QUALITY OF CARE IN CASTRATION RESISTANT PROSTATE CANCER

A DEEP DIVE INTO THE ROLE OF REAL-WORLD EVIDENCE

MALOU KUPPEN

Quality of care in castration resistant prostate cancer: a deep dive into the role of real-world evidence

Kwaliteit van zorg bij castratieresistent prostaatkanker: een duik in de rol van gegevens uit de dagelijkse praktijk

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Layout and printed by Optima Grafische Communicatie, Rotterdam, the Netherlands (www.ogc.nl)
Cover design by Malou Kuppen en Marilou Maes (www.persoonlijkproefschrift.nl)

ISBN/EAN 978-94-6361-6218

Further reading on the CAPRI registry:
And now for real - Outcomes of castration-resistant prostate cancer patients in the Netherlands (Hans Westgeest, 2022, ISBN 978-94-6421-586-1)

The CAPRI registry was funded by Sanofi-Aventis Netherlands B.V., Janssen-Cilag B.V., Astellas Pharma B.V., and Bayer B.V. The funding organizations had no role in the design and conduct of the study, collection, management, analysis, interpretation of the data, and preparation, review, or approval of the manuscripts. The PRO-CAPRI study was financially supported by the Netherlands Organisation of Health Research and Development (grant number: 836011017).

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Kwaliteit van zorg bij castratieresistent prostaatkanker: een duik in de rol van gegevens uit de dagelijkse praktijk

Proefschrift

ter verkrijging van de graad doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof. dr. A.L. Bredenoord

en volgens besluit van het college voor promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 14 januari 2022 om 13.00 uur

door

Maria Catharina Petronella Kuppen
geboren te Nijmegen

Erasmus University Rotterdam

Promotiecommissie

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LIST OF ABBREVIATIONS

ABI(+P): Abiraterone acetate (plus prednisone)

ADT: Androgen-deprivation therapy

ALP: Alkaline phosphatase

ART: Androgen-receptor targeting agents (i.e. abiraterone and enzalutamide)

CAB: Cabazitaxel

CAPRI: CAstration-resistant Prostate cancer RegIstry

CEA: Cost-effectiveness analysis

CI: confidence interval

cieBOM: "Commissie ter Beoordeling van Oncologische Middelen"

CRPC: Castration-resistant prostate cancer

DOC: Docetaxel

EAU: European Association of Urology

ECOG PS: Eastern Cooperative Oncology Group Performance Score

EMA: European Medicine Agency

ENZ: Enzalutamide

EOL: End of life

Hb: Haemoglobin

HR: Hazard ratio

HRQoL: Health-related quality of life

HTA: Health Technology Assessment

ICER: Incremental cost-effectiveness ratio

IQR: interquartile range

LDH: Lactate dehydrogenase

LPD: Life-prolonging drug (i.e. docetaxel, cabazitaxel, abiraterone, enzalutamide and radium-223)

(m)CRPC: (metastatic) Castration-resistant prostate cancer

mHSPC: Metastatic hormone-sensitive prostate cancer

OR: Odds ratio

OS: Overall survival

PRO-CAPRI: Patient-Reported Outcomes in CAstration-resistant Prostate cancer RegIstry

PSA: Prostate specific antigen

QALY: Quality-adjusted life year

Ra-223: Radium-223 dichloride

RCT: Randomized controlled trial

REF: Reference category

SAE: Serious adverse events

SRE: Skeletal-related events

SSE: Symptomatic skeletal events

SSE-FI: Symptomatic skeletal event free interval

SSE-FS: Symptomatic skeletal event free survival

TAX: Taxane based chemotherapy (i.e. docetaxel and cabazitaxel)

1

General introduction

"It is quality rather than quantity that matters."

Lucius Annaeus Seneca (4 BC – AD 65)

Measuring health care in a population has become of increasing interest due to rising health care costs. Evaluation of the care delivered is especially important in the field of oncology. The incidence of cancer is namely high in Europe due to an ageing population in combination with better screening. In 2012, the estimated cancer incidence was 2.635 million in the European Union (EU) which was 30% higher than in 1995[1]. Moreover, innovation in both diagnostics and treatments led to increasing costs[2]. In total, health care expenditure on cancer in the EU increased from €35.7 billion in 1995 to €83.2 billion in 2014[1]. The introduction of several new, innovative and costly drugs, increased the total expenditure on cancer drugs from €7.6 billion in 2005 to €19.1 billion in 2014[1].

NEW TREATMENTS: FROM DEVELOPMENT TO MARKET REGISTRATION

The development of new drugs takes several years and different research stages from the discovery of a new substance or drug to the use of the drug in daily practice. The most important research phase serves to goal to evaluate the efficacy of a treatment compared to best standard of care in a large patient population[3]. A randomized controlled trial (RCT) is the golden standard to investigate efficacy. In an RCT patients are randomly assigned to two (or more) groups: one group as the experimental group (i.e. the group that receives the drug being tested) and the other as a control group (i.e. the group with best standard of care or a placebo). All patients follow protocol mandated monitoring and response measurements at specific time points[4,5].

New treatments must show that their benefits outweigh their toxicity to the satisfaction of regulatory agencies prior to market approval. The pharmaceutical companies start the registration phase via (inter)national legislation bodies as the European Medicine Agency (EMA), the Food and Drug Administration (FDA) in the United States and/or the Dutch Medicine Evaluation Board (in Dutch: College ter Beoordeling van Geneesmiddelen, CBG)[3].

For oncolytic drugs the Dutch Society of Medical Oncologists (in Dutch: Nederlandse Vereniging voor Medische Oncologie, NVMO) has established the "Commissie ter Beoordeling van Oncologische Middelen (cieBOM)". The cieBOM has the assignment to "appraise the clinical value of new registered drugs, treatment methods and indications in medical oncology, in order to achieve better nationwide agreements on the use of new and costly drugs in the oncologic practice". The cieBOM appraises a new drug

Table 1.1 | PASKWIL criteria for appraisal of oncolytic drugs

Effectivity	Benefit on overall survival	>12 weeks or HR <0.7	+
	Benefit on progression-free survival	>12 weeks or HR <0.7	+
Grading according to ESMO-MCBS			
Adverse events	Lethal	<5%	+
	Acute, severe	<25%	+
	Chronic		+
Quality of life		Validated tests	+
Impact of treatment	Acceptable treatment burden		+
Drug costs	Median treatment duration		
	Per 28 days		
	Compared with standard of care		

Abbreviations: HR, hazard ratio; ESMO-MCBS, European Society of Medical Oncology - Magnitude of Clinical Benefit Scale

when the drug is registered in Europe by EMA and when the endpoints of the available randomized study can be assessed with the PASKWIL criteria[6]. The PASKWIL criteria exist of six items: effectivity, grading according to ESMO-MCBS (European Society of Medical Oncology - Magnitude of Clinical Benefit Scale), adverse events, quality of life, impact of treatment, and drug costs (Table 1.1).

Registration does not automatically mean that a drug is reimbursed. In the Netherlands, drugs are reimbursed when they are part of the compulsory basic health care insurance. The Dutch National Health Care Institute (in Dutch: Zorginstituut Nederland, ZiN) advises which drugs should be reimbursed. In general, all oncologic drugs as part of in hospital care are reimbursed by health care insurers. The minister of Health, Welfare and Sport can however decide to temporarily deny access of drugs to the basic health care insurance when the economic impact of drugs is estimated to be too high. High drug costs and/or high number of expected patients are main reasons for a drug to enter this so called “lock” (in Dutch: “de sluisprocedure”). A drug enters the lock when a drug costs more than €40 million per year or more than €50.000 per patient per year and in total more than €10 million per year[7]. ZiN advises the minister on reimbursement of these drugs based on four criteria: effectiveness, necessity, cost-effectiveness and feasibility[7,8].

Cost-effectiveness analyses (CEA) form a major component on the decision of reimbursement. CEAs can be used to determine the gains and extra costs of a new intervention, using the incremental cost-effectiveness ratio (ICER). The ICER expresses the cost per “quality-adjusted life year (QALY)” of one treatment compared to standard of care. Several countries use cut-off levels concerning the maximum amount to be paid for health gain (i.e. willingness to pay, WTP). In the Netherlands, a ceiling for willingness to pay according to disease burden of a specific disease is used to determine reimburse-

ment. The ceiling ranges from €20,000 per QALY for a low disease burden to €80,000 per QALY for a high disease burden[9,10]. After the advice of ZiN on treatments in the "lock", specific price arrangement can be made between the minister and pharmaceutical company of this drug before reimbursement is provided[8].

HEALTH CARE DELIVERY

National and international regulatory agents influence the accessibility of new cancer drugs as stated above. Moreover, the regulatory, financial and payment regimens directly influence the structure and performance of health care organizations and thus form an important actor in the health care system[11]. Other actors are health care organizations, care teams and patients.

Health care organizations provide infrastructure and resources to support the work and development of care teams[11]. The care teams include both formal (e.g. physicians, nurses) and informal (e.g. patients' family) caregivers. Their role is to "standardize care where possible, based on best current evidence, to stratify patients based on medical need and provide the best evidence-based care, and to customize care to meet individuals needs for patients with complex health problems"[11,12]. Professional care givers should base treatment decisions on available evidence tailored to the individual patient, which form the last actor in the health care system. The needs and preferences of individual patients should form the core of the health care system[11].

MEASURING QUALITY OF CARE

Since the views of the different actors often compete, measuring the quality of a health care system is challenging. A clear definition of quality forms the base. The most accepted definitions are from the European Commission and the World Health Organization (WHO). The European Commission states that "good quality care is health care that is effective, safe and responds to the needs and preferences of patients"[13]. These aspects or dimensions (effectiveness, safety and responsiveness/patient-centeredness) are considered as the core dimensions and directly influence the likelihood of desired outcomes[14–16]. However, the definition of quality of care changes depending on the level of health care it is assessed[14]. While the core dimensions measure quality of health care services, accessibility and efficiency should be considered when evaluating health system performances. Access to qualitative health care services is necessary to achieve overall health system goals (i.e. population health outcomes)[14]. The resources required to achieve these goals determine the efficiency of the system[14].

CASTRATION-RESISTANT PROSTATE CANCER (CRPC)

Prostate cancer is an example of an indication in which measurement of quality of care is of increasing interest, since there is a high expected number of patients and registered drugs come at high economic costs. In 2018, approximately 12,600 patients were diagnosed with prostate cancer in the Netherlands[17]. Most men are diagnosed with local prostate cancer which has a good life expectancy: 97% to 100% is still alive five years after initial diagnosis[17]. Curation of local disease does not need expensive drugs, but can be achieved by radical prostatectomy or radiation therapy.

In contrary, metastatic prostate cancer is incurable and treatment is palliative often requiring the (long-term) use of expensive drugs. Since the discovery that prostate cancer is dependent of dihydrotestosterone, androgen deprivation therapy (ADT) is the cornerstone of metastatic prostate cancer treatment[18]. From 2015 onwards several studies reported a survival benefit when adding new treatments as docetaxel, abiraterone acetate plus prednisone (hereafter abiraterone) or enzalutamide to ADT in metastatic hormone-sensitive prostate cancer (mHSPC)[19–22]. Progression to castration-resistant prostate cancer (CRPC) is however inevitable. CRPC is defined by the European Association of Urology (EAU) as castrate serum testosterone, plus either biochemical or radiologic progression[23]. Five drugs have been registered for the treatment of CRPC. Table 1.2 offers an overview of the trials leading to registration of the drugs in CRPC.

With an annual incidence of CRPC of 3,000 patients in the Netherlands and expensive treatment options, CRPC leads to both a high disease and economic burden.

Disease burden

The disease trajectory of incurable cancer as CRPC shows a slow decline over months or years followed by a rapid decline over a few months resulting in death. CRPC has an estimated life expectancy of 14 months without life-prolonging treatment[40]. All life-prolonging drugs (LPDs) have a survival benefit compared to mitoxantrone or placebo (Table 1.3). After registration of these LPDs we observed median overall survival (OS) of 26 months in current daily practice[41].

Although prolongation of life is the main goal in cancer treatment, treatments also have other objectives. CRPC impacts quality of life and deterioration occurs in both general as well as specific domains as pain, fatigue and appetite loss[40,42–46]. Moreover, CRPC patients are at risk of developing skeletal complications (known as skeletal-related events, SREs) which further impact quantity and quality of life as well as economic costs[47,48]. In general, LPDs also have a beneficial effect on these secondary outcomes (Table 1.3).

Table 1.2 | Registered drugs for treatment of CRPC in the Netherlands

Treatment	Trial	Study arm	Comparator arm	Indication	Registration date[a]
Docetaxel	TAX 327[24,25]	Docetaxel 75 mg/m^2 IV 3 wk + prednisone 5 mg BD	Mitoxantrone 12 mg/m^2 IV 3 wk + prednisone 5 mg BD	First line	June 2005
	SWOG 9916[26]	Docetaxel 60 mg/m^2 IV 3 wk + estramustine 280 mg TD + dexamethasone 20 mg TD	Mitoxantrone 12 mg/m2 IV 3 wk + prednisone 5 mg BD	First line	
Cabazitaxel	TROPIC[27]	Cabazitaxel 25 mg/m^2 IV 3 wk + prednisone 5 mg OD	Mitoxantrone 12 mg/m2 IV 3 wk + prednisone 5 mg BD	Second line	July 2011
Abiraterone	COU-AA-301[28]	Abiraterone acetate 1000 mg OD + prednisone 5 mg BD	Placebo + prednisone 5 mg BD	Second line	March 2012
Enzalutamide	AFFIRM[29]	Enzalutamide 160 mg OD	Placebo	Second line	December 2013
Radium-223	ALSYMPCA[30]	Radium-223 50 kBq/kg IV 4 wk	Placebo	First[b] and second line	February 2014
	PREVAIL[31,32]	Enzalutamide 160 mg OD	Placebo	First line	November 2014

[a] Dutch positive appraisal of cieBOM; [b] patients who were ineligible for docetaxel or refused docetaxel; [c] after initial appraisal in September 2013.
Abbreviations: CRPC, castration-resistant prostate cancer; IV, intravenously; mo, months; wk, weeks; BD, twice a day; OD, once a day; TD, three times a day; cieBOM, Commissie ter Beoordeling van Oncologische Middelen.

Table 1.3 | Endpoints in pivotal phase III trials for castration-resistant prostate cancer

Treatment	Line	Effectiveness		HRQoL			Adverse events		Costs
		OS (mo)	HR	Pain reduction	Time to HRQoL deterioration (mo)	Time to pain progression (mo)	Grade ≥3 AE[a]	Time to first SRE (mo)	Per cycle (2019)
Docetaxel[24–26]	1	19.2 vs 16.3* 17.5 vs 15.6*	0.76* 0.80*	35% vs 22%*	-	3.5 vs 4.8[b]	32% vs 22%* 16% vs 13%	-	€ 915
Cabazitaxel[27,35]	2	15.1 vs 12.7*	0.70*	9.2% vs 7.7%	-	11.1 vs NR	82% vs 58%	-	€ 4,427
Abiraterone[28,36]	2	15.8 vs 11.2*	0.66*	44% vs 22%*	-	-	8% vs 10%	25.0 vs 20.3*	€ 3,047
Enzalutamide[29,37]	2	18.4 vs 13.6*	0.63*	-	9.0 vs 3.7*	NR vs 13.8*	6% vs 7%	16.7 vs 13.3*	€ 3,338
Radium-223[30,38]	1+2	14.9 vs 11.3*	0.70*	-	-	-	26% vs 21%	15.6 vs 9.8*	€4,868
Enzalutamide[31,32,39]	1	35.3 vs 31.3*	0.73*	-	11.3 vs 5.6*	5.7 vs 5.6*	7% vs 2%	31.1 vs 31.3*	€ 3,338
Abiraterone[33,34]	1	34.7 vs 30.3*	0.79*		12.7 vs 8.3	26.7 vs 18.4[c] 10.3 vs 7.4[d]*	7% vs 4%	-	€ 3,047

* significant at p<0.05; [a] Most common type of AE; [b] Time of pain response; [c] Time to progression of mean pain intensity; [d] Time to progression of mean pain interference.
Abbreviations: OS, overall survival; mo, months; HR, hazard ratio; HRQoL, health-related quality of life; AE, adverse events; SRE, skeletal-related event; NR, not yet reached.

Economic burden

In addition to effects on an individual patient, new CRPC-drugs have a societal impact since they come at high economic costs. A systemic review showed that the annual cancer-specific costs for the treatment of metastatic CRPC ranged from $3,067 to $77,725 (approximately €2,800 to €70,000)[49]. Drug costs per cycle (i.e. every three weeks for docetaxel and cabazitaxel, and every four weeks for abiraterone, enzalutamide and radium-223) are listed in Table 1.3. A economic evaluation in the Netherlands estimated the costs per QALY of post-docetaxel drugs at €97,897 per QALY for radium-223, €99,660 per QALY for enzalutamide, €104,789 per QALY for cabazitaxel, and €108,218 per QALY for abiraterone[50]. There is no generally accepted WTP threshold, but all drugs are above the commonly accepted maximal threshold of €80,000 per QALY[51].

REAL-WORLD EVIDENCE VERSUS RANDOMIZED CONTROLLED TRIALS

Data to assess the quality of care indicators should reflect the care performed in daily practice. Data can come from a wide range of data sources, generally used sources include administrative data, medical records or (disease-specific) registries.

Although RCTs which are carried forward under optimal and carefully controlled conditions in selected populations are the golden standard to investigate treatment efficacy and toxicity, results from RCTs are not easily transferable to daily practice[52]. In the real-world the use of treatments as well as treatment monitoring and patient selection are different from the controlled conditions in RCTs. Patients in clinical trials are in general younger, have better performance scores and less comorbidities[53]. These factors can influence outcomes making the generalizability of clinical trials questionable[53]. Moreover, the treatment landscape can evolve since the execution of RCTs due to the registration of multiple alternative treatment options. RCTs form the basis of guidelines, but leave questions on the optimal treatment selection unanswered. There is thus a need for outcomes from daily practice.

CAPRI REGISTRY

Real-world evidence is often collected in patient registries, which use observational study methods to collect uniform data on specified outcomes and serve one or more scientific, clinical or policy purposes[54]. Registries can be either be intervention- or disease-based[54]. Intervention-based registries investigate appropriate use, effectiveness, cost-effectiveness and safety of one or more interventions[54]. Disease-based registries

facilitate studying the full disease course including the untreated population and treatment sequences[55].

The primary goal of patient registries is to monitor and evaluate patient care. Outcomes of patient registries can be used in the development of clinical guidelines. The data items included in the patient registries are dependent of the goal, but generally comprehend patient, process and outcome data[56].

In order to evaluate quality of care in CRPC we set up the "Castration-resistant Prostate cancer RegIstry: an observational study in the Netherlands" (CAPRI) which is an investigator-initiated, population-based registry in 20 Dutch hospitals. The objective of CAPRI is to investigate treatment patterns, resource use and outcomes of CRPC-treatments in daily practice. CAPRI is registered in the Dutch Trial Registry as Trial NL3440 (NTR3591). Before the start of the study, 20 hospitals were selected based on geographical spread and type of hospital (11 large teaching hospitals, five general hospitals, and four academic hospitals). Data collection started after approval by the local medical ethics committee and hospital board, and data extracted from the medical files included prostate cancer history, patient and disease characteristics at CRPC-diagnosis and at the start of systemic treatment, use of systemic treatments, treatment response, serious adverse events (SAEs), and resource use. Patients were retrospectively included when diagnosed with CRPC between January 2010 to December 2015 according to the EAU-definition or according to their treating physician. All data have been regularly updated for all patients until database cut-off (i.e. December 2017).

THESIS OUTLINE

In this thesis we investigated the dimensions of quality of care in the management of CRPC throughout the different chapters. The results of this thesis can add real-world results to existing evidence and aid in creating and optimizing care in CRPC patients. Prior to assessing the dimensions of quality of care we highlighted differences in outcomes between trial and real-world populations using cabazitaxel as an example (Chapter 2).

The first dimension we assessed was effectiveness in general based on two outcome measures: overall survival (Chapter 3) and health-related quality of life (Chapter 4). Moreover, effectiveness was discussed for specific treatments: sequential abiraterone and enzalutamide treatment (Chapter 5) and radium-223 (Chapter 6).

The second dimension, safety, was addressed using the prevalence of symptomatic skeletal events in a treated CRPC-population as an outcome (Chapter 7).

The dimension "patient-centeredness" is important in all chapters, but we put special emphasis on this dimension in Chapters 8 (patient selection for radium-223), 9 (additional value of a third LPD) and 10 (care in the end-of-life phase).

The last chapter (Chapter 11) provides an overview of the value of RWE in evaluating quality of health care systems, but also focuses on the possibilities to asses health system performance as a whole. We will also propose adaptations needed in future registries to continuously monitor the impact of new drugs on the quality of care in CRPC-patients.

2

Second-line cabazitaxel treatment in CRPC: clinical trials compared to standard of care

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Clinical Genitourinary Cancer 2019;17(5):e946-e956

ABSTRACT

In the Dutch CAPRI registry, cabazitaxel treatment as the standard of care and in trials was analysed. Patients treated with cabazitaxel in trials were fitter and showed outcomes comparable to registration trials. Conversely, those treated in daily practice showed features of more aggressive disease and worse outcome. This may be explained by a worse prognosis at cabazitaxel initiation.

Background: Cabazitaxel has been shown to improve overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients after docetaxel in the TROPIC trial. However, trial populations may not reflect the real-world population. We compared patient characteristics and outcomes of cabazitaxel within and outside trials (standard of care, SOC).

Design, setting and participants: mCRPC patients treated with cabazitaxel directly after docetaxel therapy before 2017 were retrospectively identified and followed to 2018. Patients were grouped on the basis of treatment within a trial or SOC. Outcomes included OS and prostate-specific antigen (PSA) response.

Results: From 3,616 patients in the CAPRI registry, we identified 356 patients treated with cabazitaxel, with 173 patients treated in the second line. Trial patients had favourable prognostic factors: fewer symptoms, less visceral disease, lower lactate dehydrogenase, higher haemoglobin, more docetaxel cycles, and longer treatment-free interval since docetaxel therapy. PSA response (≥ 50% decline) was 28% versus 12%, respectively (p=0.209). Median OS was 13.6 versus 9.6 months for trial and SOC subgroups, respectively (hazard ratio=0.73, p=0.067). After correction for prognostic factors, there was no difference in survival (hazard ratio=1.00, p=0.999). Longer duration of androgen deprivation therapy treatment, lower lactate dehydrogenase, and lower PSA were associated with longer OS; visceral disease had a trend for shorter OS.

Conclusions: Patients treated with cabazitaxel in trials were fitter and showed outcomes comparable to registration trials. Conversely, those treated in daily practice showed features of more aggressive disease and worse outcome. This underlines the importance of adequate estimation of trial eligibility and health status of mCRPC patients in daily practice to ensure optimal outcomes.

INTRODUCTION

The combination of docetaxel plus prednisone remains a recommended first-line therapy for symptomatic metastatic castration-resistant prostate cancer (mCRPC) patients who are fit to receive chemotherapy[24,57]. In patients who experienced disease progression during or after treatment with docetaxel plus prednisone, the efficacy of cabazitaxel plus prednisone was superior to mitoxantrone plus prednisone in terms of overall survival (OS), as shown in the TROPIC trial[27]. In a comparable population, abiraterone plus prednisone, enzalutamide, and radium-223 were shown to improve OS to a similar extent compared to placebo[28–30]. Results of prospective randomized trials on treatment sequences in post-docetaxel patients are lacking. Moreover, retrospective series fail to show clear hints for optimal sequencing[58]. This led to the situation that decisions on post-docetaxel treatment are made by clinicians and patients without high-level evidence informing the decision.

The benefits established in efficacy trials can frequently not be demonstrated in clinical practice at the community level[59]. The clinical effectiveness of cabazitaxel is less well known. Median OS (mOS) in retrospective studies is shorter than in the interventional TROPIC, PROSELICA, and AFFINITY trials (real-world mOS of 7.0-12.7 months vs. trial mOS of 13.4-15.1 months, respectively)[27,60–64]. However, subgroups of patients treated with an extra life-prolonging drug (LPD) in third-line (post-cabazitaxel) therapy do better with mOS, reaching 18.2 to 22.7 months[62,65–67].

Patients in clinical trials are typically selected according to strict eligibility criteria, with the aim to include a homogeneous and fit population[68]. Furthermore, clinical trial recruitment tends to concentrate in selected hospitals with an experienced clinical research team. Trial protocols optimize baseline monitoring, treatment evaluation, and treatment compliance. Real- world treatment lacks eligibility criteria and is provided in all hospitals, regardless of clinical trial experience. Real-world patients differ from trial patients and typically include older patients and patients with more comorbidities[41]. Real-world practice may also be variable in differential monitoring, compliance, (budget) constraints, and increased treatment options over time[68]. We have shown that patients who are treated in trials during the course of CRPC differ from patients who are treated outside the context of a clinical trial with respect to baseline prognostic variables at CRPC diagnosis, treatment, and outcomes[41]. Previous single-centre reports have shown differences in clinical trial and real-world populations[69] as well as differential outcomes for docetaxel treatment in CRPC[69,70].

In daily practice, it is challenging to optimize treatment efficacy by selecting the right patient for the right treatment in the right sequence. Moreover, it is challenging to extrapolate trial eligibility and results to a real-world population. The objective of this study was to compare patient characteristics, treatment, and outcomes of patients treated

with cabazitaxel in second-line therapy, both in clinical trials and outside clinical trials (standard of care, SOC) in our multicentre observational CAPRI registry.

METHODS

The study design, setting, participants, follow-up, and data collection of the CAPRI registry have been described in detail elsewhere[41]. In short, CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated observational multicentre cohort study in 20 hospitals in the Netherlands. Data collection started after approval by the local medical ethics committee and hospital board. Patients were retrospectively included from January 1, 2010, and data have been regularly updated for all patients from 2013 to 2018. The study population was an estimated 20% sample of all CRPC patients in the Netherlands in the study period. The study was registered in the Dutch Trial Registry as NTR3591.

Objective

Our objective was to assess the differences in patient characteristics, number of treatment cycles, prostate-specific antigen (PSA) response, and OS of patients treated with cabazitaxel in second-line mCRPC, defined as therapy provided directly after docetaxel regardless of pre-docetaxel treatment, both in clinical trials and outside clinical trials (SOC).

Participants

CRPC patients from the CAPRI registry diagnosed before January 1, 2016, and treated with docetaxel for mCRPC, followed by second-line cabazitaxel before January 1, 2017, were included in our analysis. If a patient was enrolled onto a clinical trial with cabazitaxel during the follow-up period, the patient was assigned to the trial subgroup; otherwise, the patient was assigned to the SOC-subgroup. Patients not treated with docetaxel for CRPC were excluded.

Follow-up and data collection

Database cut-off was set on December 31, 2017. Prognostic parameters were retrospectively registered by trained data managers and included age, Charlson comorbidity index, Gleason sum score, time receiving androgen deprivation therapy (ADT), alkaline phosphatase, lactate dehydrogenase (LDH), prostate specific antigen (PSA), haemoglobin, Eastern Cooperative Oncology Group performance status, presence of visceral disease, opioid use, and symptoms. Time of response to ADT was defined as the time from start of ADT to diagnosis of CRPC.

Serious adverse events included hospital admissions and death within 30 days of last cabazitaxel administration.

Statistical analysis

The sample size was not based on power calculations. Descriptive statistics were used. Differences in subgroups were tested for significance by either the chi-square test (categorical variables) or the Mann-Whitney U test (continuous variables). OS from start of cabazitaxel treatment to database cut-off was analysed by Kaplan- Meier methods and Cox regression analyses. Differences were considered statistically significant at $p \leq 0.05$.

For PSA response, we report the maximum decline from baseline, and in case no decline occurred, we report the response at 12 weeks (i.e. conforming to Prostate Cancer Clinical Trials Working Group 3 [PCWG3] guidelines[71]) or at last cycle (if treatment duration < 12 weeks). In our analysis, PSA response was unconfirmed, in contrast with PCWG3 guidelines. Patients with a PSA increase within 12 weeks without subsequent decrease were excluded from response analysis. Dose reduction was defined as a reduction of 20% or more; dose delay was defined as > 25 days between subsequent cycles. Severe adverse events only included hospital admissions (regardless of reason of admission) and deaths (regardless of cause of death) before 30 days after the last cabazitaxel infusion.

For imputation of missing baseline characteristics, multiple imputation by Monte Carlo Markov chain method was used. For statistical analyses, SPSS Statistics 22 (IBM, Armonk, NY) was used.

RESULTS

Population

We identified 406 patients treated with cabazitaxel after docetaxel in the study period; 2 patients were excluded because docetaxel was provided for hormone-sensitive disease and not mCRPC. A total of 173 patients were treated with cabazitaxel in the second line (i.e. after docetaxel). Of these 173 patients, 64 (37%) were treated within a trial (46, 11, 6, and 1 patients in the CABARESC, PROSELICA, Re-Cab, and CABENZA trials, respectively). A total of 184 of 406 patients received cabazitaxel in the third line (SOC n=141, trial n=43), and 47 patients received cabazitaxel in the fourth line or higher (SOC n=45, trial n=2) and were excluded from this analysis.

Median follow-up was 9.9 months (interquartile range, 5.2-18.0 months). A total of 149 patients (86%) had died at database cut-off. Baseline characteristics and treatment for CRPC are summarized in Table 2.1 and 2.2. Patients treated in trials had a more favourable prognostic profile compared to SOC patients (significantly higher haemoglobin, lower LDH, less visceral metastases and fewer symptoms, and a trend for longer time receiving

ADT). Trial patients also received more docetaxel cycles and had a longer interval between last docetaxel dose and start of cabazitaxel. Cabazitaxel trial patients participated significantly more often in other clinical trials than SOC patients. Subsequent treatment after cabazitaxel included significantly more abiraterone in trial patients (55% vs. 34%), whereas treatment with enzalutamide (22% vs. 32%), radium-223 (11% vs. 11%), and best supportive care (27% vs. 35%) was not significantly different.

Table 2.1 | Baseline characteristics at initiation of cabazitaxel therapy

		Cabazitaxel 2nd line (N=173)			TROPIC
		SOC (N=109)	**Trial (N=64)**	**p**	**CAB[a] (N=378)**
Age (years)	median (IQR)	68 (64-72)	67 (64-72)	0.502	68 (62-73)
	≥75 years (%)	17	13		18
Charlson comorbidity index (%)	6	63	75	0.112	NR
	7-8	32	25		
	9-10	4	0		
	>10	1	0		
Gleason score (%)	≤7	29	38	0.149	NR
	8-10	66	52		
	unknown	5	11		
Period of response on ADT (mo)	median (IQR)	11 (7-16)	11 (6-23)	0.780	NR
Period on ADT (mo)	median (IQR)	25 (18-37)	30 (19-45)	0.091	NR
ALP (U/L)	median (IQR)	222 (100-360)	192 (97-366)	0.799	NR
	missing (%)	18	11		
PSA (µg/L)	median (IQR)	200 (65-567)	209 (79-500)	0.711	144
	missing (%)	12	8		1
Hb (mmol/L)	median (IQR)	7.1 (6.3-7.8)	7.7 (6.7-8.1)	0.029*	NR
	missing (%)	17	11		
LDH (U/L)	median (IQR)	328 (252-504)	268 (209-397)	0.010*	NR
	missing (%)	26	14		
ECOG PS (%)	0	16	23	0.186	ECOG 0-1: 93%
	1	49	56		
	>1	9	3		NR
	missing	27	17		NR
Visceral disease (%)	no	29	45	0.038*	NR
	yes	19	11		25%
	missing	52	44		NR
Opioid use (%)	no	23	41	0.140	NR
	yes	28	27		
	missing	50	33		
Symptoms (%)	no	6	17	0.033*	NR
	yes	78	72		
	missing	16	11		

* significant at p-value <0.05; [a] cabazitaxel treatment arm in TROPIC.
Baseline period defined as 42 days before to 7 days after start of cabazitaxel therapy. Total percentages may not equal 100 because of rounding.
Abbreviations: SOC, standard of care; CAB, cabazitaxel; IQR, interquartile range; NR, not reported; ADT, androgen deprivation therapy; mo, months; ALP, alkaline phosphatase; Hb, haemoglobin, PSA, prostate specific antigen; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group Performance Score.

Table 2.2 | Treatment characteristics before docetaxel and after cabazitaxel

		Cabazitaxel 2nd line (N=173)			TROPIC
		SOC (N=109)	Trial (N=64)	p	CAB[a] (N=378)
Pre-docetaxel therapy (%)	abiraterone	10	2	0.099	NR
	enzalutamide	9	3	0.131	
	radium-223	3	0	0.181	
	anti-androgen	38	47	0.232	
	estramustine	0	2	0.191	
	ketoconazole	1	0	0.442	
	prednisone	1	0	0.442	
	study drug	3	11	0.026*	
DOC cycles	median (IQR)	7 (5-10)	10 (7-10)	0.002*	NR.
	missing (%)	1	3		
Time last DOC to progression on DOC (mo)	median (IQR)	1.2 (0.6-3.6)	2.3 (0.9-4.6)	0.097	0.8 (0.0-3.1)
	<1 (valid %)	48	33		
	missing (%)	8	9		
Time since last DOC (mo)	median (IQR)	2.2 (0.9-4.7)	3.9 (2.0-6.0)	0.001*	NR
	<6 (valid %)	86	74		
	missing (%)	5	5		
Type of progression on DOC (%)	PSA	84	91	0.095	NR
	missing	6	6		
	radiologic	37	44	0.761	
	missing	53	42		
	clinical	58	53	0.704	
	missing	16	19		
Post-cabazitaxel therapy (%)	docetaxel	2	5	0.280	10
	mitoxantrone	1	0	0.442	30
	abiraterone	34	55	0.005*	-
	enzalutamide	32	22	0.295	-
	radium-223	11	11	0.920	-
	PSMA-ligand	2	0	0.552	-
	study drug	1	16	<0.001*	-
	no treatment	35	27	0.258	NR
Total LPD duration in days (median, IQR)	Total	328 (221-508)	365 (269-534)	0.156	NR
	ART	185 (113-273)	152 (91-253)		
	Taxane	218 (134-305)	268 (217-357)		
	Radium	102 (52-148)	143 (72-217)		
Number of LPDs (%)	2	26	27	0.672	NR
	3	48	56		
	>3	27	19		
	median (IQR)	3 (2-4)	3 (2-3)		
	range	2-6	2-6		
Number of treatments (total)	median (IQR)	3 (3-4)	4 (3-5)	0.217	NR
	range	2-8	2-7		

* significant at p-value <0.05; [a] cabazitaxel treatment arm in TROPIC.

LPD treatment included docetaxel, abiraterone acetate plus prednisone, cabazitaxel, enzalutamide, and radium-223.

Abbreviations: SOC, standard of care; CAB, cabazitaxel; DOC, docetaxel; IQR, interquartile range; NR, not reported; mo, months; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen; LPD, life-prolonging drug; ART, androgen-receptor targeting therapy (i.e. abiraterone acetate plus prednisone or enzalutamide).

The number of total treatment lines was not significantly different in trial patients and SOC patients (4 vs. 3, p=0.217), and the total LPD treatment duration expressed as the sum of all LPD treatment durations in days was 365 versus 328 days (p=0.156). LPD treatment with pre-docetaxel was infrequent.

Treatment outcomes

Treatment intensity of cabazitaxel was numerically higher in trials compared to SOC, expressed by median number of cabazitaxel cycles (5 vs. 4, respectively; p=0.051), proportion of patients reaching 10 therapy cycles (24 vs. 14%, respectively), and cumulative dose (228 vs. 165 mg; p=0.026) (Table 2.3).

Serious adverse events (hospitalization and death) did not differ significantly between trial and SOC patients (Table 2.3). In the trial patients, dose adjustments were better documented (missing data, 9% vs. 31% in SOC patients). However, dose reduction or dose delay did not significantly differ between the groups.

In trial and SOC patients, PSA response (≥ 50% decline) was 28% versus 12% (p=0.209). In patients receiving cabazitaxel directly after docetaxel, mOS was 13.6 and 9.6 months for trial patients and SOC, respectively (hazard ratio 0.732; 95% confidence interval, 0.524-1.022; p=0.067) (Table 2.4, Figure 2.1). The patients who were treated with at least an additional LPD after cabazitaxel therapy had a mOS from the first cabazitaxel treatment of 15.1 months, versus 4.6 months for patients who only received best supportive care after cabazitaxel treatment.

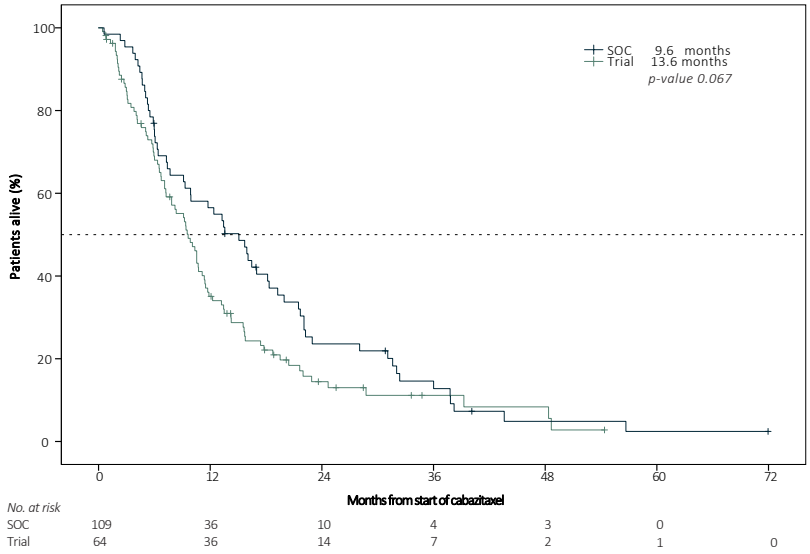

Figure 2.1 | Overall survival for recipients of second-line cabazitaxel treatment (univariable analysis)
Abbreviations: SOC, standard of care.

Table 2.3 | Treatment characteristics of cabazitaxel

		Cabazitaxel 2nd line			TROPIC
		SOC (N=104[a])	Trial (N=64)	p	CAB[b] (N=378)
Cycles (n)	median (IQR)	4 (3-6)	5 (3-9)	0.051	6 (3-10)
	≥10 (%)	14	24		28
	range	1-11	1-12		NR
	missing (%)	4	3		2
Dose adjustment (%)	no reduction or delay	36	4	0.743	
	dose mitigation	33	44		
	dose reduction	*15*	*20*		NR
	dose delay	*26*	*38*		9
	missing	31	9		
G-CSF support (%)	none	80	81	0.534	NR
	pegfilgastrim	3	5		
	missing	17	14		
Cumulative dose (mg)	median (IQR)	16 (126-300)	228 (144-422)	0.026*	NR
	missing (%)	36	28		
Severe adverse events (%)	none	30	33	0.967	
	any	44	48		
	hospital admission	*44*	*48*		NR
	death	*8*	*3*		5
	missing	26	19		
Reason of discontinuation (%)	PD	72	50	0.011	48
	patient preference	2	0		2
	toxicity	4	14		18
	death	5	2		
	max cum dose	8	19		28
	other	2	2		
	missing	8	14		

* significant at p-value <0.05; [a] 5 patients censored; [b] cabazitaxel treatment arm in TROPIC.
Treatment outcomes are censored if patient is alive or lost to follow-up at database cutoff and time between last cabazitaxel treatment and end of follow-up is shorter than 30 days. Severe adverse events only included hospital admissions (regardless reason of admission) and death (regardless cause of death) before 30 days after cabazitaxel infusion. Dose mitigation means either reduction, delay or both.
Abbreviations: SOC, standard of care; CAB, cabazitaxel; DOC, docetaxel; IQR, interquartile range; NR, not reported; G-CSF, granulocyte-colony stimulating factor; PD, progression of disease.

Table 2.4 | Treatment outcomes

		Cabazitaxel 2nd line			TROPIC
		SOC (N=109)	Trial (N=64)	p	CAB[a] (N=378)
PSA response	evaluable pts (n, %)	69 (63%)	47 (73%)	0.209	329 (87%)
	PSA decline ≥50% (valid %)	12%	28%		39%
Follow-up	median (IQR)	9.2 (4.2-14.9)	13.6 (6.0-22.2)		12.8 (7.8-16.9)
	events (deaths, %)	90 (83%)	59 (92%)		234 (62%)
Overall survival	median (95% CI)	9.6 (7.8-11.4)	13.6 (9.4-17.7)	0.067	15.1 (14.1-16.3)

[a] cabazitaxel treatment arm in TROPIC.
Abbreviations: SOC, standard of care; CAB, cabazitaxel; PSA, prostate-specific antigen; IQR, interquartile range; CI, confidence interval.

Table 2.5 | Univariable and multivariable Cox proportional hazard analysis for overall survival for cabazitaxel second-line therapy

		Univariable analysis of actual data				Multivariable analysis of pooled imputed data		
		n/N[a]	HR	95% CI	p	HR	95% CI	p
Age	cont.	149/173	1.01	0.99-1.01	0.414	1.02	0.98-1.05	0.349
Charlson comorbidity index		149/173						
	7-8 vs 6		0.97	0.68-1.39	0.884			
	9-10 vs 6		0.80	0.25-2.53	0.704			
	>10 vs 6		2.54	0.35-18.41	0.356			
Gleason sumscore	8-10 vs ≤7	138/161	1.28	0.89-1.83	0.181	1.10	0.72-1.69	0.654
Period on ADT (mo)	cont.	149/173	0.98	0.98-0.99	0.001*	0.99	0.98-0.99	0.033*
ALP (U/L)	cont.	129/146	1.00	1.00-1.00	0.241	1.00	0.99-1.00	0.589
PSA (ug/L)	cont.	134/155	1.00	1.00-1.00	0.027*	1.00	1.00-1.00	0.046*
Hb (mmol/L)	cont.	131/147	0.78	0.66-0.93	0.005*	1.01	0.82-1.24	0.957
LDH (U/L)	cont.	121/136	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	0.039*
ECOG PS		118/133						
	1 vs 0		1.57	1.01-2.44	0.047*	1.04	0.63-1.73	0.878
	>1 vs 0		2.23	1.03-4.83	0.042*	1.03	0.43-2.49	0.945
Visceral disease	yes vs no	76/88	3.10	1.87-5.15	<0.001*	2.14	0.88-5.25	0.086
Opioid use (%)	yes vs no	88/98	1.97	1.25-3.11	0.003*	1.51	0.76-2.97	0.215
Symptoms (%)	yes vs no	132/149	1.93	1.14-3.28	0.015*	1.52	0.81-2.86	0.187
Mo. since last DOC	cont.	143/166	0.90	0.85-0.96	0.001*	0.96	0.89-1.04	0.275
DOC cycles	cont.	146/170	0.94	0.88-0.99	0.044*	0.97	0.90-1.05	0.409
Trial	yes vs no	149/173	0.73	0.52-1.02	0.067	1.00	0.69-1.45	0.999

* significant at p-value <0.05; [a] number of patients with event (i.e. death) of total included in univariable analysis.
Abbreviations: HR, hazard ratio; CI, confidence interval, ADT, androgen deprivation therapy; mo, months; ALP, alkaline phosphatase; PSA, prostate specific antigen; Hb, haemoglobin; ECOG PS, Eastern Cooperative Oncology Group Performance Score; DOC, docetaxel.

Only 42 of 173 patients had no missing data for multivariate Cox regression analysis. After imputation of missing values in all patients, in a multivariate analysis trial, participation was not prognostic for survival in the pooled data (hazard ratio 1.00; 95% confidence interval, 0.69-1.45; p=0.999). Longer time receiving ADT, lower PSA, and lower LDH were prognostic for longer OS, and visceral disease had a trend for shorter survival (Table 2.5).

DISCUSSION

Differential outcomes

To our knowledge, this is the first study comparing trial patients and SOC patients treated with cabazitaxel after docetaxel in a large contemporary observational study. In this large and mature real-world cohort, patients treated with second-line cabazitaxel in a clinical trial had a mOS that was in agreement with the mOS of patients in the TROPIC trial (13.4 vs. 15.1 months)[27]. The eligibility criteria of these trial patients (enrolled onto the PROSELICA, Re-Cab, CABARESC, and CABENZA trials) were similar to the TROPIC trial, with minor differences with respect to Eastern Cooperative Oncology Group performance score and estimated life expectancy (Table 2.6)[60,72]. Although the mOS in trial patients confirms the survival outcome of the TROPIC trial, the SOC patients had a trend to shorter OS in first-line therapy after docetaxel (9.6 vs. 13.4 months).

Table 2.6 | Key eligibility criteria in trials

		TROPIC	PROSELICA	CABARESC	Re-Cab	CABENZA
Reference		NCT00417079	NCT01308580	NTR2991	NTR3233	NTR5164
Type		Phase 3 open-label randomised	Phase 3 open-label randomised	Phase 2 open-label randomised	Phase 1/2 open-label randomised	Single-arm crossover study
Inclusion	Life expectancy	>2 mo	>6 mo	any	>3 mo	any
	ECOG PS	0-2	0-2	0-1	0-1	0-1
	Adequate organ function	yes	yes	yes	yes	yes
Exclusion	CNS metastases	yes	yes	yes	no	yes
CAB mOS	25mg/m^2 arm	15.1	14.5	NA	NA	NA

[a] ClinicalTrials.gov NCT identifier and trialregister.nl (NTR number); results published[27,60,72].
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Score; CNS, central nervous system; CAB, cabazitaxel; mOS, median overall survival; NA, not applicable.

Reasons for observed difference between trial and SOC patients

Possible reasons for the differential survival of patients in the trial and SOC subgroups include differential prognostic baseline characteristics (introduced by strict eligibility criteria of trials), cabazitaxel treatment adherence (influenced by a trial protocol), exposure to other LPDs, and the Hawthorne effect (changes in behaviour or outlook associated with being under observation)[73,74].

After correction for baseline differences, time receiving ADT, PSA, and LDH were independent prognostic factors for survival, whereas treatment in a trial was not. The exclusion of patients with poorer performance status and comorbidities from clinical

trials prevented the enrolment of sicker patients and subsequently limited early cancer deaths[68]. Indeed, trial patients had significantly higher haemoglobin levels, lower LDH levels, fewer visceral metastases, and fewer symptoms compared to SOC patients. At a closer look, the cabazitaxel OS curves in first-line post-docetaxel separate directly from the start of treatment, possibly reflecting the difference in prognostic baseline parameters.

PSA response was numerically lower, but not statistically significant, for SOC patients (12%) versus trial patients (28%; p=0.209). However, the observed PSA response appears lower than in the TROPIC and PROSELICA trials (39% and 43%, respectively). In particular, the low PSA response (12%) in the SOC subgroup may be an indicator for suboptimal selection of patients for cabazitaxel treatment. In the absence of a study protocol, timing of PSA measurement may not have been at regular intervals, leading to more missing data, as seen in the SOC patients, and therefore may have negatively influenced PSA response.

The number of docetaxel cycles has been shown to affect survival in small retrospective series, which suggests that premature discontinuation is associated with shorter OS and that maximizing docetaxel exposure may lead to increased OS. However, to our knowledge, immortal time bias was not accounted for in these studies, possibly leading to overestimation of the effect[75–77]. In a retrospective analysis of 2 clinical trials including TAX-327, no OS benefit was detected in patients receiving more than 10 cycles of docetaxel. However, receiving fewer less than 10 cycles was shown to negatively affect patients without progressive disease[78]. In a post hoc analysis of the MAINSAIL trial, an independent effect on OS by the number of docetaxel cycles administered was shown[79]. It had previously been hypothesized that administration of cabazitaxel until progression, instead of the maximum of 10 cycles in the TROPIC trial, may have a positive effect on OS[80]. The median number of cabazitaxel cycles in the TROPIC and PROSELICA trials was 6 and 7, compared to 5 in the trial subgroup and 4 in the SOC subgroup (p=0.051). Unfortunately, the reason of discontinuation is not well documented, and missing data may bias the results. We hypothesize that worse prognostic baseline characteristics, in particular low haemoglobin, may play a role. It remains unclear whether treatment adherence affects outcomes, including survival. This is difficult to analyse, mainly because of methodologic reasons such as immortal time bias. However, we acknowledge the possibility that the low number of cycles may have negatively influenced survival outcomes.

Although infrequent, patients in the SOC subgroup were numerically more often treated with LPD before docetaxel, leading to potential poorer outcomes because of cabazitaxel treatment in a later line in the course of mCRPC. However, the median number of 3 LPD treatments in both groups and the total duration of LPD treatment in days did not differ.

What is known already

Data on real-world cabazitaxel use are increasingly reported. In several expanded-access and compassionate-use programs, inclusion and exclusion criteria still apply, and therefore, reports on these programs still have limited external validity on real-world patients[81–84]. Published reports on real-world cabazitaxel outcomes are summarized in Table 2.7. In retrospective studies, differential mOS is observed with regard to the registration trials (10.0-12.1 vs. 13.4- 15.1 months, respectively)[27,61,85]. Direct comparisons between trial patients and real-world patients are lacking, and to our knowledge, our analysis is the first to compare trial and SOC patients treated with cabazitaxel.

In retrospective studies, the range of mOS is broad (7.0-22.7 months), and patients treated with 3 LPD lines (docetaxel, cabazitaxel, and an extra line) have better mOS than patients treated with 2 LPD lines (docetaxel and cabazitaxel). In our study, patients treated with LPD after cabazitaxel had a mOS from the first cabazitaxel treatment of 15.1

Table 2.7 | Overview of published observational studies on second-line cabazitaxel treatment

Study	Year	N and sequence	Type of study, period	Cycles (median)	mOS (mo.)
Wissing[65]	2015	63 DCA	Multicentre retrospective, 2009-2012	7	19.1 DCA
Sonpavde[62]	2015	54 DC, 77 DCA	Multicentre retrospective, 2011-2012	5 / 6	7.0 DC, 18.2 DCA
Moriceau[63]	2016	24 DC, 17 DAC	Single centre retrospective, 2011-2014	5	11.9 DC, 12.5 DAC
Hofheinz[80]	2016	527	Multicentre prospective QoL study, 2011-2014	6	16.8
Cicero[86]	2017	30	Single centre retrospective, 2013-2016	8	14.8
Zschäbitz[87]	2017	18 DC, 5 XXC	Two-centre retrospective, 2011-2016	5	10.0 (all patients n=69; no difference between groups based on CAB line)
Suner[64]	2016	103	Multicentre retrospective, 2012-2014	5	10.6
Carles[88]	2018	160 DC, 23 XXC	Multicentre prospective QoL study, 2012-2016	6	13.2 (all patients n=189)
Delanoy[66]	2018	158 DCX	Multicentre retrospective, 2012-2016	7	21.0 DCX
Angelergues[67]	2018	267 DC, 124 DCX	Multicentre retrospective, 2012-2016	6 / 7	12.7 DC, 22.7 DCX
CAPRI (this report)	2019	55 DC, 118 DCX	Multicentre retrospective 2010-2018	4	4.6 DC, 15.1 DCX

Abbreviations: mOS, median overall survival; mo, months; D, docetaxel, C, cabazitaxel, A, abiraterone acetate plus prednisone, QoL, quality of life; X, any treatment.

months, versus 4.6 months for patients who only received best supportive care after cabazitaxel treatment. In reporting both trial and real-world outcomes, it is important to report the sequence and line of treatment as well as previous and subsequent treatments.

Limitations

Because of the retrospective nature of our registry database, the sample size was not based on power calculations but on patients available who matched the study population criteria. Furthermore, our results are limited by missing data because of the retrospective nature of our study. For multivariable analysis, we could overcome this limitation by multiple imputation methods. The comparison of SOC and trial patients is limited by the nonrandomized subgroups, reflecting trial availability and the choices of patients and physicians in real-world practice. Our results are therefore hypothesis generating.

CONCLUSION

We emphasize the important differences between patients treated in clinical trials and those treated in real-life practice. Patients treated with cabazitaxel in clinical trials were fitter and showed outcomes comparable to registration trials. Conversely, those treated in daily practice showed features of more aggressive disease and worse outcome. This underlines the importance of an adequate estimation of the trial eligibility and health status of mCRPC patients in daily practice to ensure optimal outcomes.

3

The effects of new life-prolonging drugs for mCRPC patients in a real-world population

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Prostate Cancer and Prostatic Diseases 2021; 24(3):871-879

ABSTRACT

Background: In 2004 docetaxel was the first life-prolonging drug (LPD) registered for metastatic castration-resistant prostate cancer (mCRPC) patients. Between 2011 and 2014 new LPDs for mCRPC (cabazitaxel, abiraterone, enzalutamide and radium-223) were introduced in the Netherlands.

The objective of this study is to assess the impact of the introduction of new LPDs on treatment patterns and overall survival (OS) over time.

Design, setting and participants: CRPC patients diagnosed in the years 2010-2016 in the observational, retrospective CAPRI registry (20 hospitals) were included and followed up to 2018. Two subgroups were analysed: treatment-naïve patients (subgroup 1, n=3,600) and post-docetaxel patients (subgroup 2, n=1,355).

Results: In both subgroups, the use of any LPD increased: from 57% (2010-2011) to 69% (2014-2015) in subgroup 1 and from 65% (2011-2012) to 79% (2015-2016) in subgroup 2. Chemotherapy as first mCRPC-treatment (i.e. docetaxel) and first post-docetaxel treatment (i.e. cabazitaxel or docetaxel rechallenge) decreased (46-29% and 20-9% in subgroup 1 and 2, respectively), while the use of androgen-receptor targeting treatments (ART) increased from 11% to 39% and 46% to 64% in subgroup 1 and 2, respectively. In subgroup 1, median OS (mOS) from diagnosis CRPC increased from 28.5 months to 31.0 months (p=0.196). In subgroup 2, mOS from progression on docetaxel increased from 7.9 months to 12.5 months (p<0.001). After multiple imputations of missing values, in multivariable cox-regression analysis with known prognostic parameters, the treatment period was independent significant for OS in subgroup 1 (2014-2015 vs 2010-2011 with HR 0.749, p<0.001) and subgroup 2 (2015-2016 vs 2011-2012 with HR 0.811, p=0.037).

Conclusions: Since 2010, a larger proportion of mCRPC patients was treated with LPDs, which was related to an increased mOS.

INTRODUCTION

Prolonging overall survival (OS) is an important objective of cancer treatment. Data from cancer registries show that the 5-year survival of all types of cancer increased from 50% in 1991-1996 to 65% in 2011-2016 in the Netherlands[89]. In Europe, the largest increases in cancer survival included prostate cancer survival (age-standardized five-year relative survival increased from 73% to 82% from 1999-2001 to 2005-2007)[90,91]. Five-year survival is different per stage group in prostate cancer, ranging from 100% for stage I to 51% for stage IV (TNM seventh edition) in the period 2010-2015 in the Netherlands[17]. Cancer survival may be increased by improved early detection and/or more effective therapy; however, several forms of bias may influence survival results, including lengthy-time and lead-time bias[89–91].

Prostate cancer that progresses despite androgen deprivation therapy, either metastatic (m) or non-metastatic (nm), is defined as castration-resistant prostate cancer (CRPC). In 2004 docetaxel was the first available life-prolonging drug (LPD) for mCRPC, with a significant increase of median OS (mOS)[24]. Between 2011 and 2014 new LPD for mCRPC (cabazitaxel[27], abiraterone[92,93], enzalutamide[29,31] and radium-223[30]) were introduced in the Netherlands. Sipuleucel-T was not available in these years in the Netherlands. The reimbursement of new oncolytic follows published positive treatment outcomes, regulatory drug approval, and market authorization. In the Netherlands, the use of these oncolytic is generally conditional on positive guidance by the Dutch Society of Medical Oncology (NVMO) committee 'Beoordeling van Oncologische Middelen (Appraisal of oncolytic)' (CieBOM). The publication dates of the positive guidance by the European Medicines Agency and CieBOM on the aforementioned LPD are shown in Supplementary Table S3.1.

Registration is based on the results of trials. Trial populations are subject to selection, typically enrolling younger patients with less comorbidity and features of less aggressive disease compared to real world populations[41,94]. These differential characteristics may lead to differential outcomes, raising the question what the effect is of these LPDs on OS in mCRPC. Furthermore, real world data on treatment pattern changes are scarce and limited to the first treatment after mCRPC diagnosis[95,96]. The impact of treatment pattern changes and outcomes are pivotal in the assessment of both clinical and economical effectiveness and efficacy.

The objective is to assess the impact of the introduction of new LPD treatments on treatment patterns and OS over time in a real-world population.

METHODS

The study design, setting, participants, follow up and data collection of the CAPRI registry have been described in more detail[41]. In short: CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multicentre cohort study in 20 hospitals in the Netherlands. Data collection started after approval by the local medical ethics committee and hospital board. Data have been regularly updated for all patients from 2013 to 2018. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Participants

Eligible patients had to be diagnosed with prostate cancer (defined as histologic confirmation of prostate cancer or as concluded by the treating doctor based on elevated prostate specific antigen (PSA) and metastatic pattern) and had disease progression despite androgen deprivation therapy (ADT). Disease progression was defined as in the European Urology Association (EAU) CRPC definition[23] or as progression according to the treating doctor. Anti-androgen therapy following progression on ADT was considered first-line systemic therapy for CRPC. CRPC patients were retrospectively included from 2010 to 2016. Patients treated with docetaxel in the hormone-sensitive phase were excluded from this analysis. The population is an estimated 20% sample of all CRPC patients in the Netherlands.

