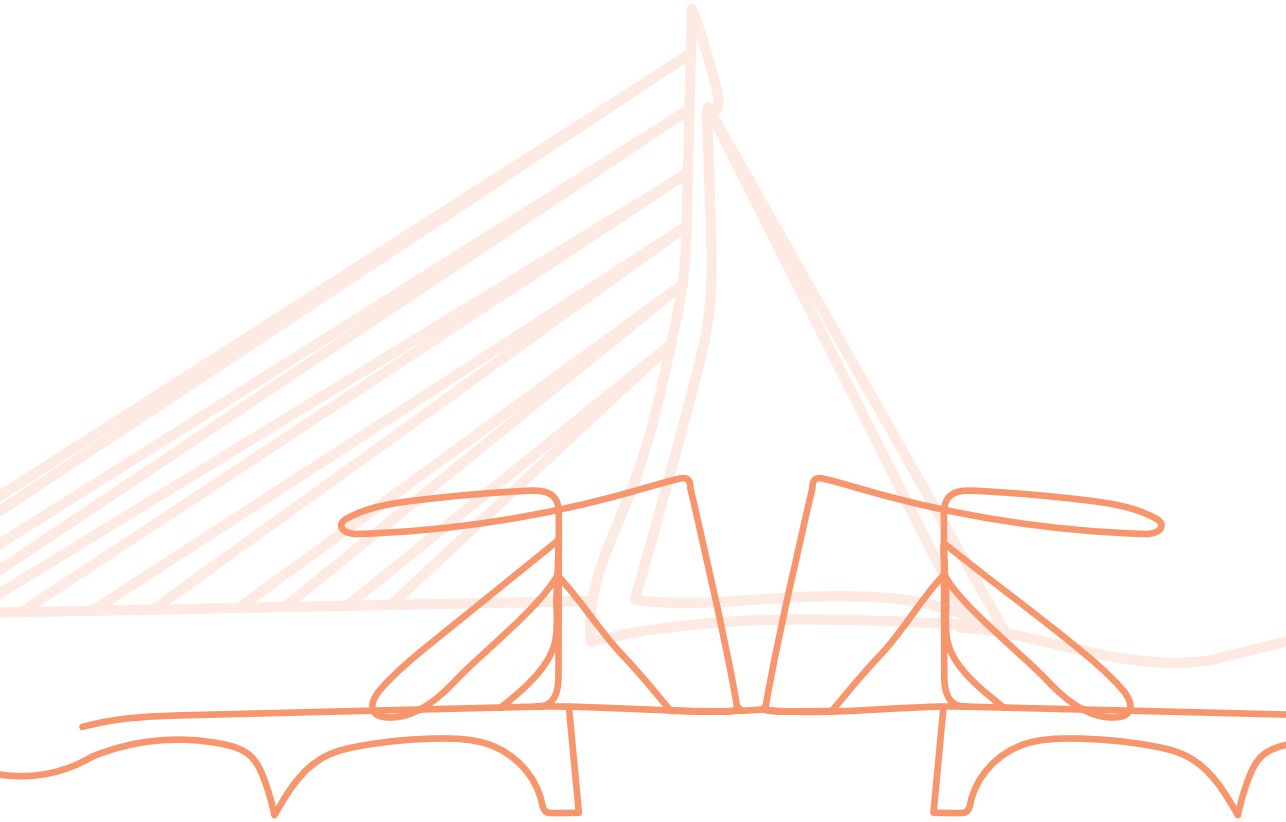
AND NOW FOR REAL

OUTCOMES OF CASTRATION-RESISTANT PROSTATE CANCER PATIENTS IN THE NETHERLANDS



HANS WESTGEEST

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Further reading:
Quality of care in castration resistant prostate cancer: a deep dive into the role of real world evidence (Malou Kuppen, 2022; ISBN 978-94-6361-6218)

And Now For Real: Outcomes Of Castration-resistant Prostate Cancer Patients In The Netherlands.

En nu in het echt: uitkomsten van castratie-resistent prostaatkanker patiënten in Nederland.

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Opgedragen aan Jitka, Joop en Lenie;
aan de patiënten die ik heb ontmoet
zij inspireren mij elke dag opnieuw

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CHAPTER 1

General introduction

My intrinsic motivation for this research came from questions arising from observations in my work as medical oncologist in the last ten years. First I worked as medical oncologist in training in an academic tertiary center, later as medical oncologist in a large teaching hospital in the Netherlands.

In the outpatient clinic, as well as in the oncology wards and outside the hospital, several thoughts have arisen. I observed that not all patients derive benefit from systemic treatment. Toxicity and complications are common in oncology treatment. And I started asking myself: what would I decide if I was a patient and in a palliative treatment setting? Moreover, I feel responsible for the ongoing debate on the financial sustainability of oncology treatment.

1. If a treatment has proven efficacy in clinical trials, will it work for my patient?
2. Do new treatments improve outcomes for my patient with regards to survival, quality of life and end of life care?
3. How can we improve routine care in domains not covered by clinical trials?

The answers may come from real world evidence. I started my research in castration-resistant prostate cancer because of the introduction of four new life prolonging drugs in the years 2010-2014 in the Netherlands.

A brief history of systemic treatment of metastatic prostate cancer

The first case of prostate cancer by histological examination was described by dr. J. Adams from London Hospital in 1853[1]. He described prostate cancer as a very rare disease at that time. At present time, prostate cancer is the second most commonly diagnosed cancer and the sixth leading cause of cancer death among men worldwide[2]. In the Netherlands, prostate cancer is the fourth most commonly diagnosed cancer (2019: 13,600 patients), however in males above age 45 it is the most common diagnosed cancer[3]. It is also the second leading cause of death among men in the Netherlands (2018: 2,896 patients)[3]. The incidence has risen since the use of Prostate-Specific Antigen (PSA) testing in blood provided an important diagnostic tool to detect prostate cancer. Screening by PSA testing and also asymptomatic patients resulted in an increase of incidence since the early 1990s (see Figure 1).

Back in 1853, Adams was correct in saying prostate cancer was a very rare disease, since life expectancy in the United Kingdom did not exceed 50 years until 1900 and prostate cancer is extremely rare below the age of 50 (see Figure 1)[4]. However, in the 20th century life expectancy increased substantially. The first to treat metastatic prostate cancer in a systematic manner was dr. Charles Huggins (1901-1997). In 1941, he reported on

serum markers of disease (serum phosphatases) and the beneficial effect of surgical castration and estrogen administration in metastatic prostate cancer. He also showed the opposite effect of androgen administration[5]. Then, he reported on the clinical findings of 45 men: in total, 31 men had a sustained improvement lasting as long as 30 months; nine men had a temporary improvement followed by recurrence of symptoms; and in five men there was no improvement following castration. Interestingly, hot flashes were a favorable prognostic sign[6]. Later he described the beneficial palliative effects on pain, weight, appetite and hematocrit. Estrogen treatment showed similar effects, but cardiovascular and thrombo-embolic adverse events were frequent. He was awarded the Nobel prize for his work in 1966[7].

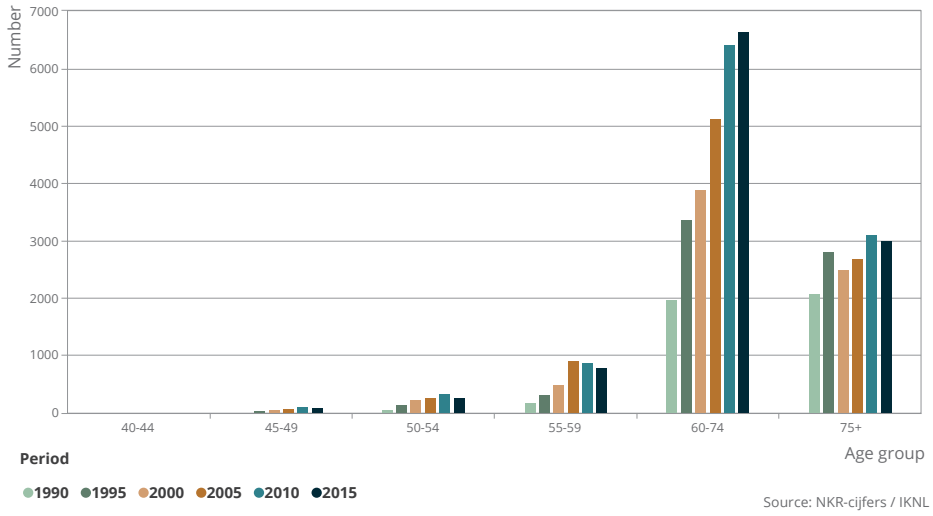

Figure 1. Incidence of prostate cancer in the Netherlands, by age group, in the years 1990-2015

In the 1970s, the effect of Luteinizing-hormone releasing hormone (LHRH) agonists was reported by dr. Schally (1926-) and others[8]. Chronic administration of LHRH agonists resulted in a decrease of the sex hormones Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) and subsequently the decrease of serum testosterone[9]. Dr. Schally was also rewarded the Nobel prize, in 1977. Nowadays, lowering testosterone (which is an important growth factor for prostate cancer cells) by medical castration with LHRH agonists (or antagonists) is still the cornerstone in treating metastatic prostate cancer[10].

The androgen receptor was discovered in the 1960s and led to the search of anti-androgens[11]. Cyproteron acetate was one of the first, to be followed by other

agents including bicalutamide [12-14]. Although overall survival benefit had not been demonstrated, use of these agents (as monotherapy or combined with castration) was widespread because of favorable toxicity profiles compared to castration, a progression free survival benefit and PSA responses.

Prostate cancer that progresses despite androgen deprivation therapy (ADT), either metastatic (m) or non-metastatic (nm), is defined as castration-resistant prostate cancer (CRPC). Various terms have been used to describe and define this disease state. In 2014 the European Association of Urology (EAU) guidelines defined CRPC as prostate cancer progressing despite castrate serum levels of testosterone, and despite consecutive hormonal manipulations followed by antiandrogen withdrawal[15]. However, the definition was simplified in the 2017 update of the EAU guidelines and the consecutive hormonal manipulations were discarded from the definition[10]:

- CRPC is defined as castrate serum testosterone <50 ng/dl or 1.7 nmol/l plus one of the following types of progression:
- Biochemical progression: Three consecutive rises in PSA 1 week apart, resulting in two 50% increases over the nadir, and PSA >2 ng/ml
- Radiologic progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumors (RECIST).
- Symptomatic progression alone must be questioned and subject to further investigation; it is not sufficient for diagnosing CRPC.

Strategies to overcome this progression included combined androgen blockade (castration combined with anti-androgen treatment). Although initially only an increased progression free survival was observed, up to 27 randomized phase III trials focused on this approach (and only three showed positive results) and 5 meta-analyses followed to conclude no survival benefit from combined androgen blockade[16]. This was known in the early 2000s, but the treatment strategy is still used in daily practice.

In the 2010s further research in androgen receptor targeting drugs (ART) resulted in the discovery and widespread use of enzalutamide for metastatic CRPC[17,18]. This was followed recently by other new generation ART for hormone sensitive prostate cancer (HSPC) and non-metastatic CRPC such as apalutamide and darolutamide[19,20].

Additional blockade of testosterone production in the adrenal glands had been sought by bilateral adrenalectomy, but surgical complexity prevented widespread use. Medical suppression of adrenal steroidogenesis was discovered in 1982. Ketoconazole,

developed as an antifungal agent, was shown to block adrenal steroid synthesis[21]. It has been used occasionally and off-label for CRPC treatment until the discovery of the more potent drug abiraterone acetate 30 years later. Abiraterone acetate is a CYP17 inhibitor (a combination of 17α-hydrolase and 17,20-lyase inhibition), and it decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the cancer cells. Abiraterone acetate is used with prednisolone to prevent drug-induced hyperaldosteronism[22].

Cytotoxic chemotherapy for cancer treatment has been used since the 1940s. The first studies in metastatic prostate cancer were done in the 1950s and 1960s, but until the 1990s studies were limited by small sample sizes, subjective response criteria and negative survival results. Mitoxantrone/prednisone became the first Food and Drug Administration (FDA, United States) approved chemotherapy for the treatment of pain in mCRPC in 2000. The approval was based on randomized trials versus a corticosteroid alone, although no survival difference was observed [23,24]. In 2004 docetaxel/prednisone was the first available life-prolonging drug (LPD) for symptomatic mCRPC patients[25]. This combination improved median overall survival compared to mitoxantrone/prednisone from 16.3 to 19.2 months (updated survival results)[26]. Docetaxel is a semi-synthetic taxane, and taxanes act by promoting and stabilizing microtubule assembly leading to inhibition of mitotic cell division. However, the mechanism of action was shown to inhibit the androgen receptor signaling axis and this may be the predominant mechanism of action[27].

Most patients (90%) with mCRPC have bone metastases[28]. Skeletal events (bone pain, pathological fractures, spinal cord compression and need for radiotherapy or surgery) are common and occur in approximately half of patients[29]. Bone resorption inhibition, either by bisphosphonates (zoledronic acid) or RANK-L inhibitors (denosumab), have shown to delay or prevent skeletal events. Radionuclides may accumulate in skeletal metastases and thereby radiate these metastases in a highly specific manner. Beta-emitting radionuclides have been shown to reduce bone pain (such as Samarium-153), whereas the alpha-emitting radionuclide Radium-223 has been shown to improve survival[30].

The discovery of the mechanisms androgen receptor blockade, adrenal androgen synthesis blockade, the discovery of taxanes and the focus on bone health led to further improvement and a myriad of new effective drugs. Between 2011 and 2014, new life-prolonging drugs (LPD) for mCRPC (cabazitaxel[31], abiraterone[32,33], enzalutamide[17,18] and radium-223[30]) were introduced in the Netherlands (see Table 1).

Table 1. Treatment options for HSPC and CRPC in the Netherlands, bases on CieBom appraisals.

