357,358]. Anchor-based methods compare change to another known outcome ("anchor"), such as laboratory measurement, psychometric evaluation or another patient-reported outcome [357,358]. The Delphi method is based on the consensus of experts [358]. The International Society for Quality of Life Research (ISOQOL) considers the use of MIDs "highly recommendable", although not mandatory [358].

2.18 Health-related quality of life in prostate cancer research and treatment

There are several questionnaires that are used for evaluating HRQoL in the setting of clinical trials studying PC. The Functional Assessment of Cancer Therapy –

Prostate (FACT-P) was validated in the 1990s [359] and remains one of the most common questionnaires in use [360]. The FACT-P is based on the Functional Assessment of Cancer Therapy – General (FACT-G) with the addition of the prostate cancer subscale (PCS), which considers questions regarding sexuality, bowel/bladder function and pain [359]. The FACT-P has been validated in Finnish [361]. The current fourth version has 39 questions that are answered using a 5-point Likert scale [361]. The questionnaire is divided into five subscales: PCS, physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB) [361]. The FACT-G score can be calculated by adding the PWB, SWB, EWB and FWB scores [361]. The FACT-P Trial Outcome Index (TOI) score can be calculated by adding the PCS, PWB and FWB scores [361]. The English version is freely available for noncommercial use on the providing organization's website [361]. Additionally, a condensed 8-item version was designed especially for men with advanced PC, called the Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 8 Item Version (FAPSI-8) [362], which has also been validated [363].

Longer questionnaires comparable to the FACT-P are two questionnaires by the European Organisation for Research and Treatment of Cancer (EORTC): EORTC Quality of Life Questionnaire (QLQ)-PR25 is designed specifically for PC patients, and EORTC QLQ-C30 is intended for cancer patients in general [49]. They are intended to be used together [49]. The EORTC QLQ-C30 has six scales (physical, role, cognitive, emotional, social, global health/QoL) and individual items related to symptoms and perceived financial worries related to the disease [49]. The EORTC QLQ-PR25 has questions regarding urinary and bowel symptoms, side effects of the treatment, and sexuality [49].

Of other questionnaires, the Expanded Prostate Cancer Index Composite (EPIC) and its condensed form, EPIC 26, assess urinary, bowel, sexual and hormonal symptoms, while the University of California, Los Angeles Prostate Cancer Index (UCLA PCI) and Prostate Cancer Outcome Study Instrument assess only urinary, bowel and sexual symptoms [49]. The Prostate Cancer Quality of Life Instrument assesses urinary, sexual and bowel symptoms and anxiety [49].

A questionnaire native to Finland called 15D can also be used to measure the HRQoL of patients and populations [364,365]. Its benefits include that the results can be used to calculate QALYs for desired purposes [365]. The 15D has 15 dimensions measured by 15 questions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity [364]. It was not developed

specifically for PC but has been studied in PC treatment and screening [365]. It was developed as an index measure but has also been validated to function as a profile measure [365]. Selected HRQoL and symptom assessment questionnaires commonly used in PC trials are presented in Figure 5.

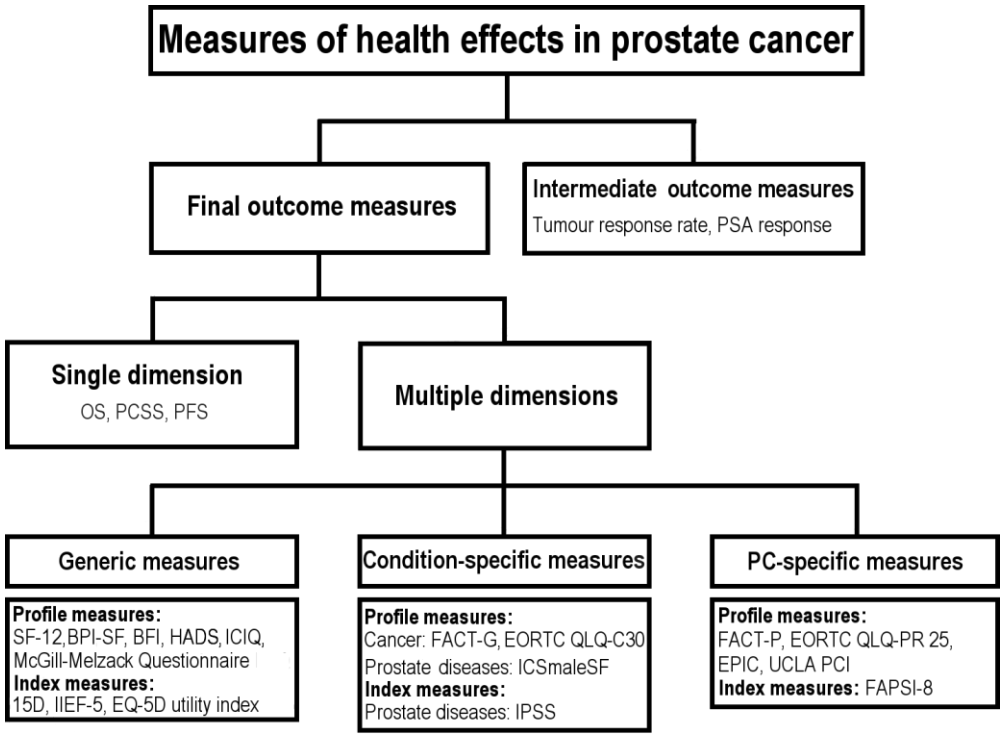

Figure 5. Measurable health outcomes are divided into single-dimension outcomes, such as overall survival (OS), and multiple-dimension outcomes that include health-related quality of life and symptom assessment questionnaires. Adapted from Drummond et al.[353]. 15D was developed as an index measure but has also been validated to function as a profile measure [365]. Abbreviations: BFI = Brief Fatigue Inventory; BPI-SF = Brief Pain Inventory Short Form; FACT-G = Functional Assessment of Cancer Therapy – General; FACT-P = Functional Assessment of Cancer Therapy – Prostate; FAPSI-8 = Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 8 Item Version; EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EPIC = Expanded Prostate Cancer Index Composite; EQ-5D = EuroQoL 5-dimension; HADS = Hospital Anxiety and Depression Scale; ICIQ = International Consultation on Incontinence Questionnaire; ICSmaleSF = International Continence Society male Short-Form (questionnaire); IIEF = International Index of Erectile Function; IPSS = International Prostatic Symptom Score; PC = prostate cancer; PCSS = prostate cancer -specific survival; PFS = progression-free survival; PSA = prostate-specific antigen; SF-12 = Medical Outcomes Study 12-Item Short-Form General Health Survey; UCLA PCI = University of California, Los Angeles Prostate Cancer Index.

2.18.1 Health-related quality of life in local or locally advanced prostate cancer

The Australian New South Wales Prostate Cancer Care and Outcomes Study (PCOS) reported prospectively collected HRQoL results for 1, 2, 3, 5, 10 and 15 years after diagnosis for men with local PC (N=1995) and compared them to an age-matched control population (N=495) [366]. The men diagnosed with PC were divided according to treatment into the AS/WW group (N=200), nerve-sparing RP group (N=494), non-nerve-sparing RP group (N=478), EBRT/HDR BT group (N=170), ADT with/without EBRT group (N=227), and LDR BT group (N=58) [366]. UCLA PCI and EPIC-26 forms were used to collect data on urinary, sexual and bowel symptoms [366]. The Medical Outcomes Study 12-Item Short-Form General Health Survey (SF-12) was used to collect data on physical and mental health [366]. One-third of the pooled SD in the control group at baseline was used as a threshold for MID, and sensitivity analyses for clinical stage, GS, and PSA at baseline were performed without significant impact on the results [366]. The results were adjusted for age, marital status, private health insurance, region, income, education, country of birth, CCI score and baseline value [366].

According to the PCOS results, urinary incontinence was significantly more bothersome in both RP groups from the first follow-up to the 15-year follow-up compared to the controls, while there were no clinically significant differences in other treatment modalities [366]. Urinary issues differed significantly from the controls only in the LDR BT group at the 1-year follow-up [366]. Sexual issues were significantly worse in the nerve-sparing RP group in years 1, 2, 3 and 5 and in the non-nerve-sparing RP group in years 1, 2, and 3 [366]. Sexual issues were alleviated in both RP groups after 1 year in a logistic growth manner [366]. Sexual issues were also significantly worse in the EBRT/HDR BT and LDR BT groups at the 1- and 2-year follow-ups [366].

In PCOS, sexual summary scores were worse in both RP groups, the EBRT/HDR BT group and the ADT group for the duration of the follow-up period [366]. However, the scores were clearly the worst in the RP groups for the first three years, after which the differences across the aforementioned groups were of the same order of magnitude compared to controls [366]. In the LDR BT group, however, the difference was significant only in the first year, possibly due to the low sample size in this group [366]. Bowel issues were significantly worse in the EBRT/HDR BT group in years 1, 2 and 3 and in the ADT group at the 1-year follow-up [366]. There

were no clinically or statistically significant differences in physical or mental health in any treatment modality [366].

Similarly, Schaake et al. compared HRQoL in men receiving EBRT for local PC (N=227) to men without PC (N=519) [367]. The majority of patients (68.7%) received adjuvant ADT, and the model was not adjusted for comorbidities [367]. The study used the EORTC QLQ-C30 form [367]. The data were collected prior to RT (baseline) and 6, 12, 24 and 36 months after the treatment [367]. However, the results for the normative population were only given for three years in comparison with the control population [367]. PC patients reported clinically and statistically worse role functioning (P=0.009), emotional functioning (P=0.008), and social functioning (P=0.001), as well as more insomnia (P=0.005) and dyspnoea (P=0.001) [367]. Selected comorbidities (coronary heart disease, obstructive pulmonary diseases) and age were included in the model, and they all had an effect on QoL [367]. There were no differences in global QoL or physical functioning [367].

Schaake et al. also compared the results against the patient baseline [367]. PC patients reported clinically and statistically more fatigue and dyspnoea (P<0.001) after the treatment for the duration of the follow-up period compared to baseline [367]. They also reported more insomnia at 6 and 12 months (P<0.001), as well as constipation and diarrhoea (P<0.001) at 12 months [367]. There were no clinically significant differences in physical, role or social functioning and neither statistically nor clinically significant differences in global QoL or emotional functioning [367].

2.18.1.1 Direct comparison of the quality-of-life effects of different treatments: evidence from randomized controlled trials

The best evidence for direct comparisons between different treatments stems from the Prostate Testing for Cancer and Treatment (ProtecT) trial, which compared EBRT (N=545, 74 Gy in 37 frs), RP (N=553) and AS (N=545) in men [368]. ProtecT used the EPIC, SF-12, Hospital Anxiety and Depression Scale (HADS), International Consultation on Incontinence Questionnaire (ICIQ) and International Continence Society Male Short-form (ICSmaleSF) questionnaires as outcome measures [368]. The data were collected at the time of biopsy (baseline) and 0.5, 1, 2, 3, 4, 5 and 6 years after the biopsy [368]. All EBRT patients received adjuvant ADT for 3−6 months [368]. MIDs for specific variables were not included in the presentation of main QoL results [368] but were provided separately for readers for certain scales (SD-based method) [369].

The ICIQ incontinence scores were clearly weakest in the RP group (P<0.001), with the lowest mean score of 5.5 at 6 months and remaining at approximately 4 thereafter [368]. ICIQ scores were relatively stable after treatment in the RT group (approximately 2 points), whereas they were between 2 and 3 in the AS group (following a slowly worsening trend) [368]. The MID for ICIQ was a 1.2-point difference [369]. The results for other incontinence items (EPIC urinary incontinence subscore, ICSmaleSF incontinence score) were similar [368].

ICSmaleSF voiding scores also followed a slowly deteriorating trend in the AS group, with mean scores of 3.8 points at 6 months and 4.2 at 6 years [368]. In the RP group, the mean score was 3.2 points at 6 months and remained stable at slightly below 3 points thereafter [368]. In the RT group, the scores were clearly the worst at 6 months (mean 5.1) and fluctuated between 3 and 3.5 thereafter [368]. The MID for ICSmaleSF voiding was 1.0 point [369].

In the EPIC urinary summary scores, the results were mostly similar between groups below the MID threshold of 4.6 points with an exception at 6 months, where the AS group scored the best (mean 90.6), while the RP and RT groups scored significantly worse (mean 80.1 and 84.7, respectively) [368,369]. The EPIC urinary issues and urinary obstruction/irritative subscores followed similar trends [368].

In the EPIC sexual summary score, the RP group again scored the worst, with 25.7 points at 6 months [368]. The scores then gradually recovered, peaking at 34.5 points at 5 years and 32.3 at 6 years [368]. In the RT group, the score was 31.9 points at 6 months and fluctuated between 40 and 43.5 thereafter [368]. The AS group again followed a deteriorating trend from 51.9 points at 6 months to 40.6 points at 6 years [368]. The MID was 11.6 points [369]. The results from the EPIC sexual function and sexual issues subscales were similar [368].

The EPIC bowel summary scores were worst in the RT group [368]. However, the absolute differences were mostly small and below the MID of 4.2 points, with an exception at 6 months, when the RT group scored 86.3, the RP group scored 92.9 and the AS group scored 92.8 [368,369]. The results were comparable in the EPIC bowel function and bowel issues subscores [368]. There were no statistically significant differences in SF-12 in either physical or mental health or in the HADS anxiety or depression subscales [368].

Giberti et al. conducted an RCT comparing RP (N=100) and BT (N=100) in low-risk PC and compared the QoL data [370]. The questionnaires used were IPSS, EORTC QLQ-C30, EORTC QLQ-PR25 and International Index of Erectile Function (IIEF-5) [370]. Only within-group comparisons were performed [370]. QoL questionnaires were collected 0.5, 1 and 5 years after the treatment [370]. In

the EORTC QLQ-C30, both groups suffered statistically significant (P<0.05) declines in physical, role and social functions at 6 months compared to baseline [370]. Both groups improved in emotional function compared to the baseline [370]. Only the RP group suffered a decline in cognitive function at 6 months (P=0.04) [370]. Both groups reported more fatigue and pain at 6 months than at baseline [370]. The RP group also reported more insomnia (P=0.04) [370]. IPSS scores worsened only in the BT group (P<0.01) at six months [370]. On the EORTC QLQ-PR25, both groups reported more urinary symptoms, treatment-related symptoms and issues related to sexual function and activity [370]. Both groups had poorer IIEF-5 scores compared to the baseline at six months [370].

The declines in the physical functioning domain of the EORTC-QLQ-C30 persisted at the 1-year follow-up in both groups, as did the improvement in emotional functioning [370]. IPSS scores remained statistically significantly worse in the BT group (P=0.01) [370]. In the EORTC QLQ-PR25, urinary symptoms were still worse in the BT group (but not the RP group), with P<0.01 [370]. Treatment-related symptoms still lowered QoL at 1 year in both groups [370]. Other differences were no longer statistically significant at one year [370]. At five years, all measures were comparable to those at baseline (P>0.05) [370].

2.18.1.2 Hypofractionated radiation therapy versus conventional radiotherapy

Three RCTs investigated the safety of moderately hypofractionated RT in comparison with conventional RT with regard to HRQoL. The CHHiP and RTOG 0415 trials found no differences of any kind [371,372]. The HYPRO trial could not rule out noninferiority for GU and GI QoL [373]. There were no differences in symptoms related to ADT or sexuality [373]. The follow-up time in all trials was five years [371–373].

Two RCTs investigating ultrahypofractionated SBRT for PC have published slightly contradictory results. PACE-B did not find any differences at its 3-month follow-up [244]. HYPO-RT-PC collected QoL data at the end of RT and 3, 6, 12, 24 and 48 months after RT [374]. The EORTC QLQ-C30 and Prostate Cancer Symptom Scale questionnaires were used [374]. There were no statistically significant differences between SBRT and conventional RT at six months or later [374]. At three months, the only difference was that the SBRT patients reported more dysuria on the PC Symptom Scale (P=0.00045). However, at the end of RT, SBRT patients experienced worse global health QoL in the EORTC QLQ-C30 (P<0.0001) [374]. Furthermore, they experienced worse role function (P=0.0014) and emotional

function (P=0.0016) and complained more of pain and diarrhoea (P<0.0001) [374]. Considering the bowel symptoms in the PC Symptom Scale at the end of RT, SBRT patients reported more stool frequency (P<0.0001), rush to the toilet in the morning because of bowel movements (P=0.0013), flatulence (P=0.0013), bowel cramps (P<0.001), mucus (P=0.0014), blood in stool (P<0.0001) and limitation in daily activity caused by bowel symptoms (P=0.0014) [374].

2.18.1.3 External beam radiotherapy and high-dose rate brachytherapy boost in terms of quality of life

Since New Wales PCOS did not separate EBRT and HDR BT or a combination of the two treatments [366], additional insight into the matter is provided. Two RCTs have investigated HDR BT boost with EBRT compared with EBRT alone. The single-centre trial (N=214) conducted in Mount Vernon Hospital, UK, collected QoL data prior to treatment (baseline) and then annually for 12 years [375]. ADT was administered to 76% of patients (for 6 months in low- and intermediate-risk patients, up to 3 years in high-risk patients) [375]. The trial found no differences in FACT-G, FACT-P, TOI or erectile function scores at any time point [375].

The Trans Tasman Radiation Oncology Group (TROG) 03.04 randomized 1071 men to four different arms: EBRT + neoadjuvant leuprorelin for 6 months + zoledronic acid for 18 months, EBRT + neoadjuvant/adjuvant leuprorelin for 18 months + zoledronic acid for 18 months, EBRT + dose escalation + neoadjuvant leuprorelin for 6 months, and EBRT + dose escalation + neoadjuvant/adjuvant leuprorelin for 18 months [376]. Dose escalation could be achieved either through HDR BT boost or by using external beams alone [376]. QoL was assessed using the EORTC QLQ PR25 and IPSS, which were reported at baseline, at the end of RT, and at 18 and 36 months [376]. IPSS scores at 18 months were worse in patients who received the HDR BT boost compared to those who did not (mean 9.5 and 6.8, respectively, P<0.001) [376]. The maximum difference for the mean EORTC QLQ-PR25 score was 7.1 at 18 months, which was considered below the clinically significant difference [376].

To date, there has not been an RCT studying HDR BT monotherapy [377]. The preliminary QoL data from phase II trials have seemed promising [377].

2.18.1.4 Adjuvant docetaxel and abiraterone: quality of life impact

Regarding adjuvant docetaxel with EBRT for local PC, GETUG-12 (where docetaxel was given with estramustine) collected data using EORTC QLQ-C30 items at baseline and at 3 and 12 months [378]. The QoL results were worse in the docetaxel group at three months regarding global health status (P=0.01), fatigue (P=0.003), role functioning (P=0.003) and social functioning (P=0.006) [378]. No differences remained at the 1-year follow-up [378]. The trial used a cut point system—for example, a global health status score ≤ 75 points was considered significant deterioration—and proportions in each group were compared [378]. The NRG Oncology RTOG 0521 study has not yet published quality-of-life results.

The STAMPEDE study compared abiraterone acetate + prednisone + ADT against docetaxel + prednisone + ADT in men with either locally advanced PC or mHSPC [379]. The abiraterone group consisted of 342 men, of which 59 (17%) were N1M0 and 191 (56%) were M1. The docetaxel group consisted of 173 men, of which 30 (17%) were N1M0 and 99 (57%) were M1. QoL was assessed using the EORTC QLQ-C30 and PR25 collected at randomization (baseline) and 6, 12, 18, 24, 36, 48, 60, 72, 84, 96 and 104 weeks after randomization [379]. The study included a subgroup analysis assessing global health status from the QLQ-C30 for the nonmetastatic and metastatic groups [379]. There was no clear difference between the abiraterone group or docetaxel group in global health status in M0 patients (P=0.275) [379]. However, in another paper about the STAMPEDE study, where docetaxel + ADT was compared against ADT alone, HRQoL was worse in the docetaxel group at 3 months (but the difference did not remain at 9 months or beyond) [380]. The result at 6 months was borderline significant: the difference in means was approximately 7 points, but P=0.09, which suggests low statistical power (the actual participation rates were not reported) [380]. At baseline, there were 125 participants in each arm [380].

2.18.1.5 Nonmetastatic castration-resistant prostate cancer and quality of life

Apalutamide combined with ADT was superior to ADT combined with placebo in terms of QoL in an RCT investigating its efficacy in nmCRPC [381]. The QoL data were collected prior to treatment (baseline) and at cycles 2−6, 7, 9, 11, 13, 17, 21, 25, 29 and 33 [381]. The duration of each cycle was 28 days, meaning that the QoL data were reported over approximately 2.5 years [381]. The FACT-P and EuroQoL 5-dimension 3-level (EQ-5D-3L) questionnaires were used, although data from the

EQ-5D-3L were reported only for VAS [381]. The differences in the FACT-P total score (TS) were statistically significant (P<0.05) in cycles 17, 21, 25 and 29 [381]. There were statistically significant differences in all FACT-P subscales, including PWB, SWB, EWB, FWB and PCS, as well as in TOI, FAPSI-8, FACT-G and VAS [381]. Most of the statistically significant differences were seen around cycle 17 and thereafter, but there were consistent trends in SWB visible as early as cycle 5 and for the most part persisting thereafter [381]. MIDs were not used [381], but most differences did not exceed the threshold, which is generally considered clinically significant [382–384]. For example, in the FACT-P TS, the difference was over five points, which is considered a lower limit for MID, only at cycle 25 [381,382].

In the RCT comparing enzalutamide + ADT against placebo + ADT, QoL results were generally similar between groups [385]. This trial defined MIDs (SD-based method) [385]. The QoL instruments used were the Brief Pain Inventory Short Form (BPI-SF), EORTC QLQ-PR25, FACT-P, and the European Quality of Life 5-dimension 5-level (EQ-5D-5L) [385]. The data were collected at baseline and 17, 33, 49, 65, 81 and 97 weeks thereafter, for an approximately 1 year 10 month follow-up [385]. There were no statistically significant differences in BPI-SF pain interference or severity, FACT-P TS, FACT-P pain or FACT-P SWB subscale [385]. In other FACT-P subscales, there were statistically significant differences at certain measurement points for PWB and FWB (favouring the placebo), as well as for EWB and PCS (favouring enzalutamide) below the MID threshold [385]. EORTC QLQ PR25 hormonal treatment-related symptoms consistently favoured the placebo [385]. However, the differences were below the MID of 6 points and can be considered clinically insignificant [385]. The results from the EORTC QLQ PR25 favoured enzalutamide regarding urinary symptoms in weeks 49, 65 and 81, while there were no differences in bowel symptoms [385]. However, the difference (approximately three points where statistical significance was found) was greatly below the MID of 9 points [385]. There were subtle statistically significant differences (approximately 2−3 mm) in the EQ-5D-5L VAS favouring enzalutamide at weeks 33, 65 and 81 greatly below the MID of 7 mm [385].

The Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) trial, which compared darolutamide + ADT against placebo + ADT, has not yet presented QoL outcomes as defined per its protocol [332]. QoL data regarding the time to deterioration of FACT-P PCS scores and EORTC QLQ PR25 subscales have been published [386]. According to these results, patients who received placebo suffered deterioration in FACT-P PCS (P=0.0005) and EORTC QLQ PR25 bowel symptoms (P=0.0027) and urinary symptoms more quickly

(P<0.0001) than patients receiving darolutamide [386]. These results cannot be interpreted as a true QoL analysis since they do not provide information about symptom intensity or persistence. The ARAMIS trial also collected data using the EQ-5D-3L and the entire FACT-P questionnaire (not just the PCS) according to its protocol [332]. The data were collected at screening, at the end of treatment, on Day 1 and every sixteen weeks up to 112 weeks (2 years and 2 months) [386]. The complete QoL results from the ARAMIS trial are yet to be reported.

2.18.2 Health-related quality of life in metastatic hormone-sensitive prostate cancer

The first RCT to investigate adding docetaxel to conventional ADT in mHSPC was a collaboration by GETUG and Association Française d'Urologie (AFU) published in 2013 [387]. In this GETUG-AFU 15 trial, docetaxel seemed initially ineffective [387]. However, in further analyses, it was shown to increase survival in high-volume disease measured according to the criteria from the CHAARTED trial [388]. GETUG-AFU 15 assessed HRQoL using the EORTC QLQ-C30 [387]. The forms were completed at baseline and 3, 6 and 12 months thereafter [387]. Global QoL was statistically significantly worse in the docetaxel group at 3 months (P=0.005) but not later [387]. The physical, role and social functioning scales were worse at 3 and 6 months in the docetaxel group [387]. Emotional functioning was worse at 6 months [387]. Patients reported more fatigue, nausea/vomiting and pain at 3 months, and for fatigue, the statistically significant difference persisted at 6 months [387]. However, there were no significant differences present at the 1-year follow-up [387]. MIDs were not used in this trial. The participants had a KPS ≥ 70% and adequate haematological, hepatic and renal function [387]. Docetaxel 75 mg/m^2 was given every three weeks up to nine cycles (6.3 months) or until treatment failure [387].

CHAARTED, also known as the E3805 study, randomized Z≤2 patients to receive six cycles of docetaxel 75 mg/m^2 + ADT or ADT alone [295]. An OS benefit was found in all patients (P=0.0018) [295]. However, in the subgroup analyses, docetaxel did not demonstrate an OS benefit in the low-volume disease group [295]. The HRQoL was measured at baseline and then every three months up to a year [389]. The questionnaires used were the BPI-SF, FACT-P, Functional Assessment of Cancer Therapy – Taxane (FACT-Taxane) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) [389]. TOI was evaluated from the FACT-P forms [389]. In the FACT-P TS, when a mixed-effects method was applied, the QoL

was worse in the docetaxel group at three months (-3.09 points, P=0.02) but superior to ADT at 1 year (+2.85 points, P=0.04) [389]. The differences were below MID, which was defined using the SEM-based method (FACT-Taxane, FACIT-F) [389]. The TOI difference at 3 months exceeded clinical significance, favouring ADT (-3.44, P<0.001) [389]. The FACT-Taxane score was also worse in the docetaxel group during the entire follow-up period, but the differences were below MID [389]. FACIT-F scores were inferior in the docetaxel group at 3 months (-4.3 points, P<0.001), and the difference exceeded clinical significance [389]. There were no differences in pain measured with the BPI-SF [389]. Considering the low- and high-volume subgroups and the differences in FACT-P TS compared to baseline, the statistically significant differences were below MID in the high-volume subgroup, but the QoL decreased in the low-volume group borderline clinically significantly at three months compared to baseline (-5.3, P<0.001) [389].

ARASENS, which compared docetaxel + darolutamide + ADT against docetaxel + ADT + placebo, has not yet published its complete HRQoL results, but the preliminary results presented at the ESMO 2022 conference showed noninferiority [390].

2.18.2.1 Abiraterone acetate in M1 hormone-sensitive prostate cancer: quality of life impact

In the subgroup analyses conducted in the STAMPEDE trial, global QoL measured using the EORTC QLQ-C30 was generally higher in patients receiving abiraterone acetate + prednisone + SOC than in those receiving docetaxel + SOC (+4.5 points, P=0.036) [379]. MIDs were not used.

In the LATITUDE trial, which compared abiraterone acetate + prednisone + conventional ADT against conventional ADT + dual placebos, the QoL results generally favoured abiraterone acetate [329,391]. The trial included only high-risk patients who met at least two of the following criteria: GS ≥ 8, ≥ 3 bone lesions or ≥ 1 visceral metastasis [329]. The QoL data were collected at baseline and for cycles 1−13, 15, 17, 19, 21, 23, 25, 27, 29, 31 and 33 [391]. The duration of one cycle was 28 days [391], meaning QoL data was collected for approximately 2.4 years. The questionnaires used were the BPI-SF, Brief Fatigue Inventory (BFI), FACT-P (including TOI) and EQ-5D-5L [391]. The results clearly favoured acetate + prednisone in the FACT-P TS, TOI, EQ-5D-5L, pain VAS from EQ-5D-5L, BPI-SF and BFI [391]. The differences were statistically significant during the first three cycles and persisted for the duration of the follow-up [391]. There were also similar

differences favouring abiraterone acetate + prednisone in all FACT-P subclasses, with the exception of SWB, for which the differences were insignificant [391]. The differences also seemed to be above the generally accepted MIDs overall or at individual timepoints [382,391]. Thus, abiraterone acetate + prednisone + ADT can be considered superior to ADT alone in terms of HRQoL in men with high-risk mHSPC with moderate confidence.

2.18.2.2 Enzalutamide and apalutamide in M1 hormone-sensitive prostate cancer: quality of life impact

Enzalutamide + ADT has been studied in two RCTs [392,393]. The Enzalutamide in the First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET) study was an open-label design, and the control group received ADT without additional placebo [392]. HRQoL was assessed using the EORTC QLQ-C30 and PR25 and was collected at baseline, weeks 4 and 12, and every 12 weeks thereafter up to three years [392]. There were no differences in global QoL [392]. There were small statistically significant differences (2.6−4 points, $P \leq 0.001$) in physical, role, social and cognitive functioning favouring enzalutamide [392]. Patients receiving enzalutamide reported significantly ($P \leq 0.05$) less fatigue, urinary symptoms, appetite loss and dyspnoea [392]. The difference was pronounced for fatigue (-5.2 points, $P < 0.001$); for other symptoms, the difference was 1.8−2.5 points [392].

A phase III, randomized, double-blind, placebo-controlled study of enzalutamide + ADT in men with metastatic hormone-sensitive prostate cancer (ARCHES) measured QoL using the EORTC QLQ-PR25, FACT-P, BPI-SF, and EQ-5D-5L [393]. These questionnaires were completed at baseline, week 13 and every 12 weeks thereafter until disease progression or 73 weeks (1 year, 5 months and 1 week) [393]. The trial used MIDs (anchor method for the EORTC QLQ-PR25 based on FACT-P; FACT-P MID was based on the literature) [393]. Overall, the differences were minimal in all parameters, demonstrating the noninferiority (and nonsuperiority) of enzalutamide in mHSPC in terms of QoL [393].

Apalutamide + ADT has been studied in one RCT compared with ADT and placebo [394]. The questionnaires in use were the BPI-SF, BFI, FACT-P and EQ-5D-5L [394]. The BPI-SF and BFI were completed every day starting six days prior to and one day after every cycle and then at months 4, 8 and 12 [394]. FACT-P and EQ-5D-5L were completed for cycles 1−7 and months 4, 8 and 12 [394]. The

duration of one cycle was 28 days [394]. The differences in all parameters were minimal and demonstrated noninferiority [394].

2.18.3 Health-related quality of life in metastatic castration-resistant prostate cancer

The Canadian RCT (N=161) that compared mitoxantrone + prednisone against prednisone alone collected HRQoL data at baseline and every three weeks thereafter [395]. There were comparable data from both groups up to approximately 33 weeks [395]. The HRQoL instruments used were the EORTC QLQ C30, Prostate Cancer-Specific Quality-of-Life Instrument (PROSQOLI), and Quality of Life Module−Prostate 14 (QOLM-P14) [395]. Crossing over from the prednisone alone group to the mitoxantrone group was allowed if there had not been improvement in pain or if there was symptom progression at 6 weeks [395]. The HRQoL results in the intergroup comparison ('head-to-head model') were similar [395]. When compared with the baseline values within groups, the prednisone alone group showed improvements in global QoL, nausea and vomiting and anorexia at six weeks ($P<0.007$) [395]. The mitoxantrone + prednisone group showed improvements in global QoL, pain, anorexia, constipation, impact of pain on mobility, degree of pain relief, and drowsiness ($P<0.009$) [395]. There was an increase in hair loss in the mitoxantrone + prednisone group ($P=0.009$) [395]. At 18 weeks, patients in the mitoxantrone + prednisone group continued to have improvements (and deterioration in hair loss) in the majority (61%) of the aspects of QoL mentioned before, whereas the prednisone only group still only had improvement in the impact of pain on mobility ($P=0.004$) [395]. The crossover group was reported separately and showed improvements in pain, impact of pain on mobility and pain relief ($P<0.003$) but greater hair loss ($P=0.01$) at 18 weeks [395].

SWOG 99-16 compared docetaxel + estramustine + dexamethasone to mitoxantrone + prednisone and collected HRQoL data at baseline (randomization), week 10, 6 months and 1 year [396]. The HRQoL questionnaires used were the Short-Form McGill Pain Questionnaire (SF-MPQ) and EORTC QLQ-C30 and PR25 [396]. The SF-MPQ results were similar [396]. There were borderline significant ($P=0.05$) findings favouring docetaxel + estramustine at 6 months (+5.1 vs. +1.6 points compared to the baseline values); the global QoL was similar at other timepoints [396]. In the EORTC QLQ-C30, docetaxel + estramustine resulted in more nausea and vomiting at week 10 ($P=0.02$) and at six months ($P<0.001$) [396].

There were no other statistically significant differences in the EORTC QLQ-C30 subclasses or symptom domains or in the EORTC QLQ-PR25 [396].

In the TAX-327 study, HRQoL was assessed using the FACT-P at baseline, every three weeks during treatment and every month thereafter [397]. Pain was assessed using the Present Pain Intensity (PPI) item from the McGill-Melzack questionnaire [397]. Docetaxel 75 mg/m^2 every three weeks + prednisone did not lead statistically more often to QoL deterioration compared to mitoxantrone + prednisone (29.1% vs. 25.5%, P=0.39) [397]. However, this was not the case with docetaxel 30 mg/m^2 (37.4% vs. 25.5%, P=0.003) [397]. The proportion of those who had QoL improvement was significantly larger in both the every 3 weeks (22% vs. 13%, P=0.009) and weekly (23% vs. 13%, P=0.005) groups [299]. This was also the case with pain improvement: 35% vs. 22% (P=0.01) and 31% vs. 22% (P=0.08), respectively [299]. QoL improvement/deterioration was defined as 16 points on the FACT-P TS compared with the baseline [299,397]. The pain response was defined as a minimum two-point reduction from baseline [299]. However, the 16-point difference for FACT-P TS MID can be considered insensitive in present-day terms (suggested threshold value according the literature is 6−10 points) [382].

2.18.3.1 Abiraterone acetate and quality of life in M1 castration-resistant prostate cancer

In chemotherapy-naïve patients, in the setting of abiraterone acetate + prednisone vs. placebo + prednisone, the COU-AA 302 trial has only been published as time to a decline in the FACT-P TS results (defined decline of minimum 10 points) [398]. The results favoured abiraterone acetate (HR=0.78, P=0.003) [398]. The FACT-P data were collected at baseline; months 3, 5 and 7; and every three months thereafter (final analysis had a median follow-up of 49.2 months) [398,399]. Pain was assessed using the BPI-SF [398]. An increase in pain was defined as an increase in the baseline pain score by at least ≥ 30% without decreasing pain medication [398]. The pain results were also published only as time to increase in pain and time to opiate use, which both favoured abiraterone acetate (P value 0.049 and <0.001, respectively) [398]. The presentation of the QoL data has been criticized by the NICE [330].

After docetaxel, the COU-AA 301 trial assessed the QoL impacts of abiraterone acetate + prednisone vs. placebo + prednisone using the BFI, BPI-SF and FACT-P [400–402]. The BFI and BPI-SF data were collected 14 days prior to treatment at baseline, during cycle 1 and on the first day of each cycle until discontinuation of the treatment [400,401]. FACT-P questionnaires were completed at baseline; on the first

day of cycles 1, 4, 7, and 10; and every six cycles thereafter with a median follow-up of 419 days in the abiraterone acetate group and 253 days in the placebo group [402]. The duration of one cycle was 28 days [401]. A larger proportion reported improvement in fatigue intensity (58.1% vs. 40.3%, P=0.001) and fatigue interference (55.0% vs. 38.0%, P=0.0075) in the abiraterone acetate + prednisone group compared to the placebo + prednisone group [400]. There were no significant differences in deteriorations (P value 0.44 and 0.22, respectively) [400]. Improvement/deterioration in BFI was defined as a 2-point difference compared to the baseline in two consecutive measurements [400].

Regarding pain in the COU-AA 301 trial, only those with clinically significant pain at baseline (minimum score 4 on BPI-SF Item 3 for pain intensity and mean score 4 or more in BPI-SF pain interference) were included in the pain improvement analyses [401]. The proportion that improved in BPI-SF pain intensity (34.3% vs. 22.7%, P<0.0001) and pain interference (30.3% vs. 20.1%, P=0.0002) was substantially higher in the abiraterone acetate + prednisone group than in the placebo + prednisone group [401]. Improvement in pain intensity was defined as a decline in BPI-SF pain intensity by at least 30% compared to the baseline at two consecutive visits, whereas progression in pain intensity was defined as either 1) BPI-SF values 30% above the baseline at two consecutive visits and no decreased pain medication or 2) an increase in the analgesic usage score by at least 30% [401]. Improvement/progression in BPI-SF pain interference was defined as a decrease/increase by at least 1.25 points at two consecutive visits [401]. Both pain intensity PFS (P=0.0018) and pain interference PFS (P=0.0006) favoured abiraterone acetate + prednisone [401].

Regarding the FACT-P results in the COU-AA 301 trial, only those with impaired QoL at baseline were included in the QoL improvement analyses [402]. Impaired QoL was defined as a score ≤ 122 in FACT-P TS, ≤ 25 in PWB, ≤ 21 in SWB, ≤ 13 in EWB, ≤ 19 in FWB, ≤ 88 in FACT-G, ≤ 34 in PCS, and ≤ 79 in TOI [402]. Improvement/deterioration was defined as a difference in points compared to the baseline according to the following criteria: 10 points on the FACT-P TS; 9 points on the FACT-G and TOI; and 3 points on the PCS, SWB, EWB, FWB and PCS [402]. Unlike the BPI-SF and BFI, there was no criterion that the result had to be confirmed in subsequent visits [402]. The proportion that improved favoured abiraterone acetate in FACT-P TS (48.1% vs. 31.9%, P<0.0001), PWB (P<0.0001), EWB (P=0.0241), FWB (P=0.0047), FACT-G (P=0.0001), PCS (P<0.0001), and TOI (P<0.0001) [402]. FACP TS deterioration-free survival and PCS deterioration-free survival favoured abiraterone acetate (P values <0.0001) [402].

2.18.3.2 Enzalutamide and quality of life in M1 castration-resistant prostate cancer

A multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy (PREVAIL) assessed the QoL effects of enzalutamide using the FACT-P, BPI-SF and EuroQoL 5-dimension (EQ-5D) [403]. BPI-SF questionnaires were completed at baseline and weeks 13 and 25 [403]. The FACT-P and EQ-5D forms were completed at baseline, weeks 5 and 13, and every 3 months thereafter (results reported up to 61 weeks) [403]. The trial used predefined MIDs (based on previous literature), which were 10 points in FACT-P TS; 3 points in PCS, PWB, FWB, EWB, and SWB; 2 points in PCS pain; 0.14 in EQ-5D utility index; 11 mm in EQ-5D VAS; and an increase of at least 30% and 2 points in the BPI-SF variables with the exception of BPI-SF pain interference, for which it was at least 50% baseline SD and two points [403].

The PREVAIL results favoured enzalutamide in a clinically and statistically significant manner after 13 weeks in FACT-P TS, PCS, FWB, and PCS pain [403]. The results also favoured enzalutamide in the EQ-5D utility index at weeks 13 and 25 and the EQ-5D VAS at weeks 37 and 71 [403]. In the enzalutamide group, a smaller proportion reported progression in BPI-SF pain intensity (P=0.0001 at 13 weeks, P=0.05 at 25 weeks) and BPI-SF pain interference (P<0.0001 at 13 weeks, P=0.0033 at 25 weeks) [403].

A multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy (AFFIRM) assessed the HRQoL by the FACT-P and BPI-SF [404]. The BPI-SF was collected only at baseline and week 13 [404]. The FACT-P was collected at weeks 1, 13, 17, 21, and 25 and every three months thereafter until treatment discontinuation [404]. Improvement or deterioration in HRQoL was compared to the baseline and defined according to the following criteria: 10-point difference in FACT-P TS and 3-point difference in PWB, SWB, EWB, FWB, and PCS [404]. The AFFIRM trial also counted death as an event for HRQoL deterioration [404], which can be considered questionable.

In the AFFIRM trial, BPI-SF results favoured enzalutamide at week 13 for both pain intensity (difference -0.65, P<0.0001) and interference (-0.74, P<0.0001) [404]. A larger proportion improved in total HRQoL in the enzalutamide group compared to the placebo group: 42% vs. 15% in FACT-P TS (P<0.0001) [404]. The findings

were similar for PWB (P<0.0001), SWB (P=0.0084), EWB (P<0.0001), FWB (P<0.0001) and PCS (P<0.0001) [404]. Death or 10-point FACT-P TS reduction-free survival favoured enzalutamide (P<0.0001) [404].

2.18.3.3 Cabazitaxel and quality of life in M1 castration-resistant prostate cancer

The original RCT that showed an OS benefit of using cabazitaxel 25 mg/m^2 every three weeks + prednisone compared with mitoxantrone + prednisone in a postdocetaxel setting did not collect HRQoL data [405]. Cabazitaxel has been evaluated in three further RCTs [406,407]. A randomized, open label, multicentre study comparing cabazitaxel at 25 mg/m^2 and at 20 mg/m^2 in combination with prednisone every 3 weeks to docetaxel in combination with prednisone in patients with metastatic castration-resistant prostate cancer not pretreated with chemotherapy (FIRSTANA) failed to show a survival benefit compared with docetaxel. HRQoL was collected at every cycle up to 16 cycles (approximately 11.2 months) using FACT-P and PPI from the McGill-Melzack questionnaire [49,406]. Improvement in HRQoL was defined as a 7-point increase in FACT-P TS compared to baseline [406]. Deterioration was defined as a 10% decrease from the baseline values [406]. The MID definition for improvement was based on the preceding literature [406]. An explanation for the deterioration criterion was not given [406]. To be definitely clinically relevant, improvement or deterioration had to be confirmed in a subsequent measurement [406]. The total HRQoL increased clinically significantly in all three arms and was maintained above the MID in the cabazitaxel 25 mg/m^2 arm for the entire duration of the follow-up, in the cabazitaxel 20 mg/m^2 arm up to the 16th cycle, and in the docetaxel arm up to the 15th cycle [406]. There were no statistically significant differences between treatments in direct comparisons of the patients who definitely improved in FACT-P or its subclasses, TOI, FACT-G, PCS Pain, PPI or fatigue [406].

A randomized, open-label multicentre study comparing cabazitaxel at 20 mg/m^2 and 25 mg/m^2 every three weeks in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen (PROSELICA) collected HRQoL data in the same way as in the FIRSTANA trial (the results were published together) and defined deterioration/improvement similarly, but the HRQoL data were collected only up to ten cycles [406]. The HRQoL results in FACT-P TS improved slightly in both arms when compared with the baseline, but the improvement was below MID [406]. There was one small difference in PCS in the proportions of the patients who did

not deteriorate, favouring 20 mg/m² dosing (P=0.0307), but not in FACT-P or other FACT-P subclasses, TOI, FACT-G, PCS pain, PPI or fatigue [406]. PROSELICA found a 20 mg/m² dose to be less toxic without a difference in survival [49].

CARD was a phase 4 RCT that compared cabazitaxel 25 mg/m² every three weeks + prednisone against enzalutamide and abiraterone acetate + prednisone and included mCRPC patients in a postdocetaxel setting [407]. The BPI-SF, FACT-P and EQ-5D-5L were used, which were collected at baseline, at the end of each treatment visit, and every three months subsequently until the patient had subsequent cancer therapy or the cut-off date was reached [407]. The following MIDs for deterioration were used (compared with the baseline): 10 points in FACT-P TS; 9 points in FACT-G and TOI; 3 points in PWB, SWB, EWB, FWB, and PCS; 2 points in FACT-P PCS pain; 0.14 difference in EQ-5D-5L utility index; 11 mm in EQ-5D-5L VAS; and at least a 30% increase in BPI-SF pain intensity [407]. The deterioration had to be confirmed in consecutive measurements [407]. No further explanation about how the MIDs were chosen was given [407] but seemed to be the same as in the FIRSTANA/PROSELICA trials [406]. There were statistically significant differences favouring cabazitaxel in FACT-P PCS pain (P<0.001) and EQ-5D-5L (P=0.030), which were both below the MID threshold [407]. In other domains, there were no statistically significant differences (P>0.05) [407].

2.18.3.4 Quality-of-life effects of the radioisotope treatments

The ALSYMPCA study collected data on the HRQoL effects of Ra-223 dichloride compared with placebo using the FACT-P and EQ-5D [408]. The EQ-5D was collected at baseline, week 16, week 24, week 36 and week 44 [408]. FACT-P was collected at baseline, week 16, week 25 and week 44 [408]. The following MIDs were used: 10 points in FACT-P TS; 2 points in FACT-P PCS pain; 3 points in PWB, SWB, EWB, FWB and PCS; and ≥0.1 increase in the EQ-5D utility index [408]. MIDs were based on the literature [408]. Regarding the proportions that improved, both the FACT-P TS (P=0.020) and EQ-5D utility index (P=0.004) results favoured Ra-223 dichloride [408]. In FACT-P subclasses, similar findings were found in EWB (P=0.006), FWB (P=0.029), PCS (P=0.012) and PCS pain (P=0.010) [408]. Regarding deteriorations, the utility index results favoured Ra-223 dichloride (P<0.001), and the FACT-P TS difference was insignificant (P=0.095) [408]. The preliminary results of the HRQoL effects of Lu-177-labelled PSMA-617 also seem promising [409].

2.18.3.5 Quality-of-life effects of other agents

A study of olaparib versus enzalutamide or abiraterone acetate in men with metastatic castration-resistant prostate cancer (PROfound) collected HRQoL data using FACT-P (at baseline and then every 8 weeks until 24 weeks or treatment discontinuation) and BPI-SF (at baseline and then every 4 weeks until 24 weeks, progression, or treatment discontinuation) [410]. The MIDs were used for FACT-P only and were six points in FACT-P TS, 5 points in TOI, 3 points in Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 6 Item Version (FAPSI-6) and PCS, and two points in PWB and FWB [410]. The MIDs were determined using adjusted least squares from the baseline [410]. The proportion that improved in FACT-P TS favoured olaparib (10% vs. 1%, P=0.0065) [410]. The BPI-SF pain interference results favoured olaparib (P=0.004) [410]. However, the absolute difference was small and less than one point [410]. There were no statistically significant differences in time to deterioration in the FACT-P TS or FACT-P subclasses or BPI-SF pain intensity or in the absolute FACT-P TS scores in any measurement [410].

The original RCT demonstrating the OS benefit of sipuleucel-T did not collect QoL data [306], and little data on HRQoL effects in mCRPC could be found. The trial investigating rucaparib has not published HRQoL results thus far.

2.18.4 Summary of health-related of quality of life findings

In the following section, the trials cited in the text that have reported (at least partially) HRQoL results have been compiled. The main finding (or limitation) of the trial is summarized. Table 11 includes studies investigating local (hormone-sensitive) PC, Table 12 nmCRPC trials, Table 13 mHSPC trials and Table 14 mCRPC trials. In Table 14, trials are further classified by their setting (docetaxel-naïve patients, post-docetaxel setting and the original docetaxel and mitoxantrone trials).

Tables also include the shortened name of the trials. Most (but not all) have already been explained in the text. The complete names of the trials are too long to be provided in abbreviations. Tables 11−14 can also be used in index-like manner.

Table 11. Summary of HRQoL findings in local (hormone-sensitive) prostate cancer

Trial	Intervention	Control	Type	Main finding/limitation	Source
PCOS	AS/WW, NS-RP, NNS-RP, EBRT/HDR BT, ADT ± EBRT, LDR BT	Men without PC	PBS	No differences in physical or mental health. PC patients reported more sexual, urinary and bowel symptoms	[366]
Schaake et al.	EBRT	Men without PC	PBS	No differences in global QoL or other QoL domains in within-group analyses. PC patients reported more symptoms	[367]
ProtecT	AS	RP, EBRT + ADT (three-arm)	RCT	No differences in physical or mental health. RP scored the worst in urinary incontinence and sexual symptoms.	[368,369]
Giberti et al.	LDR BT	RP	RCT	No differences in global QoL. IPSS scores lower in BT group.	[370]
CHHiP	Moderately hypofractionated RT	Conventional RT	RCT	Non-inferiority	[371]
RTOG 0415	Moderately hypofractionated RT	Conventional RT	RCT	Non-inferiority	[372]
HYPRO	Moderately hypofractionated RT	Conventional RT	RCT	Non-inferiority in ADT-related and sexual symptoms. Inferiority could not be ruled out for GU and GI symptoms.	[373]
PACE-B	Ultra-hypofractionated SBRT	Conventional RT	RCT	Non-inferiority	[244]
HYPO-RT-PC	Ultra-hypofractionated SBRT	Conventional RT	RCT	SBRT inferior at the end of treatment, but not later	[374]

Mount Vernon Hospital Trial	EBRT + HDR BT boost ± ADT	EBRT ± ADT	RCT	Non-inferiority	[375]
TROG 03.04	EBRT + HDR BT boost + ADT ± zoledronic acid (ZA)	EBRT + ADT ± ZA	RCT*	No significant differences in EORTC QLQ-PR 25. HDR BT group had worse IPSS scores.	[376]
GETUG-12	EBRT + ADT + docetaxel (D) + estramustine (EM) + prednisone (P)	EBRT + ADT	RCT	D+EM+P worse in global QoL and other domains at 3 months (but not at 1 year)	[378]
STAMPEDE	Standard of Care (SOC) + ADT + abiraterone acetate (AA) + P	SOC + ADT + D + P	RCT*	No difference in global QoL.	[379]

*) subgroup analysis. Abbreviations: ADT = androgen-suppression therapy; AS = active surveillance; BT = brachytherapy; EBRT = external beam radiotherapy; EORTC QLQ = European Organisation For Research and Treatment of Cancer Quality of Life Questionnaire; GI = gastrointestinal; GU = genitourinary; HDR = high-dose rate; HRQoL = health-related quality of life; IPSS = International Prostatic Symptom Score; LDR = low-dose rate; NS-RP =nerve-sparing radical prostatectomy; NNS-RP = non-nerve-sparing radical prostatectomy; PBS = population-based study; PC = prostate cancer; QoL = quality of life; RCT = randomized, controlled trial; RP = radical prostatectomy; RT = radiation therapy; SBRT = stereotactic body radiation therapy; WW = watchful waiting.

Table 12. Summary of health-related quality of life findings in non-metastatic castration-resistant prostate cancer. All studies were randomized, controlled trials.

Trial	Intervention	Control	Main finding/limitation	Source
SPARTAN	Apalutamide + ADT	Placebo (PBO) + ADT	Small differences favouring apalutamide	[381]
PROSPER	Enzalutamide + ADT	PBO + ADT	Non-inferiority	[385]
ARAMIS	Darolutamide (DAR) + ADT	PBO + ADT	Results according to the study protocol have not been published. DAR patients did not deteriorate as quickly as PBO in selected prostate cancer symptom related quality of life domains.	[332,386]

Table 13. Summary of health-related quality of life findings in metastatic hormone-sensitive prostate cancer. All studies were randomized, controlled trials.

Trial	Intervention	Control	Main finding/limitation	Source
GETUG-AFU 15	Docetaxel (D) + androgen-deprivation therapy (ADT)	ADT	Global quality of life (QoL) worse in D group at 3 months, but not later. D group results were also worse in other domains at 3 and 6 months.	[387]
CHAARTED (E3805)	D + ADT	ADT	Non-inferiority. D group reported more fatigue at 3 months.	[388]
ARASENS	D + ADT + darolutamide	D + ADT + placebo (PBO)	Non-inferiority based on a preliminary conference proceeding	[390]
STAMPEDE	Abiraterone acetate (AA) + prednisone (P) + standard of care (SOC)	D + SOC	In subgroup analysis, global QoL results favoured AA + P. Minimum important differences were not used.	[379]
LATITUDE	AA + P + ADT	Two PBOs + ADT	AA + P superior (also in pain and fatigue management)	[391]
ENZAMET	Enzalutamide + ADT	ADT	Non-inferiority	[392]
ARCHES	Enzalutamide + ADT	PBO + ADT	Non-inferiority	[393]
TITAN	Apalutamide + ADT	PBO + ADT	Non-inferiority	[394]

Table 14. Summary of health-related quality of life findings in metastatic castration-resistant prostate cancer. All studies were randomized, controlled trials.

Trial	Intervention	Control	Main finding/limitation	Source
"A Canadian randomized trial with palliative endpoints"	Mitoxantrone (M) + prednisone (P)	P only	M superior in terms of global QoL and pain	[395]
SWOG 99-16	Docetaxel (D) + Estramustine (EM) + dexamethasone	M + P	Non-inferiority in terms of global QoL. D + EM group had more nausea and vomiting.	[396]
TAX-327	D + P	M + P	3-weekly D + P superior in terms of QoL and pain. Insensitive MID definition used (16 points)	[299,397]

Trials in docetaxel-naïve patients				
COU-AA 302	Abiraterone acetate (AA) + P	Placebo (PBO) + P	AA + P group took longer to deteriorate in total QoL and in pain compared to PBO + P (no other results have been published)	[398]
PREVAIL	Enzalutamide (ENZ)	PBO	ENZ superior in terms of total QoL and pain	[403]
PROfound	Olaparib	ENZ or AA + P*	Included only patients with mutations in HRR genes. Olaparib was superior in total QoL.	[410]
Trials in post-docetaxel or docetaxel-ineligible setting				
COU-AA 301	AA + P	PBO + P	AA + P was superior in terms of total QoL, fatigue and pain	[400–402]
AFFIRM	ENZ	PBO	QoL results favoured ENZ	[404]
FIRSTANA	Cabazitaxel 25 mg/m^2 (C25) + P or cabazitaxel 20 mg/m^2 (C20) + P **	D + P	Non-inferiority result in both intervention arms in QoL and pain	[406]
PROSELICA	C20 + P	C25 + P	Non-inferiority	[406]
CARD	C25 + P	AA + P or ENZ*	Non-inferiority	[407]
ALSYMPCA	Radium-223 dichloride (Ra-223 Cl2)	PBO	Ra-223 Cl2 superior in QoL and pain	[408]
VISION	Lu-177-PSMA-617	Standard of Care	Preliminary results reported in a conference proceeding favour Lu-177-PSMA-617	[409]

*) combined arms **) arms not combined. Abbreviations: HRR = homologous recombination repair; Lu-177-PSMA-617 = lutenium-177 prostate-specific membrane antigen 617; mg/m^2 = milligrams per square metre; MID = minimum important difference; QoL = quality of life.

3 AIMS OF THE STUDY

The general aim of this thesis was to contribute to personalized and information-based decision-making in the treatment of prostate cancer (PC) by studying patient-reported health-related quality of life (HRQoL) outcomes, as well as other patient-related factors contributing to survival outcomes, such as comorbidity and fitness.

The specific aims were as follows:

1. To examine the clinical outcomes of PC patients treated with curative-intent external beam radiotherapy and the impact of patient-related factors (Charlson Comorbidity Index, ECOG performance status, age) on biochemical recurrence-free, metastasis-free, prostate cancer-specific and overall survival (Study I).

2. To study the HRQoL of intermediate-risk PC patients treated with different external beam radiotherapy techniques and fractionation schedules without neoadjuvant or adjuvant medication in comparison with a general Finnish age-matched control population (Study II).

3. To study HRQoL results from a prospective, randomized, multicentre trial studying PC patients treated with either adjuvant docetaxel and LHRH analogue or adjuvant LHRH analogue only following external beam radiotherapy for local intermediate- or high-risk PC (Study III).

4. To examine HRQoL in patients treated using two different docetaxel dosing schedules in a prospective multicentre and multinational randomized trial for metastatic, castration-resistant PC (Study IV).

4 PATIENTS AND METHODS

4.1 Patients and interventions

Study I included patients treated with external beam radiotherapy (EBRT) for PC at Tampere University Hospital between 2008 and 2013. The patients were identified directly from the clinical registry (years 2010−2013) and from the hospital's electronic patient records (years 2008−2009) using a specific code depicting EBRT for PC. This yielded a source population of 954 men. After exclusions, the final population comprised 665 men. The data were collected retrospectively between May 2015 and March 2019.

Study II included the participants of the ESKO trial. This trial included 73 men with T1c−T2cN0M0 prostate cancer and at least one intermediate-risk factor (IRF) according to the NCCN criteria. IRFs include T grade T2b–T2c, ISUP grade group (ISUP GG) 2–3 and PSA level 10–20 ng/ml [152]. All patients belonged to the favourable or unfavourable intermediate-risk group, depending on the proportion of positive biopsy cores. Patient accrual took place between May 2014 and December 2017. The patients received either conventional radiotherapy (RT) totalling 78 Gy in 39 fractions (frs), moderately hypofractionated RT totalling 60 Gy in 20 fractions or ultrahypofractionated stereotactic body RT (SBRT) totalling 36.25 Gy in five fractions. The fraction sizes were 2 Gy/fr, 3 Gy/fr and 7.25 Gy/fr, respectively. Conventional RT was given to 21 patients, moderately hypofractionated RT to 21 patients and ultrahypofractionated SBRT to 31 patients. A rectal immobilization device, Rectafix, was used in 30 of 41 patients (73.1%) who received either conventional or moderately hypofractionated RT [411]. HRQoL was a secondary endpoint in the ESKO trial, with the primary endpoint being the definition of margins for prostate SBRT and Rectafix patients. Study II did not include a subgroup analysis for Rectafix patients.

In Study II, all the participants of the ESKO trial (N=73) formed the intervention arm, whereas the control arm included 952 male participants of the National Health Survey 2011 (NHS 2011) standardized for age and representing the general Finnish population [412]. The ESKO trial was not randomized, and the choice of treatment modality was made according to the clinician's judgement. However, the SBRT

patients were enrolled following the other groups. Neoadjuvant/adjuvant ADT was not permitted. The ESKO trial was conducted at Tampere University Hospital.

Study III included the participants of the SPCG-13 randomized controlled trial (RCT). In this trial, 376 patients with local prostate cancer were randomized in a 1:1 ratio to receive either six cycles of docetaxel 75 mg/m^2 every three weeks (without prednisone), ADT with LHRH analogue for nine months starting 3 months before RT and EBRT with a total dose minimum of 74 Gy (intervention arm), or similar treatment without docetaxel (control arm). A proportion of patients received a brachytherapy (BT) boost with RT. The trial included NCCN high- and intermediate-risk patients. Of the participants, 84% had high-risk disease. The primary endpoint in the SPCG-13 was biochemical recurrence-free survival (BRFS). HRQoL was a secondary endpoint. The SPCG-13 was conducted in 11 participating hospitals in Finland and Sweden.

Study IV included the participants of the PROSTY trial (N=361). This RCT included patients with metastatic castration-resistant PC (mCRPC). The participants were randomized to receive docetaxel 50 mg/m^2 every two weeks (intervention arm, N=177) or conventional docetaxel 75 mg/m^2 every three weeks (control arm, N=188). Prednisolone 10 mg/day was given in both arms. Treatment was given indefinitely until complete response, treatment failure or the end of the study. Treatment failure was defined as grade 4 toxicity at the lowest allowed dose. Patient recruitment and data collection occurred between March 2004 and May 2009. The primary endpoint in the study was time to treatment failure. HRQoL was a secondary endpoint. The PROSTY trial included 11 participating centres in Finland, Sweden, and Ireland. The complete inclusion and exclusion criteria of the studies are shown in Table 11.

Table 15. Inclusion and exclusion criteria of Studies I-IV

Study	Inclusion criteria	Exclusion criteria
I	Treated with EBRT for PC in TaUH between 2008 and 2013	1. Patient of another health care district (no follow-up data) 2. Salvage RT or nmCRPC 3. Treatment of mamillas only, no prostatic RT 4. EBRT finalized after 2013 5. M1 disease 6. Patient-related discontinuation of EBRT
II	1. Biopsy-confirmed local N0 PC 2. T grade T1c−T2c 3. At least one IRF (T2b–T2c, ISUP GG 2–3 or PSA level 10–20 ng/ml)	1. Neoadjuvant/adjuvant ADT 2. Previous RT in the pelvic region 3. Previous TURP or hip replacement

	4. MRI eligible	4. IPSS ≥ 20 at recruitment 5. Other malignancy within five years 6. Other serious disease
III	1. Men, aged 18−75 years 2. Zubrod PS ≤ 1 3. Biopsy-confirmed PC within 12 months 4. One of the following: a. T2, ISUP GG 3 and PSA level between 10 and 70 ng/ml b. T2, ISUP GG 4−5 and PSA level < 70 ng/ml c. Any T3 PC 5. Treated with neoadjuvant LHRH-analogue 6. Adequate liver function (AST, ALT and ALP below 1.5 x ULN) 7. Adequate haematological function a. Hb > 110 g/l b. NPs > 1.5 x 10^9/l c. PLTs > 150 x 10^9/l 8. Adequate renal function (Cr below 1.5 x ULN)	1. N1 or M1 PC 2. Previous malignancy within five years excluding SCC and BCC of the skin 3. Any previous malignancy that was not considered cured 4. Chemotherapy within five years 5. Prior RT to the pelvic region 6. Use of systemic corticosteroids within 6 months 7. Unstable CVD within 6 months 8. Active infectious disease 9. Active peptic ulcer disease 10. Hypersensitivity to polysorbate 80 11. Other serious illness or medical condition
IV	1. Castration-resistant, histologically cytologically confirmed PC with PSA levels > 10 ng/ml elevated in subsequent measurements 2. Over 18 years old 3. Zubrod PS ≤ 2 9. Adequate haematological function a. Hb > 110 g/l b. NPs > 1.5 x 10^9/l c. PLTs > 100 x 10^9/l 4. Adequate renal function (Cr below 1.5 x UPN) 5. Adequate liver function a. ALT ≤ 2.5 x ULN b. AST ≤ 2.5 x ULN c. ALP ≤ 6 x ULN or extensive bone disease d. Normal bilirubin 6. No ESAs within two months, EM within 3 weeks, ADT within 3 weeks	1. Severe liver disease 2. Ischaemic heart disease 3. Thromboembolic heart disease 4. Other severe heart disease 5. Pulmonary emboli 6. Active infection 7. Autoimmune disease 8. Active peptic ulcer disease 9. Unstable diabetes 10. Iron deficiency that cannot be treated with iron supplements 11. Other severe disease or medical condition 12. Contraindications for the use of corticosteroids 13. Prior chemotherapy (excluding EM) 14. Prior radioisotope treatment 15. Prior RT covering over 25% of BM

Abbreviations: ADT = androgen deprivation therapy; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; BCC = basal cell carcinoma; BM = bone marrow; CVD = cardiovascular disease; EBRT = external beam radiotherapy; EM = estramustine; ESAs = erythropoiesis-stimulating agents; Hb = haemoglobin; IPSS = International Prostate Symptom Score; IRF = intermediate-risk factor; ISUP GG = International Society of Urological Pathology Grade Group; LHRH = luteinizing hormone-releasing hormone; MRI = magnetic resonance imaging; nmCRPC = nonmetastatic castration-resistant prostate cancer; NPs = neutrophils; PLTs = platelets; PS = performance status; PSA = prostate-specific antigen; RT = radiation therapy; SCC = squamous cell carcinoma; TaUH = Tampere University Hospital; TURP = transurethral resection of prostate; ULN = upper limit of normal.

4.2 Outcome measures

Studies II-IV assessed HRQoL with different HRQoL questionnaires, whereas Study I assessed the survival outcomes, comorbidities using the CCI and performance status (PS) using the Zubrod/ECOG/WHO PS.

The main characteristics of the studies are summarized in Table 12.

Table 16. Main characteristics of Studies I-IV

Study	Type	N	Population	Intervention	Outcomes	Instruments
I	Retrospective, single centre nonrandomized study	665	Patients treated for local PC with EBRT in TaUH between 2008 and 2013	EBRT	Survival, the effect of comorbidity and PS	CCI, ZPS
II	Prospective, single centre, nonrandomized study	1025	Participants of ESKO trial (N=73) and respondents of NHS2011 (N=952)	EBRT	HRQoL	15D, FACT-P
III	Prospective, multicentre, international, randomized trial	376	Participants of SPCG-13 trial	Docetaxel in local PC	HRQoL	FACT-P
IV	Prospective, multicentre, international randomized trial	361	Participants of PROSTY trial	Biweekly docetaxel in mCRPC	HRQoL	FACT-P, FAPSI-8, pain VAS

Abbreviations: CCI = Charlson Comorbidity Index; EBRT = external beam radiotherapy; FACT-P = Functional Assessment of Cancer Therapy – Prostate; FAPSI-8 = Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 8 Item Version; HRQoL = health-related quality of life; mCRPC = metastatic, castration-resistant prostate cancer; PC = prostate cancer; PS = performance status; VAS = visual analogue scale; ZPS = Zubrod/ECOG/WHO performance status.

4.2.1 Outcome measures in Study I

Study I differed from Studies II-IV in that HRQoL was not its endpoint. Instead, various survival outcomes of PC were examined, namely, biochemical recurrence-

free survival (BRFS), metastasis-free survival (MFS), prostate cancer-specific survival (PCSS), and overall survival (OS). The survival outcomes were examined to reveal what the contemporary state of treatment outcomes was in true, clinical, unselected populations. Biochemical recurrence (BR) was defined according to the RTOG-ASTRO Phoenix Consensus Conference criterion as an elevation of PSA concentration of 2 ng/ml or more from the nadir value (the lowest measured value after the treatment) [272]. The presence of metastatic disease was determined by the earliest radiologist report stating or suspecting metastatic disease. The date of death was determined from data from the national population registry. The cause of death was determined from the patient records, which included pathological autopsy reports in rare cases, but in most cases, it had to be determined indirectly from the patient records. To classify as a prostate cancer death, the patient had to have clinically or radiographically metastatic disease, and if there was a competing cause, the most clinically appropriate cause was classified as the cause of death (death certificates were not available). For example, if the patient had another rapidly progressing malignancy that clearly was the main cause of passing, it was not considered a PC death even if he had slowly progressing metastatic disease.

Additionally, the effects of comorbidities and performance status (PS) on survival outcomes were examined. CCI was determined by carefully examining the patient records for the history of any CCI comorbidity. As a rule, Zubrod PS was readily determined by the clinicians in the patient records, but if it was not, it was indirectly determined from verbal descriptions of the patient's performance. Laboratory and clinical examinations took place either in the oncological or urological department within Tampere University Hospital or in the primary health care of the patient's municipality of residence, typically with 6−12-month intervals, but since the data were based on 'real-world data' outside the clinical trial setting, exceptions were possible.

4.2.2 Outcome measures in Studies II and III

The ESKO trial in Study II collected HRQoL data using the 15D and FACT-P questionnaires. The data were collected prior to EBRT (baseline), at the end of treatment, and at 3 months and 3 years after treatment. FACT-P questionnaires were also collected at 1 and 2 years after EBRT. NHS 2011 respondents (the control population) did not complete the FACT-P questionnaire (FACT-P is intended for

PC patients only), and the comparisons versus the general population were performed with the 15D only.

FACT-P results were reported for the ESKO cohort in a phase II study-like manner (without a control group). Intergroup comparisons between SBRT, moderately hypofractionated RT and conventional RT were also provided (see Publication II Supplementary Table S2). Trial Outcome Index (TOI) results were also analysed from the FACT-P data.

Study III (SPCG-13) assessed HRQoL using the FACT-P. It was collected prior to treatment (baseline); at six months; and at 1, 2 and 4 years after the treatment.

4.2.3 Outcome measures in Study IV

PROSTY used the FACT-P HRQoL questionnaire and pain visual analogue scale (VAS). According to the PROSTY protocol, the FACT-P and pain VAS were collected every six weeks during the treatment, at the end of treatment and every two months after discontinuation of docetaxel ("follow-up"). The data were combined in the analyses and reported for every month, meaning that end of treatment results and follow-up results were not analysed separately but combined with the rest of the data. The number of returned forms was similar in both arms, particularly at the beginning of the treatment. Towards the end of one year (which was the last timepoint for which the results were reported), the number of returned forms in the biweekly docetaxel arm tended to be greater, reflecting the survival result from the primary endpoint publication [300].

The forms were reported for every month and not for every six weeks because there was a large number of forms (especially in the beginning of treatment) returned outside of the intended cycles in both arms, excluding the end-of-treatment forms (see Publication IV Table 1), so this information was considered beneficial to share. It is possible that a proportion of centres collected the forms for every cycle or even every half-cycle since the 28-day period (two treatment visits) was considered one cycle in the biweekly arm. Only one response per time period per participant was allowed, and in cases where more than one form had been returned, the form included in the model was decided by lot.

FAPSI-8 was also an outcome measure, but its responses could be extracted directly from FACT-P responses.

4.3 Minimum important differences

The minimum important difference (MID) was used as a threshold for clinical significance in HRQoL studies (II-IV). As most trials investigating HRQoL in PC used the MID, Studies II-IV did not determine the MID in their own statistical analysis, but it was based on the previously published literature.

All HRQoL studies used MID definitions as determined by Cella et al. for the FACT-P total score (FACT-P TS) and FACT-P prostate cancer subscale (PCS) [382]. The exact values used are presented in Table 13. Study II included FACT-G and TOI analyses, for which MID definitions were also based on Cella et al. [382]. Study IV included the FAPSI-8, for which the MID was similarly based on Cella et al. [382]. The definitions by Cella et al. were based on several methods: SD and SEM distribution-based methods and anchor-based methods using KPS, bone isoform of ALP, haemoglobin, PFS, adverse effects and OS [382]. The cohort used for MID definition consisted of patients with metastatic hormone-sensitive PC (mHSPC) [382].

Table 17. Minimum important difference (MID) definitions in health-related quality of life studies (Studies II-IV)

Study	FACT-P TS	FACT-G	FAPSI-8	TOI	PCS	PWB	SWB	EWB	FWB	15D	Pain VAS
II*	6	5	NA	5	2	**	**	**	**	0.015	NA
III	6	NA	NA	NA	2	2	2	2	2	NA	NA
IV	6	NA	2	NA	2	2	1	1	2	NA	23 mm

*) It should be clarified that Publication II presented only reference ranges for FACT-P MIDs. However, the lower limits are used in the interpretation here. **) the subdomains were analysed but MIDs were not referenced. Abbreviations: EWB = emotional well-being; FACT-G = Functional Assessment of Cancer Therapy – General; FACT-P = Functional Assessment of Cancer Therapy – Prostate; FAPSI-8 = Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 8 Item Version; FWB = functional well-being; mm = millimetres; NA = not applicable (not used); PCS = prostate cancer subscale; PWB = physical well-being; SWB = social/family well-being; TOI = Functional Assessment of Cancer Therapy – Prostate Trial Outcome Index; TS = total score; VAS = visual analogue scale.

Studies III and IV also included MIDs for FACT-P subdomains other than PCS, namely, physical well-being (PWB), emotional well-being (EWB), social/family well-being (SWB) and functional well-being (FWB). In these trials, the definitions differed. Study III extrapolated the 2-point PCS definition for other subdomains. Study IV definitions for these subdomains were based on the meta-analysis by King et al. [413]. King et al. did not use studies investigating PC patients exclusively for their MID

definitions, but they were based on studies conducted in cancer patients in general and with the FACT-G [413]. The method used for these MID definitions was the Delphi method [413].

The MID for 15D used in Study II was based upon the definition by Alanne et al., which used both distribution- and anchor-based methods (a reference question about patient overall health was the anchor) [414]. The study population in the MID reference consisted of hospital patients with 16 different conditions, including patients with PC [414].

Study IV included pain VAS, for which an MID of 23 mm was chosen based upon the systematic review by Frahm Olsen et al. [355]. The systematic review was conducted in patients with chronic pain (due to various causes) and used a distribution-based approach [355].

4.4 Statistical analysis

Regarding the statistical power, the power calculations in Studies II−IV were made for primary endpoint purposes and not HRQoL. Study IV included post hoc power analysis (see Publication IV Supplementary Table S1). In Study I, the sample size was chosen based on the confident survival results for the entire group (N=665) and not for the comorbidity and performance status analyses. The event-per-variable ratio (EPV) in Study I was over 10:1 for BRFS and OS (EPVs 17.12 and 19, respectively), over 5:1 for MFS (EPV=6.75), but under 5:1 for PCSS (EPV=4.12).

Study I used the Kaplan–Meier estimator adjusted for age for the survival curves of the entire cohort. In the subgroup analyses regarding CCI and Zubrod PS, Cox proportional hazards regression models were used. The models included CCI, Z, Gleason score (GS), T stage, N stage, neoadjuvant/adjuvant androgen deprivation therapy (ADT), PSA level when diagnosed, and age when diagnosed as variables. CCI was stratified into the following groups: CCI = 0, CCI = 1−3 and CCI ≥ 4. Zubrod PS was stratified into the following groups: Z=0, Z=1 and Z≥2. Significant multicollinearity was rejected by the calculation of variance inflation factors and analysis of variance.

Study II used an independent-samples t test for the comparisons between the ESKO and NHS 2011 cohorts. A paired-sample t test (or the corresponding nonparametric test) was used in comparisons with the baseline values. For the intergroup comparisons between different RT modalities within the ESKO cohort, Study II used the Mann–Whitney test (direct comparisons between RT modalities

'head-to-head') and Wilcoxon signed rank test (comparison with the baseline value of the specific RT modality). Study IV also used nonparametric Mann–Whitney and Wilcoxon signed rank tests in a similar manner, although for pain VAS, only the Mann–Whitney test was performed. Study III used analysis of covariance (ANCOVA).

In Study IV, nonresponse to individual questions in HRQoL questionnaires (missing data) was assessed using a pattern-mixture model (patient subdomain mean substitution) by the method suggested by Fairclough and Cella [415]. Patients with ≥ 50% nonresponse in any FACT-P subdomain were excluded. Study III used multiple imputation. Study II used a mixed-model regression.

Study IV included a multiplicity adjustment for statistical significance in the within-group model since 12 timepoints were compared against one baseline value. The Holm–Bonferroni adjustment method was used [416]. Two-tailed tests with a significance level of 0.05 were used in all studies.

The statistical analyses were conducted using SPSS Statistics in Studies I and II, version 23.0 in Study I and version 25.0 in Study II. Study III used SAS version 9.4. In Study III, the statistical analyses were performed by an external biostatistical company (EstiMates). Study IV used SPSS version 26, R software version 4.1.1 and G*Power version 3.1.9.7.

4.5 Study ethics

All studies followed the principles of the Declaration of Helsinki and the contemporary legislation of Finland, the European Union [417–419], and the participating countries. In prospective trials (Studies II-IV), all participants signed written, informed consent, which could be withdrawn at any time. Since Study I was a registry-based, retrospective, observational study, the secondary use of health data for scientific research was authorized by the director of the Tampere University Hospital Research Services, according to contemporary legislation.

All studies were approved by the ethics board in all participating countries, including the Regional Ethics Committee of the Expert Responsibility Area of Tampere University Hospital (Studies I-IV). The permit numbers were ETL R155025 (Study I), ETL R14009 (Study II), ETL R06170M (Study III) and ETL R03165M (Study IV). The national ethics committee was consulted where required (Studies II-IV). All prospective trials (Studies II-IV) were registered at

ClinicalTrials.gov with identifiers NCT02319239 (Study II), NCT00653848 (Study III) and NCT00255606 (Study IV).

The funders had no impact on study designs or the collection, analysis, or interpretation of the data. All participating authors (Studies I-IV) were required to report their conflicts of interest.

5 RESULTS

5.1 Demographics

In Study I, 95% of patients (N=633) received conventionally fractionated RT, and the remainder (N=32) received moderately hypofractionated RT with fraction sizes varying between 2.5 and 3.1 Gy. In Study II, 42% of ESKO patients (N=31) received SBRT, whereas the rest (58%) received conventionally or moderately hypofractionated RT (N=21 in both fractionation schedules). In Study III, the patients received a minimum total radiation dose of 74 Gy, but the fractionation sizes and the proportion of patients who received the BT boost was not reported. Palliative RT was allowed in Study IV.

In Study I, 55% of patients (N=367) received ADT, which was mostly conducted with LHRH analogue (84%) or a combined androgen blockade with LHRH analogue and antiandrogen (13%). Study II did not allow ADT, and Study III had mandatory neoadjuvant/adjuvant ADT with LHRH analogue for nine months. In Study IV, 92% of patients (N=319) had received ADT before docetaxel, and 9% (N=32) had received estramustine. The main characteristics of the study populations at the time of diagnosis (Study I) and at baseline (Studies II-IV) are summarized in Table 14.

Table 18. Main demographics of the studies. For Study II, only the ESKO cohort demographics are shown.

Study	N	Age (range)	PSA (range)	Z: 0/1/2+ (%)	GS 6/7/8/9+ (%)	T1/T2/T3/T4 (%)	N+ (%)	M+ (%)
I	665	71* (46−89)	9.0* (0.9−694)	52/42/5	32/39/8/21	52/37/22/2	1	0
II (ESKO)	73	69** (59−78)	9.5** (3.2−19.1)	NR	29/71/0/0	15/85/0/0	0	0
III	376	67* (63−70)	14.1 (7.8−28.0)	92/8/0	0/56/25/19	0/26/74/0	0	0
IV	346	69* (45−87)	Arm A: 116* Arm B: 109*	33/61/6	NR	NR	NR	100

*) median **) mean. For Study IV, some of the numbers are referred from the primary endpoint publication by Kellokumpu-Lehtinen et al. [300]. Abbreviations: GS = Gleason score; PSA = prostate-specific antigen; NR = not reported; Z = Zubrod/ECOG/WHO performance status.

5.2 Participation in health-related quality of life questionnaires

The number of returned forms in the ESKO cohort of Study II is shown in Publication II Table 1. The participation rate was 86% at the lowest, which occurred at the 3-year follow-up. Six patients (4%) did not return a baseline questionnaire.

In Study III, 357 patients of the 376 eligible participants (95%) returned the baseline questionnaire. The response rates for the follow-up questionnaires were 64% at six months (N=242), 47% at one year (N=176), 54% at two years (N=203), and 52% at three years (N=194).

In Study IV, 294 of the 346 eligible participants (85%) returned the baseline questionnaire. The overall participation rate was over 50% only at 3 months (N=229, 66%). Of those who responded to the baseline questionnaire, the participation rates were over 50% at two months (57%, N=168) and at four months (51%, N=149). In the first seven months (where the statistical power remained sufficient), the participation rates were 24−38% of all eligible participants. In the last five months (months 8−12), the participation rates were under 20% of all eligible participants. First and foremost, the participation rates reflect the high mortality within the trial, but on the other hand, a notable proportion (15%) did not return a single form, and a considerable proportion of the forms were also returned outside the intended 6-week periods (see Section 4.2.3), suggesting inconsistences in data collection as well. The forms included in the statistical analysis by treatment visit (an ongoing treatment evaluation, the end of treatment evaluation or a follow-up visit after treatment failure) are shown in Publication IV Table 1.

5.3 Symptomaticity of local prostate cancer

As a part of Study I, data on patient symptoms before RT were also collected. The results were presented at the PROSCA 2021 conference organized by the International Society for the Study of Exchange of Evidence from Clinical Research and Medical Experience (ISSECAM) [420].

Of Study I patients, 276 men (41.5%) did not have any symptoms. This was largely due to the ERSPC trial conducted in the Tampere region until 2007 [180] and the indirectly raised awareness caused by the trial. The three most common symptoms were weak stream (N=166, 25%), nocturia (N=154, 23%) and frequent urination during the daytime (N=146, 22%). The results are depicted in Figure 6.