To assess temporal real world LPD treatment patterns, we analysed the first LPD treatment in both treatment-naïve CRPC patients (subgroup 1) and in post-docetaxel patients (subgroup 2).

Subgroup 1 included all patients diagnosed in 2010-2016, which were divided into groups based on the date of CRPC diagnosis (2010-2011, 2012-2013, and 2014-2015). Subgroup 2 included patients treated with docetaxel for mCRPC prior to July 2016 with progression during or after docetaxel after 13 December 2010 and before 1 January 2017. Year groups were created on the docetaxel-progression date (2011-2012, 2013-2014, and 2015-2016).

Statistics

The sample size was not based on power calculations. All patients diagnosed with CRPC in the participating hospitals were included in CAPRI. Descriptive statistics were used. Differences in subgroups were tested for significance by either the Chi-square test or Kruskall-Wallis test. OS from CRPC diagnosis and progression on docetaxel to database cut off was analysed by Kaplan-Meier methods and Cox regression analyses. Differences were considered of statistical significance at a p-value of 0.05 or less. For imputation of missing baseline characteristics, multiple imputations by the Monte Carlo Markov

Chain method were applied: the distribution of the observed data was used to estimate a set of plausible values for the missing data. The outcome variables OS time and end of follow-up state were included and used as indicators. Constraints for all imputed variables were defined based on the minimum and maximum values in the observed distribution. The variables period ADT to CRPC, PSA, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) were not normally distributed and transformed to approximate normality before imputation (either by taking the natural logarithm (period ADT to CRPC, PSA, ALP) or reciprocal transformation (LDH)) and after the imputation, we transformed the imputed values back to the original scale. Using the automatic imputation function, random components were incorporated into these estimated values to reflect their uncertainty. Five data sets were created and the estimates were combined in the pooled data to obtain the overall estimates and confidence intervals[97]. IBM SPSS Statistics version 22 was used for all statistical analyses.

RESULTS

From a total of 3,616 CRPC patients in the registry, 16 patients treated with docetaxel for the hormone-sensitive disease were excluded, resulting in 3,600 patients (subgroup 1). Median follow up from CRPC-diagnosis was 25.1 months. At the end of follow up, 415 (12%) patients were alive with a median follow up of 41.0 months (range: 24.1 to 95.3 months), 2,432 (68%) patients died and 753 (21%) were lost to follow up.

In total, 1,433 patients were treated with docetaxel before 1-7-2016. After exclusion of patients with progression in 2010 (n=29) or progression after 1-1-2017 (n=49), 1,355 patients were analysed in subgroup 2.

Treatment patterns

In subgroup 1 (i.e. treatment-naïve patients) any LPD treatment increased from 57% (2010-2011) to 69% (2014-2015), Supplementary Table S3.2A and Figure 3.1A. The use of docetaxel as the first LPD decreased from 46% (2010-2011) to 29% (2014-2015), while androgen-receptor targeting drugs (ART) increased from 11% (2010-2011) to 39% (2014-2015).

In subgroup 2 (i.e. post-docetaxel patients) LPD treatment increased from 65% (2011-2012) to 79% (2015-2016). Chemotherapy as first post-docetaxel treatment (either cabazitaxel or docetaxel rechallenge) decreased from 20% (2011-2012) to 9% (2015-2016); ART increased from 46% (2011-2012) to 64% (2015-2016) (Supplementary Table S3.2B and Figure 3.1B).

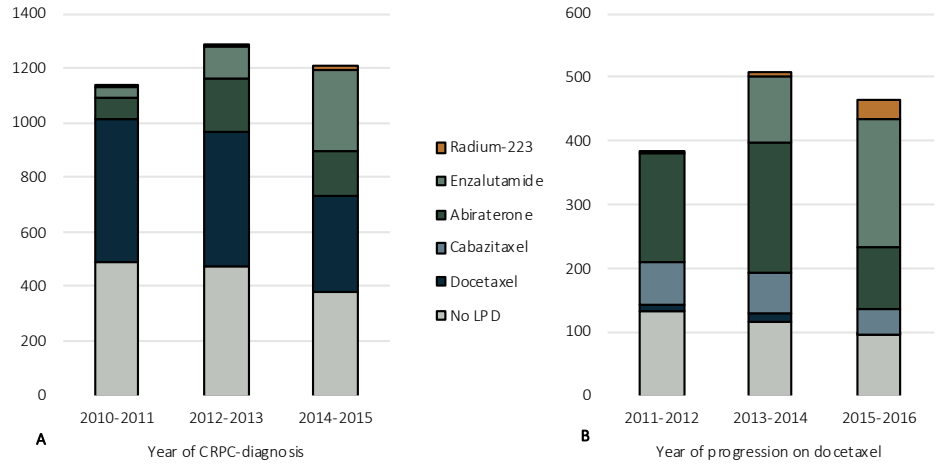


Figure 3.1 | (A) Number of first LPD-treatment after CRPC-diagnosis (subgroup 1). (B) Number of first LPD treatment after progression on docetaxel (subgroup 2).
Abbreviations: LPD, life-prolonging drug.

Baseline characteristics

In subgroup 1 during the CRPC-diagnosis years, CRPC patients showed a significant and gradual increase in age, Gleason sum score and ECOG performance score (ECOG PS), a significant increase in patients with visceral disease and a significant and gradual decrease in time from castration to CRPC diagnosis and LDH, but not PSA and ALP (Table 3.1A).

In subgroup 2, patients showed a significant and gradual increase in median age, time from castration to progression on docetaxel, time from last docetaxel to progression, number of docetaxel cycles, haemoglobin and patients with clinical progression during treatment periods (Table 3.1B). A gradual and significant decrease was shown in ALP, LDH and PSA. Missing data were especially frequent (sometimes >50%) in ECOG PS, LDH and visceral disease in both subgroups.

Overall survival

For all patients (n=3,600) the mOS was 29.6 months. In subgroup 1, the mOS was 28.5, 28.5 and 31.0 months for the CRPC-diagnosis 2010-2011, 2012-2013 and 2014-2015, respectively (p=0.196). Twelve-months and 24-months survival increased from 79% to 81% and 57% to 60%, respectively (Figure 3.2A). mOS in patients treated with LPD was 32.7 months versus 20.8 months for patients not treated with LPD (p<0.001). Univariate prognostic factors for survival were age, Charlson comorbidity score, Gleason sum score, time from ADT to CRPC, ALP, PSA, haemoglobin, LDH, ECOG PS, visceral disease, and pain and/or opioid use (Table 3.2A). Because only 223 patients had complete data,

Table 3.1A | Baseline characteristics at CRPC-diagnosis (subgroup 1)

		2010-2011	2012-2013	2014-2015	p
		N=1,140	N=1,249	N=1,211	
Age (years)	median (IQR)	74 (68-81)	75 (68-81)	76 (70-82)	<0.001*
	>75 years, %	49	51	56	
Charlson comorbidity index, %	6	60	61	63	0.794
	7-8	33	32	30	
	9-10	5	5	5	
	>10	2	2	2	
	unknown	0	0	<1	
Gleason score, %	≤7	39	33	31	<0.001*
	8-10	47	51	55	
	unknown	15	16	14	
Time from castration to CRPC (mo)	median (IQR)	15.9 (9-31)	15.2 (8-30)	14.2 (8-28)	0.011*
	unknown, %	1	<1	0	
ECOG PS, %	0	24	20	11	<0.001*
	1	22	17	13	
	2	3	4	4	
	>2	1	1	1	
	unknown	50	58	70	
ALP (U/L)	median (IQR)	105 (77-187)	105 (79-193)	108 (78-198)	0.878
	unknown, %	40	41	31	
Hb (mmol/L)	median (IQR)	8.1 (7.4-7.3)	8.0 (7.3-8.6)	8.0 (7.3-8.6)	0.247
	unknown, %	36	36	31	
PSA (µg/L)	median (IQR)	18 (6-67)	15 (6-55)	17 (5-63)	0.137
	unknown, %	4	3	2	
LDH (U/L)	median (IQR)	226 (188-329)	230 (191-313)	217 (186-268)	0.001*
	unknown, %	63	61	52	
Visceral disease, %	yes	4	3	4	0.047*
	no	18	16	12	
	unknown	78	81	85	
Pain and/or opioid use, %	yes	25	23	21	0.089
	no	42	33	16	
	unknown	33	44	63	

* significant at p-value <0.05.

Abbreviations: CRPC, castration-resistant prostate cancer; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ALP, alkaline phosphatase; Hb, haemoglobin, PSA, prostate specific antigen; LDH, lactate dehydrogenase.

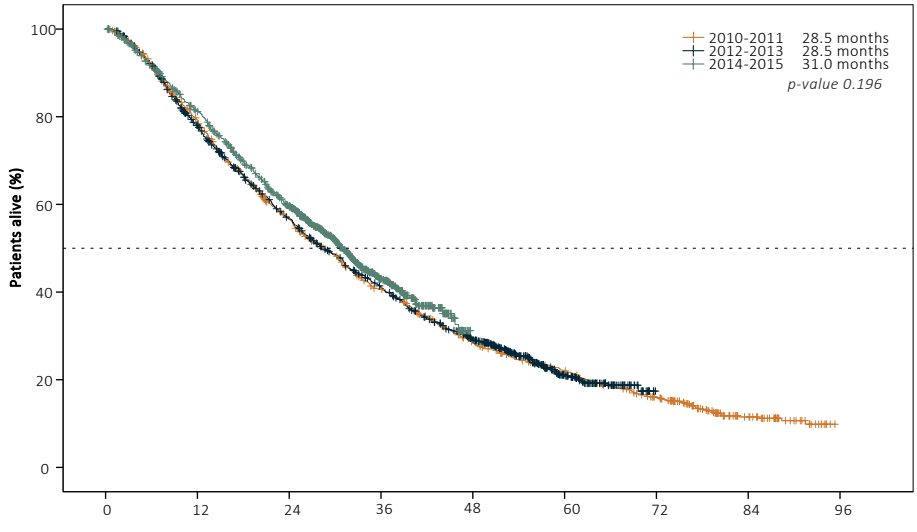
multiple imputations of missing baseline values were performed to allow for multivariable analysis with prognostic factors. After multiple imputations, in multivariable analysis the treatment period was significant for survival (HR 0.749, 95% CI 0.670-0.838 in 2014-2015 vs 2010-2011, p<0.001). Also age, time from ADT tot CRPC, ALP, PSA, Hb, LDH,

Table 3.1B | Baseline characteristics at progression date of docetaxel (subgroup 2)

		2011-2012	2013-2014	2015-2016	p
		N=348	N=508	N=463	
Age (years)	median (IQR)	71 (65-76)	72 (66-77)	72 (68-78)	0.005*
	>75 years, %	30	37	38	
Charlson comorbidity index, %	6	66	70	66	0.197
	7-8	30	26	29	
	9-10	4	4	3	
	>10	<1	<1	2	
	unknown	0	0	0	
Gleason score, %	≤7	35	34	32	0.514
	8-10	54	56	59	
	unknown	12	11	10	
Time from castration to progression on DOC (mo)	median (IQR)	24 (16-34)	28 (18-44)	30 (20-50)	<0.001*
	unknown, %	1	<1	0	
Time from last DOC to progression on DOC (mo)	median (IQR)	1.5 (0.6-3.7)	2.0 (0.7-4.3)	2.3 (0.7-5.1)	<0.001*
	≤ 0 months, %	11	9	4	
	≤ 6 months, %	91	86	81	
	unknown, %	4	3	1	
DOC cycles	median (IQR)	6 (4-9)	7 (5-10)	7 (5-10)	0.001*
	≥10, %	21	27	25	
	unknown, %	1	1	0	
ECOG PS, %	0	10	12	10	0.310
	1	31	26	25	
	2	12	13	8	
	>2	5	4	2	
	unknown	43	46	56	
ALP (U/L)	median (IQR)	161 (89-311)	144 (86-311)	120 (76-225)	<0.001*
	unknown, %	34	30	19	
Hb (mmol/L)	median (IQR)	7.1 (6.4-7.9)	7.2 (6.6-8.0)	7.5 (6.6-8.1)	0.039*
	unknown, %	30	35	41	
PSA (µg/L)	median (IQR)	128 (37-391)	108 (33-296)	73 (24-225)	<0.001*
	unknown, %	18	19	13	
LDH (U/L)	median (IQR)	304 (228-493)	276 (217-435)	255 (209-334)	0.001*
	unknown, %	43	50	51	
Visceral disease, %	yes	13	19	17	0.165
	no	34	33	37	
	unknown	53	47	47	
Clinical progression, %	yes	60	62	60	0.013*
	no	21	22	32	
	unknown	19	16	8	

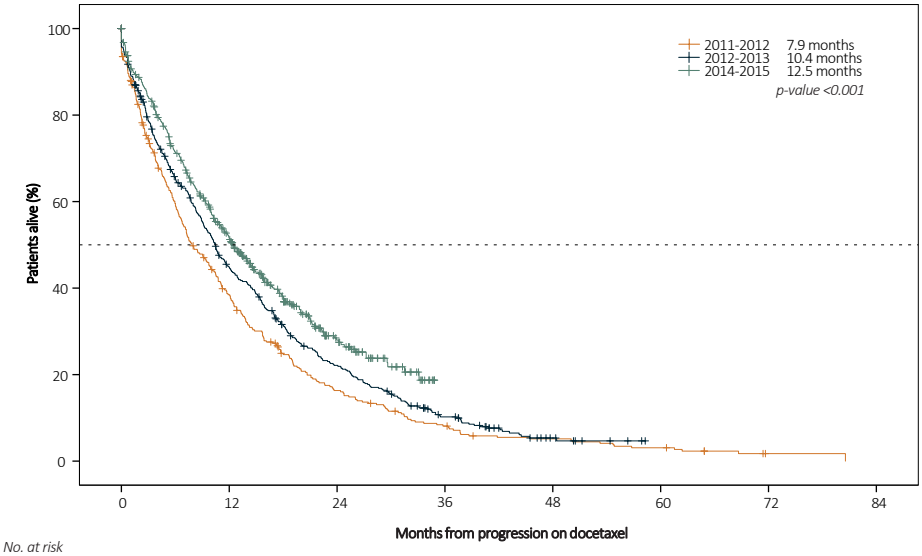
* significant at p-value <0.05.

Abbreviations: IQR, interquartile range; DOC, docetaxel; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ALP, alkaline phosphatase; Hb, haemoglobin; PSA, prostate specific antigen; LDH, lactate dehydrogenase.



No. at risk									
2010-2011	1140	874	608	421	280	202	132	43	0
2012-2013	1249	941	653	451	291	91	0		
2014-2015	1211	939	634	220	0				

Figure 3.2A | Overall survival from CRPC-diagnosis (subgroup 1)
Dotted line indicates the median overall survival
Abbreviations: CRPC, castration-resistant prostate cancer.



No. at risk								
2011-2012	384	138	55	26	15	9	1	0
2013-2014	508	213	100	39	9	0		
2015-2016	463	209	55	0				

Figure 3.2B | Overall survival from progression on docetaxel (subgroup 2)
Dotted line indicates the median overall survival

Table 3.2A | Cox-regression analysis of OS from CRPC-diagnosis (subgroup 1)

		Univariable analysis of actual data				Multivariable analysis of pooled imputed data		
		n/N[a]	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	cont.	2,432/3,600	1.02	1.01-1.02	<0.001*	1.02	1.02-1.03	<0.001*
Charlson comorbidity index		2,431/3,598						
	6		REF	-	-	REF	-	-
	7-8		1.20	1.10-1.30	<0.001*	1.10	0.99-1.22	0.086
	9-10		1.32	1.10-1.57	0.002*	1.24	0.96-1.60	0.099
	>10		2.61	1.95-3.48	<0.001*	2.17	1.56-3.02	<0.001*
Gleason score		2,055/3,078			0.003*			0.483
	≤7		REF	-		REF	-	
	8-10		1.15	1.05-1.25		1.04	0.93-1.17	
Period ADT to CRPC (mo)	cont.	2,426/3,588	0.99	0.98-0.99	<0.001*	0.99	0.99-0.99	<0.001*
ALP (U/L)	cont.	1,617/2,254	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	<0.001*
PSA (µg/L)	cont.	2,359/3,491	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	<0.001*
Hb (mmol/L)	cont.	1,701/2,361	0.61	0.58-0.64	<0.001*	0.73	0.70-0.77	<0.001*
LDH (U/L)	cont.	1,091/1,481	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	0.016*
ECOG PS		1,066/1,452						
	0		REF	-	-	REF	-	-
	1		1.79	1.57-2.04	<0.001*	1.34	1.18-1.52	<0.001*
	>1		4.69	3.88-5.67	<0.001*	2.84	2.19-3.69	<0.001*
Visceral disease		500/672			<0.001*			0.047*
	no		REF	-		REF	-	
	yes		1.56	1.26-1.94		1.22	1.00-1.49	
Pain and/or opioid use		1,432/1,916			<0.001*			<0.001*
	no		REF	-		REF	-	
	yes		2.01	1.81-2.24		1.38	1.19-1.59	
Year of CRPC diagnosis		2,432/3,600						
	2010-2011		REF	-	-	REF	-	-
	2012-2013		0.99	0.91-1.09	0.899	0.89	0.81-0.98	0.022*
	2014-2015		0.92	0.82-1.11	0.098	0.75	0.67-0.84	<0.001*

* significant at p-value <0.05; [a] number of patients with event (i.e. death) of total included in univariable analysis
Abbreviations: OS, overall survival; CRPC, castration-resistant prostate cancer; HR, hazard ratio; CI, confidence interval; REF, reference category; ADT, androgen deprivation therapy; ALP, alkaline phosphatase; PSA, prostate specific antigen; Hb, haemoglobin; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group Performance score.

Table 3.2B | Cox-regression analysis of OS from progression on docetaxel (subgroup 2)

		Univariable analysis of actual data				Multivariable analysis of pooled imputed data		
		n/N[a]	HR	95% CI	p	HR	95% CI	p
Age	cont.	1,096/1,355	1.01	1.00-1.02	0.037*	1.00	0.99-1.01	0.622
Charlson comorbidity index		1,096/1,355						
	6		REF	-	-	REF	-	-
	7-8		1.07	0.94-1.22	0.311	1.03	0.90-1.18	0.690
	9-10		1.36	1.02-1.82	0.037*	1.07	0.76-1.50	0.699
	>10		1.83	0.91-3.69	0.088	1.86	0.80-4.29	0.146
Gleason score		981/1,211			0.272			0.140
	≤7		REF	-		REF	-	
	8-10		1.08	0.95-1.22		0.90	0.77-1.04	
Period on ADT (mo)	cont.	1,091/1,350	0.99	0.99-0.99	<0.001*	0.99	0.99-1.00	<0.001*
ALP (U/L)	cont.	795/983	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	<0.001*
PSA (µg/L)	cont.	904/1,131	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	0.055
Hb (mmol/L)	cont.	726/875	0.62	0.57-0.67	<0.001*	0.75	0.70-0.80	<0.001*
LDH (U/L)	cont.	584/702	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	0.067
ECOG PS		582/698						
	0		REF	-	-	REF	-	-
	1		1.45	1.16-1.82	0.001*	1.11	0.90-1.37	0.307
	>1		3.62	2.83-4.64	<0.001*	1.52	1.07-2.15	0.022*
Visceral disease		552/695			<0.001*			<0.001*
	no		REF	-		REF	-	
	yes		1.65	1.38-1.97		1.48	1.24-1.77	
Clinical progression		942/1,167			<0.001*			0.021*
	no		REF	-		REF	-	
	yes		1.81	1.56-2.09		1.25	1.04-1.50	
Time since last DOC and progression (mo)	cont.	1,070/1,321	0.93	0.91-0.94	<0.001*	0.97	0.95-0.99	0.005*
Docetaxel cycles	cont.	1,089/1,346	0.90	0.88-0.92	<0.001*	0.95	0.93-0.97	<0.001*
Year of progression on DOC		1,096/1,355						
	2011-2012		REF	-	-	REF	-	-
	2013-2014		0.85	0.74-0.98	0.023*	0.89	0.75-1.05	0.160
	2015-2016		0.69	0.59-0.80	<0.001*	0.81	0.67-0.99	0.037*

* significant at p-value <0.05; [a] number of patients with event (i.e. death) of total included in univariable analysis.
Abbreviations: OS, overall survival; CRPC, castration-resistant prostate cancer; HR, hazard ratio; CI, confidence interval; REF, reference category; ADT, androgen deprivation therapy; ALP, alkaline phosphatase; PSA, prostate specific antigen; Hb, haemoglobin; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group Performance Score; mo, months; DOC, docetaxel.

ECOG PS, visceral disease and pain and/or opioid use remained independent prognostic factors (Table 3.2A).

In subgroup 2, mOS from progression on docetaxel increased significantly from 7.9 months to 12.5 months (p<0.001); 12-months and 24-months survival increased from 38% to 52% and 16% to 28%, respectively (Figure 3.2B). mOS in patients treated with LPD was 14.0 months versus 2.0 months for patients not treated with LPD (p<0.0001). Univariate prognostic factors for survival were age, Charlson comorbidity score, time since start castration, PSA, ALP, haemoglobin, LDH, ECOG PS, visceral disease, clinical progression, time since last docetaxel and number of docetaxel cycles, and also the treatment period (Table 3.2B). Only 229 patients had complete data. After multiple imputation, in multivariable analysis the treatment period remained significant for increased survival (HR 0.811, 95% CI 0.677-0.987 in the last period vs the first period, p=0.037; Table 3.2B). Time since start castration, ALP, Hb, ECOG PS, visceral disease, clinical progression, time since last docetaxel and the number of docetaxel cycles were all associated with increased survival.

DISCUSSION

In this large contemporary outcomes registry of CRPC patients in the Netherlands, we observed an increased survival in multivariable analyses of newly diagnosed CRPC patients and post-docetaxel patients during the years 2010-2018. In these years, several new LPDs have been approved for CRPC, both treatment-naïve and post-docetaxel. To our knowledge, this is one of the largest cohorts with long follow-up allowing for evaluation of uptake of new treatments and the effect on treatment outcomes. Results, therefore, reflect contemporary daily practice.

With the registration of new drugs, more patients were treated with at least one LPD. The observed pattern indicates the potential substitution effect of newly registered LPD, for example abiraterone for docetaxel. After the registration of enzalutamide, no further decrease in chemotherapy use was seen. However, the frequency of abiraterone use decreased after registration of enzalutamide, especially in the post-docetaxel setting. Because both abiraterone and enzalutamide are oral drugs with similarities in mode of action, potential treatment benefit and toxicity profile, enzalutamide can be seen as a substitute treatment option for abiraterone. The observed decrease in abiraterone use was probably driven by the registration of enzalutamide, but we expect that the future balance between abiraterone and enzalutamide will reflect patient and physician preferences also in treatment-naïve cohorts.

In treatment-naïve patients, we observed a trend towards older patients, higher Gleason sum score and shorter time to CRPC, regardless of the treatment given. The exact

reason for the shift in these characteristics is unclear. We speculate that this is driven mainly by the differential diagnostic and therapeutic behaviour of clinicians. Differential referral patterns from urologists to medical oncologists are not the reason, because we included all patients from both departments in all participating hospitals. One could speculate that the indication for first line ADT for hormone-sensitive metastatic disease moved towards this profile, or that more patients in this profile were referred to a participating CAPRI hospital. Moreover, clinicians may have monitored patients more strictly because of the availability of more treatment options leading to a shorter time to CRPC. Interestingly, the same shift in age and Gleason sum score was seen in a recent single-centre analysis[98]. The shift in characteristics may have influenced the observed switch from chemotherapy to ART.

Similar to the treatment-naïve cohort, the baseline profile of post-docetaxel patients showed a trend to higher age with less aggressive characteristics (i.e. longer time from castration to progression on docetaxel, longer time from last docetaxel to progression, the higher number of docetaxel cycles, higher haemoglobin and lower ALP, LDH and PSA). We hypothesize that increasing clinician experience or the availability of post-docetaxel drugs may have decreased the threshold for referral to the medical oncologist and subsequent docetaxel treatment. Moreover, patients with aggressive disease are likely to start docetaxel early and progress early, whereas patients with less aggressive disease are more likely to have a more protracted course and thus progress in later years. In contrast, with the increasing pre-docetaxel treatment options the prognostic characteristics at progression on docetaxel may be expected to shift towards more aggressive disease characteristics and a decline of patient condition. However, this was not observed in our population.

Our analysis showed that OS increased over time. Prognostic models have been developed for both treatment-naïve and post-docetaxel CRPC-patients, including ECOG PS, ALP, PSA, haemoglobin and visceral disease. The treatment-naïve prognostic model also included LDH and Gleason sum score, while the post-docetaxel model included time since docetaxel use, pain and time since castration[99,100]. We studied the same characteristics in our population with similar results: we confirmed all known prognostic factors in both univariable and multivariable analyses, in both subgroups (except for measurable disease, which was not registered in our database). Since both subgroups tended to have better prognostic profiles in later treatment periods, this can partially explain the increase in OS. However, treatment periods remained prognostic after correction for known prognostic factors. The median OS in the last period (2014-2015) of the treatment-naïve patients compares favourably to previous reports. Previously reported mOS from mCRPC diagnosis in observational studies in different periods ranges from 9-15 months (before 2004)[101–103], 11-26 months (2004-2010)[98,104,105] to 33-34 months

(from 2010)[98,105], although these studies differ in methods and should be compared with caution.

Limitations include the clinical scope that is limited by the current use of some LPD in the hormone-sensitive phase. The high number of missing values, inherent to the retrospective design of this study, leads to statistical challenges. Missing values on baseline characteristics reflect the incomplete evaluation of patients or lack of structured reporting in daily practice. This was particularly shown for ECOG PS, LDH and visceral status for subgroup 1, and to a lesser extent in subgroup 2. This warrants better documentation, especially at CRPC-diagnosis. To discard all patients with incomplete data would result in a small population and a substantial loss in precision and power. Moreover, due to the baseline and survival differences between patients with complete data and incomplete data, this would lead to invalid (non-representative) outcomes (Table S3.3). Imputation of missing baseline data did provide a valid solution for multivariable analyses and allowed to use all patients. We were also not able to analyse the reasons for the treatment decisions made. Treatment patterns could have shifted due to the preferences and experience of physicians. However, we did not have insight into these aspects, since they are not structurally captured in medical records.

CONCLUSION

The introduction of new life prolonging drugs in the Netherlands resulted in a marked increase in patients treated, a shift in the characteristics of the population treated and a significant and relevant decrease in the hazard for death.

SUPPLEMENTARY MATERIAL

Table S3.1 | Dates of positive cieBOM guidance per LPD

	LPD	EMA approval data	Publication date positive cieBOM-guidance
Chemotherapy-naive	Docetaxel	2005	2005
	Radium-223	Sep 2013	Feb 2014
	Enzalutamide	Oct 2014	Nov 2014
	Abiraterone acetate	Nov 2012	Nov 2015*
Post-docetaxel	Cabazitaxel	Jan 2011	Jul 2011
	Abiraterone acetate	Jul 2011	Mar 2012
	Enzalutamide	Apr 2013	Dec 2013
	Radium-223	Sep 2013	Feb 2014

* negative guidance in September 2013, revised to positive guidance in November 2015.
Abbreviations: CieBOM, Committee Beoordeling van Oncologische Middelen (Appraisal of oncolytics); LPD, life-prolonging drugs; EMA, European Medicines Agency.

Table S3.2A | First LPD treatment for CRPC (subgroup 1)

	Year of CRPC-diagnosis		
	2010-2011	2012-2013	2014-2015
	N=1,140	N=1,249	N=1,211
Type of treatment, n (%)			
No LPD	491 (43)	475 (38)	379 (31)
Docetaxel	522 (46)	488 (36)	351 (29)
Abiraterone	77 (7)	202 (16)	165 (14)
Enzalutamide	43 (4)	116 (9)	301 (25)
Radium-223	7 (1)	8 (1)	15 (1)

Abbreviations: LPD, life-prolonging drug; CRPC, castration-resistant prostate cancer.

Table S3.2B | First LPD treatment after docetaxel progression (subgroup 2)

	Year of progression on docetaxel		
	2011-2012	2013-2014	2015-2016
	N=384	N=508	N=463
Type of treatment, n (%)			
No LPD	134 (35)	115 (23)	96 (21)
Docetaxel	10 (3)	15 (3)	1 (<1)
Cabazitaxel	65 (17)	63 (12)	40 (9)
Abiraterone	173 (45)	205 (40)	97 (21)
Enzalutamide	2 (1)	104 (21)	200 (43)
Radium-223	0 (0)	6 (1)	30 (7)

Abbreviations: LPD, life-prolonging drug.

Table S3.3 | Baseline characteristics of patients with complete data vs patients with any missing data

		Data complete	Data incomplete	p
		N=233	N=3,377	
Age (years)	median (IQR)	70 (65-77)	75 (69-82)	<0.001*
	>75 years, %	34	53	
Charlson comorbidity index, %	6	65	61	NS
	7-8	27	32	
	9-10	7	5	
	>10	2	2	
	unknown	0	<1	
Gleason score, %	≤7	40	34	0.009*
	8-10	60	51	
	unknown	0	16	
Time from castration to CRPC (mo)	median (IQR)	10.3 (6-19)	15.4 (9-30)	<0.001*
	unknown, %	0	<1	
ECOG PS, %	0	34	17	0.004*
	1	50	15	
	2	12	3	
	>2	4	1	
	unknown	0	64	
ALP (U/L)	median (IQR)	132 (84-289)	104 (77-184)	<0.001*
	unknown, %	0	40	
Hb (mmol/L)	median (IQR)	7.9 (7.1-8.4)	8.1 (7.3-8.6)	<0.001*
	unknown, %	0	37	
PSA (µg/L)	median (IQR)	42 (13-140)	16 (5-57)	<0.001*
	unknown, %	0	3	
LDH (U/L)	median (IQR)	227 (190-320)	222 (188-288)	NS
	unknown, %	0	65	
Visceral disease, %	yes	22	2	NS
	no	78	11	
	unknown	0	87	
Pain and/or opioid use, %	yes	54	31	<0.001*
	no	47	19	
	unknown	0	50	

* significant at p-value <0.05.

Abbreviations: CRPC, castration-resistant prostate cancer; IQR, interquartile range; NS, not significant; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ALP, alkaline phosphatase; Hb, haemoglobin, PSA, prostate specific antigen; LDH, lactate dehydrogenase.

4

Health-related quality of life and pain in a real-world CRPC population

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Clinical Genitourinary Cancer 2019;18(3):e233-e253

ABSTRACT

Background: To determine generic, cancer-specific and prostate cancer-specific health-related quality of life (HRQoL), pain and changes over time in metastatic castration-resistant prostate cancer (mCRPC) patients in daily practice.

Patients and methods: PRO-CAPRI is an observational, prospective study in 10 hospitals in the Netherlands. mCRPC patients completed EQ-5D, EORTC QLQ-C30, and BPI-SF three-monthly and EORTC QLQ-PR25 six-monthly for a maximum of two years. Subgroups were identified based on chemotherapy pre-treatment. Outcomes were generic, cancer-specific and prostate cancer-specific HRQoL and self-reported pain. Descriptive statistics were performed including changes over time and minimal important differences (MID) between subgroups.

Results: In total, 151 included patients answered 873 questionnaires. Median follow-up from the start of study was 19.5 months and 84% were treated with at least one life-prolonging agent. Overall patients were in good clinical condition (ECOG 0-1 in 78%) with normal baseline haemoglobin, lactate dehydrogenase (LDH) and alkaline phosphatase (ALP). At inclusion, generic HRQoL was high with a mean EQ VAS of 73.2 out of 100. Lowest scores were reported on role and physical functioning (mean scores of 69 and 76 out of 100 respectively) with fatigue, pain, and insomnia were the most impaired domains. These domains deteriorated in >50% of patients.

Conclusion: Although most patients were treated with new treatments during follow-up, mCRPC has a negative impact on HRQoL with deterioration in all domains over time, especially role and physical functioning. These domains need specific attention during follow-up to maintain HRQoL as long as possible by timely start of adequate supportive care management.

INTRODUCTION

The survival of patients with metastatic castration resistant prostate cancer (mCRPC), that is progression of disease on androgen deprivation therapy, is not likely to extend beyond 14 months with only best supportive care[40]. Several life-prolonging drugs (LPDs), such as chemotherapy (i.e. docetaxel, cabazitaxel), androgen-receptor targeting treatments (i.e. abiraterone, enzalutamide) and radionuclide therapy (i.e. radium-223), have shown a survival benefit compared with placebo[24,27,29–31,33,92]. In a contemporary cohort with access to these new LPDs, we observed a median overall survival of 26 months[41].

mCRPC has a negative impact on health-related quality of life (HRQoL) with a decline in HRQoL over time[40,42–46,106–108]. Deterioration occurs in general domains as well as specific symptoms such as pain, fatigue and appetite loss[46]. However, these results are derived from trials performed in the era before the registration of new LPDs[40,45,46,107]. In the pivotal phase III trials, the LPDs showed a delay in HRQoL-deterioration and pain progression in both chemotherapy-naïve (CTx-naïve) and post-chemotherapy (post-CTx) disease phases[35,37,39,109], but adverse events of new agents can also add to the symptom burden in mCRPC.

There remains a paucity of data concerning treatment sequencing and direct comparisons of LPDs in randomized trials. Moreover, cumulating evidence on real-world data points towards the fact that trials utilizee highly selected populations with significantly better outcomes that are commonly not generalizable to an oncology practice[41]. Benefits of LPDs in trials are comparable and economic costs are in the same range making patient reported outcomes (PROs) of special interest in order to determine the best treatment. The use of PROs in daily practice can also inform physicians on efficacy and tolerability, increase patient satisfaction and improve symptom control and supportive care measures[110].

The high proportion of patients experiencing HRQoL deterioration owing to either disease-or treatment-related symptoms, the lack of discriminative results from trials and the gap between these trials and real-world practice, underline the necessity for PROs in daily practice. The objective of this study is therefore to determine generic, cancer-specific and prostate cancer-specific HRQoL and changes over time in patients with mCRPC using data from a patient registry in the Netherlands.

PATIENTS AND METHODS

Study design and setting

PRO-CAPRI is a prospective observational cohort study in 10 hospitals in the Netherlands. The study aimed to evaluate HRQoL, pain and resource use outside the hospital

in daily practice using validated questionnaires. The study was approved by a central and local medical ethics committee and hospital board before the start of inclusion. The PRO-CAPRI study is registered in the Dutch Trial Registry as NL3934 (NTR4096). PRO-CAPRI is a side study of the CAstration-resistant Prostate cancer RegIstry (CAPRI) registered as NL3440 (NTR3591). The methods of the CAPRI registry have been described in depth before[41].

Objective

The objectives are to determine generic, cancer-specific and prostate cancer-specific HRQoL, pain and changes over time in patients with mCRPC in daily practice.

Participants

Patients diagnosed with mCRPC between January 1 2010 and December 31 2015 were eligible for inclusion conforming to the CAPRI inclusion criteria[41]. Patients were eligible for the PRO-CAPRI study from diagnosis of CRPC to four weeks after the start of the first post-docetaxel treatment. Eligible patients provided written informed consent to the treating physician at the hospital site. All PRO-CAPRI patients were also included in the CAPRI registry.

Subgroups were created based on the disease state at inclusion, namely chemotherapy-naïve state (CTx-naïve, i.e. no prior docetaxel treatment) and (post-) chemotherapy state (post-CTx, i.e. current docetaxel or post-docetaxel treatment).

Study size

In PRO-CAPRI, 167 participants were included out of the total of 3,616 patients with mCRPC that were included in the CAPRI registry.

Follow-up and data collection

PRO-CAPRI started in June 2013 with four participating hospitals, but because of slow accrual, the protocol was amended after one year to include an additional six hospitals and prolong the inclusion period for six months. This amendment also included the addition of the pain-specific questionnaire the Brief Pain Inventory-Short Form (BPI-SF).

The baseline evaluation of consenting patients consisted of four questionnaires (EQ-5D, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30], European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module [QLQ-PR25], and after the amendment BPI-SF) and commonly used demographic items, namely age, socio-economic status, marital status, and educational level[111]. After baseline measurement EQ-5D, EORTC QLQ-C30 and BPI-SF were repeated every three months, and EORTC QLQ-PR25 every 6 months. All patients were followed until death, withdrawal of consent

or end of study duration (either a total follow-up period of two years from the start of the study or December 31st 2017).

A case record form linked the participating patient to the CAPRI database, combining HRQoL with the clinical characteristics.

Outcome

The primary outcome was generic HRQoL, measured with EQ-5D. The first part of the EQ-5D is a generic five dimensional questionnaire on a 5-point Likert scale, which was transformed into utility or EQ-5D index value based on Dutch population norms[112]. The second part is a visual analogue scale (VAS)[113].

The secondary outcomes were cancer-specific, prostate cancer-specific HRQoL, and pain. The EORTC QLQ-C30 (cancer-specific HRQOL) and EORTC QLQ-PR25 (prostate cancer-specific HRQOL) include 55 questions in different HRQOL domains, including functional scales, symptom scales, and a global health status. For the majority of items, a four-point Likert-type response scale was used. Exception is the global health status where a seven-point scale was used. All EORTC QLQ-C30 and EORTC QLQ-PR25 scales were linearly transformed to a scale from 0 to 100 according to the scoring manual[114,115]. The BPI-SF assesses severity of pain (4 items), impact of pain on daily function (7 items), location of pain, pain medication and amount of pain relief in the past 24 hours or the past week. The areas were measured on a scale from 0 to 10 with 0 indicating "no pain" and 10 indicating "worst possible pain"[116]. Clinically relevant pain was defined as a score of ≥4 on pain severity. Supplementary Table S4.1 shows an overview of the used questionnaires.

Both the primary and secondary outcomes are measured at baseline (i.e. inclusion) and over time. A minimally important difference (MID) was used to assess clinically relevant changes[116–119]. The thresholds for MIDs are also shown in Supplementary Table S4.1. Time to first MID deterioration was calculated in months from the date of first questionnaire to the date of the first MID deterioration.

Missing values

Missing values were handled based on the scoring manual for the specific questionnaires. In EQ-5D, the index value and VAS were calculated if all domains were present[113]. For EORTC QLQ-C30, EORTC QLQ-PR25 and BPI-SF averages were calculated if more than one-half of the questions were completed per scale[114–116].

Statistical analysis

The compliance rate was calculated as the number of patients returning a questionnaire divided by the total number of evaluable patients per questionnaire. Baseline characteristics were measured in the period of three months prior to three months after inclu-

sion. Descriptive statistics were used to describe the study population with subgroups per disease state at inclusion. Data on HRQoL were presented as mean changes from baseline and proportion with MID. The McNemar test was used for differences in proportion with MID between 6 and 12 months for subgroups. The independent sample t-test, Mann-Whitney U test or Chi-square test were used to compare parametric continuous, nonparametric continuous and categorical variables respectively between CTx-naïve and post-CTx patients. A p-value of 0.05 or less was considered statistically significant. IBM SPSS Statistics Version 24.0 (IBM ®, Armonk, NY, USA) was used for all analyses.

RESULTS

In total, 167 patients were included in the PRO-CAPRI study. Nine patients were excluded for failing to meet the inclusion criteria (n=7) or missing informed consent (n=2). Seven of the 158 patients who were sent the first questionnaire did not respond, either owing to death (n=4), withdrawal of consent (n=2) or inability to answer (n=1). Baseline questionnaires were evaluable for 151 patients (Figure 4.1).

In total, 873 questionnaires were completed and the median number of questionnaires per patient was six (range 1-9). The median follow-up from the first questionnaire was 19.5 months (IQR 13-25). Thirty-eight (25%) patients completed all nine questionnaires. Termination of the study before the maximum follow-up of two years occurred in 113 (75%) patients, owing to death (n=56, 37%), lost-to-follow-up (n=22, 15%), withdrawal of informed consent (n=9, 6%) or database cut-off (n=26, 17%). The compliance rate

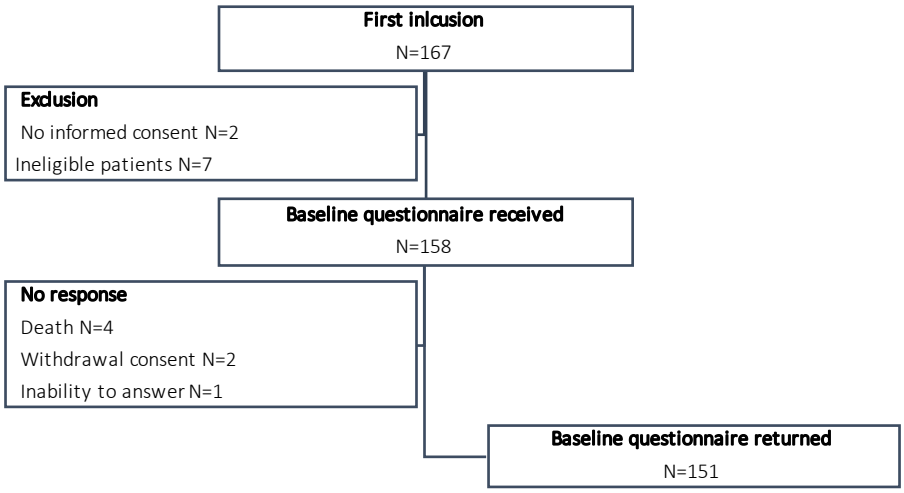

Figure 4.1 | Flowchart of patient inclusion

ranged from 94% to 100% per questionnaire, except for BPI-SF which was added during the study after a protocol amendment (Supplementary Table S4.2).

Treatment characteristics

At inclusion, 112 (74%) patients were in the CTx-naïve state and 39 (26%) patients were in the post-CTx state. At the time of the first questionnaire, 37 (33%) patients in the CTx-naïve state were treated with LPD, mainly enzalutamide (n=27, 24%) whereas in the post-CTx state most patients were treated with docetaxel (n=17, 44%). During follow-up, 84% of patients were treated with at least one LPD, mainly enzalutamide (n=89, 59%) or docetaxel (n=65, 43%) (Table 4.1).

Patient and disease characteristics

At mCRPC diagnosis, patients included in the PRO-CAPRI study were younger (72 vs 75 years, p<0.01) and had higher hemoglobin (8.3 vs 8.0 mmol/L, p=0.01) compared with the total mCRPC-population in the CAPRI registry (Supplementary Table S4.3).

CTx-naïve patients were older (median 75 vs 71 years, p=0.02), had less prevalent bone metastases (73% vs 82%, p=0.03) and had lower educational level (p=0.03) at inclusion than post-CTx patients (Table 4.1). PSA tended to be lower in CTx-naïve patients (median 36 vs 86 µg/L, p=0.06).

Table 4.1 | Patient and disease characteristics per disease state

		Total	CTx-naïve	Post-CTx	p
		N=151	N=112	N=39	
Age (years)	median (IQR)	74 (68-80)	75 (68-81)	71 (68-75)	0.020*
	range	54-95	54-95	58-84	
ECOG PS, %	0	38	39	36	0.235
	1	40	35	54	
	>1	9	10	5	
	unknown	13	16	5	
Gleason score, %	≤7	34	35	31	0.431
	8-10	56	53	64	
	no histology	3	5	0	
	metastasis biopsy	1	1	3	
	unknown	6	7	3	
Charlson comorbidity index, %	6	69	66	77	0.565
	7-8	25	27	21	
	9-10	5	6	3	
	>10	1	1	0	
	unknown	0	0	0	

Table 4.1 | Patient and disease characteristics per disease state *(continued)*

		Total	CTx-naïve	Post-CTx	p
		N=151	N=112	N=39	
Disease state, %	N1 / N0 / Nx	49 / 13 / 38	44 / 13 / 44	64 / 15 / 21	0.749
	M1 / M0 / Mx (bone)	76 / 8 / 17	73 / 5 / 22	82 / 18 / 0	0.031*
	M1 / M0 / Mx (visceral)	9 / 31 / 60	5 / 25 / 70	18 / 49 / 33	0.387
Period from ADT to mCRPC (mo)	median (IQR)	15.1 (9-28)	16.5 (9-32)	13.0 (7-22)	0.105
	unknown, %	0	0	0	
Period from mCRPC to inclusion PRO-CAPRI (mo)	median (IQR)	7.0 (2.0-21.0)	4.7 (1-14)	19.4 (10-29)	<0.001*
	unknown, %	0	0	0	
Hb (mmol/L)	median (IQR)	8.0 (7.3-8.5)	8.1 (7.5-8.5)	8.0 (7.1-8.4)	0.479
	unknown, %	2.6	3	3	
LDH (U/L)	median (IQR)	213 (185-261)	211 (182-259)	218 (187-281)	0.341
	unknown, %	7	7	5	
ALP (U/L)	median (IQR)	103 (72-173)	102 (72-168)	113 (76-254)	0.421
	unknown, %	2	3	0	
PSA (µg/L)	median (IQR)	40.4 (12-121)	36.0 (11-106)	86.0 (14-180)	0.061
	unknown, %	2	3	0	
Marital state, %	married/living together	85	83	90	0.210
	single/not living together	5	4	8	
	divorced	3	4	0	
	widowed	8	10	3	
Educational level[a], %	none	1	1	0	0.030*
	low	39	45	23	
	middle	15	11	26	
	high	38	35	46	
	other/unknown	8	9	5	
Current profession, %	employed	8	7	10	0.395
	entrepreneur	7	10	0	
	incapacitated	3	2	5	
	retired/early retired	79	78	82	
	other/unknown	3	4	3	
Treatment at inclusion[b], %	none	24	32	0	<0.001*
	no LPD	26	35	0	<0.001*
	LPD	50	33	100	<0.001*
	docetaxel	11	0	44	<0.001*
	cabazitaxel	1	0	3	0.089
	abiraterone acetate	12	9	18	0.125
	enzalutamide	27	24	36	0.001*
	radium-223	0	0	0	-
	study drug	0	0	0	-

Table 4.1 | Patient and disease characteristics per disease state *(continued)*

		Total	CTx-naïve	Post-CTx	p
		N=151	N=112	N=39	
Treatment during follow-up[c], %	none	6	9	0	0.053
	no LPD	15	18	8	0.128
	LPD	84	80	97	0.008*
	docetaxel	43	44	41	0.767
	cabazitaxel	19	14	31	0.023*
	abiraterone acetate	25	23	28	0.533
	enzalutamide	59	59	59	0.996
	radium-223	11	11	10	0.936
	study drug	3	4	3	0.762

All baseline measured are measured within three months prior or after the start of study. Percentages may exceed 100% due to rounding. p-values calculated for differences in time to first MID between CTx-naïve and post-CTx patients.
* significant at p-value <0.05; [a] Educational level converted to classes according to the Dutch Central Bureau of Statistics (CBS)[111]; [b] any systemic treatment at time of first questionnaire; [c] any systemic treatment at time of second or later questionnaires.
Abbreviations: CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ADT, androgen deprivation therapy; mCRPC, metastastic castration-resistant prostate cancer; Hb, haemoglobin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; LPD, life prolonging drug (either docetaxel, cabazitaxel, abiraterone, enzalutamide or radium-223).

Generic HRQoL (EQ-5D)

Generic HRQoL was high with a mean EQ VAS of 73.2 out of 100 and EQ-5D index value of 0.82 out of 1 at inclusion. Most problems were reported on pain/discomfort (55%) and mobility (48%). No differences between disease state were observed in generic HRQoL (Figure 4.2A; Supplementary Table S4.4).

EQ VAS deteriorated over time, but changes were small and the mean change did not reach MID during 24 months of follow-up (Figure 4.3A). There were no differences in proportion with MID deterioration at six months and twelve months (Table 4.2; Supplementary Table S4.5). The median time to MID deterioration on generic HRQoL was 10.8 months for EQ VAS without differences between CTx-naïve and post-CTx patients (Table 4.3; Supplementary Table S4.6).

Cancer-specific HRQoL (EORTC QLQ-C30)

Figures 4.2A and 4.2B show cancer-specific HRQoL at inclusion. Role (i.e. patient's ability to perform daily activities, leisure time activities, and/or work) and physical functioning were most affected in cancer-specific HRQoL (mean scores of 69 and 76 out of 100 respectively).

CTx-naïve patients had significant but not relevant lower levels of emotional functioning compared with post-CTx patients (mean scores of 81 vs 88, p=0.02). Most symptoms

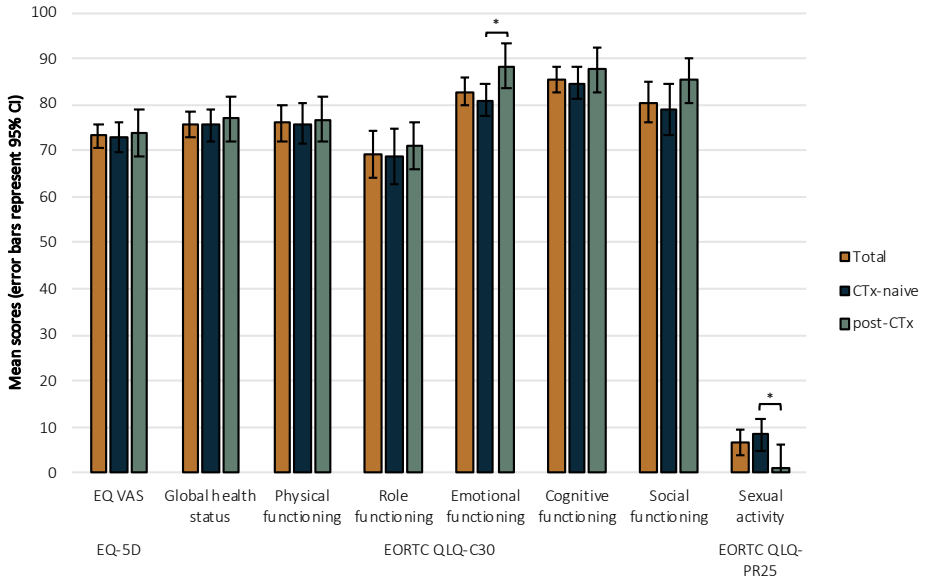

Figure 4.2A | Health-related quality of life measured at study inclusion; mean scores of functioning scales
High scores indicate high level of functioning. Error bars represent 95% confidence intervals. * significant at p-value <0.05.
Abbreviations: CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy.

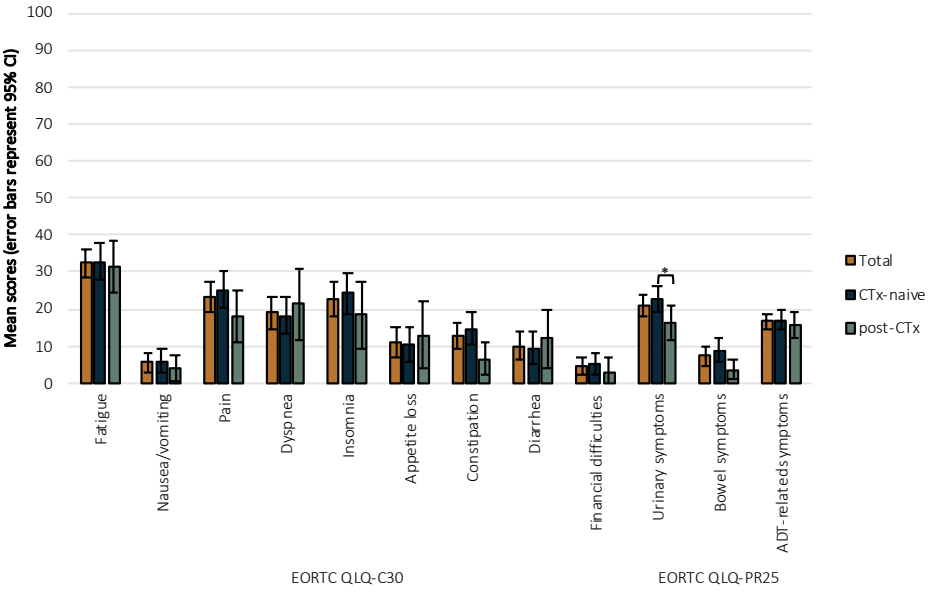

Figure 4.2B | Health-related quality of life measured at study inclusion; mean scores of symptom scales
High scores indicate high symptom burden. Error bars represent 95% confidence intervals. * significant at p-value <0.05.
Abbreviations: CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy.

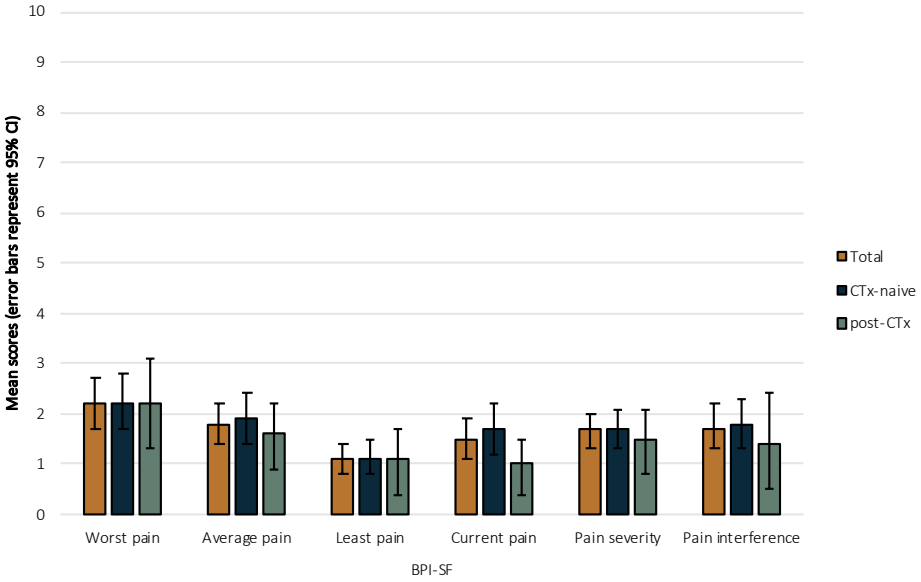

Figure 4.2C | Health-related quality of life measured at study inclusion; mean scores of pain
High scores indicate high pain severity or interference. Error bars represent 95% confidence intervals. * significant at p-value <0.05.
Abbreviations: CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy.

were measured on scales of fatigue, pain and insomnia, without differences in subgroups per disease state (Figures 4.2A-B).

Deterioration was seen on all functioning domains of EORTC QLQ-C30, except for emotional functioning (Figures 4.3B-G). The proportion of CTx-naïve patients with MID after twelve months was higher compared with after six months in global health status (32% vs 18%, p=0.03), physical functioning (44% vs 27%, p=0.02), role functioning (45% vs 27%, p=0.02) and social functioning (35% vs 19%, p=0.01). In post-CTx patients no differences in proportion with MID deterioration after six and twelve months was seen. Symptoms increased over time with the highest proportion of patients with MID in fatigue and appetite loss. The proportion of patients with MID after twelve months was higher than after six months for pain (22% vs 36%, p<0.01), which was only present in the CTx-naïve subgroup (Supplementary Table S4.5).

All functioning domains of EORTC QLQ-C30 deteriorated approximately one year after inclusion, except for emotional functioning (median 26.6 months) (Table 4.3). The median time to deterioration of the symptoms fatigue and pain were respectively 8.2 and 15.3 months.

Table 4.2 | Proportion of patients with a clinically relevant deterioration in HRQoL at month 6 and month 12

		Month 6	Month 12	p
Generic HRQoL (EQ-5D)	EQ VAS	31/115 (27.0)	31/95 (32.6)	0.281
Cancer-specific HRQoL (EORTC QLQ-C30)	global health status	27/120 (22.5)	32/96 (33.3)	0.023*
	physical functioning	38/115 (33.0)	37/90 (41.1)	0.170
	role functioning	36/117 (30.8)	43/93 (46.2)	0.009*
	emotional functioning	15/119 (12.6)	19/95 (20.0)	0.092
	cognitive functioning	37/119 (31.1)	33/95 (34.7)	0.664
	social functioning	28/119 (23.5)	33/95 (34.7)	0.015*
	fatigue	53/116 (45.7)	50/94 (53.2)	0.064
	nausea/vomiting	15/119 (12.6)	19/95 (20.0)	0.359
	pain	26/119 (21.8)	34/95 (35.8)	0.002*
	dyspnea	26/116 (22.4)	16/93 (17.2)	0.267
	insomnia	16/116 (13.8)	20/94 (21.3)	0.118
	appetite loss	24/118 (20.3)	26/93 (28.0)	0.286
	constipation	17/118 (14.4)	17/94 (18.1)	0.664
	diarrhea	20/117 (17.1)	24/95 (25.3)	0.152
	financial difficulties	8/118 (6.8)	6/95 (6.3)	0.688
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	sexual activity	14/117 (12.0)	16/93 (17.2)	0.180
	urinary symptoms	21/115 (18.3)	22/94 (23.4)	0.332
	bowel symptoms	11/93 (11.8)	10/71 (14.1)	0.508
	hormonal therapy related symptoms	19/118 (16.1)	24/94 (25.5)	0.052
Pain (BPI-SF)	pain severity	9/75 (12.0)	13/65 (20.0)	0.039*
	worst pain	15/76 (19.7)	21/65 (32.3)	0.003*
	average pain	10/74 (13.5)	18/63 (28.6)	<0.001*
	least pain	9/73 (12.3)	14/64 (21.9)	0.118
	current pain	9/75 (12.0)	9/63 (14.3)	0.289
	pain interference	7/61 (11.5)	14/51 (27.5)	0.004*

Data are presented as n/N (%) for total population (N=151). p-values calculated for differences percentage of patients with MID at month 6 and month 12; * significant at p-value<0.05.
Abbreviations: HRQOL, health-related quality of life; MID, minimal important difference; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion.