Population	Trial	Indication	Treatment arm	Comparator	End point (OS) (months)		CieBOM appraisal	
HSPC	CHAARTED	primary metastatic prostate cancer	ADT+docetaxel	ADT	57.6 vs 44.0	HR 0.61, 95% CI 0.47-0.80, p<0.001	July	2016
	STAMPEDE	metastatic prostate cancer or high risk locally advanced prostate cancer	ADT+docetaxel	ADT	81.0 vs 71.0	HR 0.78, 95% CI 0.66-0.93, p=0.006	July	2016
	GETUG-15	metastatic prostate cancer	ADT+docetaxel	ADT	58.9 vs 54.2	HR 1.01, 95% CI 0.75-1.36, p=0.955	NA	
	LATITUDE	bone metastatic prostate cancer and at least two high risk criteria	ADT+abiraterone	ADT	83% vs 76% (3-yr OS)	HR 0.63, 95% CI 0.52-0.76, p<0.001	April	2018
	STAMPEDE	metastatic prostate cancer or high risk locally advanced prostate cancer	ADT+abiraterone	ADT	66% vs 49% (3-yr OS)	HR 0.62, 95% CI 0.51-0.76, p<0.001	April	2018
	TITAN	metastatic prostate cancer or high risk locally advanced prostate cancer	ADT+apalutamide	ADT	66% vs 49% (3-yr OS)	HR 0.62, 95% CI 0.51-0.76, p<0.001	April	2018
CRPC	TAX-327	1L mCRPC	docetaxel	mitoxantrone	18.9 vs 16.5	HR 0.76, 95% CI 0.62-0.94, p=0.009	June	2005
	SWOG9916	1L mCRPC	docetaxel+estramustine	mitoxantrone	17.5 vs 15.6	HR 0.80, 95% CI 0.67-0.97, p=0.020	June	2005
	TROPIC	post-docetaxel mCRPC	cabazitaxel	mitoxantrone	15.1 vs 12.7	HR 0.70, 95% CI 0.59-0.83, p<0.001	July	2011
	COU-AA-301	post-docetaxel mCRPC	abiraterone	placebo	14.8 vs 10.9	HR 0.66, 95% CI 0.55-0.78, p<0.001	March	2012

Table 1. (Continued)

Population	Trial	Indication	Treatment arm	Comparator	End point (OS) (months)		CieBOM appraisal	
	COU-AA-302	1L mCRPC	abiraterone	placebo	34.7 vs 30.3	HR 0.81, 95% CI 0.70-0.93, p=0.003	November	2015*
	AFFIRM	post-docetaxel mCRPC	enzalutamide	placebo	18.4 vs 13.6	HR 0.63, 95% CI 0.53-0.75, p<0.001	December	2013
	PREVAIL	1L mCRPC	enzalutamide	placebo	NR vs 31.0	HR 0.73, 95% CI 0.63-0.85, p<0.001	November	2014
	ALSYMCA	1L mCRPC and post-docetaxel mCRPC	Radium-223	placebo	14.9 vs 11.3	HR 0.70, 95% CI 0.58-0.83, p<0.001	February	2014
	SPARTAN	nmCRPC	apalutamide	placebo	40.5 vs 16.2 (MFS)	HR 0.28, 95% CI 0.23-0.35, p<0.001	February	2019**
	PROSPER	nmCRPC	enzalutamide	placebo	36.6 vs 14.7 (MFS)	HR 0.29, 95% CI 0.24-0.35, p<0.001	February	2019**
	ARAMIS	nmCRPC	darolutamide	placebo	40.4 vs 18.4 (MFS)	HR 0.41, 95% CI 0.34-0.50, p<0.001	June	2020**
	PROFOUND	mCRPC post-abiraterone or enzalutamide; *BRCA1*, *BRCA2* or *ATM* mut	olaparib	ENZ or ABI	19.1 vs 1	HR 0.69, 95% CI 0.50-0.97, p=0.02	November	2020

* negative appraisal in 2013; ** could not be approved because MFS is not an established endpoint for approval.
Abbreviations: HSPC – hormone sensitive prostate cancer; CRPC – castration resistant prostate cancer; mCRPC – metastatic CRPC; nmCRPC – non-metastatic CRPC; OS – overall survival; MFS – metastasis free survival; vs – versus; yr – year; HR – hazard radio; CI – confidence interval; 1L – first line; mut – mutated; ADT – androgen deprivation therapy;

From 2015, improvements in systemic therapy focused on metastatic hormone sensitive prostate cancer (HSPC) and the nmCRPC. Addition of six cycles of docetaxel or docetaxel/prednisone increased overall survival of mHSPC in the CHAARTED and STAMPEDE trials [34,35]. Despite one negative trial (GETUG-15)[36], in a meta-analysis this treatment resulted in a significant hazard ratio of 0.77 that translates to an absolute improvement in 4-year survival of 9% [37]. In addition, adding abiraterone/prednisone to androgen deprivation therapy for 2 years also improves survival in mHSPC (LATTITUDE and STAMPEDE). Finally, also enzalutamide and apalutamide have shown to improve survival in mHSPC patients when added to androgen deprivation therapy[19,38,39].

A new disease state is nmCRPC. This is defined as rising PSA and a castrate-level of testosterone, without metastases on conventional imaging (bone scintigraphy or CT-scan)[40]. Although ADT is indicated in metastatic prostate cancer, patients may present with nmCRPC when disease progression occurs on adjuvant ADT after curative radiotherapy, or when ADT is initiated based on PSA progression without manifest metastases. Trials with enzalutamide (PROSPER) and apalutamide (SPARTAN) have been conducted in this population and showed increased metastasis free survival (MFS), and also increased OS[41-43]. This new disease state challenges the premise that palliative treatment is monitored by improving symptoms and reducing measurable disease other than a biochemical tumor marker (PSA).

Prospective, randomized trials on sequencing are scarce. Phase III trials have shown that for treatment-naïve CRPC, abiraterone, enzalutamide, docetaxel and radium-223 are life prolonging options. Cabazitaxel, abiraterone, enzalutamide and radium-223 have been shown to improve survival in mCRPC patients who show progression on docetaxel. In the CARD study, patients who progressed after docetaxel and an androgen receptor targeting agent (ARTA; either abiraterone or enzalutamide) within one year, where randomized between cabazitaxel and the other ARTA. Cabazitaxel was shown to have superior outcomes [44].

At present, research focusses increasingly on targetable molecular alterations in cancer cells, including the androgen receptor pathway, PI3K-AKT-mTOR pathway and DNA damage repair genes[45]. Precision medicine, in which a targetable alteration is treated with a specific drug, arrives in daily practice with the results of the PROFOUND trial. In patients who had disease progression while receiving enzalutamide or abiraterone and who had alterations in genes with a role in homologous recombination repair, olaparib was associated with longer overall and progression-free survival and better measures of response and patient-reported end points than either enzalutamide or abiraterone[46].

Immune therapy has been studied for years in CRPC. The first FDA-approved LPD in this class was Sipuleucel-T, based on a study that showed increased OS despite no effect on PFS[47]. This treatment is complex to administer and has not been widely used in Europe and the Netherlands. Checkpoint inhibitors have been studied in mCRPC, but until now positive results are only found in specific subgroups and several trials have found negative outcomes[48,49]. Current trials with checkpoint inhibitors focus on specific subgroups.

Despite all advances, treatment of metastatic prostate cancer remains palliative. Optimal timing and sequencing remain challenging and is often not informed by robust evidence. Debate is ongoing on nmCRPC and the role of imaging, timing of treatment in asymptomatic patients, sequencing of LPDs , potential cross-resistance between LPDs and extrapolation of treatment outcomes in populations that are not studied well (such as older patients or patients with comorbidity). General principles in oncology are challenged: in palliative care, do we treat asymptomatic patients with potential toxic drugs? Do we treat patients without a radiographic parameter of response? Does early treatment result in better survival compared to deferred treatment? Since evidence is lacking, additional data from real world may help.

Efficacy, effectiveness and efficiency

"The benefits established in efficacy trials, usually randomized, controlled trials conducted under highly controlled circumstances with maximized internal validity, can frequently not be demonstrated in clinical practice at the community level"[50]

Evidence on efficacy answers the question "Can (or might) it work?" and describes the extent to which an intervention does more good than harm under ideal circumstances; evidence on effectiveness answers the question "Does it work in practice?" and describes the extent to which an intervention does more good than harm under usual circumstances. To conclude, evidence on cost-effectiveness answers the question "Is it worth it?" and describes the effect of an intervention in relation to the resources it consumes[51].

Clinical trials are designed to maximize the internal validity and these trials eliminate factors such as doctor-patient relationship, placebo effects and patient preference (by blinding, placebo-control and exclusion of patients and clinicians with strong treatment preferences)[52]. This leads to increased internal validity and will provide evidence on efficacy. However, it will often lead to incorrect estimation of treatment effects in clinical practice, especially for patient centered outcomes, and thus is often not informative on effectiveness.

Looking back on the history of treatment of metastatic prostate cancer, many advances have been made and many lessons can be learned. Last decades, more patients are treated, and if treated they are treated with multiple drugs, earlier in the disease and have better treatment outcomes – leading to a longer duration of treatment. The impact of longer duration of treatment affects not only survival, but also quality of life and (on a population level) financial toxicity.

Relevant treatment outcomes in oncology include survival, time to disease progression, tumor response, toxicity and quality of life. Survival, progression, response and to some extent toxicity can be assessed by clinicians and researchers, whereas symptoms, patient functioning and quality of life are inaccurately assessed by others than the patients themselves. A patient reported outcome (PRO) is directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment[53]. Patient-reported outcome measures (PROMs) are the tools used to measure PROs; PROMs are usually validated questionnaires patients complete by self-assessing their health status.

In 1989, quality of life was rarely an outcome measure in clinical trials in oncology[54]. This has changed: a Pubmed search on "patient reported outcomes AND cancer" gives a total of 16,119 results on September 4th, 2020 with 2,728 results added in 2019. Although PROs in cancer have been studied since the 1980s and the literature on PROs is growing rapidly, PROs are still seldom routinely assessed in the daily oncology practice. However, potential benefits of routine PRO use are abundant: it empowers patients to actively participate in their health care, facilitates early detection and monitoring of patient symptoms, and enables clinicians to better understand and act on patients' needs; it helps communication between patient and clinician by raising specific issues on symptoms and functioning; assessing PROs itself may already improve treatment outcomes; and it may improve safety and quality of health care delivery[55].

The costs of innovative drugs increase over time: the spending on cancer drugs increased from €7.6 billion in 2005 to €19.1 billion in the European Union in 2014[56]. In the European Union, prostate cancer has been associated with high total economic costs (€8.4 billion) in 2009, consisting of healthcare costs (€5.4 billion) including medication costs (€3.1 billion), informal care costs (€1.9 billion) and costs due to productivity losses attributable to mortality (€0.7 billion)[57]. Increasing costs are challenging the affordability of anticancer agents in national health services and reimbursement systems[58]. The price of an anticancer drug should be reasonable and affordable, reflect the clinical value of the drug, ensure patients are able to access the drug and be sustainable

for both national health-care and reimbursement systems as well as pharmaceutical companies[58]. For different reasons, patient access to new treatment may be too slow, and inferior treatment strategies may persist too long, leading to unjustifiable variation in care. Data on effectiveness and cost-effectiveness are therefore needed to optimize metastatic prostate cancer care.

Effectiveness of treatment is also important in the last phase of life. Intensive end-of-life care (that is 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. However, the treatment of cancer has been shown to be increasingly aggressive over time[59].

For effectiveness, it is important to monitor real world practice and treatment outcomes. Patients and physicians should be informed on differences in trial populations and the real world population, and subsequent differences in treatment outcomes. In addition, observational research on sequencing and high intensity care in the end of life phase can also be hypothesis generating.

This thesis begins with a reflection on setting up a disease registry. Part 1 will focus on the differences in trial and real world populations in the general CRPC population and in more details in patients treated in second line with cabazitaxel (Chapters 2 and 3). Part 2 will focus on the survival and quality of life outcomes in real world. I will also focus on the end of life phase, and study high intensity care in this phase. Specific lessons from real world observations that can improve treatment in daily practice are shown in Part 3, with a focus on sequencing in real world. To conclude, I will present a case study of using registry data in developing a prediction model.

REFERENCES

1. Adams J. The case of scirrhous of the prostate gland with corresponding affliction of the lymphatic glands in the lumbar region and in the pelvis. *Lancet*. 1853(1):393.
2. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. *Eur Urol*. 2020;77(1):38-52.
3. Netherlands cancer registry (NCR) - NKR cijfers/IKNL. www.cijfersoverkanker.nl. Accessed January, 23th, 2020.
4. Our world in data. Life expectancy 1543 to 2015. https://ourworldindata.org/grapher/life-expectancy?tab=chart.
5. Huggins CB, Hodges CV. Studies on prostate cancer: 1. the effects of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Research*. 1941(1):203.
6. Huggins C. Effect of orchiectomy and irradiation on cancer of the prostate. *Ann Surg*. 1942;115(6):1192-1200.
7. Denmeade SR, Isaacs JT. A history of prostate cancer treatment. *Nat Rev Cancer*. 2002;2(5):389-396.
8. Schally AV, Kastin AJ, Arimura A. Hypothalamic follicle-stimulating hormone (FSH) and luteinizing hormone (LH)-regulating hormone: Structure, physiology, and clinical studies. *Fertil Steril*. 1971;22(11):703-721.
9. Tolis G, Ackman D, Stellos A, et al. Tumor growth inhibition in patients with prostatic carcinoma treated with luteinizing hormone-releasing hormone agonists. *Proc Natl Acad Sci U S A*. 1982;79(5):1658-1662.
10. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol*. 2017;71(4):630-642.
11. Anderson KM, Liao S. Selective retention of dihydrotestosterone by prostatic nuclei. *Nature*. 1968;219(5151):277-279.
12. Varenhorst E, Wallentin L, Carlstrom K. The effects of orchidectomy, estrogens, and cyproterone acetate on plasma testosterone, LH, and FSH concentrations in patients with carcinoma of the prostate. *Scand J Urol Nephrol*. 1982;16(1):31-36.
13. Schellhammer P, Sharifi R, Block N, et al. A controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy, in patients with advanced prostate cancer. casodex combination study group. *Urology*. 1995;45(5):745-752.
14. Iversen P. Antiandrogen monotherapy: Indications and results. *Urology*. 2002;60(3 Suppl 1):64-71.
15. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65(2):467-479.

16. Laufer M, Denmeade SR, Sinibaldi VJ, Carducci MA, Eisenberger MA. Complete androgen blockade for prostate cancer: What went wrong? *J Urol*. 2000;164(1):3-9.
17. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
18. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
19. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24.
20. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383(11):1040-1049.
21. Pont A, Williams PL, Loose DS, et al. Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med*. 1982;97(3):370-372.
22. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
23. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: A canadian randomized trial with palliative end points. *J Clin Oncol*. 1996;14(6):1756-1764.
24. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: Results of the cancer and leukemia group B 9182 study. *J Clin Oncol*. 1999;17(8):2506-2513.
25. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.
26. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: Updated survival in the TAX 327 study. *J Clin Oncol*. 2008;26(2):242-245.
27. Zhu ML, Horbinski CM, Garzotto M, Qian DZ, Beer TM, Kyprianou N. Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. *Cancer Res*. 2010;70(20):7992-8002.
28. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: A systematic review. *Int J Clin Pract*. 2011;65(11):1180-1192.
29. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer*. 2007;110(8):1860.
30. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
31. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.
32. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: Final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992.

33. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.
34. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746.
35. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163-1177.
36. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(2):149-158.
37. Sathianathen NJ, Philippou YA, Kuntz GM, et al. Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer: A cochrane review. *BJU Int*. 2019;124(3):370-372.
38. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37(32):2974-2986.
39. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381(2):121-131.
40. Mateo J, Fizazi K, Gillessen S, et al. Managing nonmetastatic castration-resistant prostate cancer. *Eur Urol*. 2019;75(2):285-293.
41. Small EJ, Saad F, Chowdhury S, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. *Ann Oncol*. 2019;30(11):1813-1820.
42. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.
43. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-2474.
44. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381(26):2506-2518.
45. Ku SY, Gleave ME, Beltran H. Towards precision oncology in advanced prostate cancer. *Nat Rev Urol*. 2019;16(11):645-654.
46. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102.
47. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.

48. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): A multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014;15(7):700-712.
49. Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. *J Clin Oncol*. 2017;35(1):40-47.
50. Sekine I, Takada M, Nokihara H, Yamamoto S, Tamura T. Knowledge of efficacy of treatments in lung cancer is not enough, their clinical effectiveness should also be known. *J Thorac Oncol*. 2006;1(5):398-402.
51. James JE. Reviving cochrane's contribution to evidence-based medicine: Bridging the gap between evidence of efficacy and evidence of effectiveness and cost-effectiveness. *Eur J Clin Invest*. 2017;47(9):617-621.
52. Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?". *Lancet*. 2005;365(9453):82-93.
53. Johnston B, Patrick D, Devji T, et al. Chapter 18: Patient-reported outcomes. . In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors)., ed. *Cochrane handbook for systematic reviews of interventions.* Version 6.0 (updated July 2019). ed. Available from www.training.cochrane.org/handbook; 2019.
54. Donovan K, Sanson-Fisher RW, Redman S. Measuring quality of life in cancer patients. *J Clin Oncol*. 1989;7(7):959-968.
55. Nguyen H, Butow P, Dhillon H, Sundaresan P. A review of the barriers to using patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs) in routine cancer care. *J Med Radiat Sci*. 2020.
56. Jonsson B, Hofmarcher T, Lindgren P, Wilking N. The cost and burden of cancer in the european union 1995-2014. *Eur J Cancer*. 2016;66:162-170.
57. Grochtdreis T, Konig HH, Dobruschkin A, von Amsberg G, Dams J. Cost-effectiveness analyses and cost analyses in castration-resistant prostate cancer: A systematic review. *PLoS One*. 2018;13(12):e0208063.
58. Uyl-de Groot CA, Lowenberg B. Sustainability and affordability of cancer drugs: A novel pricing model. *Nat Rev Clin Oncol*. 2018;15(7):405-406.
59. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol*. 2004;22(2):315-321.

CHAPTER 2

Balancing the optimal and the feasible: A practical guide for setting up patient registries for the collection of real-world data for health care decision making based on Dutch experiences

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ABSTRACT

Objectives

The aim of this paper is to provide practical guidance in setting up patient registries to facilitate real-world data collection for healthcare decision making.

Methods

This guidance was based on our experiences and involvement in setting up patient registries in oncology in The Netherlands. All aspects were structured according to i) mission and goals ("the Why"), ii) stakeholders and funding ("the Who"), iii) type and content ("the What"), and iv) identification and recruitment of patients, data handling and pharmacovigilance ("the How").

Results

The mission of most patient registries is improving patient health by improving the quality of patient care; monitoring and evaluating patient care is often the primary goal ("the Why"). It is important to align the objectives of the registry and agree on a clear and functional governance structure with all stakeholders ("the Who"). There is often a trade-off between reliability, validity and specificity of data elements and feasibility of data collection ("the What"). Patient privacy should be carefully protected, and address (inter-)national and local regulations. Patient registries can reveal unique safety information, but it can be challenging to comply with pharmacovigilance guidelines ("the How").

Conclusions

It is crucial to set up an efficient patient registry that serves its aims by collecting the right data of the right patient in the right way. It can be expected that patient registries will become the new standard alongside RCTs due to their unique value.

INTRODUCTION

Globally, there is an increasing trend to use real-world data to inform decision making in healthcare. Real-world data is often collected using a patient registry. A patient registry can be defined as "*an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes*"[1].

Regulatory authorities (United States Food and Drug Administration [FDA] and European Medicines Agency [EMA]) can require real-world data collection for safety surveillance and risk assessment (e.g., Risk Evaluation and Mitigation Strategy [REMS] by FDA, risk management plan by EMA)[2]. Furthermore, reimbursement agencies increasingly use real-world data in decision making. This was for example seen in The Netherlands where a coverage with evidence development policy was implemented in 2006[3]. This policy aims to guarantee early access to expensive drugs which have an added therapeutic value and an expected budget impact of at least 2.5 million Euros[4]. In exchange, it is required to collect data regarding appropriate drug use, effectiveness and cost-effectiveness in real-world clinical practice. These data are intended to complement the findings from clinical trial(s), and to evaluate a drug's real-world value after four years of initial reimbursement. As a consequence of the introduction of this policy, the number of patient registries has been rapidly increasing in The Netherlands.

In this paper, we provide practical guidance in setting up patient registries for the collection of real-world data. Although guidance for designing patient registries exists[1], we specifically address practical issues. This paper is based on our involvement in setting up patient registries in The Netherlands for various types of cancer (i.e., melanoma, lung, prostate, renal cell, hematological, colorectal, and head and neck cancer). We first discuss the mission and goals ("the Why") of patient registries and highlight issues related to stakeholders and funding ("the Who"). After that, challenges and solutions will be discussed regarding the type and content of a patient registry ("the What") and the identification and recruitment of patients, data handling, and pharmacovigilance ("the How"). Lastly, we discuss the main challenges in balancing the optimal and the feasible in setting up patient registries.

MISSION AND GOALS ("THE WHY")

Why use a patient registry and how to guarantee valorization of outcomes?
The mission of most registries is improving patient health by improving the quality of patient care; monitoring and evaluating patient care is therefore often the primary goal. This goal may be operationalized in several ways. For example, patient registries are one of EMA's tools to gain insight into risks of a product in real-world clinical practice[2]. Patient registries can also provide information on appropriate use (i.e., is a product used in the right way in the right patients), effectiveness, costs, and cost-effectiveness in real-world clinical practice[5]. Furthermore, registries can include essential information on patient reported outcome measures (PROMs) in case data is prospectively collected. Moreover, patient registries can inform public health planning (e.g., registering causes of disease to illustrate the need for a prevention program)[6]. It is important to be very specific about how the primary goal of monitoring and evaluating patient care will be operationalized and/or interpreted. Ultimately, this will ease the other steps in setting up patient registries.

Monitoring and evaluating patient care may not immediately improve patient health but may improve the health of future patients. It is essential to frequently discuss findings with clinicians and ensure a quality of care feedback loop. Furthermore, outcomes can be used in the development of clinical guidelines. Table 1 provides an overview of the mission and goals of the registries in which we are involved. All registries ensure transparency to the public through presentations and publications[7-14]. However, only the melanoma registry (DMTR) fortnightly provides clinicians with online benchmarked feedback regarding a predefined set of quality indicators developed by the professional organization. These quality indicators will be shared at a hospital-level with healthcare insurers, patient organizations, and the general public in the near future. Quality of care improvement by using a structured feedback loop to clinicians was not part of the initial aims of most of the registries. This may be explained by the fact that most of the registries in which we are involved were funded by manufacturers and mainly set up for reimbursement purposes. Besides reimbursement purposes, the melanoma registry (DMTR) was set up for monitoring quality of care which was obligated by the professional organization.

Important lessons to feedback loops are that agreement needs to be reached on the type of indicators that will be collected, how they will be measured and the way they will be presented. Additionally, the data need to be representative for all patients within a certain hospital (e.g., starting data collection on patients with a worse prognosis, will initially lead to biased feedback) and the data need to be case-mix corrected to

allow valid comparisons between hospitals (or clinicians), especially when it concerns outcomes indicators. To correct for differences between patients at baseline, the registry should contain a sufficient number of observations and sufficient data on the relevant prognostic factors. Lastly, a user-friendly (web-based) application is needed to facilitate a quality of care feedback loop.

STAKEHOLDERS AND FUNDING ("THE WHO")

Who are involved in the registry?

Broad support for the registry is needed to maximize its benefits. Identifying and engaging relevant stakeholders is key to the success of a patient registry. Stakeholders include clinicians, patients, researchers, governmental parties, healthcare insurers and manufacturers. Involvement from professional organizations and clinical experts (including key opinion leaders) improves the valorization of results. Involvement of patient representatives secures patient participation and may help to ensure that the aims of the registry are pursued with minimal burden to patients. Participation of manufacturers may support funding of the registry. Table 2 illustrates the involvement of stakeholders in the registries in which we are involved.

Stakeholders can, however, have conflicting interests. An essential and potentially time-consuming step is aligning the aims of the registry with these interests. It is important to determine the main objectives with key stakeholders at an early stage. It is also crucial to establish a clear and functional governance structure including a description of tasks, responsibilities, and decision-making processes. In the prostate cancer registry (CAPRI), clinical data and health-related quality of life data are collected in two separate projects with separate funding and study protocols; however, both projects are carried out by the same project team. The project team is the core executive body, responsible for the day-to-day management of the registry, coordination and adherence to the planning and protocol. The project team is advised by a clinical steering committee as well as a general assembly. The clinical steering committee has decision making power regarding the clinical and scientific aspects of the registry (e.g., data collection and publication of results) and includes balanced representatives of urologists, medical oncologists and radiotherapists of the participating hospitals and the Dutch uro-oncology study group. The general assembly represents all relevant stakeholders (including all involved manufacturers and representatives of the Dutch prostate cancer patient organization). Scientific proposals are judged by the steering committee and the writing team is composed by the involved project team members and a selection of the steering committee and the sub-investigators from the participating hospitals.

Table 1. Mission and goals ("the Why")

The Why		Name of registry	PHAROS 1	CAPRI and PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON *(not running)*	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
		Disease	CLL, MM, NHL	CRPC	Melanoma (unresectable stage IIIc/IV)	Melanoma (stage I-IV)	mCRC	mRCC	NSCLC	NSCLC	(LA) SCCHN	(RM) SCCHN
Aim:	Providing insights into patient and disease characteristics and treatment patterns		X	X	X	X	X	X	X	X	X	X
	Providing insights into clinical outcomes and economic outcomes		X	X	X	X	X	X	X	X	X	X
	Providing insights into patient reported outcomes											
	- Related to health-related quality of life		X*	X	X			X		X		
	- Related to costs (direct and/or indirect)			X	X					X		

Table 1. (Continued)

Name of registry	PHAROS 1	CAPRI and PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON *(not running)*	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
The Why										
Providing online benchmarked feedback to clinicians, hospitals and manufacturers			X							
Identifying prognostic groups based on patient material			Future aim			X		To be decided		

* Data on health-related quality of life was collected in The Profiles registry [35].

Abbreviations: PHAROS, Population-based HAematological Registry for Observational Studies; CAPRI, CAstration-resistant Prostate cancer RegIstry; PRO-CAPRI, Patient Reported Outcomes in the CAstration-resistant Prostate cancer RegIstry; DMTR, Dutch Melanoma Treatment Registry; PERCEPTION, PharmacoEconomics in Renal CEll carcinoma: a PopulaTION-based registry; POSEIDON, Prospective Observational Study Examining Investments and Derived Outcomes in NSCLC treatment; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, Non Hodgkin lymphoma; CRPC, castration-resistant prostate cancer; mCRC, metastatic colorectal carcinoma; mRCC, metastatic renal cell carcinoma; NSCLC, Non-small-cell lung carcinoma; LA SCCHN, locally advanced Squamous Cell Carcinoma of the Head and Neck; RM SCCHN, recurrent and/or metastatic Squamous Cell Carcinoma of the Head and Neck.

Table 2. Stakeholders and funding ("the Who")

The Who	Name of registry	PHAROS 1	CAPRI & PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON (not running)	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
	Disease	CLL, MM, NHL	CRPC	Melanoma (unresectable stage IIIc/IV)	Melanoma (stage I-IV)	mCRC	mRCC	NSCLC	NSCLC	(LA) SCCHN	(RM) SCCHN
Consultation*	Clinicians and/or hospitals	X	X	X	X	X	X	X	X	X	X
	Governmental party	X	X	X			X				X
	Manufacturer(s)	X	X	X	X	X	X	X	X	X	X
	Patients		X	X					X		
	Researchers / academia	X	X	X	X	X	X	X	X	X	X
Decision making/ governance**	Clinicians and/or hospitals	X	X	X			X		X		
	Governmental party	X	X	X			X				X
	Manufacturer(s)	X		X	X		X				
	Patients		X	X							
	Researchers / academia	X	X	X	X	X	X	X	X	X	X

Table 2. (Continued)

	Name of registry	PHAROS 1	CAPRI & PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON (not running)	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
The Who											
Funding	Clinicians and/or hospitals	X									
	Governmental party	X	X	X			X				X
	Manufacturer(s)	X	X	X	X	X	X	X	X	X	X

*Stakeholders involved with the registry initiative and/or design. **Stakeholders who have a formal say in decisions regarding the project when it is running.
Abbreviations: PHAROS, Population-based HAematological Registry for Observational Studies; CAPRI, CAstration-resistant Prostate cancer RegIstry; PRO-CAPRI, Patient Reported Outcomes in the CAstration-resistant Prostate cancer RegIstry; DMTR, Dutch Melanoma Treatment Registry; PERCEPTION, PharmacoEconomics in Renal CEll carcinoma: a PopulaTION-based registry; POSEIDON, Prospective Observational Study Examining Investments and Derived Outcomes in NSCLC treatment; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, Non Hodgkin lymphoma; CRPC, castration-resistant prostate cancer; mCRC, metastatic colorectal carcinoma; mRCC, metastatic renal cell carcinoma; NSCLC, Non-small-cell lung carcinoma; LA SCCHN, locally advanced Squamous Cell Carcinoma of the Head and Neck; RM SCCHN, recurrent and/or metastatic Squamous Cell Carcinoma of the Head and Neck.

Another issue may be related to data ownership (including publishing rights), (level of) data access, and data sharing. For example, when multiple manufacturers fund the registry, they may not be willing to share product-specific data. In this case, detailed product-specific data can be shared with the product-owner, while aggregated data can be shared with other companies. By allowing variation in the level of data sharing[15], competing parties can participate and benefit from collaboration within the same registry.

Who funds the registry?