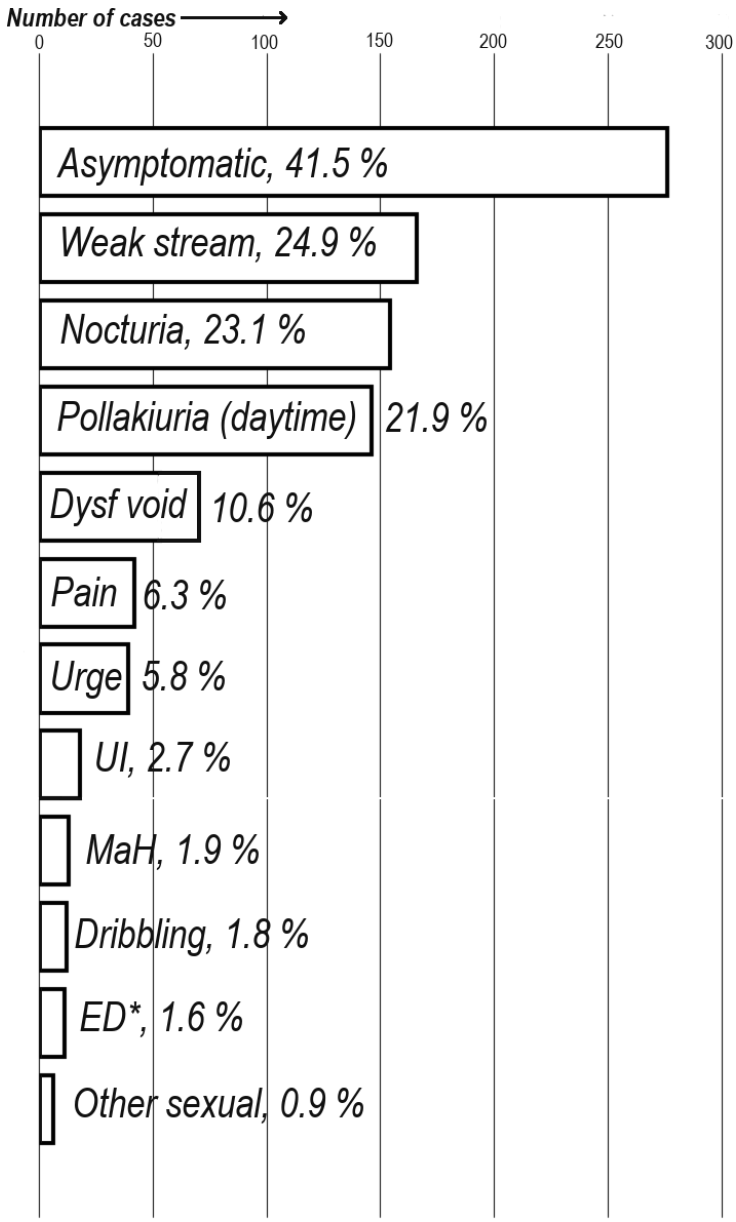

Figure 6. Bar chart depicting symptoms in Study I patients before radiation therapy. *) A new symptom within two years prior to prostate cancer diagnosis. Dysfunctional voiding (Dysf void) includes the symptoms straining, difficulty starting urination, urinary retention and the feeling of incomplete emptying of the bladder. Pain includes local lower abdominal pain and discomfort. Other sexual symptoms include hypospermia, haematospermia and painful ejaculation. Abbreviations: ED = erectile dysfunction, MaH = macroscopic haematuria; UI = urinary incontinence. Based on data from Lehtonen et al. [420].

5.4 Survival after curative-intent external beam radiotherapy and the impact of comorbidities and performance status

In Study I, the survival outcomes were calculated from the time of diagnosis, and all patients were treated with EBRT. The five-year OS was 88.9% with a 95% confidence interval (CI) of 86.5−91.3%. Among the 158 men who died during the follow-up period (7.12 years), cardiovascular disease was the most common cause (N=39, 25%), followed by other malignancies (N=33, 21%) and prostate cancer (N=31, 20%). The five-year PCSS was 97.9% (CI: 96.7−99.1%). Metastatic disease was diagnosed in 54 patients (8%), and the five-year MFS was 94.8% (CI: 93.0−96.6%). The most common primary metastatic sites were bone (N=43, 80%), lymph nodes (N=17, 32%), and lungs (N=5, 9%). Biochemical recurrence (BR), defined as a 2.0 ng/ml increase from the post-RT nadir, occurred in 137 patients (21%), and the 5-year BRFS was 88.7% (CI: 86.2−91.2%). Of the patients receiving neoadjuvant/adjuvant ADT (N=367), 24 patients (6.5%) developed castration resistance in the first-line treatment.

The most common Charlson comorbidities were diabetes without complications (N=129, 19.4%), chronic pulmonary disease (N=94, 14.1%) and moderate/severe renal disease (N=60, 9.0%). For the complete list, see Publication I Table 3. None of the patients had AIDS or metastatic solid malignancy. According to the Charlson Comorbidity Index (CCI), 298 men had a CCI score of 0 (45%), 324 men had a CCI score of 1−3 (49%), and 42 men had a CCI score ≥4 (6%). Only Charlson comorbidities diagnosed before EBRT were included in the calculation of the comorbidity index.

Neither Zubrod PS (Z) nor CCI had an impact on BRFS, MFS or PCSS (P>0.05, see Publication I for exact values). Of the variables included in the model, higher T stages and Gleason scores (GSs) increased the risk of BR, with hazard ratios (HRs) of 1.23 and 1.19, respectively (P value <0.001 and 0.036, respectively). Higher T stage (HR=1.29, P=0.004), GS (HR=1.19, P=0.036) and N+ status (HR=4.01, P=0.022) were associated with poorer MFS. Higher T stage and GS were also associated with poorer PCSS (HR 1.52 and 1.44, P value 0.0001 and 0.044, respectively).

Considering OS, two separate Cox proportional hazards regression models were performed, one for Z and one for CCI, since stratification is possible for only one variable at a time. Both Z=1 and Z≥2 patients had poorer OS than Z=0 patients, with HRs of 2.20 and 2.22, respectively (P values <0.001 and 0.010, respectively). In the Z stratification model, CCI, GS and T stage were also significant (P values <0.05,

see Publication I Table 4 for exact values and HRs). There were no statistically significant differences between the Z=1 and Z≥2 groups in OS. The 5-year OS was well above 80% in Z≥1 patients (see Publication I Figure 1).

In the CCI stratification model, only CCI≥4 was statistically significantly associated with poorer OS (HR=6.11, P<0.001) when compared with CCI=0. The P value for CCI=1−3 was 0.078 (HR=1.38). Z, GS and T stage were also significant predictors of poorer OS in this model (HR>1, P<0.05). The 5-year OS was <70% in CCI≥4 patients, while it was ≥90% in CCI=0 and CCI=1−3 patients (Publication I Figure 2).

Neoadjuvant/adjuvant ADT, age and PSA level were not associated with worse or better survival outcomes in any model.

5.5 Health-related quality of life in patients treated with external beam radiotherapy for local prostate cancer versus the general population

In Study II, there were no significant differences in total HRQoL between men treated with EBRT for PC without neoadjuvant/adjuvant ADT and the age-standardized general male population (P>0.05). The complete 15D results are shown in Publication II Table 2.

In individual dimensions, PC patients had better scores in vision (+0.029, P<0.05) at baseline but more depression and distress (-0.040 for both, P<0.05). The differences were above the MID of ±0.015, although the predefined MID applied to the total 15D index only [414] and may differ for individual dimensions.

At the end of RT, PC patients reported superior mobility (+0.048, P<0.001), hearing (+0.040, P<0.05) and mental function (+0.053, P<0.05) compared to the general population. On the other hand, the excretion QoL (-0.139, P<0.001) and sexual function (-0.143, P<0.001) were worse. The differences in depression and distress persisted (-0.045 and -0.046, P<0.001).

At three months after RT, there were only significant differences in sexual activity (-0.132, P<0.001) and depression (-0.040, P<0.05), both of which favoured the general population. At three years, there were differences in sexual activity (-0.089, P<0.05) favouring the general population and discomfort and symptoms (+0.046, P<0.01) favouring PC patients. Discomfort and symptoms is an item related to various symptoms, of which pains, aches, nausea and itching are directly mentioned in the questionnaire [364].

5.6 Quality of life before and after radiation therapy for local prostate cancer

The main FACT-P results of the ESKO cohort of Study II are shown in Publication II Table 3. Compared with the patient baseline, ESKO patients had a statistically significant deterioration in the FACT-P total score (TS) at the end of RT (-3.8, $P<0.05$). This was below the MID of 6 points and can be considered clinically insignificant. There were no statistically significant differences at 1, 2 or 3 years.

Similarly, TOI scores were worse at the end of RT (-4.2, $P<0.05$) but also below the MID of 5 points, and there were no statistically significant differences at other timepoints.

In the FACT-P subclasses, PCS was worse at the end of RT than at baseline (-2.5, $P<0.05$), which was above the MID of 2 points for clinical significance. There were also two statistically significant differences in PWB: at the end of RT (-1.3, $P<0.05$) and at three years (-0.8, $P<0.05$). Both were well below the MID of two points. There were no differences in FWB, EWB or SWB.

5.7 The impact of moderately and ultrahypofractionated radiotherapy on quality of life

Study II also performed subgroup analyses for three fractionation groups (2 Gy/fr, 3 Gy/fr and 7.25 Gy/fr) compared with the patient baseline. The main findings are presented in Supplementary Tables S1 (15D results) and S2 (FACT-P results) of Publication II, as well as in the main text. Compared with baseline, all groups reported worse scores in the 15D in excretion (at the end of treatment) and sexual activity (all timepoints). There were also statistically significant changes in the total health, vitality, depression, discomfort and symptoms, vision, hearing, breathing and sleeping dimensions of 15D, as well as FACT-P TS, TOI and PCS of FACT-P at certain timepoints. These findings are not explained in detail here due to low sample sizes, which could cause statistically significant findings in one subgroup but not in another due to low power, but the complete results are available in Publication II.

The 15D results were also analysed head-to-head between the subgroups of the ESKO cohort. The results generally favoured ultrahypofractionation in terms of total HRQoL (at the end of RT and at one year, P values 0.023 and 0.015), excretion (at the end of RT, $P=0.013$), sexual activity (at the end of RT, $P=0.034$) and usual activities (at one year, $P=0.006$). In absolute values, however, conventional RT

clearly had the worst score in the 15D total index at baseline (0.893 vs. 0.928 in SBRT and 0.911 in moderate hypofractionation), meaning that the differences were not necessarily related to the treatment. Similar differences at baseline were present in sexual activity (0.687 in conventional RT vs. 0.814 in SBRT) and usual activities (0.879 in conventional RT vs. 0.930 in SBRT). Excretion was similar between conventional RT and SBRT (0.879 vs. 0.876) at baseline.

The results also favoured SBRT over moderate hypofractionation at distress (at 3 years, P=0.045). The distress points were already worse at baseline for conventional RT (0.871 in moderate hypofractionation and 0.893 in SBRT). Moderate hypofractionation was associated with less discomfort and fewer symptoms at 1 year (P=0.028) than conventional fractionation. The differences were already large at baseline (0.815 in moderate hypofractionation vs. 0.757 in conventional RT).

5.8 The effect of ADT and risk group on quality of life in local prostate cancer: a comparative analysis between Studies II and III

An approximate evaluation of the HRQoL effects of ADT can be conducted by comparing ESKO patients in Study II and the control group in Study III who received EBRT + ADT for 9 months to obtain a perspective on the effects of LHRH analogue treatment. The groups differ in terms of characteristics, since the ESKO population included only intermediate-risk patients and the SPCG-13 included both intermediate- and high-risk patients.

The FACT-P TS was 128.5 at baseline in the ESKO cohort. In the SPCG-13 control arm, it was 118.2, which is considerably lower (MID 6−10 points). It should be noted that baseline questionnaires in the SPCG-13 were collected approximately 3 months after the initiation of the neoadjuvant LHRH analogue. At one year (after the discontinuation of ADT in the SPCG-13), the FACT-P TS scores were very similar, 126.6 in the ESKO cohort and 125.0 in the SPCG-13 control arm. At two years, the FACT-P TS scores were almost identical, 127.6 in the ESKO cohort and 127.7 in the SPCG-13 control arm. The differences at baseline were mostly attributed to the PCS domain, with scores of approximately 31 points in the SPCG-13 control arm and 37.7 points in the ESKO cohort. The PCS subclass includes items related to ADT (questions about erectile function and manliness) but also questions that

could correlate with risk group (questions regarding pains and aches, weight loss, and urinary symptoms) [361].

This comparison could indicate that ongoing ADT in local PC has an impact on HRQoL but only while it lasts, or that the deterioration in HRQoL caused by having higher-risk (more locally advanced) disease impacts HRQoL prior to EBRT but is managed with treatment at least in the short term (1−2 years), or both.

5.9 The effect of adjuvant docetaxel on quality of life in local prostate cancer

In Study III, patients with local PC belonging to the high- or intermediate-risk groups received docetaxel 75 mg/m² every three weeks for six cycles in the intervention arm, meaning that docetaxel treatment lasted approximately 4.5 months in total. Only intergroup comparisons were performed (head-to-head model). Both the control and intervention arms received EBRT and LHRH analogue for nine months. There were no statistically significant differences in FACT-P TS or any FACT-P subclasses at baseline.

Considering the HRQoL results from the FACT-P questionnaires, the docetaxel group had inferior FACT-P TS scores at six months compared to the control arm (116.6 vs. 123.7, $P<0.0001$). This was above the MID of 6 points and can be considered clinically significant. There were no statistically significant differences at 1, 2 or 4 years ($P>0.05$), and in absolute values, the results were also very similar. The results are shown in Publication III Table II and Publication III Figure 1.

In the FACT-P subclasses, both clinically and statistically significant differences favouring the control arm were found in FWB (difference 2.43 points, $P<0.0001$) and PWB (difference 2.43 points, $P<0.0001$) at 6 months. There was also only one statistically significant difference in PCS at 6 months (1.78 points, $P=0.015$). There were no statistically or clinically significant differences in other FACT-P subclasses or at other time points. The subclass results are represented in Publication III Figure 2.

5.10 Health-related quality of life and pain in patients receiving docetaxel treatment for metastatic, castration-resistant prostate cancer

In Study IV, patients with mCRPC received docetaxel in one of two different dosing schedules: 50 mg/m² every two weeks (intervention) or the conventional 75 mg/m² every three weeks (control). Prednisolone was given in both arms, and the number of cycles was not limited. The HRQoL results were compared both against patient baseline (within group) or directly between the arms (head-to-head). A synthesis of both models was created and shown in Publication IV Table 4. The pain VAS score was analysed only directly between the arms. There were no significant differences at baseline in the FACT-P, FAPSI-8, FACT-P subclasses or pain VAS score between the arms.

There were no statistically significant differences in pain VAS score between the arms. The mean pain was highest at baseline (2.4 centimetres vs. 2.6 cm, P=0.637). During treatment/follow-up, the pain VAS score peaked in the intervention arm at 9 months (N=28), with a mean of 2.4 cm. At this timepoint, the pain VAS score was 1.3 cm in the control group (N=16, P=0.101). In the control group that received conventional docetaxel dosing every three weeks, the maximum pain VAS score during the treatment was 2.3 cm at month 4 (N=74). At this timepoint, the score was 1.8 cm in the intervention arm (N=66, P=0.096). The complete pain VAS results with mean and median values are shown in Publication IV Table S13.

5.10.1 Quality of life comparisons with the patient's baseline

In the intragroup model (comparisons with the patient's baseline), there were no statistically significant differences in FACT-P TS in the intervention group at months 1, 2, 3, 4, 5, 6 or 7 (P>0.05), where the statistical power was considered sufficient for this model. However, the control group (conventional docetaxel dosing every three weeks) suffered clinically insignificant deterioration in FACT-P TS (-4.8 points, P<0.012) below the MID of 6 points during the first month but not at other timepoints during the first seven months. The complete results are shown in Publication IV Table 2. The FACT-P TS results for months 8−12 are shown in Publication IV Table S14, but there were no statistically significant differences in the comparisons with the patient's baseline.

In the FAPSI-8, both groups suffered statistically significant deteriorations in comparison to the baseline during months 1−3. However, in the every-two-weeks group, the differences were above the MID of 2 points only at the first month (-2.7, P<0.012). In the every-three-weeks group, all differences were above the MID (-2.6 at month 1, -2.9 at month 2 and -2.9 at month 3) and thus clinically significant. The complete results for the first seven months are shown in Publication IV Table 3. There were no statistically significant differences at later timepoints (Publication IV Table S14).

In the FACT-P subclasses, there were both clinically and statistically significant differences in EWB, PWB and PCS. In EWB, these were present in the intervention arm at month 2 (-1.1, P=0.012), month 5 (-1.6, P=0.027), and month 8 (-1.5, P=0.020). The MID for EWB was one point. In the control arm, EWB was worse than baseline at months 1 (-1.5, P<0.012), 2 (-1.3, P=0.020), 3 (-1.6, P<0.012) and 4 (-1.2, P=0.020). In PWB, there was a solitary improvement compared with baseline in the control group at month 4 (+2.1, P=0.022). In PCS, both arms suffered statistically and clinically significant deterioration at months 1 and 3 (P<0.012). The differences in means were -2.8 at both timepoints in the intervention arm and -3.5 and -3.2 in the control arm. The complete subclass results for the intragroup model are shown in Publication IV Tables S3 (EWB), S5 (PWB), S7 (PCS), S9 (FWB) and S11 (SWB).

P values were adjusted for multiplicity due to the number of timepoints, and the P values reported here are the multiplicity-adjusted values. The unadjusted P values are also available in Publication IV. Graphical figures of the HRQoL scores are available in Publication IV Figures S1 (FACT-P TS), S2 (FAPSI-8), S3 (PCS), S4 (PWB), S5 (EWB), S6 (FWB), and S7 (SWB).

5.10.2 Quality of life comparisons directly between the groups

In the intergroup model (head-to-head), there were no statistically significant differences between the arms in the first seven months in either the FACT-P TS or FAPSI-8 (P>0.05). The results are shown in Publication IV Table S2.

At month 8, the control group had superior FACT-P TSs (39.9 points in the intervention arm vs. 51.5 points in the control arm, P=0.020). However, the results were opposite in the following month (44.2 vs. 31.4 points, P=0.043). These differences were above the MID of 6 points. There were no significant differences

at subsequent timepoints (Publication IV Table 2) or in the FAPSI-8 (Publication IV Table 3).

In the FACT-P subclasses, there were both clinically and statistically significant differences in EWB, PWB, PCS and SWB. In EWB, there was a solitary finding favouring conventional dosing at month 8 (4.7 vs. 7.0, P=0.022). In PWB, the results favoured biweekly dosing at month 9 (7.1 vs. 4.7, P=0.034) and at month 12 (8.1 vs. 4.1, P=0.048). In PCS, the month 8 results favoured conventional dosing (13.7 vs. 17.1, P=0.040), but the month 9 results favoured biweekly dosing (15.7 vs. 11.6, P=0.045). In SWB, there was one solitary finding favouring biweekly dosing at month 9 (6.6 vs. 4.1 points, P=0.029). The complete subclass results for the intergroup model are shown in Publication IV Tables S4 (EWB), S6 (PWB), S8 (PCS), S10 (FWB) and S12 (SWB).

6 DISCUSSION

6.1 Survival outcomes in local or locally advanced prostate cancer

In studies that have included all risk groups and been conducted in comparable high-income countries, the 5-year BRFS has been reported to be approximately 82−95% after EBRT for local or locally advanced PC [421–425]. The results of Study I (BRFS=88.7%, CI: 86.2−91.2%) are in line with these studies. The 5-year MFS has varied in comparable studies between 89% and 98% [423,425–427]. Our MFS result (94.8%) was consistent with the results reported in those studies.

In regard to PCSS, Fosså et al. reported a 5-year PCSS of 96.5% in Norway in a recent study from 2014 [326]. Other trials conducted outside Nordic countries have reported 5-year PCSS results between 93% and 99.8% in the era of modern radiotherapy techniques [423–425,428–430]. Our PCSS result (97.9%) ranks in the upper half.

The 5-year OS has varied in comparable countries between 84% and 97.2% [423–425,428–432], including an OS result of 89.8% in Norway [326]. Our OS results (88.9%, CI=86.5−91.3%) are very close to those in the Norwegian cohort and in line with other studies.

For the purposes of a reasonable comparison, only trials conducted in high-income countries were included. In developing countries, clinical outcomes such as cancer-specific mortality tend to be considerably worse [433].

Nonetheless, when compared to other high-income countries, our results were as expected based on previous studies in terms of BRFS, MFS and OS. On the other hand, when all risk groups are included, cancer-specific outcomes (BRFS, MFS and PCSS) tend to be better the more low-risk patients are treated, and these outcomes not only indicate the success of a treatment but also demographics. Looking back, prostate cancer-specific mortality has decreased steadily for the past 25 years [1], indicating that much has also been accomplished and that Finland has kept up with other countries in terms of the constantly developing treatment, although overdiagnosis caused by the PSA screening trend of the 2000s also shows [434]. PCSS in our cohort was good, which could suggest that in Tampere University

Hospital, life-prolonging treatments are available to patients after the development of M1 disease.

A large proportion of PC patients treated for local PC with EBRT are men in the eighth or even ninth decade of their life (over 50% in the Study I cohort). Mäkelä and Nevala argued that the older the cancer patient is, the more likely he or she is to accept milder treatments to minimize the risk of toxicity or treatments that do not necessitate frequent hospital visits [435]. Given this, the desired extent and cost to improve PCSS and OS in local hormone-sensitive prostate cancer are questionable. If the treatment outcomes are already excellent, very many men likely have to be treated to find one that benefits (high NNT), especially in intermediate- and low-risk groups. The number needed to harm, however, is not necessarily similarly high when conducting drug or radiation trials on volunteers. Laine et al. noted a high prevalence of geriatric syndromes within a Finnish cohort and argued that such comorbidities increase treatment-related risks [436]. The inability to follow treatment instructions due to a decline in cognition was given as an example [436].

One relatively easy method of improving OS after EBRT is more careful patient selection. Those who are likely to die from causes other than PC within a few years should perhaps be monitored instead, as the current guidelines suggest [49,293]. However, the life expectancy (LE) of the patient is rarely assessed in a systematic manner in clinical practice when making the initial treatment decision. Although performance status is frequently used, even Z=0 patients may be at risk of dying within a few years if they have a significant comorbidity burden.

Indeed, it is not surprising that the current PC research has taken a step back in terms of treatment intensity with one main focus on active surveillance with trials such as ProtecT [368]. However, the requirement of possible repeated biopsies limits the usefulness of such treatment. More research with quality of life and cost-to-benefit ratio as primary endpoints in the treatment of PC is needed, with the aim of maintaining the current excellent survival results rather than necessarily improving them.

6.2 Charlson comorbidity index in local or locally advanced prostate cancer

The main finding of Study I was related to comorbidity; even if performance status was included in the model, the CCI had independent prognostic value for OS, with the CCI≥4 group having an approximately six times higher HR of all-cause mortality

versus CCI=0 patients (P<0.001), which is in line with other studies [339–341]. However, CCI=1−3 patients did not have worse OS than CCI=0 patients in our study (P=0.078), even though the EPV ratio was over 10:1, which should have been sufficient if there was a true connection [323]. The latter result is largely in conflict with the results reported by Rajan et al., who found worse other-cause mortality (OCM) for CCI=1 and CCI=2 patients versus CCI=0 patients (follow-up 8 years, HRs 1.61 and 2.04, respectively) in EBRT patients. These differences could be explained at least partially by differences in measures (5-year vs. 8-year outcomes). OCM is slightly different from overall mortality/survival, although given that there is no difference in PCSS, the results should be similar.

One explanation could be differences in sample sizes. For the RT subgroup, Rajan et al. included 13,143 CCI=0 patients, 1,834 CCI=1 patients and 825 CCI=2 patients [339]. Our Study I included 324 CCI=0 patients and 298 CCI=1−3 patients. However, a 60% increased risk, as reported by Rajan et al. [339], would likely have also been observed in a smaller population. The best explanation for the conflicting results is that even though Rajan et al. adjusted for several tumour and socioeconomical characteristics, they did not adjust for performance status [339]. Thus, the causality in their study can be questioned. It could be that people with any Charlson comorbidity are in poorer shape and thus more likely to die. On the other hand, even if the patient has Charlson comorbidities but is in excellent shape, his prognosis could be similar to those who do not have any Charlson comorbidities. The Study I results suggest that if both Zubrod PS and CCI are accounted for, CCI indeed has some independent predictive value, but only at high CCI scores. The exact threshold (CCI≥2, CCI≥3 or CCI≥4) would require more study. However, unlike Rajan et al. [339], Study I was not adjusted for marital status and educational level. Nevertheless, to my knowledge, neither has been proven to correlate with OS after EBRT, even though educational level has been shown to have an effect on which treatment is initially given [437], and marital status has been shown to be associated with a worse OS outcome after prostatectomy [438]. The other large trials (Berglund et al., Matthes et al.) included in the literature review did not have a subgroup analysis for EBRT but included various treatment modalities [340,341], which could explain the differences.

EPVs were too small to fully exclude that CCI could not affect 5-year PCSS or MFS. On the other hand, an EPV over 10:1 was more than sufficient to conclude that CCI did not affect BRFS in the study population. Our BRFS result is in line with the result reported by Goy et al. [344].

6.3 Zubrod performance status in local or locally advanced prostate cancer

Unlike the CCI, both Z groups (Z=1 and Z≥2) in Study I had an increased risk of all-cause mortality by approximately 120% when compared to Z=0 patients. The results are very similar to those reported by Fosså et al., who reported an HR of 2.03 in Z≥1 patients [326], and in line with those reported by Aas et al., although this connection was weaker (HR=1.4) [327]. However, interestingly, there was no statistically significant difference directly between Z=1 and Z≥2 patients (both groups had similarly increased risk). The confidence intervals were not completely overlapping, and the sample size in the Z≥2 group was only N=36, meaning that it cannot be fully excluded that there is no statistically significant difference. However, our results suggest that if there is a difference, the difference in hazard ratios would be relatively small if comorbidity is included as an explanatory factor. More research on the matter is needed.

Unlike previous studies [326,327], our study could not find a connection between PCSM and Zubrod PS. As stated, the number of prostate cancer deaths was too low to conclude that there was no difference. To our knowledge, we were also the first to report the results on MFS and BRFS in relation to Zubrod PS, which were nonsignificant (P>0.05). Even though the rate of metastatic disease was also too low to make definite conclusions, based on the Study I results, it can be relatively confidently argued that Zubrod PS does not have an effect on the rate of BR after EBRT for local PC.

6.4 Quality of life in patients treated with external beam radiotherapy alone in comparison with the general male population

In Study II, the most consistent difference between PC patients treated with EBRT alone and the age-standardized general male population was the difference in sexual activity, which occurred after the treatment and could be seen at both follow-up timepoints. The results support those reported previously by a PCOS study [366]. Since the 15D only assesses sexuality in one dimension (one question) on the influence of health on the amount of sexual activity [364], we can make only limited conclusions about how much this actually causes patient distress and concern. However, the PCOS results suggest that sexual issues after EBRT may not be long

term [366]. The results were distinctive from patients who had undergone surgery and reported sexual issues up to five years later compared to the two years for EBRT patients [366]. Schaake et al. assessed HRQoL only using the EORTC QLQ-C30, which does not include a measure of sexuality [367].

In contrast to PCOS [366], Study II patients reported more depression at baseline and at 3 months, as well as more distress at baseline, compared to the general population. Schaake et al. found a similar finding only at three years [367], at which point Study II could no longer find a statistically significant difference. The results suggest that psychological resilience is impacted by local factors (such as differences in genetics, culture and care), and mental QoL results suffer from a lack of generalizability. However, in Tampere University Hospital, patients with intermediate-risk PC seem to initially react mentally and acquire better mental QoL over a period of time (somewhere between three months and three years). To pinpoint the exact timeframe, more study is needed. It could be that PC diagnosis initially invoked fear in our patients, which had a detrimental impact on QoL related to psychiatric symptoms. Whether this is the case and whether the worry was in relation to the actual risk of mortality and treatment side effects would also require more study. A Swedish study conducted in screening participants and nonparticipants showed that approximately 20% of responders had a faulty impression or could not say that most men diagnosed with early PC do not die of it [439].

Regarding excretion, ESKO patients had worse scores only at 3 months. In the Australian Prostate Cancer Outcomes Study (PCOS, see also Section 2.18.1), bowel issues had a detrimental effect on QoL up to three years [366]. The excretion dimension of the 15D combines the aspects of urinary and faecal excretion [364], which limits the comparability.

No difference was found in global QoL, which was in line with the other two studies [366,367]. In many aspects (mobility, mental/cognitive function, discomfort, vision and hearing), PC patients also outperformed the general population at selected timepoints. It could be that patients referred to EBRT are in better shape than their peers. A plausible explanation is that, for example, patients with dementia are more likely to be treated with less aggressive treatment modalities or not diagnosed in the first place. The frequent hospital visits that are needed, especially for conventionally or moderately hypofractionated RT, could play a beneficial role in physical health.

6.5 Quality of life in patients treated with external beam radiotherapy alone versus the patient's pretreatment values

When compared against the patient's baseline in Study II, the only QoL difference measured by the FACT-P reaching clinical significance was the worse PCS result at the end of RT, although merely statistically significant differences in PWB and TOI were also found. The comparability to other studies is hindered by the fact that most studies that reported results in this manner did not use the FACT-P. An exception was a study by Monga et al., which reported a decline in QoL in PCS and PWB at the end of RT, but it was no longer present at the two-month follow-up (in this study the difference in PWB was over 2 points, which is usually considered the MID) [440].

Similar to the ESKO cohort in size (N=91) and design, a trial by Yamamoto et al. reported up to two years of lasting deteriorations in EPIC bowel and sexual function. Additionally, the Physical Component Summary of Medical Outcomes Study 8-Item Short-Form General Health Survey (SF-8) score was worse from 3 months up to a year (but this difference did not remain at two years) [441]. This trial included only RT monotherapy patients, similar to our study. The likely causes for the differences include the use of different forms, differences in RT technique (Yamamoto et al. included only patients receiving moderate hypofractionation) and location (Finland vs. Japan) [441].

Krahn et al. reported clinically and statistically significant deterioration of QoL in all but two (sexual issues, urinary function) UCLA PCI domains at 3 months after treatment and in some domains at one year after treatment (sexual function, bowel issues) [442]. In the EORTC QLQ-C30, there were also differences in some symptoms (fatigue and pain at both timepoints, diarrhoea at three months), although there were no differences in the QLQ-C30 QoL domains [442]. The RT cohort consisted of 66 patients [442]. The obvious explanation for the differences is the different forms used. The FACT-P does not have separate sexual, bowel or urinary domains, meaning that it can evaluate these aspects only collectively through the PCS domain, which can remain negative unless a difference is found in the majority of aspects it covers. Additionally, this trial included ADT patients (almost 60%) and patients of various risk groups and was conducted approximately 15 years ago with the contemporary RT technique and fractionation [442].

Finally, Schaake et al. (N=227) also performed comparisons with the patient's baseline, which were reported more thoroughly at 6, 12, 24 and 36 months [367]. Our results are in line with these results, since there were no clinically significant changes in any EORTC QLQ-C30 domain in their study, although there were

differences in some EORTC QLQ-C30 symptoms (dyspnoea, insomnia, fatigue) [367], which the FACT-P cannot assess. This occurred even though all patients in the study by Schaake et al. received ADT [367].

6.6 The impact of increasing fraction sizes in external beam radiotherapy for local prostate cancer

Study II was not designed to be statistically powerful enough to detect differences in HRQoL between SBRT, moderately hypofractionated RT and conventionally fractionated RT. Thus, statistical significance cannot be ruled out in domains and timepoints where it was not found. Furthermore, as the patients were not randomized into fractionation schedule groups but were allocated by the clinician, it is likely that the groups differ, and this difference causes bias that could explain the statistically significant differences that were found. Since the allocation was mostly based on time (the first patients recruited received conventionally or moderately hypofractionated RT, and the last patients recruited received SBRT), the largest bias is probably caused by differences in timeframes. Furthermore, a rectal immobilization device (Rectafix) was used only in moderately or conventionally hypofractionated RT patients (73.1%). It is certainly not implausible that such devices could negatively impact QoL. In another paper by Reinikainen et al., the use of Rectafix did not seem to have an effect on the genitourinary or gastrointestinal QoL of ESKO patients, nor did it have an impact on erectile function [411]. The only other trial that has collected HRQoL data on patients who underwent Rectafix treatment is the Australian Prostate Multicentre External beam radiotherapy Using a stereotactic boost (PROMETHEUS) trial, which investigates patients receiving SBRT boost followed by conventional radiotherapy with rectal sparing conducted with either Rectafix or SpaceOAR, which is a transperineally applicated gel [443]. The trial has not published HRQoL results as of early 2023.

Nevertheless, based on our results, nothing contraindicates further study on ultrahypofractionated SBRT since it outperformed in terms of HRQoL. Neither RCT has reported similar results [242,244,374], but in the PACE-B trial, it was not worse [244]. However, since HYPO-RT-PC assessed HRQoL in a much more multifaceted manner (much longer follow-up, more QoL instruments used) and the results at the end of treatment were quite clear (differences favouring conventional RT in global QoL, pain and various items related to bowel issues) [374], it remains the greatest authority in relation to HRQoL in the field at present. It may be that a

small proportion of SBRT patients experience high-burden gastrointestinal side effects that reflect HRQoL more often than those who undergo conventional RT, but this cannot be seen in small samples.

6.7 The impact of six cycles of adjuvant docetaxel on quality of life in patients treated with external beam therapy for local prostate cancer

In Study III, the patients in the intervention arm were given six cycles of docetaxel 75 mg/m^2 every three weeks for intermediate- or high-risk prostate cancer as an adjuvant to EBRT and LHRH analogue for 9 months, whereas the trial control arm was given the same treatment without docetaxel. Our results clearly demonstrated that adjuvant docetaxel causes a short-term decrease in total HRQoL and in the aspects of physical and functional well-being, since these domains were worse in the intervention arm at 6 months. However, such a decrease lasts less than a year from the initiation of treatment, since the HRQoL results at one year were already similar between the arms.

The SPCG-13 trial did not previously report any survival benefit [253], and thus, it is clear that based on both studies, we cannot recommend adjuvant docetaxel in general for patients with intermediate- or high-risk PC. To date, the only trial to find a survival advantage with adjuvant docetaxel for local hormone-sensitive PC has been the NRG Oncology RTOG 0521 trial [252], which has not published HRQoL results.

Our HRQoL results are in line with those reported by the GETUG-12 trial [378]. The results from the GETUG-12 trial show that a decrease in total HRQoL is already present at 3 months but similarly recovered by one year [378]. The combined results from Study III and GETUG-12 strongly suggest that the decrease in HRQoL lasts for the duration of the treatment and at least 1−2 months after the cessation of docetaxel (but less than 6 months) [378]. The estramustine used in the GETUG-12 trial may also affect the comparability of data of the two trials. Compared to the GETUG-12 trial, we found no difference in SWB, although the GETUG-12 trial found differences in social functioning [378]. The explanations for this discrepancy could include the estramustine used in the GETUG-12 trial, different timeframes (6 vs. 3 months), different forms used (FACT-P vs. EORTC QLQ-C30) and sociocultural differences (Study III was conducted in Finland and Sweden, GETUG-12 was conducted in France) [378]. Similarly, we found a difference in PWB, but the

GETUG-12 trial found no difference in physical functioning [378]. The difference found in FWB in Study III can be considered roughly to correspond with differences in role functioning in the GETUG-12 trial [378], as the role functioning domain of the EORTC QLQ-C30 depicts the ability to conduct activities at home and hobbies as before [444].

Our results are also comparable with those of the STAMPEDE trial, where the global QoL scores were considerably worse in the docetaxel + ADT group than in the ADT alone group at 3 months [380]. Although at 6 months STAMPEDE could not reach a statistically significant difference, their results, similarly to ours, showed a considerable difference at 6 months when actual mean values are investigated (66.9% vs. 73.9%), which was actually a greater difference compared to STAMPEDE results at 3 months [380], suggesting an issue related to statistical power rather than an actual contrary finding (the participation rates were not reported in STAMPEDE). The limitations of the multiarmed STAMPEDE trial that included both M0 and M1 patients treated with a variety of pharmaceuticals have been previously discussed in Sections 2.9.6, 2.11.2 and 2.18.1.4. The STAMPEDE HRQoL results were similar in both arms at 9 and 12 months (both in mean and P value) [380], corresponding to our 12-month result. STAMPEDE did not report results for domains other than EORTC QLQ-C30 global health state/total QoL [380].

6.8 Quality of life in patients with metastatic prostate cancer treated with either biweekly or triweekly docetaxel

In Study IV, patients with mCRPC received docetaxel at either two- or three-week intervals with equal dose intensity. A previous study showed that docetaxel 50 mg/m^2 every two weeks has advantages in regard to tolerability and survival [300]. Study IV now demonstrated that the total HRQoL in both arms is similar, and the biweekly regimen is noninferior in terms of total HRQoL. Furthermore, for the HRQoL subdomains, the biweekly regimen outperformed conventional dosing in the FAPSI-8, PWB and EWB and was worse only in the PCS, although the differences were small and "unconfirmed", meaning that consistent clinically and statistically significant differences did not have to be present in subsequent measurements (which has been a practice in some trials, although scientific evidence of the necessity of such a custom has not been demonstrated). The smallness of the differences is not surprising, as both treatments are very similar.

Based on the evidence provided, substituting biweekly docetaxel as a gold standard of docetaxel treatment of mCRPC in the first line should be considered. However, as overall survival was not the primary endpoint in the PROSTY trial (the endpoint was time to treatment failure, which was superior in the biweekly arm) [300], and as Study IV also had its own limitations, the attempted replication of the results in another RCT is also a suitable option before definite recommendations. Docetaxel 50 mg/m^2 is now listed as an alternative in both the EAU and NCCN guidelines [49,293].

To the author's knowledge, the HRQoL effects of docetaxel 50 mg/m^2 every two weeks have not been studied in other studies. However, a German prospective, multicentre trial demonstrated that docetaxel-related toxicity impairs the QoL of affected patients [445]. Nevertheless, reduced toxicity is not necessarily shown in RCT results: as seen from the results of the FIRSTANA and PROSELICA trials, even though dose adjustment of cabazitaxel reduced toxicity, the HRQoL results of cabazitaxel 20 mg/m^2 every two weeks and cabazitaxel 25 mg/m^2 every two weeks did not differ much, although PROSELICA found a difference in PCS favouring a smaller dose [406].

6.9 Strengths and limitations of the studies

All studies had some distinctive value. In this review, no Finnish studies similar to Study I were found covering survival outcomes of all risk groups analysed together. As stated, the CCI and Zubrod PS have not been analysed in the same model previously. Overall, most previous CCI and Zubrod PS studies covered various treatment modalities, with the exclusive EBRT results for all risk groups formerly being limited to the CCI paper published by Rajan et al. [339]. The previous Zubrod PS studies had not separated Z=1 and Z≥2 patients [326,327].

The number of studies that have compared the QoL of PC patients against that of the general population is low. PCOS was a large study, but since it combined EBRT and HDR BT + EBRT patients (without reporting the proportions of each) [366], it cannot give definitive answers for men treated with EBRT alone. Schaake et al. reported comparisons against the general population only at a single timepoint, at three years [367]. Thus, Study II provided valuable additional insight. Regional Finnish QoL information is similarly important, since as demonstrated, the results may vary between countries due to various factors.

Study III had several strengths. It was a randomized, controlled trial conducted in 11 different centres across Sweden and Finland. Thus, the amount of selection bias can be considered low. Compared to the GETUG-12 and STAMPEDE trials [378,380], it also had a longer follow-up time of up to 4 years. It also used MIDs to separate clinically significant findings from trivial ones.