Prostate cancer-specific HRQoL (EORTC QLQ-PR25)

At inclusion 31 (21%) patients reported any sexual activity measured with EORTC QLQ-PR25 with higher activity levels in CTx-naïve patients than in post-CTx patients (mean 8.5 vs 1.4, p=0.02). Prostate cancer-specific symptoms were mostly present as urinary symptoms at inclusion. CTx-naïve patients reported more bowel symptoms than post-

Table 4.3 | Time to clinical relevant deterioration in months of HRQoL for total population

		No. of events (%)	Time to MID (mo)
Generic HRQoL (EQ-5D)	EQ VAS	59.6	10.8 (6-NR)
Cancer-specific HRQoL (EORTC QLQ-C30)	global health status	54.3	14.7 (7-26)
	physical functioning	58.9	13.1 (6-26)
	role functioning	60.3	12.2 (4-28)
	emotional functioning	33.8	26.6 (10-NR)
	cognitive functioning	53.6	12.2 (6-28)
	social functioning	55.6	12.8 (7-NR)
	fatigue	66.2	8.2 (4-20)
	nausea/vomiting	47.0	19.0 (9-NR)
	pain	56.3	15.3 (6-26)
	dyspnea	43.0	22.6 (7-NR)
	insomnia	41.1	22.6 (9-NR)
	appetite loss	48.3	17.0 (9-NR)
	constipation	38.4	24.5 (10-NR)
	diarrhea	36.4	NR (9-NR)
	financial difficulties	17.9	NR (26-NR)
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	sexual activity	13.9	NR (NR-NR)
	sexual functioning	2.0	NR (NR-NR)
	urinary symptoms	26.5	NR (15-NR)
	bowel symptoms	17.2	NR (26-NR)
	incontinence aid	5.3	NR (NR-NR)
	hormonal therapy related symptoms	27.8	26.3 (13-NR)
Pain (BPI-SF)[a]	pain severity	34.2	NR (10-NR)
	worst pain	46.8	15.9 (7-NR)
	average pain	36.9	NR (10-NR)
	least pain	38.7	NR (10-NR)
	current pain	32.4	NR (10-NR)
	pain interference	31.5	NR (13-NR)

Data are presented as percentages for number of events (i.e. number of patients with MID) and median (IQR) for time to first MID in total population (N=151); a only patients with BPI-SF measurement at inclusion (N=111).
Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimal important differences; IQR, interquartile range; NR, not reached.

CTx patients (mean 8.9 vs 3.7, p=0.04). During follow-up sexual activity and prostate cancer-specific symptoms remained stable and no clinically relevant deterioration was observed.

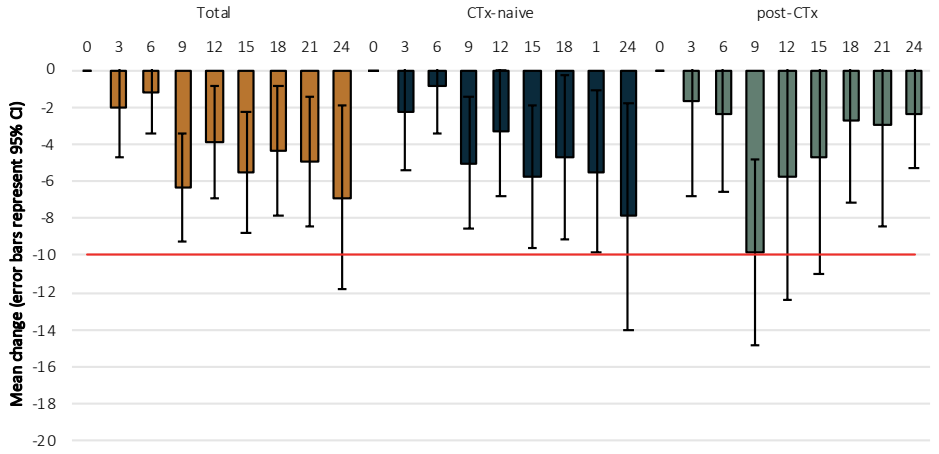

Figure 4.3A | Changes in HRQoL over time per disease state; mean changes of EQ VAS (generic HRQoL)
Mean changes from inclusion. Error bars represent 95% CI, red line is MID.
Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

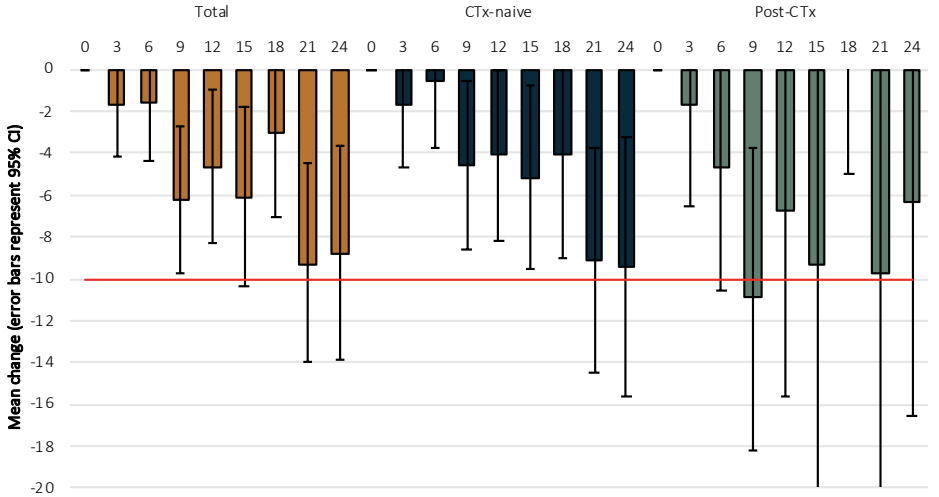

Figure 4.3B | Changes in HRQoL over time per disease state; mean changes in global health status (cancer-specific HRQoL)
Mean changes from inclusion. Error bars represent 95% CI, red line is MID.
Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

Pain (BPI-SF)

The mean pain severity and interference were low at inclusion, without differences between subgroups (Figure 4.2C). Sixteen percent (17 of 108 patients with baseline BPI-SF) reported clinically relevant pain at inclusion.

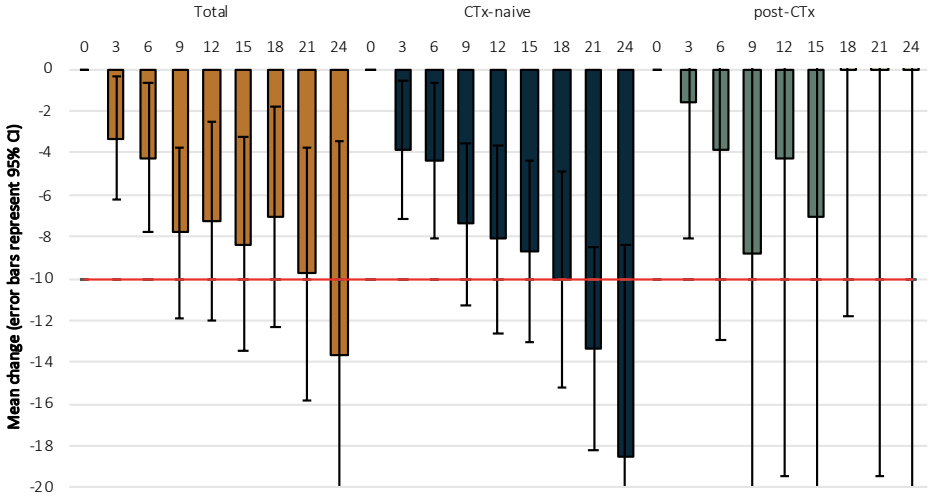

Figure 4.3C | Changes in HRQoL over time per disease state; mean changes in physical functioning (cancer-specific HRQoL)

Mean changes from inclusion. Error bars represent 95% CI, red line is MID.

Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

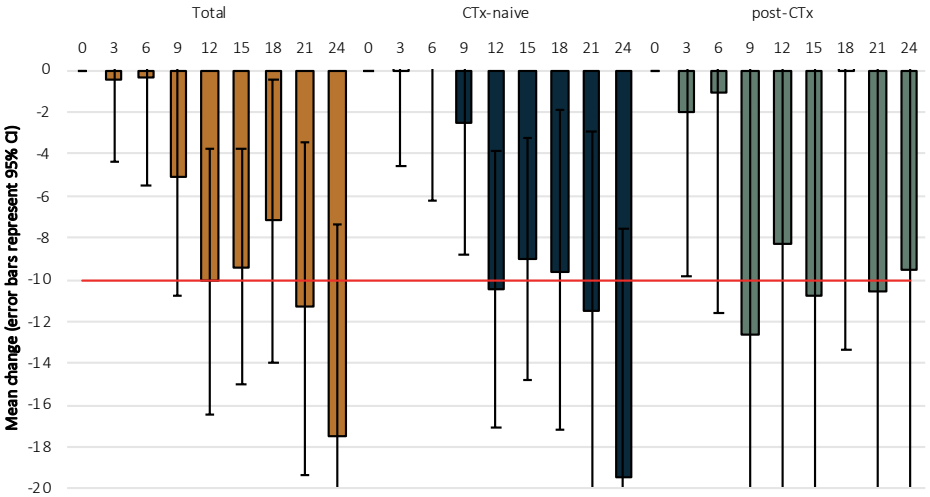

Figure 4.3D | Changes in HRQoL over time per disease state; mean changes in role functioning (cancer-specific HRQoL)

Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

Thirty-six percent of patients without clinical meaningful pain at inclusion had MID deterioration during follow-up. Eight (47.1%) of 17 patients with clinical meaningful pain at inclusion had evaluable follow-up questionnaires with four (23.5%) reporting

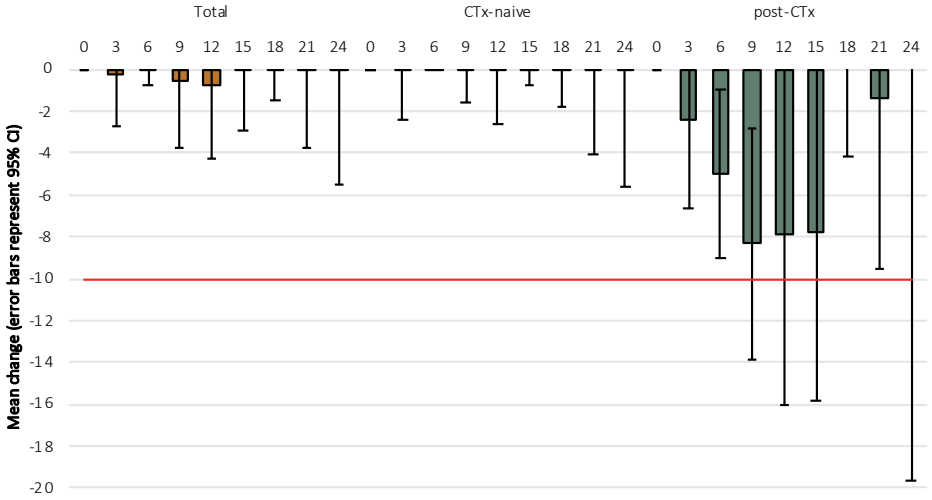

Figure 4.3E | Changes in HRQoL over time per disease state; mean changes in emotional functioning (cancer-specific HRQoL)

Mean changes from inclusion. Error bars represent 95% CI, red line is MID.

Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

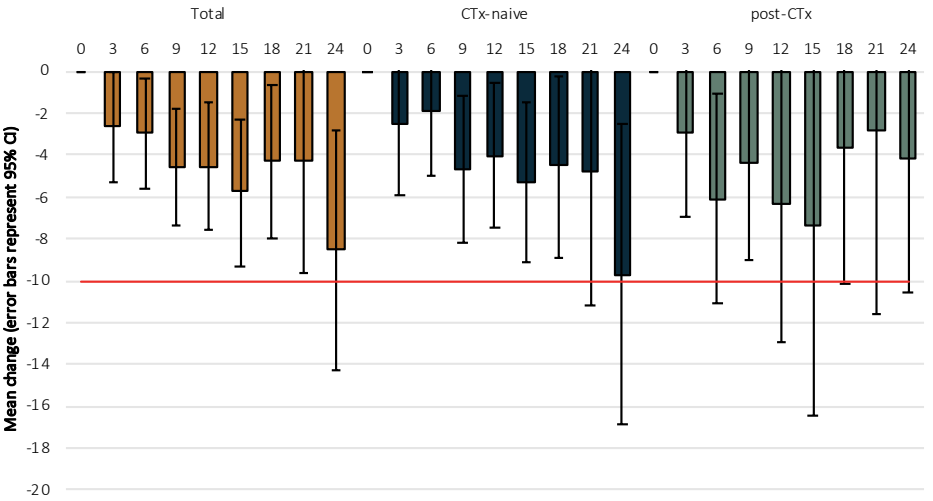

Figure 4.3F | Changes in HRQoL over time per disease state; mean changes in cognitive functioning (cancer-specific HRQoL)

Mean changes from inclusion. Error bars represent 95% CI, red line is MID.

Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

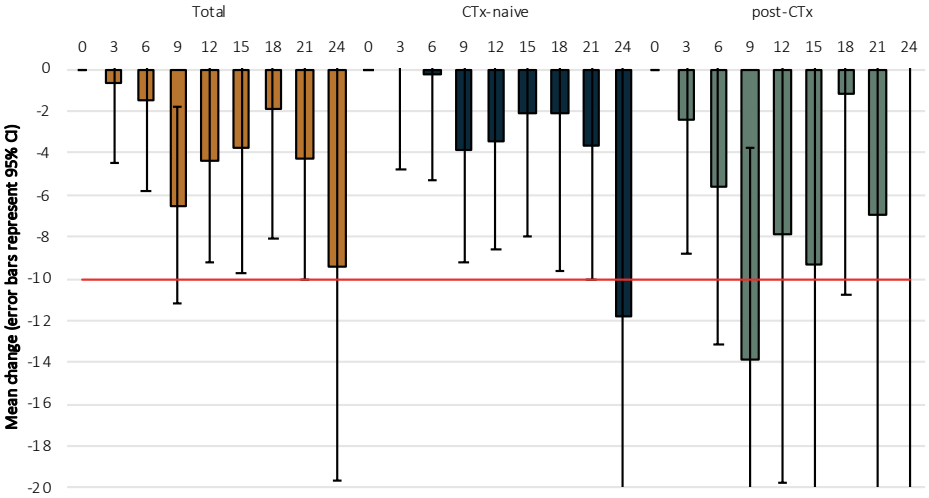

Figure 4.3G | Changes in HRQoL over time per disease state; mean changes in social functioning (cancer-specific HRQoL)

Mean changes from inclusion. Error bars represent 95% CI, red line is MID.

Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

MID improvement of pain. In CTx-naïve patients, the proportion of patients with MID after twelve months was higher for "worst" (29% vs 18%, p=0.04) and "average" (24% vs 13%, p=0.02) pain and pain interference on daily functioning (26% vs 11%, p<0.01) than after six months (Supplementary Table S4.5A).

No differences between CTx-naïve and post-CTx patients were found in time to deterioration except for "worst" pain (Supplementary Table S4.6). CTx-naïve patients had a significantly longer time to deterioration on "worst" pain than post-CTx patients (24.5 vs 9.9 months respectively, p=0.04).

DISCUSSION

To our knowledge this is the largest contemporary real-world longitudinal analysis of HRQoL during mCRPC. Previous research mainly focused on patients treated in randomized controlled trials, but results from these trials cannot be easily generalized to the real-world practice[41]. The absence of complicated inclusion and exclusion criteria in our study warrants the reflection of a real-world population in current daily practice.

In this study we showed that at inclusion, baseline HRQoL was relatively high. Most of our patients were in an early disease phase, with 75% of patients without docetaxel pre-treatment and a short interval from diagnosis of castrate-resistance to inclusion into the

study. Previously published mCRPC cohorts reported lower HRQoL[46,120]. For example, the mean EQ-5D index value was 0.82 in our study, compared with 0.64 to 0.74 in other reports[46,120]. However, differences between our study and previous reports can be explained by differences in patient selection, the availability of life-prolonging therapeutic options, and international valuation of HRQoL measurement[121,122]. This contemporary cohort indicates that in Dutch daily practice generic HRQoL is high in early mCRPC state[43,45,46,120]. Most baseline symptoms were identified in role (i.e. patient's ability to perform daily activities, leisure time activities, and/or work) and physical functioning with high symptom burden on pain, fatigue, and insomnia.

Deterioration was seen in almost all domains of HRQoL. Deterioration in HRQoL is part of the normal aging process, and scores on cognitive, emotional and social functioning are comparable to the European population norms of the same age group (≥ 70 years)[123]. However, we found low scores on role and physical functioning at inclusion, probably showing the impact of mCRPC on these domains[123]. Role and physical functioning were also prone to deterioration. Therefore, specific attention for these domains at the start of new systemic treatment and during follow-up of patients with mCRPC is needed to maintain HRQoL as long as possible.

A delay in HRQoL and pain progression has been reported in randomized controlled trials of new LPDs[35,37,39,109]. Eighty-four percent of patients in our study were also treated with LPDs during follow-up. Owing to small sample sizes, we were not able to calculate differences between treated and untreated patients, and more specifically between treatments. In our total mCRPC-population the median time to pain deterioration ("worst" pain) was 24.5 months in chemotherapy-naïve and 9.9 months in post-chemotherapy patients. This time to progression on "worst" pain is in agreement with the chemotherapy-naïve COU-AA-302 treatment arm (25.8 months)[34] and in the post-chemotherapy COU-AA-301 treatment arm (7.4 months)[36]. Comparison with clinical trials, however, warrants caution owing to differences in patient selection, outcome measures, and the definition of MID compared with our real-world population.

In prostate-cancer specific HRQoL we found low sexual activity and mostly urinary symptoms at baseline. A population-based survey in the United Kingdom showed that sexual activity was low among all stages of prostate cancer[125]. Although younger patients were concerned about the lack of sexual activity, less than one-half of the patients were offered treatment to improve sexual health[125]. The baseline assessment in individual patients with mCRPC can address problems and concerns about sexual health and guide individual treatment. However, similar to other research no trends in prostate-cancer specific HRQoL were observed during follow-up[43]. Therefore, the EORTC QLQ-PR25 seems of low additional value when it comes to monitoring treatment effects and tolerability.

An important limitation of this study was the relatively small sample size. Only four percent of all patients included in the CAPRI-registry were included in the PRO-CAPRI study. At baseline mCRPC diagnosis, patients in the PRO-CAPRI study tended to be in better clinical condition than patients in the CAPRI-registry. Therefore, results are possibly not generalizable for the total Dutch population. The second limitation of this study was the non-randomized study design that made it impossible to compare the individual new treatments. Subgroups per treatment were too small for reliable analyses of changes in HRQoL.

CONCLUSION

To conclude, in spite of the availability of life-prolonging drugs, deterioration was seen in almost all domains of HRQoL with the domains role and physical functioning especially prone to deterioration. Therefore, specific attention during follow-up is needed in order to maintain HRQoL as long as possible by timely starting supportive care management. Incorporating individual PRO assessment in daily clinical practice can possibly aid physicians in treatment decisions, monitoring treatment effects and tolerability, and improving symptom control.

SUPPLEMENTARY MATERIAL

Table S4.1 | Overview of used questionnaires and minimally important differences (MID)

		No. of items	No. of items needed[a]	Scale	MID
EQ-5D[117,118]	EQ VAS	1	1	0-100	7-11
	EQ-5D index value	5	5	-0,594 to 1	-
EORTC QLQ-C30[118,119]	physical functioning[b]	5	3	0-100	10
	role functioning[b]	2	1	0-100	10
	emotional functioning[b]	4	2	0-100	10
	cognitive functioning[b]	2	1	0-100	10
	social functioning[b]	2	1	0-100	10
	fatigue[c]	3	2	0-100	10
	nausea/vomiting[c]	2	1	0-100	10
	pain[c]	2	1	0-100	10
	dyspnea[c]	1	1	0-100	10
	insomnia[c]	1	1	0-100	10
	appetite loss[c]	1	1	0-100	10
	constipation[c]	1	1	0-100	10
	diarrhea[c]	1	1	0-100	10
	financial difficulties[c]	1	1	0-100	10
EORTC QLQ-PR25[118]	sexual activity[b]	2	1	0-100	10
	sexual functioning[b]	4	2	0-100	10
	urinary symptoms[c]	8	4	0-100	10
	bowel symptoms[c]	4	2	0-100	10
	hormonal therapy related symptoms[c]	6	3	0-100	10
	use of incontinence aid[c]	1	1	0-100	10
BPI-SF[116,118]	pain severity	4	4	0-10	≥30% and ≥2 points from baseline
	worst pain	1	1	0-10	≥30% and ≥2 points from baseline
	least pain	1	1	0-10	≥30% and ≥2 points from baseline
	average pain	1	1	0-10	≥30% and ≥2 points from baseline
	current pain	1	1	0-10	≥30% and ≥2 points from baseline
	pain interference	7	4	0-10	≥50% of baseline standard deviation and ≥2 points

[a] the number of items per domain needed to be completed to adequately calculate the score per domain; [b] functional scales (high scores indicate high level of functioning); [c] symptom scales (high scores indicate high symptom burden).
Abbreviations: MID, minimally important difference; VAS, visual analogue scale.

Table S4.2 | Compliance rate with HRQOL questionnaires

Months after inclusion	Total	EQ-5D	EORTC QLQ-C30	EORTC QLQ-PR25	BPI-SF[a]
0	151	150 (99)	146 (97)	145 (96)	111 (74)
3	136	133 (98)	134 (99)	-	107 (79)
6	124	122 (98)	123 (99)	120 (97)	99 (80)
9	119	118 (99)	118 (99)	-	103 (87)
12	101	98 (97)	98 (97)	96 (95)	85 (84)
15	83	81 (98)	82 (99)	-	71 (86)
18	70	70 (100)	70 (100)	66 (94)	57 (81)
21	55	55 (100)	55 (100)	-	50 (91)
24	39	39 (100)	39 (100)	38 (97)	34 (87)

Compliance rate: the number of patients completing at least one question divided by the total number of available patients per time point (i.e. alive and still on study). All data are presented as n (%). [a]BPI-SF was added one year after study start through protocol amendment: 27% of patients was enrolled before protocol amendment.
Abbreviations: HRQoL, health related quality of life.

Table S4.3 | Representativeness of PRO-CAPRI population based on baseline characteristics

		PRO-CAPRI	CAPRI	P
		N=151	N=3,616	
Age (years)	median (range)	72 (54-94)	75 (46-99)	0.002*
	≥75 years, %	41	52	0.006*
ECOG PS, %	0	30	18	0.078
	1	21	18	
	>1	3	5	
	unknown	46	60	
Gleason score, %	≤7	34	34	0.602
	8-10	56	51	
	no histology	3	3	
	metastasis biopsy	1	1	
	unknown	6	10	
Charlson comorbidity index, %	6	70	62	0.211
	7-8	26	32	
	9-10	4	5	
	>10	1	2	
	unknown	0	0	
Disease state, %	N1 / N0 / Nx	5 / 46 / 49	7 / 28 / 65	0.020*
	M1 / M0 / Mx (bone)	6 / 62 / 33	9 / 53 / 39	0.144
	M1 / M0 / Mx (visceral)	14 / 3/ 83	16 / 4 / 81	1.000
Period from ADT to mCRPC (mo)	median (IQR)	15.1 (9-28)	15.1 (8-29)	0.986
	unknown, %	0	<1	
Hb (mmol/L)	median (IQR)	8.3 (7.6-8.8)	8.0 (7.3-8.6)	0.014*
	unknown, %	30	34	
LDH (U/L)	median (IQR)	212 (184-249)	223 (188-294)	0.058
	unknown, %	47	59	
ALP (U/L)	median (IQR)	97 (75-150)	106 (78-192)	0.041*
	unknown, %	30	37	
PSA (µg/L)	median (IQR)	15.0 (5-44)	16.7 (6-62)	0.247
	unknown, %	1	3	

Table S4.3 | Representativeness of PRO-CAPRI population based on baseline characteristics *(continued)*

		PRO-CAPRI	CAPRI	p
		N=151	N=3,616	
Treatment during follow-up, %	none	1	12	<0.001*
	no LPD	5	25	
	LPD	94	63	
	docetaxel	66	43	<0.001*
	cabazitaxel	25	13	<0.001*
	abiraterone	38	32	0.106*
	enzalutamide	72	30	<0.001*
	radium-223	17	8	<0.001*

All baseline measurements were included if they were measured in the period of three months prior or three months after mCRPC diagnosis. Tested for statistical significance between PRO-CAPRI subgroup and rest of CAPRI-population (N=3,465); * significant at p-value<0.05.

Abbreviations: IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ADT, androgen deprivation therapy; mCRPC, metastastic castration-resistant prostate cancer; mo, months; Hb, haemoglobin, LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; LPD, life prolonging drug (either docetaxel, cabazitaxel, abiraterone, enzalutamide or radium-223).

Table S4.4 | Assessment of HRQoL with subgroups per disease state at inclusion

		Total	CTx-naïve	Post-CTx	p
		N=151	N=112	N=39	
Generic HRQoL (EQ-5D)	mobility[a],%	48	47	49	0.775
	self-care[a],%	15	16	10	0.404
	usual activities[a],%	43	43	44	0.774
	pain/discomfort[a],%	55	46	51	0.698
	anxiety/depression[a],%	27	28	23	0.630
	EQ VAS	73.2 (17)	72.9 (17)	73.9 (16)	0.848
	EQ-5D index value	0.82 (0.17)	0.82 (0.16)	0.82 (0.16)	0.796
Cancer-specific HRQoL (EORTC QLQ-C30)	global health status	75.9 (17)	75.5 (18)	76.9 (12)	0.954
	physical functioning	76.1 (23)	75.8 (24)	76.8 (23)	0.972
	role functioning	69.3 (32)	68.8 (32)	71.0 (30)	0.853
	emotional functioning	82.8 (18)	80.9 (19)	88.4 (14)	0.022*
	cognitive functioning	85.4 (18)	84.7 (18)	87.5 (17)	0.455
	social functioning	80.5 (27)	78.9 (29)	85.2 (21)	0.405
	fatigue	32.3 (25)	32.6 (26)	31.6 (21)	0.963
	nausea/vomiting	5.5 (15)	5.9 (17)	4.2 (10)	0.770
	pain	23.4 (25)	25.2 (26)	18.1 (20)	0.243
	dyspnea	18.9 (27)	18.2 (26)	21.3 (28)	0.516
	insomnia	22.8 (28)	24.3 (28)	18.5 (27)	0.235
	appetite loss	11.0 (25)	10.4 (24)	13.0 (27)	0.490
	constipation	12.8 (22)	14.8 (24)	6.5 (13)	0.083
	diarrhea	10.0 (23)	9.4 (23)	12.0 (23)	0.260
	financial difficulties	4.6 (14)	5.2 (14)	2.8 (12)	0.203
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	sexual activity	6.7 (16)	8.5 (18)	1.4 (5)	0.016*
	sexual functioning[b]	55.2 (22)	58.3 (18)	45.0 (33)	0.246
	urinary symptoms	21.1 (17)	22.7 (18)	16.4 (14)	0.057
	bowel symptoms	7.4 (14)	8.9 (16)	3.7 (8)	0.038*
	incontinence aid[c]	13.3 (29)	14.7 (23)	9.1 (22)	0.407
	hormonal therapy related symptoms	16.6 (13)	16.9 (14)	15.8 (10)	0.980

Table S4.4 | Assessment of HRQoL with subgroups per disease state at inclusion *(continued)*

		Total	CTx-naïve	Post-CTx	p
		N=151	N=112	N=39	
Pain (BPI-SF)	pain severity				
	worst pain	2.22 (2)	2.21 (3)	2.24 (2)	0.530
	average pain	1.82 (2)	1.89 (2)	1.58 (2)	0.960
	least pain	1.11 (2)	1.12 (2)	1.08 (2)	0.858
	current pain	1.52 (2)	1.67 (2)	0.96 (1)	0.407
	pain interference	1.73 (2)	1.82 (2)	1.42 (2)	0.492

All data are presented as mean (SD) unless listed otherwise. Percentages can exceed 100% due to rounding. p-values calculated for differences in time to first MID between CTx-naïve and post-CTx patients. [a] Percentage of patients reporting any problems (level 2 to 5); [b] mean scores of patients reporting any sexual activity; [c] mean scores of patients reporting any use of incontinence aid; * significant at p-value<0.05.

Abbreviations: HRQOL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; SD, standard deviation

Table S4.5A | Proportion of CTx-naïve patients with a clinically relevant deterioration and time to deterioration in HRQoL at month 6 and month 12

		Month 6	Month 12	p
Generic HRQoL (EQ-5D)	EQ VAS	22/85 (25.9)	23/73 (31.5)	0.556
Cancer-specific HRQoL (EORTC QLQ-C30)	global health status	16/90 (17.8)	24/75 (32.0)	0.027*
	physical functioning	23/85 (27.1)	30/69 (43.5)	0.019*
	role functioning	24/88 (27.3)	33/73 (45.2)	0.017*
	emotional functioning	8/89 (9.0)	13/74 (17.6)	0.096
	cognitive functioning	27/89 (30.3)	27/74 (36.5)	0.302
	social functioning	17/89 (19.1)	26/74 (35.1)	0.007*
	fatigue	38/86 (44.2)	39/73 (53.4)	0.096
	nausea/vomiting	12/89 (13.5)	13/74 (17.6)	0.791
	pain	18/89 (20.2)	25/74 (33.8)	0.019*
	dyspnea	20/86 (23.3)	14/72 (19.4)	0.549
	insomnia	13/86 (15.1)	16/73 (21.9)	0.227
	appetite loss	19/88 (21.6)	21/72 (29.2)	0.302
	constipation	14/88 (15.9)	15/73 (20.5)	0.648
	diarrhea	15/87 (17.2)	20/74 (27.0)	0.238
	financial difficulties	6/88 (6.8)	6/74 (8.1)	0.688
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	sexual activity	12/86 (14.0)	16/71 (22.5)	0.070
	urinary symptoms	16/83 (19.3)	18/71 (25.4)	0.424
	bowel symptoms	10/66 (15.2)	8/52 (15.4)	0.688
	hormonal therapy related symptoms	11/87 (12.6)	18/72 (25.0)	0.035*
Pain (BPI-SF)	pain severity	6/56 (10.7)	9/52 (17.3)	0.219
	worst pain	10/57 (17.5)	15/52 (28.8)	0.039*
	average pain	7/56 (12.5)	12/51 (23.5)	0.016*
	least pain	7/54 (13.0)	11/51 (21.6)	0.267
	current pain	6/57 (10.5)	5/50 (10.0)	1.000
	pain interference	5/46 (10.9)	11/42 (26.2)	0.008*

Data are presented as n/N (%) for total population (N=112). p-values calculated for differences between proportion of patients with MID at month 6 and month 12; * significant at p-value <0.05.

Abbreviatons: HRQOL, health-related quality of life; MID, minimal important difference; CTx-naive, no or no prior docetaxel chemotherapy at inclusion.

Table S4.5B | Proportion of post-CTx patients with a clinically relevant deterioration and time to deterioration in HRQoL at month 6 and month 12

		Month 6	Month 12	p
Generic HRQoL (EQ-5D)	EQ VAS	9/30 (30.0)	8/22 (36.4)	0.375
Cancer-specific HRQoL (EORTC QLQ-C30)	global health status	11/30 (36.7)	8/21 (38.1)	1.000
	physical functioning	15/30 (50.0)	7/21 (33.3)	0.453
	role functioning	12/29 (41.4)	10/20 (50.0)	0.453
	emotional functioning	7/30 (23.3)	6/21 (28.6)	0.688
	cognitive functioning	10/30 (33.3)	6/21 (28.6)	0.688
	social functioning	11/30 (36.7)	7/21 (33.3)	1.000
	fatigue	15/30 (50.0)	11/21 (52.4)	0.688
	nausea/vomiting	3/30 (10.0)	6/21 (28.6)	0.375
	pain	8/30 (26.7)	9/21 (42.9)	0.063
	dyspnea	6/30 (20.0)	2/21 (9.5)	0.500
	insomnia	3/30 (10.0)	4/21 (19.0)	0.625
	appetite loss	5/30 (16.7)	5/21 (23.8)	1.000
	constipation	3/30 (10.0)	2/21 (9.5)	1.000
	diarrhea	5/30 (16.7)	4/31 (19.0)	0.688
	financial difficulties	2/30 (6.7)	0/21 (0.0)	1.000
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	sexual activity	2/31 (6.5)	0/22 (0.0)	1.000
	urinary symptoms	5/32 (15.6)	4/23 (17.4)	1.000
	bowel symptoms	1/27 (3.7)	2/19 (10.5)	1.000
	hormonal therapy related symptoms	8/31 (25.8)	6/22 (27.3)	1.000
Pain (BPI-SF)	pain severity	3/19 (15.8)	4/13 (30.8)	0.250
	worst pain	5/19 (26.3)	6/13 (46.2)	0.125
	average pain	3/18 (16.7)	6/12 (50.0)	0.063
	least pain	2/19 (10.5)	3/13 (23.1)	0.500
	current pain	3/18 (16.7)	4/13 (30.8)	0.250
	pain interference	2/15 (13.3)	3/9 (33.3)	1.000

Data are presented as n/N (%) for CTx-naive population (N=39). p-values calculated for differences between proportion of patients with MID at month 6 and month 12; * significant at p-value <0.05.

Abbreviations: HRQOL, health-related quality of life; MID, minimal important difference; post-CTx, current or post-docetaxel chemotherapy at inclusion.

Table S4.6 | Time to clinical relevant deterioration in months of HRQoL per disease state

		CTx-naive		Post-CTx		p
		N=112		N=39		
		No. of events, %	Time to MID (mo)	No. of events, %	Time to MID (mo)	
Generic HRQoL (EQ-5D)	EQ VAS	56.3	12.3 (6-NR)	69.2	10.0 (4-21)	0.299
Cancer-specific HRQoL (EORTC QLQ-C30)	global health status	55.4	15.1 (7-26)	51.3	13.4 (7-NR)	0.978
	physical functioning	58.9	14.7 (6-26)	59.0	6.8 (4-NR)	0.490
	role functioning	63.4	12.3 (5-22)	51.3	12.1 (4-NR)	0.521
	emotional functioning	31.3	26.6 (12-NR)	41.0	NR (6-NR)	0.167
	cognitive functioning	52.7	12.6 (6-28)	56.4	10.0 (6-NR)	0.847
	social functioning	53.6	14.2 (9-NR)	61.5	9.5 (6-NR)	0.276
	fatigue	64.3	8.6 (4-23)	71.8	6.5 (4-13)	0.381
	nausea/vomiting	44.6	19.9 (9-NR)	53.8	15.3 (9-25)	0. 279
	pain	52.7	15.8 (6-NR)	66.7	10.2 (6-24)	0.200
	dyspnea	42.9	22.6 (8-NR)	43.6	20.1 (7-NR)	0.805
	insomnia	43.8	21.8 (9-NR)	33.3	NR (10-NR)	0.356
	appetite loss	50.9	16.5 (8-NR)	41.0	NR (9-NR)	0.459
	constipation	39.3	24.5 (9-NR)	35.9	24.1 (12-NR)	0.672
	diarrhea	35.7	NR (10-NR)	38.5	21.7 (8-NR)	0.696
	financial difficulties	20.5	NR (24-NR)	10.3	NR (NR-NR)	0.205
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	sexual activity	17.0	NR (NR-NR)	5.1	NR (NR-NR)	0.092
	sexual functioning	2.7	NR (NR-NR)	0	NR (NR-NR)	0.353
	urinary symptoms	28.6	25.6 (15-NR)	20.5	NR (19-NR)	0.571
	bowel symptoms	18.8	NR (25-NR)	12.8	NR (NR-NR)	0.783
	incontinence aid	5.4	NR (NR-NR)	5.1	NR (NR-NR)	0.941
	hormonal therapy related symptoms	26.8	26.3 (16-NR)	30.8	NR (12-NR)	0.242
Pain (BPI-SF) [a]	pain severity	32.6	NR (11-NR)	40.0	NR (9-NR)	0.408
	worst pain	41.9	24.5 (8-NR)	64.0	9.9 (7-16)	0.042*
	average pain	32.6	NR (11-NR)	52.0	12.5 (10-NR)	0.072
	least pain	39.5	NR (10-NR)	36.0	NR (11-NR)	0.833
	current pain	30.2	NR (11-NR)	40.0	NR (9-NR)	0.349
	pain interference	31.4	NR (15-NR)	32.0	NR (10-NR)	0.633

Data are presented as percentages for number of events (i.e. number of patients with MID) and median (IQR) for time to first MID. p-values calculated for differences in time to first MID between CTx-naïve and post-CTx patients. [a] only patients with BPI-SF measurement at inclusion (CTx-naïve N=86 and post-CTx N=25); * significant at p-value <0.05

Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimal important differences; IQR, interquartile range; NR, not reached.

5

Real-world outcomes of sequential androgen-receptor targeting therapies (ART) in mCRPC

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European Urology Oncology 2021;4(4):618-627

ABSTRACT

Background: Cross-resistance between androgen-receptor targeting therapies (ARTs) (abiraterone acetate plus prednisone [ABI+P] or enzalutamide [ENZ]) for treatment of metastatic castration-resistant prostate cancer (mCRPC) may affect responses to second ART (ART2).

Objective: To establish treatment duration and prostate specific antigen (PSA) response of ART2 in real-world mCRPC patients treated with or without other life-prolonging drugs (LPD: i.e. docetaxel, cabazitaxel or radium-223) between ART1 and ART2.

Design, setting and participants: castration-resistant prostate cancer (CRPC) patients, diagnosed between 2010 and 2016 were retrospectively registered in CAstration-resistant Prostate cancer RegIstry (CAPRI). Patients treated with both ARTs were clustered into two subgroups: ART1>ART2 or ART1>LPD>ART2.

Outcome measurements and statistical analysis: outcomes were ≥50% PSA response and treatment duration of ART2. Descriptive statistics and binary logistic regression after multiple imputations were performed.

Results and limitation: A total of 273 patients were included with a median follow-up of 8.4 months from ART2. Patients with ART1>ART2 were older and had favourable prognostic characteristics at ART2 baseline compared with patients with ART1>LPD>ART2. No differences between ART1>ART2 and ART1>LPD>ART2 were found in PSA response and treatment duration. Multivariate analysis suggested that PSA response of ART2 was less likely in patients with visceral metastases (odds ratio [OR] 0.143, p=0.04) and more likely in patients with a relatively longer duration of androgen-deprivation treatment (OR 1.028, p=0.01) and with ABI+P before ENZ (OR 3.192, p=0.02). A major limitation of this study was missing data, a common problem in retrospective observational research.

Conclusions: The effect of ART2 seems to be low with a low PSA response rate and a short treatment duration irrespective of interposed chemotherapy or radium-223, especially in patients with a short time on castration, visceral disease, and ENZ before ABI+P.

Patient summary: We observed no differences in outcomes of patients treated with sequential abiraterone acetate plus prednisone (ABI+P) and enzalutamide (ENZ) with or without interposed chemotherapy or radium-223. In general, outcomes were lower than those in randomised trials, questioning the additional effect of second treatment with ABI+P or ENZ in daily practice.

INTRODUCTION

Annually, 3,000 patients develop metastatic castration-resistant prostate cancer (mCRPC) in the Netherlands[127]. Multiple treatment options are available, including taxane (TAX) chemotherapy (docetaxel [DOC] and cabazitaxel [CAB]), androgen-receptor targeting therapies (ARTs; abiraterone acetate plus prednisone [ABI+P] and enzalutamide [ENZ]), and an alpha-emitting radioisotope (radium-223 [Ra-223]). One of the challenges is selecting the most optimal treatment sequence.

Sequencing of ARTs is of particular interest, since the two ARTs used target the androgen signalling pathway. Acquired resistance to ABI+P and ENZ is inevitable. Molecular mechanisms of resistance to both ARTs are similar and cross-resistance is a common phenomenon[128]. Clinical findings from one prospective and several retrospective studies support this hypothesis, showing low prostate-specific antigen (PSA) responses of second ART (ART2), especially in patients treated with ENZ before ABI+P[129–132]. A short interval between both ARTs and progression on ART1 are related to low PSA responses[133,134].

The European Association of Urology (EAU) advises the use of DOC after first line ART because of concerns about cross-resistance[23], but no solid evidence points to resensitization following the "sandwich" use of TAX prior to ART2. One small, retrospective study recently reported similar PSA responses (21-30%) in patients treated with both ARTs directly after each other or with TAX in between[135].

However, available data on the activity of ART2 are not easily translated into daily clinical practice, since data are based on small study populations (<150 patients) with highly selected patients either participating in early access programmes or treated in academic institutions, or on follow-up of patients who participated in randomized controlled trial.

The aim of this study is to investigate PSA response and treatment duration of ART2 depending on treatment sequence in a real-world setting. We provide outcomes on sequential ARTs or ARTs with interposed life-prolonging drugs (LPD) as TAX or Ra-223.

METHODS

Study design and setting

CAstration-resistant Prostate cancer RegIstry (CAPRI) is an investigator-initiated, observational multi-centre cohort study in 20 Dutch hospitals. Data collection started after approval by the local medical ethics committee and hospital board. The study design has been described before[41]. CRPC patients were included retrospectively from 1 January 2010 until 31 December 2015 with regular updates of all data until 31 December

2017. All treatment decisions as well as the use of diagnostics, response measurements, and supportive care were made by treating physicians and were not protocol amended. CAPRI is registered in the Dutch Trial Registry as NTR3591.

Participants

Patients having mCRPC who were treated with both ABI+P and ENZ before 1 July 2017 with one line of TAX or Ra-223 between both ARTs were included in this analysis. Patients treated with DOC for metastatic hormone-sensitive prostate cancer were excluded.

Outcomes were evaluated based on treatment sequence: (1) ABI+P directly followed by ENZ or vice versa (ART1>ART2) and (2) ABI+P followed by ENZ or vice versa interposed with TAX or Ra-223 treatment (ART1>LPD>ART2).

Additional subgroup analyses were performed based on the following parameters:

1. sequence of ABI+P and ENZ: ABI+P before ENZ (ABI+P>ENZ) or ENZ before ABI+P (ENZ>ABI+P),
2. ART1 treatment duration: "long ART1 treatment" (i.e. ART1 treatment duration ≥ 12 weeks according to Prostate Cancer Clinical Trials Working Group 3 [PCWG3] criteria[71]) or "short ART1 treatment" (i.e. ART1 treatment duration <12 weeks),
3. interval between ART1 and ART2: the interval between ART1 and ART2 was calculated as the time between stop of ART1 and start of ART2, with a cut off of 40 days based on previous published work[133].

Study size

In all, 273 participants were included from a total of 3,616 mCRPC patients.

Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics (including performance score, symptoms, extent of disease and laboratory values) were included in the analysis if they were documented from six weeks before to one week after the start of ART2. All patients were followed until death, loss-to-follow-up or 31 December 2017. Follow-up duration was calculated as the start date of ART2 to the last recorded date.

Outcome

Primary outcome was PSA response. PSA response was defined as the maximum change from baseline PSA levels (in percentages) without confirmation of second measure. In case no decline was present, responses were measured at 12 weeks (according to the PCWG 3 criteria for response measurement[71]) or if treatment was <12 weeks, at the end

of treatment or start of next treatment. PSA response was defined as a ≥50% PSA decline from baseline[71].

The secondary outcome was treatment duration and was calculated as the interval between the start and stop of ART2. If the stop date was unknown, treatment duration was specified as the time (1) from the start of ART2 to the start of next treatment or (2) from the start of ART2 to death if ART2 was the last treatment. Patients still alive at the end of follow-up and without a new line of therapy were censored at the date of last known visit.

Statistical analysis

The sample size was not based on power calculations. Descriptive statistics were performed. To test the significance between subgroups chi square test, Mann Whitney U test and t-test were used. Waterfall plots indicate PSA response per subgroup. Missing baseline characteristics were imputed using multiple imputations with Monte Carlo Markov Chain method. Binary logistic regression to assess the effect of baseline variables on PSA response was performed. A p-value of <0.05 was considered statistically significant. IBM SPSS Statistics version 24.0 (IBM ®, Armonk, NY, USA) was used for all analyses.

RESULTS

In total, 273 patients (8%) were treated with both ABI+P and ENZ before 1 July 2017. Of these patients, 148 were treated with ART1>ART2 and 125 patients with ART1>LPD>ART2 including 61 patients (48%) treated with DOC, 41 (33%) with CAB, and 23 (19%) with Ra-223 between ART1 and ART2 (Figure 5.1).

In ART1>ART, 86 patients (58%) received ABI+P>ENZ and 62 (44%) received ENZ>ABI+P compared with 86 patients (69%) with ABI+P>ENZ and 39 patients (31%) with ENZ>ABI+P in ART1>LPD>ART2 (Figure 5.1).

Median follow-up from ART2 was 8.4 months (range 0.3-35.8 months). At the end of the study, 202 (74%) all-cause deaths have occurred, 38 patients (14%) were lost to follow-up and 33 (12%) were still in follow-up (median follow-up from ART2 of 11.1 months).

Baseline characteristics

Patients in the ART1>ART2 sequence were older at the start of ART2 than patients in ART1>LPD>ART2 (75 vs 73 years, p<0.01) (Table 5.1). ART1>ART2 patients had favourable prognostic characteristics: less visceral metastases (12% vs 22%, p=0.04), higher haemoglobin levels (7.5 vs 6.9 mmol/L, p<0.01), lower lactate dehydrogenase (LDH) levels (240 vs 270 U/L, p=0.02) and lower PSA levels (114 vs 170 µg/L, p=0.03).

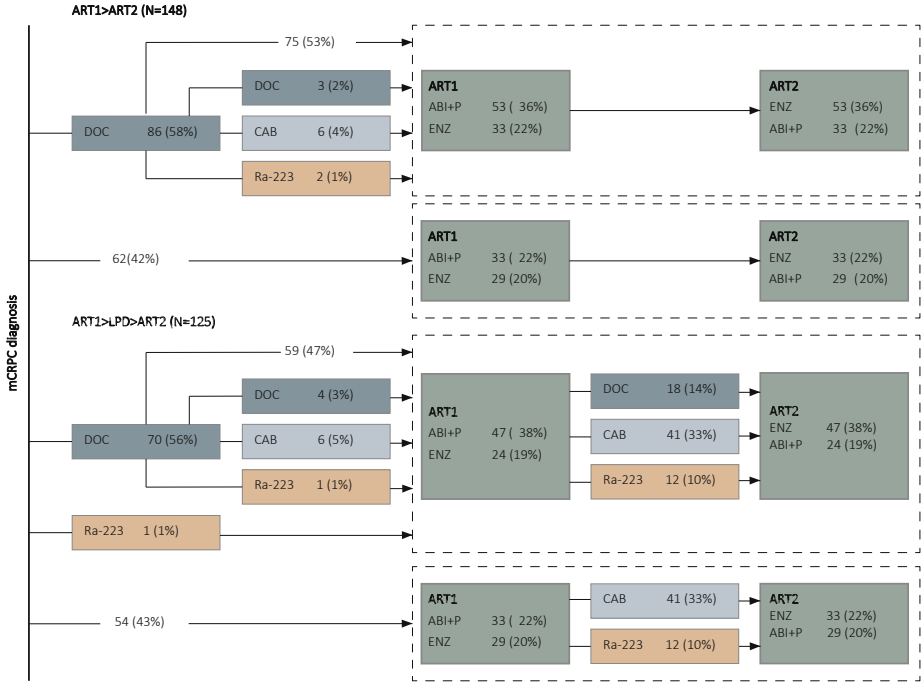

Figure 5.1 | Flowchart of treatment sequencing in patients treated with both ARTs
Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; ART1, first AR-targeting therapy; ART2, second AR-targeting therapy; DOC, docetaxel; CAB, cabazitaxel; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; Ra-223, radium-223

In ART1>ART2 more patients had short ART1 treatment (<12 weeks) than those in ART1>LPD>ART2 (24% vs 11%, p<0.01), but no differences in PSA response of ART1 were observed. In the ART1>LPD>ART2 sequence, 24% of patients had a ≥50% PSA decline on interposed LPDs (28% on TAX and 9% on Ra-223) (Table 5.1).

PSA response of ART2

PSA response of ART2 was similar in ART1>ART2 to that in ART1>LPD>ART2 (20% vs 18%, p=0.297) (Table 5.2 and Figure 5.2). PSA response of ART2 in ART1>ART2 was similar to PSA response of LPD in ART1>LPD>ART2 (respectively 20% vs 24%, p=0.80). PSA response of ART2 was lower in patients with ART1 treatment ≥12 weeks than in patients with ART1 treatment <12 weeks, but this did not reach statistical significance (18% vs 26%, p=0.08). No differences in PSA response were found based on ABI+P and ENZ sequence and interval between ART1 and ART2 (Table 5.3).

Table 5.1 | Baseline characteristics at the start of second AR-targeting therapy (ART2)

		ART1>ART2	ART1>LPD>ART2	p
		N=148	N=125	
Age (years)	median (range)	75 (53-80)	73 (50-90)	0.002*
	≥ 75 years, %	54	38	0.010*
Charlson score, %	6	57	69	0.147
	7-8	35	22	
	9-10	7	8	
	>10	1	1	
ECOG PS, %	0	16	17	0.172
	1	35	40	
	≥2	29	18	
	unknown	20	25	
Opioid use, %	yes	16	23	0.968
	no	22	33	
	unknown	62	44	
Disease state, %	N0 / N1 / Nx	14 / 41 / 45	20 / 38 / 42	0.260
	M0 / M1 / Mx (bone)	5 / 80 / 15	3 / 82 / 14	0.554
	M0 / M1 / Mx (visceral)	44 / 12 / 45	34 / 22 / 44	0.016*
Gleason score, %	≤ 7	34	37	0.715
	8-10	53	53	
	no histology	1	2	
	metastasis biopsy	1	1	
	unknown	10	7	
Time castration to mCRPC (mo)	median (IQR)	14.3 (8-27)	13.4 (9-22)	0.725
	unknown, %	0	0	
Hb (mmol/L)	median (IQR)	7.5 (6.8-8.2)	6.9 (6.0-7.8)	<0.001*
	unknown, %	10	7	
ALP (U/L)	median (IQR)	129 (88-224)	144 (86-258)	0.581
	unknown, %	11	10	
LDH (U/L)	median (IQR)	240 (190-283)	270 (204-364)	0.017*
	unknown, %	30	22	
PSA (µg/L)	median (IQR)	114 (32-391)	170 (85-444)	0.033*
	unknown, %	8	7	
ART1 treatment, %	ENZ	42	31	0.068
	ABI+P	58	69	
Number of lines prior to ART2, %	1	42	0	<0.001*
	2	51	43	
	3	7	48	
	>3	0	9	

Table 5.1 | Baseline characteristics at the start of second AR-targeting therapy (ART2) *(continued)*

		ART1>ART2	ART1>LPD>ART2	p
		N=148	N=125	
Treatment duration ART1 (mo)	median (IQR)	7.1 (3.1-13.6)	7.4 (5.2-12.3)	0.869
	≤12 weeks, %	24	11	0.005*
PSA response ART1, %	≥50% PSA decline	51	54	0.442
	<50% PSA decline	35	30	
	PSA response unknown	14	16	
Time between discontinuation ART1 and start ART2 (mo)	median (IQR)	<1 (0-2)	7 (5-10)	<0.001*
	unknown, %a	27	33	
	<40 days, %	53	0	
	≥40 days, %	20	67	
Interposed LPD[b], %	docetaxel	N/A	49	
	cabazitaxel		33	
	radium-223		18	
Treatment duration interposed LPD[b] (cycles)	median (range)	N/A	6 (1-15)	
	≥6 cycles, valid %		68	
	≥10 cycles, valid %		16	
	unknown, %		5	
PSA response interposed LPD[b], %	≥50% PSA decline	N/A	24	
	<50% PSA decline		49	
	PSA response unknown		27	

* significant at p-value <0.05; [a] patients with missing ART1 stopdate; [b] characteristics of interposed life-prolonging treatment in ART1>LPD>ART2.

Abbreviations: ART2, second AR-targeting therapy; ART1, first AR-targeting therapy; LPD, life-prolonging drug; ECOG PS, Eastern Cooperative Oncology Group Performance Score; mCRPC, metastatic castration-resistant prostate cancer; IQR, interquartile range; mo, months; Hb, hemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen.

Treatment duration

At the end of follow-up, 9% of ART1>ART2 patients were still on treatment compared with 3% of ART1>LPD>ART2 patients. Figure 5.3 shows median treatment duration of ART2: 3.2 months (interquartile range [IQR] 1.9-7.5 months) in ART1>ART2 and 3.2 months (IQR 1.8-5.9 months) in ART1>LPD>ART2 (p=0.04). Patients with ART1>ART2 had higher probability of longer treatment duration (hazard ratio 0.773, 95% confidence interval 0.603-0.993, p=0.04). Patients with a response on ART2 had a median treatment duration of 7.3 months (IQR 4.1-13.0 months).

No differences were observed in ART2 treatment duration between ABI+P and ENZ sequence, ART1 treatment duration and interval between ART1 and ART2 (Table 5.3).

Table 5.2 | PSA response and treatment duration of second AR-targeting therapy (ART2)

		ART1>ART2	ART1>LPD>ART2	p
		N=148	N=125	
PSA response	median change from baseline[a] (IQR)	-21% (-56% to +46%)	-18% (-50% to +73%)	0.315
	≥50% PSA decline, %	20	18	0.297
	<50% PSA decline, %	45	57	
	unknown, %	35	25	
Treatment duration ART2 (mo)	median (IQR)	3.2 (1.9-7.5)	3.2 (1.8-5.9)	0.042*
	censored, %[b]	9	3	
	≤3 months, valid %	52	49	0.621
	>3 months, valid %	48	51	
PSA response on line after ART1, %[c]	≥50% PSA decline	20	24	0.801
	<50% PSA decline	45	49	
	unknown	35	27	

* significant at p-value<0.05; [a] measured as relative change from baseline value (negative values indicate a PSA decline, positive values a PSA increase); [b] still on treatment at end of follow-up; [c] PSA response rate of ART2 in ART1>ART2 and of interposed LPD in ART1>LPD>ART2.

Abbreviations: PSA, prostate-specific antigen; ART2, second AR-targeting therapy; ART1, first AR-targeting therapy; LPD, life-prolonging drug; IQR, interquartile range; mo, months.

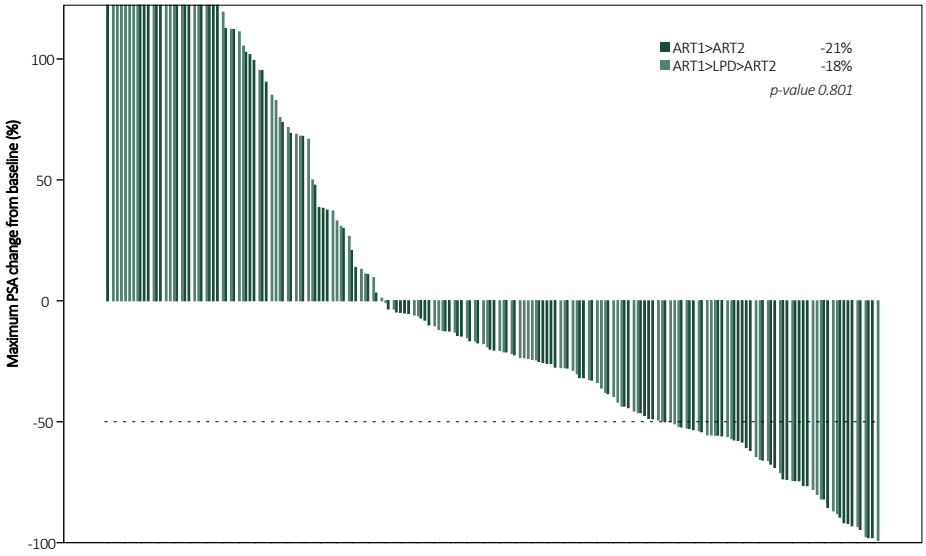

Figure 5.2 | Waterfall plot of PSA response during second AR-targeting therapy (ART2)

Maximum percentage change from baseline PSA per patient. Dotted line indicate the threshold of ≥50% PSA decline. Abbreviations: PSA, prostate-specific antigen; ART2, second AR-targeting therapy; ART1, first AR-targeting therapy; LPD, other life-prolonging drug (docetaxel, cabazitaxel or radium-223).

Table 5.3 | PSA response and treatment duration of second AR-targeting therapy (ART2) based on different subgroups

		ABI+P and ENZ sequence			ART1 treatment duration			Interval between ART1 and ART2		
		ENZ>ABI+P	ABI+P>ENZ	p	≥ 12 weeks	< 12 weeks	p	< 40 days	≥ 40 days	p
		N=101	N=172		N=223	N=50		N=119	N=154	
PSA response, %	≥50% PSA decline	14	23	0.159	18	26	0.078	20		0.461
	<50% PSA decline	51	50		53	38		45		
	unknown	36	27		29	36		35		
Treatment duration (mo)	median (IQR)	3.2 (1.8-7.3)	3.2 (1.9-5.9)	0.158	3.2 (1.9-6.7)	3.2 (1.8-5.8)	0.573	3.2 (1.9-6.4)	3.2 (1.8-6.5)	0.364
	censored, %[a]	12	3		6	6		8		
	3 months, valid %	55	48	0.276	51	49	0.825	53		0.437
	>3 months, valid %	45	52		49	51		47		

[a] still on treatment at end of follow-up.