It is crucial to secure sufficient funding for all activities related to the registry to ensure viability and sustainability. Activities include designing the registry (e.g., stakeholder meetings, writing and revising the study protocol, defining data sets and ethical approval) and running the registry (e.g., data collection, data analyses, writing and reporting). Ensuring funding can be challenging, especially in case of extensive data collection and/or long-term follow-up. Long-term funding arrangements are essential for the sustainability of a registry.

Registries can be funded from one or multiple sources including public and private sources. Potential funding sources are manufacturers, healthcare insurers, governmental parties, patient organizations, professional associations, private foundations and advocacy groups. Funding for the registries in which we are involved was often provided by multiple manufacturers. These registries were largely motivated by the need to collect real-world data on the performance of drugs in line with the Dutch coverage with evidence development policy. Some of these registries also received governmental funding (including [unrestricted] research grants).

Multi-sponsor registries have the advantage of decreasing the financial burden for each party and securing wider support. However, sponsors may have conflicting interests and different ideas about the design and planning of the registry. For example, multiple manufacturers were involved in the hematological registry (PHAROS 1). They had products for various indications in different treatment lines. Since the optimal approach to collect data may differ per party (e.g., dependent on treatment line), priorities needed to be set and needed to be acceptable for all parties.

Another example is the (POSEIDON) lung cancer registry, aimed to start in four hospitals. Although the set-up started three years ago, it is currently unknown if data collection will actually commence. Over time, more stakeholders became involved and the objectives became concurrently broader. For example, one of the objectives was to collect detailed biomarker information for scientific purposes and in order to conduct economic evaluations of targeted therapies. However, collecting data on biomarkers increases the requirements for infrastructure and funding. Furthermore, different

stakeholders had different ideas about the type of biomarker data to be included. Agreement between all stakeholders has not yet been reached.

A practical solution for future registries is to carefully consider the number and type of stakeholders and their specific role in decision making. The inclusion of more stakeholders increases potential benefits, but it can also complicate decision making.

TYPE AND CONTENT ("THE WHAT")

What is a suitable type and content?

A patient registry can be intervention-based or disease-based[1]. An intervention-based registry addresses research questions regarding appropriate use, effectiveness, cost-effectiveness, and safety. Disease-based registries provide additional information and facilitate studying the full disease course including (sequential) treatment pathways[11]. Furthermore, such a registry provides information on the number of untreated patients and whether these patients would have been eligible for treatment. It should be noted, however, that this also adds to complexity, time and costs of a registry. Table 3 provides an overview of the type and content of the registries in which we are involved.

Both intervention-based and disease-based registries can include all patients that meet the inclusion criteria or include a sample of this population. Including all patients adds to time and costs, whereas selecting a sample can be more efficient but can have pitfalls as well. In particular, the representativeness of the patient population may be hampered (external validity). Whereas causal studies about how nature works do not necessarily need a representative sample, representativeness is crucial in studies describing a specific population at a specific point in time[16]. As a consequence, a representative sample is needed when monitoring and evaluating patient care. A random sample or a cluster sample can enhance representativeness. A cluster sample includes patients in a certain cluster (e.g., a region or a hospital) based on the assumption that the cluster is representative for other clusters.

To increase efficiency, it may be an option to use multiple-phase sampling. For example, in a two-phase design, limited data is first collected in a large sample, after which detailed data is collected in a subsample. The melanoma registry (DMTR) uses such an approach. Minimal data is collected on patients who are not treated in a melanoma center (due to a worse prognosis), whereas full data (clinical, economic, PROMs) are collected for all patients who received treatment in one of the fourteen melanoma centers. In addition, more detailed data (additional healthcare resource use, productivity losses and informal care) are only collected in a selection of four of the fourteen centers.

Table 3. Type and content of the registry ("the What")

The What	Name of Registry	PHAROS 1	CAPRI and PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON *(not running)*	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
	Disease	CLL, MM, NHL	CRPC	Melanoma (unresectable stage IIIc/IV)	Melanoma (stage I-IV)	mCRC	mRCC	NSCLC	NSCLC	(LA) SCCHN	(RM) SCCHN
Type:	Disease-based	X	X	X	X		X	X	X		
	Intervention-based					X				X	X
Scope:	Population-based			X							
	Sample-based	X	X		X	X	X	X	X	X	X
Content:	Patient and disease characteristics/ treatment	X	X	X	X	X	X	X	X	X	X
	Clinical outcomes	X	X	X	X	X	X	X	X	X	X
	Economic outcomes	X	X	X	X	X	X	X	X	X	X
	Patient reported outcomes	X*	X	X			X		X		
	Quality of care indicators**			X							
	Patient material			Future aim			X		To be decided		
Data-collection:	Prospective		X	X			X		X		
	Retrospective	X	X	X	X	X	X	X		X	X
	Start and end date	From 2010	2012-2017	From 2013	2012-2015	2010-2013	2011-2014	2012-2014	To be decided	2011	2011-2013

Table 3. (Continued)

The What	Name of Registry	PHAROS 1	CAPRI and PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON *(not running)*	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
	Years of diagnosis	From 2004	2010-2015	From 2012	2003-2011	2003-2013	2008-2013	2009-2011	To be decided	2007-2010	2006-2013

* Data on health-related quality of life was collected in The Profiles registry [31] ** Quality of care indicators can be derived from all registries (e.g., length of a stay in a hospital). However, the DMTR is the only registry providing online benchmarked feedback to clinicians, hospitals and manufacturers.
Abbreviations: PHAROS, Population-based HAematological Registry for Observational Studies; CAPRI, CAstration-resistant Prostate cancer REgIstry; PRO-CAPRI, Patient Reported Outcomes in the CAstration-resistant Prostate cancer REgIstry; DMTR, Dutch Melanoma Treatment Registry; PERCEPTION, PharmacoEconomics in Renal CEll carcinoma: a PopulaTION-based registry; POSEIDON, Prospective Observational Study Examining Investments and Derived Outcomes in NSCLC treatment; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, Non Hodgkin lymphoma; CRPC, castration-resistant prostate cancer; mCRC, metastatic colorectal carcinoma; mRCC, metastatic renal cell carcinoma; NSCLC, Non-small-cell lung carcinoma; LA SCCHN, locally advanced Squamous Cell Carcinoma of the Head and Neck; RM SCCHN, recurrent and/or metastatic Squamous Cell Carcinoma of the Head and Neck.

Despite of the sampling procedures, which initially enhance representativeness, representativeness is hampered in case patients who do not want to participate differ from those who participate, or in case patients are not randomly lost to follow-up. Additionally, sampling from a complete sampling frame is not always feasible, especially for registries using a prospective design.

What data elements?

What data elements to include largely depends on the goal of the registry. If the goal is to improve the quality of patient care by providing information on appropriate use, effectiveness, and cost-effectiveness in real-world clinical practice, comprehensive data is needed on patient and disease characteristics, treatment and outcomes (health and economic outcomes). However, if the goal is explicitly focused on effectiveness and safety in order to improve the quality of patient care, the choice of data elements can be more selective. In order to select the most important data elements, an analysis plan can be created. Describing the future data analyses helps identifying those data elements that are essential and those elements that are academically "interesting"[17].

Data elements should, preferably, be based on data standards (e.g., Clinical Data Interchange Standards Consortium [CDISC]), current data sets (e.g., national disease registry), and/or standard terminology (e.g., Systematized Nomenclature of Medicine [SNOMED]). This facilitates comparison to other studies and creates the opportunity to link different data sets.

Consultation of experts ensures the selection of appropriate data elements[18]. It is important to involve clinical experts as well as experts in using real-world data. Clinical experts who are not experienced with real-world data may advise on data elements that are difficult to collect in a real-world setting. It is always recommended to test the availability of data elements. In case there is a lack of reliable data about a certain variable, it may be possible to use a proxy (e.g., time to next treatment as a proxy for time to progression).

Using real-world data always implies balancing between reliability, validity and specificity of data elements on the one hand, and the feasibility of data collection (affordability and completeness) on the other hand. The available sources will set boundaries to what can be collected and influence the manner of data collection. For example, data on adverse events in clinical trials is commonly reported using the Common Terminology Criteria for Adverse Events (CTC AE) as graded by the clinician. This is, however, often not feasible in a registry, unless the CTC AE are consistently used and concisely reported in medical charts in clinical practice. In the lung cancer study, data were retrospectively

collected from medical charts. Only 8.5% of adverse events (81 out of 956) were graded by a clinician using a standardized grading system and reported in the medical chart. Only 51% was sufficiently reported to retrospectively derive a grade, as judged by data managers. Therefore, a tension may exist between optimizing reliability (only register and grade an adverse event if recorded by the treating clinician) and optimizing other properties of the registry such as data completeness. When selecting the data-elements, one has to be aware of such trade-offs in order to optimize the attributes most important to the registry.

IDENTIFICATION AND RECRUITMENT OF PATIENTS, DATA HANDLING, AND PHARMACOVIGILANCE ("THE HOW")

How to identify patients?

Any type of registry may have issues regarding the identification of eligible patients. In population-based patient registries, it is essential to identify and include all eligible patients (e.g., with the diagnosis of interest or treated with the intervention of interest). In contrast, a sample of the population can be drawn, and existing databases can be used to identify eligible patients. It is crucial to ensure representativeness when using an existing database (e.g., national databases, hospital databases, clinicians [databases]). Drawing a sample from patients joining a patient association may, for example, lead to selection bias (e.g., a higher educated group of patients). The potential for bias can be evaluated by examining different studies addressing similar research questions and comparing patient and disease characteristics to the characteristics of the patients in the registry. Table 4 illustrates how patients were identified in the registries in which we are involved.

In the retrospective part of the renal cancer registry (PERCEPTION), eligible patients were identified through the Netherlands Cancer Registry, which includes basic information on 95% of all cancer patients. A cluster sample was selected for inclusion in this registry (i.e., all patients with metastatic renal cell carcinoma in 42 from 51 hospitals in four regions, covering approximately half of the country). A practical hurdle arises when (sufficient) information is not available on the population. For the prospective part of this registry, the Netherlands Cancer Registry could not provide a timely and complete list of eligible patients. Therefore, lists of patients diagnosed with metastatic renal cell carcinoma were fortnightly derived from hospitals' financing systems, in addition to the Netherlands Cancer Registry.

Table 4. Identification and recruitment of patients, handling data and pharmacovigilance ("the How")

The How	Name of registry	PHAROS 1	CAPRI & PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON (not running)	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
	Disease	CLL, MM, NHL	CRPC	Melanoma (unresectable stage IIIc/IV)	Melanoma (stage I-IV)	mCRC	mRCC	NSCLC	NSCLC	(LA) SCCHN	(RM) SCCHN
Identification of patients:	National database(s)	X			X		X		To be decided		
	Hospital database(s)		X			X	X	X	To be decided		X
	Clinicians (database(s))			X					To be decided	X	X
Handling data:	Paper-based case report form	X			X					X	
	Electronic case report form	X	X	X	X		X	X	X		X
Handling PROMS:	Paper-based questionnaire	X	X	X*			X		X		
	Electronic questionnaire	X		X					X		
Patient privacy protection:	Anonymization and/ or pseudonomization	X	X	X	X		X	X		X	X
	Trusted third party			X					X		

Table 4. (Continued)

	Name of registry	PHAROS 1	CAPRI & PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON (not running)	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
The How											
(S)AE:	Collection	X	X	X	X	X	X	X	X	X	X
	Reporting to pharmacovigilance authority	X	Yes, (S)AE level						To be decided		

* At the convenience of the patient. Abbreviations: PHAROS, Population-based HAematological Registry for Observational Studies; CAPRI, CAstration-resistant Prostate cancer RegIstry; PRO-CAPRI, Patient Reported Outcomes in the CAstration-resistant Prostate cancer RegIstry; DMTR, Dutch Melanoma Treatment Registry; PERCEPTION, PharmacoEconomics in Renal CEll carcinoma: a PopulaTION-based registry; POSEIDON, Prospective Observational Study Examining Investments and Derived Outcomes in NSCLC treatment; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, Non Hodgkin lymphoma; CRPC, castration-resistant prostate cancer; mCRC, metastatic colorectal carcinoma; mRCC, metastatic renal cell carcinoma; NSCLC, Non-small-cell lung carcinoma; LA SCCHN, locally advanced Squamous Cell Carcinoma of the Head and Neck; RM SCCHN, recurrent and/or metastatic Squamous Cell Carcinoma of the Head and Neck; (S)AE, (serious) adverse event.

How to recruit patients?

The recruitment of patients can be a serious challenge. Participation can be voluntary or compulsory for patients and/or clinicians. To increase participation rates, it could be made compulsory to gain access to and/or reimbursement of a product, (e.g., an expensive drug). This was partly the case in the melanoma registry (DMTR). The Dutch minister made the financing of an expensive melanoma drug conditional on the set-up of a population-based registry and centralization of melanoma care in fourteen specialist centers (endorsed by health insurers).

However, participation in most registries is voluntary. Patients can have multiple incentives to participate. Because a registry most likely does not change current treatment, improving future patients' health may be the most important incentive. Clinicians or hospitals may be incentivized by a particular research interest or the ability to achieve other goals (e.g., reimbursement, transparency and improvement of quality of care)[1]. Furthermore, a (financial) compensation for time invested by either clinicians or patients may help to increase participation.

How to handle the data?

Paper or electronic case report forms (CRFs) can be used to record information. Electronic CRFs offer the advantage of automatic validation checks and do not require transferring data from paper to an electronic database. The database needs to be suitable for the registry, including the level of detail of the data.

Furthermore, electronic and paper-based patient questionnaires can be used to collect PROMs. In the PERCEPTION registry, patients were sent a health-related quality of life questionnaire every three months in the first year of participation in the study, and every six months in the second year. Experiences from the PERCEPTION registry showed that most patients who gave informed consent returned the questionnaire on a short notice; response rates varied between 80% and 90%. However, response rates can vary substantially between studies, and may depend on the study population and the burden of the questionnaire(s). To increase participation and response, it may be an option to use both electronic and paper-based patient questionnaires especially in case most patients are elderly. Additionally, in case this matches the required measuring moments, questionnaires can be completed at clinic visits, for example in the waiting room (e.g. by using a tablet). Furthermore, especially in case of immobile or terminally ill patients, telephone calls or house visits by study staff may be needed to collect the required patient reported data. The process of data collection should be designed to maximize participation and response, data quality and efficiency while minimizing patient burden.

To improve the quality of clinical data, clinicians can be requested to register or verify data. This is, however, often not feasible since clinicians often lack time to review large volumes of patient data. In case registry data is used for the evaluation of the quality of care in multiple hospitals, external data managers may increase objectivity and may ensure uniformity of data collection. In the melanoma registry (DMTR), all data recorded by data managers need to be validated by clinicians. This validation process is, however, time-consuming. Validation efforts should therefore preferably focus at the most important variables (such as toxicities) that may not reliably be captured by data managers. Uniformity of data collection in the DMTR was improved by initially recording data on 10% of all patients by two data managers (one external).