Additionally, Study IV was a multinational RCT and included a non-Nordic dimension, as it included Irish patients, although the proportion of Irish participants was small. The trial had plenty of timepoints. It did not exclude patients who had treatment failures from the follow-up. The statistical model was adjusted for multiplicity where needed. The pattern-mixture model used for nonresponse has been found to be the least biased method possible by one study [415]. The data were analysed nonparametrically as required and thus avoided the risks of bias related to categorization of continuous data ('cut-point system'), which is one method often used to make data more parametrically accessible. The trial used MIDs.

6.9.1 Limitations of Study I

The retrospective, unrandomized setting of Study I naturally predisposes it to various kinds of bias, such as missing data, recall and selection bias [446]. Relatively good survival outcome results could be at least partially explained by lead time bias, since a proportion of patients directly participated in the ERSPC PSA screening trial, and others could seek consultation due to the increased awareness caused by the ERSPC trial, although they did not have symptoms or risk factors for PC. As shown in Section 5.3, 42% of participants did not have any symptoms. As stated, EPVs were too small to fully exclude that the CCI and Z could not affect 5-year PCSS or MCS.

Furthermore, Study I was a single-centre study comprising solely patients of Tampere University Hospital. The generalizability of results is limited even within Finland, which has large regional differences in morbidity between the Southern and Western regions and between the Eastern and Northern regions [447]. We did not perform a subgroup analysis for different D'Amico subgroups for survival outcomes, which could be considered a weakness.

6.9.2 Limitations of Study II

As previously stated, the main limitations of Study II include its nonrandomized design, sample size and the use of a rectal immobilization device in proportion to patients (hindering generalizability). The sample size was underpowered particularly for the subgroup analysis of different fractionations, but the entire intervention arm (N=73) preferably should have been larger (>200) to increase confidence, even though the control arm was a large cohort (NHS 2011 participants, N=952). Additionally, the data collection differed between NHS 2011 and ESKO participants, since the National Health Survey was conducted in 2011 and ESKO was conducted between 2014 and 2017. This causes bias in relation to time. Similar to Study I, this was also a single-centre study with similar issues related to generalizability.

Additionally, the comparisons with the patient baseline values were not corrected for multiplicity, which could have an impact particularly for FACT-P results, since 5 timepoints were compared against the same baseline value (for the 15D, there were only two). The interpretation of MIDs could have been clearer, since even though MIDs are described in the Material & Methods section of Publication II, they are described as a reference range (not exact values), and the statistical and clinical significances are not clearly separated in the interpretation of the original publication.

6.9.3 Limitations of Study III

Although Study III was a generally well-implemented study, it also has limitations. The study was conducted only in two countries, which means that while the results are well generalizable to the Nordic countries, they are not necessarily internationally generalizable. The statistical model used, ANCOVA, has been claimed not to be the least biased method available [448]. However, the high participation rates in the study limit the amount of bias. The decision of the model was made by the team statistician, not by the author.

Furthermore, there was no separate measure for pain, unlike in many trials. In retrospect, the FACT-P pain item could have been analysed in the absence of other pain questionnaires, or a separate measure such as BPI-SF could have been used. The use of specific questionnaires related to fatigue or mental symptoms also could have been informative. Additionally, the number of data collection points (baseline, 6 months, 1 year and 4 years) was quite low, and the data could have also been collected at 3 and 9 months, for example.

6.9.4 Limitations of Study IV

In PROSTY data collection, judging by the crude data, there were clearly varying practices regarding how often HRQoL forms were collected, which did not vary by arm but could vary by centre. As there were many forms returned outside the intended timeframes, the investigator had to decide whether to exclude a large number of forms (which could also be considered unethical) or to change the time interval for reporting, as was eventually done. However, the results may be biased to a small extent in that they overrepresent the data from some centres.

The number of timepoints was a strength but also a weakness due to low power in later samples, the informative value of which is questionable. However, to prevent selective publishing, these data were reported since they were analysed and included in the analysis. Acquiring data on late survivors of mCRPC may be difficult, and gaining powerful samples, for example, at one year after mCRPC treatment intervention, could require data from several studies.

Data collection for the PROSTY trial ended over ten years ago, which is another limitation. The late reporting was not attributed to the author, however. Currently, more treatment options are already available for nmCRPC and mHSPC. PSMA PET/CT and high/low burden classification in mPC are also quickly changing treatment practices. This means that the current patients may differ from the ones studied. However, in my view, it is better to report HRQoL results from any RCT late than to not report them. No novel prostate cancer drug should be implemented in clinical guidelines before evaluating its impacts on quality of life, as 'the best life possible' is preferable to 'the longest life possible' for many PC patients.

6.10 Considerations for future studies

As stated, it is a matter of opinion to what extent PCSS results close to 100% in local hormone-sensitive PC should be aimed to improve. In my view, the research should focus on high-risk patients and patients whose LE is at least 10−15 years. The novel treatments found to be beneficial in nongeriatric populations should not be regularly used in geriatric populations, except for treatment palliation if such is found. If new agents are introduced, they should have very favourable side effects and HRQoL profiles. Perhaps the resources would be best spent on studies that investigate patients whose cancer has already biochemically failed or metastasized.

Clinical decision-making would also benefit from easy-to-use tools for the estimation of LE, such as those that utilize data on patient comorbidities. As explained in this review (see Section 2.16), the conventional CCI is still a useful prognostic tool in present-day medicine (including in regard to PC) [337]. Additionally, it is supported by the strongest evidence of the instruments currently available [337]. However, in some regards it can also be considered outdated, since it includes comorbidities whose impact on public health in present-day Western medicine is minute (i.e., AIDS), causing needless work in data collection. On the other hand, the prognoses of certain comorbidities (for example, peptic ulcer disease and lymphoma) are different compared to 35 years ago, and one could question whether they still have a similar impact or weight in modern medicine. There is a demand for new comorbidity indices in oncological studies, but they should also be supported by sufficient evidence.

Compared to the general population, sexual activity seemed to be the most commonly affected area in local PC. Sexuality and its impact on quality of life in PC patients are very complicated entities that can be affected by age itself, relationship status, comparison with peers and even timely trends. Katz and Dizon argued that male sexuality is too often evaluated only through the presence of a dysfunction and the ability to perform intercourse [449]. However, based on PCOS results and in part supported by Study II, it is clear that PC patients suffer from sexual side effects of the treatment at least within the first few years. A major question is whether future interventions to improve sexual QoL should be targeted to all PC patients or whether we should try to identify subgroups that are most affected by the decline in sexual activity. After all, there are already several methods to manage the issue: we can delay the decline in sexual QoL, possibly by years, by selecting AS instead of EBRT [368], and the treatment options for ED range from simple oral medication to implant surgery [368]. However, even these cannot cure effects on self-esteem or on the perception of manliness.

Data collection of health-related quality of life forms in randomized controlled trials should be carefully designed. The protocol should have predefined MIDs or state clearly that MIDs are defined in a separate analysis from the study population, and the method for the MID definition should be included in the protocol. The reason for this is to minimize the risk of biased data presentation. It is already too easy to select either sensitive or unsensitive MIDs (or even not to use them) according to the known characteristics of the treatment (chemotherapy likely causes more side effects than novel antiandrogens added to already commonly used conventional antiandrogens), and the decision on MID thresholds should not be

made even easier by letting the investigator know the primary endpoint results before the HRQoL analysis. Unsensitive MIDs are likely one major reason why the HRQoL results in the intervention arms are often either noninferior or superior and very rarely inferior.

Furthermore, the protocols should clearly state at which point HRQoL forms are collected and intervene if there are large number of forms returned outside these timepoints. Specifically, in trials that differ in cycle duration, data collection should be designed carefully to be as little biased possible towards any arm but also in a simple manner (i.e., not as intended in the PROSTY trial, where the first HRQoL form was to be collected in the middle of the second cycle of the intervention arm, which was the third treatment visit, and before the second cycle in the control arm, which was the second treatment visit). Otherwise, it could be too complicated for data collectors/clinicians to determine when to collect the HRQoL form, leading to the wrong number of forms collected at the wrong timepoints. If there are forms returned outside of the intended periods, they should preferably be destroyed by the facility before implementing them to crude data, so that the investigator does not have to make the decision whether to include or exclude a large number of forms from the analysis. Electronically collected patient-reported outcome information is one solution to tackle this problem [450]. However, even this represents its own challenges within generations that have not grown up as digital natives.

Moreover, this literature review clearly showed that HRQoL research is still in a 'Wild West' kind of state, meaning that there are no established practices regarding which forms are acceptable to use, when to use them, and which methodology should be used for analyses. Adam et al. attempted to perform a meta-analysis for the HRQoL effects in PC but encountered such great heterogeneity among the studies that pooled analysis could not even be attempted [451]. Organizations such as ISOQOL as well as the EAU and NCCN should take greater responsibility by giving recommendations, for example, through a certificate system (the forms and methods that are sufficiently researched and acceptable could be given such a certificate).

Patients should be well informed before they receive curative or life-prolonging treatment, as treatment-regret remains a problem [452]. Patient-shared decision making is a novel way of questioning the narrative that the maximum achievable lifespan is always the most desired goal for the patient, as the harms of the treatment may show immediately but the benefits of treating low-risk disease may show only after 5 years or even longer [5]. A tools to make decision-making process easier, such as decision-aid tools [453], are needed.

7 CONCLUSIONS

The survival outcomes of local prostate cancer treated with external beam radiotherapy in Tampere University Hospital are similar to those in other high-income countries. Both the comorbidity and performance status of the patient affect overall survival after external beam radiotherapy for prostate cancer.

Patients treated with external beam radiotherapy alone for prostate cancer do not have worse total health-related quality of life than the age-standardized general population, nor is it worse as an entirety compared to their life preceding treatment. However, some aspects, such as sexual activity, are affected, and this effect is long-lasting.

Adjuvant docetaxel treatment to external beam radiotherapy for local prostate cancer causes a short-term decline in total health-related quality of life and physical and functional well-being. The decrease in quality of life is recovered in a year, and the quality of life of patients who receive docetaxel is comparable to that of other radiotherapy patients at least until four years.

Docetaxel 50 mg/m^2 every two weeks is as good as docetaxel 75 mg/m^2 every three weeks in the treatment of metastatic castration-resistant prostate cancer when health-related quality of life is considered. It may be even superior in some respects, such as in emotional well-being, but this is more uncertain.

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PUBLICATIONS

PUBLICATION I

Both comorbidity and worse performance status are associated with poorer overall survival after external beam radiotherapy for prostate cancer

Miikka Lehtonen, Lauri Heiskanen, Petri Reinikainen, and Pirkko-Liisa Kellokumpu-Lehtinen

BMC Cancer. 2020 Apr 15;20(1):324.
https://bmccancer.biomedcentral.com/articles/10.1186/s12885-020-06812-6
DOI: 10.1186/s12885-020-06812-6

Lehtonen et al. BMC Cancer (2020) 20:324
https://doi.org/10.1186/s12885-020-06812-6

BMC Cancer

RESEARCH ARTICLE Open Access

Both comorbidity and worse performance status are associated with poorer overall survival after external beam radiotherapy for prostate cancer

Miikka Lehtonen[1*], Lauri Heiskanen[1], Petri Reinikainen[1,2] and Pirkko-Liisa Kellokumpu-Lehtinen[1,2]

Abstract

Background: In this retrospective study, we evaluated the biochemical recurrence rate, metastatic disease progression, and prostate cancer-specific and overall survival in patients curatively treated with external beam radiotherapy (EBRT) for early prostate cancer (PC). We also examined the prognostic effect of comorbidity by Charlson Comorbidity Index (CCI) and overall performance status by Eastern Clinical Oncology Group (ECOG) score.

Methods: A total of 665 men treated between 2008 and 2013 were enrolled from Tampere University Hospital, Finland. Prostate-specific antigen (PSA) tests and hospital records were used to determine the 5-year survival for each aforementioned endpoint using a Kaplan-Meyer estimate. To analyze the impact of the selected prognostic factor, we used a Cox regression model to calculate the corresponding hazard ratio (HR) and 95% confidence interval (CI).

Results: With a median follow-up-time of 7.12 years, the 5-year overall survival (OS) after EBRT was 88.9% [86.5 -91.3%], prostate cancer-specific survival (PCSS) was 97.9% [96.7 -99.1%], metastasis-free survival (MFS) 94.8% [93.0 -96.6%] and biochemical recurrence-free survival (BRFS) 88.7% [86.2 -91.2%]. Both CCI (HR = 1.38, [1.25–1.51]) and ECOG score (HR = 1.63, [1.29–2.05]) declined OS, as well as Gleason score and T score ($P < 0.05$). Gleason score and T grade also associated to worse PCSS, MFS and BRFS.

Conclusions: CCI and ECOG score are useful tools in evaluating the overall life expectancy of the patient after EBRT for PC. T-stage and Gleason score remain still the major prognostic factors.

Background

Prostate cancer (PC) is the most common cancer among men in developed countries worldwide. In Finland, 5162 new cases were reported in 2016 [1]. PC primarily affects older males, with a peak incidence in men over 65 years [2] and it accounted for 13.3% of all cancer-related deaths among men in 2016 [3]. With earlier diagnostics in the PSA (prostate-specific antigen) era and advancements in treatment options, the prognosis has steadily improved in the past 15 years. The most recent register data reported a 5-year survival rate as high as 93% in the entire country [4].

External beam radiotherapy (EBRT) is one of the most common treatments of early PC and is often combined with androgen deprivation therapy (ADT) for patients with intermediate and high-risk disease. For localized disease, radical prostatectomy is also a viable option, especially for younger patients with few comorbidities. Other treatment options include brachytherapy, active and passive surveillance and ADT [5, 6].

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The present study aimed to evaluate the treatment outcomes of prostate cancer patients in Tampere University Hospital receiving EBRT as a curative treatment for localized PC and how comorbidity and overall fitness affect the results. We used Charlson Comorbidity Index (CCI) in measurement. CCI was developed in 1980's and is eponymously named after its developer [7], and is still in common use. To measure overall performance in patients, we used Eastern Clinical Oncology Group (ECOG) score [8], which was also developed nearly 40 years ago and is equally still widespread.

Register data shows that the prostate cancer-specific survival (PCSS) rates of all patients treated in Tampere University hospital are among the best in Finland with 1-year and 5-year survival rates of 99 and 95%, respectively [4]. However, no previous study has exclusively evaluated the outcomes of patients treated with EBRT in this region.

Methods

Study population, data collection, treatment, and follow-up

The study population was comprised of PC patients enrolled in The Clinical Registry at the Department of Oncology in Tampere University Hospital between 2010 and 2013, as well as patient data retrieved from the hospital information system from 2008 and 2009. Patients were identified from the hospital information system with a specific code depicting EBRT for PC. All patients receiving EBRT as a first-line treatment with curative intent, regardless of tumor T-score and pre-existing risk factors, were included. Only patients who met the following criteria were excluded from this five-year patient population: 1) The EBRT ended after December 31, 2013; 2) The patient was not a resident of a municipality belonging to the Pirkanmaa Healthcare District (detailed follow-up data were unavailable); 3) Metastatic disease (M1); 4) Premature cessation of EBRT due to a sudden illness (unrelated to prostate cancer); 5) EBRT as a second-line treatment (failed androgen deprivation monotherapy or salvage radiation therapy after radical prostatectomy); and 6) No radical treatment (palliative radiotherapy).

The final population was comprised of 665 men (Fig. 1). The study was approved by the ethical committee of the region, and permission to access patient report inquiries was granted by the director of the faculty of science (ETL R155025). The data collection occurred between May 2015 and March 2019 and included an assessment of the patient demographics, medical history and carcinoma-related details from the patient records of Tampere University and Tampere City Hospital.

Most men received treatment in the form of intensity-modulated radiation therapy (IMRT) with image-guided assistance ($N = 646$, 97.1%). The remaining cases were treated with either volumetric-modulated arc therapy (VMAT, $N = 7$, 1.1%) or three-dimensional conformal radiotherapy (3D-CRT, $N = 12$, 1.8%). Altogether, 367 men (55.1%) received androgen deprivation therapy (ADT) with a median duration of 20.3 months (range 1.6–127.4, N=). In 9 cases (2.5%), the duration of hormonal treatment could not be determined due to

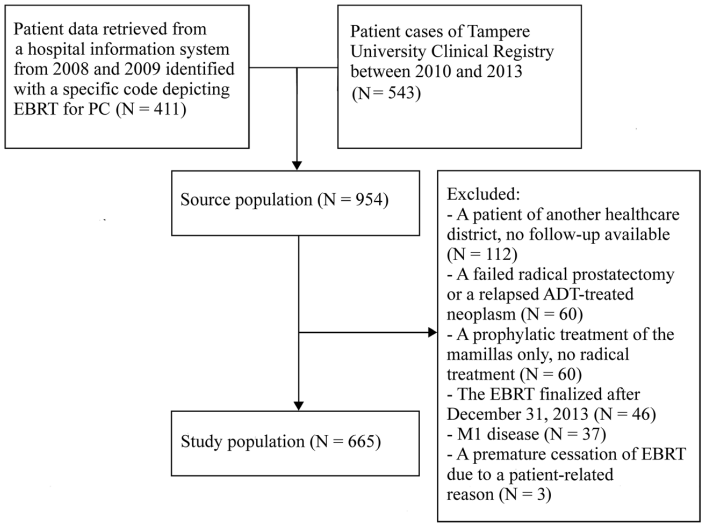

Fig. 1 A model depicting the formation of the final study population. EBRT = External Beam Radiotherapy; PC = Prostate Cancer

missing data. Among patients receiving ADT, 283 patients (76.9%) patients received a combined neoadjuvant-adjuvant –treatment, 74 patients (20.1%) received only the neoadjuvant and 11 patients (3.0%) only the adjuvant treatment.

Of patients belonging to a high recurrence risk group ($N = 360$) in the D'Amico classification [9], 295 men (81.9%) received ADT. In the intermediate-risk group ($N = 183$), 62 men (33.8%) received ADT. The median duration of the medicinal treatment in the high-risk group was 25.0 months (range [2.0–127.4], $N = 288$), and in the intermediate-risk group, it was 6.0 months (range [1.5–33.7], $N = 61$). In the low-risk group ($N = 121$), ADT was given to 10 men (8.3%). One patient could not be classified using the D'Amico system because of the inaccurate T grade documenting. A urologist decided to begin a neoadjuvant or adjuvant medication, based on the risk group and individual factors such as quality of life concerns. The patient had the right to decline from hormonal treatment. The long-term follow-up after EBRT was also mainly carried out by the department of urology and in lower-risk groups partly transferred back to primary healthcare.

ADT used most frequently was luteinizing-hormone-releasing hormone (LHRH) analog monotherapy with either leuprorelin or goserelin ($N = 308$, 83.9%). In 46 (12.5%) cases, this treatment was combined with antiandrogen bicalutamide. Two men (0.54%) received bicalutamide monotherapy, and 9 men (2.5%) received an LHRH-agonist (degarelix). Furthermore, two men (0.54%) participated in the SPCG-13 adjuvant phase III clinical trial and were treated with six cycles of docetaxel combined with a hormonal adjuvant treatment after radiotherapy [10].

The initial diagnosis was performed through a pathological examination of core needle biopsies of the prostate in a vast majority of the cases ($N = 656$, 98.6%). In nine cases (1.4%), cancer was an incidental finding after a routine examination of the surgical pathology slides after transurethral resection of the prostate (TURP). Standardly, a transrectal 12-core biopsy procedure was used, although there were patients with fewer or more biopsy cores (median 12.0, range [2–19], $N = 612$). The median percent of positive biopsy cores (PPC) was 40.0% (range 5.9% – 100%).

TNM-staging was established using both a pathology report and MRI imaging, through which the physician determined the clinical stage. Bone scans were performed to high-risk patients to exclude metastatic progression. The risk of lymph node and seminal vesicle metastasis was assessed by Memorial Sloan Kettering Cancer Center (MSKCC)-nomogram [11], and the radiation plan was selected accordingly. If the risk of seminal vesicle invasion was over 15% seminal apices were included in the treatment site and if lymph node involvement risk was over 35% pelvic lymph nodes were included in the radiation fields. Based on the nomogram, 452 men (67.9%) received treatment to the prostate gland and the bases of seminal vesicles alone. In 111 men (16.7%), seminal apices were included, and in 102 men (15.3%), both seminal apices and pelvic lymph nodes were radiated in addition to the prostate. Prostate and the bases of seminal vesicles were treated with 5 mm marginal. Treatment marginal to the seminal vesicle apices and lymph nodes was 7 mm. Most patients ($N = 536$, 80.6%) were treated with conventional fractionation (2 Gy, 5 times a week) with a dose of 78 Gy, which has been the standard of care until the recent introduction of hypofractionated schedules. A total of 32 men (4.8%) received hypofractionated radiotherapy treatment with fractions between 2.5–3.1 Gy. The detailed characteristics of the disease profiles and treatments are shown in Tables 1 and 2, respectively.

Patient follow-up data were collected from the medical records of the urological or oncological departments at Tampere University Hospital and the urological department at the Tampere City Hospital. The PSA-levels were obtained from the Fimlab laboratory database used in every public health institution in Pirkanmaa Hospital District. Each patient attended a PSA laboratory control every 6 to 12 months and a doctor's appointment at least once a year after the finalization of EBRT. If the patient had symptoms that could indicate a relapse, then the controls were taken more often. The dates of death were obtained from the Tampere University hospital patient records, which are directly synchronized with the Finnish Population Information System.

Outcomes and statistical analysis

The endpoint for biochemical recurrence-free survival (BRFS) was defined as a PSA increase by 2.0 μg/l or more from the lowest accomplished value after EBRT (nadir). The endpoint for metastasis-free survival (MFS) was determined by metastatic lesions shown in imaging. The date of death was used to determine the endpoint for overall survival (OS) and prostate-cancer specific survival (PCSS). The cause of death was determined by examining the patient records before death or by an autopsy report in selected cases.

No routine CT-scans or plain X-rays were used in the follow-up, and patients were only imaged if they had symptoms that could indicate metastatic disease or if they experienced a biochemical failure. For patients who did not reach the primary endpoint, the last registered PSA-value, physical examination (physician's appointment) or data collection date (whether the patient had died or not) was used to determine the follow-up time. Survival and follow-up times were determined from the date at which PC was diagnosed by a pathologist.

Table 1 Cancer and treatment characteristics of the study population

Characteristics	
Median age at the time of diagnosis (years; range)	70.9 (46.1–89.0)
T stage, n (%)	
T1	347 (52.2%)
T2a-b	62 (9.3%)
T2c	92 (13.8%)
T3	147 (22.1%)
T4	16 (2.4%)
unknown	1 (0.15%)
N1-disease, n (%)	5 (0.75%)
Gleason score, n (%)	
6	211 (31.7%)
7	260 (39.1%)
8	53 (8.0%)
9	138 (20.8%)
10	3 (0.45%)
Percentage of positive biopsy cores, n (%)	
1–10%	65 (9.8%)
11–20%	95 (14.3%)
21–30%	82 (12.3%)
31–40%	63 (9.5%)
41–50%	108 (16.2%)
51–60%	45 (6.8%)
61–70%	32 (4.8%)
71–80%	20 (3.0%)
81–90%	30 (4.5%)
91–100%	67 (10.1%)
Diagnostic transurethral resection of the prostate (TURP)	9 (1.4%)
Missing data	49 (7.4%)
Median PSA-level at the time of the diagnosis (range)	9.0 (0.9–694.0)
Median time from diagnosis to EBRT, months (range)	3.80 (0.77–83.6)
Median duration of ADT, months (range)	20.0 (1.6–125.7)
Fractionation type, n (%)	
conventional	633 (95.2%)
hypofractionated	32 (4.8%)
Average performance status *(ECOG score)*, n (%)	
0	348 (52.3%)
1	281 (42.3%)
2	33 (5.0%)
3	3 (0.45%)
Charlson Comorbidity Index, n (%)	
0	298 (44.8%)
1	190 (28.6%)
2	98 (14.7%)
3	37 (5.6%)
4	20 (3.0%)
5	13 (2.0%)
6	6 (0.90%)
7	2 (0.30%)
8	1 (0.15%)

The data were analyzed using SPSS Statistics 23.0 (IBM Corporation, Armonk, NY, USA) statistical analysis software. By using the aforementioned endpoints, we plotted age-adjusted Kaplan-Meyer curves for BRFS, MFS, PCSS, and OS. To study potential prognostic factors, we used Cox proportional hazards regression model *(Forward: LR method)*. The factors included in the analysis were age at the time of diagnosis, Gleason score, PSA-level at diagnosis, T-stage, N-stage, ADT, ECOG-score and Charlson Comorbidity Index (CCI) score. The variables included in final models were chosen based on their significance preliminary models. *P*-values below 0.05 were considered statistically significant. The frequencies and weights of different Charlson comorbidities are shown in Table 3. CCI points are determined by summing the weights of the patient's comorbidities.

Table 2 Radiotherapy schedules of the study population

Characteristics	N	%
EBRT dose (Gy)		
60	3	0.45
62	7	1.1
66	1	0.15
67.5	1	0.15
70.2	20	3.0
72	61	9.2
74	27	4.1
75	1	0.15
76	4	0.60
78	536	80.6
80	4	0.60
Fraction size (Gy)		
2	633	95.2
2.5	1	0.15
2.6	1	0.15
2.7	20	3.0
3	3	0.45
3.1	7	1.1

Table 3 Patient comorbidities characteristics

Charlson Comorbidity	Weight	N	%
Diabetes without complications	1	129	19.4
Chronic pulmonary disease	1	94	14.1
Cerebrovascular disease	1	58	8.7
Myocardial infarction	1	57	8.6
Connective tissue disease	1	53	8.0
Congestive heart failure	1	30	4.5
Dementia	1	22	3.3
Peripheral vascular disease	1	18	2.7
Peptic ulcer disease	1	15	2.3
Liver disease, mild	1	2	0.30
Renal disease, moderate or severe	2	60	9.0
Diabetes with end organ damage	2	22	3.3
Malignant tumor (within five years)	2	17	2.6
Leukemia, polycythemia	2	4	0.60
Lymphoma, multiple myeloma	2	3	0.45
Hemiplegia	2	2	0.30
Liver disease, moderate or severe	3	2	0.30
Metastatic solid malignancy	6	0	0
Acquired immunodeficiency syndrome (AIDS)	6	0	0

To study the effects of performance status and comorbidity separately, we plotted two distinct models. In the first model, the CCI score was used as a categorical variant. Comorbidity was classified into three categories: no comorbidity (CCI = 0), mild to moderate comorbidity (CCI = 1–3) and severe comorbidity (CCI = 4 or more). In the second model, ECOG score was used as a categorical variant. Overall performance was classified: normal (ECOG = 0), mild restrictions (symptoms only during strenuous exercise, ECOG =1) and from moderate to severe restrictions (symptomatic during normal daily activities, ECOG = 2 or more). To assess the potential presence of multicollinearity in the models, we calculated variance inflation factors (VIFs). With all VIFs being under 1.4, no significant multicollinearity was found. A one-way ANOVA test was also performed.

Results

In a median follow-up time of 7.12 years (standard deviation ±2.4 years, range 6.2–176.8 months), biochemical recurrence was observed in 137 (20.6%) patients. Among 367 men receiving ADT, 94 (25.6%) experienced a relapse, and for 24 of those (6.5%), the relapse occurred during the ongoing ADT treatment. The 5-year age-adjusted BRFS for the entire study population was 88.7% with a standard error (ste) of 0.013. The 95-% confidence interval (CI) was [86.2 -91.2%].

Altogether, 54 (8.1%) patients were diagnosed with metastatic disease during the follow-up. The 5-year MFS was 94.8% (ste: 0.009, [93.0 -96.6%]). The primary metastatic sites were bone ($N = 43$, 79.6%), lymph nodes ($N = 17$, 31.5%), lungs ($N = 5$, 9.3%), adrenal glands ($N = 2$, 3.7%), orbit (N = 1, 1.9%) and liver (N = 1, 1.9%).

158 men (23.8%) died during the follow-up. The 5-year age-adjusted PCSS was 97.9% (ste: 0.006, [96.7 -99.1%]), and the 5-year OS was 88.9% (ste: 0.012, [86.5 -91.3%]). Three leading causes of death were cardiovascular disease ($N = 39$, 24.7%), followed by other malignancies than prostate cancer ($N = 33$, 20.9%) and finally prostate cancer ($N = 31$, 19.6%). The cause of death remained unknown in 13 cases (8.2%) but was unlikely prostate cancer-related, as no biochemical recurrence or metastatic disease was registered for these cases. Other causes included neurological (including dementia, $N = 18$, 11.4%), infection ($N = 10$, 6.3%), pulmonary fibrosis or COPD ($N = 9$, 5.7%), trauma (N = 3, 1.9%) and uremia ($N = 2$, 1.3%).

Prognostic factors

The main findings considering prognostic factors on overall survival are listed in Table 4. In the first model, we evaluated how Charlson Comorbidity Index influenced overall survival after EBRT (Fig. 2). Overall, CCI had a statistically significant effect (P = < *0.001*). Compared to the baseline patients with no comorbidity

Table 4 Prognostic factors associated with overall mortality after EBRT

Model 1. *Charlson Comorbidity Index used as categorical variant.*

Factor	HR	95-% CI	*P*-value
CCI = 0 *(N = 298)*			< 0.001
CCI = 1–3 *(N = 324)*	1.38	[0.97–1.97]	0.078 ***(NS)***
CCI = 4 or more *(N = 42)*	6.11	[3.76–9.92]	< 0.001
Gleason score	1.21	[1.04–1.41]	0.015
T-grade	1.11	[1.01–1.21]	0.030
Zubrod score	1.63	[1.29–2.05]	< 0.001

Not significant: Androgen deprivation therapy (P = 0.70), age (P = 0.27), N-grade (P = 0.75), PSA-value before diagnosis (P = 0.15).

Model 2. *Performance status used as categorical variant.*

Z = 0 *(N = 348)*			< 0.001
Z = 1 *(N = 281)*	2.20	[1.54–3.13]	< 0.001
Z = 2 or more *(N = 36)*	2.22	[1.21–4.09]	0.010
Charlson Comorbidity Index	1.38	[1.25–1.51]	< 0.001
Gleason score	1.19	[1.02–1.39]	0.026
T-grade	1.11	[1.02–1.22]	0.022

Not significant: Androgen deprivation therapy ($P = 0.88$), age ($P = 0.18$), N-grade ($P = 0.77$), PSA-value before diagnosis ($P = 0.080$)
$N = 665$. Abbreviations: *NS* not significant, *HR* hazard ratio, *CI* confidence interval

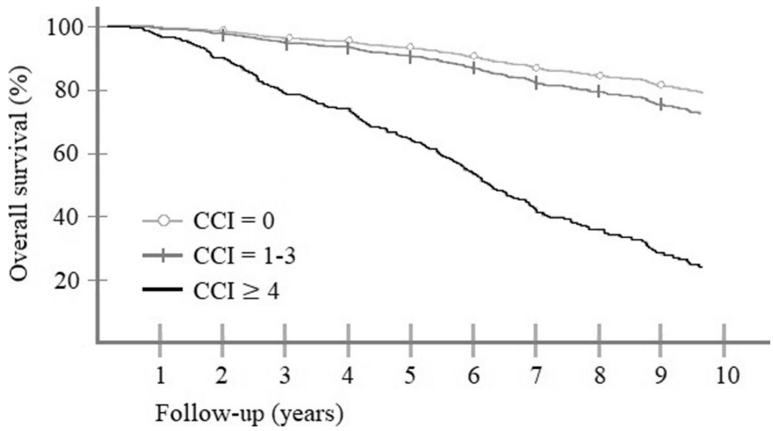

Fig. 2 Cox proportional hazards model of overall survival after EBRT in different Charlson Comorbidity groups. Otherwise healthy men are the baseline, CCI ≥ 4 are severely comorbid, and CCI = 1–3 are men with mild to moderate comorbidity. CCI = Charlson Comorbidity Index

(CCI = 0, *N = 298*), the population with severe comorbidity (CCI = 4, *N = 42*) had over 6-fold increased a risk of death with a hazard ratio (HR) of 6.11 (95-% CI = [3.76–9.92], P = < 0.001). Men with mild to moderate comorbidity (CCI = 1–3, *N = 324*), had not a statistically significant difference compared to the CCI = 0 population (HR = 1.38, [0.97–1.97], *P* = 0.078). Other factors that had an effect on overall survival were Gleason score (HR = 1.21, [1.04–1.41], *P* = 0.015), T-stage (HR = 1.11, [1.01–1.21], *P* = 0.030) and overall performance score (HR = 1.63, [1.29–2.05], P = < 0.001). Androgen deprivation therapy (*P* = 0.70), age (*P* = 0.27), N-grade (*P* = 0.75) and PSA-value before diagnosis (*P* = 0.15) were not a statistically significant prognostic factors in these patients.

In the second model, overall performance score was used as categorical variant (Fig. 3). Compared to the baseline (ECOG = 0, *N = 348*), men with mild restrictions (Z = 1, *N = 281*) had an increased risk of death (HR = 2.20, [1.54–3.13], P = < 0.001). Similarly, men with moderate to severe restrictions (ECOG ≥2, *N = 36*) had an increased risk (HR = 2.22, [1.21–4.09, *P* = 0.010) compared to the ECOG = 0 patients. There was not a statistically significant difference between groups ECOG = 1 and ECOG ≥2. Other factors that increased the risk (as in Model 1) were Gleason score (HR = 1.19, [1.02–1.39, *P* = 0.026) and T-stage (HR = 1.11, [1.02–1.22], *P* = 0.022), as well as CCI score (HR = 1.38, [1.25–1.51], P = < 0.001).

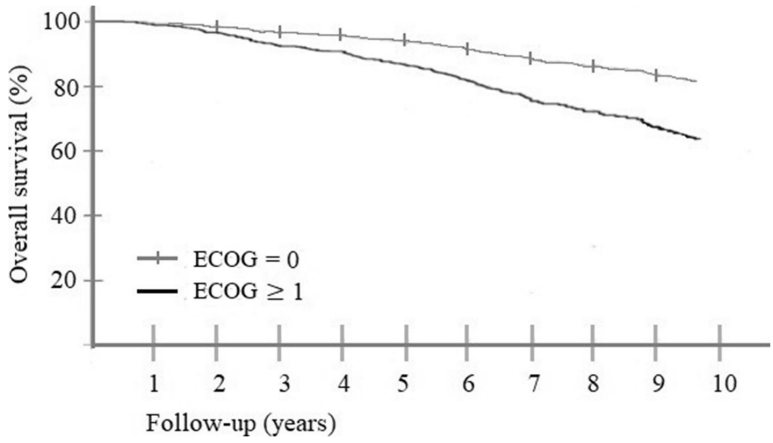

Fig. 3 Cox proportional hazards model of overall survival in different ECOG score groups. ECOG = 0 have no disability, ECOG ≥1 have mild to severe disability. ECOG = Eastern Clinical Oncology Group score

Neither comorbidity nor overall performance score increased the risk of biochemical recurrence (*P*-values 0.24 and 0.15, respectively), emergence of the first metastasis (P-values 0.59 and 0.83) or prostate-cancer related mortality (P-values 0.076 and 0.31). T-stage (HR = 1.23, [1.11–1.36], $P < 0.001$) and Gleason score (HR = 1.19, [1.02–1.41], $P = 0.036$) increased the risk of biochemical relapse. T-stage (HR = 1.29, [1.08–1.53], $P = 0.004$), N-stage (HR = 4.01, [1.22–13.1], P = 0.022) and Gleason score (HR = 1.63, [1.24–2.15], $P < 0.001$) declined the metastasis-free survival. T-stage (HR = 1.52, [1.19–1.94], $P = 0.001$) and Gleason score (HR = 1.44, [1.01–2.06], $P = 0.044$) increased the risk of prostate-cancer death. In sub-group analysis, whether the patient was hypofractionated or not, had not any effect on OS, PCSS, MFS or BRFS ($P > 0.9$).

Discussion

Our results show that the radical radiotherapy treatment results of early prostate cancer are excellent. Overall the 5-year OS (88.9%), PCSS (97.9%), MFS (94.8%) and BRFS (88.7%) were similar or better compared with the figures reported in other studies [12–18]. In recent years, there have been some large high-quality population-based studies that have demonstrated an association between increased overall mortality and comorbidity [19–21]. Smaller studies have found similar results earlier [22–24]. CCI has been shown to be a continuous variable in larger studies [19, 20], and we would probably have noticed a statistically significant effect with greater *N* in group CCI = 1–3.

Radiotherapy remains still a very important curative treatment of early prostate cancer with or without ADT. ADT increases the risk of myocardial infarction and diabetes, but the absolute risk increases similarly whether the patient has pre-existing conditions or not according to previous studies [25]. Adjuvant chemotherapy with docetaxel did not improve biochemical disease-free survival after radical RT according to the recent results of Scandinavian Prostate Cancer Group trial-13 (SPCG-13) [10]. Based on our results we should more carefully take into account patients' comorbidities and performance status when selecting treatment options for the elderly patient population.

Compared to earlier studies, this study showed that comorbidity and overall performance score affect overall survival independently. Most previous studies have focused on the Charlson Comorbidity Index alone. This study also used a differed stratification compared to previous studies. Both Rajan and Berglund used CCI ≥ 3 as a threshold for severe comorbidity [19, 20], but we demonstrated with a quite small $N = 62$ that in group CCI ≥ 4 patients have a 3.8–10 times the risk of dying after EBRT compared to healthy. CCI ≥ 4 could be a threshold value if the Charlson Comorbidity Index is used in daily practice in deciding the suitable treatment.

The present study had several limitations. This was an observational retrospective study without randomization or blinding. The number was quite small and comprised of 665 men. However, all the patients were treated in the same institution according to the same guidelines. Additional strengths of this study include very careful data collecting and non-selectiveness. We did not exclude any patients due to age, general condition or functioning-related factors, and the present cohort is hence comparable to the actual patient population treated with radiation therapy in general hospitals. The analysis of the material was quite comprehensive. However, we did not collect data on all possible contributing factors, such as familial history of prostate cancer or marital status. Some additional factors, such as the percentage of cancer volume (PCV), were investigated in preliminary models but then dropped due to lacking significance compared to other factors. We focused on survival and did not address matters such as quality of life or adverse effects of the treatment, which could be important from patient's perspective.

Conclusion

Charlson comorbidity is associated with weaker overall survival after EBRT for prostate cancer even if the overall performance status of the patient is considered, and both CCI and ECOG score have an independent effect. More study is needed, at which point exactly patient's disease burden and overall fitness should exclude EBRT.

Abbreviations

3D-CRT: Three-dimensional Conformal Radiotherapy; ADT: Androgen Deprivation Therapy; ANOVA: Analysis of Variance; BRFS: Biochemical recurrence-free Survival; CI: Confidence Interval; CCI: Charlson Comorbidity Index; COPD: Chronic Obstructive Pulmonary Disease; CT: Computer Tomography; EBRT: External Beam Radiotherapy; ECOG: Eastern Clinical Oncology Group; Gy: Gray; HR: Hazard Ratio; IMRT: Intensity-modulate Radiation Therapy; LHRH: Luteinizing-hormone-releasing Hormone; MFS: Metastasis-free Survival; MRI: Magnetic Resonance Imaging; MSKCC: Memorial Sloan Kettering Cancer Center; OS: Overall Survival; PC: Prostate Cancer; PCSS: Prostate Cancer-specific Survival; PCV: Percentage of Cancer Volume; PPC : Percentage of Positive Biopsy Cores; PSA: Prostate-specific Antigen; SPCG: Scandinavian Prostate Cancer Group; TURP: Transurethral Resection of the Prostate; VIF: Variance Inflation Factor; VMAT: Volumetric-modulated Arc Therapy

Acknowledgments

The authors would like to thank Tiina Luukkaala for assistance with the statistical analysis, Timo Lohiranta for assistance with the initial data extractions and Irja Kolehmainen for contributions to the required permits and general arrangements.