Abbreviations: PSA, prostate-specific antigen; ART2, second AR-targeting therapy; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; ART1, first AR-targeting therapy; IQR, interquartile range; mo, months.

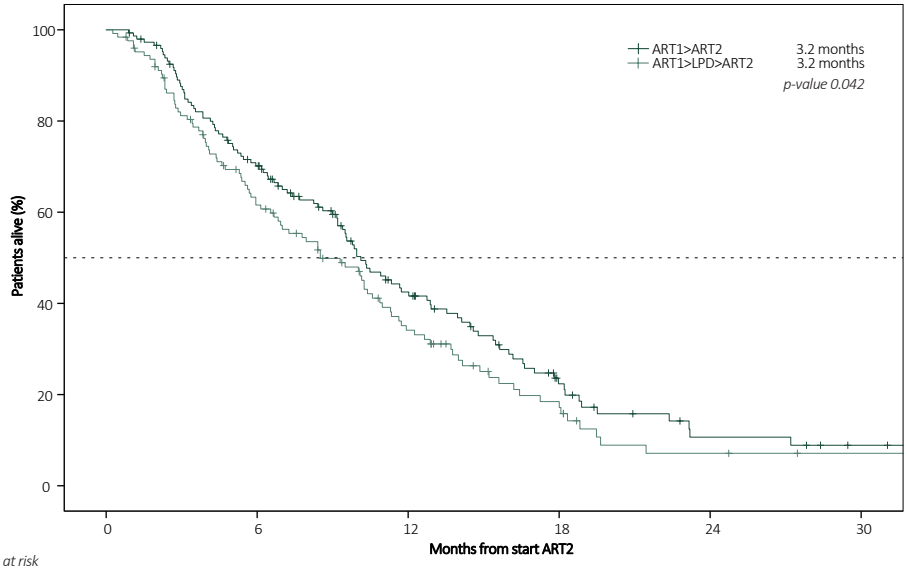

Figure 5.3 | Treatment duration (months) during second AR-targeting therapy (ART2)
Abbreviations: ART2, second AR-targeting therapy; ART1, first AR-targeting therapy; LPD, other lifeprolonging drug (docetaxel, cabazitaxel or radium-223).

Multivariable analysis

Eighty-three patients (30%) were excluded from multivariable binary logistic regression due to missing PSA response of ART2 (Table 5.4). There was no difference in PSA response on ART2 between ART1>ART2 and ART1>LPD>ART2 (odss ratio [OR] 0.890, p=0.89). Visceral metastases were associated with lower PSA response rates (OR 0.143, p=0.04), while longer time on androgen-deprivation therapy (OR 1.028, p=0.01) and ABI+P before ENZ (OR 3.192, p=0.02) were associated with higher PSA response rates (Table 5.4).

After the exclusion of 32 patients treated with ART1 for <12 weeks from multivariate analysis, time on androgen-deprivation therapy remained the only significant factor for PSA response (OR 1.034, p=0.02).

DISCUSSION

In this retrospective analysis of real-world data, we reported outcomes of sequential treatment with both ARTs with or without interposed TAX or Ra-223. To our knowledge, this is the largest multicentre population in which patients are treated according to the views and opinions of their medical oncologists and urologists. Outcomes therefore reflect current daily practice.

Table 5.4 | Univariable and multivariable binary logistic regression for PSA-response

		Univariable analysis of original data				Multivariable analysis of pooled data after imputation		
		N	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (years)	cont.	190	1.03	0.99-1.07	0.199	1.01	0.96-1.07	0.643
Charlson score	6	27	REF	-	-	REF	-	-
	7-8	52	0.61	0.35-1.55	0.266	0.58	0.22-1.57	0.283
	> 9	11	0.82	0.38-5.03	0.684	1.16	0.21-6.56	0.865
ECOG PS	0	36	REF	-	-	REF	-	-
	1	81	0.71	0.26-1.45	0.412	0.40	0.14-1.12	0.081
	≥2	38	0.90	0.30-2.18	0.814	0.50	0.13-1.96	0.316
Opioid use	no	54	REF	-	-	REF	-	-
	yes	40	1.20	0.47-3.04	0.707	1.31	0.46-3.72	0.609
Disease state	lymph nodes[a]	107	0.63	0.27-1.49	0.293	0.70	0.22-2.19	0.532
	bone[a]	162	1.24	0.24-6.37	0.798	5.41	0.70-41.77	0.104
	visceral[a]	91	0.34	0.10-1.11	0.074	0.14	0.02-0.88	0.037
Gleason score	≤ 7	65	REF	-	-	REF	-	-
	8-10	104	0.58	0.29-1.14	0.113	0.69	0.29-1.67	0.411
Time from ADT to mCRPC (mo)	cont.	190	1.02	1.00-1.04	0.013*	1.03	1.01-1.05	0.013*
Hb (mmol/L)	cont.	183	0.98	0.73-1.32	0.888	0.71	0.42-1.18	0.180
ALP (U/L)	cont.	183	1.00	0.99-1.00	0.720	1.00	0.99-1.00	0.760
LDH (U/L)	cont.	151	1.00	0.99-1.00	0.500	1.00	0.99-1.00	0.725
PSA (µg/L)	cont.	190	1.00	1.00-1.00	0.931	1.00	0.99-1.00	0.535
Docetaxel prior to ART1	no	75	REF	-	-	REF	-	-
	yes	115	0.72	0.38-1.36	0.309	0.67	0.29-1.53	0.337
ART sequence	ENZ>ABI+P	65	REF	-	-	REF	-	-
	ABI+P>ENZ	125	1.65	0.82-3.33	0.161	3.19	1.20-8.53	0.021*
Sequence	ART1>ART2	95	REF	-	-	-	-	-
	ART1>LPD>ART2	94	0.71	0.38-1.35	0.298	0.89	0.36-2.21	0.890
Duration ART1	> 12 weeks	158	REF	-	-	REF	-	-
	≤ 12 weeks	32	2.02	0.92-4.45	0.082	3.29	0.99-11.09	0.054
≥50% PSA decline ART1	no	56	REF	-	-	REF	-	-
	yes	109	0.91	0.44-1.89	0.807	1.13	0.40-3.21	0.824

* significant at p-value<0.05; [a] odds ratio of present metastases on disease site vs not present (yes vs no).
Abbreviations: OR, odds ratio; CI, confidence interval; REF, reference category; ECOG, Eastern Cooperative Oncology Group; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; ADT, androgen deprivation therapy; mo, months; Hb, haemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen. ART1, first AR-targeting therapy; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; LPD, life-prolonging drug; ART2, second AR-targeting therapy.

Patients with ART1>ART2 had better prognostic factors at the start of ART2 (less visceral disease, higher haemoglobin, lower LDH, and lower PSA) than ART1>LPD>ART2 patients. One could speculate that physicians decided to administer TAX or Ra-223 rather than the other ART in younger patients with more adverse prognostic factors, and seemingly have little faith in a meaningful response to ART2 in patients with progression on ART1. This seems unjustified based on similar response rates to ART2 in ART1>ART2 (20%) to that on LPDs in ART1>LPD>ART2 (24%).

We observed a PSA response of ART2 in 20% of patients with or without interposed TAX or Ra-223, and a median treatment duration of 3 months. PSA response is in line with previously published reports on ART2 (4-30%[130–132,136–139]), but low compared with phase III randomized controlled trials for ABI+P and ENZ (62%-78% in chemotherapy-naïve and 38%-54% in post-chemotherapy treatment[28,29,31,33]). Low PSA responses and short treatment duration can be a result of cross-resistance between ABI+P and ENZ. Mechanisms of resistance are complex and not completely understood, but it is proposed that they include both androgen receptor(AR)-dependent (e.g. AR aberrations, including amplification, genomic structural variants or splice variants such as AR-V7) and AR-independent mechanisms (e.g. neuroendocrine transformation or glucocorticoid receptor overexpression)[128]. Since mechanisms of resistance are overlapping between ABI+P and ENZ, cross-resistance may lead to low efficacy of ART2.

However, a low PSA response rate and.a short treatment duration of ART2 can also be the result of the advanced disease state. Most patients were treated with ART2 in line 3 (47%) or line ≥4 (30%). An Italian multicentre study showed that the biochemical response rates decreased to 38%, 24% and 16% on respectively second, third, and fourth lines irrespective of the treatment sequence[140].

Presence of visceral disease and shorter time between the start of androgen deprivation therapy and mCRPC were predictive of a poor PSA response of ART2. Visceral disease and a rapid time to castration resistance are known prognostic factors for overall survival[141,142], but can possibly impact PSA response due to a correlation between survival and PSA response rate[143,144].

We hypothesized that patients who discontinued ART1 due to other reasons than progression would have better effect of ART2, since resistance (either primary or acquired) to ART1 has not occurred. Since the exact reason of discontinuation was not easily evaluable due to missing values and the absence of strict progression criteria, treatment duration was used as a proxy for the reason of discontinuation. Toxicity mainly occurs in the initial months making a duration <12 weeks an indicator of toxicity. These patients tended to have higher PSA response rates than patients with ART1 treatment ≥12 weeks (26% vs 18%), but this difference was not clinically relevant.

Treatment sequence of ABI+P and ENZ has also been argued to affect the response of ART2 with favourable effects for ABI+P>ENZ than for ENZ>ABI+P[130–133,136,145,146]. In our

study, patients with ABI+P>ENZ also had better PSA-response rates of ART2 (OR 3.192, p=0.02) without differences in treatment duration. The beneficial effect of ABI+P>ENZ on PSA response did not hold after exclusion of patients with ART1 treatment <12 weeks (OR 2.060, p=0.19).

We used PSA kinetics and treatment duration as indicators for treatment efficacy of ART2, but the effect on overall survival and progression-free survival could not be estimated. Post-hoc analyses of phase III trials of ABI+P and ENZ demonstrated a strong correlation between PSA kinetics during ABI+P and ENZ and overall survival[143,144].

Although the PSA response rate of ART2 is fairly low and the median treatment duration is short, patients who had a PSA response of ART2 had a clinically relevant duration of ART2 treatment (7.3 months). ART2 may therefore offer a benefit in a selected patient population, which may include patients who are AR copy neutral and those without ARv7[128].

Monitoring treatment efficacy in mCRPC is complex[147]. The decision to discontinue treatment should not be based on a single indicator for progression, but on the association between different outcome measures (e.g. clinical, biochemical, patient-reported outcomes, and imaging)[71]. Consistent evaluation and reporting of clinical, biochemical and radiologic changes during treatment are advised, since these can aid future research of treatment efficacy in daily practice[71].

The first limitation of our study was the high number of missing values, which is inherent to the retrospective design. Missing values on baseline characteristics reflect incomplete evaluation of patients or lack of structured reporting in daily practice. This underlines the need for better documentation at the start of a new treatment. Imputation of missing baseline data offers a valid solution for multivariate analysis. However, 83 patients (30%) were excluded from the imputed analysis, which decreased the statistical power. Moreover, because of the retrospective database the sample size was not based on power calculations, but on patients available matching the study population criteria.

The second limitation was the fact that this study was not able to capture all data on treatment decisions. Other factors than the known patient and disease characteristics may play a role in the decision for a particular sequence, for example, preferences of both patients and physicians. In sequencing ABI+P and ENZ the possible contraindications for prednisone could also be considered. These unknown factors may affect outcomes. Furthermore, biomarkers could not be evaluated in our patient population. Accumulating evidence points at a subgroup, identified by non-invasive biomarkers, that benefits from ART2. These limitations indicate the need of prospective research in a large population to confirm the findings of this retrospective research and putative predictive biomarkers: such research work is currently being conducted (e.g. CARD study: ClinicalTrials.gov Identifier NCT02485691 and Phase 2 randomised cross-over trial of ART: NCT02125357).

In conclusion, our study suggests that PSA responses rates of ART2 are low with a short treatment duration irrespective of sequencing both ARTs directly after each other or with interposed TAX or Ra-223. The effect of ART2 seems to be low, especially in patients with a short time on castration, visceral disease, and ENZ before ABI+P. Further prospective research incorporating other outcome measures such as overall and progression-free survival, pain, and quality of life is necessary to aid in the optimal treatment decision after ART1 and to possibly identify subgroups that can benefit from ART2.

6

Real-world outcomes of radium-223 dichloride for mCRPC

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Future Oncology 2020;16(19):1371-1384

ABSTRACT

Background: Timing of radium-223 (Ra-223) in metastatic castration-resistant prostate cancer (mCRPC) remains challenging due to alternative options and short window of opportunity.

Methods: Ra-223 treated patients in the CAPRI-registry were included. Outcomes were evaluated based on treatment line of Ra-223.

Results: Out of 285 patients, 49% received Ra-223 in line ≥3. 51% completed six Ra-223 injections and 34% had a symptomatic skeletal event after first Ra-223 without differences between subgroups. After correction of known prognostic factors Ra-223 in line ≥3 (HR 3.267, 95% CI 1.689-6.317, p<0.01) remained associated with worse OS.

Conclusions: In the Netherlands, Ra-223 was mainly started as second or third mCRPC-treatment in 2014-2018. Later timing of Ra-223 did affect OS, but not treatment completion and occurrence of symptomatic skeletal events.

INTRODUCTION

The management of metastatic castration-resistant prostate cancer (mCRPC) is palliative, but in recent years several new life-prolonging drugs (LPDs) have been developed, including taxane chemotherapy (docetaxel and cabazitaxel), androgen-receptor (AR)-targeting therapies (abiraterone acetate plus prednisone and enzalutamide), and a targeted alpha-emitting isotope (radium-223 dichloride, Ra-223)[148,149].

Ra-223 has been registered for the treatment of mCRPC patients with symptomatic bone metastases, limited lymph node metastases and no visceral metastases since February 2014, based on the phase 3 ALSYMPCA trial[30]. An increased overall survival (OS) of Ra-223 compared with placebo has been established in both docetaxel pre-treated (median OS 14.4 months) and docetaxel untreated (median OS 16.1 months) patients[150]. Ra-223 also improved quality of life and reduced the risk of symptomatic skeletal events (SSEs)[38,124].

Optimal patient selection and timing of treatment for the best possible treatment in mCRPC is challenging with multiple treatment options available[151]. In general, there is a lack of prospective comparative data and data on sequencing of LPDs in mCRPC leading to unrestricted sequences. Recently in July 2018, after our database lock (in December 2017), the European Medicines Agency (EMA) has recommended restricting the use of Ra-223 to patients who received two prior systemic lines for mCRPC or to patients ineligible for other systemic treatments which is the only definitive restriction for sequencing in mCRPC patients[152]. However, especially for Ra-223 optimal timing of treatment is important, due to the short window of opportunity. After the occurrence of extensive nodal metastases or visceral disease, often later in the disease stage, patients are ineligible for Ra-223[153].

Adequate monitoring of treatment efficacy in mCRPC should be based on a combination of prostate-specific antigen (PSA) changes, clinical and radiological parameters[71,154]. Since Ra-223 is an isotope targeting bone metastases, monitoring is different from other LPDs due to the lack of reliability for PSA-changes as a marker of disease progression[155]. It has therefore been recommended to combine PSA changes with alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) changes in order to determine efficacy[154].

Results on treatment efficacy from randomized controlled trials are not easily translated to daily practice due to patient selection[53]. Therefore, real-world evidence on sequencing and outcomes is becoming more and more important. The aim of this study was to evaluate outcomes of Ra-223 treatment in a real-world setting in the Netherlands. We provide data on the use and experience with Ra-223 in a contemporary mCRPC cohort, treated prior to EMA restrictions.

PATIENTS AND METHODS

Study design and setting

CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multicentre cohort study in 20 Dutch hospitals (11 large teaching hospitals, 5 general hospitals and 4 academic hospitals). The study design has been described before[41]. The study was approved by a central medical ethics committee and hospital board before the start of inclusion. Patients diagnosed with CRPC were included retrospectively from 1 January 2010 until 31 December 2015. CRPC was either defined by the criteria set by the European Association of Urology (EAU)[23] or defined by the treating physician. All data have been regularly updated for all patients until 31 December 2017. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Participants

mCRPC patients that were treated with Ra-223 monotherapy during follow-up were included in this analysis. Outcomes were evaluated based on the position of Ra-223 in the treatment sequence: line 1 (no prior systemic treatment with docetaxel (DOC) and androgen-receptor targeting therapies (ART), i.e. abiraterone acetate plus prednisone or enzalutamide), line 2 (prior systemic treatment with one line of DOC or ART), and line ≥3 (prior systemic treatment with two or more systemic treatments).

Patients treated with DOC or ART for hormone-sensitive metastatic prostate cancer were excluded from the analysis.

Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics were included in the analysis if they were documented six weeks prior to one week after the start of Ra-223. All patients were followed until death, lost-to-follow-up or December 31, 2017. Follow-up duration was calculated as time from first Ra-223 injection to last recorded date.

Outcomes

Primary outcomes were treatment duration, occurrence of SSEs and OS. Treatment duration was calculated as the number of Ra-223 injections. Reason for discontinuation included PSA, radiological and clinical progression and was collected retrospectively without protocol mandated progression assessment. Registration did not include ALP and LDH progression as reason for discontinuation. SSEs were defined as either radiotherapy to the bone, surgery to the bone, spinal cord compression, and pathological fractures. SSE analyses included only patients with structured SSE registration, which was performed from 2016 onwards. All SSEs were clinically apparent and occurred after

first Ra-223 injection to end of follow-up. Time to SSE was calculated as time in months from first Ra-223 injection to SSE and SSE-free survival as time to SSE or death. OS was measured as time in months from first Ra-223 injection to time of death from any cause. Patients alive or lost-to-follow-up at the end of study were censored at last recorded date.

Secondary outcomes were biochemical responses and serious adverse events (SAE). Biochemical responses (i.e. PSA and alkaline phosphatase (ALP)) were calculated as maximum change in PSA and ALP up to four weeks after last Ra-223 injection and change per Ra-223 injection. Responses were not confirmed by a second value. Patients who did not finish Ra-223 treatment at end of follow-up (either due to early discontinuation or maximum of six injections), were excluded from biochemical response analyses. SAE were defined as hospital admission during Ra-223 treatment or within 30 days after last Ra-223 injection. Hematologic events were calculated as anemia grade 2 or higher (hemoglobin < 6.2 mmol/L), thrombocytopenia grade 2 or higher (platelets < 75 x 10^9 / L), and the need of blood transfusion during this time period. Other hematologic events as leukopenia or neutropenia were not evaluable. No distinction between SAE or hematologic events related to Ra-223 treatment, to underlying disease or to other conditions could be made.

Statistical analysis

Descriptive statistics were performed. To test significance between subgroups, Chi-square tests were used for categorical variables and Kruskall-Wallis and ANOVA for nonparametric continuous, and parametric continuous variables, respectively. Kaplan-Meier analysis was used to estimate OS, with log-rank test to test for differences between subgroups. Missing baseline characteristics were imputed using multiple imputations with Monte Carlo Markov Chain method. Binary logistic regression and Cox-proportional hazard analysis were performed on pooled data after multiple imputation for treatment completion and OS respectively. A p-value of 0.05 or less was considered statistically significant. IBM SPSS Statistics version 24.0 (IBM ®, Armonk, NY, USA) was used for all analyses.

RESULTS

At the end of the study 3,616 CRPC-patients were included in 20 hospitals. Fourteen patients were excluded due to docetaxel-treatment in hormone sensitive prostate cancer. In total, 285 patients (8%) treated with Ra-223 were included in this analysis.

Median follow-up from Ra-223 was 8.5 months (range 0.2-44.7 months). At the end of study, 161 deaths (57%) had occurred, 63 patients (22%) were lost to follow-up and

61 patients (21%) were still on follow-up with a median follow-up period from start of Ra-223 of 10.5 months (range 1.3 – 44.7 months).

Treatment sequence

Twenty-nine patients (10%) were treated with Ra-223 as first line and 106 patients (37%) with Ra-223 as second line: 22 patients (8%) after DOC and 84 patients (29%) after ART. Overall, 150 patients (49%) were treated with Ra-223 in line ≥ 3: 92 patients (32%) in line 3 and 63 patients (22%) in line ≥4. Seven patients (2%) were retreated with Ra-223 (Supplementary Figure S6.1).

Baseline characteristics

Baseline characteristics of patients at start of Ra-223 are shown in Table 6.1. Patients treated with Ra-223 in line ≥ 3 were younger (median 72 vs 76 and 76 years, p<0.01) and had lower hemoglobin (Hb) (median 7.4 vs 8.1 and 7.8 mmol/L, p=0.02) than patients treated with Ra-223 in line 1 and 2.

Bone health agents (i.e. bisphosphonates or denosumab) were given prior to or during Ra-223 in 16 patients in line 1 (55%), in 67 patients (63%) in line 2 and in 120 patients (80%) in line ≥3 (p<0.01).

Biochemical response

In total, 267 patients had ended Ra-223 treatment at end of follow-up and were included in response analyses (Figure 6.1A-B). Eight patients (4%) had a ≥50% PSA decline and 122 patients (58%) had a ≥30% ALP decline during follow-up. Maximum ALP response during treatment was less in Ra-223 in line ≥3 (-34%) compared with line 1 and 2 (-48% and -39% respectively, p=0.05) (Table 6.2).

Adverse events

Ninety-two patients (32%) were admitted during Ra-223 or within 30 days after last Ra-223 injection without differences between treatment lines (Table 6.3). Anemia ≥ grade 2 occurred in 74 patients (26%): 4 patients in line 1 (14%), 20 patients in line 2 (19%) and 50 patients (33%) in line ≥ 3 (p<0.01). In total, 61 patients (21%) needed at least one blood transfusion during Ra-223, most frequently in line ≥ 3 (29 % in line ≥3 vs 7% in line 1 and 14% in line 2). Thrombocytopenia ≥ grade 2 was also more prevalent in line ≥ 3, namely in 14 patients (9%) compared with 0 patients (0%) in line 1 and 2 patients (2%) in line 2 (p=0.02).

Treatment completion

Six percent of patients were still on treatment at the end of follow-up and were excluded from analysis of treatment completion. Overall, 135 (51%) patients were treated with 6

Table 6.1 | Baseline characteristics at the start of radium-223

		Ra-223 line 1 N=29	Ra-223 line 2 N=106	Ra-223 line ≥ 3 N=150	p
Age (years)	median	76	76	72	0.001*
	range	58-80	51-92	54-89	
	≥ 75 years, n (%)	16 (55)	62 (59)	52 (35)	
Charlson score, n (%)		21 (72)	68 (64)	93 (62)	0.822
	6	7 (24)	33 (31)	44 (29)	
	7-8	1 (3)	4 (4)	11 (7)	
	9-10	0 (0)	1 (1)	2 (1)	
	>10	0 (0)	0 (0)	0 (0)	
	unknown				
ECOG PS, n (%)	0	7 (24)	22 (21)	27 (18)	0.760
	1	12 (41)	52 (49)	71 (47)	
	≥2	5 (17)	11 (10)	21 (14)	
	unknown	5 (17)	21 (20)	31 (21)	
Lymph node involvement, n (%)	yes	7 (24)	22 (21)	29 (19)	0.990
	no	18 (62)	60 (57)	76 (51)	
	unknown	4 (14)	24 (23)	45 (30)	
Visceral disease, n (%)	yes	0 (0)	4 (4)	5 (3)	0.549
	no	25 (86)	84 (79)	103 (69)	
	unknown	4 (14)	18 (17)	42 (28)	
Opioid use, n (%)	yes	7 (24)	16 (15)	38 (25)	0.196
	no	12 (41)	39 (37)	48 (32)	
	unknown	10 (35)	51 (48)	64 (43)	
Time ADT to mCRPC (mo)	median	15.6	16.9	12.6	0.239
	IQR	7-29	10-29	8-22	
Period mCRPC to Ra-223 (mo)	median	12.6	25.8	34.0	<0.001*
	IQR	5-42	18-36	21-46	
Hb (mmol/L)	median	8.1	7.8	7.4	0.016*
	IQR	7.4-8.6	7.0-8.3	6.6-8.2	
	unknown, n (%)	4 (14)	10 (9)	15 (10)	
ALP (U/L)	median	157	140	153	0.480
	IQR	106-273	80-227	93-276	
	unknown, n (%)	6 (21)	11 (10)	22 (15)	

* significant at p-value <0.05. Percentages may exceed 100% due to rounding.

Abbreviations: Ra-223, radium-223; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mo, months; IQR, interquartile range; Hb, hemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen.

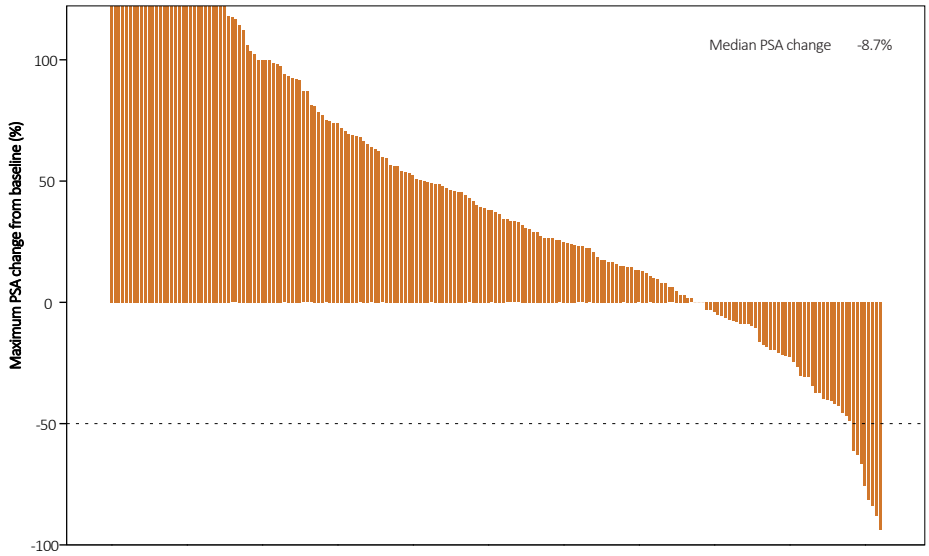


Figure 6.1A | Biochemical response on radium-223; maximum percentage change in PSA
Dotted line indicates the threshold of ≥50% PSA decline.
Abbreviations: PSA, prostate-specific antigen

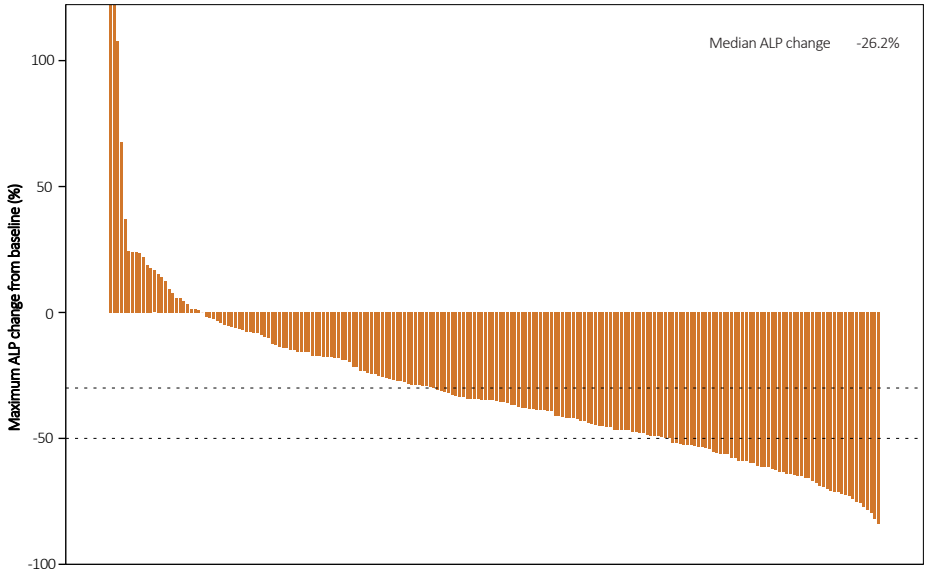


Figure 6.1B | Biochemical response on radium-223; maximum percentage change in ALP
Dotted lines indicate the threshold of ≥30% and ≥50% ALP decline.
Abbreviations: ALP, alkaline phosphatase.

Table 6.2 | Efficacy outcomes of radium-223

		Ra-223 line 1	Ra-223 line 2	Ra-223 line ≥ 3	p
Treatment injections	N	29	106	150	0.185
	median	6	6	5	
	IQR	3-6	3-6	3-6	
	unknown, n (%)	1 (3)	0 (0)	3 (2)	
	on treatment, n (%)	1 (3)	8 (8)	9 (6)	
	<6, n (valid %)	12 (44)	43 (44)	73 (53)	
	6, n (valid %)	15 (56)	55 (56)	65 (47)	
Biochemical responses during Ra-223	N[a]	28	98	141	
	Max. PSA response, median	+15%	+39%	+37%	0.766
	IQR	-20% - +137%	0% - +81%	+7% - +90%	
	unknown, n (%)	10 (36)	19 (19)	33 (23)	
	≥50% PSA decline (n, valid %)	1 (6)	4 (5)	3 (3)	0.677
	Max. ALP response, median	-48%	-39%	-34%	0.046*
	IQR	-63% - -28%	-53% - -18%	-50% - -5%	
	unknown, n (%)	8 (29)	14 (14)	35 (25)	
	≥30% ALP decline, n (valid %)	13 (65)	51 (61)	58 (55)	0.570
	≥50% ALP decline, n (valid %)	7 (35)	25 (30)	26 (25)	0.537
SSEs	N	28	96	124	
	During Ra-223[b], n (%)	2 (7)	13 (14)	17 (14)	0.622
	radiation to bone	2 (7)	13 (14)	17 (14)	0.622
	orthopedic surgery	1 (4)	0 (0)	0 (0)	0.019*
	spinal cord compression	0 (0)	1 (1)	3 (2)	0.541
	pathologic fracture	0 (0)	0 (0)	1 (1)	0.595
	During follow-up[c], n (%)	8 (29)	32 (33)	44 (36)	0.824
	radiation to bone	7 (25)	31 (32)	44 (36)	0.604
	orthopedic surgery	2 (7)	1 (1)	0 (0)	0.007*
	spinal cord compression	0 (0)	5 (5)	3 (2)	0.292
	pathologic fracture	0 (0)	2 (2)	2 (2)	0.741
Time to SSE (mo)	median, IQR	35.1 (13-35)	18.9 (7-22)	14.6 (6-NR)	0.124
	censored, n (%)	18 (64)	60 (63)	75 (60)	
	unknown, n, (%)	2 (7)	5 (5)	6 (5)	
SSE-FS (mo)	median, IQR	12.5 (6-35)	8.7 (5-18)	7.5 (4-11)	0.003*
	censored, n (%)[d]	9 (32)	36 (38)	30 (24)	
	unknown, n (%)	2 (7)	5 (5)	6 (5)	

Table 6.2 | Efficacy outcomes of radium-223 *(continued)*

		Ra-223 line 1	Ra-223 line 2	Ra-223 line ≥ 3	p
OS (mo)	N	29	106	150	<0.001*
	median, IQR	23.8 (11-39)	17.0 (8-26)	10.4 (6-19)	
	censored, n (%)[e]	15 (52)	54 (51)	55 (37)	

* significant at p-value <0.05; [a] patients still on treatment with Ra-223 at end of follow-up were excluded from response analyses; [b] in time period from start of first Ra-223 injection to 30 days after last Ra-223 injection; [c] in time period from start of first Ra-223 injection to last recorded date; [d] patients alive without SSE were censored at end of follow-up date; [e] patients alive or lost-to-follow-up were censored at end of follow-up date.
Abbreviations: Ra-223, radium-223; PSA, prostate specific antigen; IQR, interquartile range; ALP, alkaline phosphatase; SSE, symptomatic skeletal events; mo, months; SSE-FS, symptomatic skeletal event free survival; OS, overall survival.

Ra-223 injections and 128 (48%) with 1-5 Ra-223 injections. Median number of injections was 6 in Ra-223 as 1st or 2nd line and 5 in Ra-223 as 3rd line treatment (Table 6.3).

Patients who completed 6 Ra-223 injections had better known prognostic factors at start of Ra-223 than patients who had 1-5 Ra-223 injections, namely higher Hb (7.9 vs 7.3 mmol/L, p<0.01), lower ALP (122 vs 189 U/L, p<0.01), lower LDH (231 vs 263 U/L, p<0.01) and lower PSA (84 vs 165 µg/L, p<0.01). Patients with 6 Ra-223 injections less frequently needed a hospital admission (21% vs 47%, p<0.01) and blood transfusion (13% vs 32%,

Table 6.3 Hospital admissions and hematologic events of radium-223[a]

		Ra-223 line 1 N=29	Ra-223 line 2 N=106	Ra-223 line ≥ 3 N=150	p
Hospital admission during Ra-223, n (%)	yes	8 (28)	27 (26)	57 (38)	0.075
	no	16 (55)	61 (58)	68 (45)	
	unknown	5 (17)	18 (17)	25 (17)	
Anemia ≥ grade 2[b], n (%)	yes	4 (14)	20 (19)	50 (33)	0.007*
	no	16 (55)	53 (50)	56 (37)	
	unknown	9 (31)	33 (31)	44 (29)	
Thrombocytopenia ≥ grade 2[c], n (%)	yes	0 (0)	2 (2)	14 (9)	0.015*
	no	20 (69)	71 (67)	91 (61)	
	unknown	9 (31)	33 (31)	45 (30)	
Blood transfusion during Ra-223, n (%)	yes	2 (7)	15 (14)	44 (29)	0.001*
	no	26 (90)	90 (85)	100 (67)	
	unknown	1 (3)	1 (1)	6 (4)	

* significant at p-value <0.05; [a] in time period from start of first Ra-223 injection to 30 days after last Ra-223 injection; [b] defined as hemoglobin < 6.2 mmol/L according to CTCAE v3.0[32]; [c] defined as platelets < 75 x 10^9 / L according to CTCAE v3.0[32].
Abbreviations: Ra-223, radium-223; CTCAE, Common Terminology Criteria for Adverse Events.

p<0.01) during Ra-223 compared with patients with 1-5 injections. After correction for known prognostic characteristics, higher Hb (OR 1.464, 95% CI 1.082-1.982, p=0.01) was associated with higher odds and higher LDH (OR 0.966, 95% CI 0.992-1.000, p=0.03) with lower odds for treatment completion (6 injections vs 1-5 injections) (Table 6.4).

At the last Ra-223 injection, 20 patients (7%) had an ALP increase ≥25% and 105 patients (39%) a PSA increase ≥25% without differences between 1-5 or 6 Ra-223 injections. Recorded reasons for early discontinuation were progressive disease (PD) in 83 patients (65%) and toxicity in 14 patients (11%). PD was defined by one of the parameters (i.e. PSA, radiological or clinical deterioration) in 25% (n=20), by a combination of two parameters in 54% (n=44) and all three parameters in 21% (n=17). Other reasons for discontinuation were death (n=11, 9%), patient preference (n=4, 3%) and unknown reasons (n=16, 13%).

Table 6.4 | Univariable and multivariable binary logistic regression for treatment completion (6 vs 1-5)

		Univariable analysis of original data (N=267)				**Multivariable analysis of pooled data after imputation (N=267)**		
		N[a]	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (years)	cont.	263	0.98	0.95-1.02	0.328	0.97	0.94-1.01	0.181
Charlson score	6	165	REF	-	-	REF	-	-
	7-8	79	1.18	0.70-2.02	0.546	1.22	0.65-2.30	0.530
	> 9	19	0.89	0.34-2.30	0.809	1.15	0.38-3.46	0.799
ECOG PS	0	51	REF	-	-	REF	-	-
	1	124	0.68	0.35-1.32	0.250	0.89	0.40-2.01	0.782
	≥2	35	0.31	0.13-0.76	0.011*	0.79	0.27-2.37	0.676
Lymph node involvement	yes vs. no	194	0.87	0.46-1.64	0.664	1.08	0.52-2.26	0.832
Visceral disease	yes vs. no	194	0.51	0.12-2.18	0.359	0.63	0.17-2.35	0.480
Time ADT to CRPC (mo)	cont.	263	1.01	0.99-1.02	0.062	1.01	0.99-1.02	0.080
Hb (mmol/L)	cont.	240	1.78	1.35-2.34	<0.001*	1.46	1.08-1.98	0.014*
ALP (U/L)	cont.	227	0.99	0.99-1.00	0.074	1.00	0.99-1.00	0.728
LDH (U/L)	cont.	180	0.99	0.99-0.99	0.003*	0.99	0.99-1.00	0.029*
PSA (µg/L)	cont.	229	1.00	0.99-1.00	0.107	1.00	0.99-1.00	0.666
Prior treatment	line 1	27	REF	-	-	REF	-	-
	line 2	98	1.02	0.43-2.41	0.958	0.99	0.38-2.65	0.998
	line ≥ 3	138	0.71	0.31-1.63	0.423	0.87	0.33-2.26	0.768

* significant at p-value <0.05; [a] number of patients included in univariate analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; cont, continuous; REF, reference category; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; mo, months; Hb, haemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen.

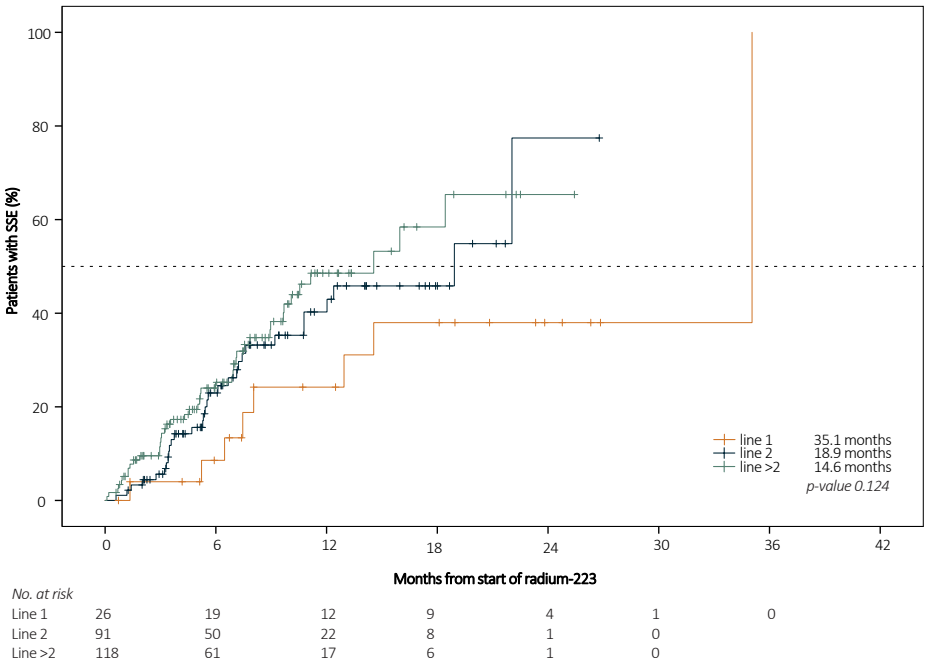


Figure 6.2A | Time to first SSE from start of radium-223
Dotted lines indicate the median time to first SSE.
Abbreviations: SSE, symptomatic skeletal events.

Symptomatic skeletal events

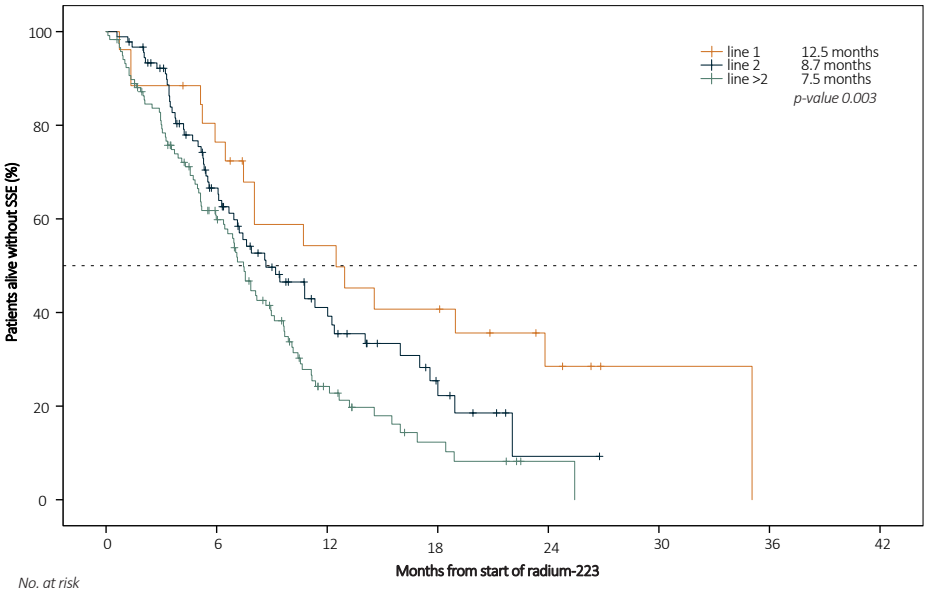
In total, 248 patients were available for SSE analyses. Eighty-four patients (34%) had a SSE during total follow-up after 1st Ra-223 injection. SSE concerned mostly radiation therapy (n=82, 33%). Eight patients (3%) had a spinal cord compression, 4 patients (2%) a pathologic fracture and 3 patients (1%) orthopaedic surgery. During Ra-223 32 patients (13%) experienced a SSE. There were no differences in rate of SSE between treatment line of Ra-223, except for orthopaedic surgery (Table 6.2).

Median time to first SSE was 16.0 months with SSE-free survival of 8.0 months (Figure 6.2A-B). SSE-free survival was longer in patients treated in line 1 (12.5 months), than line 2 (8.7 months) and line ≥3 (7.5 months).

Overall survival

In total, 161 deaths (57%) occurred during follow-up. Median OS was 12.2 months (IQR 8-29 months). Median OS was shorter in patients treated in line ≥ 3 (10.4 months) and line 2 (17.0 months) compared with line 1 (23.8 months) ($p<0.01$; Figure 6.3).

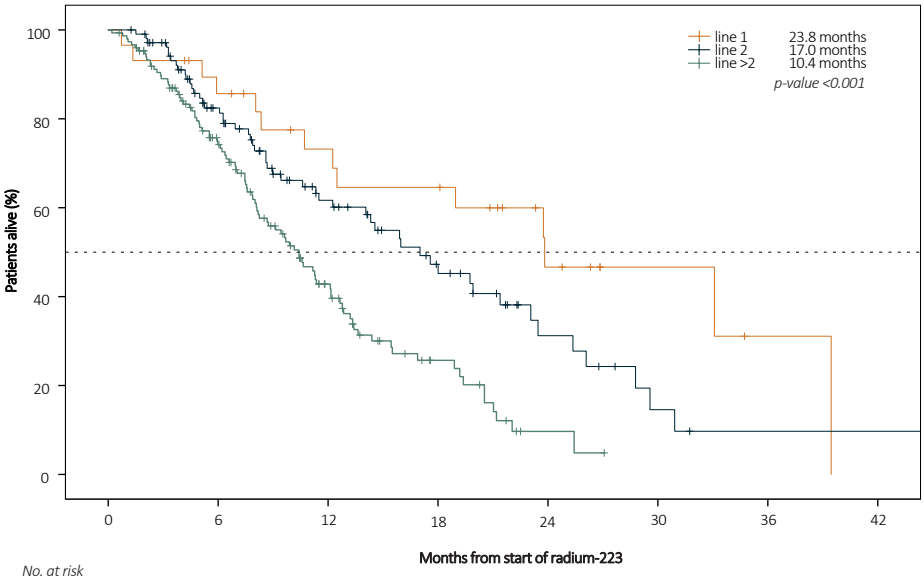
In univariable analyses, Ra-223 in line 2 (HR 1.744, $p=0.07$) and line ≥ 3 (HR 3.293, $p<0.01$) were associated with shorter OS. After correction for known prognostic factors



No. at risk

Line 1	26	19	12	9	4	1	0
Line 2	91	50	22	8	1	0	
Line >2	118	61	17	6	1	0	

Figure 6.2B | SSE-free survival from start of radium-223
Dotted lines indicate the median SSE-free survival
Abbreviations: SSE, symptomatic skeletal events.



No. at risk

Line 1	29	22	16	15	7	3	1	0
Line 2	106	71	40	23	9	3	1	1
Line >2	150	94	40	14	2	0		

Figure 6.3 | Overall survival from start of radium-223
Dotted line indicates median overall survival.

in multivariable analysis, this remained significant for Ra-223 treatment in line ≥ 3 (HR 3.267, p<0.01; Table 6.5). ECOG ≥2 (HR 2.206, p=0.03), higher ALP (HR 1.001, p=0.03) and higher LDH (HR 1.002, p=0.02) were also associated with worse survival, while higher Hb (HR 0.796, p=0.02) was associated with longer survival (Table 6.5).

Table 6.5 | Univariable and multivariable Cox-proportional hazard analysis for overall survival

		Univariable analysis of original data (N=285)				**Multivariable analysis of pooled data after imputation (N=285)**		
		n/N[a]	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age (years)	cont.	161/285	1.01	0.99-1.03	0.378	1.01	0.98-1.03	0.653
Charlson score	6	100/182	REF	-	-	REF	-	-
	7-8	46/84	0.98	0.69-1.39	0.903	0.97	0.64-1.45	0.864
	> 9	15/19	1.97	1.14-3.41	0.015*	1.70	0.90-3.20	0.100
ECOG PS	0	26/56	REF	-	-	REF	-	-
	1	70/135	1.26	0.82-2.02	0.276	1.00	0.61-1.65	0.998
	≥2	29/37	3.95	2.30-6.78	<0.001*	2.21	1.07-4.55	0.032*
Lymph node involvement	yes vs. no	116/211	1.20	0.80-1.80	0.384	0.97	0.59-1.60	0.910
Visceral disease	yes vs. no	121/220	2.52	1.23-5.19	0.012*	1.44	0.64-4.23	0.490
Time ADT to mCRPC (mo)	cont.	161/285	0.99	0.99-1.00	0.207	0.99	0.99-1.00	0.232
Hb (mmol/L)	cont.	145/256	0.62	0.52-0.73	<0.001*	0.80	0.66-0.97	0.022*
ALP (U/L)	cont.	136/246	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	0.028*
LDH (U/L)	cont.	114/191	1.00	1.00-1.00	<0.001*	1.00	1.00-1.00	0.016*
PSA (µg/L)	cont.	138/248	1.00	1.00-1.00	0.009*	1.00	1.00-1.00	0.463
Prior treatment	line 1	14/29	REF	-	-	REF	-	-
	line 2	52/106	1.74	0.96-3.18	0.070	1.82	0.95 -3.52	0.073
	line ≥ 3	55/150	3.29	1.82-5.96	<0.001*	3.27	1.69-6.32	<0.001*

* significant at p-value <0.05; [a] number of patients with event (i.e. death) of total included in univariable analysis.
Abbreviations: HR, hazard ratio; CI, confidence interval; cont, continuous; REF, reference category; ECOG, Eastern Cooperative Oncology Group Performance Score; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mo, months; Hb, hemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen.

DISCUSSION

In this retrospective analysis, we report the outcomes of Ra-223 in the real world. To our knowledge, so far this is the largest multicentre population without strict patient selection criteria in which patients are treated according to the views and opinions of their treating physicians and outcomes therefore reflect current daily practice.

In our cohort, 79% was treated with Ra-223 prior to line 4, mostly in second (37%) or third (32%) line. Only 29 patients were treated with Ra-223 in line 1, since only part of our cohort could be treated with Ra-223 in first line due to the fact that Ra-223 was registered in the Netherlands in February 2014 and our patient population included patients with mCRPC diagnosis between 2010 and 2016. In the Netherlands, the start of Ra-223 tends to be earlier in the disease stage compared with an Italian retrospective study of 158 Ra-223-treated patients in 2013-2018[156]. It has been proposed that earlier treatment utilization is related to higher treatment completion rates and better outcomes[157], but prospective data on the outcomes of treatments in third line or higher are lacking.

Median OS in our cohort was lower than in the ALSYMPCA trial (12.2 vs 14.9 months)[30], while previous retrospective cohorts of Ra-223 treated patients reported a wide range of OS (8.1 to 17.5 months)[151]. As we have shown before, outcomes from trials are not easily generalizable to the real-world mainly due to patient selection[41]. In our unselected patient cohort, patients were older than in the ALSYMPCA trial (46% vs 28% aged ≥ 75 years), but other known prognostic factors were comparable. In the ALSYMPCA trial with all patients treated in line 1 or 2 the OS differed between the docetaxel pre-treated (14.4 months) and docetaxel untreated (16.1 months) cohorts [30,150]. In our cohort positioning of Ra-223 was later in the disease trajectory (49% with Ra-223 in line 3 or higher). OS in patients with Ra-223 in line ≥ 3 was lower than in line 1 or 2 (respectively 10 vs 24 and 17 months). However, OS in earlier treatment lines has to be interpreted with caution due to the cumulative effect of subsequent treatments after Ra-223 and the small number of patients with Ra-223 in line 1 (N=29). Differences in OS between different positions of Ra-223 in the treatment sequence can partially be explained by the fact that patient and disease characteristics in higher treatment lines reflect a more advanced disease stage. In mCRPC, cancer biology becomes more aggressive due to the progressive nature of the disease and resistance to previous systemic treatments with also an increase in the incidence of visceral metastases[153,157]. In our cohort, this is reflected by worse prognostic factors at the start of Ra-223 in patients treated with Ra-223 in line ≥3, especially lower Hb and higher PSA. Worse ECOG and higher ALP were also associated with worse OS. Complete assessment of known prognostic factors is necessary before the start of Ra-223 especially in patients who had two or more previous systemic treatment lines[151].

In our cohort, 51% of patients completed all 6 injections of Ra-223 which is similar to previous large unselected cohorts (51% to 63%)[158–161], but lower than in the pivotal phase

3 ALSYMPCA trial (63%)[30]. The main reason for early discontinuation was progressive disease recorded as PSA, radiological and/or clinical progression, which were the only factors for disease progression included in our study protocol. Progression assessment was not protocol mandated and performed based on the views and opinions of treating physicians. Ra-223 could be discontinued earlier than necessary for example based on incomplete progression assessment or flare in PSA or pain not related to progression. We found a negative association with treatment completion for higher LDH and lower Hb, which was consistently found in retrospective studies[158,160,162,163]. More hospital admissions and blood transfusions occurred in patients with 1-5 Ra-223 injections, which were likely a sign of disease progression since Ra-223 has a low myelotoxic profile with no differences in rate of hematologic complications (i.e. anemia and blood transfusion) compared with placebo in ALSYMCPA[164,165]. Treatment completion could have a positive effect on OS as reported by previous studies[158,166,167]. However, results on the effect of treatment completion and OS have to be interpreted with caution due to the effect of immortal time bias.

Forty-three percent experienced at least one SSE after first Ra-223 injection, mostly radiation therapy to the bone in agreement with ALSYMPCA[38]. Although our cohort was more frequently pre-treated with other LPDs, this did not seem to affect the occurrence of clinically relevant SSEs after first Ra-223 injection. Bone metastases and loss of bone mineral density due to ADT cause significant risk of SSEs in mCRPC-patients[47]. In our population only 4 patients (2%) experienced a clinically apparent pathologic fracture, which is comparable to the findings from the ALSYMPCA trial (5%)[38]. We found that most physicians combine Ra-223 treatment with bone health agents, especially in higher treatment lines. The reasons not to initiate bone health agents were unclear, but could include contra-indications as hypocalcemia or renal insufficiency or an estimated low risk of SSE by clinicians. Post-hoc analyses have shown that the combination of bone health agents could have potential extra benefit on SSE and OS[168].

We observed similar biochemical response rates in our real-world population (4% with ≥50% PSA decline and 58% with ≥30% ALP decline) as in ALSYMPCA. Changes in PSA levels indicate a response on androgen-receptor level, because PSA expression is regulated by the androgen-receptor axis. However, Ra-223 does not target the androgen-receptor axis, but the tumor growth in bones and tumor-induced osteoblastic bone growth. This may be one of the reasons for low PSA responses during Ra-223 (6% to 15%)[158,159,163 and frequent] ALP responses (33% to 47%)[30,163,169]. It is suggested that decline in ALP, but also LDH, is associated with longer survival, but biomarker changes have not been proven to be surrogates for survival[155]. Especially in Ra-223 which has little effect on PSA, evaluation of treatment response and the decision for treatment discontinuation should be based on a combination of changes in biochemical markers as ALP and

LDH and changes in other response measurements, such radiologic assessment and clinical condition[71,154,155,157,169].

Our study was performed in the era without the registration of docetaxel and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer and without the current EMA restriction for Ra-223 (i.e. restriction of Ra-223 after two prior systemic treatments for mCRPC or in patients ineligible for other systemic treatments). These changes will probably have an effect on the clinical practice of Ra-223 treatment in the Netherlands. While in this cohort Ra-223 was mainly started after no or one prior LPD (47%), it seems inevitable that in the future more patients will be treated with more than one LPD before Ra-223. However, patients progressing after two previous treatment lines are more likely to have developed visceral metastases, missing the window of opportunity for Ra-223. Moreover, it is likely that the efficacy of Ra-223 is lower in later treatment lines due to more advanced disease phase[170].

In our study, we showed that hematologic events are more prevalent and OS is shorter when Ra-223 is initiated in line ≥3. Moreover, there is a short window of opportunity for Ra-223 due to the occurrence of visceral metastases in later disease stage[153]. By restricting the use of Ra-223 in later treatment lines, the window of opportunity may be passed causing loss of a treatment option in mCRPC.

The first limitation of our study was the high number of missing values, which is inherent to the retrospective design. Missing values on baseline characteristics reflect incomplete evaluation of patients or lack of structured reporting in daily practice. Our evaluation of optimal patient selection can therefore be incomplete. This underlines the need for better documentation at the start of a new systemic treatment. However, imputation of missing baseline data could offer a solution for multivariable analysis but residual confounding could still be present in multivariable analysis.

The second limitation was the fact that this study was not able to capture all data on treatment decisions. Other factors than the known patient and disease characteristics as for example availability of Ra-223 in the hospital may play a role in the patient selection for Ra-223 and the choice of specific sequences. These unknown factors may also affect outcomes such as treatment completion and early discontinuation. Moreover, ALP progression as a reason of Ra-223 discontinuation was not registered in our protocol. Due to the lack of protocol mandated progression assessment, progression-free survival could not be evaluated. This limitation indicates the need of prospective research in a large population to provide better guidance on the optimal patient selection and timing of Ra-223.

CONCLUSION

Our study suggests that in the Netherlands Ra-223 was mainly prescribed at the second and third line after prior docetaxel and/or androgen-receptor targeting therapies in the years 2014-2018. Later timing of Ra-223 did not affect treatment completion or occurrence of SSE, but adverse events were more frequent and OS was significantly shorter in patients treated with Ra-223 in line ≥3 compared with earlier treatment lines. Poorer survival was only partially explained by worse baseline characteristics at the start of Ra-223. Further prospective research is necessary to investigate optimal timing and monitoring of Ra-223 in the treatment landscape with multiple treatment options, especially in light of the registration of LPDs for metastatic hormone sensitive prostate cancer and current restrictions provided in the EMA guidance.

SUPPLEMENTARY MATERIAL

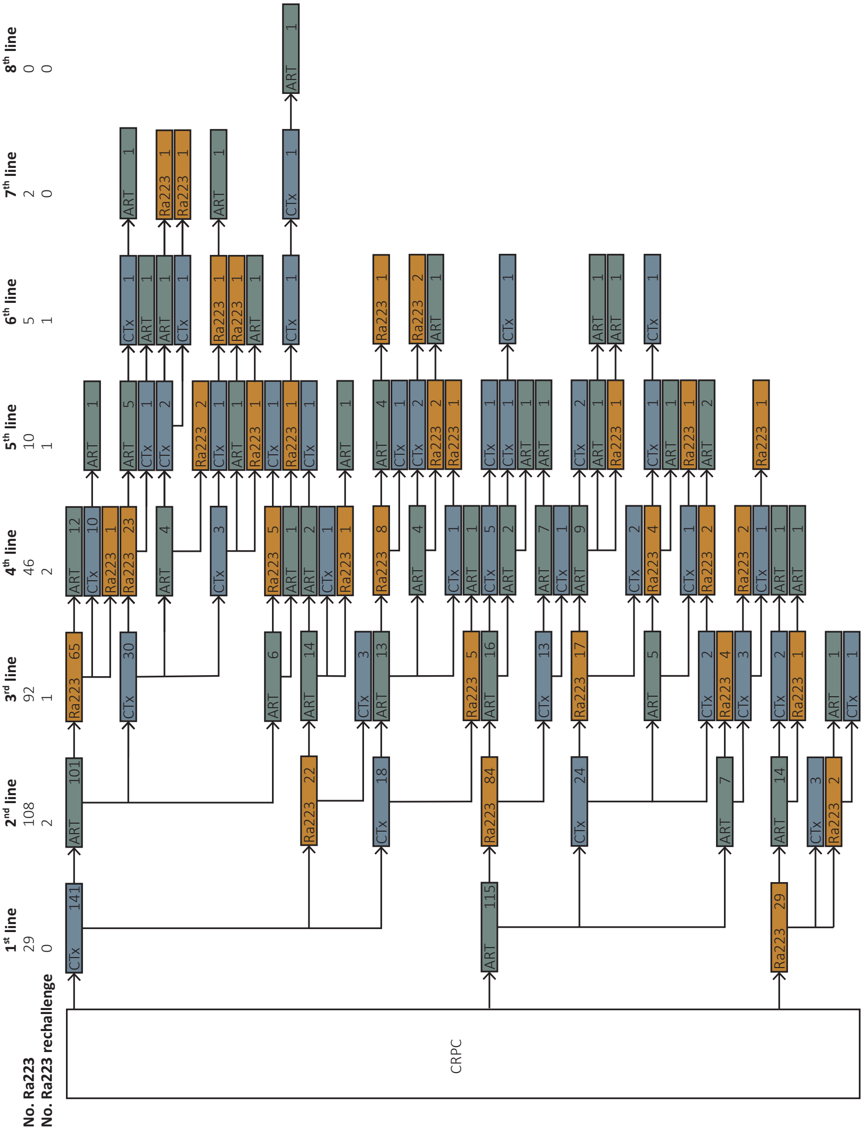


Figure S6.1 | Flowchart of treatment sequencing in patients treated with radium-223
Abbreviations: CTx, chemotherapy (docetaxel or cabazitaxel); ART, androgen-receptor targeting therapies (abiraterone or enzalutamide); Ra-223, radium-223.