It is essential to adequately and continuously train data managers supported by a detailed and up-to-date manual. This also includes guidance on when to record a value as missing, unknown, or as negative. For example, there is a difference between a patient who had no test for locating metastases and a patient who had a test but no metastases were found. Inconsistencies in data recording hamper a valid interpretation of the results. Training data managers and preliminary analyses of the collected data allow for identification of and sharing information on common mistakes.

Furthermore, it is crucial to ensure patients' privacy in particularly for patient identifiers. Training in Good Clinical Practice (GCP) (to the extent the principles are relevant for patient registries) and awareness of (inter-)national and local regulations will help designing a registry which guarantees patient privacy. This includes anonymization or pseudonymization of data to ensure that information cannot be traced back to an individual patient. Anonymization may hamper specific registry functionalities (e.g., combining different data sources). Pseudonymization involves replacing identifying items by artificial identifiers, or pseudonyms. Pseudonymization can be performed by a Trusted Third Party (TTP), guarding the encryption to the procedure while enabling re-identification when required. However, even in case a TTP is used, the inclusion of patient identifiers in the CRF should be carefully scrutinized and only allowed when absolutely necessary; approval should be obtained from a medical-ethical committee.

How should pharmacovigilance be incorporated?

Patient registries have the potential to reveal unique pharmacovigilance information since their follow up allows identification of long term toxicity. Moreover, real-world toxicities may differ from toxicity profiles in clinical trials because of differential populations, treatment patterns, adverse event handling and clinician experience[19].

However, it can be challenging to comprehensively collect safety data within a registry, especially in case data is collected retrospectively.

With respect to pharmacovigilance requirements, the EMA guideline on good pharmacovigilance practices differentiates between non-interventional post-authorization studies with primary data collection, and non-interventional post-authorization studies based on secondary use of data[20]. First, in case of post-authorization studies with primary data collection, "*for all collected adverse events comprehensive and high quality information should be sought in a manner which allow for valid individual case safety reports to be reported within the appropriate timeframes*"[20]. These timeframes are intended to allow manufacturers and authorities to take immediate action when needed to prevent serious adverse events occurring in other patients. However, this requires a clear workflow and an appropriate infrastructure. Second, in case of secondary use of data (e.g. medical chart reviews), the reporting of suspected adverse reactions in the form of individual case safety reports is not required; "*reports of adverse events should be summarized as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting*"[20]. The distinction between non-interventional post-authorization studies with primary data collection and non-interventional post-authorization studies based on secondary use of data, and its' consequences regarding pharmacovigilance was not always interpreted similarly between stakeholders in some of the registries in which we are involved. This has resulted in substantial registration burden (e.g. reporting within 24 hours of recording) under pressure from manufacturers.

Designing a solid plan for pharmacovigilance is part of setting up any patient registry. This plan needs to be consistent with national and international guidelines, and agreed upon by all stakeholders and the relevant medical-ethical bodies. Ideally, all safety information should be registered and reported by the clinician at the moment of occurrence.

It may be difficult to comprehensively collect safety information within a registry, while being dependent on the available data sources. It may be impossible to determine causality without involving the treating clinician. It is therefore crucial to have short communication lines with treating clinicians, and ensuring medical expertise in the study team is recommended. Alternatively, adverse event reporting can be outsourced to knowledgeable hospital personnel.

Interim analyses in the prostate cancer registry (CAPRI) revealed that about half of the patients had a recorded hospitalization or death during treatment. Although this

percentage included both related and unrelated adverse events, all needed to be reported (see Table 4). This illustrates that SAEs are common and may significantly add to data management time and thus costs of running a registry. However, it also emphasizes that pharmacovigilance may be an important aspect in improving patient health.

LESSONS LEARNED

Patient registries provide valuable information on real-world patients, real-world practice, real-world costs, real-world effects, and real-world cost-effectiveness. If well-designed and well-executed, registries can support decision making at different levels. Regulatory authorities and local reimbursement agencies can use real-world data in market access and reimbursement decisions. Furthermore, sharing real-world outcomes can improve decision making at the patient level, and, ultimately, can improve patient health.

Since patient registries can serve multiple goals and inform decision making at different levels, practical guidance in setting up a registry is important to ensure a proper design and execution. This paper provides practical guidance on "the Why", "the Who", "the What" and "the How" in setting up a patient registry, which is based on our experiences and involvement in multiple registries in The Netherlands for various types of cancer. It is essential to cooperate with all relevant stakeholders and collect the right data from the right patients in the right way. The "right" is, however, not always the most extensive approach. It is crucial that the registry is designed in such a way that it serves its aims and is as efficient as possible. It is, therefore, particularly important to balance the optimal and the feasible to maximize the gains within the constraints of the available resources.

This paper has a number of limitations. First, our experiences in setting up patient registries are based on registries in cancer only, nevertheless we believe that this practical guidance is applicable to patient registries in other disease areas. Additionally, in most of the registries in which we are involved, patients were selected using existing databases, such as the Netherlands Cancer Registry, and most of the registries were largely informed by chart reviews conducted by trained data managers. Nevertheless, we believe that our experiences in The Netherlands will benefit researchers in other contexts and other countries.

FUTURE PROSPECTS OF REGISTRIES

The number of patient registries will continue to rise in the near future[21]. Their importance was shown in many areas including general practice[22], neurology[23,24], orthopedics[25,26], and oncology[27,28].

Various initiatives exist that facilitate designing high quality registries, such as the High-Value Health Care Project[29] and the cross-border PAtient REgistries iNiTiative (PARENT) project. The PARENT project supports member states of the European Union with the implementation of interoperable patient registries and created a registry of registries which is available online[30].

Several trends may influence the design of future patient registries. First of all, there will be a further evolution of data standards and an improvement of interoperability of registries with electronic health records[31]. Moreover, there is an increasing trend in setting up multi-institution and multi-country registries[32]. Especially in rare diseases, multi-country registries are needed to include sufficient numbers of (comparable) patients. Finally, the content of registries will reflect important clinical developments (e.g., biobanking)[33].

Considering the unique value of and increasing demand for real-world evidence, we expect that patient registries will become the new standard alongside RCTs.

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REFERENCES

1. Gliklich RE, Dreyer NA. *Registries for evaluating patient outcomes: A user's guide.* 2nd ed. Rockville: Agency for Healthcare Research and Quality; 2010.
2. Lis Y, Roberts MH, Kamble S, J Guo J, Raisch DW. Comparisons of food and drug administration and european medicines agency risk management implementation for recent pharmaceutical approvals: Report of the international society for pharmacoeconomics and outcomes research risk benefit management working group. *Value in Health.* 2012;15(8):1108-1118.
3. Dutch National Health Care Institute (ZIN) (formerly named CVZ). Assessment procedure for inpatient drugs [in dutch: Procedure beoordeling intramurale geneesmiddelen]. 2006;26022597.
4. Dutch National Health Care Institute (ZIN) (formerly named CVZ). Specialist drugs package management [in dutch: Pakketbeheer specialistische geneesmiddelen]. 2013;2013077869.
5. Dutch National Health Care Institute (ZIN) (formerly named CVZ). Guidance for outcomes research [in dutch: Leidraad voor uitkomstenonderzoek 'ten behoeve van de beoordeling doelmatigheid intramurale geneesmiddelen']. 2008;28113706.
6. Baxter SL, Wormald RP, Musa JM, Patel D. Blindness registers as epidemiological tools for public health planning: A case study in belize. *Epidemiology Research International.* 2014;2014:1-8.
7. Blommestein HM, Issa DE, Pompen M, et al. Cost-effectiveness of rituximab as maintenance treatment for relapsed follicular lymphoma: Results of a population-based study. *Eur J Haematol.* 2014;92(5):398-406.
8. Oerlemans S, Issa DE, van den Broek EC, et al. Impact of therapy and disease-related symptoms on health-related quality of life in patients with follicular lymphoma: Results of the population-based PHAROS-registry. *Eur J Haematol.* 2014;93(3):229-238.
9. Oerlemans S, Issa DE, van den Broek EC, et al. Health-related quality of life and persistent symptoms in relation to (R-)CHOP14, (R-)CHOP21, and other therapies among patients with diffuse large B-cell lymphoma: Results of the population-based PHAROS-registry. *Ann Hematol.* 2014;93(10):1705-1715.
10. van den Broek EC, Oerlemans S, Nijziel MR, Posthuma EF, Coebergh JW, van de Poll-Franse LV. Impact of active surveillance, chlorambucil, and other therapy on health-related quality of life in patients with CLL/SLL in the netherlands. *Ann Hematol.* 2015;94(1):45-56.
11. Blommestein HM, Verelst SG, de Groot S, Huijgens PC, Sonneveld P, Uyl-de Groot CA. A cost-effectiveness analysis of real-world treatment for elderly patients with multiple myeloma using a full disease model. *Eur J Haematol.* 2015.
12. van der Linden N, van Gils CW, Pescott CP, Buter J, Uyl-de Groot CA. Cetuximab in locally advanced squamous cell carcinoma of the head and neck: Generalizability of EMR 062202-006 trial results. *Eur Arch Otorhinolaryngol.* 2014;271(6):1673-1678.

13. van der Linden N, van Gils CW, Pescott CP, Buter J, Vergeer MR, Groot CA. Real-world cost-effectiveness of cetuximab in locally advanced squamous cell carcinoma of the head and neck. *Eur Arch Otorhinolaryngol*. 2015;272(8):2007-2016.
14. van der Linden N, Buter J, Pescott CP, et al. Treatments and costs for recurrent and/or metastatic squamous cell carcinoma of the head and neck in the netherlands. *Eur Arch Otorhinolaryngol*. 2015.
15. Bellgard MI, Macgregor A, Janon F, et al. A modular approach to disease registry design: Successful adoption of an internet-based rare disease registry. *Human Mutation*. 2012;33(10):E2356-66.
16. Rothman KJ, Gallacher JE, Hatch EE. Why representativeness should be avoided. *Int J Epidemiol*. 2013;42(4):1012-1014.
17. Saczynski JS, McManus DD, Goldberg RJ. Commonly used data-collection approaches in clinical research. *Am J Med*. 2013;126(11):946-950.
18. Wattigney WA, Croft JB, Mensah GA, et al. Establishing data elements for the paul coverdell national acute stroke registry: Part 1: Proceedings of an expert panel. *Stroke*. 2003;34(1):151-156.
19. Willis CD, McNeil JJ, Cameron PA, Phillips LE. Monitoring drug safety with registries: Useful components of postmarketing pharmacovigilance systems. *Journal of Clinical Epidemiology*. 2012;65(2):121-125.
20. European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP), module VI - management and reporting of adverse reactions to medicinal products (rev 1). 2014;EMA/873138/2011 Rev 1.
21. Molsen E, Trotter J, Smith MD. Use of patient registries: Results of the ISPOR patient registry special interest group survey. *ISPOR Connections*. 2005;11(6).
22. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the general practice research database: A systematic review. *British Journal of General Practice*. 2010;60(572):e128-36.
23. Reeves MJ, Nickles AV, Roberts S, Hurst R, Lyon-Callo S. Assessment of the completeness and accuracy of case ascertainment in the michigan stroke registry. *Circulation: Cardiovascular Quality and Outcomes*. 2014;7(5):757-763.
24. Korngut L, Johnston M, Pringsheim T, Jetté N. The future of neurological patient registries. *Clinical Practice*. 2014;11(5):509-516.
25. Arthursson AJ, Furnes O, Espehaug B, Havelin LI, Söreide JA. Validation of data in the norwegian arthroplasty register and the norwegian patient register: 5,134 primary total hip arthroplasties and revisions operated at a single hospital between 1987 and 2003. *Acta orthopaedica*. 2005;76(6):823-828.
26. van Steenbergen LN, Denissen GA, Spooren A, et al. More than 95% completeness of reported procedures in the population-based dutch arthroplasty register: External validation of 311,890 procedures. *Acta orthopaedica*. 2015;86(4):1-8.
27. Kearney T, Donnelly C, Kelly J, O'Callaghan E, Fox C, Gavin A. Validation of the completeness and accuracy of the northern ireland cancer registry. *Cancer epidemiology*. 2015.

28. Londero SC, Mathiesen JS, Krogdahl A, et al. Completeness and validity in a national clinical thyroid cancer database: DATHYRCA. *Cancer epidemiology*. 2014;38(5):633-637.
29. Engelberg Center for Health Care Reform at Brookings. How registries can help performance measurement improve care. 2010.
30. PARENT, cross-border PAtient REgistries iNiTiative. http://patientregistries.eu/. Accessed 01/04, 2014.
31. Richesson RL. Data standards in diabetes patient registries. *Journal of Diabetes Science and Technology*. 2011;5(3):476-485.
32. Catarinella F, Stavast I, Wittens C. A european venous registry: Pitfalls and opportunities. *Phlebology*. 2014;29(1 suppl):188-192.
33. Van der Velde E, Vriend J, Mannens M, Uiterwaal C, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the netherlands: Rationale, design, and first results. *European Journal of Epidemiology*. 2005;20(6):549-557.
34. Van de Poll-Franse LV, Horevoorts N, van Eenbergen M, et al. The patient reported outcomes following initial treatment and long term evaluation of survivorship registry: Scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer*. 2011;47(14):2188-2194.

PART 1

Differences in clinical trial populations and real world populations

CHAPTER 3

Differences in trial and real-world populations in the Dutch Castration-resistant Prostate Cancer Registry

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ABSTRACT

Background
Trials in castration-resistant prostate cancer (CRPC) treatment have shown improved outcomes including survival. However, as trial populations are selected, results may not be representative for the real world population.

Objective
To assess the differences between patients treated in a clinical trial versus standard care during the course of CRPC in a real world CRPC population.

Design, setting and participants
CAPRI is a population based, observational, retrospective registry. CRPC patients from 20 hospitals in the Netherlands have been included from 2010 to 2013.

Outcome measurements and statistical analysis
Baseline characteristics, systemic treatment and overall survival (OS) were the main outcomes. Descriptive statistics, multivariate Cox regression and multiple imputation by Monte Carlo Markov Chain method were used.

Results and limitation
In total 1,524 patients have been enrolled of which 203 patients had participated in trials at any time. The median follow up period was 23 months. Patients in the trial group were significantly younger and had less comorbidity. Docetaxel treatment was more frequently used in trial patients (85% vs 40%). Despite an observed unadjusted median OS difference of 35 versus 24 months between the trial and standard care group, this difference was not retained after adjustment for baseline characteristics and treatment effect.