Authors' contributions

P.K. designed, directed and coordinated this study. M.L. and L.H. performed data collecting. M.L. performed the statistical analysis. M.L., L.H., P.R., and P.K. participated in the writing of the article. All authors have read and approved the manuscript.

Funding

This study was financially supported by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital,

grant number 9 U020. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The research was approved by the ethics board at Tampere University Hospital. As this was a retrospective, observational study the patient's consent was unnecessary according to national regulations (Finnish Date Protection Law 31 §). All patient data was treated confidentially and ethically.

Consent for publication
The authors consent for publication.

Competing interests
The authors declare no competing interests.

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Received: 6 December 2019 Accepted: 31 March 2020
Published online: 15 April 2020

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Publisher's Note

PUBLICATION II

Health-related Quality of Life of Patients Treated With Different Fractionation Schedules for Early Prostate Cancer Compared to the Age-standardized General Male Population

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Clinical Genitourinary Cancer, 2022 Aug 3:S1558-7673(22)00168-9
https://www.clinical-genitourinary-cancer.com/article/S1558-7673(22)00168-9/
DOI: 10.1016/j.clgc.2022.07.013

Original Study

Health-related Quality of Life of Patients Treated With Different Fractionation Schedules for Early Prostate Cancer Compared to the Age-standardized General Male Population

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Abstract

This prospective study investigated the health-related quality of life (HRQoL) of the patients with an early prostate cancer (PC) treated with radiotherapy (RT) without hormonal treatment compared to that in the age-standardized general male population. Patients have equal overall HRQoL measured with the 15D instrument compared to the general male population. Patients had more depression at the beginning of RT, and their sexual activity remained at a lower level after RT.

Background: The effects of radiotherapy (RT) patients' health-related quality of life (HRQoL) are usually compared to those of other treatment modalities instead of HRQoL of the general population in oncological studies. We examined HRQoL of patients with an early prostate cancer (PC) not receiving hormonal treatment up to 3 years after RT using the 15D instrument and the FACT-P questionnaire. **Methods:** The 15D results were compared to those in the age-standardized general male population (N = 952) using an independent-sample *t* test. The study population (N = 73) received RT either with 78/2 Gy, 60/3 Gy or 36.25/7.25 Gy fractionation. **Results:** No significant differences in the mean total HRQoL scores were found between the RT groups and the general male population at any time point. Patients with PC had more depression ($P = .015$) and distress ($P = .029$) than the general male population before the treatment and depression up to 3 months after treatment ($P = .019$), which did not persist at 3 years. The sexual activity dimension had declined by the end of treatment, and this decline persisted 3 years later ($P = .033$). Excretion functions were worse compared to those in peers at the end of treatment ($P < .001$) but no longer at 3 months and later after RT. Regarding the FACT-P, HRQoL remained good at 3 years after RT in all the treatment groups and there were no significant differences between the different RT groups at this time point. **Conclusion:** This study demonstrated that patients treated with RT for early PC had similar HRQoL compared to the age-standardized general male population at 3 years after treatment.

Clinical Genitourinary Cancer, Vol. 000, No.xxx, 1–9 © 2022 The Author(s). Published by Elsevier Inc.

Keywords: Hypofractionated radiotherapy, Radiotherapy, The FACT-P questionnaire, 15D instrument, Stereotactic Body Radiation Therapy

Introduction

External beam therapy (EBRT) along with radical prostatectomy (RP), is the gold standard for the treatment of local prostate cancer (PC).[1] Over the past decades, the reporting of health-related quality of life (HRQoL) results and other patient-related outcome measures have become a norm in modern oncological research, including in EBRT for PC.[2,3] Although PC had global the fourth highest incidence of all cancers in 2020, and the highest incidence of all cancers in Finland in 2019, the independent effects of external beam therapy on HRQoL have been relatively poorly studied in the absence of other treatments.[4-6] Androgen-deprivation therapy (ADT) seems to have a detrimental effect on HRQoL, which implies

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Submitted: Mar 29, 2022; Revised: Jul 6, 2022; Accepted: Jul 30, 2022; Epub: xxx

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https://doi.org/10.1016/j.clgc.2022.07.013

that the results of studies consisting of men receiving hormonal treatment cannot be generalized to men not receiving ADT.[7]

The primary objective of this trial was to investigate, how radiation therapy for the prostate affects HRQoL in the absence of treatment-related confounding factors. We could not find any previous studies that would have been comparing differences in HRQoL between men treated with EBRT for PC and the age-standardized general population and excluded men receiving ADT. In the New South Wales Prostate Cancer Care and Outcomes Study (PCOS) men receiving either EBRT or brachytherapy had a predetermined clinically significant difference in quality of life (QoL) in terms of bowel function up to 10 years and in terms of sexual function during the whole 15 year follow-up.[8,9] In another population-based study by Schaake et al., men treated with EBRT had worse QoL measured in role functioning, emotional functioning, social functioning, dyspnea and insomnia compared to the general population at 3 years after EBRT.[10] This study included both men with and without hormonal treatment (proportions of 69% and 31%, respectively).[10]

After the development of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), both an increase in the fraction dose and a decrease in the target volume without additional toxicity have become possible, thus reducing side-effects and hospital visits, costs and patient inconvenience.[11-13] Hypofractionated radiotherapy is currently the preferred form of radiotherapy for local PC recommended by National Cancer Comprehensive Network (NCCN) guidelines.[1,14] Current research, as well as our trial, focuses on ultrahypofractionated radiotherapy, which employs stereotactic body radiation therapy (SBRT), aiming to further increase the fraction dose, reduce toxicity and limit the treatment schedule even to 5 to7 visits.[13]

The secondary objectives were to compare HRQoL between groups undergoing either conventional, hypofractionated or ultrahypofractionated, (Stereotactic Body RT, SBRT) treatment schedules. HRQoL in men treated with ultrahypofractionated schedules has been previously studied only in 2 randomized controlled trials (RCTs), neither of which permitted androgen-deprivation.[15,16] Both trials had both low- and intermediate-risk patients, the HYPO-RT-PC trial used the ASTRO classification and the PACE-B trial used the NCCN classification.[15,16] In the HYPO-RT-PC trial, HRQoL was weaker compared in global health, role functioning, emotional functioning, pain, and diarrhea at the end of radiation of therapy than after conventional therapy, but no difference was observed at follow-ups.[15] The PACE-B trial did not find differences in HRQoL between the ultra-hypofractionation and control group during the 3-month follow-up at any point (the control group consisted of men receiving either conventional or hypofractionated therapy).[16] Moderate hypofractionation has been studied in at least 3 RCTs, which reported acceptable toxicity profile and no differences in HRQoL between hypofractionated therapy and conventional therapy.[17-19]

At present, the treatment results of modern RT for early prostate cancer are excellent in Finland.[20] Therefore, studying the patients' mental and overall health after PC diagnosis is important, as the vast majority of patients are expected to recover (the metastasis-free 5-year survival almost 95 %) and compare HRQoL between the patients with PC treated using 3 RT fractionating schemes and the age-standardized general male population to explore the need for individual psychosocial support for patients with radically treated PC.

Materials and Methods

Patients and Radiation Therapy Planning

Men up to 85 years of age with a biopsy-confirmed localized T1c-T2cN0M0 prostate cancer with 1 or 2 intermediate risk factors (IFRs) according to NCCN criteria were eligible for this study.[21] IFRs were T2b-T2c disease, Gleason score of 7 or a prostate-specific antigen (PSA) level of 10 to 20 ng/mL. Androgen deprivation therapy (ADT) or need of transurethral resection of the prostate (TURP) were exclusion criteria. Between May 2014 and December 2017, a total of 73 patients (approximately 90%-95% of eligible patients) were recruited from Tampere University Hospital. The first 42 patients were treated with a fraction dose of 2 Grays (Gy), 5 fractions per week to a total dose of 78 Grays (78/2 Gy) or 60/3 Gy according to the clinician's decision, and the next 31 patients were then treated with a higher fraction dose: 7.25 Gy and only 5 times = 36.25/7.25 Gy. The Tampere University Hospital Ethics Committee approved the study (R14009), and patients provided written informed consent. The clinical trial identifier was NCT02319239 at www.ClinicalTrials.gov.

Prior to RT, all patients had 3 gold fiducial markers implanted into the prostate gland under transrectal ultrasound guidance. After implantation, planning computed tomography (CT) and magnetic resonance imaging (MRI) were performed (with empty bladder and rectum). The prostate and the base of the seminal vesicles were delineated as the prostate clinical target volume (CTV). A symmetric 5-mm margin was used to achieve prostate planning target volume (PTV). If the seminal invasion (SV) risk was greater than 15%, SV sites were contoured and given 7-mm expansion as SV-PTV in the RT 78/2 Gy and 60/3 Gy groups, and the RT doses to the SV-PTV were 56/2 Gy and 46/2.3 Gy, respectively.[22] In the 36.25/7.25 Gy group SV sites were not included. The bladder, rectum, and femoral heads were defined as organs at risk. Treatment localization was performed by orthogonal kilo voltage (kv) imaging. In the 36.25/7.25 Gy group cone beam CT (CBCT) was used to evaluate the bladder and rectum before every treatment session. In the 78/2 Gy and 60/3 Gy groups radiotherapy was administered daily from Monday to Friday, and the 36.25/7.25 Gy group received treatment every other day for ten days. Volumetric modulated arch therapy (VMAT) with 2 full arcs and 6-MV flattened beams was used for treatment in all groups.

Health-related Quality of Life Instruments

In this study, we used 2 internationally validated patient-reported outcome questionnaires in Finnish to evaluate the HRQoL of patients with PC treated with RT: the 15D instrument and the Functional Assessment of Cancer Therapy-Prostate (FACT-P). These questionnaires were completed before RT (baseline), at the end of treatment, and 3 months, 1 year, 2 years and 3 years after the RT. Altogether, 787 questionnaires were collected during the study, yielding a response rate of 92%.

Please cite this article as: Petri Reinikainen et al, Health-related Quality of Life of Patients Treated With Different Fractionation Schedules for Early Prostate Cancer Compared to the Age-standardized General Male Population, Clinical Genitourinary Cancer, https://doi.org/10.1016/j.clgc.2022.07.013

The 15D is a generic instrument with 15 dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity) and developed in Finland and used in different type of diseases, interventions, and compare costs using Quality Adjusted Life Years (QALYs) and is comparable to EQ-5D.[23-27] Each dimension has 5 different answers ranging from no problems to extreme problems.[28] The 15D score ranges from 0 to 1, where 1 indicates full health. The minimum clinically important change in the 15D score is interpreted as follows: |0.015-0.035| for slightly better/worse and over |0.035| for much better/worse. A 15D score change of ≥ 0.015 is considered clinically meaningful, with the patient feeling the difference in his or her wellbeing.[29] An age-standardized sample of the Finnish male population (N = 952) was used as a comparison group for patients treated with RT, which was obtained from the National Health 2011 Survey.[30] The National Health 2011 Survey was a combination of health interview and health examination aimed to obtain information on public health problems in working-aged and the aged population. It captured 7964 persons aged 30 and over living in the mainland Finland.

The FACT-P is a validated 39-item questionnaire that was developed to measure HRQoL in men with prostate cancer and consists of 5 subscales: 7 items for physical wellbeing (PWB), 7 items for social and family wellbeing (SWB), 6 items for emotional wellbeing (EWB), 7 items for functional wellbeing (FWB) and 12 items for the prostate cancer subscale (PCS).[31] Items are scored from 0 to 4 and it can be worded in a positive or negative direction. The FACT-P total score ranges from 0 to 156. Higher values of total or any subscales indicate better HRQoL. The FACT-G (general) measures general HRQoL in patients with cancer and consist of 27 items (PWB, SWB, EWB and FWB). The FACT-P Trial Outcome Index (TOI) is based on physical, functional and prostate cancer -specific subscales of the FACT-P (PWB, FWB and PCS).

One method to evaluate meaningful changes in the FACT-P total score or in its subscales at different timepoints, is to compare scores to the published minimal important difference (MID) scores. Most of the publications in this area correspond to men with metastatic prostate cancer. Meaningful changes vary from 6 to 10 points for the total FACT-P score, from 5 to 7 points for the FACT-P TOI score, from 2 to 3 points for the FACT-P PCS score and 5 to 8 points for the FACT-G score, respectively.[32,33]

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics version 25.0 for Windows (SPSS Inc. Chicago, IL). The statistical significance of the difference between mean 15D scores between the general male population and patients treated with RT was tested using independent-sample *t* tests. The same test was used for differences between 15D scores and FACT-P scores in the RT treatment groups. Treatment changes within the RT groups before the RT and at the appointed follow-up timepoint were analyzed using paired-sample *t* tests. If the 15D or FACT-P variables were not normally distributed, a corresponding nonparametric test was performed. The Mann-Whitney 2 independent samples test was used to compare 2 RT groups, and changes within the RT group between different time points were analyzed using the Wilcoxon signed-rank test. All tests used a 2-sided $P < .05$ for statistical significance.

Results

The mean and median age of the patients treated with RT was 69 years (range 59-78 years). Most of the patients had a Gleason 3 + 4 disease, and the mean PSA was 9.5 ng/mL. After 3 years of follow-up, 66 patients were included in the study. Of the 7 discontinuations, 3 were in 78/2 Gy group, and 2 in 60/3 Gy and 36.25/7.25 Gy groups. Four men developed another aggressive malignant disease that was not related to RT, and 1 man in 78/2 Gy group and 2 men in 60/3 Gy group had a biochemical relapse according to the Phoenix definition.[34] All 3 relapses had a Gleason 3+4 disease at baseline. The clinical demographics of the patients treated with RT are presented in Table 1.

Results from the 15D Instrument

Changes in the 15D score and scores for different dimensions in patients treated with RT are demonstrated in Figure 1. No statistically significant differences in the mean 15D score were found between patients treated with RT and the general male population at the beginning of treatment or at the 3-year follow-up (Table 2). The acute toxicity of RT treatments did not correspond to the 15D score at the end of RT, or at any timepoint compared to observations in the general male population. The 15D scores of the patients treated with RT ranged from 0.735 to 1.000 (mean 0.913) at the baseline. Six patients were in full health (15D score 1.000). At the end of the treatment 2 patients were in full health and 15D scores ranged from 0.675 to 1.000 (mean 0.898). Three years after RT, 4 patients had a 15D score of 1 and, 15D scores ranged from 0.504 to 1.000 (mean 0.890). The 15D score difference decrease between baseline and the 3-year follow-up was statistically significant ($P = .001$).

At the baseline, patients treated with RT had lower mean scores for depression and distress ($P = .015$ and $P = .029$, respectively) than the general male population. At the end of RT, these mental problems continued, and 3 months after the treatment, the mean dimension score for depression was still significantly lower ($P = .019$). However, in the end of the follow-up at 3 years, the mental health of the patients treated with RT was similar to the general population ($P > .05$ for both distress and depression). The sexual activity of patients treated with RT was also non significantly lower at the baseline. Immediately and 3 years after the treatment sexual activity was significantly lower than that in the general male population. When bowel and bladder symptoms (Excretion) were compared, patients treated with RT had better mean scores at baseline and significantly worse scores at the end of RT ($P < .001$), but subsequently, no differences compared to the general male population were identified. Patients seemed to score better than the general male population for physical discomfort and symptoms at 3 years after RT ($P = .027$). Patients also had better cognitive function scores at all timepoints.

When observing the changes within the RT groups (supplementary Table S1), the HRQoL measured by the 15D score worsened significantly in the 78/2 Gy and 60/3 Gy groups, but not in the SBRT 36.25/7.25 Gy group between baseline and 3 years after treatment ($P = .034$, $P = .044$ and $P = .153$, respectively). Bowel and

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Table 1 Patients Clinical Demographs

	Radiation Therapy Group			
	All N = 73	39 × 2 Gy N = 21	20 × 3 Gy N = 21	5 × 7.25 Gy N = 31
Age, years				
Mean (range)	69 (59-78)	68 (59-78)	70 (60-78)	70 (63-78)
BMI				
Mean (range)	28.1 (21.4-40.6)	28.4 (21.4-40.4)	27.8 (22.4-34.8)	28.1 (21.8-40.6)
BMI ≥ 30, N (%)	19 (26)	6 (29)	5 (24)	8 (26)
Comorbidities, N (%)				
Diabetes type II	17 (23)	4 (19)	6 (29)	7 (23)
Hypertension	44 (60)	11 (52)	10 (48)	23 (74)
ASO	11 (15)	4 (19)	3 (14)	4 (13)
AF	8 (11)	3 (14)	3 (14)	2 (7)
Gleason score, N (%)				
3 + 3	21 (29)	7 (33)	8 (38)	6 (19)
3 + 4	49 (67)	13 (62)	13 (62)	23 (74)
4 + 3	3 (4)	1 (5)	0 (0)	2 (7)
T stage, N (%)				
T1c	11 (15)	2 (10)	3 (14)	6 (19)
T2a	18 (25)	5 (24)	4 (19)	9 (29)
T2b	9 (12)	3 (14)	3 (14)	3 (10)
T2c	35 (48)	11 (52)	11 (52)	13 (42)
PSA baseline, ng/mL				
Mean (range)	9.5 (3.2-19.1)	10.5 (4.0-15.2)	8.7 (3.4-18.4)	9.5 (3.2-19.1)
Questionnaires returned, N (%)				
Baseline	70 (96)	21 (100)	21 (100)	28 (90)
End of RT	67 (92)	21 (100)	21 (100)	25 (81)
3 months	70 (96)	21 (100)	21 (100)	28 (90)
12 months	68 (93)	19 (90)	21 (100)	28 (90)
24 months	64 (88)	17 (81)	20 (95)	27 (87)
36 months	63 (86)	18 (86)	18 (86)	27 (87)

Abbreviations: Gy = Gray; BMI = Body mass index; ASO = Atherosclerosis; AF = atrial fibrillation; PSA = Prostate specific antigen; N = number of patients

bladder problems (Excretion) were present in all RT groups at the end of treatment. According to the mean dimension scores at 3 years after the RT, the scores in the 78/2 Gy and 60/3 Gy groups were worse than the baseline scores. Sexual activity worsened in all RT groups from baseline to the 3-year of follow-up. The men in the 60/3 Gy group felt less energetic (Vitality) and more depressed (Depression) 3 years after RT, but they had less physical discomfort and fewer symptoms. The men in the 36.25/7.25 Gy group had more discomfort and symptoms during the follow-up. Three years after RT the men in the 78/2 Gy group had more symptoms related to ageing than the men in the other groups. The dimensions related to vision, hearing, breathing and sleeping became worse between the baseline and the 3-year follow-up.

At the end of RT, the 36.25/7.25 Gy group had a better HRQoL than the 78/2 Gy group when comparing 15D total scores ($P = .023$) (Figure S1). The men in the 36.25/7.25 Gy group had fewer problems with excretory functions ($P = .014$) and were more satisfied with their sexual activity ($P = .013$) at the end of RT than men in the 78/2 Gy group. The difference in the dimension of sexual activity was at 3 months after RT in favor of the 36.25/7.25 Gy group ($P = .034$). One year after treatment, the men in the 36.25/7.25 Gy group reported better HRQoL with respect to the 15D total score than the men in the 78/2 Gy group ($P = .015$). The men in the 36.25/7.25 Gy group were more content with usual activities (UACT) than the men in the 78/2 Gy group ($P = .006$). Between the 60/3 Gy and 36.25/7.25 Gy groups, the men treated with SBRT had less distress at 3 years after RT ($P = .045$), and between the 78/2 Gy and 60/3 Gy groups, men treated with hypofractionated RT had less discomfort and symptoms ($P = .028$) at 1 year after RT.

Results from the FACT-P Questionnaires

The baseline FACT-P total score of the whole study population was 128.5 (SD 16.9). The treatments had a transient negative effect on HRQoL (Table 3.). At the end of the RT, the FACT-P total score declined significantly (124.7, SD 18.1, $P = .013$). However, after 3 years of follow-up the FACT-P total score returned to baseline level (128,5, SD 18.8, $P = .364$). At the end of RT, significant negative changes in physical activity (PWB, $P = .002$), the prostate-cancer-specific subscale (PCS, $P = .002$), and the trial outcome index (TOI) ($P = .002$) were observed. Negative changes in physical activ-

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Figure 1 **The mean 15D dimension scores of RT patients and the age-standardized general male population at different timepoints. Population 1 is the control population for the treatment group at baseline until 3 months and population 2 is the control population for the treatment group at 36 months. Statistically significant changes in RT patients' dimension scores between the baseline and follow-up timepoints are marked with asterisks (*).**

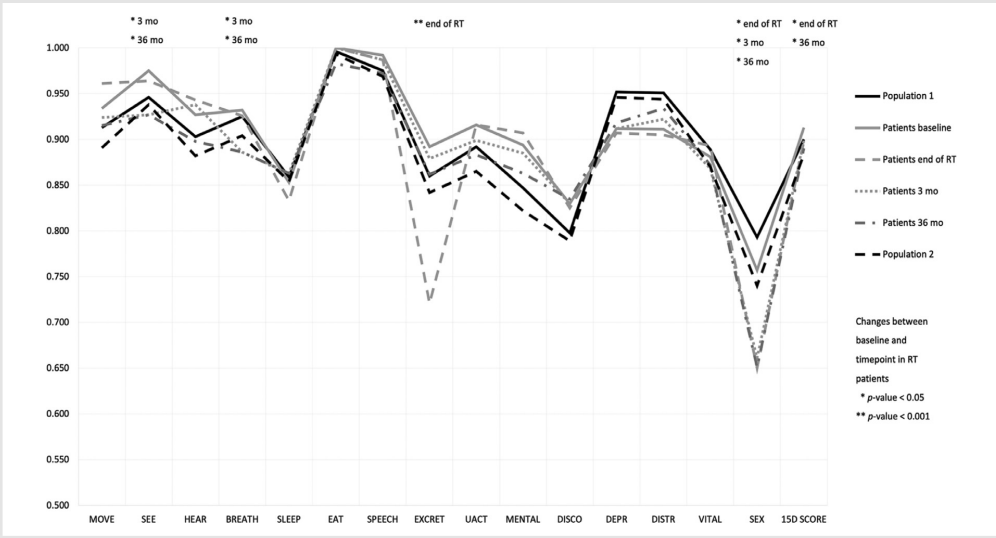

Table 2 **The Mean 15D Scores and Dimension Values of RT Patients at Different Timepoints Compared to The Age-Standardized General Male Population**

	Baseline		End of RT		3 Months After RT		3 Years After RT	
	Mean	Δ	Mean	Δ	Mean	Δ	Mean	Δ
15D score	0.913	0.013	0.898	-0.012	0.899	-0.011	0.890	0.006
Mobility	0.934	0.023	0.961	0.048[b]	0.924	0.011	0.915	-0.019
Vision	0.975	0.029[a]	0.964	0.018	0.927	-0.019	0.927	-0.011
Hearing	0.927	0.024	0.943	0.040[a]	0.938	0.035	0.898	0.016
Breathing	0.932	0.007	0.926	0.001	0.886	-0.039	0.886	-0.018
Sleeping	0.853	-0.006	0.833	-0.026	0.863	0.004	0.863	0.009
Eating	1.000	0.004	1.000	0.004	1.000	0.004	0.983	-0.010
Speech	0.992	0.017	0.987	0.012	0.987	0.012	0.972	0.003
Excretion	0.892	0.032	0.721	-0.139[b]	0.879	0.019	0.862	0.020
Usual activities	0.916	0.024	0.916	0.024	0.899	0.007	0.883	0.018
Mental function	0.894	0.047[a]	0.907	0.053[a]	0.885	0.038	0.863	0.041
Discomfort and symptoms	0.830	0.032	0.825	0.027	0.830	0.032	0.835	0.046[a]
Depression	0.912	-0.040[a]	0.907	-0.045[a]	0.912	-0.040[a]	0.918	-0.028
Distress	0.911	-0.040[a]	0.905	-0.046[a]	0.922	-0.029	0.934	-0.010
Vitality	0.881	-0.008	0.893	0.004	0.868	-0.021	0.872	0.002
Sexual activity	0.757	-0.036	0.650	-0.143[b]	0.661	-0.132[b]	0.651	-0.089[a]

Δ, difference compared to the age-standardized male population (positive values for better score to RT patients in comparison to general population).
Differences between RT population and age-standardized male population were analyzed using independent-sample *t* test
[a] $P < .05$
[b] $P < .001$.

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Table 3 The Mean FACT-P Scores and Standard Deviations (SD) of RT Patients (N = 73)

	Baseline (N = 70)	End of RT (N = 67)	3 Months (N = 70)	12 Months (N = 68)	24 Months (N = 64)	36 Months (N = 63)
FACT-P total	128.5 (16.9)	124.7 (18.1)[a]	126.9 (18.9)	126.6 (16.9)	127.6 (17.0)	128.5 (18.8)
FACT-G total	90.8 (12.3)	89.3 (13.5)	89.9 (14.5)	89.0 (12.3)	89.8 (12.0)	90.7 (13.7)
Physical (PWB)	25.7 (2.7)	24.4 (3.4)[a]	25.1 (3.2)	25.2 (3.2)	25.1 (3.1)	24.9 (3.4)[a]
Social (SWB)	22.0 (4.9)	21.9 (5.1)	21.8 (5.9)	21.2 (5.6)	21.7 (4.5)	22.0 (5.0)
Emotional (EWB)	20.4 (3.0)	20.7 (3.0)	20.8 (2.7)	20.8 (3.0)	20.4 (2.9)	20.9 (3.0)
Functional (FWB)	22.4 (4.9)	22.1 (5.3)	22.2 (5.8)	21.9 (5.3)	22.3 (4.3)	22.7 (4.6)
Prostate cancer specific (PCS)	37.7 (6.0)	35.2 (6.4)[a]	37.2 (5.7)	37.4 (5.8)	37.7 (5.9)	37.9 (6.1)
Trial Outcome Index (TOI)	85.9 (11.2)	81.7 (12.9)[a]	84.4 (12.5)	84.5 (12.0)	85.2 (12.1)	85.5 (12.9)

The FACT-P, FACT-G and subscales score (range); FACT-P (0-156); FACT-G (0-108); PWB, SWB, FWB (0-28); EWB (0-24); PCS (0-46); TOI (0-104). Changes between baseline and timepoints were analyzed using paired-sample *t* test
[a] $P < .05$; $P < .001$.

ity in the whole study population were still observed after 3 years of follow-up ($P = .019$).

No significant changes in the FACT-P total scores were identified in any of the RT groups between baseline and the 3-year of follow-up (Table S2). The highest scores were in the 36.25/7.25 Gy group. The 60/3 Gy group was the only group in which the FACT-P total score decreased between baseline and 3 years after RT. At the end of RT, the mean TOI worsened in the 60/3 Gy group by 6 points ($P = .011$). Between baseline and the end of RT, the mean score in PCS of the 60/3 Gy group decreased by 3.9 points ($P = .006$), and at 3 months after RT, these patients still had more symptoms than at baseline ($P = .014$). None of the RT groups had significant changes in the PCS scores between baseline and the 3-year of follow-up.

Discussion

This study had several strengths. According to our review, this is the first prospective trial comparing short-term (< 5 year) results in patients of exclusively after EBRT for early prostate cancer treated with modern RT techniques to results in an age-standardized general male population. The PCOS study reported results for a combined group of EBRT and brachytherapy group, which does not accurately depict the effects of EBRT since the QoL effects differ, particularly considering urinary functions.[8,35] To our knowledge, this study is also the first to compare short-term results in men exclusively without ADT, therefore accurately depicting the HRQoL effects of EBRT without confounding factors. However, this factor can also be considered a limitation, because most men treated with EBRT will receive adjuvant or neoadjuvant ADT (approximately 80% in Finland).[10,20] HRQoL effects of EBRT for prostate cancer seem tolerable, and acceptable, and minor compared with those of adjuvant EBRT treatment of breast cancer, for instance.[36]

Overall, our results are in line with those in the PCOS study and Schaake et al., considering general HRQoL and sexual functions.[8,10] Compared to the PCOS study results, no decrease in excretory functions was observed at 3 months or later after EBRT.[8] However, the 15D instrument does not separate urinary and fecal excretory functions, which could also be viewed as a limitation. Compared to our study, in the PCOS study, the mental well-being scores were lower in the patient population than in the reference population at 1, 2 and 3 years after EBRT, but the result did not exceed the clinically significant difference.[8] Our study did not use an identical time frame, and the results are therefore not directly comparable, but our results support the results of the PCOS study considering 3-year HRQoL.[8] In our study, depression was more common in the patient population than in the general population for at least 3 months, and distress was more common until the end of treatment. Our results suggest that mental health interventions may be beneficial. However, according to the previous research, nontargeted approaches are unlikely to improve mental health-related QoL.[37] A recent review by Mundle et al., suggested screening of mental problems in men treated for PC and targeted treatment, although more study is needed on what exact form or method should be used for screening.[38] Sexual rehabilitation programs seem to reduce sexual bother and improve adherence to the standard pharmaceutical treatments for erectile dysfunction, but whether they actually improve HRQoL or its sexual domain, requires more study and one of the

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key issues is to include an uro-oncological nurse to PC team and she/he should have enough time to discuss with the patient and his spouse about the multidimensional issues related to PC and its treatments.[39] Electronic patient reported outcomes (PROs) is a modern way to follow-up patients HRQoL life and increase it as we have first done with patients with breast cancer.[40] The same system was initiated in 2019 for patients with prostate cancer treated with RT.

Compared to those in Schaake et al., our patients did not have weaker sleep- or breathing-related HRQoL at 3 years.[10] As Schaake et al., showed that increased reported dyspnea was related to the prevalence of chronic obstructive pulmonary disease (COPD) and asthma in this cohort, indicating that the difference was likely caused by differences in the characteristics of the study populations.[10] However, the difference in sleep-related quality of life cannot be explained and remains a topic for further study.[10]

Considering the FACT-P results, Monga et al. reported a similar decline in PWB and PCS subdomains at the end of radiotherapy.[41] In their study, the differences in FACT-P were not present any longer at 2 months, similar to our 3-month result.[41] This suggests that HRQoL declines are transient. Compared to the HYPO-RT-PC and PACE-B trials, our study included only intermediate-risk patients.[15,16] Compared to the PACE-B study, which also used the NCCN classification, we report HRQoL results up to 3 years vs. the 3 months in the PACE-B study.[16] No results from RCTs that combine ADT and SBRT have yet been published, although studies are ongoing.[18,42]

Limitations

This study has also several limitations. First, the number of patients with PC in our study was quite small compared to those in the HYPO-RT-PC and PACE-B trials for evaluating the secondary objective.[15,16] The sample size was large enough to evaluate patients as 1 group (N = 73) in relation to the general population but unfortunately is too small to account for statistically powerful comparisons between different fractionation groups. Small sample size bears a risk for false negative results. However, as the results of HYPO-RT-PC and PACE-B are in conflict with each other considering the HRQoL at the end of treatment, our trial provides further information on the long-term HRQoL and thus we decided to report also the results for different fractionation groups briefly.[15,16] Our study reports also HRQoL results for 3 years after RT, which neither of the aforementioned trials do not, since PACE-B HRQoL results were reported up to a year and HYPO-RT-PC long-term results 1, 2, 4 and 6 years after RT.[15,16]

The study was not randomized, which predisposes to both unknown and known types of confounders, such as selection bias.[43] Our study was also single-center design, which may limit its generalizability. The study population was superior compared to the age-matched general population in some features (vision and mental/cognitive functions at baseline), likely because we did not account for possible differences in educational levels between populations. There is also some possible bias in relation with time, since the population sample (N = 952) used in comparison was collected in 2011, and the study took place between 2014 and 2017. Also, the first patients were assigned either 78/2 Gy or 60/3 Gy fractionation, but the later participants were systematically assigned to 36.25/7.25 Gy fractionation, which is another source of possible bias. It is known that certain phenomena that occur periodically, such as economic crises or pandemics, may affect physical and mental health and thus also HRQoL.[44–46]

Finally, our results only apply to those men belonging to NCCN intermediate-risk group and treated with EBRT. There are currently many good care options for men belonging to those group, including active surveillance, brachytherapy and RP.[1] According to the current NCCN guideline, observation is preferable to the EBRT, if life expectancy is under 10 years and the disease belongs to the favourable intermediate risk group.[1] Our study did not distinguish between favorable and unfavorable intermediate risk groups.

Conclusion

The HRQoL of our patients treated with RT for PC seems to be at a high level except for sexuality-related issues, and more attention should be devoted to this important aspect of HRQoL and to the development of possible therapeutic interventions/approaches according to patients' personal needs. SBRT was also tolerated as conventional and moderately hypofractionated treatment, and the overall HRQoL of EBRT-treated PC patients in this study compared with the age-standardized general population was good. SBRT seems to be a convenient treatment in daily clinical practice.

Clinical Practice Points

- There are limited studies comparing the effects of curative-intent RT on early PC patients' to HRQoL in the general population. In this study we demonstrated that the overall HRQoL of early PC patients treated with modern image guided RT techniques and without hormonal treatment is equal at 3 years after treatment to the age-standardized general male population measured with the 15D instrument. The patients with prostate cancer had more depression and distress in the time of active treatment to their cancer when compared to the age-standardized male population. Patients' sexual activity declined during RT and remained at the lower level during 3-year follow-up. In the future, more support should be given to the PC patients at the beginning of the treatment to mental issues and also later to address sexual issues.
- The HRQoL of 3 different RT groups; conventional fractionation (78/2 Gy), moderate hypofractionation (60/3 Gy) or stereotactic body radiotherapy (36.25/7.25 Gy), were compared with the 15D instrument and the FACT-P questionnaire. The changes within the RT groups measured by the 15D score worsened significantly in the 78/2 Gy and 60/3 Gy groups, but not in the SBRT 36.25/7.25 Gy group, but there were no significant changes in the FACT-P total scores in any of the RT groups, between baseline and 3 years after treatment. This study confirms the rationale of treating early PC with stereotactic body radiotherapy.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Expert Responsibility area of Tampere University Hospital (protocol code R14009, 2014-02-24).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Acknowledgments

To Irja Kolehmainen, research coordinator and research nurses Tuula Nuuttila and Jasmin Salmi. This research was funded by Seppo Nieminen foundation, Grant number 15012, Tampere University Hospital and by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, Grant numbers 9V019, 9AA027, 9AB027 and 9U020, Tampere University Hospital.

Disclosure

Harri Sintonen is the developer of the 15D and obtains royalties from its electronic versions. The other authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.07.013.

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Please cite this article as: Petri Reinikainen et al, Health-related Quality of Life of Patients Treated With Different Fractionation Schedules for Early Prostate Cancer Compared to the Age-standardized General Male Population, Clinical Genitourinary Cancer, https://doi.org/10.1016/j.clgc.2022.07.013

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Table S1. Changes in the mean 15D scores and mean dimension values in different radiation therapy groups between baseline and follow-up timepoints.

	Radiation therapy group											
	Conventional fractionation (78/2 Gy)				Moderate hypofractionation (60/3 Gy)				Stereotactic body radiotherapy (36.25/7.25 Gy)			
	baseline mean	Δ end of RT	Δ 3 months	Δ 3 years	baseline mean	Δ end of RT	Δ 3 months	Δ 3 years	baseline mean	Δ end of RT	Δ 3 months	Δ 3 years
15D score	0.893	-0.020	-0.014	-0.036*	0.911	-0.015	-0.010	-0.040*	0.928	-0.013	-0.015	-0.019
Mobility	0.890	0.054*	-0.009	-0.026	0.986	0.000	-0.011	-0.045	0.928	0.012	-0.010	-0.011
Vision	0.969	0.000	-0.041*	-0.050	0.989	-0.020	-0.065*	-0.090*	0.969	0.009	-0.025	-0.008
Hearing	0.950	0.000	-0.011	-0.073*	0.902	0.049*	0.011	-0.013	0.928	0.010	0.037	-0.011
Breathing	0.888	0.000	-0.074*	-0.099*	0.956	-0.014	-0.014	-0.055	0.946	-0.009	-0.038	-0.041
Sleeping	0.839	-0.044	0.000	-0.039	0.805	0.013	0.025	0.025	0.897	-0.020	-0.001	-0.000
Eating	1.000	0.000	0.000	-0.039	1.000	0.000	0.000	-0.019	1.000	0.000	0.000	0.000
Speech	1.000	0.000	-0.014	-0.033	0.971	-0.014	0.000	0.000	1.000	0.000	0.000	-0.023
Excretion	0.879	-0.234**	-0.015	-0.051	0.924	-0.192**	-0.043	-0.068	0.876	-0.099*	0.023	-0.009
Usual activities	0.879	0.000	-0.014	-0.032	0.933	0.013	-0.014	-0.082	0.930	-0.025	-0.021	-0.032
Mental function	0.881	0.000	0.000	-0.020	0.868	0.004	0.004	-0.049	0.923	0.016	-0.026	-0.028
Discomfort and symptoms	0.757	0.010	0.057	0.017	0.815	0.056	0.000	0.062*	0.893	-0.054	-0.046	-0.047*
Depression	0.932	0.011	0.000	-0.026	0.876	-0.028	-0.001	-0.036	0.923	-0.009	0.009	0.019
Distress	0.947	-0.013	0.000	-0.030	0.871	0.005	0.013	-0.005	0.912	0.012	0.009	0.064*
Vitality	0.878	-0.010	-0.020	-0.025	0.868	0.009	-0.001	-0.074	0.892	0.032	-0.018	0.019
Sexual activity	0.687	-0.143*	-0.120*	-0.036	0.749	-0.116*	-0.106	-0.116	0.814	-0.063	-0.074	-0.187*

Δ, difference compared to baseline score (positive values for better score when compared to baseline).

Changes between baseline and timepoints were analyzed using paired-sample t test: * $P < .05$; ** $P < .001$.

Minimum important changes for 15D scores: >0.035, much better; 0.015 - 0.035, slightly better; 0.015 - -0.015, no change; -0.015 - -0.035, slightly worse; <-0.035, much worse.

Table S2. Radiation therapy groups' mean scores and standard deviations (SD) on the FACT-P, FACT-G and FACT-P subscales at different timepoints during the follow-up.