7

Symptomatic skeletal events and the use of bone health agents in a real-world treated mCRPC population

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Accepted for publication in Clinical Genitourinary Cancers

ABSTRACT

Background: Patients with metastatic castration-resistant prostate cancer (mCRPC) are at risk of symptomatic skeletal events (SSE). Bone health agents (BHA, i.e. bisphosphonates and denosumab) and new life-prolonging drugs (LPDs) can delay SSEs. The aim of this study is to investigate the use of BHAs in relation to SSEs in treated real-world mCRPC population.

Methods: We included patients from the CAPRI registry who were treated with at least one LPD and diagnosed with bone metastases prior to the start of first LPD (LPD1). Outcomes were SSEs (external beam radiation therapy (EBRT) to the bone, orthopaedic surgery, pathological fracture or spinal cord compression) and SSE-free survival (SSE-FS) since LPD1.

Results: 1,923 patients were included with a median follow-up from LPD1 of 16.7 months. Fifty-two percent (n=996) started BHA prior or within four weeks after the start of LPD1 (early BHA). In total, 41% experienced at least one SSE. SSE incidence rate was 0.29 per patient year for patients without BHA and 0.27 for patients with early BHA. Median SSE-FS from LPD1 was 12.9 months. SSE-FS was longer in patients who started BHA early vs patients without BHA (13.2 vs 11.0 months, p=0.001).

Conclusion: In a real-world population we observed an undertreatment with BHAs, although patients with early BHA use had lower incidence rates of SSEs and longer SSE-FS. This finding was irrespective of type of SSE and presence of risk factors. In addition to LPD treatment, timely initiation of BHAs is recommended in bone metastatic CRPC patients with bone pain and/or opioid use and prior SSE.

INTRODUCTION

Bone metastases occur in approximately 90% of patients with (metastatic) castration-resistant prostate cancer (mCRPC)[40]. Bone health in mCRPC is further affected by the loss of bone mineral density due to ADT and higher age[48,171]. The result is ineffective haematopoiesis, bone pain and skeletal related events (SREs) which can lead to significant deterioration in quality of life and worsened survival[40,47,172–174].

SREs, defined as pathologic fractures, spinal cord compression, and the need for surgery or external beam radiation (EBRT) to the relieve bone pain, occur in 40-50% of all mCRPC-patients[175–178]. Asymptomatic SREs are not considered clinically relevant, thus symptomatic skeletal events (SSE) have been proposed as an important new trial end point[71,179].

New life-prolonging drugs (LPD, i.e. docetaxel, cabazitaxel, abiraterone acetate plus prednisone, enzalutamide and radium-223 dichloride) have been registered for the treatment of mCRPC based on a survival benefit compared with mitoxantrone or placebo[24,27–31,33], but abiraterone acetate plus prednisone (AA+P), enzalutamide (ENZ) and radium-223 (Ra-223) have also shown a prolongation in time to first SRE[36,37,39].

Bone health agents (BHAs) also prevent SREs without improving survival. Patients treated with zoledronic acid were less likely to experience an SRE than placebo treated patients (38% vs 49%)[177,178]. Denosumab, a monoclonal antibody, reduced the incidence of SREs to a greater extent than zoledronic acid (36% vs 41% with any SRE, respectively), but hypocalcaemia was more common (13% vs 6%, respectively)[180].

The optimal management of patients with bone metastatic CRPC remains unclear due to a lack of comparative data and low generalizability of trials results to daily practice[41]. Treatment decisions are highly variable and based on personal clinical judgement[181]. There seems however a general undertreatment with BHAs in bone metastatic CRPC patients The number of patients with concomitant BHA use in the ERA-223 trial was low (41%) possibly explaining the high rate of mostly osteoporotic fractures in the combination arm (AA+P plus Ra-223)[182]. This increased the awareness of bone health in these patients. The objective of our study is to investigate the use and outcomes of BHAs in a treated real-world mCRPC cohort.

METHODS

Study design and setting

CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multicentre cohort study in 20 Dutch hospitals (11 large teaching hospitals, 5 general hospitals and 4 academic hospitals). The study design has been described

before[41]. The study was approved by a central medical ethics committee and hospital board before the start of inclusion. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Participants

Patients diagnosed with CRPC were included in CAPRI retrospectively from January 1, 2010 until December 31, 2015. CRPC was either defined by the criteria set by the European Association of Urology (EAU)[23] or defined by the treating physician. All data have been regularly updated until December 31, 2017. Patients treated with at least one LPD for mCRPC and diagnosed with bone metastases before the start of first LPD (LPD1) were included in this analysis.

We identified groups based on timing of BHA. Patients without BHA use during follow-up were classified as "no BHA", while "early BHA" was defined as start of BHA prior to or within four weeks after the start LPD1 and "late BHA" as the start of BHA after four weeks after the start of LPD1.

Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers in an electronic case report form (eCRF), and included all radiotherapy, hospital admissions, operations and treatment given (including LPD, radionuclides and BHA). The eCRF was updated in 2016 to allow for structural registration of spinal cord compression and pathologic fractures. These types of SSEs were derived from hospital admission reasons before 2016. Baseline characteristics were included if they were documented six weeks prior to one week after the start of new systemic treatment. All patients were followed until death, lost-to-follow-up or December 31st, 2017.

Outcome

Outcomes were clinically relevant skeletal complications: SSEs and SSE-free survival (SSE-FS). SSEs were defined as the occurrence of either external beam radiotherapy to the bone (EBRT), symptomatic pathological fractures, spinal cord compression or surgery to the bone. All SSEs were clinically detected and there was no protocol mandated routine radiological assessment. All SSEs were calculated during total follow-up defined as period from LPD1 to end of follow-up.

SSE-FS was defined as time in months from first occurrence of SSE to death. Patients without an event (either death or SSE) were censored at last recorded date.

Statistical analysis

Descriptive statistics were performed. Missing baseline characteristics were imputed using multiple imputations with Monte Carlo Markov Chain method. Binary logistic

regression was performed on pooled data after multiple imputation to assess the effect of baseline variables on SSE incidence. Kaplan-Meier analysis was used to estimate SSE-FS. A p-value of 0.05 or less was considered statistically significant. IBM SPSS Statistics Version 24.0 (IBM ®, Armonk, NY, USA) was used for all analyses.

RESULTS

In total, 3,616 patients were included in the CAPRI registry, of which 2,540 (70%) had bone metastases and 2,274 (63%) were treated with an LPD. Patients with known bone metastases and ≥1 LPD treatment were included in the analyses (n=1,923; 53%). Median follow-up from LPD1 was 16.7 months (range 0-86 months).

Baseline characteristics

Baseline characteristics at the start of LPD1 are listed in Table 7.1. Median age was 73 years (range 46-99 years) and 62% (n=1,194) had an ECOG performance score of 0-1. Thirty-nine percent (n=746) had pain and/or used opioids. Median ALP was 157 U/L (IQR 99-335 U/L) and PSA 110.0 µg/L (IQR 43-264 µg/L). Twenty-seven percent (n=519) experienced at least one SSE prior to LPD1.

Treatment characteristics

The median time from CRPC diagnosis to LPD1 was 6.9 months (IQR 2-16 months). In total 717 patients (37%) were treated with 1 LPD, 589 (31%) with 2 LPDs, 617 (32%) with 3 or more LPDs. AA+P and ENZ were most commonly used (52% and 46% respectively).

Sixty percent (n=1,158) used BHA during follow-up, mostly zoledronic acid (n=626, 33%) or denosumab (n=276, 14%). Fifty-two percent (996/1,923) start BHA prior or within 4 weeks after the start of LPD1 (Table 7.2).

Patients who started BHA early were younger than patients without BHA (73 vs 75 years) and more frequently experienced a prior SSE (31% vs 22%) (Supplementary Table S7.1). Patients with late BHA use were the youngest (71 years) and had less frequently a ECOG PS ≥2 (5% vs 14% in patients with no BHA and 11% in patients without BHA, p=0.018).

Symptomatic skeletal events

SSE and SSE-FS was evaluable in 1,866 patients (97%): 717 (38%) without BHA, 976 (52%) with early BHA and 162 (9%) with late BHA. Forty-three percent (n=797) experienced one or more SSEs after the start of LPD1, mostly EBRT to the bone (41%) followed by spinal cord compression (6%), pathologic fracture (3%) and orthopaedic surgery (3%). The incidence of SSE was 0.26 per patient year for the total population (Table 7.2), 0.29

Table 7.1 | Baseline characteristics at the start of LPD1

		Total N=1,923
Age (years)	median (range)	73 (46-99)
	≥ 75 years (n, %)	869 (45)
ECOG PS, n (%)	0	390 (20)
	1	804 (42)
	≥2	224 (12)
	unknown	505 (26)
Charlson comorbidity index, n (%)	0	1,258 (65)
	1-2	557 (29)
	3-4	88 (5)
	> 4	20 (1)
	unknown	0 (0)
Pain and/or opioid use, n (%)	yes	746 (39)
	no	222 (12)
	unknown	955 (50)
Visceral metastases, n (%)	yes	223 (12)
	no	811 (42)
	unknown	889 (46)
Time ADT to mCRPC (mo)	median (IQR)	13.1 (8-24)
	unknown, n (%)	6 (<1)
Time ADT to LPD1 (mo)	median (IQR)	22.4 (13-41)
	unknown, n (%)	6 (<1)
Hb (mmol/L)	median (IQR)	7.8 (7.0-8.4)
	unknown, n (%)	284 (15)
LDH (U/L)	median (IQR)	237 (193-328)
	unknown, n (%)	537 (28)
ALP (U/L)	median (IQR)	157 (99-335)
	unknown, n (%)	269 (14)
PSA (µg/L)	median (IQR)	110 (43-264)
	unknown, n (%)	184 (10)
SSE prior to LPD1, n (%)	yes	519 (27)
	no	1,211 (63)
	unknown	193 (10)

All baseline parameters are measured in the period 6 weeks prior to 1 week after the start of LPD1. Total percentages can exceed 100% due to rounding.

Abbreviations: LPD, life-prolonging drug; ECOG PS, Eastern Cooperative Group Performance Score; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mo, months; Hb, haemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; SSE, symptomatic skeletal event.

Table 7.2 | Treatment characteristics

		Total N=1,923
Life-prolonging drugs		
Number of LPDs during follow-up, n (%)	1	717 (37)
	2	589 (31)
	3	393 (20)
	>3	224 (12)
Type of LPDs, n (%)	docetaxel	575 (30)
	cabazitaxel	415 (22)
	abiraterone acetate	992 (52)
	enzalutamide	885 (46)
	radium-223	272 (14)
Time from mCRPC diagnosis to first LPD (mo)	median	6.9
	IQR	2-16
Bone health agents		
BHA during follow-up, n (%)	no	750 (39)
	yes	1,158 (60)
	unknown	15 (1)
Type of BHA, n (%)	zoledronic acid	626 (33)
	other bisphosphonates[a]	161 (8)
	denosumab	276 (14)
	combination[b]	90 (5)
	unknown	5 (<1)
Time to BHA, n (%)	early use[c]	996 (52)
	use after LPD1	162 (8)

Total percentages can exceed 100% due to rounding.
[a] other includes pamidronic acid (n=95), alendronic acid (n=53), risedronic acid (n=7), clodronic acid (n=3), unknown bisphosphonates (n=3); [b] switch between bisphosphonates and denosumab during follow-up; [c] start of BHA prior to or within four weeks after the start of LPD1.
Abbreviations: LPD, life-prolonging drug; mo, months; IQR, interquartile range; BHA, bone health agents.

and 0.27 for patients without BHA and with early BHA use respectively (Figure 7.1). The incidence rate for each type of SSE was lower in patients with early BHA compared with no BHA or late BHA, but only statistically significant for orthopaedic surgery and pathologic fractures (Figure 7.1).

At database cut-off, 1,340 patients (70%) had died, 244 (13%) were still alive and 339 patients (17%) were lost-to-follow-up. Median SSE-FS was 12.9 months (IQR 6-24 months). Patients with late BHA use were excluded from time-to-event analyses due to immortal time bias. SSE-FS was slightly longer in patients who started BHA early vs patients without BHA (13.2 vs 11.0 months, p=0.001) (Table 7.3; Figure 7.2).

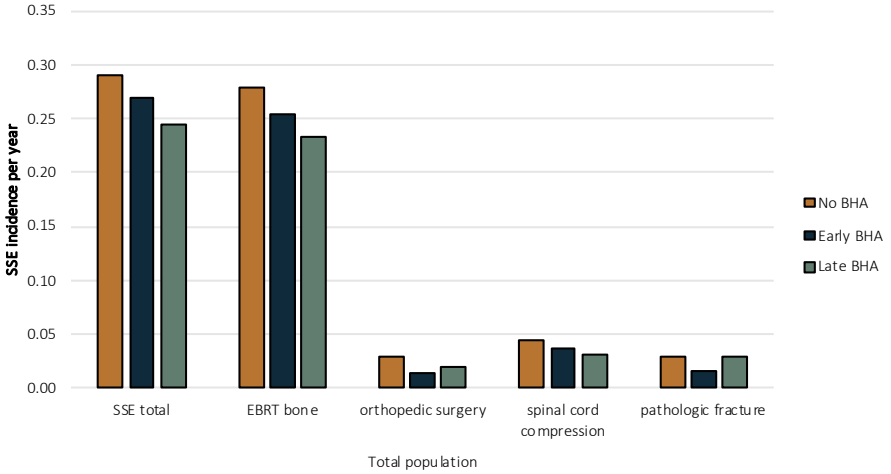


Figure 7.1 | SSE incidence rate per patient year
Abbreviations: SSE, symptomatic skeletal events; BHA, bone health agents; EBRT, external beam radiation therapy..

Table 7.3 | Symptomatic skeletal events during follow-up

		Total N=1,866
SSE during follow-up, n (%)	SSE total	797 (43)
	EBRT bone	759 (41)
	orthopedic surgery	57 (3)
	spinal cord compression	112 (6)
	pathologic fracture	64 (3)
Number of SSEs, n (%)	1	617 (33)
	2	150 (8)
	≥3	30 (2)
SSE-FS (mo)	median (IQR)	12.9 (6-24)
	event SSE, n (%)	797 (43)
	event death, n (%)	721 (39)
	censored, n (%)	348 (19)
All person-time (years)		2,935
SSE, n per patient year		
	SSE total	0.27
	EBRT bone	0.26
	orthopedic surgery	0.02
	spinal cord compression	0.04
	pathologic fracture	0.02

Total percentages can exceed 100% due to rounding.
Abbreviations: IQR, interquartile range; BHA, bone health agents; SSE, symptomatic skeletal events; EBRT, external beam radiation therapy; SSE-FS, SSE-free survival.

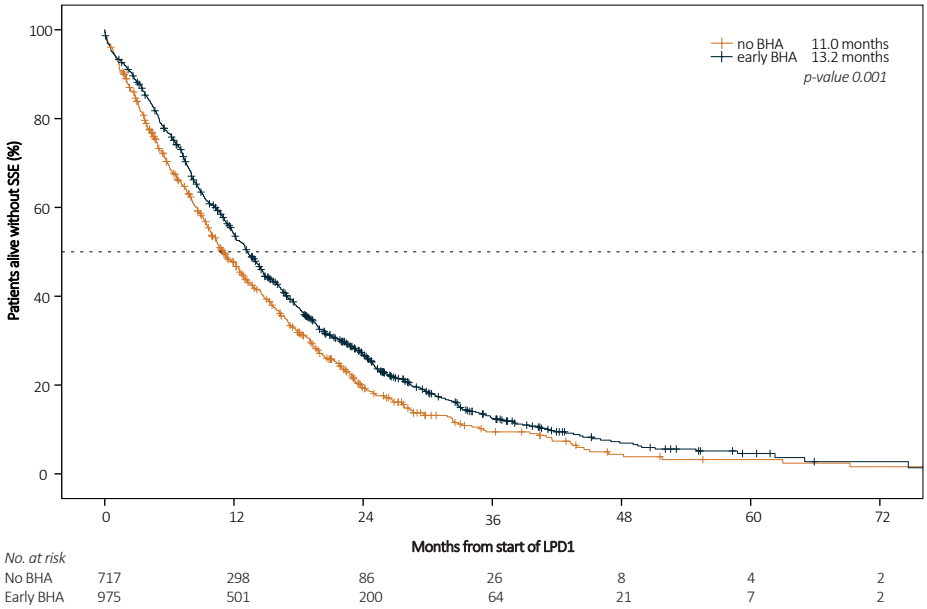


Figure 7.2 | SSE-FS based on BHA use
Dotted line indicates median SSE-FS.
Abbreviations: BHA, bone health agents; SSE-FS, symptomatic skeletal event free survival.

Subgroup analysis

After correction for known prognostic factors, the presence of pain and/or opioid use at the start of LPD1 (OR 1.42, 95% CI 1.08-1.86, p=0.01) and an SSE prior to LPD1 (OR 4.00, 95% CI 3.16-5.07, p<0.01) were strong predictors for development of an SSE (Supplementary Table S7.2). We have created subgroups based on the presence of none (subgroup 1), one (subgroup 2) or both (subgroup 3) of these characteristics. BHA early use was the highest in patients with the highest risk (i.e. subgroup 3), namely 60.8% compared with 48.8% in subgroup 1 and 53.8% in subgroup 2 (p=0.044). Although early BHA use, 28% in subgroup 1, 49% in subgroup 2 and 65% in subgroup 3 experienced at least one SSE during follow-up (p<0.001).

The SSE incidence rate per patient year increased per subgroup: 0.18 in subgroup 1, 0.32 in subgroup 2, and 0.49 in subgroup 3 (p<0.001). Patients with early BHA use had lower SSE incidence rate per patient year compared with patients without BHA use in all subgroups, which was only statistically significant for subgroup 3 (Figure 7.3).

SSE-FS was better for patients in subgroup 1 and 2 than patients in subgroup 3 (16.3 and 10.4 vs 6.9 months respectively, p<0.001). Patients with early use of BHA had longer SSE-FS than patients without BHA in subgroup 2 and 3 (12.1 vs 8.7 months, p=0.001 and 7.2 vs 5.9 months, p=0.033 respectively; Figure 7.4B and 7.4C), but not subgroup 1 (16.6 vs 15.9 months, p=0.307; Figure 7.4A).

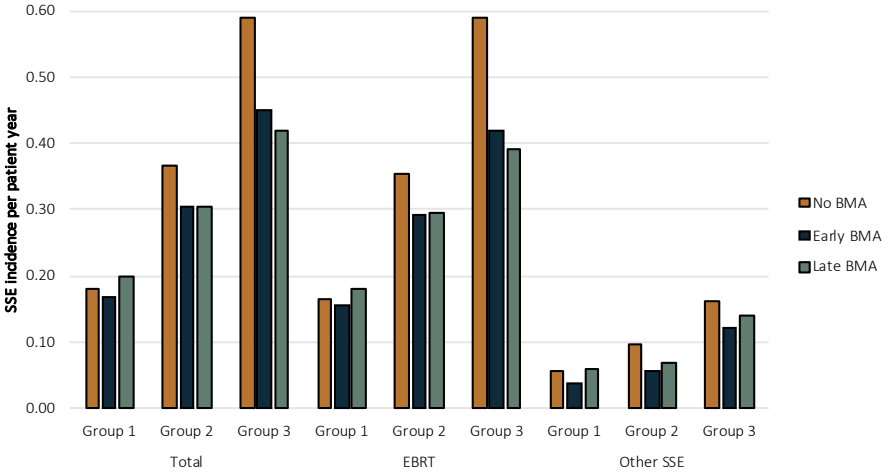


Figure 7.3 | SSE incidence rate per patient year per subgroup
Subgroup 1 i.e. patients without pain and/or opioid use and without prior SSE; Subgroup 2 i.e. patients with only pain and/or opioid use or only prior SSE; subgroup 3 i.e. patients with both pain and/or opioid use and prior SSE.
Abbreviations: SSE, symptomatic skeletal events; BHA, bone health agents; EBRT, external beam radiation therapy.

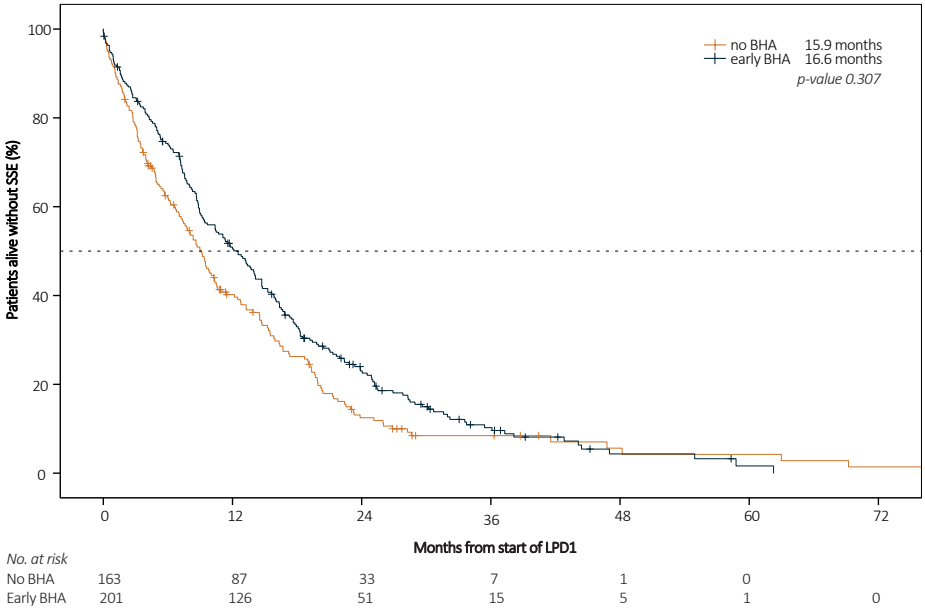
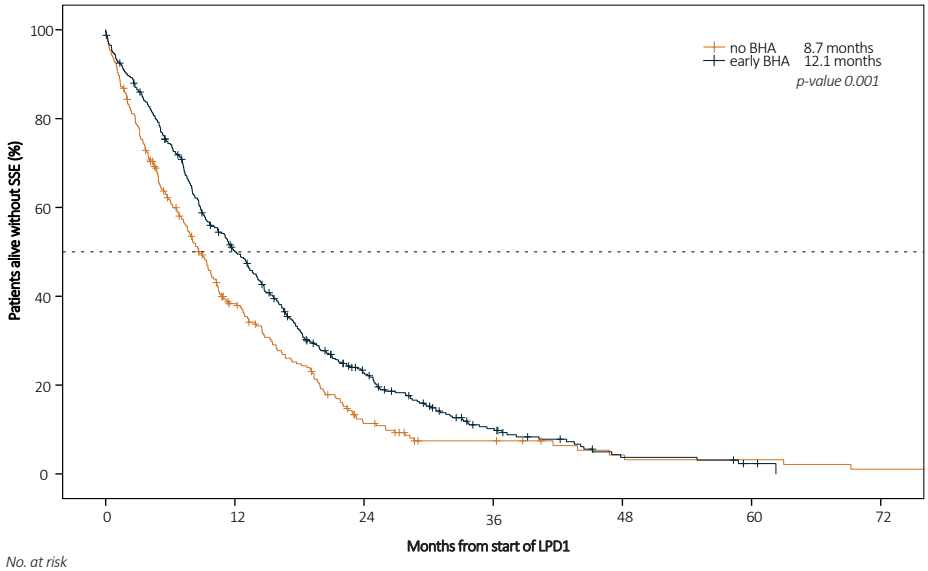


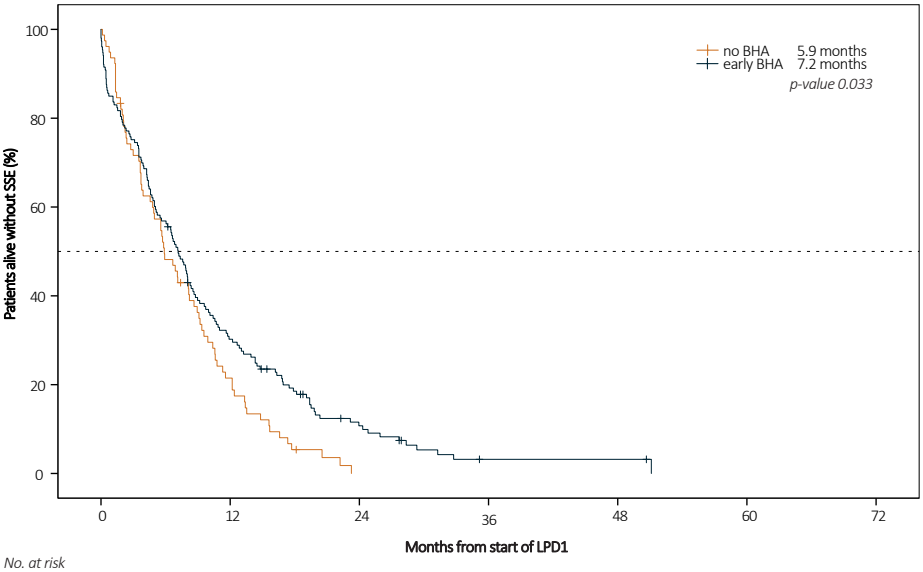
Figure 7.4A | SSE-FS based on BHA use for subgroup 1; no pain and/or opioid use and no prior SSE
Abbreviations: BHA, bone health agents; SSE-FS, symptomatic skeletal event free survival.



No. at risk

No BHA	281	93	23	10	4	3	1
Early BHA	401	191	73	24	6	2	0

Figure 7.4B | SSE-FS based on BHA use for subgroup 2; only pain and/or opioid use or only prior SSE
Dotted line indicates median SSE-FS.
Abbreviations: BHA, bone health agents; SSE-FS, symptomatic skeletal event free survival.



No. at risk

No BHA	78	16	0			
Early BHA	153	45	13	2	2	0

Figure 7.4C | SSE-FS based on BHA use for subgroup 3; both pain and/or opioid use and prior SSE
Dotted line indicates median SSE-FS.
Abbreviations: BHA, bone health agents; SSE-FS, symptomatic skeletal event free survival.

DISCUSSION

In this cohort analysis, we report SSEs in a real-world mCRPC population treated with LPDs. To our knowledge, this is the largest multicentre population without strict patient selection criteria in which patients are treated according to the views and opinions of their treating physicians. Outcomes therefore reflect current daily practice. Moreover, we used SSEs as an outcome which is clinically more relevant than SREs that also include asymptomatic skeletal events found on radiologic assessment.

All patients in this real-world mCRPC population were at risk for SSEs due to the presence of bone metastases and the prolonged use of ADT[48]. Forty-one percent actually experienced at least one SSE during follow-up, which was on the high end of previously reported rates ranging between 29% to 44%[177,184]. Patients who started BHAs early (prior or within the first month after the start of LPD1) had a lower incidence rate of SSEs and longer SSE-FS compared with patients without BHA use. Phase III trials have shown the effect of bisphosphonates (zoledronic acid) and denosumab on SREs and both prolong the time to first on-study SRE (20.7 months for denosumab and 17.1 months for zoledronic acid)[183]. This effect was similar when using only symptomatic events (i.e SSEs) as an endpoint[184]. Results from trials performed in selected patients are in general not easily generalizable to clinical practice, but in addition to our findings a recently published paper of 625 real-world CRPC-patients showed a reduction in SSE incidence rate with concomitant BHA use (0.34 vs 0.37 in with and without concomitant BHA respectively[185].

Although both randomized trials and real-world evidence support the beneficial effect of BHAs and the guidelines BHAs promote the use of BHAs in all bone-metastatic CRPC-patients, only 60% of our population was treated with BHAs during follow-up [23,186–188]. This undertreatment is not new and similar to the 40-55% of patients with concurrent BHA in similar populations[182,185]. The reasons not to start a BHA were not included in our database, but an European analysis reported that clinicians mainly withhold BHA treatment since they wanted to wait until first line LPD had failed or they estimated that the risk of bone complications was low[189]. The LPDs AA+P, ENZ and Ra-223 prolong the time to first SRE with approximately 3-6 months compared with placebo [30,36,37,39]. However, post-hoc analyses of these pivotal trials have shown an additional effect (i.e. longer OS, longer time to opiate use, and longer time to deterioration in ECOG PS) of combining LPDs with BHA[190,191].

We also investigated which patients can benefit from BHAs based on their risk of SSEs. Although other studies report elevated ALP, visceral metastases, Gleason score ≥7 and short interval between the initiation of ADT and CRPC diagnosis as risk factors, we have found that only patients with a prior SSE and with pain and/or opioid use were at higher risk of developing an SSE[192–194]. Patients who had either a prior SSE or pain and/or opioid use (or both) benefited the most from early BHA use. However, patients

without these two characteristics who started BHA early also had a lower SSE incidence per patient year, although SSE-FS was not different from patients without BHA use. Our observation further supports timely initiation of BHAs (prior to or early after the start of LPD1) in patients with bone metastases, especially in patients with a prior SSE or pain and/or opiate use (or both). Based on our data we were not able to determine optimal timing and duration of BHA).

The most common SSE was EBRT which can offer an adequate treatment for bone pain with an overall pain response in ranging from 66% to 84%[195,196]. Since bone pain is frequent and severe in mCRPC patients especially later disease phases, this could explain the high need for EBRT for symptom management[197]. Patients who started BHAs early had lower incidence rates of EBRT and of all other SSEs, but the incidence of other SSEs was low in our population (<10%). Our results on spinal cord compressions are similar to other studies, but we observed less pathologic fractures (3% vs 25%)[198]. We only captured symptomatic skeletal complications (SSEs) and not SREs which also include asymptomatic fractures on protocol mandated radiologic assessment. Changing the definition from SREs to SSEs mainly impacts the prevalence of pathologic fractures[184]. A phase III trial namely showed that the rate of pathologic fractures was 17% when the endpoint was SREs compared with 2% when the endpoint was SSEs[184].

In addition to SSEs which are more clinically relevant than SREs, SSE-FS offers a new clinical trial end point combining survival and SSEs into a single outcome. This provides an objective measurement of clinically meaningful benefit. The ERA-223 trial also used SSE-FS as an endpoint[182]. The ERA-223 trial included asymptomatic or minimally symptomatic mCRPC patients with bone metastases randomized between AA+P with placebo or Ra-223 and after a median follow-up of 21.2 months, SSE-FS was 26.0 and 22.3 months, respectively[182]. In our cohort, median SSE-free survival was 12.9 months. The difference in SSE-FS in our observation can be explained by a high prevalence of SSEs compared with other studies [37,39,192,194,199]. We only included real-world patients who tend to have worse prognostic features than trial populations and thus are likely to have shorter SSE-FS.

The limitation of our study was the high number of missing values on baseline characteristics. This reflects incomplete evaluation of patients or lack of structured reporting in daily practice. High number of missing values leads to exclusion of many patients in multiple regression analysis, however imputation of missing baseline data offers a valid solution. Moreover, we miss data that might be of influence on the risk of SSEs (e.g. site of metastases and metastatic burden). Residual confounding could therefore still be present in multivariable analysis.

We were not able to determine if skeletal complications occurred at the tumour site and information to discriminate with osteoporotic complications as serum levels of vitamin D or calcium or dual energy X-ray absorptiometry (DEXA) scans were not available

in this study. Discriminating between tumour-related or osteoporotic complications is necessary, since they need different treatment strategies.

In this real-world analysis 41% of bone metastatic CRPC patients experienced an SSE during follow-up, even though all were treated with at least one LPD. Patients who started BHA early had lower incidence rate of SSEs and longer SSE-FS, irrespective of risk factors (prior SSE or pain and/or opioid use) and type of SSE. However, we found a possible undertreatment of BHAs since only 52% started BHA early. This warrants timely combining LPDs with BHAs in all bone metastatic CRPC-patients, but especially in patients with risk factors. Further prospective research should provide information about the optimal timing and duration of BHAs, especially in light of the availability of new LPDs.

SUPPLEMENTARY MATERIAL

Table S7.1 | Baseline characteristics at the start of LPD1 based on BHA subgroups

		No BHA N=750	Early BHA N=996	Late BHA N=162	p
Age (years)	median (range)	75 (46-99)	73 (46-95)	71 (53-90)	<0.001*
	≥ 75 years (n, %)	375 (50)	432 (43)	54 (33)	
ECOG PS, n (%)	0	142 (19)	208 (21)	39 (24)	0.018
	1	295 (39)	437 (44)	66 (41)	
	≥2	102 (14)	113 (11)	8 (5)	
	unknown	211 (28)	238 (24)	49 (30)	
Charlson comorbidity index, n (%)	0	498 (66)	637 (64)	114 (70)	0.117
	1-2	202 (27)	304 (31)	46 (28)	
	3-4	41 (6)	44 (4)	2 (1)	
	> 4	9 (1)	11 (1)	0 (0)	
	unknown	0 (0)	0 (0)	0 (0)	
Pain and/or opioid use, n (%)	yes	285 (38)	404 (41)	52 (32)	0.614
	no	241 (32)	320 (32)	50 (31)	
	unknown	224 (30)	272 (24)	60 (37)	
Visceral metastases, n (%)	yes	101 (14)	100 (10)	20 (12)	0.084
	no	304 (41)	429 (43)	73 (45)	
	unknown	345 (46)	467 (47)	69 (43)	
Time ADT to mCRPC (mo)	median (IQR)	14 (8-24)	13 (7-23)	12 (8-22)	0.265
	unknown, n (%)	3 (<1)	2 (<1)	0 (0)	
Time ADT to LPD1 (mo)	median (IQR)	23 (12-44)	22 (13-40)	19 (12-38)	0.124
	unknown, n (%)	3 (<1)	2 (<1)	0 (0)	
Hb (mmol/L)	median (IQR)	7.8 (6.9-8.4)	7.8 (7.0-8.4)	8.0 (7.4-8.6)	0.202
	unknown, n (%)	116 (15)	130 (13)	29 (18)	
LDH (U/L)	median (IQR)	231 (190-334)	240 (198-323)	248 (195-337)	0.496
	unknown, n (%)	230 (31)	243 (24)	55 (34)	
ALP (U/L)	median (IQR)	154 (98-319)	160 (99-345)	161 (99-365)	0.570
	unknown, n (%)	105 (14)	126 (13)	28 (17)	
PSA (µg/L)	median (IQR)	119 (45-273)	100 (40-270)	113 (49-230)	0.370
	unknown, n (%)	60 (8)	95 (10)	24 (15)	
SSE prior to LPD1, n (%)	yes	161 (22)	312 (31)	45 (28)	<0.001*
	no	502 (67)	598 (60)	104 (64)	
	unknown	87 (12)	86 (9)	13 (8)	

*significant at p-value<0.05.

All baseline parameters are measured in the period 6 weeks prior to 1 week after the start of LPD1. Total percentages can exceed 100% due to rounding.

Abbreviations: LPD, life-prolonging drug; BHA, bone health agent; ECOG PS, Eastern Cooperative Group Performance Score; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mo, months; Hb, hemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; SSE, symptomatic skeletal event.

Table S7.2 | Univariable and multivariable binary logistic regression for SSE

		Univariable analysis of original data				Multivariable analysis of pooled data after imputation		
		N	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (years)	cont.	1,866	0.94	0.93-0.95	<0.001*	0.94	0.93-0.96	<0.001*
Charlson score	6	1,224	REF	-	-	REF	-	-
	7-8	536	0.90	0.73-1.10	0.297	1.03	0.81-1.30	0.831
	≥ 9	106	0.54	0.35-0.84	0.006*	0.58	0.36-0.93	0.024*
ECOG PS	0	368	REF	-	-	REF	-	-
	1	782	1.12	0.88-1.44	0.363	0.99	0.73-1.37	0.986
	≥2	222	0.71	0.51-1.01	0.055	0.59	0.39-0.91	0.016*
Pain and/or opioid use	no	588	REF	-	-	REF	-	-
	yes	737	1.57	1.26-1.96	<0.001*	1.42	1.08-1.86	0.012*
Visceral metastases	no	777	REF	-	-	REF	-	-
	yes	220	0.91	0.67-1.23	0.517	0.84	0.54-1.29	0.402
Time ADT to mCRPC (mo)	cont.	1,861	0.99	0.99-1.00	0.098	1.00	0.99-1.00	0.891
Hb (mmol/L)	cont.	1,596	1.05	0.96-1.16	0.307	0.98	0.87-1.11	0.782
ALP (U/L)	cont.	1,608	1.00	1.00-1.00	0.566	1.00	1.00-1.00	0.930
LDH (U/L)	cont.	1,347	1.00	0.99-1.00	0.005*	0.99	0.99-1.00	0.007*
PSA (µg/L)	cont.	1,692	1.00	1.00-1.00	0.861	1.00	1.00-1.00	0.363
Prior SSE	no	1,166	REF	-	-	REF	-	-
	yes	511	3.83	3.07-4.77	<0.001*	4.00	3.16-5.07	<0.001*

*significant at p-value<0.05.

Abbreviations: SSE, symptomatic skeletal event; OR, odds ratio; CI, confidence interval; REF, reference category; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mo, months; Hb, haemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate specific antigen.

8

Radium-223 therapy in patients with advanced CRPC with bone metastases: lessons from daily practice

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Clinical Nuclear Medicine 2018;43(1):9–16

ABSTRACT

Purpose: To identify pre-therapeutic variables associated with overall survival (OS) in patients treated with Ra-223.

Methods: Data from 45 CRPC patients treated with Ra-223 were retrospectively analyzed. All patients who received at least one Ra-223 injection were included in the study. Cox proportional hazard regression models were used to estimate hazard ratio's (HR) and to test for association.

Results: Twenty-one patients (47%) received six Ra-223 injections and 24 patients (53%) received one to five Ra-223 injections. Median OS since start of Ra-223was 13.0 months (95%confidence interval (CI) 8.2–17.8). Patients who completed Ra-223 therapy had a median OS of 19.7 months (95% CI 14.9–24.6), while patients who received one to five Ra-223 injections had a median OS of 5.9 months (95% CI 3.8–8.1; $P < 0.001$). Univariable analysis showed poor baseline ECOG performance status (PS), baseline opioid use, lowered baseline haemoglobin, and elevated prostate specific antigen, alkaline phosphatase and lactate dehydrogenase (LDH) levels were significantly associated with OS. Multivariable Cox regression analysis demonstrated that poor baseline ECOG PS (HR 10.6) and high LDH levels (HR 7.7) were pre-therapeutic variables that predicted poor OS.

Conclusion: In a multivariable Cox regression model, good baseline ECOG PS and low LDH levels were significantly associated with longer OS in patients treated with Ra-223. These variables may be used for stratification of CRPC patients for Ra-223 therapy. Prospective studies to evaluate these variables are warranted, to develop a nomogram to select patients properly. In this retrospective study, predictors of overall survival in 45 metastatic castration-resistant prostate cancer patients treated with Ra-223 therapy were evaluated. Baseline ECOG performance status and lactate dehydrogenase levels turned out to be significant in a multivariable prediction model for overall survival.

INTRODUCTION

Radium-223 (Ra-223) is a registered palliative therapy for castration-resistant prostate cancer (CRPC) patients with symptomatic bone metastases. This radioisotope is very similar to calcium and binds selectively to areas of increased bone turnover in bone metastases. There it emits high-energy alpha particles of short range (<100 µm; 2-10 cell layers), causing double-strand DNA breaks leading to a cytotoxic effect on tumour cells and cells in the tumour microenvironment[200,201].

In the phase 3 ALSYMPCA trial, CRPC patients were treated with Ra-223 or placebo, either before or after docetaxel chemotherapy[30]. The outcome was a significant median overall survival (OS) benefit of 3.6 months in favour of Ra-223 over placebo. Subsequent analyses demonstrated survival benefit of Ra-223 in chemotherapy-naïve CRPC patients as well as in post-chemotherapy CRPC patients[150]. In addition, Ra-223 reduced the risk of symptomatic skeletal events and was accompanied by significant improvement of quality of life[38,124].

To date, clinical data on Ra-223 in daily practice are scarce. In the ALSYMPCA trial, 63%of CRPC patients treated with Ra-223 received six injections, whereas only 42% of the Dutch patients received six Ra-223 injections in 2016, with a median number of four injections[30]. This may indicate that real-world patients treated with Ra-223 differ from those included in the ALSYMPCA trial[41].

In addition, effect monitoring during Ra-223 therapy is challenging. Therefore, optimal patient selection is crucial. It is important to identify pre-therapeutic factors to estimate whether a patient will achieve OS benefit of Ra-223. Knowledge of these factors can lead to better patient selection and might lead to a reduction of health care costs. The objective of this study was to evaluate real-world data of CRPC patients treated with Ra-223, in order to determine pre-therapeutic variables that predict OS and to describe baseline differences between patients who completed and patients who discontinued Ra-223 therapy.

METHODS

Study design and patient population

CRPC patients treated with Ra-223 between September 2013 and March 2016 were retrospectively evaluated. Patients who received at least one Ra-223 injection were included in the study. There were no exclusion criteria. All patients continued androgen deprivation therapy and patients were castration-resistant according to the European Association of Urology definition[23].

The medical records of the patients were reviewed to collect information about demographic characteristics, comorbidity, histology, surgical procedures and medical therapies for prostate cancer, laboratory evaluations, imaging studies, the occurrence of skeletal related events (SREs) and survival. All patients were followed until death or June 1, 2017.

Ra-223 therapy standard of care

Ra-223 was injected intravenously every 4 weeks up to six cycles according to standard of care[202]. Institutional criteria for initiation of Ra-223 therapy included CRPC patients with bone metastases, no or small (<3 cm in short-axis diameter) lymph node metastases and no visceral metastases. Laboratory requirements were baseline absolute neutrophil count >1.5 x 10^9/L and platelet count >100 x 10^9/L. Laboratory evaluation was carried out within 60 days before Ra-223 initiation. Within 3 months prior to start of Ra-223 therapy imaging studies were performed, including a bone scintigraphy and computer tomography (CT) of thorax and abdomen. Before every injection, performance status (PS) was scored according to the Eastern Cooperative Oncology Group (ECOG) criteria. Laboratory evaluation before every Ra-223 injection included haemoglobin (Hb), platelets, lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and prostate specific antigen (PSA) measurements. All eligible patients were discussed in our multidisciplinary team meeting before initiation of Ra-223 therapy.

Adverse events

Adverse events during Ra-223 therapy were scored using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. SREs were defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression[147].

Biochemical and radiological response evaluation

Changes in PSA and ALP were calculated from baseline to week 12 (after three injections), from baseline to end of therapy (approximately 1 month after the last injection) and as maximal percentage change at any time from baseline. Patients who had no baseline level, no follow-up measurements or received concomitant enzalutamide or abiraterone were excluded from biochemical response evaluation. More than 25% decline or increase from baseline of PSA, ALP and LDH was considered to be clinically significant, according to Prostate Cancer Working Group 3 criteria[147]. Radiological evaluation was performed in patients who underwent evaluation of soft tissues within 3 months after completion or discontinuation of therapy.

Statistical methods

Survival time was defined as the time interval from date of first Ra-223 injection to the date of death. Cox proportional hazards models were used to assess the prognostic significance of baseline variables in univariable and multivariable analysis. A multivariable Cox regression model was fitted by including variables in the model with a forward selection strategy based on Wald's test at a significance level of 0.10 at every step. In case baseline variables were heavily skewed distributed or the proportional hazard assumption was not likely to hold, log transformation or categorization of variables was performed.

To compare baseline characteristics between patients who completed and discontinued Ra-223 therapy, the chi-square test or Fisher exact test was used. Statistical tests were performed two sided, with P values <0.05 considered statistically significant. Survival curves for patients who completed therapy and patients who discontinued therapy were estimated by the Kaplan-Meier estimator. The Mantel-Cox log rank test was used to compare the survival distributions.

Statistical analyses were performed using SPSS 22.0 (IBM®, Armonk, NY, USA). Figures were created with SPSS and GraphPad Prism 5.03 (GraphPad Software, Inc., La Jolla, CA, USA).

Ethics

This study was approved by the medical ethics review committee. The principles of the Helsinki Declaration were followed.

RESULTS

Patient characteristics

Patient characteristics of the 45 CRPC patients who received Ra-223 are shown in Table 8.1. The median number of prior registered therapies for CRPC was 2 (range 0-4). Twenty-five patients (56%) received prior docetaxel chemotherapy and 35 patients (78%) received prior enzalutamide and/or abiraterone (Table 8.2).

Overall survival

Thirty-eight patients (84%) had died at time of analysis. The median OS since start of Ra-223 in the whole study population was 13.0 months (95% CI 8.2-17.8). Univariable analysis showed that baseline ECOG PS, baseline opioid use and baseline haemoglobin, PSA, ALP and LDH levels were variables significantly associated with OS (Table 8.3). With the multivariable analysis we found a model that included baseline ECOG PS and baseline LDH levels (Table 8.4). However, the multivariable analysis was restricted to 32

Table 8.1 | Baseline patient characteristics

		Complete cohort (N=45)		1-5 Ra-223 injections (N=24)		6 Ra-223 injections (N=21)		p
		N		N		N		
Age (years)		45	71 (51-84)	24	71 (51-83)	21	70 (55-84)	0.666
Non-metastatic initial tumor (n, %)		45	14 (31.1)	24	7 (29.2)	21	7 (33.3)	0.763
Gleason-score 8-10, n (%)		45	27 (60.0)	24	16 (66.7)	21	11 (46.7)	0.329
Time diagnosis PCa to CRPC (mo), median (range)		45	29 (5-200)	24	30 (5-200)	21	26 (12-173)	0.716
Time start ADT to CRPC (mo), median (range)		45	22 (5-85)	24	20 (5-85)	21	24 (12-75)	0.539
Time CRPC to Ra-223 (mo), median (range)		45	23 (1-80)	24	20 (0-51)	21	30 (6-80)	0.082
Prior therapies for localized PCa, n (%)	Radical prostatectomy[a]	45	10 (22.2)	24	4 (16.6)	21	6 (28.6)	0.476
	Radiotherapy prostate (initial or salvage)	45	17 (37.8)	24	8 (33.3)	21	9 (42.9)	0.511
	Pelvic lymph node dissection	45	11 (24.4)	24	6 (25.0)	21	5 (23.8)	1.000
	Pelvic lymph node irradiation	45	4 (8.9)	24	1 (4.2)	21	3 (14.3)	0.326
Prior therapies for CRPC, n (%)	No. of therapies, median (range)	45	2 (0-4)	24	2 (0-4)	21	2 (0-4)	0.744
	None	45	6 (13.3)	24	5 (20.8)	21	1 (4.8)	0.193
	Abiraterone and/or enzalutamide	45	35 (77.8)	24	17 (70.8)	21	18 (85.7)	0.296
	Abiraterone	45	31 (68.9)	24	13 (54.2)	21	18 (85.7)	0.028*
	Enzalutamide	45	11 (24.4)	24	9 (37.5)	21	2 (9.5)	0.040*
	First-line chemotherapy[b]	45	25 (55.6)	24	14 (58.3)	21	11 (52.4)	0.688
	Second-line chemotherapy[c]	45	13 (28.9)	24	8 (33.3)	21	5 (23.8)	0.528
	Radiotherapy to bone metastases	45	27 (60.0)	24	13 (54.2)	21	14 (66.7)	0.393
Concomitant abiraterone or enzalutamide, n (%)		45	5 (11.1)	24	4 (16.7)	21	1 (4.8)	0.352
Body mass index (kg/m2), mean (SD)		42	26.6 (3.3)	21	26.1 (3.3)	21	26.8 (3.5)	0.782
Opioid use, n (%)		45	20 (44.4)	24	14 (58.3)	21	6 (28.6)	0.045
ECOG PS, n (%)	ECOG PS 0	44	21 (47.7)	24	8 (33.3)	20	13 (65.0)	0.104
	ECOG PS 1	44	15 (34.1)	24	10 (41.7)	20	5 (25.0)	
	ECOG PS 2-3	44	8 (18.2)	24	6 (25.0)	20	2 (10.0)	

* significant at p-value <0.05; [a]Either open (40%) or laparoscopically (10%) or robot assisted (50%); [b]96% docetaxel, 4% mitoxantrone; [c] 62% cabazitaxel, 38% docetaxel. Total percentages may exceed 100%

because of rounding. *Abbreviations*: Ra-223, radium-223; PCa, prostate cancer; CRPC, castration resistant prostate cancer; mo, months; ADT, androgen deprivation therapy; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance Score.

Table 8.2 | Baseline laboratory and imaging characteristics

		Complete cohort (N=45)		1-5 Ra-223 injections (N=24)		6 Ra-223 injections (N=21)		p
		N		N		N		
Hemoglobin (g/dL), median (range)		45	12.0 (9.3)	24	11.8 (9.3-14.9)	21	12.6 (9.9-15.4)	0.136
	Hb > 10, n (%)	45	40 (88.9)	24	20 (83.3)	21	20 (95.2)	0.352
	Hb ≤ 10, n (%)	45	5 (11.1)	24	4 (16.7)	21	1 (4.8)	
Platelet count (x 10^9/L), median (range)		45	240 (140-466)	24	238 (140-461)	21	254 (142-466)	0.794
WBC count (x 10^9/L) , median (range)		45	7.5 (3.4-12.7)					
NLR (x 10^9/L), median (range)		35	4.20 (0.9-11.8)	19	2.90 (1.0-11.8)	16	4.59 (0.9-9.0)	0.466
	NLR ≤ 3.0, n (%)	35	15 (42.9)	19	10 (52.6)	16	5 (31.3)	0.203
	NLR > 3.0, n (%)	35	20 (57.1)	19	9 (47.4)	16	11 (68.8)	
PSA level (µg/L), median (range)		44	130.0 (1-6472)	23	170.0 (9-3000)	21	61.0 (1-6472)	0.142
ALP (U/L), median (range)		43	147 (60-2640)	24	180 (73-1958)	19	125 (60-2640)	0.304
	ALP < 115, n (%)	43	16 (37.2)	24	7 (29.2)	19	9 (47.4)	0.220
	ALP ≥ 115, n (%)	43	27 (62.8)	24	17 (70.8)	19	10 (52.6)	
LDH level (U/L), median range		33	216 (165-1045)	19	288 (175-1045)	14	208 (165-341)	0.011*
	LDH <250, n (%)	33	20 (60.6)	19	8 (42.1)	14	12 (85.7)	0.015*
	LDH ≥ 250, n (%)	33	13 (39.4)	19	11 (57.9)	14	2 (14.3)	
Extent of disease, n (%)	6-20 metastases	45	9 (20.0)	24	5 (20.8)	21	4 (19.0)	0.912
	>20 metastases	45	28 (62.2)	24	14 (58.3)	21	14 (66.7)	
	Superscan[a]	45	8 (17.8)	24	5 (20.8)	21	3 (14.3)	
	Lymph node metastases	41	10 (24.4)	20	5 (25.0)	21	5 (23.8)	0.929
	Visceral metastases	41	4 (10.0)	20	2 (10.0)	21	2 (9.5)	1.000

* significant at p-value <0.05; [a] Superscan referes to a bone scan showing diffuse, intense skeletal uptake of the races without renal and background activity. Total percentages may exceed 100% because of rounding.

Abbreviations: Ra-223, radium-223; Hb, hemoglobin; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; PSA, prostate specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase CRPC, castration resistant prostate cancer; ADT, androgen deprivation therapy; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance Score.

Table 8.3 | Univariable analysis of overall survival

		N	mOS (mo)	HR	95% CI	p
Age (years)		45	13.0	1.01	0.97-1.06	0.59
ECOG PS						<0.01*
	ECOG PS 0	21	19.7	REF	-	-
	ECOG PS 1	15	5.9	3.35	1.59-7.06	<0.01*
	ECOG PS 2-3	8	7.3	4.15	1.66-10.33	<0.01*
Opioid use	No	25	15.7	REF	-	-
	Yes	20	5.9	2.00	1.05-3.81	0.03*
Initial Gleason score	≤7	18	11.0	REF	-	-
	8-10	27	13.6	0.88	0.46-1.69	0.71
Extent of disease						0.16
	6-20 metastases	9	17.0	REF	-	-
	>20 metastases	28	13.5	1.32	0.56-3.13	0.52
	Superscan[a]	8	7.9	2.62	0.92-7.49	0.07
Prior chemotherapy	No	20	15.7	REF	-	-
	Yes	25	8.9	1.77	0.90-3.49	0.10
Prior abiraterone or enzalutamide	No	10	8.6	REF	-	-
	Yes	35	13.0	1.74	0.72-4.19	0.22
No of prior CRPC therapies	0-1	18	14.3	REF	-	-
	≥2	27	10.0	1.47	0.75-2.85	0.26
No of prior CRPC therapies						0.24
	0	6	5.1	REF	-	-
	1	12	14.3	1.24	0.38-4.06	0.72
	2	10	8.9	1.10	0.32-3.77	0.88
	3	9	11.0	1.80	0.55-5.92	0.33
	4	8	6.0	3.07	0.87-10.80	0.08
Haemoglobin (g/dL)		45	13.0	0.74	0.58-0.93	<0.01*
Haemoglobin (g/dL), dichotomized	>10	40	13.6	REF	-	-
	≤10	5	5.7	3.81	1.39-10.38	<0.01*
Platelet count (x 10^9/L)		45	13.0	1.00	1.00-1.00	0.21
ANC (x 10^9/L)		36	11.0	0.98	0.84-1.14	0.78
NLR (x 10^9/L)		35	11.0	1.08	0.94-1.24	0.30
Log PSA		44	13.0	1.23	1.03-1.48	0.03*
Log ALP		43	12.2	1.66	1.16-2.35	<0.01*
ALP (U/L), dichotomized	<115	16	15.7	REF	-	-
	≥115	27	8.6	2.16	1.05-4.44	0.04*
Log LDH (U/L)		33	11.0	7.39	2.54-21.54	<0.01*
LDH (U/L), dichotomized	<250	20	15.7	REF	-	-
	≥250	13	5.9	2.78	1.23-6.30	0.01*
Albumin (g/L)		33	13.6	0.96	0.87-1.05	0.34

*significant at p-value <0.05; [a] superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.

Abbreviations: mOS, median overall survival; mo, months; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Co-operative Oncology Group Performance Score; REF, reference category; CRPC, castration resistant prostate cancer; ANC, absolute neutrophil count; NLR, neutrophil-to-lymphocyte ratio; PSA, prostate specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase.

Table 8.4 | Multivariable analysis of overall survival

		N	HR	95% CI	p
Prior abiraterone or enzalutamide		32			
	No	9	REF	-	-
	Yes	23	2.38	0.91-6.23	0.08
ECOG PS		32			<0.01*
	ECOG PS 0	17	REF	-	-
	ECOG PS 1	9	10.62	3.07-36.73	<0.01*
	ECOG PS 2-3	6	5.67	1.74-18.47	<0.01*
Log LDH		32	7.67	1.75-33.53	<0.01*

*significant at p-value <0.05.
Abbreviations: HR, hazard ratio; CI, confidence interval; REF, reference category; ECOG PS, Eastern Cooperative Oncology Group Performance Score; LDH, lactate dehydrogenase.

subjects (71%) due to limited availability of baseline LDH levels (complete case analysis). When the baseline LDH level variable was left out from analysis, 41 subjects (91%) were included in the analysis and baseline ECOG PS, baseline haemoglobin level and opioid use were selected in multivariable analysis (hazard ratios 2.6 (95% CI 1.1-5.8); 0.8 (95% CI 0.6-1.0) and 2.2 (95% CI 1.0-4.7), respectively).

The number of injections

Twenty-one (47%) patients received all six injections. The median number of injections was five. Four patients (9%) received one or two injections, seven patients (16%) received three injections, four patients (9%) received four injections and nine patients (20%) received five injections. We found significant differences between patients who received one to five injections and those who completed therapy regarding baseline LDH levels, baseline opioid use and prior use of abiraterone or enzalutamide (Tables 8.1 and 8.2). Patients who completed Ra-223 therapy had a median OS of 19.7 months (95% CI 14.9-24.6), while patients who received one to five Ra-223 injections had a median OS of 5.9 months (95% CI 3.8-8.1; p<0.001) (Figure 8.1). This significant finding in survival was substantiated by the OS difference between five (n=9) and six Ra-223 injections (7.3 vs 19.7 months, p<0.01).

Adverse events

Persistent hematologic toxicity was the reason to discontinue Ra-223 therapy in nine of 24 patients (38%; pancytopenia in four patients, thrombocytopenia in three patients, anaemia in two patients). No grade 3-4 non-hematologic adverse events occurred during and after therapy.