Conclusions
At CRPC diagnosis, baseline characteristics of patients who have been enrolled in trials notably differed from patients who received standard treatment options only. The survival difference between the trial and standard care group could be explained by baseline differences and treatment effect. These results indicate that trial results cannot easily be translated to real world practice.

Patient summary
We observed that patients treated in clinical trials differed from patients who were not. We concluded that this may lead to differential treatment and survival. Caution is warranted when real world outcomes are compared to trial results.

INTRODUCTION

Prostate cancer is a common cause of cancer in men[1]. The incidence and mortality in the Netherlands in 2010 were 104 and 25 per 100,000 (European Standardized Rate), respectively[2]. The relative survival for patients with prostate cancer in the Netherlands and Europe is comparable[3].

Palliative treatment in metastatic prostate cancer starts with androgen deprivation therapy (ADT) by either medical or surgical castration. The addition of chemotherapy in hormone sensitive metastatic prostate cancer was not applicable in the study period. Once progression on ADT occurs the condition is called castration-resistant prostate cancer (CRPC). Key items in the definition of CRPC are a castration level of testosterone and a rising PSA (biochemical progression) and/or radiologic progression[4-7].

Treatment recommendations mainly depend on the presence of metastases and the presence of symptoms, and include (year of introduction in the Netherlands in brackets): secondary hormonal manipulations (including abiraterone (post-docetaxel 2012, chemotherapy naïve 2013) and enzalutamide (post-docetaxel 2013, chemotherapy naïve 2014)), chemotherapy (including docetaxel (2005) and cabazitaxel (2011)), bone directed therapy (including radium-223 (2014)), immune therapy (sipuleucel-T, not available in the Netherlands during the study period) and treatment in clinical trials[4-7].

Trial outcomes form the basis of guidelines and treatment decisions in daily practice. However, trial populations are selected and therefore results may not be representative for the real world population[8]. Moreover, new treatment options in CRPC have changed treatment practice and can influence baseline and post treatment characteristics. Real world data on CRPC patient characteristics, treatment and outcomes are scarce, and reports are often outdated[9]. Therefore we have initiated the CAPRI registry to investigate the clinical outcomes, treatment patterns and economic outcomes of CRPC treatment in daily practice.

In this paper we report the first results of the CAPRI registry. The aim of this analysis is to assess differences in baseline characteristics at CRPC diagnosis, systemic treatment and survival in patients treated in trials versus standard care during the course of CRPC.

METHODS

Study design and setting

CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multi-center cohort study in 20 hospitals in the Netherlands. Before the start of the study, 20 hospitals were selected on the basis of geographical spread, as well as by type of hospital (11 large teaching hospitals, 5 general hospitals and 4 academic hospitals) and accepted the invitation. Data collection started after approval by the local medical ethics committee and hospital board. Patients were retrospective included from January 1, 2010 and data has been regularly updated for all patients from 2013 to 2015. The study population is an estimated 20% sample of all CRPC patients in the Netherlands in the study period. The study is registered in the Dutch Trial Registry as NTR3591.

Objective

To assess the differences in a real world CRPC population between patients treated in a clinical trial ("trial") versus standard care during the course of CRPC.

Participants

Patients were screened for inclusion in both the urology and medical oncology departments of each hospital, and were identified by the diagnosis code prostate cancer from the hospital information systems based on encoded "Diagnosis Treatment Combinations", a nationwide coding and reimbursement system providing information about the type of care, diagnosis and all treatment modalities. 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 PSA and metastatic pattern), and had disease progression despite ADT. Disease progression was defined as in the EAU CRPC definition[6], or as progression according to the treating doctor. Anti-androgen therapy following progression on ADT was considered first line systemic therapy for CRPC. In addition, patients had to be diagnosed with CRPC in years 2010, 2011 or 2012 and have more than two outpatient clinic visits. Eligible patients treated in more than 1 hospital were included only once.

In case a patient was enrolled in a phase I, II, or III trial during the follow up period, the patient was assigned to the "trial" group, otherwise the patient was assigned to the "standard care" group.

Follow up and data collection

Predefined and readily available data from medical records were collected retrospectively by trained data managers. Database cut-off was set on March 1, 2015. See Appendix 1 for full overview of data variables.

Study size
Here we report the first analysis after registration of the first 1,524 consecutive patients.

Statistics
Descriptive statistics were used. Differences in groups were tested by either Chi-square test (categorical variables) or Mann-Whitney U (continuous variables). Survival analyses were done 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 imputation by Monte Carlo Markov Chain method was performed.[10]. For statistical analyses, IBM SPSS Statistics version 22 was used.

RESULTS

At the time of this analysis (March 2015), 29,565 prostate cancer patients were identified. A flow diagram of the screened population, exclusion and inclusion of patients is shown in Figure 1.

The median follow up period from CRPC diagnosis was 23 months (Inter quartile range (IQR) 11 - 34 months). At the time of the database cutoff, 983 deaths (65%) had occurred, 180 patients (12%) were lost to follow up and 361 patients (24%) were still in follow up with a median follow up period of 39 months (range 26 – 62 months).

Baseline characteristics
Baseline characteristics of the patients at CRPC diagnosis, and differences between the groups, are shown in Table 1. Data about the CRPC criteria are provided in supplementary Table S5. The population included 6% of patients without a histologic diagnosis of prostate cancer and 4% with unknown histologic status. The inclusion of these patients was based on PSA and clinical characteristics. Testosterone was not measured in 51% at baseline, however in 10% of patients testosterone was measured later in the course of CRPC. Patients in the trial group were significantly younger (67 vs 76 years, $p<0.001$) and had less comorbidity (No comorbidity 76% vs 54%, $p<0.001$). At CRPC diagnosis, patients in the trial group had higher hemoglobin (8.4 vs. 8.0 mmol/L, $p<0.001$), lower LDH (215 vs 228 U/L, $p=0.033$), and better clinical performance score (ECOG ≥2 2% vs 7%, $p=0.015$).

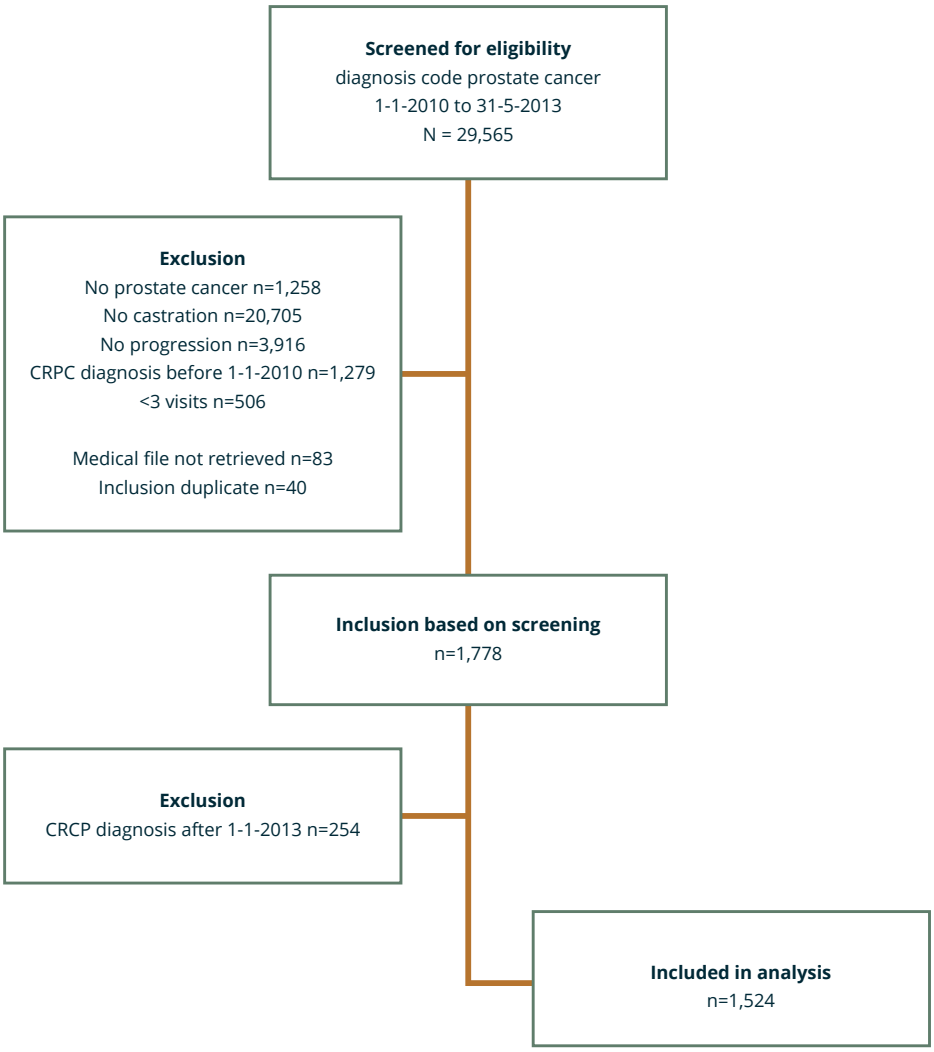


Figure 1. Flow diagram of study population.

1,524 CRPC patients were included, diagnosed with CRPC in 2010 (30%), 2011 (37%) or 2012 (33%). 203 patients (13%) were treated in at least one trial (range 1-4; 48 patients participated in more than 1 trial) during the course of disease (trial group). The remaining 87% had not been treated in a trial (standard care group). The most common trials are shown in supplementary Table S4. Life prolonging drugs have been given to patients in the trial group in both trials and as standard care: docetaxel 46/173 (27%) in trials, cabazitaxel 69/94 (73%) in trials, abiraterone 3/114 (3%) in trials, enzalutamide 0/46 (0%) in trials and radium-223 4/7 (57%) in trials. Life-prolonging drugs have been given as study drug in randomized placebo-controlled trials in a minority of cases (abiraterone/placebo n=5, enzalutamide/placebo n=18).

Table 1. Baseline characteristics at inclusion (CRPC).

			subgroups		
		n=1,524	**n=1,321**	**n=203**	
		Total	**Standard care**	**Trial**	**p value**
Age	median, range (yr)	75 (46-97)	76 (46-97)	67 (46-87)	<0.001
	≥75 yr (n, %)	772 (51%)	737 (56%)	35 (17%)	
Charlson comorbidity index	6 (n, %)	870 (57%)	716 (54%)	154 (76%)	<0.001
	7-8	493 (32%)	448 (34%)	45 (22%)	
	9-10	91 (6%)	88 (7%)	3 (2%)	
	≥11	38 (3%)	37 (3%)	1 (1%)	
	unknown	32 (2%)	32 (2%)	0 (0%)	
Gleason sumscore	≤7 (n, %)	577 (38%)	496 (38%)	81 (40%)	0.971
	8-10	723 (47%)	621 (47%)	102 (50%)	
	no histology	89 (6%)	84 (6%)	5 (3%)	
	metastasis biopsy	16 (1%)	12 (1%)	4 (2%)	
	unknown	119 (8%)	108 (8%)	11 (5%)	
Period on ADT	median, range (months)	15 (0-248)	15 (0-248)	16 (0-164)	0.940
	IQR	8-29	9-29	8-31	
	unknown (n, %)	44 (3%)	37 (3%)	7 (3%)	
Stage	PSA only (%)	11	12	6	0.012
	N0 / N+ / Nx	9 / 35 / 56	8 / 34 / 58	12 / 44 / 43	0.358
	M0 / M+ / Mx (bone)	10 / 61 / 29	10 / 59 / 30	11 / 71 / 17	0.713
	M0 / M+ / Mx (visceral)	19 / 4 / 77	18 / 4 / 78	26 / 3 / 71	0.206
Hemoglobin	median (mmol/L)	8.1	8.0	8.4	<0.001
	IQR	7.4-8.6	7.3-8.6	8.0-8.8	
	unknown/missing (n, %)	491 (32%)	432 (33%)	59 (29%)	
ALP	median (U/L)	105	105	99	0.059
	IQR	78-183	79-190	74-144	
	unknown/missing (n, %)	578 (38%)	516 (39%)	62 (31%)	
LDH	median (U/L)	224	228	215	0.033
	IQR	188-315	189-341	184-265	
	unknown/missing (n, %)	902 (59%)	800 (61%)	102 (50%)	
PSA	median (µg/L)	18.4	17.6	21.1	0.202
	IQR	6.7-62.9	6.6-62.2	8.4-68.8	
	unknown/missing (n, %)	85 (6%)	62 (5%)	23 (11%)	
ECOG performance score	0 (n, %)	315 (21%)	271 (21%)	44 (22%)	0.015
	1	391 (26%)	334 (25%)	57 (28%)	
	≥2	101 (7%)	97 (7%)	4 (2%)	
	unknown/missing	717 (47%)	619 (47%)	98 (48%)	

Total percentages may exceed 100% because of rounding. * total more than 100% because of patients receiving sequential medical and surgical castration; ** indication: adjuvant treatment, initial complete androgen blockade or adverse effects of castration (flushes). Short term (<8 weeks) anti-androgen use to prevent flare at start of luteinizing hormone releasing hormone (LHRH) agonists is excluded. Hemoglobin, ALP, LDH, PSA and ECOG performance score counted as unknown if not present within 90 days prior to and 90 days after CRPC diagnosis. Abbreviations: TUR-P: transurethral resection prostate; EBRT: external beam radiotherapy; ADT: androgen deprivation therapy; IQR: interquartile range; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; PSA: prostate specific antigen; ECOG: Eastern cooperative oncology group.

Treatment

All systemic treatments until end of follow up are summarized in Table 2.