	Radiation therapy group																	
	Conventional fractionation (78/2 Gy)						Moderate hypofractionation (60/3 Gy)						Stereotactic body radiotherapy (36.25/7.25 Gy)					
	bl	eRT	3 mo	12 mo	24 mo	36 mo	bl	eRT	3 mo	12 mo	24 mo	36 mo	bl	eRT	3 mo	12 mo	24 mo	36 mo
FACT-P total	123.9 (17.3)	120.5 (16.3)	125.2 (19.6)	122.8 (15.9)	129.6 (16.7)	125.3 (18.3)	128.9 (15.6)	122.9 (20.6)	126.0 (18.1)	122.8 (18.8)	123.6* (19.8)	125.8 (20.8)	131.7 (17.5)	130.4 (16.5)	128.9 (19.5)	132.9 (14.6)	129.0* (15.3)	132.8 (17.6)
FACT-G total	89.3 (11.7)	88.6 (11.2)	88.9 (14.9)	86.9 (11.7)	91.7 (11.5)	89.0 (13.6)	89.8 (12.8)	87.7 (15.8)	89.5 (14.3)	86.2 (13.9)	87.1* (13.4)	88.0 (16.2)	92.8 (12.7)	91.4 (13.5)	90.9 (14.9)	93.0 (10.9)	90.3* (11.4)	93.8 (11.6)
Physical (PWB)	25.4 (2.6)	23.9* (3.0)	24.3 (3.4)	24.1* (3.2)	25.5 (2.4)	24.3 (4.2)	25.5 (3.0)	23.8* (4.6)	24.8 (3.6)	24.9 (4.2)	24.7 (3.7)	24.6 (3.6)	26.1 (2.5)	25.4 (2.1)	25.8 (2.6)	26.3 (1.9)	25.2 (3.2)	25.5 (2.8)
Social (SWB)	22.2 (5.1)	21.6 (4.8)	22.3 (6.2)	21.4 (4.9)	22.6 (4.4)	21.8 (5.2)	22.3 (4.7)	22.9 (3.6)	22.7 (3.7)	20.0 (6.6)	22.0 (3.8)	21.9 (5.0)	21.6 (5.1)	21.3 (6.5)	20.8 (6.9)	22.0 (5.4)	21.0 (5.0)	22.2 (5.2)
Emotional (EWB)	19.6 (2.3)	20.7 (2.6)	20.3 (2.2)	20.4 (3.3)	21.0* (2.2)	20.6 (2.9)	20.2 (3.5)	20.0 (3.9)	20.0 (3.5)	20.2 (3.4)	19.6 (3.4)	20.1 (3.7)	21.2 (2.9)	21.3 (2.3)	21.7 (2.1)	21.4 (2.4)	20.7 (2.9)	21.8 (2.2)
Functional (FWB)	22.0 (5.9)	22.4 (3.7)	21.9 (6.4)	21.0 (5.9)	22.6 (4.3)	22.2 (4.7)	21.7 (4.5)	21.0 (5.8)	21.9 (5.3)	21.8 (4.3)	21.1 (4.8)	21.6 (5.6)	23.3 (4.4)	22.7 (6.0)	22.6 (5.9)	22.6 (5.7)	23.0 (4.0)	23.8 (3.6)
Prostate cancer specific (PCS)	34.8 (7.0)	31.8 (6.8)	36.2 (6.6)	35.9 (5.3)	37.8 (6.3)	36.3 (6.2)	39.0 (4.4)	35.1* (6.2)	36.5* (5.1)	37.0 (6.3)	36.6 (6.5)	38.2 (6.0)	38.9 (5.7)	38.2 (4.7)	38.4 (5.5)	38.8 (5.5)	38.3 (5.4)	38.7 (6.2)
Trial Outcome Index (TOI)	82.0 (12.3)	78.1 (12.3)	82.5 (13.6)	81.0 (12.0)	85.9 (11.8)	82.9 (13.5)	86.3 (10.0)	80.0* (15.0)	83.3 (12.1)	83.0 (12.7)	82.4* (14.0)	84.1 (13.9)	88.7 (10.7)	86.5 (10.4)	86.7 (12.0)	88.3 (10.5)	86.6 (10.9)	88.3 (11.7)

Changes between baseline and timepoints were analyzed using paired-sample t test: * $P < .05$; ** $P < .001$.

The FACT-P, FACT-G and subscales score (range): FACT-P (0-156); FACT-G (0-108); PWB, SWB, FWB (0-28); EWB (0-24); PCS (0-46); TOI (0-104).

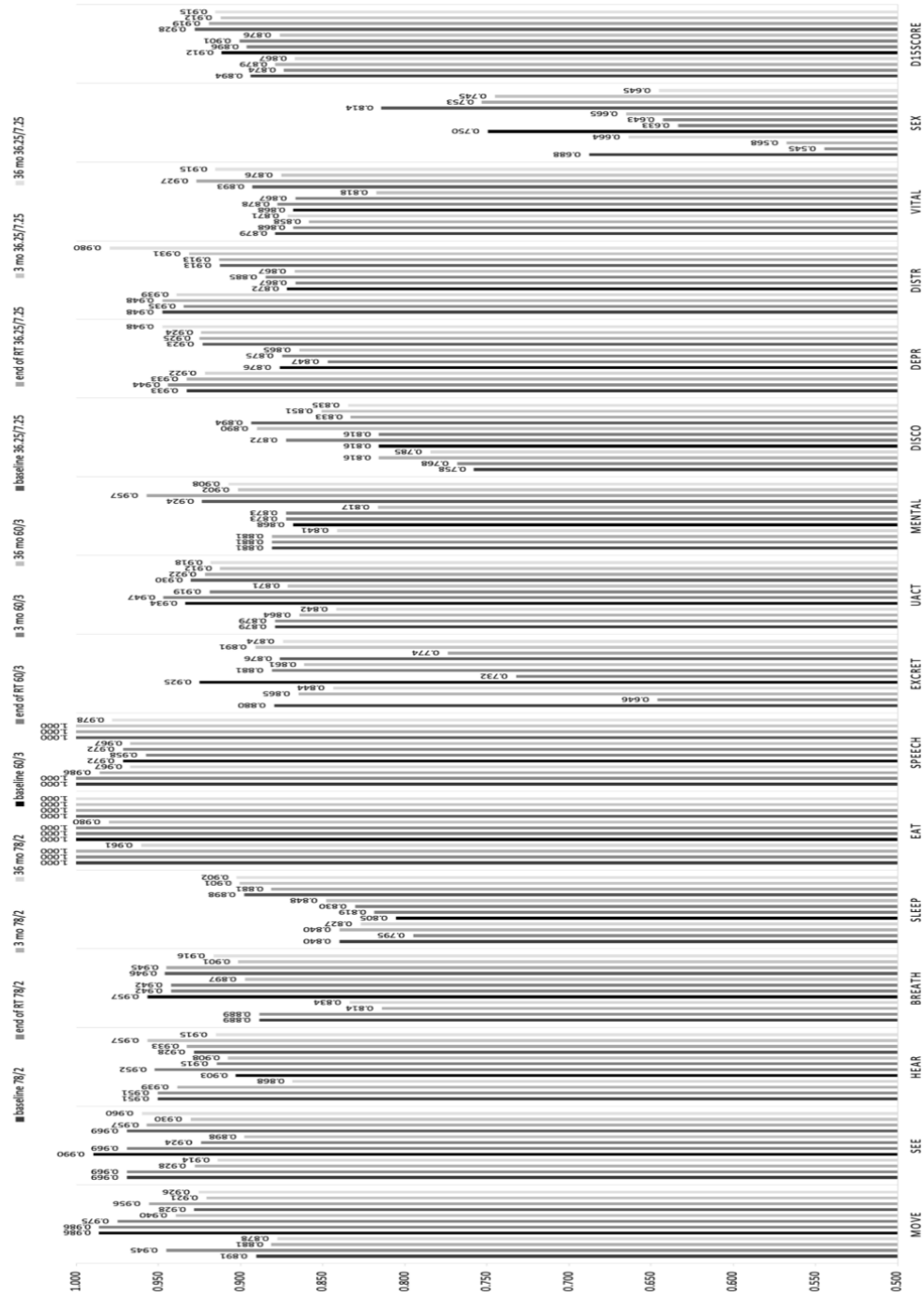

Figure S1. The mean 15D scores and mean dimension values at different timepoints in RT groups.

PUBLICATION III

Health-related Quality of Life in Intermediate- or High-risk Patients Treated With Radical External Radiotherapy and Adjuvant Docetaxel for Localized Prostate Cancer: A Randomized, Phase III SPCG-13 Study

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Anticancer Research, 2022 Jan;42(1):87-92
https://ar.iiarjournals.org/content/42/1/87
DOI: 10.21873/anticanres.15460

ANTICANCER RESEARCH *42*: 87-92 (2022)
doi:10.21873/anticanres.15460

Health-related Quality of Life in Intermediate- or High-risk Patients Treated With Radical External Radiotherapy and Adjuvant Docetaxel for Localized Prostate Cancer: A Randomized, Phase III SPCG-13 Study

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Abstract. *Background/Aim: The goal of this study was to investigate whether health-related quality of life (HRQoL) was affected in patients with high- or intermediate-risk localized prostate cancer treated with docetaxel following radiation therapy (RT). Patients and Methods: A total of 376 patients treated with RT and androgen deprivation were randomized to receive 6 cycles of docetaxel 75 mg/m^2 (N=188, Arm A) or surveillance (N=188, Arm B). FACT-P HRQoL questionnaires were gathered at baseline, six months and 1, 2 and 4 years after randomization. The data were analysed using analysis of covariance. Results: FACT-P scores decreased in Arm A at the end of treatment and remained unchanged in Arm B (p<0.0001). The HRQoL scores in Arm A matched Arm B in the 1-year follow-up (p=0.0528) and remained similar in further follow-up. Conclusion: Docetaxel transiently decreased HRQoL during chemotherapy but not after treatment for up to four years of follow-up.*

Adjuvant treatment with docetaxel for local prostate cancer (PC) has been studied in few prospective randomized trials after radical prostatectomy (RP) and radiotherapy (RT) during the past two decades (1-4). After local treatment, the risk of biochemical recurrence for a high-risk disease is approximately 50% at five years (5-9). A docetaxel-based treatment has been shown to increase survival in both hormone-naïve and castration-resistant metastatic prostate cancer (10-14). In early-stage breast cancer, an adjuvant taxane-based regimen has been accepted as standard treatment over the past twenty years (15-17).

The Scandinavian Prostate Cancer Group (SPCG) initiated two prospective open-label, randomized trials, SPCG-12 and SPCG-13, to evaluate a possible benefit of docetaxel as adjuvant treatment after local curative treatment in localized high- or intermediate-risk prostate cancer. In the SPCG-12 trial, the patients were randomized to receive six cycles of docetaxel without androgen-deprivation therapy (ADT) or surveillance after RP and in the SPCG-13 they received six cycles of docetaxel with ADT or surveillance with ADT after curative-intent external beam radiotherapy (EBRT) without continuous prednisone. ADT treatment was continued for three months and was ended before the beginning of docetaxel treatment. The adjuvant docetaxel did not improve biochemical progression-free survival (BPFS) in either of the trials (2, 3). In the NRG Oncology RTOG 0521 trial, which included only high-risk patients after EBRT, docetaxel with ADT improved not only BPFS but also metastasis-free survival (MFS) and overall survival (OS) (1). In the GETUG-12 trial, BPFS was improved with a combination of docetaxel and estramustine, but MFS

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Key Words: Radiotherapy, prostate cancer, quality of life, docetaxel.

Table I. *Baseline characteristics of included patients.*

Factor	Adjuvant treatment with docetaxel (N=180)	Surveillance (N=183)
Age (yrs), median (IQR)	67 (63.5-70)	67 (63-71)
PSA before RT (ng/ml), median (IQR)	14.1 (7.8-28.0)	14.1 (7.1-26.0)
PSA after RT (ng/ml), median (IQR)	0.49 (0.15-2.70)	0.60 (0.12-1.75)
T-stage T2/T3 (%)	26/74	25/75
Gleason 7/8/9-10	56/25/19	50/25/25
WHO status 0/1 (%)	92/8	95/5

IQR: Interquartile range; PSA: prostate-specific antigen; RT: radiotherapy; WHO: World Health Organization.

was not (4, 18). Currently, we cannot exclude the possibility that docetaxel could be beneficial in some subgroups of early prostate cancer after EBRT.

If docetaxel is to be considered in the treatment for local PC after EBRT, it is important to know how it affects the quality of life (QoL) of the patient. The reporting of QoL results after treatment of a local PC with docetaxel has been sparse. In the STAMPEDE trial, which included high-risk PC patients with rising PSA values, the combination of docetaxel and ADT after either EBRT or RP did not decrease patients' QoL compared to ADT alone (9). In the GETUG 12 trial, QoL was decreased at three months but not at one year of follow-up (4). The goal of this study was to investigate whether health-related quality of life (HRQoL) was affected by adjuvant docetaxel given after radical RT in the randomized SPCG-13 trial.

Patients and Methods

The main inclusion criteria for the SPCG-13 trial were men between 18 and 75 years, World Health Organization (WHO) performance status 0-1, and histologically confirmed adenocarcinoma of the prostate within 12 months before randomization. Additionally, one of the following features was required: T2 with Gleason 7 (4+3) and prostate-specific antigen (PSA) level between 10-70 ng/ml, T2 with Gleason 8-10 and PSA under 70 ng/ml, or any T3 tumours. Thus, all of the SPCG-13 patients belonged to an intermediate- or high-risk group according to the National Comprehensive Cancer Network (NCCN) guidelines (8). Other key inclusion and exclusion criteria were described in detail in our previous publication (2). Every patient signed an informed consent form before they were enrolled in the study. Before signing, they had the possibility to ask questions and consider their participation. The trial was approved by the ethics committee of Tampere University Hospital. The trial identifier at the Clinical Trials website (https://clinicaltrials.gov) is NCT00653848.

The primary endpoint of the trial was BPFS. The secondary endpoints were PSA doubling time, safety (using CTCAE version 3.0, https://ctep.cancer.gov/), MFS, OS and QoL. QoL was measured by version 4 of the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire, which is a validated tool for the evaluation of QoL in men with prostate cancer (19, 20).

The FACT-P questionnaire includes 27 general cancer-specific questions divided into four subscales (physical well-being, social/family well-being, emotional well-being, and functional well-being) as well as 12 prostate cancer-specific items in this prostate cancer subscale to assess function during the previous 7 days. The FACT-P total score is a summary of general subscale scores and prostatic cancer-specific subscale scores, where each item is rated on a Likert-type scale of 0-4 (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much), for which higher scores indicate better HRQoL.

A total of 378 patients who met the inclusion and exclusion criteria were randomized after completion of RT to six courses of docetaxel (Arm A, N=188) or surveillance (Arm B, N=188). The randomization took place between May 2007 and August 2012. All patients received ADT (luteinizing hormone-releasing hormone (LHRH) analogue), for nine months starting three months before RT. Arm A additionally received six courses of docetaxel, 75 mg/m^2 every three weeks starting three months after completion of RT. RT was 3-D conformal RT or intensity-modulated RT. In addition, a boost of brachytherapy was allowed. Total tumour dose had to be ≥74 Gy.

In Arm A 177 patients were followed more than three months. 171 patients completed follow-up. Eight patients withdrew consent, 4 patients were lost to follow-up, 4 patients were excluded due to protocol violations, and one patient had no follow-ups. In Arm B (surveillance), all 188 patients were followed for more than three months. A total of 186 patients completed the follow-up, one was lost to follow-up, and one withdrew consent (2). This HRQoL analysis included 183 patients in Arm A and 180 patients in Arm B who completed the FACT-P questionnaire at baseline.

FACT-P QoL questionnaires were gathered at baseline, during and after docetaxel treatment and yearly in the follow-ups at 1 year, 2 years and 4 years after treatment) in both groups and analysed using an analysis of covariance (ANCOVA) model adjusted for baseline. The calculations were performed by a statistician using SAS version 9.4 statistical software. The clinically significant difference was defined as the minimum 6-point difference in the total FACT-P score and the minimum 2-point difference in the FACT-P subdomains, based on the evidence by Cella *et al.* (21).

Results

The baseline characteristics are shown in Table I. A total of 147 (78.2%) patients completed all six cycles of docetaxel in arm A. The mean age was 66.2 years (range=47-75) in arm A and 66.4 years (range=46-76) in arm B. The median follow-up was 59.4 months (range=1-111 months).

The total HRQoL scores at baseline did not differ between arms. In Arm A (docetaxel group, N=177), the mean total

Table II. *Total scores from FACT-P questionnaires.*

Time		N	Mean	SD	95-% CI	*p*-Value
Baseline	Arm A (docetaxel)	177	119.0	18.86	[116.2-121.7]	0.701 (NS)
	Arm B (surveillance)	180	118.2	18.14	[115.5-120.8]	
Six months	Arm A (docetaxel)	120	116.6	14.0	[114.1-119.1]	<0.0001
	Arm B (surveillance)	122	123.7	13.4	[121.3-126.1]	
1 year	Arm A (docetaxel)	91	123.0	13.88	[120.2-125.9]	0.344 (NS)
	Arm B (surveillance)	85	125.0	13.6	[122.1-127.9]	
2 years	Arm A (docetaxel)	99	124.4	14.14	[121.6-127.2]	0.097 (NS)
	Arm B (surveillance)	104	127.7	13.6	[125.0-130.4]	
4 years	Arm A (docetaxel)	91	125.0	13.89	[122.1-127.8]	0.764 (NS)
	Arm B (surveillance)	103	125.6	14.1	[122.8-128.3]	

SD: Standard deviation, CI: confidence interval, NS: not significant.

score from the FACT-P questionnaire was 119.0 with a 95% confidence interval (CI)=116.2-121.7, while it was 118.2 (95% CI=115.5-120.8) in Arm B (surveillance, N=180).

At the end of treatment (24 weeks or earlier if docetaxel had to be halted prematurely), the mean HRQoL score significantly declined in Arm A to 116.6 (as estimated with the ANCOVA model, adjusting for baseline values), while it was 123.7 in Arm B ($p<0.0001$, ANCOVA model for difference between groups). This difference (–7.1 points) was also clinically significant.

However, at one year, the total HRQoL scores did not differ between arms (123.0 *vs.* 125.0, respectively), as estimated with the ANCOVA model, ($p=0.344$) and remained at the same level in both arms during subsequent follow-ups (Figure 1). All *p*-values and 95%CI are listed in Table II.

A clinically significant decline in HRQoL scores during treatment with docetaxel in Arm A was seen in two domains: functional (difference –2.43 points, $p<0.0001$) and physical (–2.89 points, $p<0.0001$). A statistically significant difference was also found in the prostate-specific subdomain (–1.78, $p=0.015$), but this did not reach the threshold of clinical significance. Graphs for all subcategories are shown in Figure 2.

Discussion

Our results show that docetaxel treatment decreases HRQoL during chemotherapy, but the effect is temporary, and no difference in HRQoL can be seen after one year. Furthermore, the decline in HRQoL is limited to the physical and functional domains in FACT-P, and differences in other domains (social, emotional, or prostate-specific categories) were not observed even during the treatment.

Our results are in line with those reported in the STAMPEDE and GETUG-12 trials (9, 18). In the STAMPEDE trial, which included only high-risk patients with rising PSA, QoL similarly decreased in the docetaxel group (with ADT) during treatment compared to the surveillance group (only ADT), but had recovered by the first follow-up in 9 months, and this persisted in the second follow-up in 1 year (9). In the GETUG-12 trial, docetaxel was given for high-risk local PC in combination with estramustine and ADT or ADT only (4). GETUG-12 did not use the FACT-P questionnaire, but EORTC QLQC-30 (4). QoL was worse at 3 months, but no difference was seen at 1 year (4). Statistically significant differences were seen at 3 months in global health status, fatigue, role functioning and social functioning (4). Because the questionnaire was different in the GETUG-12, the results of our study are not directly comparable, but our study showed no decline in the social subscale. Both studies used similar treatment plans (6 cycles, 3-week cycle), but the dosage of docetaxel was slightly lower (70 mg/m^2) than in our study (4, 9).

Our study had several strengths. This was a randomized, prospective clinical trial conducted in two very similar Nordic countries with relatively low margins for bias. Our follow-up time (up to almost 5 years) was longer than in the STAMPEDE and GETUG-12 trials, where QoL results were reported for only one year. Thus, our results demonstrated that HRQoL is not affected due to the possible long-term toxicity of adjuvant docetaxel after the curative intent EBRT for at least four years. This was a multicentre study with 11 hospitals from Sweden and Finland, which means that sample bias was also low. To the best of our knowledge, this is the largest report of QoL results for docetaxel treatment for early local PC after radical RT.

Some limitations can be identified as well. Double blinding might have been used in this setting. However, the use of intravenous placebo is considered ethically questionable in academic oncological studies because of the risk of toxicity, infusion-related decline in QoL and because otherwise well-performed trials are considered statistically adequate (22). Placebo was not used either in comparable NRG Oncology RTOG 0521, STAMPEDE or GETUG-12 trials (1, 4, 9). According to the declaration of Helsinki of World Medical Association (WMA), the use of placebo cannot subject patient to a risk of serious or irreversible harm (23).

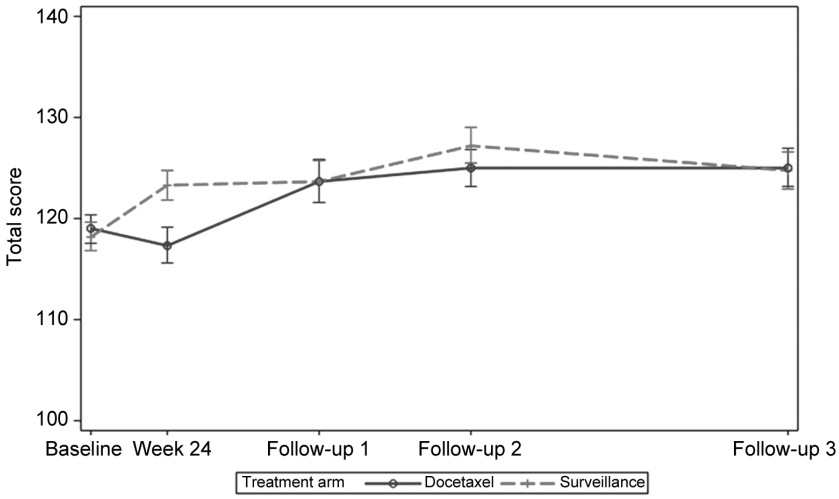

Figure 1. *Quality of life total scores in the SPCG-13 trial. The FACT-P forms were collected at 6 months (the end of scheduled treatment) and follow-ups at 1, 2 and 4 years. There was a significant difference favouring surveillance at week 24, but no difference in subsequent follow-ups.*

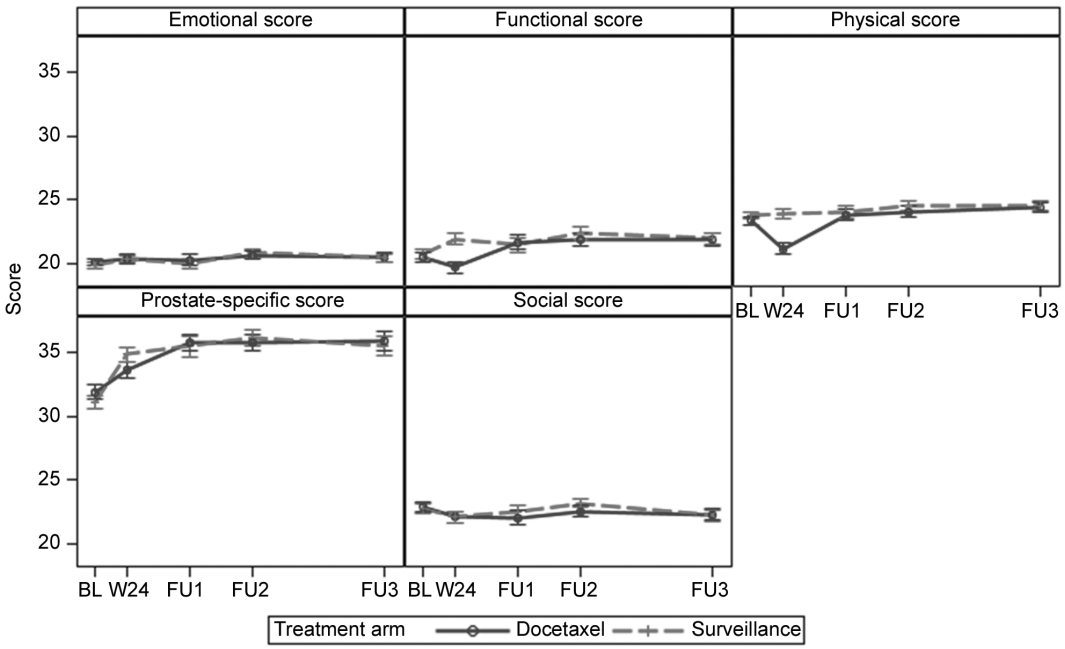

Figure 2. *Quality of Life Sub-Scores in the SPCG-13 trial. The FACT-P forms were at 6 months (the end of scheduled treatment) and follow-ups at 1, 2 and 4 years. The decline in HRQoL in docetaxel group at week 24 was seen only in functional and physical well-being. BL: Baseline; W24: week 24; FU: follow-up.*

The statistical method used was an ANCOVA-model, which can be considered inferior compared to the mixed model approaches if there are a significant number of missing data points (24). The decision for the ANCOVA-model was made by the statistician of the team based on the features of the data. Our results do not differ from the STAMPEDE trial, which used a mixed model (9). ANCOVA yields similar results to the mixed model, when missingness is 40-50% and has higher power with low missingness (20-40%) (25). Missingness exceeded 50% only in one time-point (1-year control in Arm B), and the 2-point difference in total FACT-P score mean is clearly unsignificant regardless of the model. On the other hand, missingness was under 30% at six months, which means that ANCOVA was superior to the mixed model at this timepoint. We lost more patients during follow-up in the treatment arm compared to the surveillance arm due to consent withdrawals, protocol violations or unattendance. It is plausible that the difference is related to the QoL factors and should be considered in the interpretation of the results.

In conclusion, adjuvant docetaxel after EBRT causes a transient decline in HRQoL during chemotherapy, with a progressive recovery to the HRQoL level of the control arm at one year. As the results from clinical trials have been conflicting, more research is needed to determine whether docetaxel is beneficial or not in men with high-risk local PC.

Conflicts of Interest

Marie Hjälm-Eriksson is a member of the advisory board of Bayer. Camilla Thellenberg-Karlsson: Speaker's fee: Janssen.

Author's Contributions

M.L. and J.S.: Writing of the article and the interpretation of statistical data, with ML being the primary writer and JS providing commentary. M. H-E., C. T-K.: acquisition of data, revision, study design. T.H.: statistical analysis, study design, writing (methodology). C.G.: study design, acquisition of data. P-L. K-L.: design, data interpretation, revision, study design, data acquisition, supervision. All Authors accepted the final manuscript.

Acknowledgements

We would like to thank all the investigators, study coordinators and nurses within the SPCG-13 participating centres: Karolinska University Hospital, Uppsala University Hospital, Örebro University Hospital, Karlstad, Sundsvall, Eskilstuna, Växjö and Jönköping Hospitals in Sweden and Tampere University Hospital, Hospitals in Lahti and Seinäjoki in Finland. We would also like to thank all patients who participated in the SPCG-13 trial, their families and Sanofi for their financial contribution to the SPCG-13 trial. The SPCG-13 investigator-sponsored trial received funding from Sanofi. This study was also partly supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital. The funders had no impact on the study design, collection of data, data analysis, interpretation of results or contents of the article.

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Received October 20, 2021
Revised November 15, 2021
Accepted November 22, 2021

PUBLICATION IV

2-weekly versus 3-weekly docetaxel for metastatic castration-resistant prostate cancer: complete quality of life results from the randomised, phase-III PROSTY trial

Miikka Lehtonen, Jorma Sormunen, Tiina Luukkaala, Timo Marttila, Ray McDermott, Timo Joensuu, Ilari Lehtinen, Claes Ginman, and Pirkko-Liisa Kellokumpu-Lehtinen

Acta Oncologica, 2022 Aug;61(8):963-971
https://www.tandfonline.com/doi/10.1080/0284186X.2022.2098680
DOI: 10.1080/0284186X.2022.2098680

Acta Oncologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

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To cite this article: Miikka Lehtonen, Jorma Sormunen, Tiina Luukkaala, Timo Marttila, Ray McDermott, Timo Joensuu, Ilari Lehtinen, Claes Ginman & Pirkko-Liisa Kellokumpu-Lehtinen (2022) 2-weekly versus 3-weekly docetaxel for metastatic castration-resistant prostate cancer: complete quality of life results from the randomised, phase-III PROSTY trial, Acta Oncologica, 61:8, 963-971, DOI: 10.1080/0284186X.2022.2098680

To link to this article: https://doi.org/10.1080/0284186X.2022.2098680

ACTA ONCOLOGICA
2022, VOL. 61, NO. 8, 963–971
https://doi.org/10.1080/0284186X.2022.2098680

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ORIGINAL ARTICLE

2-weekly versus 3-weekly docetaxel for metastatic castration-resistant prostate cancer: complete quality of life results from the randomised, phase-III PROSTY trial

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ABSTRACT

Introduction: Treatment with 2-weekly docetaxel 50 mg/m^2 was shown to improve overall survival and was better tolerated than the standard 75 mg/m^2 3-weekly regimen in men with metastatic castration-resistant prostate cancer (mCRPC) in the original randomised PROSTY trial. The aim of this study was to investigate, whether quality of life (QoL) effects would differ between the 2-weekly docetaxel 50 mg/m^2 regimen from the standard 3-weekly 75 mg/m^2 treatment.

Materials and Methods: QoL data were collected with the Functional Assessment of Cancer Therapy – Prostate (FACT-P) and Functional Assessment of Cancer Therapy Advanced Prostate Symptom Index – 8 Item version (FAPSI-8). Pain was measured using the Visual Analogue Scale (VAS). A total of 743 forms from 163 patients were analysed in Arm A (2-weekly docetaxel), and 704 forms from 173 patients were analysed in Arm B (3-weekly docetaxel). The data were analysed using both the Wilcoxon signed rank test (with Holm–Bonferroni adjustment) and Mann–Whitney U models.

Results: No major differences were found in total QoL. Total QoL was higher at month 8 in Arm B ($p = .020$), but this was reversed in the following month ($p = .043$), and no statistically significant differences were found during other months. Compared to Arm A, participants in Arm B had longer-lasting deterioration in FAPSI-8 scores and emotional well-being subdomain at the beginning of treatment ($p < .05$). Various one-month differences were found in FACT-P subdomains (except for functional well-being), and these favoured participants in Arm A, except for the prostate-cancer subdomain. There were no differences in pain.

Conclusion: Based on our results, 2-weekly docetaxel was not inferior to 3-weekly docetaxel in terms of total health-related QoL and seemed to be superior at least in terms of the FAPSI-8 and emotional well-being subdomain in the first three to four months of treatment. More research on the topic is suggested to confirm the results.

ARTICLE HISTORY
Received 16 April 2022
Accepted 1 July 2022

KEYWORDS
Prostate cancer; metastatic prostate cancer; metastatic castration-resistant prostate cancer; docetaxel; quality of life

Introduction

Although novel therapeutics have emerged, docetaxel remains a mainstay in the treatment of metastatic castration-resistant prostate cancer (mCRPC) [1–5]. The expected treatment response and tolerance are moderate with the standard 75 mg/m^2 3-weekly regimen. As drug-related toxicity does exist, it is still important to search for new alternatives for these patients [6,7].

The PROSTY trial was a phase III, prospective randomised multinational trial that compared 2-weekly administration of docetaxel 50 mg/m^2 to the standard 75 mg/m^2 3-weekly regimen [7]. The 2-weekly regimen had a favourable Grade 3–4 toxicity profile on Common Toxicity Criteria (CTC) of National Cancer Institute (NCI) version 2.0 and led to 2.5 months gain in median overall survival (OS, $p = .021$) when compared to the standard 3-weekly regimen [7,8]. This led to an acknowledgement in the National Comprehensive Cancer Network® (NCCN) guideline on prostate cancer as an alternative dosing for mCRPC, as well as in the European Association of Urology (EAU). Moreover, International Society of Geriatric Oncology (SIOG) guidelines on prostate cancer recommended 2-weekly regimen particularly for elderly patients [3,4,9]. However, the 2-week regimen is not mentioned in the American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (AUA/ASTRO/SUO), European Association of Urology (EAU) or European Society of Medical

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Supplemental data for this article is available online at https://doi.org/10.1080/0284186X.2022.2098680.

Oncology (ESMO) guidelines [5,10]. Furthermore, only 10% of experts preferred 2-weekly regimen over 3-weekly or weekly dosing in Advanced Prostate Cancer Consensus Conference (APCCC) 2017 [11]. Perhaps this is because the health-related quality of life (HRQoL) results have not been previously published. The aim of this study was to investigate, whether 2-weekly docetaxel 50 mg/m^2 would differ from the standard 75 mg/m^2 3-weekly regimen in terms of HRQoL, and thus find out if HRQoL effects would support the use of 2-weekly docetaxel or not. The quality of life (QoL) was classified as a secondary endpoint of PROSTY trial. The null hypothesis was that QoL would not differ (clinically) significantly between the treatment groups.

Material and methods

The PROSTY trial was a multicentre investigator-initiated study that took place in 11 hospitals in Finland, Ireland and Sweden. All participants signed a written, informed consent form. The trial was registered to the clinicaltrials.gov database (number NCT00255606) before the enrolment period. The study was approved by ethics committees in each participating country. Patient accrual and data collection were conducted between 2004 and 2009. The rate of treatment failures was 100% at the end of the study. Treatment failure was defined as disease progression, intolerable toxicity, patient refusal to continue treatment or death. Time to treatment failure was the primary endpoint in the study. The power calculations were based on the primary endpoint purposes [7]. Consolidated Standards of Reporting Trials (CONSORT) guidelines were used in the reporting of this trial [12].

The main inclusion criteria for the study were adult men with World Health Organisation (WHO) performance scores of 0–2, the presence of distant metastases of prostate cancer (M1) on (conventional) imaging and biochemically confirmed castration-resistant status by plasma testosterone levels under 1.7 nmol/l and elevating prostate-specific antigen (PSA) during castration treatment. No previous chemotherapy except estramustine was allowed. Exclusion criteria are described in detail in the primary publication [7]. Individuals with a previous history of other malignancies, significantly increased serum creatinine or major blood count or liver enzyme abnormalities were not allowed.

QoL instrument used in this study was the Finnish, English or Swedish version of the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire [13,14]. This is a validated tool for evaluating QoL in patients with prostate cancer, and it contains 39 questions that are divided into physical, social/family, emotional and functional well-being subdomains and the prostate cancer specific subdomain [13]. Additionally, FACT Advanced Prostate Symptom Index-8 (FAPSI-8) data were analysed [15,16]. The FAPSI-8 contains eight key questions derived from the FACT-P questionnaire and is specifically designed for men with advanced prostate cancer, which was the reason it was used along with the complete FACT-P questionnaire [15]. Higher scores indicate better QoL in the FACT-P and its subdomains. Both FACT-P and FAPSI-8 are validated to evaluate QoL during the treatment [13,15,17]. Pain was assessed with the Visual Analogue Scale (VAS) [18]. Possible VAS values range from 0 to 100 mm, where 0 mm equals for no pain and 100 mm the worst imaginable pain.

According to the power calculations, which were conducted for the primary end-point purposes, 361 patients were randomised to either 2-weekly docetaxel 50 mg/m^2 (Arm A, $N = 177$) or docetaxel 75 mg/m^2 every three weeks (Arm B, $N = 184$). The number of the treatment cycles was not limited, but the treatment was continued until complete response, treatment failure or the end of study (the treatment failure rate was 100% at the end of the study). After randomisation, 15 noneligible patients according to the inclusion and exclusion criteria were additionally identified, meaning that the cohorts consisted of 170 patients in Arm A and 176 patients in Arm B. However, only 163 men in Arm A and 173 men in Arm B returned FACT-P questionnaires, meaning that seven patients in Arm A and three patients in Arm B were lost to HRQoL follow-up.

According to the protocol, FACT-P forms were collected every six weeks (before docetaxel infusion), at the end of treatment and every two months after treatment failure until subsequent therapy was initiated. The collected data were analysed for every month, up to a year, to increase accuracy in relation to time. The early responders were considered to be similar to the late responders except for the probability of progression and treatment burden. These both correlate with time and are likely less biased due to this procedure. The patients responded to the questionnaires in paper format at home. The patients visited doctor every six weeks during the treatment, within a month after the treatment failure and every 12 weeks during the follow-up (after the treatment failure) in both arms. A nurse checked the patient before infusion, made sure that the patient had received the possible premedication (e.g., antiemetic agents), administered docetaxel and followed the patient during the intravenous administration for possible side-effects.

Statistical analysis

The method for handling the missing data in the study was a pattern mixture model with a patient subdomain mean substitution. Patients with $\geq$50% nonresponse in any subdomain were excluded ($N = 45$), as suggested by Fairclough et al. [19]. Nonresponse in the final model was 2.1%, which is acceptable [19]. Only one form for each patient for a single time period was allowed. If the patient returned more than one form for a single month, the form included in the analysis was chosen by lot ($N = 28$). The majority of forms returned in this manner were of the same content, meaning that a patient had filled two identical copies, one for the last treatment and one for the required end of treatment evaluation. The end of treatment FACT-P questionnaires and follow-up visits after treatment failure were not analysed separately for this study design, but along with patients still in active treatment of the corresponding month.

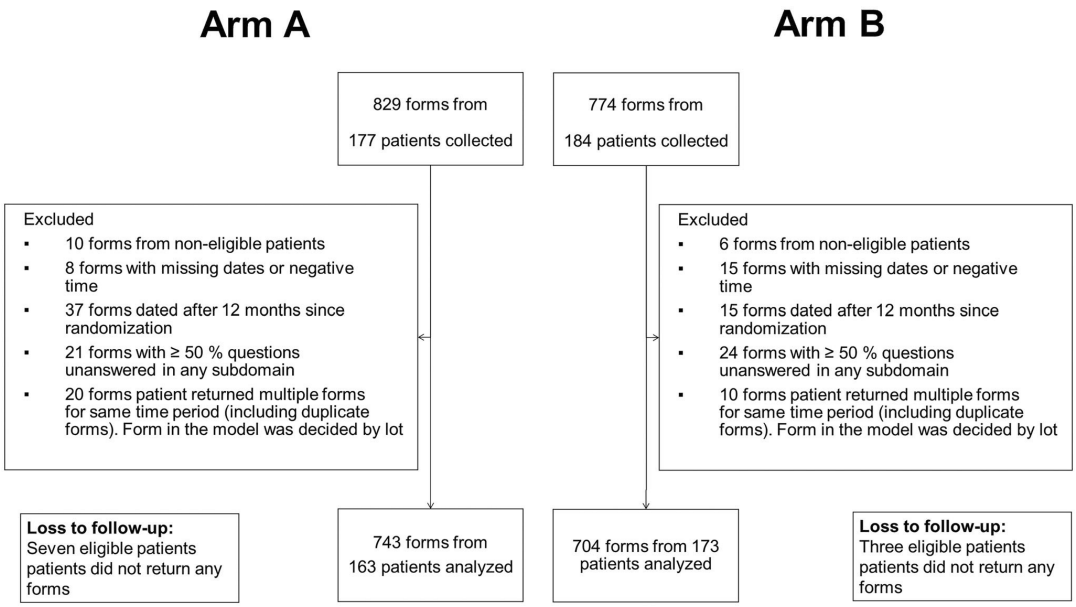

Figure 1. Flowchart depicting included and excluded FACT-P questionnaires. Additional two forms were excluded from the in-group model only due to a missing baseline questionnaire. Arm A: docetaxel 50 mg/m^2 every two weeks; Arm B: docetaxel 75 mg/m^2 every three weeks.

Table 1. Forms by type of the visit for each Arm.

Arm A								Arm B							
	Ongoing treatment		EoT evaluation		Control after TF		Total		Ongoing treatment		EoT evaluation		Control after TF		
Month	*N*	%	*N*	%	*N*	%	*N*	Month	*N*	%	*N*	%	*N*	%	Total
1	50	98.0	1	2.0	0	0.0	51	1	51	94.4	3	5.6	0	0.0	54
2	82	95.3	3	3.5	1	1.2	86	2	80	90.9	8	9.1	0	0.0	88
3	105	88.2	14	11.8	0	0.0	119	3	102	86.4	15	12.7	1	0.8	118
4	62	89.9	6	8.7	1	1.4	69	4	63	78.8	15	18.8	2	2.5	80
5	35	68.6	14	27.5	2	3.9	51	5	17	47.2	16	44.4	3	8.3	36
6	46	69.7	15	22.7	5	10.6	66	6	43	63.2	18	26.5	7	10.3	68
7	33	70.2	10	21.3	4	8.5	47	7	24	55.8	9	20.9	10	23.3	43
8	18	58.1	7	22.6	6	19.4	31	8	9	34.6	11	42.3	6	23.1	26
9	18	60.0	5	16.7	7	23.3	30	9	7	36.8	5	26.3	7	36.8	19
10	17	53.1	6	18.8	9	28.1	32	10	8	66.6	0	0.0	4	33.3	12
11	8	47.1	4	23.5	5	29.4	17	11	3	37.5	3	37.5	2	25.0	8
12	7	70.0	1	10.0	2	20.0	10	12	5	45.5	2	18.2	4	36.4	11

Two patients in Arm A that had not filled the baseline forms were excluded from the Wilcoxon signed rank model but not from the Mann–Whitney U-tests. Only one form for each patient for time patient was allowed. If the patient returned more than one forms for a single month, the form included in the analysis was chosen by lot ($N = 28$), which are not separated for this qualitative table, but were excluded from the statistical analysis. Arm A: docetaxel 50 mg/m^2 every two weeks; Arm B: docetaxel 75 mg/m^2 every three weeks; EoT: End of Treatment; *N*: sample size; TF: Treatment Failure.