At baseline, 33 patients (73%) had grade 1 anaemia and five patients (11%) had grade 2 anaemia. Only one patient with initial grade 2 anaemia completed therapy. During

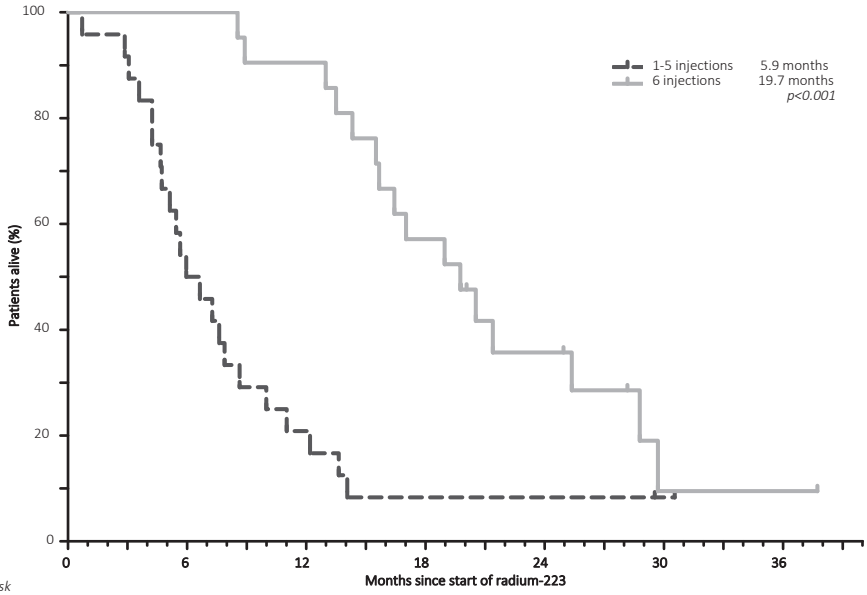

Figure 8.1 | Overall survival from the start of radium-223

therapy, 16 patients received red blood cell transfusion. Seventy-five percent of these patients did not complete therapy and 81% of these patients had received two or more prior CRPC therapies. OS was significantly worse when compared to patients who did not need blood cell transfusion (8 versus 14 months). At any time during therapy, grade 1 thrombocytopenia occurred in 11 patients (24%) and grade 2 (2%) or 3 (2%) occurred in one patient each. Flare-up of pain immediately after Ra-223 administration occurred in 16 patients (36%) at any time during therapy.

Physical health deterioration was the reason to stop therapy in six (25%) patients. Five of these six patients had a baseline ECOG PS of 1 (33%) or 2 (50%).

During therapy, 14 SREs were reported in 11 patients (24%). In seven patients spinal cord compression occurred, which was treated by external beam radiotherapy (EBRT) plus dexamethasone. In two patients a pathological fracture occurred; these patients both discontinued therapy. Additionally, three patients underwent EBRT because of increase of pain at a solitary lesion.

Biochemical response evaluation

Figure 8.2 shows PSA and ALP dynamics in patients treated with Ra-223 monotherapy. Significant increase of PSA was observed in 65% of patients after three injections. Significant decrease of ALP was found in 53% of patients after three injections. All of

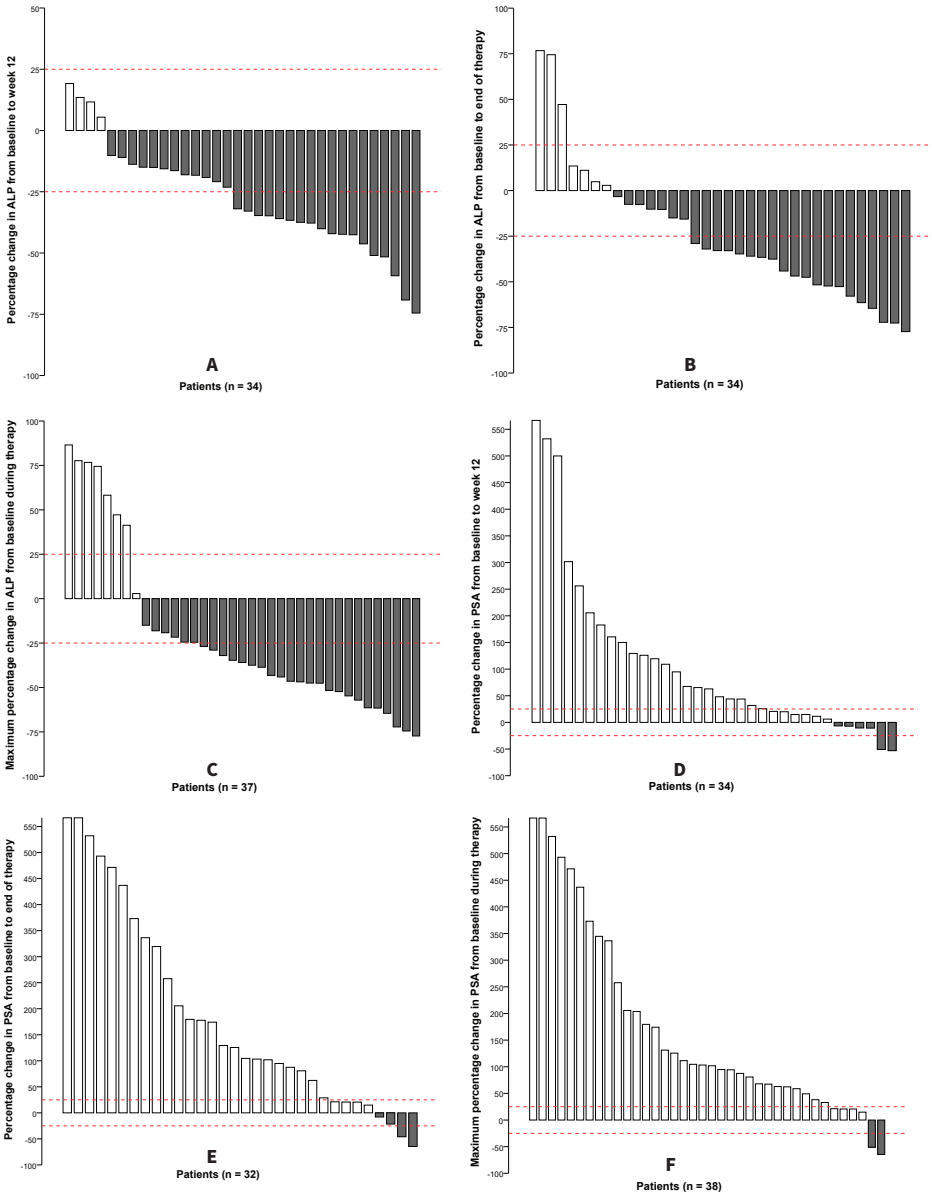

Figure 8.2 | Waterfall plots showing percentage change in ALP and PSA levels
Percentage change from baseline to week 12, to end of therapy and maximum percentage change in ALP (A-C) and PSA (D-F).
Abbreviations: ALP, alkaline phosphatase; PSA, prostate specific antigen.

the patients with PSA decrease showed remarkable ALP decrease (range 23%-75%). ALP at end of therapy was significantly lower in patients who completed therapy when compared to patients who discontinued therapy ($p<0.01$).

Radiological response evaluation

In retrospect, four patients (10%) had small visceral metastases in either liver (n=2) or lungs (n=2) prior to start of Ra-223 therapy. The two patients with lung metastases completed Ra-223 therapy, while both patients with liver metastases discontinued therapy after the fourth injection.

After Ra-223 therapy, 20 patients (44%) underwent evaluation of lymph nodes and soft tissues. Radiological evaluation was mainly performed in patients that completed therapy (90% versus 38%). New lymph node enlargement (≥15 mm in the short axis) was shown in 17% of patients. New visceral metastases to liver, lung, spleen and/or brain were found in 41%of patients. All of these patients were heavily pretreated. Among the 24 patients who discontinued therapy, radiological disease progression was the main reason to stop therapy in five (21%) patients.

Therapies after Ra-223 therapy

In patients who discontinued Ra-223 therapy, best supportive care (67%) or a second-generation anti-hormonal agent (33%) was started. In patients who completed Ra-223 therapy, subsequent therapy was a second-generation anti-hormonal agent in 15 patients (71%). Two patients (10%) received docetaxel without any toxicity during chemotherapy and three patients (14%) received best supportive care after completion of Ra-223 therapy.

DISCUSSION

Overall survival

Median OS in this cohort was 13.0 months, which is similar to the ALSYMPCA trial[30]. Multivariable analysis selected baseline ECOG PS and LDH levels to be significantly associated with OS in this study. The post hoc multivariable analysis of the ALSYMPCA trial also selected baseline ECOG PS and LDH were correlated with OS. In addition, that analysis identified albumin level, total ALP, PSA and age to be correlated with OS as well[155]. The analysis of the early access program demonstrated median OS was longer for patients with low baseline ALP levels, Hb > 10.0 g/dL, ECOG performance score of 0, no reported baseline pain, concomitant use of abiraterone or enzalutamide and concomitant use of denosumab[203]. Recent retrospective analyses stated low baseline ALP levels, no or less prior therapies, and a low number of bone metastases are correlated with better OS[159,161,204]. In fact, all of these pre-therapeutic variables reflect less advanced disease. These findings, and the fact that the prevalence of visceral metastases increases towards advanced disease stage, seem to underline the need for early application of Ra-223 in CRPC patients[153].

Number of injections

Remarkable difference in OS between patients who completed and discontinued Ra-223 therapy was found. Recently, several retrospective studies described significant associations between the received number of Ra-223 injections and OS[159–161]. However, these results have to be interpreted with caution, due to immortal time bias[205]. After all, patients must survive sufficiently long to complete Ra-223 therapy. In addition, the question remains whether the completion of therapy is the cause of the difference in OS, rather than better patient selection.

Response evaluation

At week 12 of therapy, ≥25% reduction in PSA was found in 6% of patients. This low PSA response rate is comparable to findings in the ALSYMPCA trial and the early access program[30,203]. According to the proportional treatment effect analysis of the ALSYMPCA trial, ALP decrease at 12 weeks from baseline was found to be the best indicator for risk of death, but accounted only for 34% of the survival benefit from Ra-223 treatment[155]. This indicates response evaluation of Ra-223 should consist of more than biochemical evaluation alone. There is a clinical need for reliable biomarkers for optimal patient selection and effect monitoring during Ra-223 therapy.

In this study, only 44% of patients underwent CT within 3 months after termination of Ra-223 therapy. New visceral metastases were found in 41%of the patients. This percentage may be overestimated due to selection of patients for radiological evaluation. However, a recent study described radiological extra-skeletal disease progression in even 46% of patients[169]. Advanced imaging techniques, such as ^{68}Ga-PSMA-11 PET-CT, may be helpful to rule out extra-skeletal disease prior to Ra-223 therapy initiation and was also described to be useful as a gatekeeper during Ra-223 therapy[206–209].

Study limitations

The impact of this study is limited by its retrospective single center design and relative small sample size. It is, therefore, susceptible to recall and interpretation bias. The sample size restricted extensive regression analysis. However, this real-world study was able to discriminate important baseline variables which are associated with OS. These results were similar to outcomes of other studies.

Learning curve

Our team experienced a learning curve towards optimal patient selection for Ra-223 therapy. In 2014, only 27% of the patients completed therapy. In 2016, 65% of the patients completed therapy. Nationwide, only 42% of the Dutch patients completed therapy in 2016. According to recent recommendations and our experience, patients should be discussed in a multidisciplinary tumour board with presence of a nuclear physician

before start of therapy[23,210]. In addition, all patients must be radiologically evaluated before and after therapy. During therapy, additional imaging may be considered in case of extraordinary elevation of tumour markers, in order to rule out extra-skeletal disease[169].

CONCLUSIONS

In CRPC patients treated with Ra-223, we found a remarkable difference in OS between patients who discontinued and completed therapy. Baseline ECOG PS and LDH levels were selected in a multivariable Cox regression model to predict OS. Prospective observational multicentre studies with larger patient populations are needed to confirm our findings and to develop a nomogram to select patients properly.

9

Third-line life-prolonging drug treatment in a real-world mCRPC population

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European Urology Focus 2021;7(4):788-796

ABSTRACT

Background: Evidence concerning third-line life-prolonging drugs (LPDs) in the treatment of metastatic castration-resistant prostate cancer (mCRPC) patients is incomplete.

Objective: To evaluate third-line LPD outcomes in a real-world cohort of mCRPC patients, identify variables associated with overall survival (OS), and establish a prognostic model.

Design, setting and participants: Patients with mCRPC who were progressive on second-line LPD before July 1, 2017 were retrospectively identified from the Dutch Castration-resistant Prostate Cancer Registry (CAPRI) and followed until December 31, 2017.

Outcome measurements and statistical analysis: Association of potential risk factors with OS was tested by Cox proportional hazard models after multiple imputation of missing baseline characteristics. A predictive score was computed from the regression coefficient and used to classify patients into risk groups.

Results and limitations: Of 1,011 mCRPC patients progressive on second-line LPD, 602 (60%) received third-line LPD. Patients receiving third-line LPD had a more favourable prognostic profile at baseline and longer median OS than patients with best supportive care (10.4 vs 2.4 mo, p<0.001). Eastern Cooperative Oncology Group performance status 1 and ≥2 (hazard ratio [HR] 1.51, p<0.007 and HR 3.08, p<0.001, respectively), opioid use (HR 1.55, p=0.019), visceral metastases (HR 2.09, p<0.001), haemoglobin <7 mmol/l (HR 1.44, p<0.002), prostate-specific antigen ≥ 130 μg/l (HR 1.48, p=0.001), alkaline phosphatase ≥ 170 U/l (HR 1.52, p<0.001), and lactate dehydrogenase ≥ 250 U/l (HR 1.44; p=0.015) were associated with shorter survival. Harrell's C-index was 0.74. The median OS values for low-, low-intermediate-, high-intermediate-, and high-risk groups were 14, 7.7, 4.7, and 1.8 mo, respectively. Limitations include the retrospective design.

Conclusions: We developed a prognostic model and identified a subgroup of patients in whom third-line LPD treatment has no meaningful benefit. Our results need to be confirmed by prospective clinical trials.

Patient summary: We reported outcomes from third-line life-prolonging drugs in metastatic prostate cancer patients and developed a prognostic model that could be used to guide treatment decisions.

INTRODUCTION

Prostate cancer is the most common cancer among men in the Western world[211]. Part of these patients will eventually progress and develop metastatic castration-resistant prostate cancer (mCRPC)[212]. In 2004, docetaxel, a member of the taxane drug class, was the first treatment to improve overall survival (OS) of mCRPC patients[24]. In the past years, several new therapeutic agents, including cabazitaxel, abiraterone acetate, enzalutamide, and radium-233, have also been registered for the treatment of mCRPC based on a survival benefit. The outcomes of these life-prolonging drugs (LPDs) as first- and/or second-line (post-docetaxel) treatment have been well established[27,29,30,32,33,92].

It is common practice to use these drugs as a third-line LPD treatment, after first- and second-line LPD treatment, in the hope to obtain a cumulative benefit[58]. To date, randomized controlled trials of third-line LPDs in mCRPC patients are scarce[213]. The reports on third-line LPDs are particularly retrospective and based on small cohorts of patients receiving one specific third-line LPD[140,146,214–216]. Patients with mCRPC who are on third-line LPD may have worse outcomes, compared with those on first- and second-line LPD treatment, due to more advanced stages in general, decreased performance status, worse tolerance to treatments[138], and possible cross-resistance[217].

Thus, third-line LPDs might not be appropriate for all patients. Selection of patients with mCRPC who will benefit from third-line LPD treatment is crucial to improve outcomes, reduce unnecessary toxicity, improve quality of life (QoL), and reduce costs[218]. Prediction of treatment out-come may allow for better patient selection. Nevertheless, current prognostic models for survival using clinical and laboratory baseline variables in mCRPC patients have been described only in first- or second-line LPDs[99,219–221].

The aim of this retrospective study was to evaluate outcomes of third-line LPD treatment in a real-world cohort of mCRPC patients, to identify clinical and laboratory variables associated with survival, and to finally assess the impact of these variables in a risk score.

PATIENTS AND METHODS

Study design and setting

Castration-resistant Prostate Cancer Registry (CAPRI) is an investigator-initiated, observational, multicentre cohort study in 20 hospitals in The Netherlands. The study design has been previously described[41]. Patients with mCRPC were included retrospectively from January 1, 2010 until December 31, 2015. Metastatic CRPC was defined either by the criteria set by the European Association of Urology[23] or by the treating physician. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Objectives

The aim of this study is to investigate the outcomes of third-line LPD treatment in a real-word population of mCRPC patients, identify clinical and laboratory variables related to survival outcomes, and assess the impact of these variables in a risk score.

Participants

Metastatic CRPC patients with progressive disease on or after a second-line LPD, before July 1, 2017, were included in the analysis. All patients had received two lines of LPD treatment, of which at least one of the two previous lines was docetaxel. They were categorized into two groups: patients receiving a third-line LPD and patients receiving best supportive care (BSC).

Patients previously treated with docetaxel for hormone-sensitive metastatic prostate cancer (n=14) were excluded from the analysis.

Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics were included in the analysis if they were documented 3 wk prior to 3 wk after the progression date after a second-line LPD. All patients were followed until death, loss to follow-up, or December 31, 2017. Follow- up duration was calculated as the time from the date of progression on a second-line LPD to the last recorded date.

Outcomes

Outcomes were OS, treatment duration (TD), and prostate-specific antigen (PSA) response. OS was calculated in months from the date of progression after second-line LPD treatment to the date of death from any cause. Patients alive at the end of the study or lost to follow-up were censored at the last recorded date.

TD was defined as the interval between the start and stop of third-line LPD treatment. If the stop date was unknown, TD was specified as the time from the start of third-line LPD to the start of next treatment, or as the time from the start of third-line LPD to the end of follow-up if third-line treatment was the last treatment. Patients on treatment at the end of follow-up were censored at the last recorded date.

PSA response was defined as the maximum change from baseline PSA levels (in percentages) without confirmation of a second measure. In case no decline was present, responses were measured at 12 wk (according to Prostate Cancer Clinical Trials Working Group 3 criteria for response measurement[71]) or if treatment was <12 wk, at the end of treatment or start of next treatment. PSA response was defined as a ≥50% PSA decline from baseline.

Statistical analysis

Descriptive statistics were performed. The t test (or Mann-Whitney U test for non-parametric variables) was used for continuous variables and the Pearson chi-square was used for categorical variables. OS and TD were estimated using the Kaplan-Meier method and were compared between groups using the log-rank test. A waterfall plot was made to indicate PSA response. Missing baseline characteristics were imputed using multiple imputation with Monte Carlo Markov Chain method. Selection of prognostic factors was based on clinical applicability (routinely collected and used by clinicians), previous research, and expert opinion[222]. Continuous variables were categorized using the median cut-off or clinically applicable cut-offs. Multivariable Cox proportional hazard analysis using a backward stepwise procedure was performed on pooled data for OS. A simplified prediction rule was obtained by rounding the regression coefficients to half points, which were multiplied by two for easier clinical applicability. A risk score for the prediction of OS was then calculated for each patient. Patients could be categorized into different risk groups based on the survival curves of each risk score. The prognostic performance of the prediction model was evaluated using Harrell's concordance index (C-index) in the original dataset. A p value of ≤0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

At the end of the study, 3,616 CRPC patients were included in 20 hospitals. A total of 1,011 mCRPC patients (28%) had progression on or after a second LPD treatment and were included in the analysis. At database cut-off, 826 deaths (82%) had occurred, 127 patients (13%) were lost to follow-up, and 58 patients (6%) were still alive.

All patients were previously treated with docetaxel and with abiraterone acetate (n=525, 52%), enzalutamide (n=282, 28%), cabazitaxel (n=155, 15%), docetaxel rechallenge (n=31, 3.0%) or radium-223 (n=18, 2.0%).

Of these 1,011 mCRPC patients, 602 (60%) received a third-line LPD. The third-line LPD consisted of cabazitaxel (n=213, 35%), abiraterone acetate (n=137, 23%), enzalutamide (n=129, 21%), radium-223 (n=78, 13%), and docetaxel (n=45, 8.0%). An overview of previous treatment lines and third-line treatment is provided in Supplementary Table S9.1.

Baseline characteristics

Baseline characteristics of mCRPC patients at the progression date of a second-line LPD, according to the subsequent third-line LPD or not, are shown in Table 9.1. Patients receiving a third-line LPD had a more favourable prognostic profile (significantly younger,

Table 9.1 | Baseline characteristics at time of progression on a second-line LPD in mCRPC patients

		Total group[a]	BSC	Third-line LPD	p
		N=1,011	N=409	N=602	
Age (years)	mean ± SD	71.6 ± 7.5	73.0 ± 7.8	71.0 ± 7.3	0.032*
	unknown, n (%)	21 (2)	0 (0)	21 (3)	
ECOG PS, n (%)	0	93 (9)	15 (4)	78 (13)	<0.001*
	1	280 (28)	67 (16)	213 (35)	
	≥2	130 (13)	98 (24)	32 (5)	
	unknown	508 (50)	229 (56)	279 (46)	
Opioid use, n (%)	yes	219 (22)	127 (31)	92 (12)	<0.001*
	no	187 (18)	57 (14)	130 (22)	
	unknown	605 (60)	225 (55)	380 (63)	
Symptomatic disease, n (%)	yes	704 (70)	346 (85)	358 (60)	<0.001*
	no	226 (22)	50 (12)	130 (22)	
	unknown	81 (8)	13 (3)	68 (11)	
Bone metastases, n (%)	yes	871 (86)	355 (87)	516 (86)	0.139
	no	44 (4)	13 (3)	31 (5)	
	unknown	96 (10)	41 (10)	55 (9)	
Visceral metastases, n (%)	yes	169 (17)	91 (22)	78 (13)	<0.001*
	no	349 (35)	116 (28)	233 (39)	
	unknown	493 (49)	202 (49)	291 (48)	
Lymph node metastases, n (%)	yes	469 (46)	195 (48)	274 (46)	0.030*
	no	160 (16)	51 (12)	109 (18)	
	unknown	382 (38)	163 (40)	219 (36)	
Hb (mmol/l)	mean ± SD	7.1 ± 1.2	6.8 ± 1.2	7.4 ± 1.1	<0.001*
	unknown, n (%)	303 (30)	111 (27)	192 (32)	
Platelets (10^9/L)	median (IQR)	250 (193-315)	238 (167-322)	256 (205-313)	0.032*
	unknown, n (%)	314 (31)	117 (29)	197 (33)	
PSA (µg/l)	median (IQR)	133 (42-413)	174 (42-491)	118 (42-358)	0.058
	unknown, n (%)	126 (13)	64 (16)	62 (10)	
ALP (U/l)	median (IQR)	170 (99-353)	260 (128-506)	139 (88-253)	<0.001*
	unknown, n (%)	182 (18)	72 (18)	110 (18)	
LDH (U/l)	median (IQR)	289 (213-420)	389 (241-730)	251 (203-360)	<0.001*
	unknown, n (%)	411 (41)	154 (38)	257 (43)	

* significant at p-value <0.05. [a] total group of patients progressive on or after a second-line LPD.
Abbreviations: mCRPC, metastatic castration-resistant prostate Cancer; LPD, life prolonging drug; BSC, best supportive care; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance score; Hb, haemoglobin; IQR, interquartile range; PSA, prostate specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase.

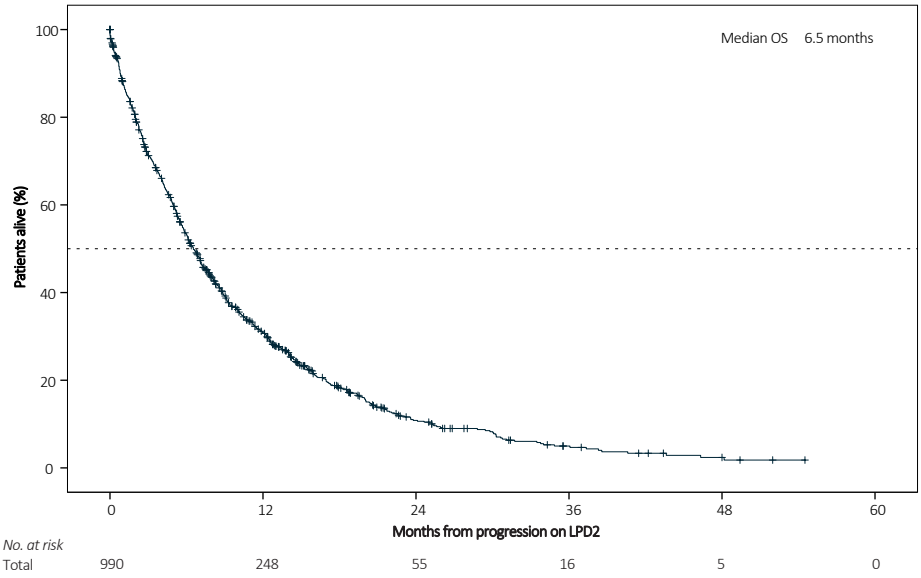


Figure 9.1A | Overall survival from progression after LPD2 for the total group (n=1,011)
21 patients were excluded from analysis due to missing progression date on LPD2. Dotted line indicates the median overall survival
Abbreviations: LPD2, second-line life-prolonging drug.

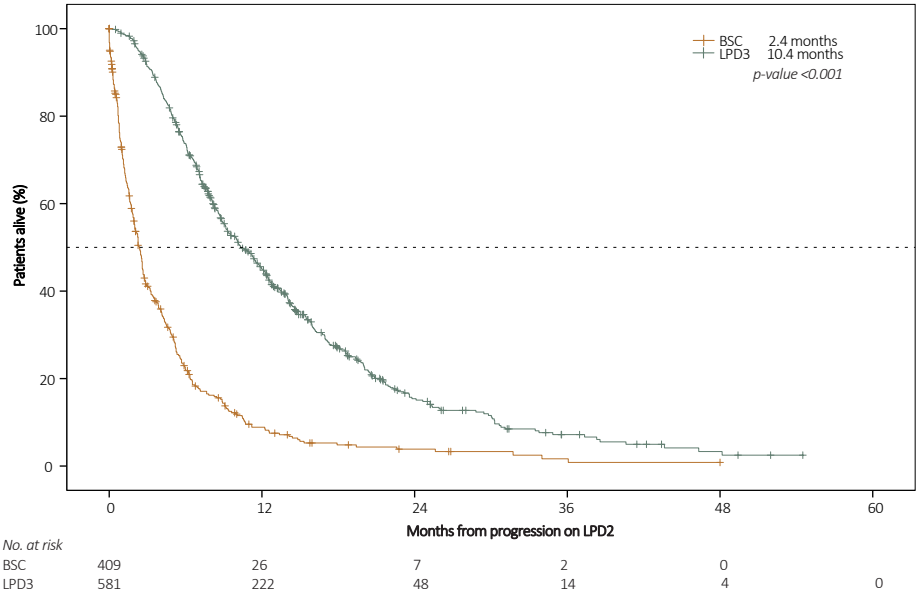


Figure 9.1B | Overall survival from progression after LPD2 classified by LPD3 (n=602) or BSC (n=409)
21 patients were excluded from analysis due to missing progression date on LPD2. Dotted line indicates the median overall survival
Abbreviations: LPD2, second-line life-prolonging drug; BSC, best supportive care; LPD3, third-line life-prolonging drug.

better Eastern Cooperative Oncology Group performance status [ECOG PS], less opioid use, less visceral metastases, higher haemoglobin [Hb], lower alkaline phosphatase [ALP], and lower lactate dehydrogenase [LDH]) compared with patients who received BSC.

Overall survival and risk-scoring system

The median OS (mOS) from progression on a second-line LPD was 6.5 mo (95% confidence interval [CI] 5.9-7.2). The mOS was longer for patients receiving a third-line LPD (10.4 mo, 95% CI 9.2-11.6) compared with patients who received BSC (2.4 mo, 95% CI 2.1-2.7; Figure 9.1B).

Univariable analysis revealed baseline ECOG PS, opioid use, symptoms, visceral metastases, lymph node metastases, Hb, PSA, ALP, LDH, and period from castration to CRPC as being significant variables for the prediction of survival in mCRPC patients progressing on a second-line LPD (Table 9.2).

The multivariable Cox regression analysis of pooled data identified seven variables independently associated with OS: ECOG PS of 1 and ≥2 (HR 1.51, 95% CI 1.13-2.00, p=0.007 and HR 3.08, 95% CI 2.31-4.10, p<0.001, respectively), opioid use (HR 1.55, 95% CI 1.10-2.19, p=0.019), visceral metastases (HR 2.09, 95% CI 1.76-2.49, p<0.001), Hb <7.0 mmol/l (HR 1.44, 95% CI 1.15-1.84, p=0.002), PSA ≥130 mg/l (HR 1.48, 95% CI 1.20-1.82, p=0.001), ALP ≥170 U/l (HR 1.52, 95% CI 1.26-1.84, p<0.001), and LDH >250 U/l (HR 1.44, 95% CI 1.09-1.90, p=0.015); these were related to worse survival and included in the final model. The Harrell's C-index was 0.74.

Based on their regression coefficients, we assigned a score of 1 point to ECOG PS of 1, opioid use, Hb < 7.0 mmol/l, PSA ≥ 130 mg/l, ALP ≥ 170 U/l, and LDH > 250 U/l. A score of 2 points was assigned to ECOG PS ≥ 2 and presence of visceral metastases (Supplementary Table S9.2A). Taking into account the survival curves of the calculated risk scores, patients could be categorized into different risk groups: low-risk (score 0), low-intermediate risk (score 1-3), high-intermediate risk (score 4-6), and high-risk (score 7-9; Supplementary Table S9.2B). The low-risk group included 103 patients (10%), the low-intermediate-risk group included 467 patients (46%), the high-intermediate-risk group included 341 patients (34%), and the high-risk group included 56 patients (6%). Median survival times for these low-, low- intermediate-, high-intermediate-, and high-risk groups were 14.0 mo (95% CI 10.7-17.3), 7.7 mo (95% CI 6.6-8.9), 4.7 mo (95% CI 4.0-5.4), and 1.8 mo (95% CI 1.4-2.2), respectively (p<0.001; Figure 9.2A).

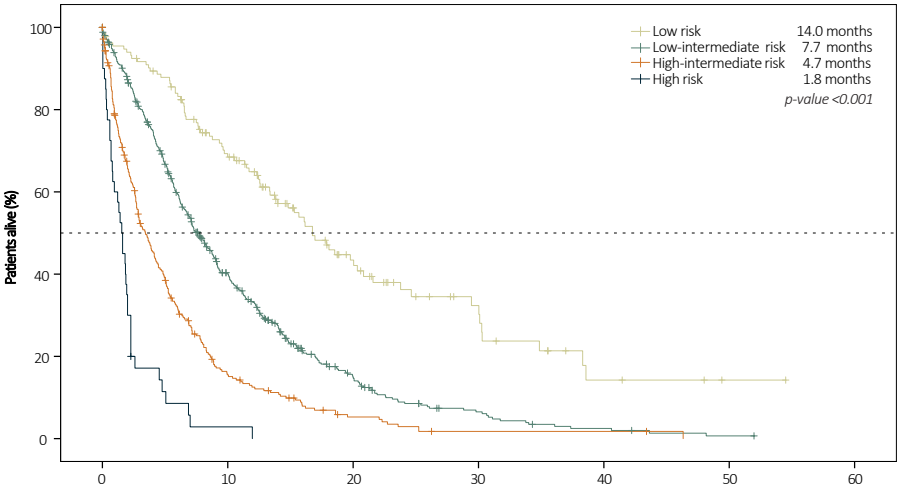
A third-line LPD was started in 69% patients (71 out of 103) in the low-risk group, 64% patients (299 out of 467) in the low-intermediate-risk group, 53% patients (181 out of 341) in the high-intermediate-risk group, and 30% patients (17 out of 56) in the high-risk group. The mOS for these risk groups, according to whether or not treated with a third-line LPD, are depicted in Figure 9.2.

Table 9.2 | Univariable and multivariable analysis of different prognostic variables for overall survival

	Univariable analysis				Multivariable analysis				
	n/N[a]	HR	95% CI	p	HR	95% CI	p	β[b]	pt
ECOG PS	420/503			<0.001*					
0		REF	-		REF	-	-	0	
1		1.74	1.33-2.29		1.51	1.13-2.00	0.007*	0.409	1
≥2		4.55	3.35-6.18		3.08	2.31-4.10	<0.001*	1,123	2
Opioid use	350/406			<0.001*			0.019*		
no		REF	-		REF	-		0	
yes		2.18	1.75-2.73		1.55	1.10-2.19		0.438	1
Symptomatic	754/925			<0.001*					
no		REF	-						
yes		2.07	1.73-2.47						
Visceral metastases	409/511			<0.001*			<0.001*		
no		REF	-		REF	-		0	
yes		2.13	1.73-2.62		2.09	1.76-2.49		0.738	2
LN metastases	508/622			0.002*					
no		REF	-						
yes		1.38	1.12-1.69						
Hb (mmol/l)	594/708			<0.001*			0.002*		
<7		2.22	1.88-2.62		1.44	1.15-1.84		0.372	1
≥7		REF	-		REF	-		0	
Platelets (10^9/L)	584/697			0.535					
<250		REF	-						
≥250		1.05	0.89-1.24						
PSA (µg/l)	723/885			<0.001*			0.001*		
<130		REF	-		REF	-		0	
≥130		1.73	1.49-2.00		1.48	1.20-1.82		0.393	1
ALP (U/l)	682/833			<0.001*			<0.001*		
<170		REF	-		REF	-		0	
≥170		2.23	1.91-2.60		1.52	1.26-1.84		0.421	1
LDH (U/l)	505/600			<0.001*			0.015*		
<ULN		REF	-		REF	-		0	
≥ULN		2.24	1.86-2.69		1.44	1.09-1.90		0.365	1
Time from ADT to CRPC (mo)	806/988			0.012*					
<12		1.19	1.04-1.37						
≥12		REF	-						

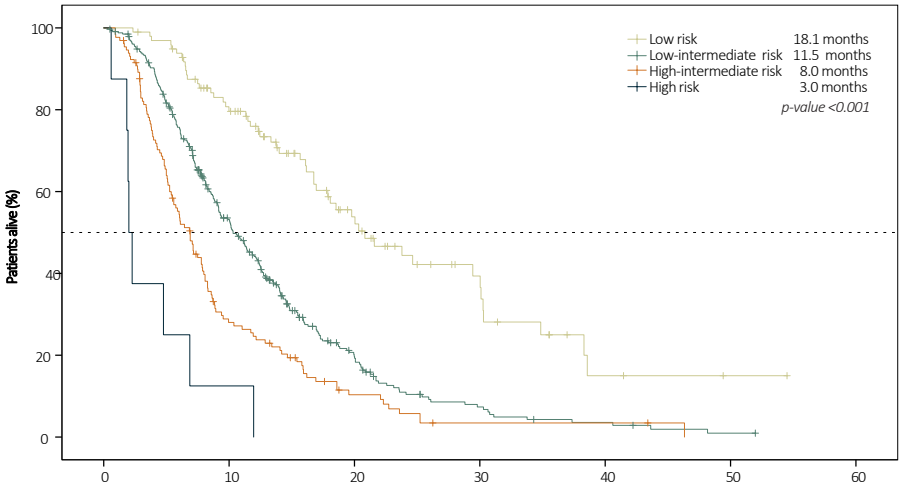
* significant at p-value <0.05; [a] number of patients with event (i.e. death) of total included in univariable analysis; [b] The coefficient of each variable was rounded to half point and then multiplied by a contant (2) for easier clinically applicability. *Abbreviations*: mCRPC, metastatic castration-resistant prostate cancer; LPD, life prolonging drug; HR, hazard ratio; CI, confidence interval; β, beta regression coefficient; pt, points; ECOG PS, Eastern Cooperative Oncology Group Performance Score; REF, reference category; LN, lymph nodes; Hb, haemoglobin; PSA, prostate-specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; ULN, upper limit of normal; ADT, androgen deprivation therapy; mo, months.

A nomogram, integrating the significant independent variables for OS, is provided in Supplementary Figure S9.1.



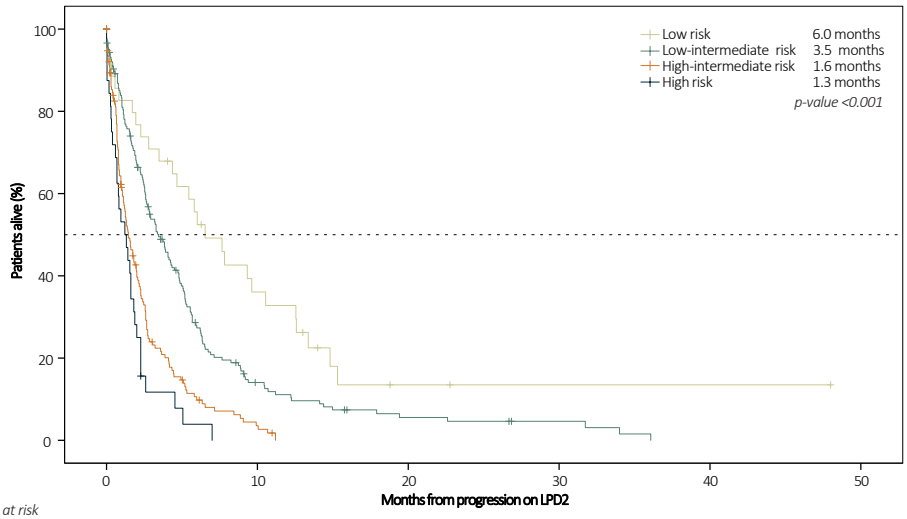
No. at risk						
Low	97	47	14	8	2	0
Low-intermediate	448	154	50	19	5	1
High-intermediate	324	60	15	3	3	0
High risk	55	2	0			

Figure 9.2A | Overall survival from progression after LPD2 according to risk groups: total (N=1,011)
Dotted line indicates the median overall survival
Abbreviations: LPD2, second-line life-prolonging drug; BSC, best supportive care; LPD3, third-line life prolonging drug.



No. at risk						
Low	67	40	13	7	1	0
Low-intermediate	288	136	45	16	5	1
High-intermediate	173	54	15	3	3	0
High risk	17	2	0			

Figure 9.2B | Overall survival from progression after LPD2 according to risk groups: LPD3 (N=602
Dotted line indicates the median overall survival
Abbreviations: LPD2, second-line life-prolonging drug; third-line life-prolonging drug.



No. at risk

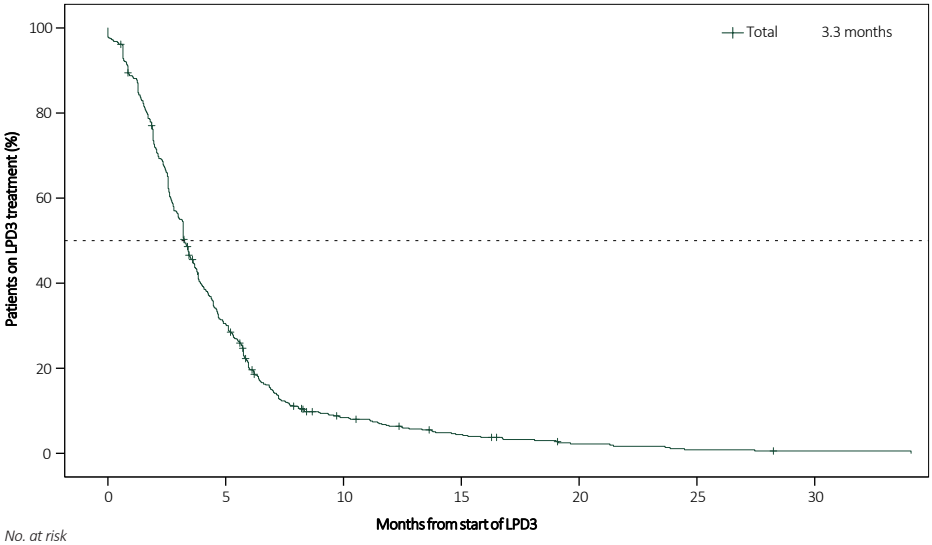
Low	30	7	1	1	1	0
Low-intermediate	160	18	5	3	0	
High-intermediate	151	6	1	0		
High risk	38	0				

Figure 9.2C | Overall survival from progression after LPD2 according to risk groups: BSC (N=409)
Dotted line indicates the median overall survival
Abbreviations: LPD2, second-line life-prolonging drug; BSC, best supportive care.

Treatment duration and prostate-specific antigen response of third-line LPD treatment

At the end of follow-up, 26 patients (4.3%) with a third-line LPD were still on treatment. The median TD (mTD) for a third-line LPD was 3.3 mo (95% CI 3.0-3.5). PSA decline on the third-line LPD was assessable in 560 (93%) patients and observed in 130 (22%) patients.

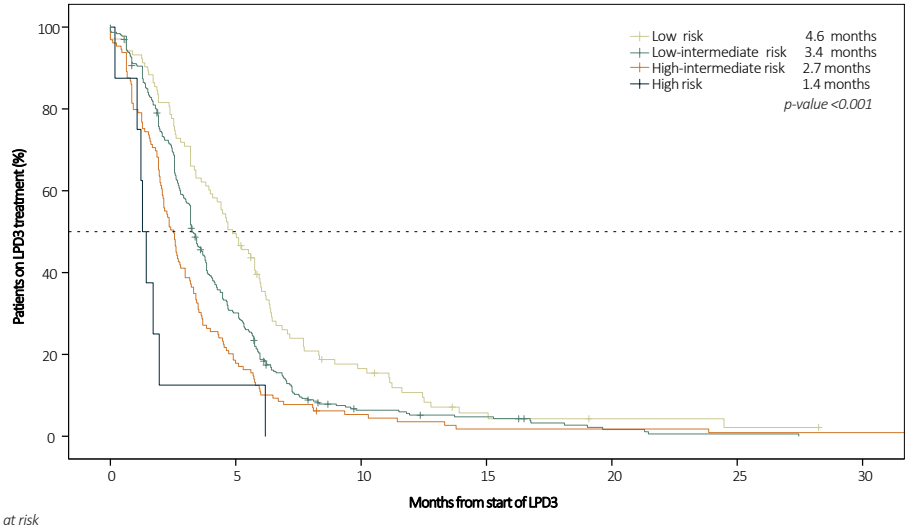
The mTD for the four risk groups (low-, low-intermediate-, high-intermediate-, and high-risk groups) were 4.6 mo (95% CI 3.8-5.4), 3.4 mo (95% CI 3.2-3.6), 2.7 mo (95% CI 2.4-3.0), and 1.4 mo (95% CI 1.1-1.7), respectively (p<0.001; Figure 9.3). PSA response rates (>50% PSA response) were 24% (18/76 patients), 22% (66/301 patients), 23% (41/181 patients), and 6% (one/17 patients), respectively. Waterfall plot of the PSA responses are shown in Figure 9.4.



No. at risk

Total	364	80	11	6	4	0

Figure 9.3A | Treatment duration of LPD3: all patients (n=602)
Abbreviations: LPD3, third-line life-prolonging drug.



No. at risk

Low	76	27	7	2	1	1	0
Low-intermediate	297	77	19	10	4	1	0
High-intermediate	180	38	7	3	2	1	1
High risk	17	2	0				

Figure 9.3B | Treatment duration of LPD3 according to the risk groups: all patients (n=602)
Abbreviations: LPD3, third-line life-prolonging drug.

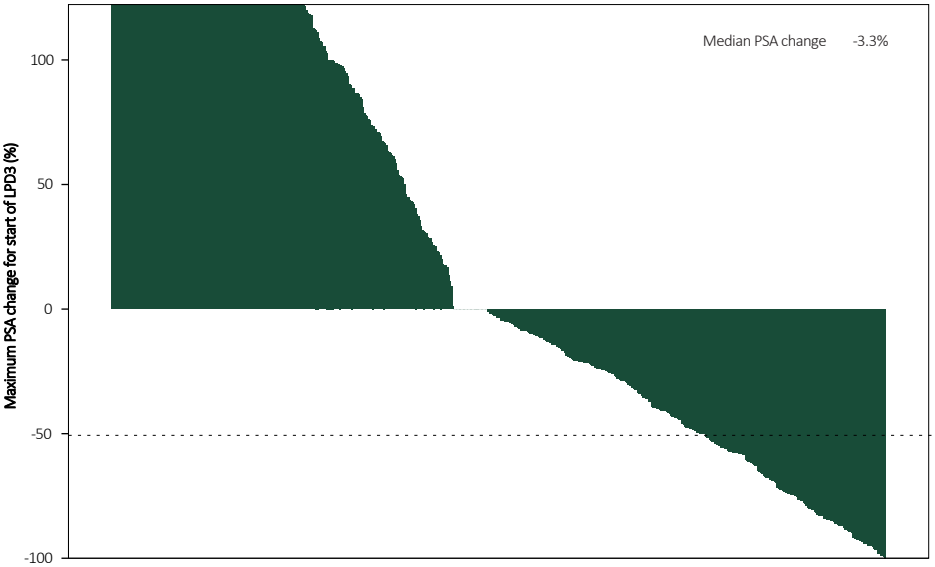


Figure 9.4 | Waterfall plot of maximum PSA change from baseline for patients treated with LPD3
Abbreviations: PSA, prostate specific-antigen; LPD3, third-line life prolonging drug.

DISCUSSION

To our knowledge, this is the first large multicentre real- world cohort, evaluating the outcomes of mCRPC patients progressing on a second-line LPD, treated according to the views and opinions of their treating physicians.

We observed the mOS of 6.5 mo from progression of second-line LPD. The mOS was longer in patients with a third-line LPD than in patients receiving BSC (10.4 vs 2.4 mo), but TD was short (3.3 mo) and PSA response was low (22%). Our results confirm the potential cumulative survival benefit (mOS 7.1-15.8) of previous retrospective studies on third-line LPD treatment[146,215,216].

Pivotal phase 3 trials on first- and second-line LPD treatment in mCRPC patients reported the mOS of 14.0- 34.7 mo. The difference in OS can partially be explained by the fact that patients treated in trials notably differ from patients who receive standard treatment options only[41] and the more advanced disease state of patients after two systemic treatment lines. This is reflected by poor performance score, high disease burden, and high ALP, LDH, and PSA. As mCRPC progresses, disease control becomes more difficult[223]. Possible cross-resistance with previous treatments can further decrease treatment effect[217]. Moreover, tolerability to new systemic treatments can be worse[138], leading to early discontinuation.

Evidence concerning optimal sequencing of third-line LPDs is limited, but suggests that patients may not respond to androgen receptor-targeted therapies (ARTs;

abiraterone or enzalutamide) in third line after progression on prior ARTs due to cross-resistance[58,138,224]. This is recently prospectively confirmed by a study of de Wit et al.[213], which reported increased mOS in patients receiving cabazitaxel compared with those receiving an ART (13.6 vs 11.0 mo) after prior docetaxel and the other ART. Since all patients had progression on an alternative ART within 12 mo, they were not comparable with our study population. Our analysis identified seven independent prognostic variables associated with survival, namely ECOG PS, opioid use, visceral metastases, Hb, PSA, ALP, and LDH. These variables were able to distinct four risk groups (low-, low-intermediate-, high-intermediate-, and high-risk) for patients who had progressive disease after a second-line LPD, with corresponding median survival times of 14.0, 7.7, 4.7, and 1.8 mo, respectively ($p<0.001$).

Especially, high-risk patients had remarkably short mOS. Moreover, high-risk patients treated with a third-line LPD had worse mOS than patients receiving BSC in low- or low-intermediate-risk groups. These results suggest that high-risk patients may derive no meaningful benefit from third-line LPDs in clinical practice, which is supported by the short mTD and low PSA responses. Therefore, high-risk patients should not be treated with third-line LPDs; instead, they should be treated with BSC.

Our prognostic model allows for the stratification of four risk groups with widely differing mOS. It is important for physicians to consider these different survival times in medical decision making. Proper patient selection for third-line LPD treatment is crucial to improve outcomes, reduce unnecessary toxicity, and improve QoL. Also, careful consideration is warranted considering possible low cost effectiveness.

This study is not without limitations. First, our results are limited by the absence of previously identified risk factors such as albumin level[222]. However, albumin is not a routinely assessed parameter in real-world clinical practice. Moreover, many patients had missing values of one or more baseline variables at progression on second-line LPD due to the retrospective nature of the study. Imputation of missing baseline data offers a valid solution for multivariable analysis[225]. Second, the effect of third-line LPD in other out-comes such as QoL and cost effectiveness could not be included in this analysis. Lastly, the identified prognostic model has not yet been externally validated and is therefore not yet suitable for clinical use.

Nevertheless, our prognostic model was developed using a large number of patients with mCRPC who were progressive after second-line LPD, and the number of deaths in the pooled analysis was substantial, providing good statistical power. Furthermore, this prognostic model is based on readily available clinical and laboratory variables, and risk groups can be calculated easily. Although our prognostic model is based on retrospective data, it was able to identify four risk groups with differing survival times, suggesting that the identified variables may assist in the selection of patients for third-line LPD

treatment in daily clinical practice and thereby improving efficacy of these potentially toxic and expensive LPD.

CONCLUSION

Third-line LPDs might not be appropriate for all mCRPC patients, which is supported by the short mTD and low PSA responses observed in our study. We developed a simple prognostic model, based on routinely used clinical and laboratory parameters, and identified a high-risk subgroup in whom no meaningful benefit from third-line LPD is derived in clinical practice. Our results need to be confirmed by further prospective trials.

SUPPLEMENTARY MATERIAL

Table S9.1 | Overview of treatment lines

		First-line	Second-line	Third-line
		N=1,011	**N=1,011**	**N=602**
Docetaxel	N (%)	872 (87)	170 (17)	45 (8)
Cabazitaxel	N (%)	0 (0)	155 (15)	213 (35)
Abiraterone acetate plus prednisone	N (%)	89 (9)	436 (43)	137 (23)
Enzalutamide	N (%)	49 (5)	233 (23)	129 (21)
Radium-223	N (%)	1 (<1)	17 (2)	78 (13)

Table S9.2A | Risk factors to calculate risk score

Risk variables	Points[a]
ECOG PS 1	1
ECOG PS ≥2	2
Opioid use	1
Visceral metastases	2
Haemoglobin	1
Prostate-specific antigen	1
Alkaline phosphatase	1
Lactate dehydrogenase	1

[a] points assigned to risk variables are based on their regression coefficients.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table S9.2B | Definition of risk groups

Risk groups	Risk score
Low-risk	0 points
Low-intermediate-risk	1-3 points
High-intermediate-risk	4-6 points
High-risk	7-9 points

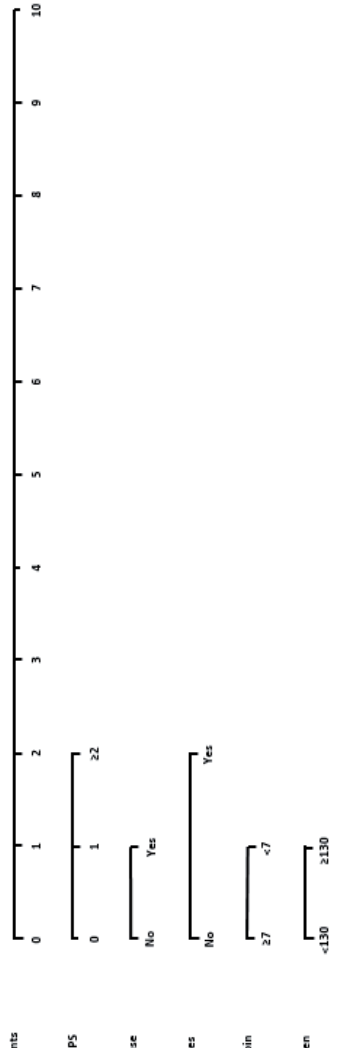


Figure S9.1 | Nomogram for overall survival in patients with mCRPC.
Points are assigned for each risk factor by drawing a line upward from the corresponding values to the line. The total sum of points for seven risk factors is plotted on the total points line. A line is drawn down to the corresponding predictions of 6-, 12-, 18-, 24-, and 30-month survival probability.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ULN, Upper Limit of Normal.

10

High intensity care in the end of life phase of CRPC patients

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Journal of Palliative Medicine 2021; online ahead of print

ABSTRACT

Background: Intensive end-of-life care (i.e. the overuse of treatments and hospital resources in the last months of life), is undesirable since it has a minimal clinical benefit with a substantial financial burden. The aim was to investigate the care in the last three months of life (EOL) in castration-resistant prostate cancer (CRPC).

Methods: CAPRI is an investigator-initiated, observational multicentre cohort study in 20 hospitals retrospectively including patients diagnosed with CRPC between 2010 and 2016. High intensity care was defined as the initiation of life-prolonging drugs (LPD) in the last month, continuation of LPD in last 14 days, >1 admission, admission duration ≥14 days and/or intensive care admission in last 3 months of life. Descriptive and binary logistic regression analyses were performed.

Results: High intensity care was experienced by 41% of 2,429 patients in EOL period. Multivariable analysis showed that age (OR 0.98, 95% CI 0.97-0.99), performance status (OR 0.57, 95% CI 0.33-0.97), time from CRPC to EOL (OR 0.98, 95% CI 0.97-0.98), referral to a medical oncologist (OR 1.99, 95% CI 1.55-2.55), prior LPD treatment (>1 line OR 1.72, 95% CI 1.31-2.28) and opioid use (OR 1.45, 95% CI 1.08-1.95) were significantly associated with high intensity care.

Conclusions: High intensity care in EOL is not easily justifiable due to high economic cost and little effect on life span, but further research is awaited to give insight in the effect on patients' and their caregivers' quality of life.

INTRODUCTION

Several life-prolonging drugs (LPDs) have been registered for treatment of metastatic castration-resistant prostate cancer (mCRPC): taxane chemotherapy (TAX, i.e. docetaxel, cabazitaxel), androgen receptor-targeting therapies (ART, i.e. abiraterone acetate, enzalutamide), and an alpha-emitting isotope (radium-223 dichloride).

The disease trajectory of incurable cancer as mCRPC shows a slow decline over months or years, followed by a rapid decline over the last few months resulting in death[226]. In a contemporary real world cohort we previously reported a median overall survival (OS) of 26 months[41]. Several prognostic models and individual factors have been studied to aid in the identification of the beginning of the end-of-life (EOL)[100,219,227]. However, the overestimation of survival by clinicians shows that identification of EOL remains challenging[228–230]. This optimism about survival can lead to suboptimal delivery of palliative care. This does not only come at high economic costs, but is also not in line with patient's preferences[229].

The focus of EOL-care should shift from active LPD treatment to symptom management and meeting the subjective needs of patients[231]. In EOL, patients are less willing to accept treatment complications and want a dignified end of life, as comfortable as possible[232–235]. Intensive use of hospital care in EOL does not meet patient's needs, since the contribution to survival is minimal and the effect on quality of life is not evident[236–238].

Potential indicators for high intensity care near the EOL have been identified and include the intensive use of chemotherapy, low rates of hospice use, and interventions resulting in emergency room (ER) visits, hospitalization, or intensive care unit (ICU) admissions[236,237]. Although high intensity care in EOL can have possible substantial financial and clinical harms, population-based, disease-specific data are lacking. We aim to investigate the use of high intensity care, more specifically the use of treatments and hospitalization in EOL in CRPC. We will focus on changes in care during the disease trajectory and differences between treated and untreated patients.

METHODS

Study design and setting

CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multi-center cohort study in 20 Dutch hospitals, which were selected on the basis of geographical spread and the type of hospital (i.e. four academic hospitals, 11 large teaching hospitals and five general hospitals). The study design has been described before[41]. The study was approved by a medical ethics committee and in accordance to

Dutch law no informed consent was necessary for this observational registry. The study is registered in the Dutch Trial Registry as NL3440.

Participants

All CRPC-patients diagnosed between 2010 and 2016 in the 20 hospitals were included retrospectively. CRPC was either defined by the criteria set by the European Association of Urology[23] or by the treating physician (e.g. starting treatment, including agents as bicalutamide based on PSA progression). Predefined and readily available data from medical records were collected retrospectively by trained data managers. CRPC patients with docetaxel for metastatic hormone-sensitive prostate cancer (n=14) were excluded.

In the current analysis, we only included patients with a registered date of death in their medical files. We assumed all deaths were related to CRPC since the reason of death was not registered.

Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics were included in the analysis if they were registered during a hospital visit or admission one month prior or after the start of the last three months of life. All data has been regularly updated for all patients until December 31st, 2017.

Outcome

Outcomes were treatment utilization and hospital admissions in the last 3 months of life. Firstly, outcomes were evaluated during the course of CRPC: from CRPC diagnosis to the last 6 months of life (CRPC- 6mo), from the last 6 to the last 3 months of life (6-3mo) and in last 3 months of life (3mo-death). Secondly, we investigated outcomes in subgroups based on LPD treatment (i.e. docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, or radium-223) in last 3 months of life: patients without LPD in last 3 months of life ("no LPD treatment"), patients with LPD started before last 3 months of life but continued in last 3 months of life ("LPD continuation") and patients initiating new LPD in last 3 months of life ("LPD initiation").

The second outcome parameter was high intensity care which was defined as the occurrence of at least one of these items: initiation of LPD in the last month of life (1), continuation of LPD within the last 14 days of life (2), more than one hospital admission in the last 3 months of life (3), admission duration of ≥ 14 days in the last 3 months of life (4) and intensive care unit (ICU) admission in the last 3 months of life (5). Hospice use and ER-visits were not evaluable from our database and were excluded as indicators in this analysis.