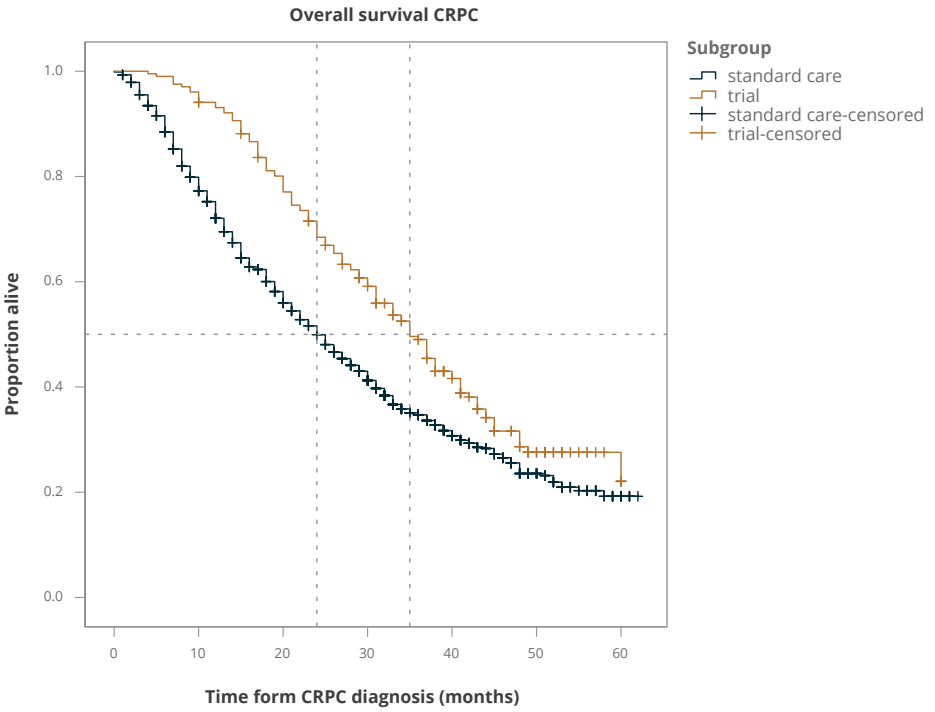
During the follow up period, 46% of all patients were treated with docetaxel. In the trial group, 85% of patients were treated with docetaxel as compared to 40% of patients in the standard care group (p<0.001). In the trial group, cabazitaxel (46% vs 7%, p<0.001), abiraterone post-docetaxel (50% vs 22%, p<0.001), enzalutamide post-docetaxel (20% vs 15%, p<0.001), enzalutamide chemo-naïve (5% vs 1%, p<0.001) and radium-223 post-docetaxel (3% vs 1%, p=0.003) were initiated more often, whereas prescription of abiraterone (6% vs 8%, p=0.419) and radium-223 (0% vs <1%, p=0.377) in chemotherapy-naïve patients was more equally spread.

Survival

Median overall survival (OS) of all patients was 26 months (IQR 12 – 48 months). Median OS was 35 months (IQR 21 –60 months) for the trial group, as compared to 24 months (IQR 12 – 48 months) for the standard care group (p<0.001) (Figure 2). Univariate analysis of baseline variables, trial enrollment and treatment strategy were performed: variables were dichotomized and patients with missing values were analyzed separately (see supplementary Table S6). After multiple imputation of missing values, we performed multivariate analysis of the pooled imputed data. After correction for baseline differences, independent prognostic factors for survival were Gleason score, period on ADT, hemoglobin, alkaline phosphatase (ALP), PSA and ECOG performance status (see Table 3). Treatment with abiraterone, enzalutamide and radium-223 in chemotherapy-naïve patients, as well as treatment with cabazitaxel, abiraterone, enzalutamide and radium-223 post-docetaxel were associated with longer survival (Hazard ratio (HR) 0.53; p<0.0001 and HR 0.46; p<0.0001, respectively). However, trial enrollment was no longer significant for OS (HR 0.95, p=0.658).

Table 2. CRPC systemic treatment (baseline prior therapy including castration therapy and anti-androgens before inclusion are not shown). Abbreviations: IQR: Inter quartile range.

			subgroups		P value
		n=1,524	**n=1,321**	**n=203**	
		Total	**Standard care**	**Trial**	
Systemic treatment	Yes (n, %) No	1,290 (85%) 232 (15%)	1,087 (82%) 232 (18%)	203 (100%) 0 (0%)	<0.001
Hormonal	Anti-androgen Ketoconazole Estradiol Estramustine	860 (56%) 17 (1%) 8 (<1%) 37 (3%)	766 (58%) 11 (1%) 7 (1%) 32 (2%)	94 (46%) 6 (3%) 1 (<1%) 5 (3%)	0.002 0.007 0.945 0.921
Docetaxel naive	Prednisone	87 (6%)	81 (6%)	6 (3%)	0.064
	Abiraterone *Open label in trial*	118 (8%)	105 (8%)	13 (6%) *0 (0%)*	0.419
	Enzalutamide *Open label in trial*	23 (2%)	12 (1%)	11 (5%) *0 (0%)*	<0.001
	Study drug *Abiraterone/placebo* *Enzalutamide/placebo* Radium-223 *Open label in trial*	28 (2%) 5 (<1%)	0 (0%) 5 (<1%)	28 (14%) *5 (2%)* *18 (9%)* 0 (0%) *0 (0%)*	<0.001 0.377
Docetaxel	Docetaxel *Open label in trial*	697 (46%)	524 (40%)	173 (85%) *46 (23%)*	<0.001
Post docetaxel	No treatment Cabazitaxel *Open label in trial*	196 (28%) 190 (13%)	170 (32%) 96 (7%)	26 (13%) 94 (46%) *69 (34%)*	<0.001 <0.001
	Abiraterone *Open label in trial*	385 (25%)	284 (22%)	101 (50%) *3 (1%)*	<0.001
	Enzalutamide *Open label in trial*	115 (8%)	80 (15%)	35 (20%) *0 (0%)*	<0.001
	Docetaxel rechallenge	76 (4%)	50 (4%)	16 (8%)	0.007
	Mitoxantrone	13 (1%)	8 (1%)	7 (3%)	<0.001
	Study drug Radium-223 *Open label in trial* Prednisone	72 (4%) 19 (1%) 6 (<1%)	0 (0%) 12 (1%) 6 (<1%)	72 (35%) 7 (3%) *4 (2%)* 0 (0%)	<0.001 0.003 0.333
Treatment lines	Median (range) IQR	2 (0-9) 1-3	1 (0-8) 1-3	3 (1-9) 3-4	<0.001



Number at risk

Standard care	1,321	986	674	426	191	60	9
Trial	203	191	153	111	61	21	4

Figure 2. Unadjusted overall survival from CRPC diagnosis; median overall survival standard care vs trial subgroup 24 vs 35 months (p<0.001).

DISCUSSION

This is the first large registry in which outcomes are collected independent of the treating doctors. The design of the registry allowed the inclusion of patients without histologic confirmation of prostate cancer or not meeting the CRPC definition by the EAU, but regarded as CRPC by the treating doctor. Therefore, the outcomes in this study truly reflect daily practice.

The population included 6% of patients without a histologic diagnosis of prostate cancer. However, patients who started treatment for CRPC had primary metastatic disease and an elevated initial PSA, making the diagnosis of metastatic prostate cancer likely. The population included 41% of patients without measurement of testosterone during the course of disease. It is unlikely that patients are enrolled in trials an objective

CRPC status, however the baseline period in our study (90 days before to 90 days after CRPC diagnosis) differs from the date of trial enrollment. This explains missing or unknown data on CRPC status in the trial subgroup.

We observed a median OS in the total population of 26 months, and a longer OS in the trial group compared to standard care (35 vs 24 months, p<0.001). This difference may at least partly be explained by confounding factors, including baseline differences or differences in treatment. After correction for baseline prognostic factors and treatment effect, trial participation was not associated with a significantly lower risk of death (HR 0.95, p=0.658).

Trial patients mainly differed from standard care patients with regards to age (67 vs 76 years), comorbidity (no comorbidity 76% vs 54%) and treatment strategy (docetaxel treatment 85% vs 40%).

Baseline characteristics of recent clinical trials in docetaxel-naïve populations are relatively similar to this study, particularly to the trial group[11-13]. However, the median OS in our trial group compares slightly favorably to the median OS of comparator groups in recent chemotherapy-naïve CRPC trials: 35 months vs 21.7-30.2 months[11-13]. We observed subsequent docetaxel therapy in the trial group in 85% of patients, whereas this percentage ranged from 50-70% in the comparator groups of the recent trials[11-13]. In a single-center analysis of trial participants only, chemotherapy-naïve CRPC patients (median age 67 years) had a median OS of 30.6 months and subsequent docetaxel treatment was given in 64%[14]. In conclusion, the baseline characteristics, systemic treatment and outcomes of our trial subgroup are representative for known trial populations.

Missing values are a limitation of our study, but this is inherent to the retrospective method. For this analysis, baseline characteristics at the moment of CRPC diagnosis and not the characteristics at the start of each subsequent treatment were analyzed. In the baseline period, evaluation of disease stage (CT-scan and bone scintigraphy) and laboratory parameters (hemoglobin, ALP, LDH), as well as performance status registration, were frequently incomplete. LDH and visceral disease status were missing in >50% of cases, but were included because of known prognostic relevance. Missing values were less frequent at the start of subsequent treatment, especially in life-prolonging drugs (data not shown). The high number of missing values in prognostic factors is a reflection of daily practice and the absence of direct need of documentation of these parameters at progression on ADT. Gleason scores may be missing if no histologic biopsy was taken, or if the biopsy dates from the period prior to

the introduction of the Gleason scoring system in 2004[15]. However, we adapted tumor grades to Gleason scores if possible (see Appendix 1). When excluding all patients with missing values in prognostic factors, only 113 patients could be included in the multivariate analysis. This obviously would have lacked statistical power. Imputation of missing data may provide a valid and reproducible solution for this problem, allowing multivariate analysis on the complete study population[10].

Known predictors of survival in metastatic CRPC include disease site (visceral disease), Gleason score, performance status, ALP, hemoglobin, PSA and LDH[16]. After imputation of missing values, we confirmed these predictors of survival in our population (see supplementary Table S7). Moreover, after correction for baseline differences, independent significant prognostic factors for survival did also include period on ADT.

The treatment effect is difficult to assess in this analysis. Treatments were given sequentially with differential sequences and in a non-protocolled way. Therefore we analyzed the prescription of life-prolonging drugs (abiraterone, enzalutamide, radium-223, docetaxel and cabazitaxel) as a proxy for treatment effect. We observed that patients in the trial group were treated with more treatment lines and more life-prolonging drugs. Treatment with life-prolonging drugs was associated with increased OS in multivariate analysis.

Trial patients were enrolled in more than 15 different trials. A total of 264 trial treatments were registered, with a substantial number of treatments in either a trial with survival benefit but placebo-controlled (n=28), a trial with no difference in outcome between the study arms (n=96) or a trial that has no results yet (n=93). Although we did not aim to answer the question if trial participation is an independent prognostic factor for survival, we hypothesized that placebo treatment or treatment in trials without proven survival benefit over standard treatment may have diluted a positive effect of trial treatment on survival, if present.

Based on a systematic review in 2001, it was concluded that there is weak evidence to suggest that clinical trials have a positive effect on the outcome of participants, possibly through enhancing quality of care, stringent patient selection criteria, and adapting aggressive measures for treating patients in trials[17]. Two recent reports on patients treated with docetaxel for metastatic CRPC resulted in a differential independent effect of trial participation on OS in multivariate analysis [18;19]. We hypothesized that our results may reflect the high availability of novel treatment options and mandatory health care insurance in the Netherlands. A limitation may therefore be the lack of

external validity to populations outside the Netherlands, especially those populations with different access to healthcare.

In conclusion, we have shown that baseline characteristics of patients enrolled in a trial differed from patients who are not, as well as the percentage of patients treated with docetaxel. The difference in OS between trial patients and standard care patients did not retain statistical significance after correction for baseline differences and treatment effect. These results may indicate that trial results cannot easily be translated to real world practice. Further studies are needed to assess clinical outcomes, patient reported outcomes and cost-effectiveness of treatment in real world populations.

REFERENCES

1 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63:11-30.

2 www.cijfersoverkanker.nl. Nederlandse Kankerregistratie, beheerd door IKNL (c) maart 2015. 2015.

3 Cremers RG, Karim-Kos HE, Houterman S, et al. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. Eur J Cancer 2010; 46:2077-2087.

4 Cookson MS, Roth BJ, Dahm P, et al. Castration-resistant prostate cancer: AUA Guideline. J Urol 2013; 190:429-438.

5 NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline) version 1.2014. www.nccn.org . 27-11-2013. 24-3-2014.

6 Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014; 65:467-479.

7 Horwich A, Hugosson J, de Reijke RT, et al. Prostate cancer: ESMO Consensus Conference Guidelines 2012. Ann Oncol 2013; 24:1141-1162.

8 Elting LS, Cooksley C, Bekele BN, et al. Generalizability of cancer clinical trial results: prognostic differences between participants and nonparticipants. Cancer 2006; 106:2452-2458.

9 Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract 2011; 65:1180-1192.

10 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011; 30:377-399.

11 Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-422.

12 Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138-148.

13 Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371:424-433.

14 Omlin A, Pezaro C, Mukherji D, et al. Improved survival in a cohort of trial participants with metastatic castration-resistant prostate cancer demonstrates the need for updated prognostic nomograms. Eur Urol 2013; 64:300-306.

15 Epstein JI AFAJeal. Acinar adenocarcinoma. In Eble JN SGEJeae, editor. World Health Organization Classification of Tumours. Pathology & Genetics: Tumours of the Urinary System and Male Genital Organs. Lyon, France: IARC Press, 2004, pp. 179-184.

16 Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 2003; 21:1232-1237.

17 Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". J Clin Epidemiol 2001; 54:217-224.

18 Goyal J, Nuhn P, Huang P, et al. The effect of clinical trial participation versus non-participation on overall survival in men receiving first-line docetaxel-containing chemotherapy for metastatic castration-resistant prostate cancer. BJU Int 2012; 110:E575-E582.

19 Templeton AJ, Vera-Badillo FE, Wang L, et al. Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials. Ann Oncol 2013; 24:2972-2977.

Appendix 1: Outcome measures

Age at inclusion was calculated by subtracting the year of birth from the year of inclusion, and dichotomized to <75 years and ≥75 years. Comorbidity was registered based on the complete medical file, and Charlson comorbidity index was calculated and categorized as described before[1]. Since all patients had CRPC, minimum Charlson comorbidity index was 6. Gleason sumscore was registered from the first pathology report at prostate cancer diagnosis, as described by the local pathologist. If Gleason sumscore was absent, but tumor grading was known, the tumor grade was converted as follows: Anderson/UICC grade 1 to Gleason 2-6; Anderson/UICC grade 2 to Gleason 7; Anderson/UICC grade 3 to Gleason 8-10. Total Gleason sumscore was dichotomized to <8 and 8-10. The period on ADT was calculated by subtracting the date of CRPC diagnosis from the date of first administration of palliative castration therapy (in case of progression during adjuvant therapy, the date of first administration of adjuvant castration therapy). Disease stage was registered based on previous and actual staging; either N+/M+ (known lymph node/visceral/bone metastases), N0/M0 (no known lymph node/visceral/bone metastases with assessment within 2 months, Nx/Mx (no known lymph node/visceral/bone metastases and no assessment within 2 months). Laboratory results (hemoglobin (Hb), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and prostate specific antigen (PSA)), presence of symptoms and performance status were only included for baseline assessment if measured within 90 days prior to or 90 days after CRPC diagnosis and before initiation of first-line therapy. Performance status was registered according to the Eastern Cooperative Oncology Group (ECOG) grading or Karnofsky index in the medical file, and when absent, performance status was scored by the datamanager based on the narrative in the status if possible[2].