All the exclusions are depicted graphically in Figure 1. Qualitative analysis of the returned questionnaires by the type of visit is available in Table 1. Overall, 743 forms in Arm A and 704 forms in Arm B were analysed. The distributions were highly skewed, meaning that parametric models could not be used. The data were analysed using both the paired Wilcoxon signed rank test (comparisons within groups towards the baseline value) and the independent Mann–Whitney U-test (direct comparisons between groups). The multiplicity adjustment was made for in-group comparisons towards the baseline since a repeated measure was used for comparison 12 times [20]. The multiplicity adjustment was made using the Holm–Bonferroni method [21]. For VAS, which also had skewed distributions, only Mann–Whitney U-tests were performed.

Although QoL was classified as a secondary endpoint in PROSTY trial per protocol, the minimally clinically important differences (MCIDs) were not defined in protocol but decided prior the statistical analysis according to the current scientific knowledge on HRQoL analysis of FACT-P published after the initiation of PROSTY trial [22–24]. MCIDs were defined as 6 points in mean for the total FACT-P score, 2 points for the FAPSI-8 and each subdomain, with exceptions of the social/family well-being (SWB) score and emotional well-being (EWB) score, for which 1-point limits were used. MCIDs for FACT-P total score, prostate cancer subscale (PCS) and FAPSI-8 were based on the study by Cella *et al.* with patients with metastatic castration-resistant prostate cancer [22]. MCIDs for the remaining subdomains were based on the meta-analysis by King *et al.*, which consisted of patients from 71 trials with

different kinds of cancer surveyed with Functional Assessment of Cancer Therapy – General (FACT-G), which is identical to FACT-P except it omits the PCS subdomain [23,24]. Studies determining MCID for other FACT-P subdomains than PCS consisting of mCRPC patients do not exist to our knowledge. VAS was defined as a 23 mm difference in medians, based on Olsen *et al.* [25]. The statistical analysis was conducted using IBM® SPSS® version 26 and R-software version 4.1.1. The *post hoc* power analysis was conducted using G*Power software version 3.1.9.7.

Power analysis

Power calculations were originally made for primary endpoint purposes. Power analysis was performed *post hoc* to interpret the results reliably within this trial, and its results are available in the supplementary material (Supplementary Material Table S1). The number of returned forms diminished steadily towards the end of follow-up, reflecting mortality and the rate of treatment failures, and was more prominent in Arm B.

Considering comparisons within groups compared to the baseline, the power remained acceptable (with one exception at 5 months at Arm B) until 7 months, which means that direct comparisons towards the baseline considering differences between arms are recommended only until 7 months, and tabulated results for in-group comparisons towards the baseline are reported only until 7 months in the main article to avoid misinterpretation. The tabulated results for the remaining timepoints are available in the supplementary material and are described for the significant part.

The power does not affect similarly to the comparability of head-to-head model, which means all the statistically significant differences are to be interpreted in terms of superiority or inferiority regardless of power. However, the observed power was over 80% only at baseline and months 2, 3 and 4, warranting caution when drawing conclusions outside these perimeters due to the potential type-II error. We recommend using in-group data for interpretation until the seven-month timepoint, after which we recommend using head-to-head comparisons as complementary data.

Results

There were no statistically significant differences at baseline in total FACT-P scores, FAPSI-8 scores, VAS scores or any FACT-P subdomains. The median age of the participating patients was 68 years in Arm A (range 46–85 years) and 69 years in Arm B (range 45–87 years). In Arm A, 62% of the patients and in Arm B, 60% belonged to WHO performance status category 1 ('restricted in strenuous activity'), while 32% and 34% (respectively) belonged to performance status category 0 ('normal performance'). The remainders (6% in both arms) belonged to category 2 ('unable to work, up and about over a half of the day'). The total FACT-P score means at baseline were 46.8 in Arm A and 46.6 in Arm B (medians 43.0 and 44.0, respectively, $p > .99$), while the FAPSI-8 score means were 9.5 and 10.0 ($p = .64$). A total of 147 men in Arm A and 149 men in Arm B completed the baseline questionnaire.

The baseline characteristics were similar in both Arms. The median serum PSA was 116 nanograms per microlitre (ng/ml) in arm A and 109 ng/ml in arm B, and the difference was statistically nonsignificant. Twelve percent in Arm A and 13% in Arm B had previous prostatectomy, 58% versus (vs.) 53% had received radical-intent radiotherapy, 91% vs. 93% had been treated with hormonal therapy and 7% vs. 11% had been treated with estramustine.

The first seven months

There were no clinically significant changes in total HRQoL during the first seven months of follow-up in either model (Table 2). In Arm B, there was a decline compared to the

Table 2. Total FACT-P scores compared to the baseline values for months 1 – 7 and directly between groups for months 8 – 12.

	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Mth.	N	Diff. (mean)	Diff. (median)	*P* (exact)	*P* (adj.)	N	Diff. (mean)	Diff. (median)	*P* (exact)	*P* (adj.)
1	51	−6.2	−5.3	.010	.120	54	−4.8	−4.9	<.001	<.012*
2	83	−3.0	+3.0	.072	.792	85	−6.1	−3.6	.033	.330
3	111	−1.6	+1.0	.284	>.999	117	−4.6	−3.0	.008	.088
4	69	−3.5	−0.3	.505	>.999	80	+0.9	+5.3	.823	>.999
5	51	−4.5	−6.0	.637	>.999	33	−0.1	+1.3	.995	>.999
6	65	−2.3	+0.0	.178	>.999	68	−1.7	−1.3	.479	>.999
7	46	−5.8	−5.5	.972	>.999	43	+2.3	+3.9	.718	>.999

Total FACT-P scores: head-to-head comparisons

	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Mth.	*N*	Mean	Median	IQR	*N*	Mean	Median	IQR	*p Value*
8	30	39.9	41.5	[23.8 – 52.3]	26	51.5	51.0	[36.5 – 66.1]	.020*,†
9	29	44.2	38.7	[29.0 – 61.1]	19	31.4	29.9	[25.0 – 43.0]	.043*,†
10	32	44.2	45.8	[25.1 – 61.0]	12	43.7	45.5	[26.2 – 61.5]	.985
11	17	46.3	46.0	[32.0 – 59.2]	8	38.5	37.8	[25.0 – 55.6]	.344
12	10	45.4	45.0	[29.2 – 62.7]	10	31.9	30.0	[13.8 – 45.3]	.184

Both models were performed for all the timepoints, and complete results are available in the supplementary material. Statistically significant *P*-values (<.05) are marked with an asterisk (*). Both statistically and clinically significant differences are marked with a dagger symbol (†). Minimally clinically significant difference is ≥ 6 points of difference in means. Adj.: adjusted for multiplicity with Holm-Bonferroni method; diff.: difference; IQR: interquartile range; mth.: month; *N*: sample size; *P*: *P* value. Total FACT-P scores compared to the baseline.

Table 3. FAPSI-8 compared to the baseline values for months 1 – 7 and directly between groups for months 8 – 12.

FAPSI-8 scores compared to the baseline.

	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Mth.	*N*	Diff. (mean)	Diff. (median)	*P* (exact)	*P* (adj.)	*N*	Diff. (mean)	Diff. (median)	*P* (exact)	*P* (adj.)
1	51	−2.7	−3.0	<.001	<.012*,†	54	−2.6	−2.0	<.001	<.012*,†
2	83	−1.9	−2.0	<.001	<.012*	85	−2.9	−3.0	.001	.012*,†
3	111	−1.9	−2.0	<.001	<.012*	117	−2.9	−2.1	<.001	<.012*,†
4	69	−2.5	−3.0	.049	.392	80	−1.6	−1.0	.006	.054
5	51	−3.9	−4.0	.024	.216	33	−1.9	−2.0	.099	.594
6	65	−1.8	−2.0	.839	>.999	68	−2.5	−3.0	.040	.320
7	46	−3.1	−3.0	.176	>.999	43	−1.6	−2.0	.083	.581

FAPSI-8: head-to-head comparisons

	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Mth.	*N*	Mean	Median	IQR	*N*	Mean	Median	IQR	*p* Value
8	30	6.3	5.5	[2.0 – 10.3]	26	8.7	8.0	[5.0 – 12.3]	.053
9	29	7.7	7.0	[3.0 – 13.5]	19	5.6	5.0	[2.0 – 8.0]	.190
10	32	7.4	6.5	[3.0 – 11.8]	12	7.0	6.5	[4.0 – 10.3]	.974
11	17	7.1	6.0	[3.0 – 11.7]	8	6.3	6.0	[2.3 – 10.3]	.763
12	10	8.2	8.0	[3.8 – 11.0]	10	5.7	5.0	[0.0 – 9.5]	.286

Both models were performed for all the timepoints, and complete results are available in the supplementary material. Statistically significant *p*-values (< .05) are marked with an asterisk (*). Both statistically and clinically significant differences are marked with a dagger symbol (†). Minimally clinically significant difference is ≥ 2 points of difference in means. Adj.: adjusted for multiplicity with Holm-Bonferroni method; diff.: difference; IQR: interquartile range; mth.: month; *N*: sample size; *P*: *p* Value.

baseline HRQoL not exceeding the clinically significant threshold in the first month (difference in means −4.8, $p < .012$, adjusted for multiplicity [adj.]). In the FAPSI-8, however, differences compared to the baseline were observed (Table 3). In Arm B, QoL measured in the FAPSI-8 remained both clinically and statistically decreased for the first three months (mean differences −2.6, −2.9, −2.9; adj. *P*-values <.012, .012, <.012). In Arm A, however, FAPSI-8 scores decreased both clinically and statistically significantly only for the first month (−2.7; adj. $p < .012$). In the following two months, the FAPSI-8 score decreased statistically but not clinically significantly (−1.9 and −1.9; adjusted *P*-values <.012 and <.012). At the remaining time points, statistically significant differences were not found (adj. *P*-values >.05). The results for direct comparisons between groups for total FACT-P and FAPSI-8 are available in Supplementary Material Table S2 (there were no significant differences). Graphical boxplot presentations of median, interquartile range (IQR) and range values between arms are shown for total FACT-P score in Supplementary Material Figure S1 and for FAPSI-8 in Supplementary Material Figure S2 for the entire analysis period.

In the emotional well-being subdomain, Arm B suffered a longer-lasting decrease in EWB, which lasted for the first four months (-1.5, −1.3, −1.6 and −1.2; adj. *P*-values < .012, .020, < .012 and .020). In Arm A, the decrease in EWB was clinically significant only for months 2 and 5 (−1.1 and −1.6; adj. *P*-values .012 and .027). Additionally, there was one non-clinically significant decrease in month 3 (−0.9, adj. $p < .012$). The complete tabulated results are available in Supplementary Material Table S3. In head-to-head comparisons, there was only one not clinically significant but statistically significant difference favouring Arm A in the third month (6.3 points vs. 5.5 points; $p = .031$; Supplementary Material Table S4) during the first seven months.

In physical well-being (PWB) scores, there was one solitary clinically significant improvement in Arm B in month 4 (+2.1, adj. $p = .022$) compared to the baseline (Supplementary Material Table S5). In addition, there was one non-clinically significant improvement in month 6 (+1.5, adj. $p = .012$). Participants in Arm A had a consistent trend of statistically significant, but clinically unimportant improvements between months 4 – 7 (+0.8, +1.0, +1.97 and +0.9; adj. *P*-values < .012, .040, < .012 and < .012). There were no statistically significant differences in direct comparison between the groups in PWB during the first seven months (Supplementary Material Table S6).

In the PCS score, participants in both groups suffered similar deterioration compared to the baseline in month 1 (Arm A: −2.8 and Arm B: −3.5, adj. $p < .012$ for both) and 3 (Arm A: −2.8 and Arm B: −3.2, adj. $p < .012$ for both). Additionally, there was one clinically insignificant deterioration in Arm A in month 2 (-1.8, adj. $p = .040$). The complete results are shown in Supplementary Material Table S7. There were also no statistically significant differences in PCS in direct comparison between groups during the first seven months (Supplementary Material Table S8).

In functional well-being (FWB) scores, there was one solitary, clinically nonsignificant improvement in the fourth month in Arm B (+1.0, adj. $p < .012$, Supplementary Material Table S9) and no differences in the head-to-head model (Supplementary Material Table S10). In social/family well-being, there were no statistically significant differences in either model during the first seven months (Supplementary Material Tables S11 and S12) or in VAS (Supplementary Material Table S13). Graphical boxplot presentations depicting medians, interquartile ranges and total ranges for the entire analysis period are available in Supplementary Material Figures S3 – S7 (for PCS, PWB, EWB, FWB and SWB, respectively).

Months 8 – 12

In the head-to-head model, total FACT-P scores favoured Arm B in month 8 (means Arm A: 39.9 vs. Arm B: 51.5 points,

$p = .020$). However, in the following month, the results were reversed (Arm A: 44.2 vs. Arm B: 31.4, $p = .043$). At eight months, differences were seen in EWB (Arm A: 4.7 vs. Arm B: 6.0, $p = .022$) and PCS (Arm A: 13.7 vs. Arm B: 16.5, $p = .022$). The FAPSI-8 behaved in a borderline significant manner (Arm A: 6.3 vs. Arm B: 8.7, $p = .053$). In the ninth month, Arm A was superior in PWB (Arm A: 7.1 vs. Arm B: 4.7, $p = .034$) and SWB (Arm A: 6.6 vs. 4.0, $p = .029$), meaning the differences were attributed to different subdomains of FACT-P. In the last three months, the rate of participation was quite low due to the progression of the disease (remaining greater in Arm A, reflecting the difference in OS), but there was one additional clinically significant difference in PWB in the final month ($N = 20$) of the analysis period (Arm A: 8.1 vs. Arm B: 4.1, $p = .048$). The VAS scores remained similar (grand means 1.9 for Arm A and 1.7 for Arm B) in both groups for months $8-12$ ($p > .05$). As discussed previously, the in-group comparisons are not comparable after the seventh month due to the decreasing number of patients in both groups. However, no statistically significant deteriorations compared to the baseline were observed with these sample sizes in months $8-12$. A clinically nonsignificant improvement trend in PWB persisted in Arm A from 8 months until 10 months (difference in means: $+0.4$, $+1.1$, $+1.2$; adj. P-values $< .012, .040, .042$). The remaining total FACT-P scores and FAPSI-8 scores compared to the baseline scores are shown in Supplementary Material Table S14. No statistically significant differences were present in total FACT-P or FAPSI-8 even in unadjusted (exact) P values. A summary of the complete results for the entire analysis period is shown in Table 4.

Discussion

Since it was already known that patients who received docetaxel 50 mg/m^2 with 2-weekly dosing gained a 2-month-benefit in OS compared to those receiving the standard regimen, the most important matter to investigate was if these patients would have inferior QoL compared to those who received 75 mg/m^2 of docetaxel every three weeks [7]. Our results do not support this view regarding the total QoL and key elements of QoL measured by the FAPSI-8. Only for PCS, non-inferiority could not be shown, as Arm B outranked Arm A once in the eight months in head-to-head model, and declines compared to the baseline values were similar in both groups. However, similar one-month differences were also found to favour Arm A in EWB, SWB and PWB scores. In the FIRSTANA and PROSELICA trials, which studied cabazitaxel for mCRPC, a deterioration or improvement had to be present in two subsequent measurements to confirm the results [26]. Arguments for such a definition were not given, but as seen in this study, the QoL in patients with mCRPC can fluctuate somewhat, and such a definition may indeed be reasonable [26]. If the results confirmed in this manner had been considered significant, the declines in QoL would have only been observed in the FAPSI-8 and EWB in Arm B during the first months. This would support the claim that biweekly docetaxel is not inferior and, based on our results, seems to be superior to triweekly docetaxel, at least in the FAPSI-8 and EWB, during the beginning of treatment.

The biweekly docetaxel 50 mg/m^2 had reduced incidence of grade 3–4 neutropenia and febrile neutropenia compared to triweekly 75 mg/m^2 [7]. In QoliTax trial, which investigated the impact of adverse effects of docetaxel on QoL in cancer patients in general (of which 48.1% were PC patients), grade 3–4 leukopenia during docetaxel treatment did not affect significantly QoL [27]. However, grade 3–4 infections did have a negative impact on patients' total HRQoL, although not linked to emotional functioning [27]. On the other hand, grade 3–4 nausea was associated with a detrimental effect on patients' emotional functioning as well as total HRQoL [27]. In PROSTY trial, biweekly docetaxel had no reduced rate

Table 4. Summary of the clinically and statistically significant results from both models.

	In-group			Head-to-head	
	Months improved	Months deteriorated	Difference	Months superior to the other arm	'Grade'
Total FACT-P					
Arm A	0	0	0	1	1
Arm B	0	0	0	1	1
FAPSI-8					
Arm A	0	1	−1	0	−1
Arm B	0	3	−3	0	−3
PWB					
Arm A	0	0	0	2	2
Arm B	1	0	1	0	1
SWB					
Arm A	0	0	0	1	1
Arm B	0	0	0	0	0
EWB					
Arm A	0	2	−2	0	−2
Arm B	0	4	−4	1	−3
FWB					
Arm A	0	0	0	0	0
Arm B	0	0	0	0	0
PCS					
Arm A	0	2	−2	0	−2
Arm B	0	2	−2	1	−1

A grade for comparability was formed by calculating the difference of improved and deteriorated months compared to the baseline and the months the arm outranked the other (sum). PWB: physical well-being; SWB: social well-being; EWB: emotional well-being; FWB: functional well-being; PCS: prostate cancer subdomain in FACT-P.

of grade 3–4 nausea compared to the triweekly docetaxel, but there was smaller incidence of grade 1–2 nausea (34% vs. 48%). Whether milder nausea is also associated with worse emotional QoL, requires more study. There could also be other explanations to differences: more frequent visits to the hospital required by biweekly dosing could give a stronger sense of safety, which could be linked to the EWB.

The shifting behaviour of the total FACT-P in the eighth and ninth months was interesting. The total QoL remained rather stable in Arm A (means 39.9 and 44.2, *N*s 30 and 29), although 39.9 was the minimum QoL in Arm A during the analysis period. In Arm B, the QoL was at the maximum in the eighth month (51.5, $N = 26$) and then dropped to the minimum in the ninth month (31.4, $N = 19$). Small sample sizes are known to overestimate effect sizes (absolute differences); however, this does not erase significance [28]. The proportion of end of treatment (EoT) evaluations was high in the eighth month in Arm B (42.3%). However, no similar effect was found in the fifth month, when the proportion of EoT evaluations was even higher (44.4%). The reason for EoT was also collected, and we noticed that in the fifth month, most EoT decisions in Arm B were due to progression (68.7%), while in the eighth month, the majority (54.5%) were due to other reasons, that is, side effects or an individual decision by the patient. This could suggest that QoL could decrease more substantially in the subsequent follow-ups if the treatment failure is due to a patient refusal to continue or side effects compared to those with progression. More research on the topic is needed.

The statistical method (a pattern-mixture model with patient subdomain mean substitution) is the least biased method possible for FACT-P to our knowledge, meaning that the results are very accurate when the power is over 80% [19]. Mixed models are mostly used in similar studies. However, they produce biased results when the data are not missing at random (MNAR), for example, if the missingness is related to mortality [29,30]. We postulated that missingness was related to mortality in this setting and that patients near death would return fewer forms and have weaker quality of life, thus representing another MNAR mechanism. Another issue in mixed models is related to the handling of missing data, which still frequently go unreported in clinical trials [31]. If the exclusion is based on a relatively low nonresponse (over 20%, for example), this will lead to unnecessary loss of power and larger bias if the nonresponse is not due to random factors [32,33]. Fairclough *et al.* demonstrated that nonresponse is associated with higher age and living alone, so a mixed model approach would have been biased towards younger men and men living with a partner [19]. However, a linear mixed model produced similar results to the pattern mixture model in the AFFIRM trial comparing enzalutamide versus placebo in men with mCRPC [34]. The non-parametric approach may be difficult to fathom, and solutions based on the categorical classification into groups ('maintained QoL', 'deteriorated QoL', 'improved QoL'), which make the data more parametric, have been used [26]. However, such procedures reduce statistical power and have a higher rate of type-I and type-II errors [35,36].

Limitations of the study and design

Our study has several limitations as well. The most obvious concern is the declining power after 7 months, a phenomenon also depicted in other similar studies [26]. The power calculations were not made for QoL data for which it is expected that response rate is more around 50% than close to 100% [37]. The MCIDs were not defined until before the statistical analysis, not per protocol. This is understandable from the historical perspective, since the first consensus statements about the use of MCIDs were not published until year after the initiation of the trial in 2005, although there had been a consensus meeting in 2002, which only mainly concluded that more research on the topic was needed at the time [38,39]. Even if the MCIDs would have been defined per protocol, the contemporary definitions from 2000s based on the standard deviation would be outdated now. However, due to the aforementioned limitations, it could be argued that the design was not truly developed to substantiate QoL differences, and the present study can be considered exploratory in this regard. The evidence presented would therefore benefit from support from other trials designed to investigate exclusively QoL.

Towards the end of the analysis period the sample sizes are small due to the incurable nature of mCRPC. However, this is emphasised in the interpretation. If the analysis period were selected solely based on power, then months 8 and 9 would not have been analysed, and many significant findings would have been lost. Collecting QoL information of patients in their final months of life from trials is difficult but important for the general view [40]. Combining data for several studies may be the only solution to yield powerful results. However, QoL of patients after treatment failure was followed more seldom than patients in ongoing treatment, and in retrospect, if the follow-up schedule had been equal, slightly more power would have been preserved. Treatment cycles differed in duration between arms, which means that cumulative dose at the time of average response also differ slightly. The difference in cumulative dose was highest in month 7 (800 mg/m^2 in Arm A and 750 mg/m^2 in Arm B), with no apparent effect on QoL results.

Another limitation is the age of the study. The trial was conducted between 2004 and 2009, and the primary results were published in 2013 [7]. Over the past 10 years, the second- and third-line treatment of mCRPC has improved, and thus, the QoL of patients with mCRPC in clinical practice may be different compared to that 10 to 15 years ago [41–46]. However, because fewer patients received second-line treatment, fewer patients were lost to follow-up since this was an exclusion criterion, although some patients enrolled in subsequent trials. Imaging was based on conventional methods, and the results may not be extrapolated to patients who are negative for M1 disease on conventional imaging but positive on prostate-specific membrane antigen (PSMA) -labelled positron emission tomography or PSMA-labelled computer tomography [3]. Because of greatly changing landscape of PC treatment due to the developments in radioisotope imaging, we suggest the future trials on the topic to be based on PSMA-imaging. The results also apply

only to those patients who receive docetaxel in first-line chemotherapy for mCRPC or after estramustine.

This study also was not intended to compare the cost-effectiveness of biweekly docetaxel treatment to the triweekly treatment in relation to the benefit gained. Since biweekly regimen requires 1.5 times more frequent visits to the hospital, it also increases the costs. The patent of docetaxel has expired in Europe, and it is currently quite affordable, meaning that the increased costs would mainly be caused by personnel costs, which greatly vary between different countries [47]. The rate of febrile neutropenic infections was also higher with the standard triweekly docetaxel ($p = .001$) [7]. As these infections usually require ward care in the hospital, they are also costly.

Conclusions

Based on our results, two-weekly docetaxel 50 mg/m^2 is equal to the standard 75 mg/m^2 every three weeks in terms of total HRQoL and seems to be superior at least in terms of the FAPSI-8 and emotional well-being in the first three to four months. However, we suggest additional research with QoL-exclusive design to confirm the results.

Acknowledgments

To all patients and participating centres of PROSTY trial.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committees in all participating countries (Decision No. ETL R03165M).

Informed consent statement

Written informed consent has been obtained from the patients to publish this paper.

Disclosure statement

RMcD: honoraria from Bayer, Sanofi, Janssen, Astellas Pharma, Bristol-Myers Squibb, Merch Sharp & Dohme, Pfizer, Novartis and Clovis Oncology. Speaker's Bureau from MSD Oncology. Travel expenses from Pfizer, Janssen-Cilag, Roche and Ipsen. JT: founder and part owner of Docrates Hospital in Helsinki. P.K.: honoraria from BMS, Merck and travel expenses from Sanofi.

Funding

This study was supported by Sanofi and the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital and Cancer Society of Finland. The funders of the study had no impact on study design, data collection, data analysis, data interpretation or writing of the report. The representatives of Sanofi were regularly informed on how the study was proceeding and participated in the investigators' meetings. The last author had full access to the data in the study and had final responsibility for the decision to it to submit for publication.

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Data availability statement

The anonymized version of the data presented in this are available on a reasonable request from the corresponding author. The data are not publicly available due to statutory reasons.

Appendices

CONSORT statement; Supplementary material including Figures S1 – S5 and Tables S1 – S14.

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Reporting checklist for randomised trial

For 2-weekly versus 3-weekly docetaxel for metastatic castration-resistant prostate cancer: complete quality of life results from the randomized, phase III PROSTY trial by Lehtonen et al.

Based on the CONSORT guidelines (Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials)

.		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2−3
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	4−5
Background and objectives	#2b	Specific objectives or hypothesis	4−5
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	5−7
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7−9
Participants	#4a	Eligibility criteria for participants	5−6
Participants	#4b	Settings and locations where the data were collected	5
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4−7

Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	7−9
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	7−9
Sample size	#7a	How sample size was determined.	9−10
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	Central
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	N/A
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Minimisation
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	Allocation sequence generation by TL, patient enrollment by PK, participant assignment by research nurse
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	N/A
Blinding	#11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	7−9

Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Figure 1
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	5
Recruitment	#14b	Why the trial ended or was stopped	N/A
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1; also described in text pp. 10−11
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 2−3 and S1−S14
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11−14
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Post-hoc power analysis Table S1
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	See primary end-point publication (Kellokumpu-Lehtinen et al. Lancet Oncol. 2013

Feb;14(2):117–24.)

Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17−19
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	14−19
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19
Other information			
Registration	#23	Registration number and name of trial registry	5
Protocol	#24	Where the full trial protocol can be accessed, if available	Link here
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	20−21

Supplementary Table S1. Observed power in both models

Comparisons towards the baseline					**Comparisons head-to-head**			
	Arm A		Arm B			Arm A	Arm B	
Month	*N*	1 – β	*N*	1 – β	Month	*N*	*N*	1 – β
BL	147	0.999	149	0.999	BL	147	149	0.978
1	51	0.900	54	0.916	1	51	54	0.653
2	83	0.986	85	0.988	2	84	85	0.850
3	111	0.998	117	0.998	3	112	117	0.938
4	69	0.966	80	0.983	4	69	80	0.801
5	51	0.957	33	0.730	5	51	33	0.536
6	65	0.980	68	0.964	6	65	68	0.756
7	46	0.867	43	0.842	7	46	43	0.580
8	30	0.686	26	0.619	8	30	26	0.397
9	29	0.670	19	0.475	9	29	19	0.336
10	32	0.716	12	0.304	10	32	12	0.266
11	17	0.429	8	0.198	11	17	8	0.177
12	10	0.251	10	0.251	12	10	10	0.163

Arm A: docetaxel 50 mg/m^2 every two weeks; Arm B: docetaxel 75 mg/m^2 every three weeks; BL: baseline; *N* = sample size; 1 – β: observed power.

Supplementary Table S2. Total FACT-P scores and FAPSI-8 scores compared directly between the arms

Total FACT-P scores: head-to-head comparisons									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	*N*	Mean	Median	IQR	*N*	Mean	Median	IQR	*P* value
BL	147	46.8	43.0	[33.1−60.9]	149	46.6	44.0	[31.8−59.9]	0.999
1	51	40.6	37.7	[29.0−50.0]	54	41.8	39.1	[27.3−55.1]	0.912
2	84	43.8	46.0	[30.0−54.9]	85	40.5	40.4	[27.0−53.0]	0.304
3	112	45.2	44.0	[31.3−58.2]	117	42.0	41.0	[28.5−53.0]	0.156
4	69	43.3	42.7	[29.5−55.8]	80	47.4	49.3	[33.2−61.6]	0.268
5	51	42.3	37.0	[26.0−59.8]	33	46.5	45.3	[29.3−61.5]	0.272
6	65	44.5	43.0	[30.5−58.5]	68	44.9	42.8	[27.3−62.7]	0.889
7	46	41.0	37.5	[27.4−56.4]	43	48.9	47.9	[32.3−67.1]	0.090
FAPSI-8 scores: head-to-head comparisons									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	*N*	Mean	Median	IQR	*N*	Mean	Median	IQR	*P* value
BL	147	9.5	9.0	[5.0−13.0]	149	10.0	9.0	[5.0−14.5]	0.644
1	51	6.9	6.0	[4.0−9.0]	54	7.5	7.0	[4.0−10.3]	0.502
2	84	7.7	7.0	[4.0−11.8]	85	7.2	6.0	[3.0−11.0]	0.394
3	112	7.6	7.0	[4.0−10.0]	117	7.1	6.9	[4.0−10.0]	0.339
4	69	7.0	6.0	[4.0−10.5]	80	8.4	8.0	[4.0−12.0]	0.214
5	51	6.5	5.0	[3.0−9.0]	33	8.1	7.0	[4.0−12.0]	0.131
6	65	7.7	7.0	[4.0−11.0]	68	7.5	6.0	[3.0−11.0]	0.450
7	46	6.4	6.0	[3.0−10.0]	43	8.4	7.0	[3.0−12.0]	0.243

There were not any statistically significant differences ($P < 0.05$). Minimal clinically significant difference is ≥ 6 points of difference in means for total FACT-P and ≥ 2 points for FAPSI-8. BL = baseline; IQR = interquartile range; *N* = sample size.

Supplementary Table S3. Emotional well-being scores (EWB) compared to the baseline

Emotional well-being subdomain scores compared to the baseline.										
	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Month	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)
1	51	-1.4	-1.0	0.020	0.140	54	-1.5	-2.00	<0.001	<0.012*,†
2	83	-1.1	+0.0	0.001	0.012*,†	85	-1.3	-1.00	0.002	0.020*,†
3	111	-0.9	+0.0	< 0.001	< 0.012*	117	-1.6	-2.00	<0.001	<0.012*,†
4	69	-1.3	+0.0	0.078	0.312	80	-1.2	-0.50	0.002	0.020*,†
5	51	-1.6	-1.0	0.003	0.027*,†	33	-1.1	-1.00	0.732	> 0.999
6	65	-1.5	-1.0	0.021	0.140	68	-1.5	-1.50	0.066	0.462
7	46	-2.3	-1.0	0.008	0.064	43	-0.7	+0.00	0.011	0.088
8	30	-2.5	-1.5	0.002	0.020*,†	26	-0.1	+0.00	0.913	> 0.999
9	29	-1.4	+0.0	0.868	> 0.999	19	-2.9	-2.00	0.120	0.72
10	32	-1.4	+0.0	0.020	0.140	12	-2.4	-2.00	0.828	> 0.999
11	17	-0.8	+1.0	0.390	> 0.999	8	-1.5	-1.00	0.875	> 0.999
12	10	-1.2	-0.5	0.630	> 0.999	10	-2.8	-1.50	0.352	> 0.999

Statistically significant (< 0.05) Holm-Bonferroni adjusted P-values with an asterisk (*). Both statistically and clinically significant changes are marked with a dagger mark (†). Minimal clinically significant difference is ≥ 1 points of difference in means. Adj. = adjusted for multiplicity with Holm-Bonferroni method.

Supplementary Table S4. Emotional well-being scores (EWB) compared directly between groups

Emotional well-being subdomain scores compared directly between groups									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	N	Mean	Median	IQR	N	Mean	Median	IQR	*P* value
BL	147	7.2	6.0	[4.0−10.0]	149	7.1	6.0	[4.0−10.0]	0.795
1	51	5.8	5.0	[4.0−8.0]	54	5.6	4.0	[2.0−9.0]	0.382
2	84	6.0	6.0	[3.0−8.8]	85	5.8	5.0	[3.0−8.0]	0.607
3	112	6.3	6.0	[4.0−8.0]	117	5.5	4.0	[3.0−8.0]	0.031*
4	69	5.8	6.0	[2.0−8.0]	80	5.9	5.5	[2.3−8.8]	0.934
5	51	5.6	5.0	[2.0−8.4]	33	6.0	5.0	[3.0−9.5]	0.706
6	65	5.7	5.0	[3.0−8.0]	68	5.6	4.5	[2.0−8.9]	0.577
7	46	4.9	5.0	[1.8−8.0]	43	6.4	6.0	[4.0−10.0]	0.094
8	30	4.7	4.5	[3.0−6.3]	26	7.0	6.0	[4.0−10.0]	0.022*, †
9	29	5.8	6.0	[2.5−9.0]	19	4.1	4.0	[3.0−6.0]	0.129
10	32	5.8	6.0	[3.3−8.3]	12	4.7	4.0	[1.8−7.0]	0.412
11	17	6.4	7.0	[3.0−8.0]	8	5.6	5.0	[4.0−6.0]	0.555
12	10	5.9	5.5	[3.0−7.8]	10	4.3	4.5	[1.0−6.5]	0.287

Statistically significant (< 0.05) exact P-values are marked with an asterisk (*). Minimal clinically significant difference is ≥ 1 point of difference. Both statistically and clinically significant changes are marked with a dagger mark (†). BL: baseline; IQR: interquartile range.

Supplementary Table S5. Physical well-being (PWB) compared to the baseline

Physical well-being scores compared to the baseline.										
	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Month	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)
1	51	+0.1	+0.0	0.285	0.430	54	+0.2	+0.0	0.354	> 0.999
2	83	+0.5	+1.0	0.217	0.430	85	+0.3	+1.0	0.231	> 0.999
3	111	+1.2	+0.0	0.011	0.055	117	+0.6	+0.0	0.237	> 0.999
4	69	+0.8	+2.0	<0.001	<0.012*	80	+2.1	+2.0	0.002	0.022*,†
5	51	+1.0	+2.0	0.005	0.040*	33	+2.4	+2.0	0.068	0.544
6	65	+1.97	+1.5	<0.001	<0.012*	68	+1.5	+1.5	0.001	0.012*
7	46	+0.9	+2.0	<0.001	<0.012*	43	+2.4	+2.0	0.012	0.108
8	30	+0.4	+2.0	<0.001	<0.012*	26	+2.2	+2.0	0.010	0.100
9	29	+1.1	-1.0	0.005	0.040*	19	-1.0	-1.0	0.130	0.910
10	32	+1.2	+0.0	0.007	0.042*	12	-0.0	+0.0	0.203	> 0.999
11	17	+1.4	+0.5	0.020	0.080	8	+0.5	+0.5	0.563	> 0.999
12	10	+2.1	-3.0	0.078	0.234	10	-1.6	-3.0	0.770	> 0.999

Statistically significant (< 0.05) Holm-Bonferroni adjusted P-values with an asterisk (*). Both statistically and clinically significant changes are marked with a dagger mark (†). Minimal clinically significant difference is ≥ 2 points of difference in means. Adj. = adjusted for multiplicity with Holm-Bonferroni method.

Supplementary Table S6. Physical well-being (PWB) scores compared directly between groups

Physical well-being subdomain scores compared directly between groups									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	N	Mean	Median	IQR	N	Mean	Median	IQR	*P* value
BL	147	6.0	5.0	[2.0−8.2]	149	5.7	5.0	[2.0−8.1]	0.722
1	51	6.1	5.0	[2.0−9.0]	54	5.9	5.0	[3.0−9.0]	0.789
2	84	6.5	6.0	[2.0−10.0]	85	6.0	6.0	[2.0−9.0]	0.537
3	112	7.2	7.0	[3.0−10.0]	117	6.3	5.0	[3.0−9.0]	0.123
4	69	6.8	6.0	[3.5−10.0]	80	7.8	7.0	[3.0−11.0]	0.332
5	51	7.0	5.0	[3.0−11.0]	33	8.1	7.0	[4.0−11.5]	0.277
6	65	8.0	7.0	[4.8−11.0]	68	7.2	6.5	[2.3−10.8]	0.230
7	46	6.9	6.0	[3.8−9.3]	43	8.1	7.0	[4.0−12.0]	0.332
8	30	6.4	5.0	[2.0−10.0]	26	8.0	7.0	[4.8−10.3]	0.196
9	29	7.1	6.0	[4.0−10.5]	19	4.7	4.0	[1.0−8.0]	0.034*,†
10	32	7.2	7.0	[4.0−10.4]	12	5.7	5.0	[1.5−8.5]	0.286
11	17	7.4	8.0	[4.0−9.5]	8	6.2	5.5	[2.0−11.5]	0.558
12	10	8.1	8.5	[3.9−11.3]	10	4.1	2.0	[1.0−7.0]	0.048*,†

Statistically significant (< 0.05) exact P-values are marked with an asterisk (*). Minimal clinically significant difference is ≥ 2 point of difference. Both statistically and clinically significant changes are marked with a dagger mark (†). BL: baseline; IQR: interquartile range.

Supplementary Table S7. Prostate cancer subdomain (PCS) scores compared to the baseline

Prostate cancer subdomain scores compared to the baseline										
	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Month	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)
1	51	-2.8	-2.0	< 0.001	< 0.012*,†	54	-3.5	-2.4	< 0.001	< 0.012*,†
2	83	-1.8	-1.0	0.004	0.040*	85	-3.2	-3.0	0.007	0.070
3	111	-2.8	-2.0	< 0.001	< 0.012*,†	117	-3.2	-3.0	< 0.001	< 0.012*,†
4	69	-3.2	-3.0	0.066	0.594	80	-1.8	-1.1	0.040	0.360
5	51	-3.7	-4.0	0.066	0.594	33	-2.3	-2.0	0.132	> 0.999
6	65	-2.4	-3.0	0.676	> 0.999	68	-2.9	-3.0	0.200	> 0.999
7	46	-3.5	-3.5	0.425	> 0.999	43	-1.8	-2.0	0.372	> 0.999
8	30	-4.2	-4.0	0.237	> 0.999	26	-1.2	-1.5	0.694	> 0.999
9	29	-2.2	-2.0	0.700	> 0.999	19	-6.7	-7.0	0.368	> 0.999
10	32	-3.6	-3.0	0.451	> 0.999	12	-2.8	-3.5	0.473	> 0.999
11	17	-2.4	-5.0	0.468	> 0.999	8	-5.5	-6.0	0.438	> 0.999
12	10	-2.1	-2.0	0.930	> 0.999	10	-5.6	-7.5	0.625	> 0.999

Both arms suffered similar clinically significant decrease in months 1 and 3. Statistically significant (< 0.05) Holm-Bonferroni adjusted P-values with an asterisk (*). Both statistically and clinically significant changes are marked with a dagger mark (†). Minimal clinically significant difference is ≥ 2 points of difference in means. Adj. = adjusted for multiplicity with Holm-Bonferroni method.