Statistical analysis

The sample size was not based on power calculations. Descriptive statistics were performed using Cochranes Q test or Friedman test. One-way ANOVA, Kruskall-Wallis or Chi-square test were used to test for differences between LPD-subgroups. Post-hoc analyses using pairwise comparison with Bonferroni correction were performed in case of significant differences. Univariable and multivariable binary logistic regression incorporating known prognostic factors were performed on original data and pooled data after multiple imputation using Markov Chain methods. A p-value of 0.05 or less was considered statistically significant. IBM SPSS Statistics Version 24.0 (IBM ®, Armonk, NY, USA) was used for all analyses.

RESULTS

In total 2,432 of 3,616 (68%) CRPC patients included in the CAPRI registry died during follow-up; 3 patients (<1%) were excluded due to missing date of death. The median follow-up duration was 19.4 months (range 0.4-92 months) from CRPC diagnosis.

Treatment characteristics

In CRPC-6mo 52% (n=1,256) was treated with an LPD compared to 44% (n=1,074) in the last 6-3mo, and 39% (n=951) in last 3 months of life (p<0.01). Most patients started LPD prior to last 3 months of life and continued treatment in this period (729 of 951 patients). The number of patients initiating new LPD declined between CRPC-6mo and last 6-3mo (52% vs 21%, p=0.05) and remained stable between last 6-3mo and last 3 months of life (21% vs 15%, p=0.45) (Table 10.1). In the last 3 months of life TAX was prescribed in 6%, ART in 9% and radium-223 rarely (1%).

Patient and disease characteristics

Median age at the start of last 3 months of life was 77 years. Performance score declined from CRPC diagnosis to last 3 months of life (valid percentages ECOG >1 of 14% and 47%, respectively) with increasing bone and visceral metastases (valid percentages of respectively 88% vs 93% and 21% vs 30%). Laboratory values also deteriorated with higher PSA, LDH, ALP and lower Hb at start of last 3 months of life (Supplementary Table S10.1).

Patients initiating a new LPD in last 3 months of life had a better clinical condition than patients without LPD treatment: they were younger (median 74 vs 80 years, p<0.01), had better ECOG PS (valid percentages for ECOG PS 0-1 in 61% vs 46%, p<0.01) and less comorbidities (Charlson score 6 in 58% vs 47%, p<0.01). However, known prognostic factors were less favorable: more opioid use (valid percentages of 72% vs 60%, p=0.01), higher PSA (median 160 vs 96 ng/ml, p<0.01), higher ALP (median 216 vs 170

Table 10.1 | Treatment characteristics during the course of CRPC

		CRPC-6 mo	6-3 mo	EOL phase	Adjusted p-value
Total systemic treatment utilization, %	no	13	30	41	<0.001*
	yes	75	66	59	
	unknown	12	4	0	
Type of utilized therapy, %	non-LPD	23	21	20	<0.001*
	LPD	52	44	39	
	docetaxel	40	13	10	<0.001*
	cabazitaxel	9	7	6	<0.001*
	abiraterone	25	18	16	<0.001*
	enzalutamide	16	11	10	<0.001*
	radium-223	4	3	3	0.001*
New therapy initiated, %	no	13	67	80	<0.001*
	yes	75	28	20	
	unknown	12	4	0	
Type of new initiated therapy, %	non-LPD	23	8	4	0.001*
	LPD	52	21	15	
	docetaxel	40	6	4	<0.001*
	cabazitaxel	9	4	2	<0.001*
	abiraterone	25	6	5	<0.001*
	enzalutamide	16	4	4	<0.001*
	radium-223	4	2	1	<0.001*

*significant at p-value <0.05
Abbreviations: CRPC, castration-resistant prostate cancer; mo, months; EOL, end-of-life phase (i.e. last 3 months of life); LPD, life-prolonging drugs (i.e. docetaxel, cabazitaxel, abiraterone acetate, enzalutamide or radium-223).

U/L, p<0.01), higher LDH (median 328 vs 299 U/L, p=0.04) at the start of last 3 months of life (Table 10.2).

Hospital admissions

The number of admissions per 3 months was higher in last 3 months of life: ≥2 admissions in 24% in last 3 months of life compared to 11% in last 6-3 mo and 5% CRPC-6mo, (p<0.01) with a median admission duration of respectively 9 and 7 vs 1.5 days (p<0.01). In last 3 months of life, admissions were more likely due to complications of the disease CRPC (n=582, 24%) and blood transfusions (n=183, 8%) than in CRPC-6mo and last 6-3mo (Table 10.3).

Table 10.2 | Baseline characteristics at start of EOL phase based on LPD treatment

		No LPD treatment	LPD continuation	LPD initiation	Adjusted p-value[a]
		N=1,327	N=729	N=373	
Age (years)	median (range)	80 (51-99)	74 (46-96)	74 (50-93)	<0.001*
	≥ 75 years, %	72	48	48	
ECOG PS, %	0	2	4	6	0.007*
	1	12	24	37	
	> 1	17	24	28	
	unknown	69	48	30	
Charlson score, %	6	47	62	58	<0.001*
	7-8	38	30	32	
	9-10	9	7	8	
	>10	5	1	2	
	unknown	<1	0	0	
Bone metastases, %	yes	65	88	82	<0.001*
	no	7	3	6	
	unknown	28	9	14	
Visceral metastases, %	yes	8	16	16	0.181
	no	21	36	30	
	unknown	71	49	54	
Opioid use, %	yes	16	27	38	0.007*
	no	10	12	15	
	unknown	74	60	48	
PSA (µg/ml)	median (IQR)	96 (25-307)	200 (65-607)	160 (61-365)	<0.001*
	unknown, %	80	58	9	
Hb (mmol/L)	median (IQR)	6.8 (5.9-7.6)	6.6 (5.9-7.4)	6.9 (6.1-7.5)	0.049*
	unknown, %	54	33	16	
ALP (U/L)	median (IQR)	170 (100-371)	213 (113-457)	216 (125-381)	0.001*
	unknown, %	57	25	17	
LDH (U/L)	median (IQR)	299 (224-450)	342 (230-530)	328 (248-536)	0.021*
	unknown, %	70	44	29	
Referred to medical oncologist, %	yes	59	92	94	<0.001*
	no	39	7	6	
	unknown	2	1	0	
Prior LPD treatment lines, %	0	68	33	33	<0.001*
	1	15	29	34	
	2	10	25	19	
	≥3	8	13	14	

Table 10.2 | Baseline characteristics at start of EOL phase based on LPD treatment *(continued)*

		No LPD treatment	LPD continuation	LPD initiation	Adjusted p-value[a]
		N=1,327	N=729	N=373	
Prior treatment, %	docetaxel	22	60	58	<0.001*
	cabazitaxel	6	12	13	<0.001*
	abiraterone acetate	16	28	26	<0.001*
	enzalutamide	12	15	13	0.252
	radium-223	5	5	5	0.109

* significant at p-value<0.05; [a] adjusted for multiple testing using Bonferroni correction.
Total percentages may exceed 100% because of rounding. Characteristics measured in period of one month prior or after the start of last 3 months of life.
Abbreviations: CRPC, castration-resistant prostate cancer; EOL, end-of-life phase (i.e. last 3 months of life); ECOG PS, Eastern Cooperative Oncology Group performance score; PSA, prostate specific antigen; Hb, haemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; IQR, interquartile range.

Table 10.3 | Hospital admissions during the course of CRPC

		CRPC-6 mo	6-3 mo	EOL phase	Adjusted p-value[a]
Hospital admission, %	0	37	55	39	<0.001*
	1	41	19	32	
	≥2	5	11	24	
	unknown	9	15	5	
Admission duration[b]	valid median	1.5	7	9	<0.001*
	IQR	1-3	3-13	4-16	
	missing (%)	<1	<1	1	
	< 14 days, %	43	23	38	<0.001*
	≥ 14 days, %	2	7	17	
Admission reason, %	diagnostic evaluation	10	4	7	0.178
	therapeutic	12	6	10	0.001*
	complication of therapy	10	4	5	<0.001*
	complication of CRPC	13	10	24	0.049*
	blood transfusion	3	4	8	<0.001*
	other	10	4	9	<0.001*
ICU admission, %	yes	1	1	2	0.006*
	no	81	85	93	
	unknown	18	15	5	

* significant at p-value <0.05; [a] adjusted for multiple testing using Bonferroni correction; b number of admissions and admission duration calculated per 3 months.
Total percentages may exceed 100% because of rounding.
Abbreviations: CRPC, castration-resistant prostate cancer; mo, months; EOL, end-of-life phase (i.e. last 3 months of life); IQR, interquartile range; CRPC, castration-resistant prostate cancer; ICU, intensive care unit.

More patients initiating LPD in the last 3 months of life (n=281, 75%) were admitted to the hospital than patients without LPD treatment (n=655, 49%) and with LPD continuation (n=429, 59%) (p<0.01). Admission duration was significantly longer in patients initiating LPD compared to patients continuing LPD (median 11 days vs 9 days, p=0.02). Although infrequent in absolute numbers, significantly more patients (n=11, 3%) initiating new LPD in the last 3 months of life were admitted to the ICU (Table 10.4).

Table 10.4 | Hospital admission in EOL phase based on LPD treatment

		No LPD treatment	LPD continuation	LPD initiation	Adjusted p-value[a]
		N=1,327	N=729	N=373	
Hospital admission, %	0	43	38	24	<0.001*
	1	30	33	35	
	≥2	19	26	40	
	unknown	8	3	1	
Admission duration	valid median	9	9	11	0.021*
	IQR	4-16	4-15	5-18	
	unknown, %	2	1	2	
	< 14 days, %	34	41	46	0.040*
	≥ 14 days, %	15	17	28	
Admission reason, %	diagnostic evaluation	6	8	11	0.418
	therapeutic	8	11	12	0.607
	complication of therapy	1	6	14	<0.001*
	complication of CRPC	17	29	40	<0.001*
	blood transfusion	5	11	11	<0.001*
	other	8	9	12	0.698
ICU admission, %	yes	1	2	3	0.013*
	no	91	95	96	
	unknown	8	3	1	
Total number of high intensity care indicators, %	0	76	48	21	<0.001*
	1	14	34	32	
	> 1	10	18	46	

* significant at p-value <0.05; [a] adjusted for multiple testing using Bonferroni correction.
Total percentages may exceed 100% because of rounding.
Abbreviations: EOL, end-of-life phase (i.e. last 3 months of life)); LPD, life-prolonging drugs (i.e. docetaxel, cabazitaxel, abiraterone acetate, enzalutamide or radium-223); IQR, interquartile range; CRPC, castration-resistant prostate cancer; ICU, intensive care unit.

High intensity care

High intensity care was experienced by 992 patients (41%): >1 hospital admission (n=592, 24%), admission duration of ≥14 days (n=423, 17%), continuation of LPD in the last 14 days (n=397, 16%), initiation of LPD in last month (n=81, 3%) or ICU admission (n=39, 2%).

Table 10.5 | Univariable and multivariable logistic regression predicting any high intensity care in EOL phase

		Univariable analysis of original data				**Multivariable analysis of pooled data after imputation**		
		N	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (years)	cont.	2.429	0.96	0.95-0.97	<0.001*	0.98	0.97-0.99	0.002*
ECOG PS	0	82	REF	-	-	REF	-	-
	1	475	0.87	0.54-1.39	0.562	0.83	0.49-1.42	0.487
	≥2	494	0.69	0.43-1.10	0.118	0.57	0.33-0.97	0.038*
Visceral metastases	no	656	REF	-	-	REF	-	-
	yes	276	1.12	0.84-1.48	0.433	0.96	0.67-1.38	0.819
Hb (mmol/L)	cont.	1.414	0.91	0.83-0.99	0.037*	0.90	0.80-1.02	0.093
LDH (U/L)	cont.	1.066	1.00	1.00-1.00	0.209	1.00	0.99-1.00	0.106
ALP (U/L)	cont.	1.424	1.00	0.99-1.00	0.043*	1.00	0.99-1.00	0.121
PSA (U/L)	cont	913	1.00	1.00-1.00	0.902	1.00	1.00-1.00	0.320
Opioid use	no	282	REF	-	-	REF	-	-
	yes	546	1.54	1.15-2.06	0.004*	1.45	1.08-1.95	0.015*
Time from CRPC to EOL phase (mo)	cont.	2.429	0.99	0.98-0.99	<0.001*	0.98	0.97-0.98	<0.001*
LPD started prior to EOL phase	0	1.023	REF	-	-	REF	-	-
	1	556	1.94	1.57-2.40	<0.001*	1.53	1.19-1.96	0.001*
	≥2	850	1.94	1.60-2.34	<0.001*	1.72	1.31-2.28	<0.001*
Referral to medical oncologist	no	598	REF	-	-	REF	-	-
	yes	1.807	2.61	2.12-3.21	<0.001*	1.99	1.55-2.58	<0.001*
Year of death	2010-2011	226	REF	-	-	REF	-	-
	2012-2013	684	0.96	0.71-1.31	0.802	1.05	0.75-1.46	0.782
	2014-2015	837	1.13	0.84-1.53	0.416	1.18	0.84-1.65	0.343
	2016-2017	682	0.91	0.67-1.24	0.541	1.08	0.74-1.57	0.686

*significant at p-value <0.05

Abbreviations: EOL phase, end-of-life phase (i.e. last 3 months of life); OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; REF, reference category; Hb, haemoglobin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer; mo, months; LPD, life-prolonging drugs (i.e. docetaxel, cabazitaxel, abiraterone acetate, enzalutamide or radium-223).

Multivariable analysis of pooled data after multiple imputation showed that high intensity care was less likely in older patients (OR 0.980, 95% CI 0.968-0.993, p<0.01), patients with ECOG ≥2 (OR 0.569, 95% CI 0.334-0.968, p=0.04), and longer time from CRPC diagnosis to EOL (OR 0.977, 95% CI 0.970-0.984, p<0.01). Opioid use (OR 1.453, 95% CI 1.083-1.951, p=0.02), one or two prior LPD treatments (OR 1.527, 95% CI 1.192-1.957, p<0.01 and OR 1.723, 95% CI 1.305-2.275, p<0.01 respectively) and referral to medical oncologist (OR 1.988, 95% CI 1.551-2.547, p<0.01) were associated with higher odds of high intensity care (Table 10.5).

DISCUSSION

This analysis of real-world data on EOL care in Dutch CRPC-patients showed that 41% of all patients experienced high intensity care in EOL. To our knowledge, this is the first study on EOL care in a large, unselected prostate cancer population within the timeframe in which new LPDs became available. Moreover, since we collected prognostic factors over time we were able to evaluate which factors were associated with high intensity care.

We observed a shift in treatment choices from TAX in early CRPC-phases to ART in the last 3 months of life. In comparison to other studies use of TAX was low (16% vs 30%)[238–240], which was explained by the fact that our study was performed in the era with the availability of newer LPDs as ART. Clinicians seem more reluctant to treat patients with TAX and may prefer ART because of less impact (oral vs intravenous administration) and a milder adverse event profile, especially later in the disease trajectory when ECOG PS declines.

The reasons to initiate LPD were not documented. In EOL LPDs add little to a patient's survival making the use LPDs seem unreasonable. However, since clinicians often overestimate a patients' survival, it is possible that they not adequately identify the start of EOL[228–230]. This is supported by the fact that patients initiating new LPD were younger with better performance score. Moreover, treatment could also have been considered a necessity since these patients had more aggressive disease characteristics (i.e. higher PSA, ALP and LDH). In addition to a survival benefit, LPDs could be started for the prevention of complications and/or symptoms with preservation of quality of life, which seems reasonable since pain and/or opioid use were common in patients starting an LPD in EOL. However, the advantages on quality of life in EOL are not widely studied, so the initiation of a new LPD in patients with aggressive disease should be carefully considered based on the little effect on survival[100,219,227].

We showed that patients with more aggressive disease characteristics and good performance score were more likely to experience high intensity care in EOL. As stated

before, clinicians were more likely to initiate an LPD in patients with aggressive disease states and an adequate level of fitness. It has been reported that patient preference in treatment initiation also plays an important role, since patients often strive for survival when time from diagnosis is short, they are young and feel fit[235]. Aggressive disease characteristics can also lead to a higher risk for admission related to complications or the underlying disease. Patients who continued or initiated LPD in the last 3 months of life were more frequently admitted to the hospital than patients who did not use LPDs, mostly due to disease-related complications (40%). However, treatment-related admissions were also prevalent (37%) in patients initiating LPD.

Forty-one percent experienced high intensity care in our CRPC cohort. While Dutch clinicians may be more reserved in starting new LPDs, they were likely to admit a patient to the hospital for supportive care even in EOL. This is supported by an admission rate of 35% in the last week of life in a Dutch general oncologic population[241]. The threshold for hospitalization in the Netherlands may be low, since the population has mandatory insurance including hospital care. It is also notable that some patients with mCRPC, including those with refractory cancer-related pain, may need and benefit from hospital admission near EOL for symptom control. Although the effect of high intensity care on patients' quality of life is unknown, an adequate organization of palliative care either in or outside the hospital (e.g. by general practitioners, GPs) improves quality of life of both patients and caregivers and may lead to reduce costs by reducing the amount of time spend in hospitals[242]. During our study period a transmural palliative care team was not available in all treatment centers and specific arrangements differed between centers, which could affect hospital admission rate[243]. A palliative care team should play a key role in the collaboration between various specialists and can proactively manage symptoms such as pain which might otherwise acquire hospital admissions.

In the Netherlands, CRPC is generally treated by multidisciplinary teams including both urologists and medical oncologists, but the arrangements within multidisciplinary teams differ between hospitals. Referral from urologist to medical oncologist increased the odds of high intensity care in EOL. Although this can possibly be explained by an overall more aggressive treatment approach, it is more likely that the decision to initiate LPD was made by multidisciplinary teams based on patients' general health and disease characteristics and that these patients were referred to medical oncologists to start LPD, while patients opting for best supportive care remained treated by urologists.

This study reflects Dutch clinical practice, but may not be easily generalizable due to potential international differences (e.g. different organization of EOL care, treatment culture and reimbursement systems). Our results concern a population with CRPC and cannot be generalized to other cancer types[244].

Moreover, the indicators for high intensity care in our analysis is commonly used[245]. We were not able to include hospice use and ER visits which are well known indicators

for high intensity care, since they were not captured in our registry. We chose a period of last three months of life as a cutoff for EOL. This period was appropriate for CRPC according to the experts in our steering committee, but might differ in other cancer types.

A limitation is that we only captured in-hospital data. Firstly, we excluded patients if the death date was not known in the participating hospitals, which were probably patients without in-hospital care in EOL. Therefore, the use of high intensity care in the total population could be overestimated. Secondly, high intensity care included only specific hospital resources and data on the role of the GP and palliative care teams was unavailable. The fact that we were not able to include all relevant data as ER visits and hospice stays is a major limitation. The overuse of hospital resources in patients who are likely to die soon seems not easily justifiable from both a patient's perspective (i.e. there is little to no effect on patient's life span) and from a societal perspective (i.e. the economic burden of the use of LPDs and hospital resources is high). However, the effect of this high intensity care on other aspects of a patient's wellbeing as quality of life is not yet known. Adequate guidance can improve quality of life, satisfaction and prevent high intensity care in EOL with unnecessary hospital admissions[246–249], but we could not evaluate the role of the GP and palliative care teams.

Another limitation is the missing data particularly in baseline characteristics. Missing data is inherent to the retrospective observational nature of this study. Multiple imputation offers a valid solution for missing data in multivariable analysis. The exact reason of death was also not registered. We assumed all deaths were related to CRPC, which seems a safe assumption because of the progressive nature of this disease and general relative short median OS, but this may be an overestimation.

CONCLUSION

High intensity care in EOL in CRPC occurred in 41%. While Dutch clinicians seemed reserved to start LPD in last 3 months of life, hospital admissions were frequent especially in patients starting a new LPD. Higher age and poor performance score were associated with lower chances of high intensity care. High intensity care is not easily justifiable from both patient and economic perspective, but further research is warranted to give insight in the effect on quality of life.

SUPPLEMENTARY MATERIAL

Table S10.1 | Baseline characteristics at CRPC diagnosis and at start of EOL phase

		CRPC diagnosis	EOL phase
Age (years)	median (range)	75 (46-99)	77 (46-99)
	≥ 75 years, %	54	61
ECOG PS, %	0	18	3
	1	20	20
	> 1	6	20
	unknown	56	57
Charlson score, %	6	59	54
	7-8	33	35
	9-10	6	8
	>10	2	3
	unknown	<1	<1
Bone metastases, %	yes	59	75
	no	8	5
	unknown	34	20
Visceral metastases, %	yes	4	11
	no	16	27
	unknown	79	62
Opioid use, %	yes	10	23
	no	23	12
	unknown	68	66
PSA (µg/ml)	median (IQR)	22.7 (8-79)	159 (44-410)
	unknown, %	3	62
Hb (mmol/L)	median (IQR)	7.9 (7.2-8.5)	6.7 (5.9-7.5)
	unknown, %	30	42
ALP (U/L)	median (IQR)	116 (81-224)	192 (108-404)
	unknown, %	33	41
LDH (U/L)	median (IQR)	232 (192-330)	321 (230-506)
	unknown, %	55	56
Referred to medical oncologist, %	yes	14	74
	no	84	25
	unknown	2	1

Total percentages may exceed 100% because of rounding. Characteristics measured in period of 6 weeks prior to 1 week after CRPC diagnosis and one month prior or after the start of last 3 months of life.
Abbreviations: CRPC, castration-resistant prostate cancer; EOL, end-of-life phase (i.e. last 3 months of life); ECOG PS, Eastern Cooperative Oncology Group performance score; PSA, prostate specific antigen; Hb, haemoglobin; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; IQR, interquartile range.

11

General discussion

New treatments for castration-resistant prostate cancer (CRPC) were approved in Europe by the European Medicine Agency (EMA) and reimbursed in the Netherlands between 2011-2015 (Table 11.1). Treatments are palliative with the aim to prolong life span (median 4 months in overall survival; OS) and improve or maintain quality of life[23,40]. However, these treatments are expensive (between 3,000-4,500 euros per patient per month) and with approximately 3,000 new CRPC-patients per year the budget impact is considerable. This warrants the need to evaluate the use and outcomes of the CRPC treatments and assess the overall quality of care in this population. Here, qualitative care is defined as "health care that is effective, safe and responds to the needs and preferences of patients"[13,250]. In this last chapter we discuss the use and challenges of using real world evidence (RWE) to evaluate quality of care and propose adaptations needed in future registries to continuously monitor the impact of new drugs on the quality of care in CRPC-patients.

Table 11.1 | Dates of approval for CRPC drugs

Treatment	Indication	RCT publication	EMA approval	cieBOM approval
Docetaxel	First line	Oct 2004	Jan 2005	Jun 2005
Cabazitaxel	Second line	Oct 2010	Jan 2011	Jul 2011
Abiraterone	Second line	May 2011	Jul 2011	Mar 2012
Abiraterone	First line	Jan 2013	Nov 2012	Oct 2015 (Sep 2013[a])
Enzalutamide	Second line	Sep 2012	Apr 2013	Dec 2013
Radium-223	First and second line	Jul 2013	Sep 2013	Feb 2014
Enzalutamide	First line	Jul 2014	Oct 2014	Nov 2014

[a] abiraterone could not be positively appraised in September 2013 using the PASKWIL criteria
Abbreviations: CRPC, castration-resistant prostate cancer; RCT, randomized controlled trial; EMA, European Medicine Agency; cieBOM, commissie ter Beoordeling van Oncologische Middelen; mo, months.

OUR EXPERIENCE MEASURING QUALITY OF CARE

The benefit of drugs for patients is the induction of responses and prolongation of survival while maintaining or improving quality of life[14]. This is of special importance for new drugs prescribed in a palliative phase of cancer such as CRPC. Effectiveness, safety and patient-centeredness are universally accepted as the core dimensions of quality of health care services, since only these dimensions can improve the likelihood of these desired benefits[14].

Effectiveness

Effectiveness is roughly made up of two components: 1) care should benefit the patient and 2) care should match scientific knowledge (evidence-based medicine)[251,252]. Clinicians play a critical role in selecting the right treatment for the right patient. Guidelines could aid clinicians and assure that the prescription of new drugs is based on the latest scientific knowledge[253]. Meta-analyses or systemic reviews of multiple randomized controlled trials (RCTs) provide the most important input for guidelines. However, since RCTs evaluate the outcomes of an intervention given randomization to treatment and ideal circumstances, outcomes of RCTs differ from outcomes of real-world patients. We showed that OS of real-world CRPC-patients treated with standard of care was worse than patients treated in trials in Chapter 2[41].

Patients are selected for clinical trials on strict criteria while in daily practice usually less strict selection is applied[74]. Patients treated with cabazitaxel in clinical trials had better patient and disease characteristics than patients treated with cabazitaxel in daily practice. These differences resulted in differential survival outcomes between the groups. This emphasizes proper patient selection in clinical practice.

While patient selection offers a valid explanation for differences between trials and real-world, it could not be the only explanation. For example, patient characteristics were similar in our subgroup treated with radium-223 dichloride (Ra-223) compared to the ALSYMPCA trial, while OS in our real-world cohort was worse as shown in Chapter 6[30,254]. Unknown and/or unmeasured prognostic factors could attribute to this difference in survival. Participation in trials may differ from real-world in method of treatment delivery (protocol effect) or care (care effect). Therefore differences can also be caused due to the fact that patients participate in trials (participation effect)[254]. Moreover, trial participation may lead to changes in behavior of both clinicians and patients due to the knowledge that they are under observation (Hawthorn effect) or psychologically mediated benefits from patients' awareness of trial participation (placebo effect)[74]. To conclude, outcomes of RCTs are in general not easily generalizable to the real-world clinical practice due to patient selection and participation effect.

The use of guidelines that are purely based on RCTs is thus of limited value to the real-world patient population. Physicians should be aware that prescribing a new treatment to patients with less favourable prognostic factors could translate in less survival benefit. Therefore, guidelines should incorporate real-world evidence (RWE). Disease-based registries are a proper method to evaluate real-world effectiveness taken account for different patient characteristics, treatment delivery and monitoring. Additionally, guidelines should not only be evidence-based, but also based on physician experience (i.e. experienced-based medicine) and on the expectations and wishes of the patients and their family (i.e. preference-based medicine)[253]. The combination of these aspects

supports physicians and patients to choose the treatment that is most beneficial to the patient.

RWE of all outcomes including quality of life should be available to physicians and patients. In Chapter 4, we have shown that although the majority of patients were treated with newly registered treatments, patients scored lower on almost all quality of life domains lower when time progresses than at the start of the study. This was especially true for patients with more aggressive disease aspects and more prior treatment lines[37,39,109]. Knowing which symptoms can occur and affect quality of life can better manage patients' expectations and guide treatment decisions and supportive care.

However, RWE cannot replace RCTs, but should be considered as complementary. Comparative effectiveness can best be addressed when patient populations, treatment delivery and follow-up are comparable. A challenge in RWE is the impact of differences in prognostic factors between treatment arms, since in RWE you do not stratify for important prognostic variables[56]. Methodologies for statistical analyses such as propensity score matching and multivariable regression analyses can partially overcome these difficulties, but can only be applied for known values and thus leave potentially residual bias. Another known problem in RWE is confounding due to immortal time bias, which can occur when for example evaluating differences in outcomes based on number of cycles in retrospect. This is best illustrated by our analyses using a real-world population of 45 patients treated with radium-223 (Ra-223) in Chapter 8. Patients who received six injections of Ra-223 had better median OS than patients with one to five injections (19.7 vs 5.9 months). This difference can be caused by immortal time bias, since patients have to life sufficiently long to complete all cycles of Ra-223. The confounding in RWE should be carefully considered in treatment decisions and health care policy decisions, since they can be misleading and potentially dangerous[56].

In addition to providing clinicians and patients with sufficient information on outcomes, RWE could also be used by policy makers in regulatory approval of new drugs. In the first place, policy makers value new drugs based on their benefits. For cancer treatments, benefits can be expressed in terms of both quantity (i.e. OS and progression free-survival or PFS) and quality of life. Improvement of OS or PFS is the most important criteria for market authorization in Europe and the Netherlands[6,255]. However, surrogate endpoints (i.e. outcomes of biological activity as tumour marker responses) are often used instead[256]. These surrogate endpoints promote faster access to new drugs, but it is unknown if they provide meaningful information on effectiveness in terms of OS or PFS[257,258]. Conditional market authorization could be granted by EMA, when the benefits of immediate access to the market outweigh the risks to need further data. However, the lack of evidence on OS or PFS is often not made up for after (conditional) market authorization. This is where RWE could also step in as we have shown in Chapter 3. We

observed a benefit of new drugs after market authorization with an improvement in OS from 28.5 months in 2010-2011 to 31.0 months in 2014-2015. Policy makers have incorporated post-marketing RWE: the Dutch Health Care Institute (in Dutch: Zorginstituut Nederland, ZiN) obligated RWE effectiveness analyses four years after market approval for all expensive drugs between 2006 and 2012 and for drugs with a high budget impact after 2012[259].

In addition to OS and PFS, quality of life is another important outcome for oncologic treatments. Patients often value quality of life when being treated even if it means they may not live as long[232–235,260–262]. While over half of the drugs approved by EMA between 2009-2013 included quality of life as an outcome measure, only 10% showed an improvement in quality of life at the time of authorization[256]. This discrepancy between regulatory bodies and patients should be addressed through stimulating quality of life research and making this obligatory both prior to market approval or post-marketing period.

Health-related quality of life (HRQoL)is a complex outcome to measure[263]. In contrary to mortality which is a binary outcome (either a patient is alive or death), HRQoL consists of multiple domains including essentially four core domains: psychological, social, occupational and physical health[263]. Over the years, multiple questionnaires have been developed, but there is no consensus on analyzing and interpreting these data which hinders the application of HRQoL outcomes in clinical guidelines and policy making[264]. Measuring HRQoL starts with a clear research question in order to select the most appropriate questionnaire, but there is a gap between outcomes of interest to patients and of interest of policy makers making it difficult to select a proper questionnaire[265].

In order to inform patients about treatment decisions, outcomes that are relevant for that specific disease are a necessity. A cancer-specific questionnaire (e.g. EORTC QLQ-C30) is useful to evaluate HRQoL domains and changes over time in palliative cancer as CRPC (Chapter 4). However, a prostate-cancer specific questionnaire as EORTC QLQ-PR25 mainly focusses on problems of local prostate cancer which are not in the foreground in CRPC-patients. Therefore, these questionnaires are little use when evaluating care for a CRPC-population as shown in Chapter 4.

For policy makers, HRQoL measurements are mainly used in economic evaluations. Questionnaires for such evaluations should translate in one general outcome that is easily comparable between diseases (i.e. not disease specific) and can be weighed against reference values of a healthy population. The EQ-5D-5L is one of the best questionnaires that fits this goal.

Safety

The dimension "safety" refers to the fact that health care should be provided in order to prevent harm to patients[14–16]. Safety can be evaluated by measuring what goes wrong (safety-I) or what goes right (safety-II). It is a challenge in RWE to determine safety especially safety-II, but an estimation of safety-I can be done by measuring hospitalizations as a sign of adverse events. However, determining if these events are really an adverse event and thus a sign of what goes wrong, is difficult.

In CRPC, skeletal-related events (SREs) have a great impact on morbidity, mortality and economic costs, especially when symptomatic[175]. Recently the phase III ERA-223 had to be unblinded due to a higher rate of fractures in the treatment arm (abiraterone; ABI+P plus Ra-223) compared to the control arm (ABI+P), which also led to an adjustment in the indication of Ra-223[182]. Although life-prolonging drugs (LPDs) showed a decline in incidence of symptomatic skeletal events (SSEs) in RCTs[36,37,39], we observed that 41% of patients treated with an LPD had at least one SSE (Chapter 7). SSEs can be a result of an advance disease stage rather than shortcomings in care, but when they could have been prevented this might indicate that there is a safety issue. Studies have proven that bisphosphonates and denosumab reduce the risk reduction of SSEs, but 40% of the patients at risk were not treated with bone health agents[168]. Although the reasons not to start bone-supporting treatments are unknown, this might indicate undertreatment in this group and puts patients at risk for complications. This illustrates an opportunity to improve quality in CRPC-care.

The difficulty analyzing endpoints of severe AEs (grade ≥3) as hospitalizations and death in RWE is to assess whether they could have been prevented. We found that the admission rate increased during the course of CRPC, with especially high admission rate near the end-of-life: 24% of the patients was admitted more than once in the end-of-life phase (Chapter 10). The cause is probably that in more advanced disease stages, i.e. later in the CRPC-trajectory, patients are prone to complications of the disease as pain and are likely to need short hospital admissions for symptom management. However, unplanned hospitalizations can have a negative impact on quality of life of both patients and caregivers[266–268]. Caregivers play an essential role in caring for cancer patients, not only in emotional support, but often also in assisting with medication, self-care and daily activities[269]. Disruption of social life and lost productivity costs may lead to reduced quality of life in caregivers[269]. Stressors as unplanned hospitalizations add to the caregivers' burden[269]. In order to properly investigate if admissions are unwanted, the causality and admission reason need to be captured in a structurally manner in the source documents for RWE, e.g. patients' medical records.

Safety-management should not only ensure that "as few things as possible go wrong" (safety-I), but also that "as many things as possible go right" (safety-II)[270]. Prescribing the most effective treatment can be considered a sign of safety-II. Knowing why things

go right, can improve care in general, but as with safety-I the "why"-question is often difficult to answer.

Patient-centeredness

"Patient-centeredness" states that care should be tailored to an individual patient[15]. CRPC management has the opportunity to be patient-cantered due to multiple treatment options. Figure 11.1 shows the many different treatment sequences that were given in daily practice. This variety can be explained by the fact that there is no (inter) national consensus on the best treatment option, since outcomes of treatments are in the same range and the lack of comparative data. There is thus a need to consider other aspects to tailor treatment to an individual patient[23,154,271,272]. RWE can provide information for both clinicians and patients to support treatment decisions.

Figure 11.1 | Treatment patterns of CRPC patients treated with at least one line of systemic treatment
Each shell represents a line of treatment starting from the center (i.e. CRPC-diagnosis).
Abbreviations: CRPC, castration-resistant prostate cancer; no LPD, no life-prolonging drug; DOC, docetaxel; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; Ra-223, radium-223.

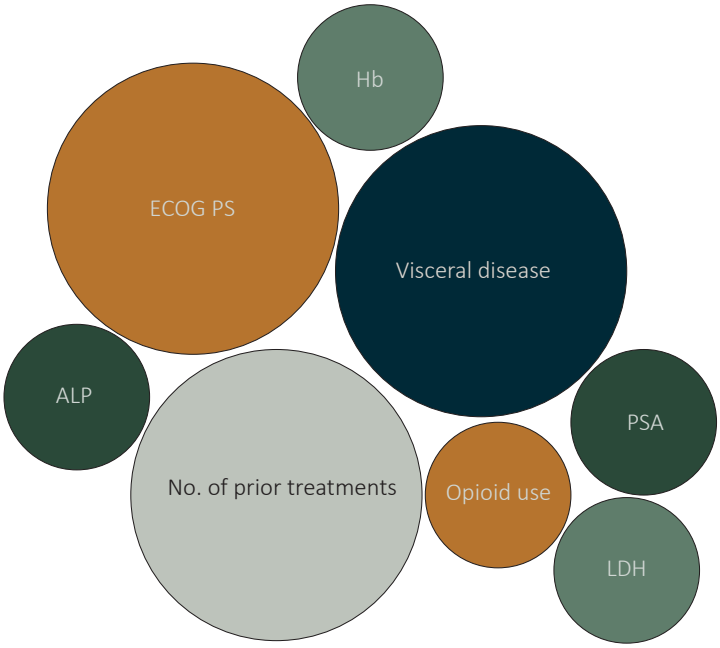

Figure 11.2 | Prognostic factors in CRPC treatments in CAPRI
Larger circles indicate a stronger association. Abbreviations: CRPC, castration-resistant prostate cancer; CAPRI, castration-resistant prostate cancer registry; Hb, hemoglobin; ECOG PS, Eastern Cooperative Oncology Group Performance score; ALP, alkaline phosphatase; PSA, prostate specific antigen; LDH, lactate dehydrogenase.

Patient and disease characteristics are important factors to consider, since they can impact outcomes of certain treatments or treatment sequences. Knowledge of these factors can help treatment selection and improve outcomes, as we have shown in Chapter 8. Moreover, prognostic models using multiple characteristics can thus to aid clinical decision making. Models developed for CRPC include 4 to 11 variables, mostly haemoglobin, baseline prostate-specific antigen (PSA), alkaline phosphatase, performance status and lactate dehydrogenase[222]. These were similar to the variables we found related to outcomes (Figure 11.2) with the addition of opioid use and number of prior treatments.

Prior treatments may negatively affect the subsequent treatment due to cross-resistance, lower tolerability, and more advanced disease state. The median OS in CRPC-patients declines from 21 months at the start of second line to 11 and 5 months at the start of third or fourth line respectively[140], which was similar to our observation (Table 11.2). The early start of treatment thus seems beneficial for outcomes as OS, but this was not prospectively validated[157]. The disadvantage of an early start is that there might not be any treatment left in later lines, which is especially disadvantageous when patients are still in good quality of life.

Table 11.2 | Overall survival of CRPC-treatments per life-prolonging treatment line

Line	n/N[a]	Median OS	IQR
First line	1,532/2,216	20.3	10.9-34.4
Second line	984/1,397	12.3	6.5-24.5
Third line	506/701	9.6	5.1-16.9
Fourth line	184/261	9.4	4.6-13.8

[a] number of events (= death) of total number of patients at the start of each treatment line
Abbreviations: CRPC, castration-resistant prostate cancer; OS, overall survival; IQR, interquartile range.

Cross-resistance, the phenomenon that occurs when resistance to one treatment makes the disease resistant to an other treatment, can explain lower effectiveness of later treatment lines. The type of prior treatment delivered to the patient should be considered for in later treatment decisions. Knowledge of pathogenesis is key. The development of CRPC is largely driven by the androgen pathway and treatments targeting the androgen pathway (i.e ABI+P, enzalutamide and first-generation antiandrogens as bicalutamide) have overlapping mechanisms of resistance and are thus prone to cross-resistance[128]. Our RWE suggested that the effect of ABI+P after enzalutamide (ENZ) or vice versa was particularly low (Chapter 5). This was recently prospectively validated in the CARD study, showing that cabazitaxel improved several clinical outcomes compared to ABI+P and ENZ after prior treatment with docetaxel and the other androgen signalling inhibitor[213]. Measuring androgen-receptor (AR)-biology could help to select patients who benefit from AR-targeting drugs or other systemic treatments. For example, AR-V7 was shown to be associated with resistance to AR-targeting drugs, but not chemotherapy[273–275]. However, these technologies are not broadly implemented in clinical practice yet, warranting other guidance in treatment decisions.

To support clinicians with knowledge on effectiveness of a given treatment especially after prior treatments, we incorporated known risk factors (Figure 11.2) into a simple prognostic score for patients treated with at least docetaxel and one line of AR-targeting drugs in Chapter 9. The prognostic model was able to identify a subgroup of patients with short survival (< 6 months) after progression on the second treatment line. The score incorporates simple, clinically available items which can be used by clinicians in treatment decisions (Chapter 9).

Prognostic models as above can not only provide information on the best treatment option, but also support the decision not to start a new treatment when life expectancy is short. Treatment near the end-of-life can namely cause physical and psychological distress[276]. Moreover, patients continuing chemotherapy in the last 14 days of life had no survival benefit and were less likely to receive hospice care[277]. The reasons to continue treatment in this phase are unclear, but they might be driven by patient preferences,

expected treatment benefits or overestimation of life expectancy by clinicians[228–230]. Although treating patients with expensive treatments in the end-of-life phase seems not justifiable since it adds little to survival and comes at high societal costs, treatments could have been initiated to maintain quality of life and prevent or treat symptoms of CRPC. However, the treatment effect on quality of life in this phase is not widely studied[100,219,227]. Investigating the effects of treatments near the end-of-life is important, but challenging from RWE since it is often unclear beforehand that the end-of-life period has started. This warrants the need for prognostic models as the Halabi-models or the model developed by us in Chapter 9 to adequately estimate life span. These models can aid in clinical decision making and prevent inefficient use of treatments.

Although prognostic models can be used in clinical decision making, most of them are not used in clinical practice due to methodological pitfalls, complexity and user-friendliness[222]. In addition, most available models for the treatment of CRPC are based on results of RCTs which lack external validity as stated before[222,278]. This could be the explanation that models failed to predict survival in 21-31% of CRPC-patients[222]. Prognostic models based on RWE as described by us in the third-line treatment in Chapter 9, offer a valid solution and are easily applicable in clinical practice.

In order to provide the input needed for prognostic models, RWE should be able to capture all relevant patient and disease characteristics, as well as outcomes. Moreover, treatment populations should be large enough to adequately estimate survival. All challenges of RWE (e.g. lack of internal validity and missing data) can put prognostic models at risk of all sorts of bias. Supplementing data from RCTs with real-world data might offer the best of both worlds.

Many patients express that they want to receive information on the possible risks and benefits of care[279]. Moreover, they want to be involved in decisions about care, a process known as shared-decision making. The involvement of patients in treatment decisions improves satisfaction[280,281]. Clinicians also feel strongly about patient involvement in treatment decisions, but more than half of the clinicians do not feel adequately trained[282].

The most important aspect to ensure patient involvement is providing information that is suitable to the individual patient. Patient information is available in all sorts and forms and the offer is enormous. It can thus be challenging for patients to find the information that best suits their situation.

Information should therefore be offered in an understandable manner, preferably by clinicians or nurses that can guide patients in their individual situation. However, tailored communication is difficult and it is suggested that clinicians often provide a one-size-fits-all approach with a fixed information set on treatments due to time constraints[283]. This warrants the need for the development of decision tools, which

increase disease-specific knowledge and improve involvement in the decision-making process[282,284]. The CRPC-population is an older population (often aged > 75 years), which asks for specific techniques to adequately exchange information. RWE should form the basis of decision tools, since they are better generalizable to clinical practice than RCTs.

A decision tool should not only incorporate survival, since this might not be in line with patients' needs and wants[285]. A discrete choice experiment (DCE) can cover a range of outcomes of different treatment options (including survival, quality of life and complications) to determine the most important values of a patient and their caregivers[260]. The specific items to be covered by the DCE should be firstly determined in focus groups. Working closely together with patient advocates or support groups (as for example the Dutch Prostaatkanker Stichting) is therefore important to better tailor to patient's needs. These groups can also aid in making information easily accessible to patients.

THE ROLE OF RWE IN ASSESSMENT OF HEALTH CARE SYSTEMS

The definition of quality of care differs depending on the level of health care it is assessed: either health care services or health care systems as a whole[14].

Quality of health care systems can be considered as good access to qualitative health care services to achieve health system goals (i.e. population health outcomes)[14]. The resources required determine the efficiency of the system[14]. In this part we show how RWE can assess accessibility and efficiency.

Accessibility

Access to health care is a human right first recorded in the Universal Declaration of Human Rights in 1948 by the United Nations[286]. For drugs to be accessible to patients several steps have to be undertaken, including a positive review by international (EMA) and national (cieBOM and ZiN[1]) regulatory agencies. This can result in a substantial delay (Table 11.1). A second delay can occur after the necessary approvals when treatments are not prescribed either due to hospital policies or clinician inexperience with new drugs.

The time of prescription of new drugs offers information on the uptake. New CRPC drugs were in general rapidly used after registration as seen from CAPRI (Figure 11.3 and 11.4). However, data are based on a selection of hospitals and feedback of results to the participating hospitals might have influenced the prescription rates.

1 Commissie ter Beoordeling van Oncologische Middelen (cieBOM)

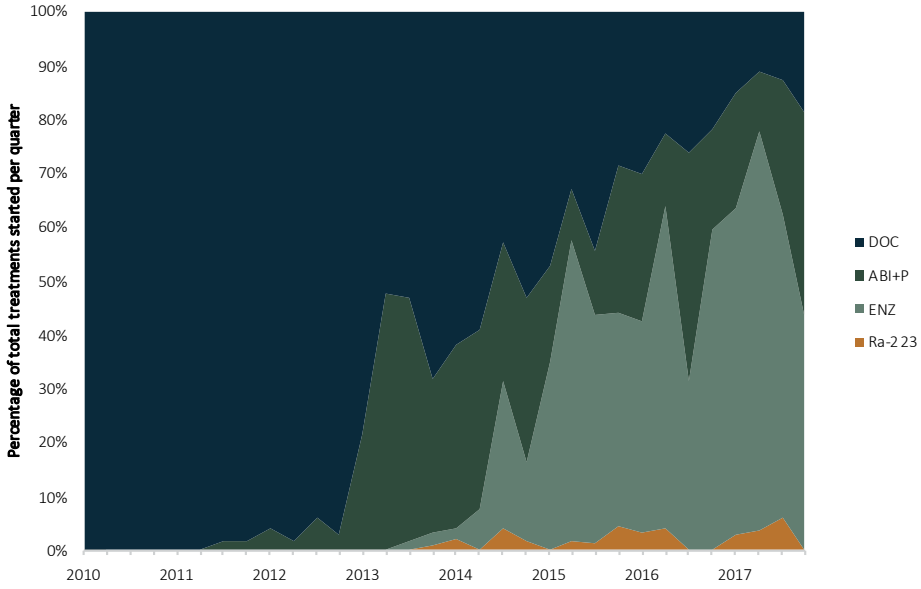

Figure 11.3 | Choice of first line treatment over time
Abbreviations: DOC, docetaxel; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; Ra-223, radium-223.

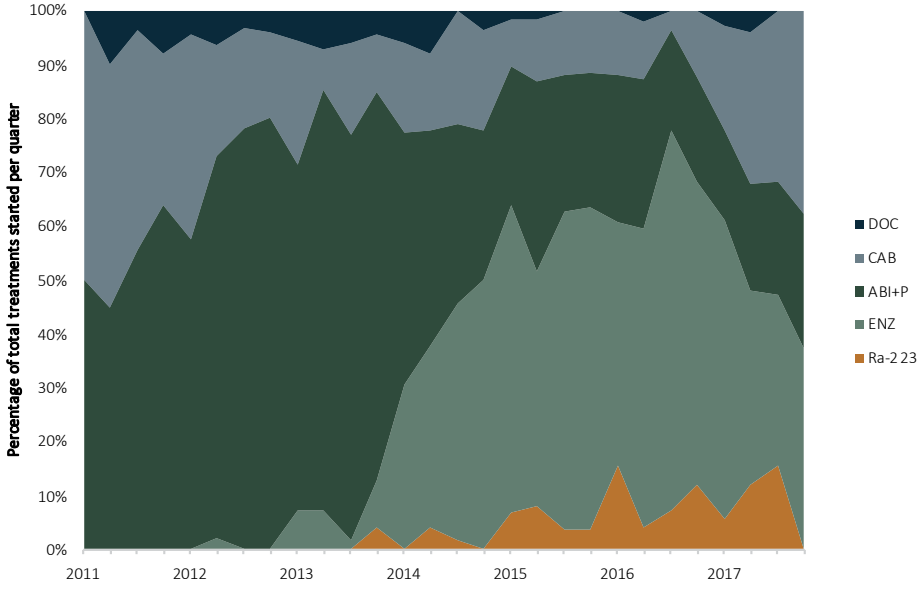

Figure 11.4 | Choice of first post-docetaxel treatment over time
Abbreviations: DOC, docetaxel; CAB, cabazitaxel; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; Ra-223, radium-223.

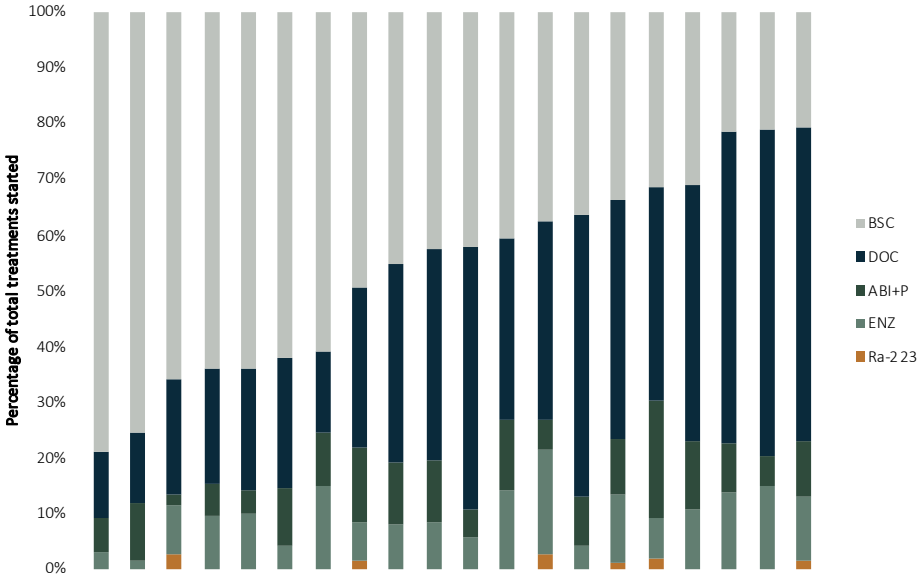

Figure 11.5 | Choice of first line treatment per hospital
Each bar represents a hospital. Treatment was considered as first line as it was started within 24 months of CRPC-diagnosis; no treatment or treatment after 24 months was recorded as BSC. *Abbreviations*: BSC, best supportive care; DOC, docetaxel; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; Ra-223, radium-223.

RWE can indicate when there are problems with the uptake of one or more treatments. This can be a sign for inappropriate access if either the patient has an indication for this specific treatment. In our interim population (n=1,524 diagnosed with CRPC in 2010-2013) we observed that only 46% of patients were treated with docetaxel, while docetaxel was the only treatment option for CRPC at that time[51]. Forty percent of our patients who met the indication criteria of docetaxel (i.e. ECOG PS 0-2, symptomatic disease or asymptomatic with visceral metastases or signs of rapid progression), were not treated with docetaxel[51,287]. Since these patients had other signs of less aggressive disease and were fitter than patients who started docetaxel, we proposed that clinicians had chosen to wait until the time that treatment was necessary since from an historical perspective docetaxel was only used in patients with symptomatic and advanced disease stages. However, the exact reasons for this observation are difficult to unravel and RWE is not able to exclude all arguments for withholding treatment.

In addition to access over time, RWE can also investigate the treatment use between hospitals as sign of differential access. In CAPRI the choice of CRPC-treatment varied widely between the twenty hospitals (Figure 11.5 and 11.6). In addition to differences in patient populations between hospital, hospital structures can be a valid explanation. The odds of receiving any first post-docetaxel treatment was highly related to type of

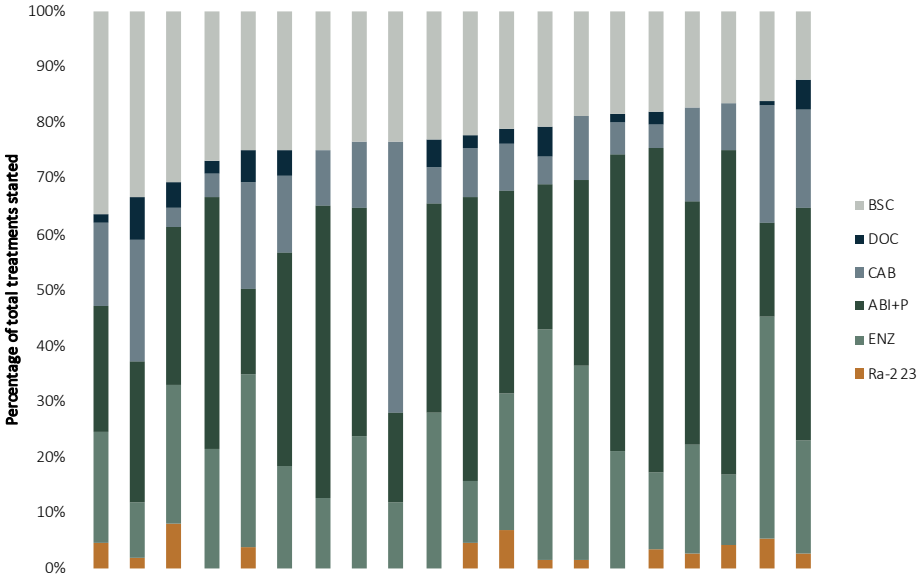

Figure 11.6 | Choice of first post-docetaxel treatment per hospital
Each bar represents a hospital. Treatment was considered as first post-docetaxel treatment as it was started within 12 months of progression on docetaxel; no treatment or treatment after 12 months was recorded as BSC.
Abbreviations: BSC, best supportive care; DOC, docetaxel; CAB, cabazitaxel; ABI+P, abiraterone acetate plus prednisone; ENZ, enzalutamide; Ra-223, radium-223.

hospital: in semi-specialized or specialized hospitals more patients were treated with any post-docetaxel treatment. Hospital infrastructure to allow for specialty medications as Ra-223 or trial treatments is likely to affect referral for these treatments and thus cause variation[288].

RWE is able to indicate variation in access to treatments, either in time as well as in geographic location. The reasons why access might be less than expected are difficult to unravel. As stated before, differences in patient characteristics can explain differences in access. When patients don't have to indication for a specific treatment, this can lead to less prescriptions of that treatment. However, treatment decisions are not only based on patient characteristics, but are a complex process of shared decision making. Especially patient preferences can hardly be assessed from electronic medical records (EMRs). In order to get more insight in treatment decisions, a qualitative research approach is necessary. Combining the clinical data in registries with patient and clinician questionnaires could fill this information gap.

Variation by itself is not a bad thing when the outcomes are equal. We observed that receiving a second treatment after docetaxel varied widely between hospitals (from 35% to 87%), but these differences were explained by differential patient characteristics between hospitals. The same case-mix affected OS. Although there was a variation

between hospitals in both prescription rate and outcomes, this variation was thus not related to hospital characteristics. Future studies should not only report that there is variation, but also address what is causing the variation (e.g. case-mix) and if the variation leads to differential outcomes.

Efficiency

The expenditure on health care for an individual patient has its effect on the total population, especially with rising costs of treatments. This led to an increased focus on health-economic outcomes. Efficiency can be used to measure effectiveness on a population level, where not only outcomes but also costs are considered. The best method to investigate efficiency is by cost-effectiveness analyses (CEA) in which costs per quality-adjusted life years (QALYs) are calculated. In simple cost-effectiveness analyses the costs and QALYs of one treatment are compared with the costs and QALYs of one other treatment (often best standard of care) by calculating the incremental cost effectiveness ratio (ICER). However, in daily practice multiple treatments can be given in different sequences. A registry can provide input for all clinically relevant costs and outcomes for the full disease spectrum, creating the possibility for CEA for different treatments and sequences. These outcomes can be used by policy makers to consider alternatives, but also coverage decisions[289].

We performed a CEA for different sequences including one to four registered life-prolonging drugs for CRPC. Most sequences gained between 1.3 to 2.0 QALYs costing €60,000 to €150,000. There was little variation between sequences with similar numbers of life-prolonging drugs. As costs for treatments are a main driver for high ICERs, CEA may open up the conversation about drug pricing and be used in price negotiations. Moreover, CEAs based on RWE provide policy makers with representative results to guide policy decisions (e.g. reimbursement).

Cost-effectiveness thresholds are set to identify interventions that are good value for money. In the Netherlands, a maximum willingness to pay threshold was set at €80,000 per QALY depending on the burden of the disease. Results of CEAs are estimates based on several assumptions and are prone to errors. Therefore, specific sensitivity and scenario analyses are performed to make it technically solid. However, they do not provide information on affordability or budget impact. CEAs are thus not the only argument in policy decisions as effectiveness (in both survival and quality of life) and safety of a treatment, necessity and feasibility are as or even more important.

While CEAs generally consider costs and benefits from a societal perspective, value-based health care (VBHC) covers the patient perspective[289,290]. Patient value is defined as for the patient-relevant outcomes relative to the cost spent to achieve these outcomes[290]. The value in VBHC cannot be compromised into one single outcome and does not have to be in line with the outcomes of CEAs[289]. The concept of VBHC can be used in

clinical practice in order to support treatment decisions and thus tailor treatment to the individual patient.

THE FUTURE OF (PROSTATE CANCER) REGISTRIES

Using the CAPRI registry, we were able to provide insight in the quality of care of CRPC between 2010 and 2018. However, our journey was not without challenges.

The challenges and considerations for future patient registries

The first challenge we encountered in our CAPRI registry was collecting the data and assuring data quality[56,291]. We started with patient identification based on diagnosis codes used for reimbursement. Since there was no specific code for CRPC, we screened all patients with the code for "prostate cancer" in the urology and medical oncology department. To include the total of 3,616 patients we had to screen over 40,000 records. We then manually entered data from the EMRs into the data warehouse. This process is time consuming (4-5 hours per patient) and prone to errors. One solution to secure good qualitative data is consistently capturing data using clear definitions. Moreover, data should be checked regularly by datamanagers or researchers to improve accuracy[292]. In CAPRI, data managers were trained by one of the two investigators and used a pre-defined guideline for data collection. This left little room for own interpretation by the data managers. Future registries can build on these experiences using training programs and guidelines for data managers.

Although manual data collection is the golden standard, IT-based solutions for patients identification and data collection are emerging. These solutions can streamline data collection using artificial intelligence and minimize human errors. The intelligent search engine CTcue Clinical Data Collector (CDC) makes it possible to search through all fields of EMRs and allows the export to a data warehouse. We compared data quality of data automatically collected by CDC with our own data. In conclusion, we could classify automatically collected data items into three categories based on quality (high, medium or low). High quality data were mainly data structurally captured in EMRs (e.g. laboratory values), while data from text fields or dates (e.g. date of diagnosis) were less reliable. This indicates that structured data items can be collected automatically to minimize human errors, but manual revision is needed for data collected from less reliable items.

There remains a potential risk of measurement error or misclassification of data items. However, these items were also prone to error when manually collecting data. For example, progression was not captured in a structured manner in the EMRs and we were thus not able to use progression-free survival as an end point. The only solution to tackle this problem would be by protocol mandating registration of important items in

EMRs. However, medical files serve the purpose of individual care and not registration for research purposes. Researchers should consider in advance which data items are a necessity and weigh this against the drawbacks in quality.

Quality monitoring can improve data accuracy, but RWE are often not as closely monitored and checked as RCTs. In CAPRI, a central quality check was performed on a sample of the data by one of the two investigators. Quality assurance should be structured using a preplanned quality control plan[292]. Insight in the quality of the data can help improve data management.

Data items that are not available or available against low quality introduce the second challenge of patient registries: missing values[291]. Not all data of interest were available in our registry and available data were often incomplete, since there was no protocol-mandated registration. The high number of missing values makes statistical analyses more difficult, but when completeness of data cannot be solved with improving data collection, multiple imputation of missing data using Markov-Chain method offers a valid solution[293]. Residual confounding could still be present especially when missing data are not completely at random.

The last challenge of registries is methodological and mentioned before: data analyses are prone to different forms of confounding[56,291]. Treatment choices are not randomized leading to confounding by indication. Although statistical solutions as multivariable analyses or propensity score matching allow for the comparison of different treatments, residual confounding can remain due to unknown confounders or by measurement errors or misclassification of the confounding factors[291]. It is important for researchers to keep in mind the possibilities as well as the impossibilities of RWE and sometimes withhold from drawing conclusions when statistical pitfalls are too large.

The changing treatment landscape of prostate cancer

For prostate cancer specifically, the treatment landscape changes rapidly. Several ongoing studies will be published in the upcoming years and probably lead to registration of new treatments. Research mainly focusses on therapies addressing resistance after prior treatments, targeted-therapies, and checkpoint inhibitors[128,294–298]. In addition to new drugs, existing CRPC-drugs are registered for a new indication: metastatic hormone-sensitive prostate cancer (mHSPC)[19–22,299]. Future registries should move forward and not only include CRPC-patients, but start data collection from mHSPC.

Moreover, the landscape of patient selection and treatment monitoring changes. Multiparametric magnetic resonance imaging, positron emission tomography (PET)- CT, and prostate-specific membrane antigen (PSMA)-PET have better accuracy to identify metastatic tumour load in CRPC-patients than conventional imaging modalities, but the use of these techniques is limited due to high costs and lack of widespread availability[23,300]. In addition to imaging modalities, research focusses on molecular profiling

to properly identify patients. Molecular characterization could further match patients to therapies and can be incorporated in a future registry.

Trials for new drugs, imaging modalities and molecular technologies are largely centred around academic medical centers[301]. Travel distance to academic medical centres can form a barrier, since longer distances are associated with increased indirect costs for traveling and economic productivity for both patients and their caregivers[302,303]. The differential access to high-quality health care also causes disparities in clinical trial participation, since trials can be stratified by genomic alterations[301,304]. Consequently, since genomic alterations and high-quality radiographic imaging can guide subsequent therapy, this can limit treatment delivery. A future prostate cancer registry should therefore pay extra attention to the availability of new technologies and the effect on equal access to health care.

FINAL REMARKS

Disease-specific patient registries can provide a valuable source of data for the evaluation of quality of care. Results of real-world data can indicate areas of concern, for example access to health care or inappropriate use of treatments or hospital resources. RWE can therefore initiate policy changes on either national or hospital level to improve health care delivery and as important, monitor the effect of these changes to direct future health care decisions[305].

Moreover, RWE has the potential to impact outcomes for an individual patient. Incorporating real-world outcomes in guidelines or decision tools offers both clinicians and patients better insight in expected outcomes. This is especially of value when outcomes not only include survival, but also quality of life and adverse events. Results of registries can open up the conversation between clinician and patient, improve patient involvement in shared decision making and eventually lead to improved patient satisfactory. The ultimate goal of health care should be that the patient receives the best possible care in his situation. RWE from registries can aid in reaching this goal.

Summary

Measuring health care quality in a population has come of increasing interest especially in fields with costly new treatments and/or high incidence as for example in oncology. The first step to properly evaluate quality of care is a clear definition. Commonly used are the definition of the European commission and the World Health Organization (WHO): "good quality care is health care that is effective, safe and responds to the needs and preferences of patients"[13]. These dimensions (i.e. effectiveness, safety and patient-centeredness) are considered the core dimensions to evaluate quality of health care services[14]. However, health care systems also need to be assessed on accessibility and efficiency.

CASTRATION-RESISTANT PROSTATE CANCER

Prostate cancer is an example of an indication in which measurement of quality of care is of increasing interest, because it is one of the most common types of cancer in men. Although localized disease is curable, treatment in metastatic disease is palliative. Androgen deprivation therapy (ADT) is the main treatment for metastatic prostate cancer. Recent studies have shown a positive effect on survival of the addition of docetaxel, abiraterone acetate (hereafter abiraterone) or enzalutamide to ADT. Progression to a phase known as CRPC is however inevitable.

CRPC has a great impact on survival and is related to the presence of symptoms (mainly pain, fatigue and appetite loss), a decline in health-related quality of life (HRQoL) over time, and a high risk of skeletal complications due to frequent bone metastases and bone mineral density loss due to ADT. Several life-prolonging drugs (LPDs) have been registered for the treatment of CRPC based on a survival benefit, but they also maintain quality of life and delay skeletal complications.

Docetaxel (DOC), a taxane-based chemotherapy, was approved as first line treatment of CRPC in 2005[24]. Cabazitaxel (CAB), a different taxane-based chemotherapy, was registered for the treatment after docetaxel failure[27], as were the androgen-receptor targeting agents (ART) abiraterone (ABI+P) and enzalutamide (ENZ) and an alpha-emitting isotope radium-223 dichloride (Ra-223)[28–30]. Ra-223 is only advised as treatment in patients with bone metastases and no visceral metastases or extensive lymph node metastases. ABI+P, ENZ, and Ra-223 are also approved for the first line treatment[31–34]. However, the European Medicine Agency (EMA) recently advised the use of Ra-223 in line 3 or higher unless patients are ineligible for other LPDs[306]. Although treatments have positive effects on survival and quality of life, they come at high economic costs making appropriate use of treatments an important subject of discussion.

THESIS AIM

In this thesis we aimed to highlight the quality of care in the management of CRPC. Our results can add to existing evidence and aid in optimizing care. To evaluate quality of care in the Netherlands we set up the "Castration-resistant Prostate cancer RegIstry (CAPRI)" in which we collected data on patient and disease characteristics, treatments, outcomes and resource use of over 3,500 CRPC-patients from twenty different hospitals.

REAL-WORLD EVIDENCE VERSUS RANDOMIZED CONTROLLED TRIALS

The first part of this thesis focusses on real-world evidence (RWE) in comparisons to randomized controlled trials (RCTs). RCTs are carried forward under optimal and controlled conditions in selected populations. Available data on treatment effectiveness and safety for CRPC comes from RCTs and is used for clinical guidelines and treatment protocols. In **Chapter 2** we investigated differences between RCTs and RWE from our CAPRI registry for cabazitaxel. Cabazitaxel is a registered treatment after progression on docetaxel. We identified 173 patients treated with cabazitaxel in the second line. Patients treated with cabazitaxel in a clinical trial had better median overall survival (mOS) compared to patients treated with cabazitaxel in standard of care (13.6 versus 9.6 months; hazard ratio (HR) 0.73, p=0.067). This difference was caused by differences in patient characteristics with fitter patients treated in trial, since after correction for prognostic factors there were no differences in survival (HR 1.00; p=0.999). This underlines the need for outcomes based on real-world data to ensure optimal outcomes, since trial data are not easily generalizable to daily practice.

QUALITY OF CARE: THE CORE DIMENSIONS

Effectiveness

"Effectiveness" is the dimension that describes that care delivered should have desirable outcomes based on scientific knowledge. We investigated the effectiveness of new LPDs in general in **Chapter 3**. We observed a marked increase in the number of patients treated after registration. The number of patients without any LPD (i.e. DOC, CAB, ABI+P, ENZ or Ra-223) decreased from 43% in 2010-2011 to 31% in 2014-2015. Better access to new treatments can improve outcomes. We have shown that the overall survival increased from 28.5 months in 2010-2011 to 31.0 months in 2014-2015. This difference was only partially explained for by changes in known prognostic factors.

Although survival improved with the availability of new treatments for CRPC, many patients experience a decline in health-related quality of life (HRQoL) as observed in our prospective PRO-CAPRI study ("Patient Reported Outcomes in the Castration-resistant Prostate cancer RegIstry") including 151 patients from 10 CAPRI-hospitals. As discussed in **Chapter 4**, this deterioration was seen in almost all domains, but was especially present in physical functioning and role functioning (i.e. patient's ability to perform daily activities, leisure time activities, and/or work). Since patients often favor maintaining HRQoL over survival, evaluation of symptoms and HRQoL should be one of the cornerstones in CRPC management. Implementing HRQoL-measurements in clinical practice can improve shared-decision making and optimize supportive care and symptom management.

Choosing the optimal treatment strategy in CRPC to obtain the best outcomes (either quantity or quality of life) for an individual patient is challenging due to a lack of comparative results and low generalizability of trail results to daily practice. The choice of a treatment should be based on patient and disease characteristics, aspects of the proposed treatments and treatment history[23,154,271]. We consistently investigated patient and disease characteristics and their association with outcomes. A summary of these factors is listed in Figure 11.2.

One of the main factors associated with outcomes is prior treatments. The effect of a subsequent treatment can namely be affected by cross-resistance. In **Chapter 5** we discussed the potential cross-resistance between drugs targeting the androgen receptor (AR). The suspected cross-resistance between ABI+P and ENZ has led to the advice of the use of chemotherapy (TAX) after failure of one of these drugs in the guidelines. In **Chapter 5**, we present the results of this so-called "sandwich" use of other LPDs between ARTs (ABI+P or ENZ). Of the 273 patients treated with both ARTs, 125 patients were treated with the "sandwich method" (i.e. ART1>LPD>ART2) and 148 patients with both ARTs directly after each other (i.e. ART1>ART2). Patients with ART1>ART2 were older, but had favourable prognostic factors at the start of ART2. These differences in baseline characteristics did not result in a different response. In general, the effect of a second ART was low: only 20% had a PSA response and median treatment duration was 3 months. Especially patients with visceral metastases, a short duration of ADT, and ENZ followed by ABI+P were less likely to obtain a PSA response. However, we also showed that patients who had a PSA response had a clinically relevant treatment duration. A second ART should therefore only be offered in a selected patient population and does seem of little value in patients with the aforementioned prognostic factors. Future research should focus on identifying patients who will likely benefit from a second ART, which may include putative predictive biomarkers as androgen-receptor splice variant 7 (ARv7).

A second explanation for the association between number of prior treatment lines and outcomes, is the fact that patients with multiple prior treatments often have more aggressive disease characteristics and worse clinical performance at the start of a later treatment line. We have illustrated this with the outcomes of Ra-223 in respect to the line of treatment in **Chapter 6**. Since Ra-223 has a small window of opportunity because it has to be started before the presence of visceral metastases, which occur later in the disease trajectory, optimal timing of Ra-223 is of special interest. We found that of the 285 patients treated with Ra-223, 49% of patients received Ra-223 in line three or higher. Patients with Ra-223 in line ≥3 had more hematologic events and shorter overall survival (OS) which was partially explained by worse prognostic factors at the start of treatment. However, the line of treatment remained significant after correction for known prognostic factors. The initiation of Ra-223 should be carefully considered in patients with two or more previous CRPC-treatments, especially when worse prognostic factors are present.

Safety

The core dimension "safety" focusses on the fact that the health care system has the right services in ways to prevent harm to the patient. CRPC patients are especially at risk of skeletal complications as (symptomatic) pathologic fractures, spinal cord compression, the need for surgery, or external beam radiation to the bone. The recent published data of the ERA-223 trial suggest that combination therapy of ABI+P and Ra-223 increases the risk of skeletal complications, mainly fractures. This led to an analysis of the safety of LPDs in a treated population with bone metastatic CRPC. The prevalence of symptomatic skeletal events (SSEs) was considered an outcome indicator for safety. In **Chapter 7** we showed that 41% of the 1,923 patients develop an SSE during follow-up, mostly radiation to the bone. The median time to the first SSE was 23.1 months and median SSE-free survival 12.9 months. Although RCTs have shown a beneficial effect of LPDs on SSEs, the incidence of SSEs was still high in this real-world population. Bone health agents (BHA) have shown a reduction in the risk of SSEs, however this was prior to the registration of LPDs. In our treated population, there seems to be a little delay in the SSE-free survival (13.2 vs 11.0 months, $p<0.01$) in patients who start BHA prior to or within four weeks after the start of the first LPD. This warrants the timely start of BHA to delay the time to SSE onset, especially in patients at high risk (i.e. with factors that reflect bone involvement as prior SSE and pain and/or opioid use).

Patient-centeredness

The core dimension "patient-centeredness" focusses on the degree to which the patient is placed in the centre of health care delivery. Care should be tailored to meet the needs of an individual patient. The importance of choosing the right treatment for the right

patient is seen in **Chapter 8**. We focussed on 45 CRPC patients treated with Ra-223 and only 47% was able to complete all cycles of Ra-223. Although prone to bias (i.e. immortal time bias), patients with all 6 cycles had better overall survival. Overall survival was also influenced by baseline performance status and lactate dehydrogenase levels. These variables can be used to stratify CRPC patients for Ra-223 therapy.

Patient and disease characteristics can also aid in the choice not to start a new LPD when an additional treatment is considered of little value. Although registered LPDs have only been investigated in first and/or second line, treatment beyond line 2 is common practice. The additional effect of third line LPD (LPD3) is however questioned. We assessed the outcomes of a LPD3 in patients previously treated with DOC and any other LPD and developed a simple prognostic model to identify patients who would derive no or little benefit. These results are presented in **Chapter 9**. We found that the 1,011 patients with progression on LPD2 had a median OS of 6.5 months. LPD3 was started in 602 patients (60%). Although these patients had favourable prognostic factors over patients without LPD3, treatment with LPD3 was short (3 months) and only 22% had a PSA response. We have created a simple prognostic score based on seven variables negatively associated with OS: ECOG performance score 1 and ≥2, opioid use, visceral metastases, high PSA, alkaline phosphatase and lactate dehydrogenase. Patients classified in higher risk groups had less benefit from LPD3 (i.e. shorter survival, shorter treatment duration and lower PSA response rates). The prognostic model can aid physicians in stratification of four risk groups with widely differing OS, which can be used in medical decision making. Proper patient selection for LPD3 is crucial to improve outcomes, reduce unnecessary toxicity, improve HRQoL, and prevent unnecessary costs.

Treatment decisions become more challenging after multiple treatment lines especially when patients have characteristics of aggressive disease. In this phase, the life expectancy is low and the end-of-life (EOL) near. During this phase of life, decisions should be made on the expected effectiveness and safety and should be highly patient-centred. The focus should shift from active LPD treatment to symptom management. Intensive cancer care should be avoided, since it adds little to survival and comes at high costs. We reported intensive care defined as the use of LPDs and hospital resources in the EOL (i.e. last three months of life) in **Chapter 10**. Of all CRPC-patients, 41% experienced high intensity care in the last three months, mainly caused by hospitalization. LPD treatment rate was 39% in the EOL phase, but only 15% started a new LPD. These LPDs mainly included ABI+P or ENZ, which may be preferred by clinicians over chemotherapy due to less impact (oral versus intravenous administration) and milder toxicity profiles. Patients using LPD in the last three months were more frequently admitted to the hospital. Although LPDs in this phase of the disease add little to survival, they can prevent of symptoms and preserve of quality of life. The benefits of starting or continuing an LPD in the last phase should be carefully weighed against possible disadvantages (e.g.

hospitalization). Strong predictors for high intensity care were a short period between CRPC diagnosis and EOL, younger age, better performance score, and prior LPD treatment. A specialized palliative care team should play a key role in the organization of care in individuals who likely die soon of metastatic disease. Although high intensity care is not easily justifiable due to high economic cost and little effect on life span, future research should focus on the possible benefits in quality of life for both patients and their caregivers.

We have showed our experiences using RWE to evaluate quality of care on its core dimensions effectiveness, safety and patient-centeredness. In summary, outcomes in daily practice differ from RCTs, since patient characteristics, treatment delivery and monitoring differ. RWE should be used complementary to RCTs and incorporated in guidelines to support clinical decision making. RWE can provide information on outcomes related to specific treatments and patient characteristics, making it possible to select the right treatment for an individual patient.

EVALUATING QUALITY OF HEALTH CARE SYSTEMS

The definition of quality of care differs on the level of health care it is assessed. Quality of health care systems is defined as good access to qualitative health care services (evaluated by the core dimensions) to achieve population health goals. The resources needed to reach these goals determine the efficiency. Accessibility and efficiency are evaluated in **Chapter 11**.

Access can be assessed either in time or in geographic location. Although the uptake of new CRPC-drugs was quick after market authorization, RWE can indicate if there are problems with the uptake. For example, 40% of our patients who met the inclusion criteria for docetaxel were not treated with docetaxel at the time that this was the only treatment option. Variation in treatment choices between hospitals is a sign of geographic access. However, variation itself is not a bad thing when outcomes are equal. We did not find a relation between hospital characteristics and outcomes.

Efficiency can be used to measure effectiveness on a population level, considering not only outcomes, but also costs. Cost-effectiveness analyses (CEA) can show differences in efficiency between treatments and treatment sequences. In CRPC, most sequences gained between 1.3 and 2.0 quality-adjusted life years (QALYs) costing €60,000 to €150,000 with little variation between sequences of similar number of treatments. While CEAs can be used by policy makers on a societal level, value-based health care (VBHC) is more important on a patient level. The value in VBHC cannot be compromised into a

single outcome. RWE can provide the input for VBHC and help tailor treatment to the individual patient.

THE FUTURE

A disease-specific patient registry can provide a valid source of data for the evaluation of quality of care. However, our journey was not without challenges. One challenge was collecting the data and assuring data quality. Manual identification and collection from electronic medical records (EMRs) and transferring data into the data warehouse is time consuming and prone to errors. Future registries should explore the possibilities of automatic data collection using IT-based solutions. Especially in the field of oncology, treatment landscapes are changing rapidly and quicker data collection that is able to adapt to these changes is a necessity. Moreover, a preplanned quality control plan should be used to guarantee data quality. Another challenge is the fact that data analyses are prone to confounding. The possibilities and especially impossibilities of RWE should be kept in mind by researchers.

The ultimate goal of health care should be that the patient receives the best possible care in his situation. RWE from registries may aid in reaching this goal.

Samenvatting

Het meten van kwaliteit van gezondheidszorg in een populatie heeft toenemende belangstelling, vooral in sectoren met dure nieuwebehandelingen en of een hoge ziekte incidentie zoals in de oncologie. De eerste stap in het evalueren van kwaliteit van zorg is een duidelijke definitie. De meest gebruikte definities zijn van de Europese Commissie en de Wereld Gezondheidsorganisatie: “goede kwaliteit van zorg is gezondheidszorg die effectief en veilig is en voldoet aan de behoeften en voorkeuren van patiënten” [13]. Deze dimensies (effectiviteit, veiligheid en patiëntgerichtheid) worden beschouwd als de kerndimensies om kwaliteit van gezondheidsdiensten te evalueren[14]. Gezondheidssystemen worden echter beoordeeld op toegankelijkheid en efficiëntie.

CASTRATIERESISTENT PROSTAATCARCINOOM

Prostaatkanker is een voorbeeld van een indicatie waarin het meten van kwaliteit van zorg toenemende belangstelling heeft, omdat het een van de meest voorkomende kankersoorten is bij mannen. Hoewel gelokaliseerde ziekte te genezen is, is de behandeling van de uitgezaaide ziekte palliatief. Androgeendeprivatie therapie (ADT) is de belangrijkste behandeling voor gemetastaseerd prostaatcarcinoom. Recent hebben studies aangetoond dat er een positief effect is op de overleving als aan ADT docetaxel, abirateron of enzalutamide wordt toegevoegd. Progressie naar een fase bekend als castratieresistent prostaatcarcinoom (CRPC) is echter onontkoombaar.

CRPC heeft een grote impact op de overleving en gaat gepaard met symptomen (vooral pijn, vermoeidheid en verlies van eetlust), een vermindering in gezondheid gerelateerde kwaliteit van leven in de loop van de tijd en een hoog risico op skeletcomplicaties door het frequent aanwezig zijn van botuitzaaiingen en verlies van botdichtheid door ADT. Verschillende levensverlengende behandelingen (LPD) zijn geregistreerd voor de behandeling van CRPC gebaseerd op overlevingswinst, maar zij behouden ook kwaliteit van leven en vertragen skeletcomplicaties.

Docetaxel (DOC), een taxaan chemotherapie, werd geregistreerd als eerstelijnsbehandeling voor CRPC in 2005[24]. Cabazitaxel (CAB), een andere taxaan chemotherapie, werd geregistreerd voor gebruik na docetaxel[27]. Hetzelfde gold voor de androgeenreceptor targeting behandelingen (ART) abirateron (ABI+P) en enzalutamide (ENZ) en de alfa-stralende isotoop radium-223 dichloride (Ra-223)[28–30]. Ra-223 wordt alleen geadviseerd als behandeling bij patiënten met botmetastasen en zonder uitzaaiingen in de organen of met uitgebreide lymfekliermetastasen. ABI+P, ENZ, en Ra-223 zijn ook geregistreerd voor het gebruik in de eerste lijn[31–34]. Het Europees Medicijn Agentschap (EMA) heeft echter recent geadviseerd dat Ra-223 alleen in lijn 3 of hoger gebruikt mag worden tenzij patiënten niet in aanmerking komen voor andere LPDs[306]. Hoewel de behandelingen een positief effect hebben op overleving en kwaliteit van leven, zijn de economische kosten

hoog waardoor het zinnig gebruik van deze behandelingen een belangrijk discussiepunt is geworden.

DOEL VAN DIT PROEFSCHRIFT

In dit proefschrift willen we nadruk leggen op de kwaliteit van zorg in de behandeling van CRPC. Onze resultaten zijn van toegevoegde waarde op de bestaande literatuur en kunnen ondersteunen in de optimalisatie van de zorg. Om de kwaliteit van zorg in Nederland te kunnen evalueren hebben we het 'Castratieresistent Prostaatkanker RegIster (CAPRI)' opgezet waarin we data verzamelden over patiënt- en ziektekarakteristieken, behandelingen, uitkomsten en zorggebruik van meer dan 3.500 CRPC-patiënten uit twintig verschillende ziekenhuizen.

GEGEVENS UIT DE DAGELIJKSE PRAKTIJK VERSUS GERANDOMISEERDE STUDIES

In het eerste deel van dit proefschrift focussen we op de gegevens uit de dagelijkse praktijk, 'real-world evidence (RWE)', in vergelijking tot gerandomiseerde studies, 'randomized controlled trials (RCTs)'. RCTs worden uitgevoerd onder optimale en gecontroleerde omstandigheden in geselecteerde patiëntpopulaties. De beschikbare gegevens over de effectiviteit en veiligheid van CRPC-behandelingen komen voort uit RCTs en worden gebruikt voor klinische richtlijnen en behandelprotocollen. In **Hoofdstuk 2** onderzochten we de verschillen tussen RCTs en RWE voor cabazitaxel in ons CAPRI register. Cabazitaxel is geregistreerd als behandeling na progressie op docetaxel. We identificeerden 173 patiënten behandeld met cabazitaxel in de tweede lijn. Patiënten die behandeld werden met cabazitaxel in een klinische studie hadden een betere mediane overleving dan patiënten behandeld met cabazitaxel als onderdeel van de dagelijkse zorg (13,6 versus 9,6 maanden; hazard ratio (HR) 0,73, p=0,067). Dit verschil werd verklaard door verschillen in patiëntkarakteristieken. Patiënten die behandeld werden in een klinische studie waren namelijk fitter en na correctie voor verschillen in prognostische factoren, was er geen verschil in overleving (HR 1,00; p=0,999). Dit benadrukt de noodzaak voor het gebruik van gegevens uit de dagelijkse praktijk om voor zo optimaal mogelijke uitkomsten te zorgen, gezien gegevens uit klinische studies niet makkelijk generaliseerbaar zijn naar de dagelijkse praktijk.

KWALITEIT VAN ZORG: DE KERNDIMENSIES

Effectiviteit

"Effectiviteit" is de dimensie die beschrijft dat de geleverde zorg de gewenste uitkomsten moet hebben gebaseerd op de wetenschappelijke kennis. We onderzochten de effectiviteit van nieuwe LPDs in het algemeen in **Hoofdstuk 3**. We zagen een toename in het aantal patiënten dat behandeld werd na registratie van de nieuwe medicijnen. Het aantal patiënten zonder LPD (te weten DOC, CAB, ABI+P, ENZ or Ra-223) nam af van 43% in 2010-2011 tot 31% in 2014-2015. Betere toegang tot nieuwe behandelingen kan de uitkomsten verbeteren. We toonden aan dat de overleving (overall survival of OS) toenam van 28,5 maanden in 2010-2011 tot 31,0 maanden in 2014-2015. Dit verschil werd slechts gedeeltelijk verklaard door veranderingen in bekende prognostische factoren.
Ondanks dat de overleving verbeterde met het beschikbaar komen van nieuwe behandelingen voor CRPC, ondervonden veel patiënten een afname in gezondheid gerelateerde kwaliteit van leven (health-related quality of life, HRQoL) zoals we zagen in onze prospectieve PROCAPRI-studie waarin we 151 patiënten includeerden uit 10 CAPRI-ziekenhuizen. Zoals besproken in **Hoofdstuk 4** werd deze verslechtering gezien in bijna alle domeinen, maar was vooral aanwezig in fysiek functioneren en rol functioneren (de mogelijkheid voor de patiënt om de dagelijkse activiteiten, vrije tijd en/of werk uit te oefenen). Gezien patiënten veelal het behoud van kwaliteit van leven prefereren boven overleving, moet het evalueren van symptomen en HRQoL een van de hoekstenen zijn van de behandeling van CRPC. Het opnemen van HRQoL-metingen in de dagelijkse praktijk kan gezamenlijke besluitvorming tussen arts en patiënt bevorderen en de ondersteunende zorg en symptoomgerichte behandeling optimaliseren.

De keuze voor de meest optimale behandelstrategie in CRPC voor een individuele patiënt om de beste uitkomsten (of kwantiteit of kwaliteit van leven) te bereiken is uitdagend gezien het gebruik aan vergelijkende studies en de lage generaliseerbaarheid van resultaten uit studies naar de dagelijkse praktijk. De keuze van de behandeling moet gebaseerd worden op patiënt- en ziektekarakteristieken, aspecten van de voorgestelde behandelingen en de voorgaande behandelingen[23,154,271]. We onderzochten deze patiënt- en ziektekarakteristieken en hun relatie met uitkomsten. Een samenvatting van deze factoren wordt weergeven in figuur 11.2.

Een van de belangrijkste factoren die geassocieerd is met uitkomsten zijn de voorgaande behandelingen. Het effect van een volgende behandeling kan namelijk beïnvloed worden door kruisresistentie. In **Hoofdstuk 5** lieten we de mogelijke kruisresistentie tussen middelen die werkzaam zijn via de androgeenreceptor (AR) zien. De mogelijke kruisresistentie tussen ABI+P en ENZ heeft ertoe geleid dat na progressie op een van beide middelen chemotherapie met een taxaan wordt geadviseerd in de richtlijn.

In **Hoofdstuk 5** presenteerden we de resultaten van het zogenaamde “sandwich” gebruik van andere LPDs tussen ARTs (ABI+P of ENZ). Van de 273 patiënten die behandeld zijn met beide ARTs zijn 125 patiënten behandeld met de “sandwich methode” (ART1>LPD>ART2) en 148 patiënten met beide ARTs direct na elkaar (ART1>ART2). Patiënten met ART1>ART2 waren ouder, maar hadden betere prognostische kenmerken bij de start van ART2. Deze verschillen in karakteristieken bij de start resulteerden niet in een verschillende respons. Het effect van een tweede ART was in het algemeen laag: slechts 20% had een PSA-respons en de mediane behandelduur was 3 maanden. Vooral patiënten met viscerale uitzaaiingen, een korte behandelduur van ADT en ENZ gevolgd door ABI+P hadden minder kans op een PSA-respons. Patiënten die een PSA-respons hadden, hadden echter een klinische relevante behandelduur. Een tweede ART moet daarom alleen aangeboden in een geselecteerde patiëntpopulatie en lijkt van weinig toegevoegde waarde bij patiënten met de bovengenoemde prognostische factoren. Verder onderzoek is noodzakelijk om patiënten te identificeren die waarschijnlijk baat hebben bij een tweede ART. Dit zijn mogelijk patiënten met voorspellende biomarkers zoals de androgeen-receptor splice variant 7 (ARv7).

Een tweede verklaring voor de associatie tussen het aantal voorgaande behandelingen en uitkomsten is het feit dat patiënten met meerdere voorgaande behandelingen vaak tekenen hebben van agressievere ziekte en slechtere klinische conditie op het moment dat zij starten met een latere behandellijn. Wij hebben dit laten zien met de uitkomsten van Ra-223 per behandellijn in **Hoofdstuk 6**. De periode waarin Ra-223 gestart kan worden is kort, gezien het gestart moet worden voor de aanwezigheid van viscerale metastasen, die vaak ontstaan later in het ziekteproces. Een optimale timing van Ra-223 is derhalve van belang. Wij zagen dat 49% van de 285 patiënten die behandeld zijn met Ra-223 startten met Ra-223 in een derde of hogere behandellijn. Patiënten met Ra-223 in lijn 3 of hoger hadden meer hematologische toxiciteit en kortere OS wat deels verklaard werd door slechtere prognostische factoren bij de start van de behandeling. De start van Ra-223 moet goed overwogen worden bij patiënten met twee of meer voorgaande CRPC-behandelingen, vooral als er slechte prognostische kenmerken aanwezig zijn.

Veiligheid

De kerndimensie “veiligheid” richt zich op het feit dat de gezondheidszorg de diensten inzet op een manier dat deze de patiënt niet schaadt. CRPC-patiënten lopen vooral het risico op skeletcomplicaties zoals (symptomatische) pathologische fracturen, myelumcompressie, de noodzaak tot chirurgie of externe radiotherapie op het bot. De recent gepubliceerde gegevens van de ERA-223 studie suggereerden dat de combinatie van ABI+P en Ra-223 het risico op skeletcomplicaties en dan vooral fracturen verhoogd. Dit leidde tot een analyse naar de veiligheid van LPDs in een behandelde populatie met botuitzaaiingen. De prevalentie van symptomatische skelet events (SSEs) werd beschouwd

als een uitkomstmaat voor veiligheid. In **Hoofdstuk 7** toonden we aan dat 41% van de 1.923 patiënten een SSE vooral radiotherapie op het bot ontwikkelden tijdens de follow-up. De mediane tijd tot de eerste SSE was 23,1 maanden en de mediane SSE-vrije overleving 12,9 maanden. Ondanks dat RCTs een positief effect op SSEs hebben laten zien voor LPDs, was de incidentie van SSEs hoog in deze populatie uit de dagelijkse praktijk. Botbevorderende middelen (bone health agents of BHA) hebben een verlaagd risico op SSEs laten zien, echter is dit aangetoond in de periode voordat LPDs geregistreerd waren voor CRPC. In onze behandelde populatie leek er een kleine verlenging te zijn in SSE-vrije overleving (13,2 versus 11,0 maanden, p<0,01) voor patiënten die snel starten met BHA (voor of binnen vier weken na de start van de eerste LPD). Dit benadrukt het belang van het tijdig starten van BHA om de tijd tot eerste SSE te verlengen, vooral bij patiënten met een verhoogd risico te weten factoren van botbetrokkenheid zoals eerdere SSE en pijn en/of gebruik van opioïden.

Patiëntgerichtheid

De kerndimensie “patiëntgerichtheid” richt zich op de maat waarop de patiënt in het centrum van de gezondheidszorg geplaatst wordt. Zorg moet passen bij de behoeften van de individuele patiënt. Het belang van de keuze voor de beste behandeling voor de patiënt is te zien in **Hoofdstuk 8**. We evalueerden 45 CRPC-patiënten behandeld met Ra-223 en slechts 47% was in staat om de behandeling van 6 kuren af te maken. Ondanks dat de analyse onderhevig was aan bias (immortal time bias), hadden patiënten met 6 kuren een betere overleving. De overleving werd ook beïnvloed door performance status en hoogte van lactaat dehydrogenase bij de start van de behandeling. Deze variabelen kunnen gebruikt worden om CRPC-patiënten te stratificeren voor Ra-223 behandeling.

Patiënt- en ziektekarakteristieken kunnen ook helpen in de keuze om niet te starten met een nieuwe behandeling als geschat wordt dat een additionele behandeling geen meerwaarde heeft. Ondanks dat de geregistreerde LPDs alleen onderzocht zijn in de eerste en/of tweede behandellijn, een behandeling in lijn 3 of hoger is de gangbare praktijk. Een additioneel effect van een derdelijns LPD (LPD3) wordt echter betwijfeld. We onderzochten de uitkomsten van een LPD3 in patenten die behandeld waren met DOC en een andere LPD en ontwikkelden een simpel prognostisch model om patenten te identificeren die geen of weinig voordeel hebben van een LPD3. Deze resultaten werden gepresenteerd in **Hoofdstuk 9**. We zagen een mediane OS van 6,5 maanden in de 1.011 patiënten met progressie op LPD2. 602 patiënten (60%) werden behandeld met LPD3. Hoewel deze patiënten betere prognostische factoren hadden dan patiënten zonder LPD3, was de behandelduur van LPD3 kort (3 maanden) en slechts 22% had een PSA-respons. We creëerden een simpele prognostische score gebaseerd op zeven variabelen die negatief geassocieerd waren met OS: ECOG performance status van 1 en ≥2, gebruik van opioïden, viscerale metastasen, hoog PSA, alkalisch fosfatase en lactaatdehydrogena-

se. Patiënten geclassificeerd in de hogere risicogroepen hadden minder voordeel van LPD3 namelijk kortere overleving, kortere behandelduur en minder PSA-respons. Het prognostisch model kan artsen helpen met de onderverdelen van patiënten in een van de vier risicogroepen met verschillende uitkomsten in overleving en dus ondersteunen bij de behandelkeuze. Goede patiëntselectie voor LPD3 is cruciaal bij het verbeteren van uitkomsten en kwaliteit van leven en het voorkomen van onnodige toxiciteit en kosten.

Behandelkeuzes worden lastiger na verscheidende voorgaande behandellijnen vooral bij patiënten met tekenen van agressieve ziekte. In deze fase de levensverwachting is kort en het einde van het leven (end-of-life of EOL) is nabij. Keuzes in deze fase moeten gemaakt worden op basis van effectiviteit en veiligheid en moeten uiterst patiëntgericht zijn. De nadruk moet verschuiven van een actieve behandeling met LPDs naar een symptoomgerichte behandeling. Intensieve oncologische zorg moet voorkomen worden, gezien het weinig voordeel heeft op de overleving maar wel gepaard gaat met hoge kosten. In **Hoofdstuk 10** rapporteerden we de intensieve zorg gedefinieerd als het gebruik van LPDs en zorggebruik in het ziekenhuis in de EOL (de laatste drie maanden van het leven). 41% van alle CRPC-patiënten ervaarde intensieve zorg in de laatste drie maanden, vooral veroorzaakt door ziekenhuisopnames. De mate van LPD-behandeling was 39% in de EOL fase, maar slechts 15% startte met een nieuwe LPD-behandeling. Nieuw gestarte LPD-behandeling was vooral ABI+P of ENZ, die voor artsen mogelijk de voorkeur hebben boven chemotherapie omdat ze minder impact hebben (orale versus intraveneuze toediening) en mildere toxiciteitsprofielen. Patiënten die een LPD gebruikten in de laatste drie maanden werden vaker opgenomen in het ziekenhuis. Hoewel LPDs in deze fase van ziekte weinig toevoegen aan de overleving, kunnen ze symptomen voorkomen en kwaliteit van leven behouden. De voordelen van het starten of continueren van een LPD in de laatste levensfase moet afgewogen worden tegen de mogelijke nadelen zoals hospitalisatie. Sterke voorspellers voor intensieve zorg waren een korte periode tussen de CRPC-diagnose en de EOL, lagere leeftijd, betere performance status en voorgaande LPD behandeling. Een gespecialiseerd palliatief team moet een belangrijke rol spelen in de organisatie van de zorg in individuen die waarschijnlijk snel zullen overlijden aan gemetastaseerde ziekte. Ondanks dat intensieve zorg slecht te verantwoorden is door de hoge economische kosten en weinig effect op levensduur, moet toekomstig onderzoek aantonen of er mogelijk voordeel is op de kwaliteit van leven van zowel patiënten als hun verzorgers.

We hebben onze ervaringen laten zien met het gebruik van RWE om de kwaliteit van zorg op de kerndimensies effectiviteit, veiligheid en patiëntgerichtheid te evalueren. Samenvattend, de uitkomsten in de dagelijkse praktijk verschillen van gerandomiseerde studies, omdat de patiëntkarakteristieken, behandelingen en monitoring verschillen. RWE moet complementair aan RCTs gebruikt worden en opgenomen worden in de richt-

lijnen om de klinische besluitvorming te ondersteunen. RWE kan voorzien in informatie over uitkomsten gerelateerd aan specifieke behandelingen en patiëntkarakteristieken waardoor het mogelijk wordt om de beste behandeling voor een individuele patiënt te kiezen.

EVALUATIE VAN DE KWALITEIT VAN GEZONDHEIDSZORGSYSTEMEN

De betekenis van kwaliteit van zorg verschilt per niveau van de gezondheidszorg waarop het onderzocht wordt. Kwaliteit van gezondheidszorgsystemen wordt gedefinieerd als goede toegang tot kwalitatieve gezondheidszorgdiensten (geëvalueerd door de kerndimensies) om gezondheidsdoelen op populatieniveau te bereiken. De middelen die nodig zijn om deze doelen te bereiken bepalen de efficiëntie van de systemen. Toegankelijkheid en efficiëntie worden geëvalueerd in **Hoofdstuk 11**.

Toegankelijkheid kan onderzocht worden in de tijd of per geografische lokalisatie. Ondanks dat de middelen voor CRPC snel na markttoelating toegepast werden in de dagelijkse praktijk, kan RWE ook aangeven of er problemen zijn met deze uptake. Een voorbeeld: 40% van onze patiënten die in aanmerking kwamen voor een behandeling met docetaxel werden niet met docetaxel behandeld in de tijdsperiode dat dit de enige mogelijke behandeling was. Variatie in behandelkeuzes tussen ziekenhuizen is een teken van geografische toegankelijkheid. Variatie is echter niet onwenselijk als de uitkomsten gelijk zijn. Wij vonden geen relatie tussen ziekenhuiskarakteristieken en uitkomsten.

Efficiëntie kan gebruikt worden om de effectiviteit op een populatieniveau te bepalen, waarbij niet alleen gekeken wordt naar de uitkomsten maar ook naar de kosten. Kosteneffectiviteitsanalyses (KEA) kunnen de verschillen in efficiëntie tussen behandelingen en sequenties van behandelingen aantonen. De behandelsequenties bij CRPC-patiënten levereden tussen de 1,3 en 2,0 voor kwaliteit gecorrigeerde levensjaren (quality-adjusted life years of QALYs) op en kosten tussen de €60.000 en €150.000. Er was weinig variatie in deze uitkomsten tussen sequenties met een gelijk aantal behandelingen. KEAs kunnen gebruikt worden door beleidsmakers op een maatschappelijk niveau, maar value-based health care (VBHC) is belangrijker voor de patiënt. De ‘value’ in VBHC kan niet door een enkele uitkomstmaat bepaald worden. RWE kan de zorgen voor de input voor VBHC en hierdoor helpen om de behandeling of te stemmen op de individuele patiënt.

DE TOEKOMST

Een ziekte specifiek register is een belangrijke bron van gegevens die nodig zijn voor het evalueren van kwaliteit van zorg. Echter was onze ervaring niet zonder uitdagingen.

Een uitdaging was het verzamelen van data en zorgen dat deze data van goede kwaliteit waren. Het handmatig identificeren en verzamelen van gegevens uit elektronische patiëntendossier en het overzetten van deze gegevens naar de dataopslag kost veel tijd en is vatbaar voor fouten. Toekomstige registers moeten kijken naar de mogelijkheden voor het automatisch verzamelen van data gebruikmakend van ICT-oplossingen. Vooral in de oncologie veranderen de behandellandschappen snel, waardoor snelle data verzameling die snel aan te passen is aan deze veranderingen wenselijk is. Een vooropgesteld plan voor de kwaliteitscontrole is nodig om de kwaliteit van de data te garanderen. Een andere uitdaging is het feit dat analyses van de data vatbaar zijn voor 'confounding' (verstoringen). Onderzoekers moeten dan ook de mogelijkheden en onmogelijkheden van RWE in gedachte houden bij het analyseren van de data.

Het uiteindelijke doel van de gezondheidszorg is dat de patiënt de beste mogelijke zorg in zijn situatie ontvang. RWE uit registers kan mogelijk helpen om dit doel te bereiken.

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PhD portfolio

List of publications

About the author

PHD PORTFOLIO

PhD candidate	Malou Kuppen
Institute	Erasmus School of Health Policy and Management Erasmus University Rotterdam, The Netherlands
PhD period	2015-2022
Promotors	prof. dr. C.A. Uyl-de Groot prof. dr. W.R. Gerritsen

PhD training

- European Society of Medical Oncology annual congress. ESMO: Barcelona, Spain. 2019
- 10th European Multidisciplinary Meeting on Urologic cancer. EMUC: Amsterdam, the Netherlands. 2018
- European Society of Medical Oncology annual congress. ESMO: Munich, Germany. 2018
- Economic evaluations of medical interventions. ME-TA: Sint-Martens-Latem, Belgium. 2018
- European Association of Urology 33rd annual congress. EAU: Copenhagen, Denmark. 2018
- Use of propensity scores in observational studies of treatment effects. ISPOR short course: Glasgow, United Kingdom. 2017
- Adjusting for time-dependent confounding and treatment switching bias in observational studies and clinical trials. ISPOR short course: Glasgow, United Kingdom. 2017
- 20th annual European congress. ISPOR: Glasgow, United Kingdom. 2017
- Annual congress. DUOS: Utrecht, the Netherlands. 2016
- Health Economics. NIHES summer course: Rotterdam, the Netherlands. 2016
- Basic course on Regulations and Organisation for clinical investigators (BROK). NFU: Rotterdam, the Netherlands. 2016

Teaching activities

- Bachelor theses: bachelor programme Erasmus School of Health Policy and Management, Erasmus University Rotterdam. Supervisor. 2016-2019
- Participating in Health Technology Assessment research: master programme European Master in Health Economics and Management, Erasmus University Rotterdam. Presenter. 2015-2019
- Introduction in Health Policy and Management: bachelor programme Erasmus School of Health Policy and Management, Erasmus University Rotterdam. Tutor. 2015-2017

Podium presentations

- Post docetaxel survival in metastatic castration-resistant prostate cancer (mCRPC) is improving in the Netherlands [award for best unmoderated poster]. 10th European Multidisciplinary Meeting on Urologic cancer: Amsterdam, the Netherlands. 2018
- Outcomes of crossover between androgen receptor targeting drugs in the Castration-resistant Prostate cancer RegIstry (CAPRI) in the Netherlands. EAU 33rd annual congress: Copenhagen, Denmark. 2018
- Use of new therapies and hospital admission near the end of life in castration-resistant prostate cancer (CRPC) in the Castration-resistant Prostate cancer RegIstry (CAPRI) in the Netherlands. ISPOR 20th annual European congress: Glasgow, United Kingdom. 2017
- Differences in trial and real-world populations in the Dutch Castration-resistant Prostate cancer RegIstry (CAPRI). RadboudUMC symposium: Nijmegen, Netherlands. 2016
- Differences in trial and real-world populations in the Dutch Castration-resistant Prostate cancer RegIstry (CAPRI) [award for best PhD presentation]. DUOS jaarsymposium: Utrecht, Netherlands. 2016

Poster presentations

- Treatment outcomes of 3rd treatment in real-world metastatic castration-resistant prostate cancer (mCRPC) population: results from the Dutch CAPRI-registry. ESMO annual congress: Barcelona, Spain. 2019
- Real-world use of radium-223 for treatment of metastatic castration-resistant prostate cancer (mCRPC): results from the Dutch CAPRI registry. ESMO annual congress: Barcelona, Spain. 2019
- Post docetaxel survival in metastatic castration-resistant prostate cancer (mCRPC) is improving in the Netherlands [award for best unmoderated poster]. 10th European Multidisciplinary Meeting on Urologic cancer: Amsterdam, the Netherlands. 2018
- Enzalutamide with or without prior anti-androgens for castration-resistant prostate cancer (CRPC): results from the Dutch CAPRI Registry. 10th European Multidisciplinary Meeting on Urologic cancer: Amsterdam, the Netherlands. 2018
- Patient reported outcomes in the castration-resistant prostate cancer registry (PRO-CAPRI). ISPOR 21st annual European congress: Barcelona, Spain. 2018
- Symptomatic skeletal related events (SSE) and SSE-free survival in real-word castration-resistant prostate cancer patients. ESMO annual congress: Munich, Germany. 2018
- Cabazitaxel treatment in metastatic castration-resistant prostate cancer (mCRPC) clinical trials compared to usual care in CAPRI. ESMO annual congress: Munich, Germany. 2018

- Outcomes of crossover between androgen receptor targeting drugs in the Castration-resistant Prostate cancer RegIstry (CAPRI) in the Netherlands. EAU 33rd annual congress: Copenhagen, Denmark. 2018
- Guideline adherence in docetaxel treatment of castration-resistant prostate cancer (CRPC) patients in a real-world population: Castration-resistant Prostate cancer RegIstry (CAPRI) in the Netherlands. ISPOR 20th annual European congress: Glasgow, United Kingdom. 2017
- Use of new therapies and hospital admission near the end of life in castration-resistant prostate cancer (CRPC) in the Castration-resistant Prostate cancer RegIstry (CAPRI) in the Netherlands. ISPOR 20th annual European congress: Glasgow, United Kingdom. 2017

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Scientific publications

Westgeest HM, **Kuppen MCP**, Van den Eertwegh AJM, Van Oort IM, Coenen JLLM, Van Moorselaar RJA, Aben KKH, Bergman AM, Ten Bokkel Huinink D, Van den Bosch J, Hendriks MP, Lampe MI, Lavalaye J, Mehra N, Smilde TJ, Somford DM, Tick L, Weijl NI, Van de Wouw AJ, Gerritsen WR, Uyl-de Groot CA. High-intensity care in the end-of-life phase of castration-resistant prostate cancer patients: results from the Dutch CAPRI registry. J Palliat Med 2021: [Online ahead of print]

Westgeest HM, **Kuppen MCP**, Van den Eertwegh AJM, De Wit R, Bergman AM, Van Moorselaar RJA, Coenen JLLM, Van den Bergh ACM, Somford DM, Mehra N, Van Oort IM, Aben KKH, Gerritsen WR, Uyl-de Groot CA. The effects of new life-prolonging drugs for metastatic castration-resistant prostate cancer (mCRPC) patients in a real-world population. Prostate Cancer Prostatic Dis 2021;24(3):871-879.

Schmid S, Omlin A, Higano C, Sweeney C, Martinez Chanza N, Mehra N, **Kuppen MCP**, Beltran H, Condeduca V, Vargas Pivato de Almeida D, Cotait Maluf F, Oh WK, Tsao CK, Sartor O, Ledet E, Di Lorenzo G, Yip SM, Chi KN, Bianchini D, De Giorgi U, Hansen AR, Beer TM, Pernele L, Morales-Barrera R, Tucci M, Castro E, Karalis K, Bergman AM, Linh Le M, Zürrer-Härdi U, Pezaro C, Suzuki H, Zivi A, Klingbiel D, Schär S, Gillessen S. Activity of platinum-based chemotherapy in patients with advanced prostate cancer with and without DNA repair gene aberrations. JAMA Netw Open 2020;3(10):e2021692.

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Notohardjo JCL, **Kuppen MCP**, Westgeest HM, van den Eertwegh AJM, van Moorselaar RJA, Mehra N, Coenen JLLM, van Oort IM, van den Bergh ACM, Aben KKH, Somford DM, de Wit R, Bergman AM, Lavalaye J, Uyl-De Groot CA, Gerritsen WR. Treatment outcomes of 3rd treatment in real-world metastatic castration-resistant prostate cancer (mCRPC) population: results from the Dutch CAPRI-registry. Annals of Oncology 2019;30(suppl 5):v325-v355. Presented at ESMO 2019 Annual congress Barcelona (poster)

Westgeest H, **Kuppen M**, Van Den Eertwegh A, Van Moorselaar R, Mehra N, Coenen J, Van Oort I, Van Den Bergh A, Aben K, Somford D, De Wit R, Bergman A, Lavalaye J, Uyl-De Groot C, Gerritsen W; Post-docetaxel survival in metastatic castration-resistant prostate cancer (mCRPC) is improving in the Netherlands. European Urology Suppl 2018;17(14):e2858. Presented at 10th European Multidisciplinary Meeting on Urological Cancers Amsterdam (poster: award for best unmoderated poster)

Kuppen M, Westgeest H, Van Den Eertwegh A, Van Moorselaar R, Mehra N, Coenen J, Van Den Bergh A, Aben K, Bergman A, Somford D, Lavalaye J, Uyl-De Groot C, Gerritsen W; Enzalutamide with or without prior anti-androgens for castration-resistant prostate cancer (CRPC): results from the Dutch CAPRI Registry. European Urology Suppl 2018;17(14):e2891. Presented at 10th European Multidisciplinary Meeting on Urological Cancers Amsterdam (poster)

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Kuppen MCP, Westgeest HM, van den Eertwegh AJM, van Moorselaar RJA, Mehra N, Coenen JLLM, van Oort IM, van den Bergh ACM, Aben KKH, Somford DM, Lavalaye J, Gerritsen WR, Uyl-de Groot CA. Patient Reported Outcomes in the Castration-resistant Prostate cancer RegIstry (PRO-CAPRI). Value in Health 2018;21(suppl 3):S80. Presented at 21th Annual European Congress ISPOR Barcelona (poster).

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Kuppen MCP, Westgeest HM, van den Eertwegh AJM, van Moorselaar RJA, de Wit R, van Oort IM, Aben KKH, Verhoeven R, van den Bergh ACM, Coenen JLLM, Uyl-De Groot CA, Gerritsen WR. Outcomes of crossover between androgen receptor targeting drugs in the Castration-resistant Prostate cancer RegIstry (CAPRI). Eur Urol Suppl 2018;17(2):e878. Presented at 33rd Annual EAU Congress Copenhagen (podium)

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Westgeest HM, **Kuppen MCP**, van den Eertwegh AJM, Gerritsen WR, Uyl-de Groot CA. Guideline adherence in docetaxel treatment of castration-resistant prostate cancer (CRPC) patients in a real-world population: the Castration-resistant Prostate cancer RegIstry (CAPRI) in the Netherlands. Value in Health 2017;20(9):A471–A472. Presented at 20th Annual European Congress ISPOR Glasgow (poster)

Policy-related publications

Kuppen MCP, Westgeest HM, van den Eertwegh AJM, Gerritsen WR, Uyl-de Groot CA. Meaningful care: meaningful use of expensive treatments in patients with castration-resistant prostate cancer [in Dutch: Zinnige gebruik van geneesmiddelen bij patiënten met castratie refractair prostaatcarcinoom]. Advise to Dutch National Health Care Institute, 2016

ABOUT THE AUTHOR

Malou Kuppen was born in Nijmegen on May 6th 1989. In 2007 she started the bachelor programme of Medicine at Maastricht University (2007-2010). In 2013, she obtained her master's degree in Medicine and started as an intern (in Dutch: ANIOS, arts-assistent niet in opleiding) at the department of Urology at the Catharina Hospital in Eindhoven, the Netherlands. Since 2015 she works as a researcher for the CAPRI registry at the institute for Medical Technology Assessment (iMTA) and Erasmus School of Health Policy and Management (ESHPM), Erasmus University Rotterdam. She combined research with clinical work at the department of Medical Oncology at Radboudumc. Her work focusses on the real-world outcomes of castration-resistant prostate cancer, especially clinical outcomes, health-related quality of life, and economic evaluations. During her PhD trajectory she further developed an interest in the field of radiation oncology and she continued her studies as a resident (in Dutch: AIOS, arts-assistant in opleiding) at the department of Radiation Oncology at Maastro from January 2020 onwards.

DANKWOORD

Dit proefschrift was niet tot stand gekomen zonder de steun van velen. Een aantal wil ik in dit laatste hoofdstuk bedanken.

Allereerst mijn promotoren. Carin, niet alleen was jij mijn hoop in bange dagen toen er een ziektemodel gemaakt moest worden, maar je gaf me het vertrouwen het proefschrift tot een goed einde te brengen. Bedankt daarvoor! Je bent als begeleider enorm betrokken bij het reilen en zeilen van je PhD's, iets wat ik enorm waardeer.

Winald, je bent een bron van kennis als het gaat om het doen van onderzoek en je ideeën zijn eindeloos. Als er geen uitweg meer mogelijk leek, wist jij altijd weer een creatieve oplossing te vinden door het van een andere kant te belichten. Bedankt ook voor al je wijze raad!

Hans, ik kan niet anders zeggen dan dat dit proefschrift er niet was geweest zonder jou. Dank voor het vertrouwen om CAPRI onder jouw vleugels door te zetten. De wekelijkse koffiemomentjes op de oranje bank waren perfect om de dagelijkse koers te bepalen en te spuien. Ook wil ik je bedanken voor alles wat ik van je heb mogen leren buiten het onderzoek om. Soms moet je een onconventionele route nemen om je doel te bereiken.

Graag wil ik de commissieleden bedanken voor het lezen van het proefschrift en het opponeren tijdens de verdediging.

De leden van de stuurgroep, jullie kritische blik bij de vergaderingen hield ons scherp en bij de les. De kwaliteit van dit proefschrift is een stuk hoger door jullie inbreng. Daarnaast ben ik alle coauteurs dankbaar voor het meelezen en de feedback tijdens schrijfproces.

De CAPRI-data waren er niet geweest zonder de inzet van vele datamanagers als ook de deelnemende ziekenhuizen, lokale onderzoekers, alle andere betrokkenen en degene die dit register financieel mogelijk hebben gemaakt. Een speciale plek is gereserveerd voor alle deelnemende patiënten. Hun deelname zorgde voor inzicht in de dagelijkse praktijk en helpt met verbeteringen voor toekomstige patiënten.

Het nieuwe CAPRI-3 team, jullie enthousiasme is aanstekelijk en the future of CAPRI is bright!

Alle collega's in Rotterdam en Nijmegen, jullie hebben mijn nomadisch bestaan dragelijk gemaakt! Ondanks dat ik er vaker niet dan wel was, voelde ik me toch onderdeel van het team.

Maarten, of het nu ging om dataverzameling en statistiek of een goede kop koffie, je was altijd bereid te luisteren en te sparren. Ik heb vooral genoten van ons werkbezoek aan Heidelberg en ons optreden tijdens de EAU in Kopenhagen.

Speciale dank ook voor iedereen bij ESHPM en iMTA, in het speciaal het Rotterdams registerclubje en mijn kamergenoten. Dank voor alle momenten waarop ik gebruik heb mogen maken van jullie kennis. Het multidisciplinaire is van onschatbare waarde!

Alle nieuwe collega's bij Maastro en CZE, wat een warm welkom na jaren onderzoek! Jullie hebben me de ruimte gegeven om dit proefschrift af te ronden, waarvoor hartelijk dank. Ik zal vanaf nu minder over prostaten en euro's praten, beloofd.

Degenen die het dichtst bij je staan, moeten altijd het langst wachten:

Lieve vrienden, of het nu gaat om digitale meetings met de andere kant van de wereld, lunchen in Utrecht met het crimineel quintet, vogelen in de Biesbosch, avondjes Ticket to Ride of gewoon een goede kop koffie, jullie boden een welkome afleiding van de dagelijkse sleur tijdens het maken van dit proefschrift. Nu het klaar is, komt er meer tijd voor leuke momenten!

Lieve (schoon)familie, jullie zijn altijd geïnteresseerd geweest in de vorderingen van "het boekje". Hier issie dan! Lieve ome Wim, wat had ik dit resultaat ook graag aan jou laten zien…

Lieve pap en mam, wat moet ik hier dan nog zeggen om jullie te bedanken? Jullie zijn er altijd voor ons geweest, en nog. Dank dat jullie alles laten vallen als er nood aan de man is. Zonder alle uurtjes aan de telefoon vanaf onbekende snelwegen was dit boekje er ook niet geweest.

Liefste Fallon, de laatste regels van dit proefschrift zijn voor jou: hou van jou <3