Supplementary Table S8. Prostate cancer subdomain (PCS) scores compared directly between groups

Prostate cancer subdomain scores compared directly between groups									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	N	Mean	Median	IQR	N	Mean	Median	IQR	*P* value
BL	147	17.9	17.0	[13.0−23.0]	149	18.3	18.0	[12.0−23.0]	0.674[a]
1	51	15.1	15.0	[11.0−20.0]	54	14.9	15.6	[9.8−19.0]	0.938
2	84	16.1	16.0	[10.3−20.0]	85	15.2	15.0	[10.0−19.0]	0.282
3	112	15.5	15.0	[11.0−19.0]	117	15.1	15.0	[10.0−19.0]	0.666
4	69	14.7	14.0	[10.0−20.0]	80	16.5	16.9	[10.3−22.0]	0.182
5	51	14.2	13.0	[8.4−19.0]	33	16.1	16.0	[11.0−21.0]	0.161
6	65	15.4	14.0	[11.0−20.5]	68	15.4	15.0	[9.8−20.0]	0.850
7	46	14.4	13.5	[10.0−18.5]	43	16.5	16.0	[11.0−20.0]	0.215
8	30	13.7	13.0	[8.8−18.0]	26	17.1	16.5	[12.0−22.2]	0.040*,†
9	29	15.7	15.0	[9.5−21.0]	19	11.6	11.0	[7.0−16.0]	0.045*,†
10	32	14.3	14.0	[8.0−20.0]	12	15.6	14.5	[12.3−18.8]	0.536
11	17	15.5	12.0	[10.5−23.5]	8	12.9	12.0	[12.0−20.4]	0.307
12	10	15.8	15.0	[9.3−19.8]	10	12.7	10.5	[4.0−21.0]	0.286

Statistically significant (< 0.05) exact P-values are marked with an asterisk (*). Minimal clinically significant difference is ≥ 2 points of difference. Both statistically and clinically significant changes are marked with a dagger mark (†). [a] = asymptotic significance (due to computational reasons). BL: baseline; IQR: interquartile range

Supplementary Table S9. Functional well-being (FWS) scores compared to the baseline

Functional well-being scores compared to the baseline										
	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Month	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)
1	51	-1.2	-1.0	0.165	0.846	54	+0.0	+0.8	0.876	> 0.999
2	83	-0.5	+0.0	0.683	0.846	85	-0.8	-0.2	0.209	> 0.999
3	111	+0.6	+2.0	0.077	0.616	117	-0.0	+0.8	0.427	> 0.999
4	69	-0.3	+0.0	0.052	0.468	80	+1.0	+1.8	<0.001	<0.012*
5	51	+0.3	+1.0	0.014	0.168	33	+1.4	+1.8	0.569	> 0.999
6	65	+0.4	+2.0	0.026	0.286	68	+1.0	+1.8	0.006	0.066
7	46	-0.1	+1.0	0.101	0.707	43	+2.0	+2.8	0.148	> 0.999
8	30	-0.4	+1.0	0.369	0.846	26	+2.1	+2.6	0.031	0.31
9	29	-0.4	+0.0	0.257	0.846	19	-2.2	-0.2	0.606	> 0.999
10	32	+0.9	+2.8	0.036	0.360	12	-0.7	-0.2	0.320	> 0.999
11	17	+1.2	+2.0	0.176	0.846	8	+0.3	-0.2	0.438	> 0.999
12	10	+0.9	-0.5	0.141	0.846	10	-2.9	-3.8	0.941	> 0.999

Statistically significant (< 0.05) Holm-Bonferroni adjusted P-values with an asterisk (*). Both statistically and clinically significant changes are marked with a dagger mark (†). Minimal clinically significant difference is ≥ 2 points of difference in means. Adj. = adjusted for multiplicity with Holm-Bonferroni method.

Supplementary Table S10. Functional well-being (FWS) scores compared directly between groups

Functional well-being scores compared directly between groups									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	N	Mean	Median	IQR	N	Mean	Median	IQR	*P* value
BL	147	9.5	8.0	[5.0−14.0]	149	9.0	8.2	[5.0−12.0]	0.712
1	51	8.3	7.0	[5.0−12.0]	54	9.1	9.0	[5.8−12.3]	0.509
2	84	9.0	8.0	[5.0−12.0]	85	8.3	8.0	[5.0−11.0]	0.290
3	112	10.1	10.0	[6.0−13.8]	117	9.0	9.0	[6.0−12.4]	0.097
4	69	9.2	8.0	[6.0−12.9]	80	10.1	10.0	[7.0−13.0]	0.265
5	51	9.8	9.0	[5.0−13.0]	33	10.4	10.0	[7.0−15.0]	0.480
6	65	9.9	10.0	[6.0−14.0]	68	10.1	10.0	[6.0−14.8]	0.994
7	46	9.4	9.0	[6.0−14.0]	43	11.0	11.0	[7.0−15.0]	0.198
8	30	9.1	9.0	[4.9−13.0]	26	11.2	10.8	[8.0−15.0]	0.141
9	29	9.1	8.0	[4.5−14.5]	19	6.9	8.0	[3.0−9.0]	0.190
10	32	10.4	10.8	[6.0−14.0]	12	8.3	8.0	[2.0−15.3]	0.364
11	17	10.7	10.0	[8.0−14.5]	8	9.3	8.0	[4.8−14.5]	0.520
12	10	10.4	7.5	[6.0−16.8]	10	6.1	4.3	[2.0−9.8]	0.077

There were not any statistically significant differences ($P < 0.05$). Minimally clinically significant difference is ≥ 1 point of difference.

BL: baseline; IQR: interquartile range.

Supplementary Table S11. Social/family well-being (SWB) scores compared to the baseline

Social/family well-being scores compared to the baseline										
	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Month	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)
1	51	-1.0	-1.0	0.656	> 0.999	54	-0.1	+0.0	0.370	> 0.999
2	83	-0.1	+0.0	0.244	> 0.999	85	-1.1	-0.3	0.096	> 0.999
3	111	-0.1	+0.0	0.628	> 0.999	117	-0.3	+0.1	0.713	> 0.999
4	69	+0.6	+1.0	0.446	> 0.999	80	+0.7	+1.1	0.263	> 0.999
5	51	-0.5	+0.0	0.894	> 0.999	33	-0.5	-1.0	0.748	> 0.999
6	65	-0.7	-0.1	0.232	> 0.999	68	+0.2	+1.0	0.861	> 0.999
7	46	-0.8	-0.5	0.306	> 0.999	43	+0.5	+1.7	0.183	> 0.999
8	30	-0.3	+1.0	0.795	> 0.999	26	+1.8	+2.4	0.132	> 0.999
9	29	+0.3	+1.0	0.573	> 0.999	19	-2.3	-1.3	0.132	> 0.999
10	32	+0.3	+0.7	0.975	> 0.999	12	+3.0	+2.1	0.461	> 0.999
11	17	+0.2	+1.0	0.587	> 0.999	8	-1.9	+0.2	0.438	> 0.999
12	10	-1.0	-0.5	> 0.999	> 0.999	10	-1.7	-0.3	0.219	> 0.999

There were not any statistically significant differences ($P < 0.05$). Minimal clinically significant difference is ≥ 1 points of difference in means. Adj. = adjusted for multiplicity with Holm-Bonferroni method.

Supplementary Table S12. Social/family well-being (SWB) scores compared directly between groups

Social/family well-being scores compared directly between groups									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	N	Mean	Median	IQR	N	Mean	Median	IQR	*P* value
BL	147	6.3	5.0	[3.4−8.0]	149	6.4	5.3	[3.0−9.0]	0.853
1	51	5.2	4.0	[3.0−7.0]	54	6.3	5.4	[3.3−8.7]	0.170
2	84	6.1	5.0	[3.3−8.0]	85	5.3	5.0	[2.1−7.0]	0.188
3	112	6.2	5.0	[3.6−8.9]	117	6.1	5.4	[3.0−8.0]	0.835
4	69	6.9	6.0	[4.0−9.0]	80	7.1	6.5	[4.0−8.0]	0.767
5	51	5.8	5.0	[3.0−8.0]	33	5.9	4.3	[3.1−8.6]	0.987
6	65	5.5	4.9	[2.0−8.0]	68	6.6	6.3	[4.0−8.0]	0.116
7	46	5.4	4.5	[2.3−8.1]	43	6.9	7.0	[4.0−8.1]	0.190
8	30	6.0	6.0	[3.0−10.0]	26	8.2	7.7	[4.9−9.0]	0.132
9	29	6.6	6.0	[4.0−9.5]	19	4.1	4.0	[3.7−5.3]	0.029*,†
10	32	6.6	5.7	[3.1−10.0]	12	9.4	7.4	[4.0−14.5]	0.415
11	17	6.4	6.0	[4.1−9.5]	8	4.5	5.6	[2.3−6.0]	0.219
12	10	5.3	4.5	[3.0−7.0]	10	4.7	5.1	[3.0−6.6]	0.867

There were not any statistically significant differences ($P < 0.05$). Minimally clinically significant difference is ≥ 1 point of difference.

BL: baseline; IQR: interquartile range.

Supplementary Table S13. Visual analogue scale (VAS) results compared directly between groups

VAS results									
	Docetaxel 50 mg/m^2 every 14 days				Docetaxel 75 mg/m^2 every 21 days				
Month	N	Mean	Median	IQR	N	Mean	Median	IQR	*P* value
BL	141	2.4	2.0	[0.5−3.5]	138	2.6	2.0	[0.8−3.5]	0.637
1	48	1.8	1.4	[0.5−2.4]	51	2.2	2.0	[0.5−3.4]	0.188
2	80	1.9	1.0	[0.4−2.8]	75	1.7	1.0	[0.3−3.0]	0.685
3	105	1.9	1.5	[0.5−2.5]	107	1.9	1.3	[0.5−2.5]	0.783
4	66	1.8	1.0	[0.3−2.9]	74	2.3	1.6	[0.5−3.5]	0.096
5	49	1.5	1.0	[0.3−2.3]	31	2.2	1.5	[0.5−3.8]	0.152
6	57	1.9	1.0	[0.3−3.6]	65	2.0	0.9	[0.3−3.6]	0.975
7	42	1.9	1.5	[0.3−2.7]	40	1.9	1.0	[0.6−3.3]	0.669
8	28	1.6	0.8	[0.3−2.5]	25	1.8	1.4	[0.7−3.0]	0.362
9	28	2.4	1.3	[0.4−3.7]	16	1.3	0.5	[0.2−1.2]	0.101
10	30	2.1	1.0	[0.4−3.3]	13	1.9	1.0	[0.5−3.3]	0.750
11	17	1.9	0.8	[0.4−2.5]	7	1.7	2.5	[0.5−2.6]	0.709[e]
12	10	1.4	0.8	[0.4−1.4]	9	1.7	1.0	[0.4−2.4]	0.660[e]

There were not any statistically significant differences ($P < 0.05$). Minimally clinically significant difference is ≥ 1 point of difference. Asymptotic significances if not otherwise noted. [e] = exact significance. BL: baseline; IQR: interquartile range.

Supplementary Table S14. Total FACT-P Scores compared to the baseline for months 8−12

Total FACT-P scores compared to the baseline for months 8−12										
	Docetaxel 50 mg/m^2 every 14 days					Docetaxel 75 mg/m^2 every 21 days				
Month	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)
8	30	-6.89	-1.50	0.939	> 0.999	26	+4.92	+7.00	0.175	> 0.999
9	29	-2.58	-4.28	0.479	> 0.999	19	-15.16	-14.14	0.152	> 0.999
10	32	-2.52	+2.80	0.441	> 0.999	12	-2.89	+1.50	0.844	> 0.999
11	17	-0.47	+3.00	0.142	> 0.999	8	-8.05	-6.22	0.652	> 0.999
12	10	-1.34	+2.00	0.461	> 0.999	10	-14.68	-14.00	0.175	> 0.999
FAPSI-8 scores compared to the baseline for months 8−12										
Month	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)	N	Difference (mean)	Difference (median)	*P* value (exact)	*P* value (adj.)
8	30	-1.85	-2.00	0.631	> 0.999	26	-1.30	-1.00	0.514	> 0.999
9	29	-2.13	-2.50	0.575	> 0.999	19	-4.39	-4.00	0.460	> 0.999
10	32	-2.36	-3.00	0.349	> 0.999	12	-3.03	-2.50	0.824	> 0.999
11	17	-1.30	-1.00	0.668	> 0.999	8	-3.78	-3.00	0.625	> 0.999
12	10	-1.85	-2.00	0.631	> 0.999	10	-4.33	-4.00	0.559	> 0.999

Statistically significant (< 0.05) Holm-Bonferroni adjusted P-values with an asterisk (*). Both statistically and clinically significant changes are marked with a dagger mark (†). Minimal clinically significant difference is ≥ 6 points of difference in means for total FACT-P and ≥ 2 points for FAPSI-8. Adj. = adjusted for multiplicity with Holm-Bonferroni method. There were not any statistically significant differences ($P < 0.05$). BL = baseline; IQR = interquartile range; *N* = sample size.

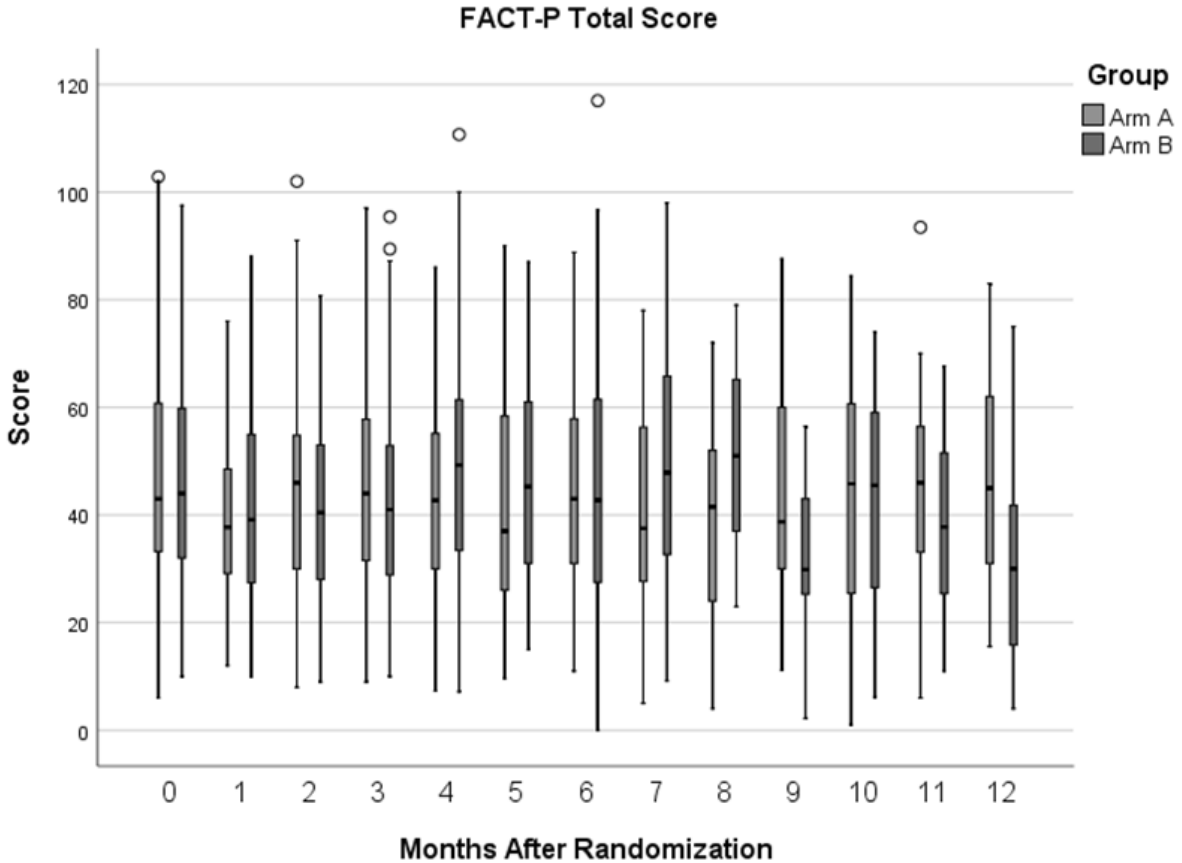

Figure S1. Total FACT-P scores for Arm A (blue) and Arm B (red) in different months during the follow-up. Median is depicted as a black line inside the coloured box. The coloured box represents interquartile range. Lines in indicate the ranges. Dots indicate outliers, but they were not excluded from the analysis. The differences were significant in month 8 (favouring Arm B) and month 9 (favouring Arm A). Arm A: docetaxel 50 mg/m^2 every 14 days; Arm B: docetaxel 75 mg/m^2 every 21 days.

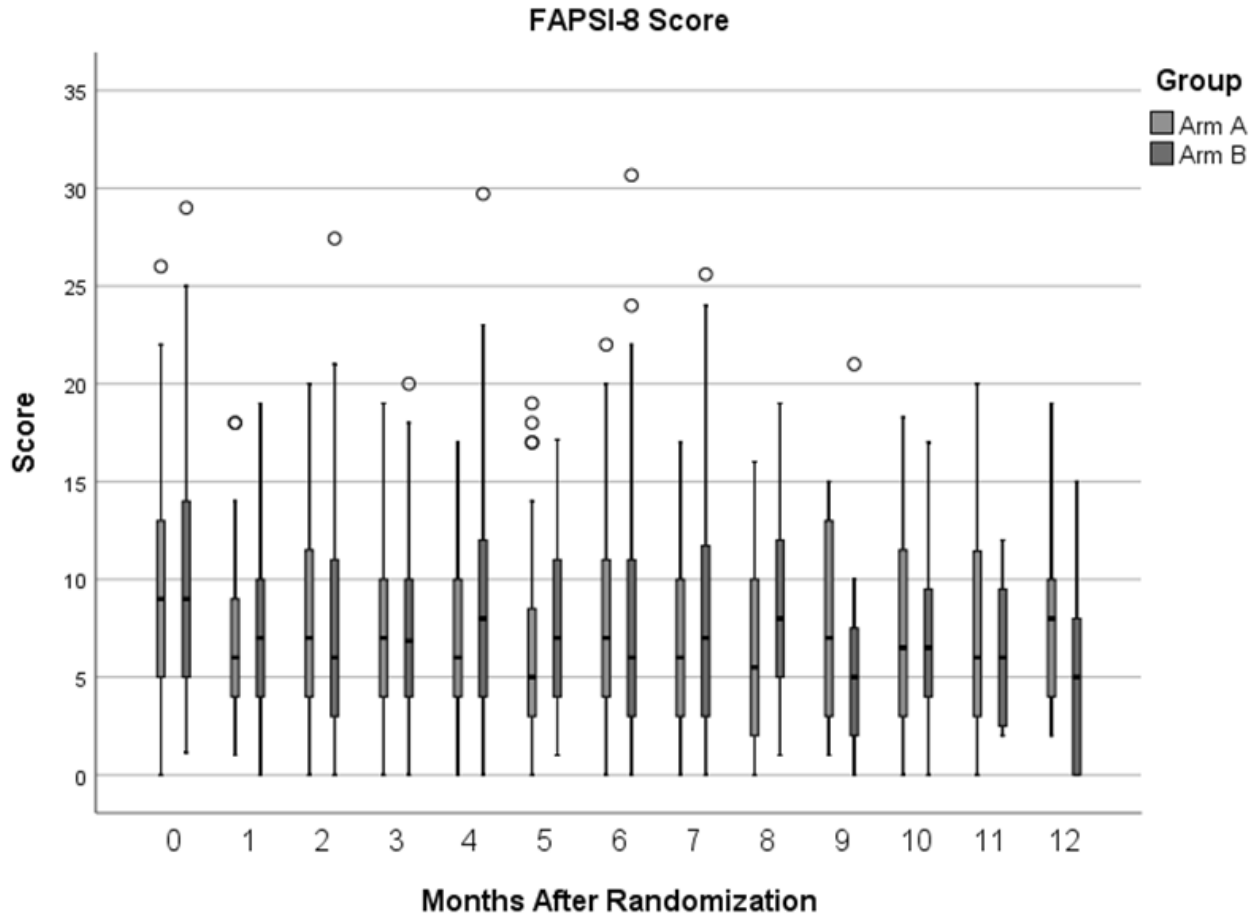

Figure S2. FAPSI-8 scores for Arm A (blue) and Arm B (red) in different months during the follow-up. Median is depicted as a black line inside the coloured box. The coloured box represents interquartile range. Lines in indicate the ranges. Dots indicate outliers, but they were not excluded from the analysis. Arm A: docetaxel 50 mg/m^2 every 14 days; Arm B: docetaxel 75 mg/m^2 every 21 days.

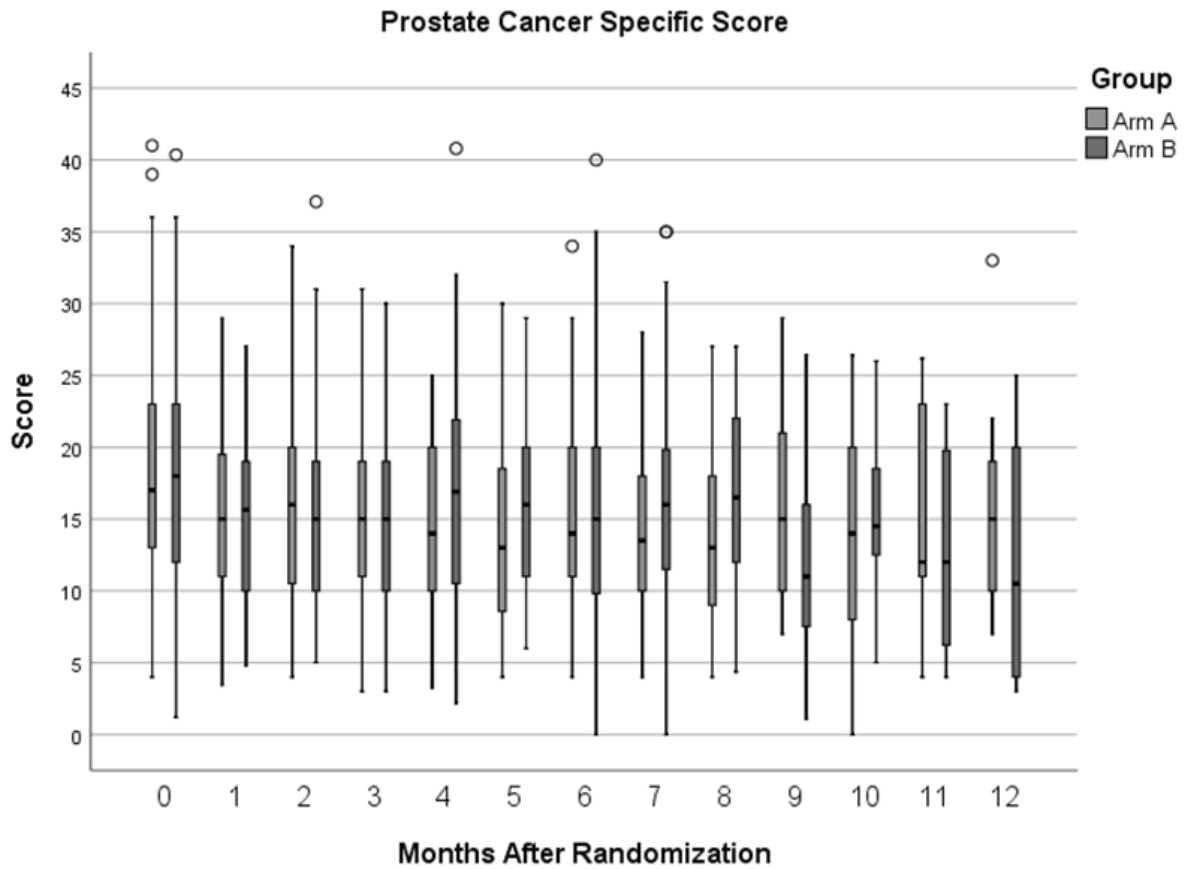

Figure S3. PCS results for Arm A (blue) and Arm B (red) in different months during the follow-up. Median is depicted as a black line inside the coloured box. The coloured box represents interquartile range. Lines in indicate the ranges. Dots indicate outliers, but they were not excluded from the analysis. Arm A: docetaxel 50 mg/m^2 every 14 days; Arm B: docetaxel 75 mg/m^2 every 21 days.

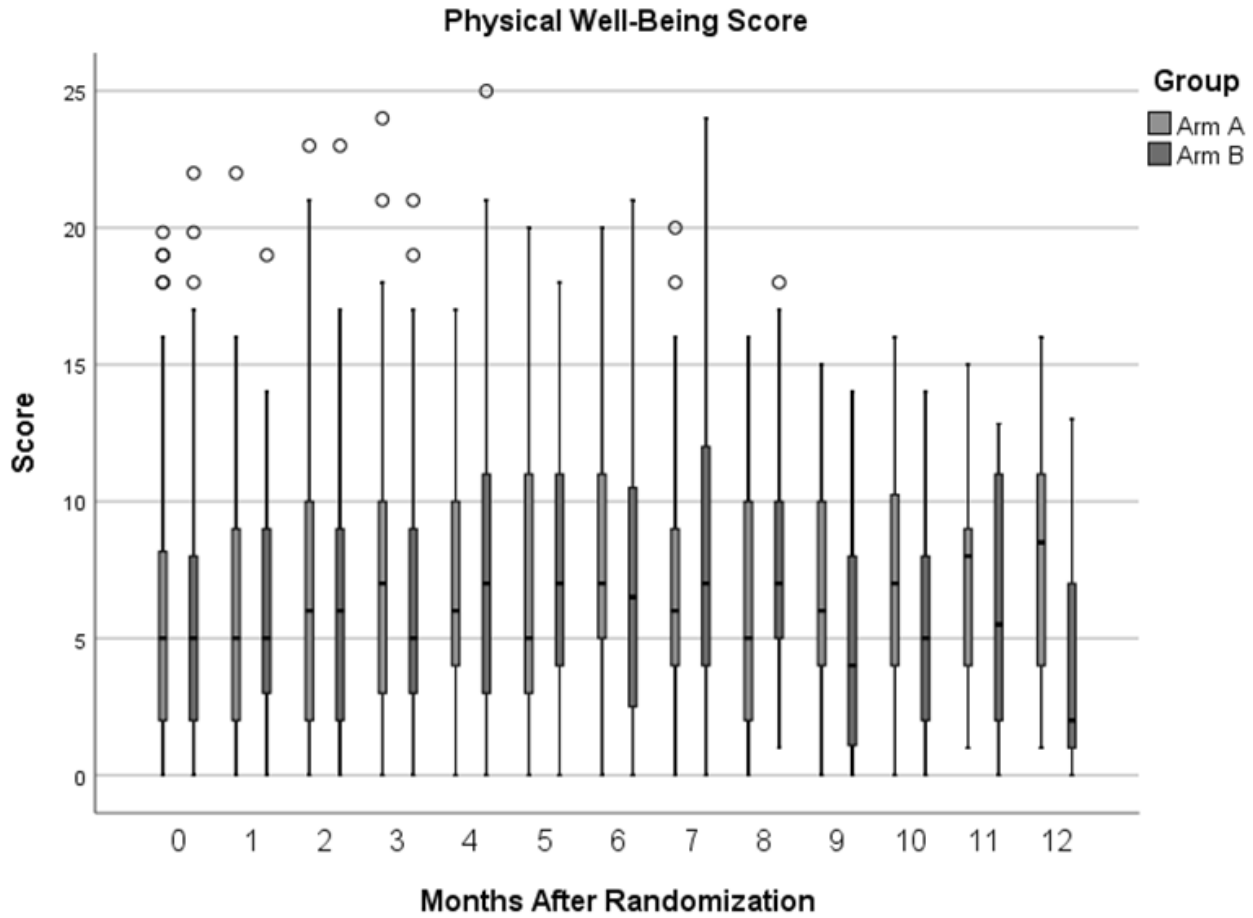

Figure S4. PWB results for Arm A (blue) and Arm B (red) in different months during the follow-up. Median is depicted as a black line inside the coloured box. The coloured box represents interquartile range. Lines in indicate the ranges. Dots indicate outliers, but they were not excluded from the analysis. Arm A: docetaxel 50 mg/m^2 every 14 days; Arm B: docetaxel 75 mg/m^2 every 21 days.

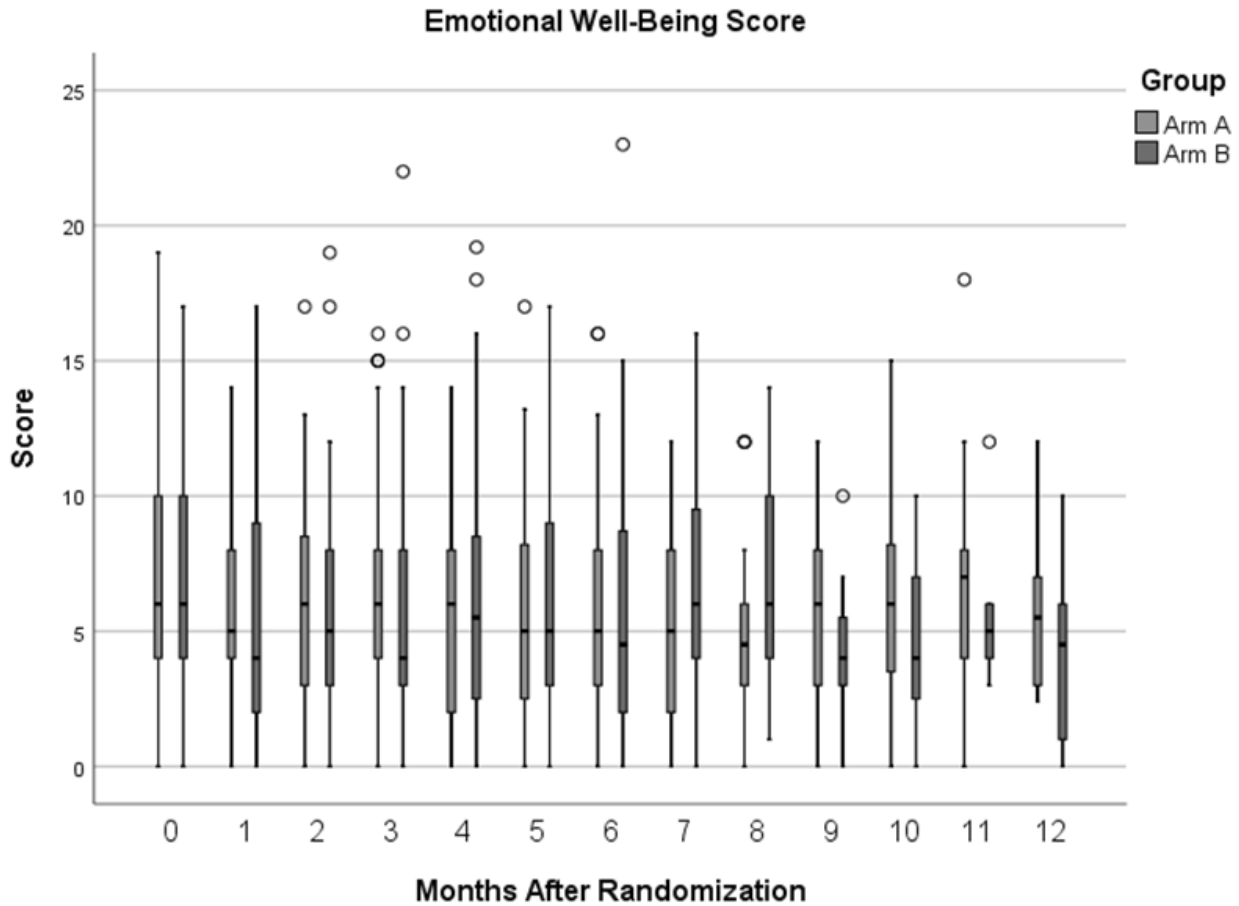

Figure S5. EWB results for Arm A (blue) and Arm B (red) in different months during the follow-up. Median is depicted as a black line inside the coloured box. The coloured box represents interquartile range. Lines in indicate the ranges. Dots indicate outliers, but they were not excluded from the analysis. Arm A: docetaxel 50 mg/m^2 every 14 days; Arm B: docetaxel 75 mg/m^2 every 21 days.

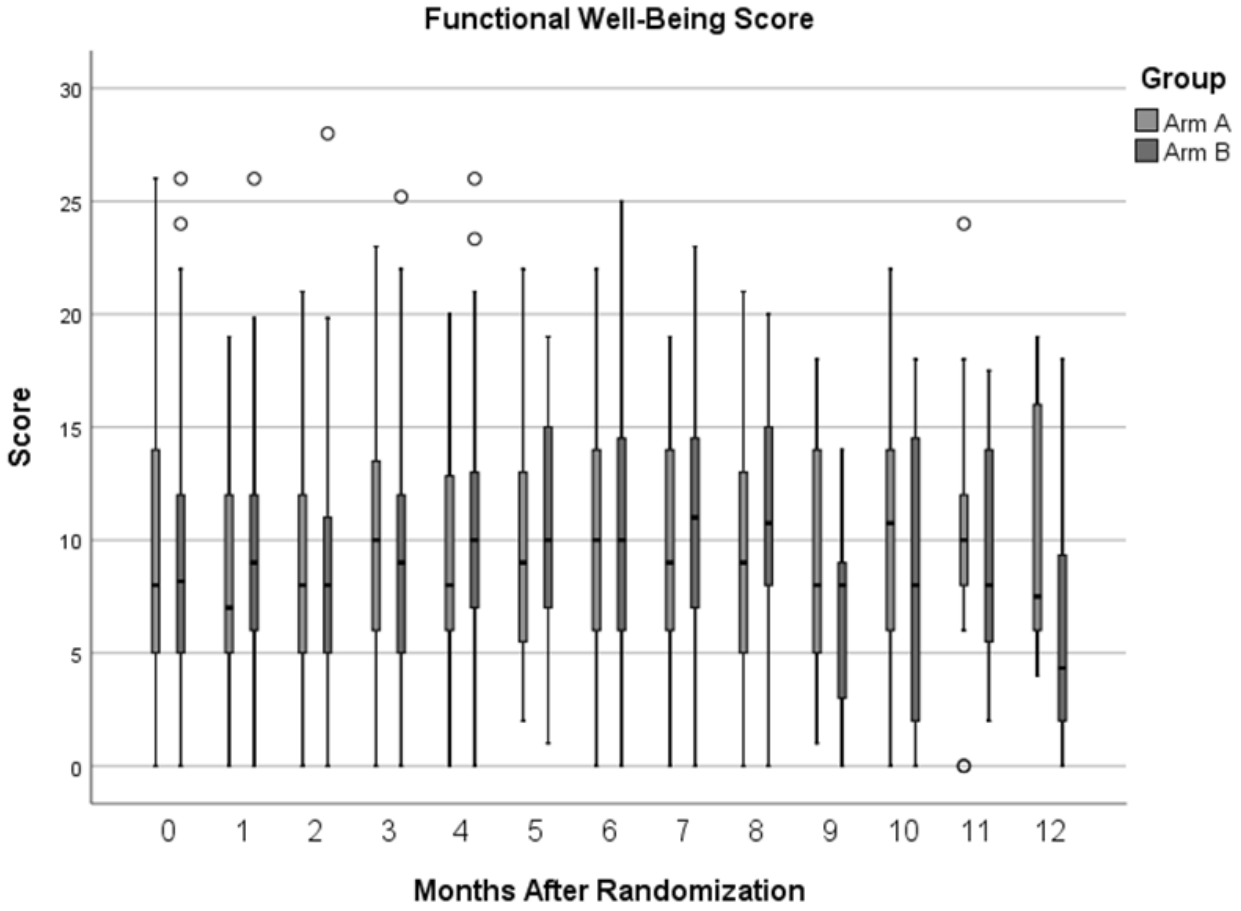

Figure S6. FWB results for Arm A (blue) and Arm B (red) in different months during the follow-up. Median is depicted as a black line inside the coloured box. The coloured box represents interquartile range. Lines in indicate the ranges. Dots indicate outliers, but they were not excluded from the analysis. Arm A: docetaxel 50 mg/m^2 every 14 days; Arm B: docetaxel 75 mg/m^2 every 21 days.

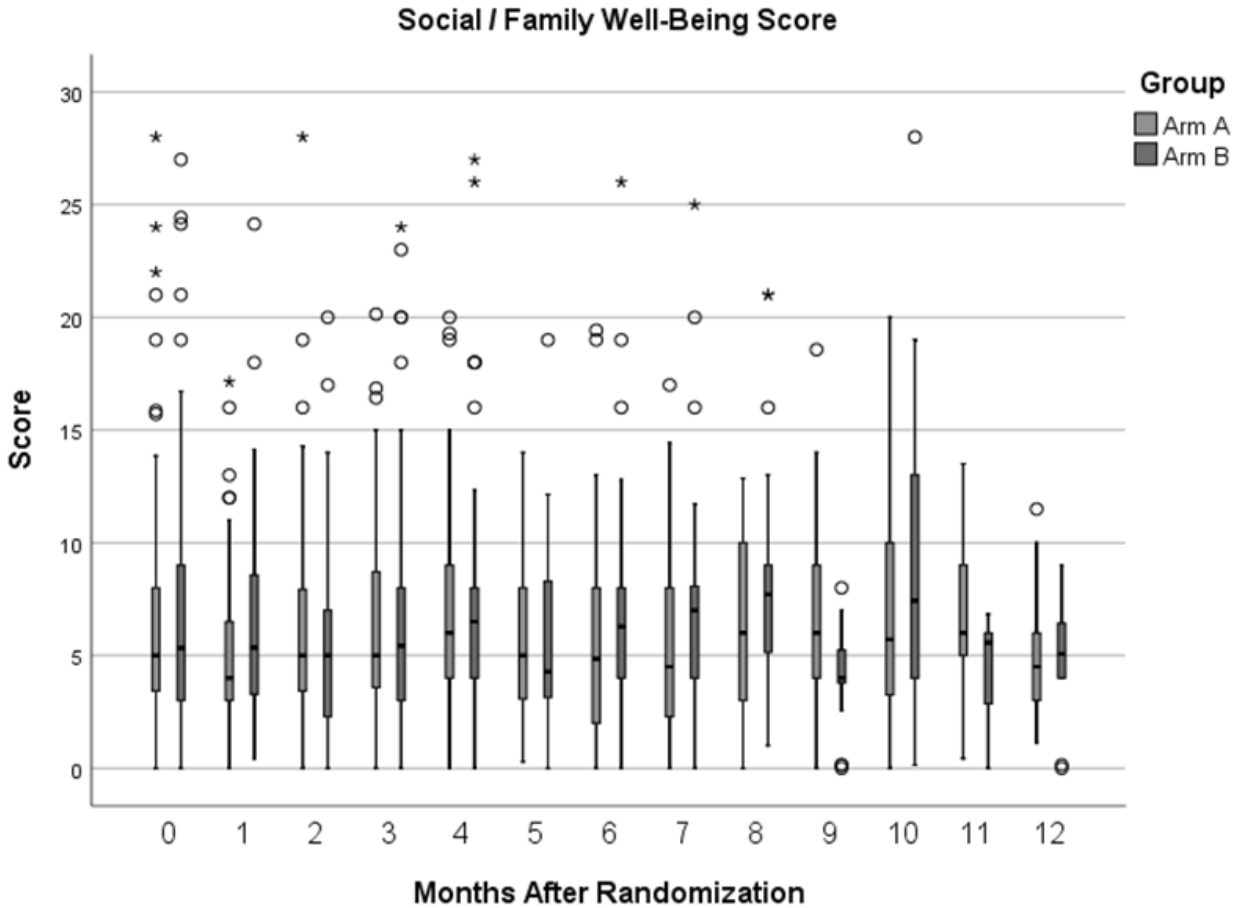

Figure S7. SWB results for Arm A (blue) and Arm B (red) in different months during the follow-up. Median is depicted as a black line inside the coloured box. The coloured box represents interquartile range. Lines in indicate the ranges. Dots indicate outliers and asterisks extreme outliers, but they were not excluded from the analysis. Arm A: docetaxel 50 mg/m^2 every 14 days; Arm B: docetaxel 75 mg/m^2 every 21 days.