REFERENCES

1 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373-383.

2 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.

Table S4. overview of trial treatment. If possible, trial identifier is shown for trials that not have been published (clinicaltrials.gov and trialregister.nl). DOC = docetaxel, CAB = cabazitaxel.

Comparator drug	Intervention drug	Trial examples	Total number of treatments
docetaxel	DOC+lenalidomide, DOC+risedronate, DOC+rhenium-188, DOC+carboplatin DOC+custirsen	MAINSAIL [3], NEPRO [4], TAXIUM-II, RECARDO (NTR3070), SYNERGY (NCT01188187)	46
cabazitaxel	CAB+budesonide, CAB 20mg/m2, CAB+rhenium-188	CABARESC (NTR2991), PROSELICA (NCT01308580), Re-Cab (NTR3233)	69
placebo	abiraterone	COU-AA-302 [5]	8
placebo	enzalutamide	PREVAIL [6]	18
placebo	orteronel	ELM-PC4 [7], ELM-PC5 [8]	20
placebo	ipilimumab	CA184-095 (NCT01057810), CA184-043 [9]	30
placebo	cabozantinib	COMET-1 (NCT01605227)	18
other	other		55

REFERENCES

3 Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2015; 16:417-425.

4 Meulenbeld HJ, van Werkhoven ED, Coenen JL, et al. Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro). Eur J Cancer 2012; 48:2993-3000.

5 Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138-148.

6 Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371:424-433.

7 Saad F, Fizazi K, Jinga V, et al. Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. Lancet Oncol 2015; 16:338-348.

8 Fizazi K, Jones R, Oudard S, et al. Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. J Clin Oncol 2015; 33:723-731.

9 Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2014; 15:700-712.

Table S5. Distribution of CRPC diagnosis criteria at baseline.

			subgroups		
		n=1,524	**n=1,321**	**n=203**	
		Total	**Standard care**	**Trial**	**p value**
Testosterone	≥1,7 nmol/L (non-castrate) (n,%)	57 (4%)	49 (4%)	8 (4%)	<0.001
	<1,7 nmol/L ≤90 days after CRPC	610 (40%)	487 (37%)	123 (61%)	
	<1,7 nmol/l >90 days after CRPC	153 (10%)	134 (10%)	19 (9%)	
	Not measured	624 (41%)	589 (45%)	35 (17%)	
	Unknown/missing	80 (5%)	62 (5%)	18 (9%)	
Histology	Histology confirmed (n,%)	1371 (90%)	1182 (89%)	189 (93%)	0.088
	No histology	89 (6%)	84 (6%)	5 (3%)	
	Unknown/missing	64 (4%)	55 (4%)	9 (4%)	
PSA progression at baseline CRPC	No (n,%)	45 (3%)	40 (3%)	5 (3%)	0.656
	Yes	1,447 (95%)	1,253 (95%)	194 (96%)	
	Unknown/missing	32 (2%)	28 (2%)	4 (2%)	
Radiologic progression at baseline CRPC	No (n,%)	214 (14%)	190 (14%)	24 (12%)	0.115
	Yes	357 (23%)	300 (23%)	57 (28%)	
	Unknown/missing	953 (63%)	831 (63%)	122 (60%)	
Radiologic or PSA progression according to definition CRPC	No (n,%)	22 (1%)	18 (1%)	4 (2%)	0.378
	Yes	1068 (70%)	940 (71%)	128 (63%)	
	Unknown/missing	434 (29%)	363 (28%)	71 (35%)	

Table S6. univariate analysis of predictors of overall survival duration, at inclusion (CRPC). Nr=not reached; Ref=reference; CI: confidence interval; ADT: androgen deprivation therapy; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; PSA: prostate specific antigen; ECOG: Eastern cooperative oncology group; abi: abiraterone acetate; enz: enzalutamide; rad: radium-223; doc: docetaxel; cab: cabazitaxel.

		Patients	**Events**	**Survival (median, IQR)**	**Hazard ratio (95% CI)**	
		n	**n**	**Months**		**p value**
Age (years)	<75	752	460	31 (15-53)	ref	<0.001
	≥75	772	523	23 (11-42)	1.13 (1.20-1.54)	-
	missing	0	-	-	-	
Charlson comorbidity index	6	870	556	28 (14-48)	ref	0.024
	≥7	622	411	23 (11-47)	1.16 (1.02-1.32)	0.246
	missing	32	16	39 (20-nr)	0.75 (0.45-1.23)	
Gleason sumscore	≤7	577	338	32 (15-nr)	Ref	<0.001
	8-10	723	490	23 (12-43)	1.41 (1.22-1.62)	<0.001
	missing	224	155	21 (11-43)	1.49 (1.13-1.78)	
Period on ADT (months)	<15*	719	537	20 (10-34)	Ref	<0.001
	≥15	761	419	35 (17-nr)	0.50 (0.44-0.56)	0.020
	missing	44	27	28 (12-53)	0.63 (0.43-0.93)	
Visceral disease	No**	619	373	31 (16-nr)	Ref	<0.001
	Yes	61	48	20 (7-38)	1.80 (1.34-2.44)	<0.001
	missing	844	562	23 (11-45)	1.43 (1.25-1.63)	
ECOG Performance status	0	315	165	37 (21-nr)	Ref	<0.001
	1	391	281	20 (10-38)	1.97 (1.63-2.39)	<0.001
	>1	101	92	6 (3-13)	6.52 (5.03-8.44)	0.002
	missing	717	445	29 (14-58)	1.33 (1.11-1.59)	
Hemoglobin	<8.1*	492	383	15 (8-30)	2.15 (1.85-2.50)	<0.001
	≥8.1	541	320	30 (15-nr)	Ref	0.158
	missing	491	280	34 (19-58)	0.89 (0.76-1.05)	
ALP	<105*	465	265	33 (18-nr)	Ref	<0.001
	≥105	481	381	15 (8-28)	2.39 (2.04-2.80)	0.663
	missing	578	337	33 (15-53)	1.04 (0.89-1.22)	
PSA	<18*	711	393	35 (19-nr)	Ref	<0.001
	≥18	728	536	18 (9-34)	2.06 (1.81-2.35)	0.083
	missing	85	54	31 (15-48)	1.29 (0.97-1.71)	
LDH	<224*	311	206	25 (15-44)	Ref	<0.001
	≥224	311	248	14 (7-29)	1.73 (1.44-2.08)	0.003
	missing	902	529	31 (15-60)	0.79 (0.67-0.92)	
Trial participation	No	1,321	854	24 (12-48)	Ref	<0.001
	Yes	203	129	35 (21-60)	0.69 (0.57-0.82)	
Abi/Enz/Rad chemotherapy-naive	No	1,390	924	24 (12-47)	Ref	<0.001
	Yes	134	59	41 (29-60)	0.45 (0.35-0.59)	

Table S6. (Continued)

		Patients	Events	Survival (median, IQR)	Hazard ratio (95% CI)	
		n	n	Months		p value
Docetaxel	No	827	509	24 (10-60)	Ref	0.274
	Yes	697	474	28 (15-46)	0.93 (0.82-1.06)	
Cab/Abi/Enz/Rad post-docetaxel	No	1,049	669	22 (10-52)	Ref	<0.001
	Yes	475	314	32 (21-48)	0.72 (0.63-0.83)	

* dichotomized on the basis of the median value.
** if visceral disease was absent in subsequent assessment, no visceral disease at time of CRPC was assumed.

Table S7. multivariate model predicting overall survival using Cox-regression of known prognostic variables only (pooled imputed data); Abbreviations: Sig: significance; HR: hazard ratio; CI: confidence interval; Cont = continuous variable; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; PSA: prostate specific antigen; ECOG: Eastern cooperative oncology group.

			95% CI for HR	
Pooled imputed data (n=1,524)	Sig. (p value)	HR	Lower	Upper
ECOG performance 1 vs 0	<0.001	1.613	1.291	2.016
ECOG performance >1 vs 0	<0.001	4.731	3.317	6.748
Gleason sumscore 8-10 vs ≤7	0.015	1.234	1.044	1.459
Log (LDH (cont, U/L))	0.225	1.408	0.793	2.500
Log (ALP (cont, U/L))	<0.001	2.342	1.818	3.016
Log (PSA (cont, µg/L))	<0.001	1.396	1.227	1.587
Visceral metastasis yes vs no	0.035	1.464	1.030	2.079
Hemoglobin (cont, mmol/L)	<0.001	0.802	0.738	0.871

CHAPTER 4

Second line cabazitaxel treatment in castration-resistant prostate cancer (CRPC) clinical trials compared to standard of care in CAPRI: an observational study in the Netherlands.

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ABSTRACT

Aim

Cabazitaxel has been shown to improve overall survival (OS) in mCRPC patients after docetaxel in the TROPIC trial. However trial populations may not reflect the real world population. The objective is to compare patient characteristics and outcome of cabazitaxel within and outside trials (standard of care - SOC).

Methods

mCRPC patients treated with cabazitaxel directly after docetaxel before 2017 were retrospectively identified and followed to 2018. Patients were grouped based on treatment within a trial or SOC. Outcomes included OS and PSA response.

Results

From 3,616 patients in the CAPRI registry, we identified 356 patients treated with cabazitaxel, of whom 173 patients in second line. Trial patients had favorable prognostic factors: less symptoms and visceral disease, lower LDH, higher hemoglobin, more docetaxel cycles and a longer treatment-free interval since docetaxel. PSA response (≥ 50% decline) was 28 vs 12%, respectively (p=0.209). mOS was 13.6 vs 9.6 months for trial and SOC subgroups, respectively (HR 0.73, p=0.067). After correction for prognostic factors, there was no difference in survival (HR 1.00, p=0.999). Longer duration of ADT treatment, lower LDH and lower PSA were associated with longer OS; visceral disease had a trend for shorter OS.

Conclusion

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 an adequate estimation of the 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 for chemotherapy[1,2]. In patients who progressed 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[3]. In a comparable population, abiraterone plus prednisone, enzalutamide and radium-223 were shown to improve OS to a similar extent compared to placebo[4-6]. 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[7]. 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[8]. 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 7.0-12.7 months versus trial mOS 13.4-15.1 months, respectively)[3,9-13]. However, subgroups of patients treated with an extra life prolonging drug (LPD) in third line (post-cabazitaxel) do better with mOS reaching 18.2-22.7 months[11,14-16].

Patients in clinical trials are typically a selected population based on strict eligibility criteria, with the aim to include a homogeneous and fit population[17]. 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 given 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 [18]. Real world practice may also be variable in differential monitoring, compliance, (budget) constraints and increased treatment options over time[17]. We have recently 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[18]. Previous single center reports have shown differences in clinical trial and real world populations[19] and differential outcomes for docetaxel treatment in CRPC[19,20].

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 the real world population. The objective of this study is to compare patient characteristics, treatment and outcomes of patients treated with cabazitaxel in second line both in clinical trials and outside a clinical trial (standard of care, SOC), in our multicenter observational CAPRI registry.

METHODS

The study design, setting, participants, follow up and data collection of the CAPRI registry has been described in more detail[18]. In short: CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multi-center 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 has been regularly updated for all patients from 2013 to 2018. The study population is an estimated 20% sample of all CRPC patients in the Netherlands in the study period. The study is registered in the Dutch Trial Registry as NTR3591.

Objective

To assess the differences in patient characteristics, number of cycles, PSA response and OS of patients treated with cabazitaxel in second line mCRPC, defined as directly post-docetaxel regardless of pre-docetaxel treatment, both in clinical trials and outside clinical trial (standard of care, SOC).

Participants

CRPC patients from the CAPRI registry diagnosed before 1-1-2016 and treated with docetaxel for mCRPC, followed by second line cabazitaxel before 1-1-2017 were included for this analysis. If a patient was enrolled in 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 on androgen deprivation therapy (ADT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH),

prostate specific antigen (PSA), hemoglobin, ECOG performance status, presence of visceral disease, opioid use and symptoms. Time of response to ADT was defined as the time from start ADT to diagnosis of CRPC.

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

Statistics

The sample size was not based on power calculations. Descriptive statistics were used. Differences in subgroups were tested for significance by either Chi-square test (categorical variables) or Mann-Whitney U (continuous variables). OS from start of cabazitaxel treatment to database cut off was analyzed by Kaplan-Meier methods and Cox regression analyses. Differences were considered of statistical significance at a p-value of 0.05 or less.

For PSA response, we report the maximum decline from baseline, and in case no decline occurred, we report the response at 12 weeks (conform PCWG3 guidelines[21]) 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 rise 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, IBM SPSS Statistics version 22 was used.

RESULTS

Population

We identified 406 patients treated with cabazitaxel after docetaxel in the study period; 2 patients were excluded because docetaxel was given for hormone sensitive disease and not mCRPC. 173 patients were treated with cabazitaxel in second line (ie after docetaxel). Of these 173 patients, 64 (37%) patients were treated within a trial (46, 11, 6, 1 patients in the CABARESC, PROSELICA, Re-Cab and CABENZA trial, respectively). 184 patients out of 406 received cabazitaxel in third line (SOC n=141, trial n=43) and

47 patients received cabazitaxel in fourth line or higher (SOC n=45, trial n=2) and were excluded from this analysis.

Median follow up was 9.9 months (IQR 5.2-18.0 months). 149 patients (86%) had died at database cutoff. Baseline characteristics and treatment for CRPC is summarized in Table 1a and 1b. Patients treated in trials had a more favorable prognostic profile compared to SOC patients (significantly higher hemoglobin, lower LDH, less visceral metastases and less symptoms, and a trend for longer time on 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 standard care patients. Subsequent treatment after cabazitaxel included significant 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.

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

Table 1a. baseline characteristics at start cabazitaxel (baseline period defined as 42 days before to 7 days after start of cabazitaxel).

	Cabazitaxel 2nd line (n=173)			**TROPIC**
	SOC (n=109)	**Trial (n=64)**	**p-value**	**cabazitaxel arm (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 (%)			0.112	
6	63	75		n.r.
7-8	32	25		
9-10	4	0		
>10	1	0		
Gleason score (%)			0.149	
≤7	29	38		n.r.
8-10	66	52		
unknown	5	11		
Time of response to ADT (months)			0.780	
Median (IQR)	11 (7-16)	11 (6-23)		n.r.
Time on ADT (months)			0.091	
Median (IQR)	25 (18-37)	30 (19-45)		n.r.

Table 1a. (Continued)

	Cabazitaxel 2nd line (n=173)			TROPIC
	SOC (n=109)	**Trial (n=64)**	**p-value**	**cabazitaxel arm (n=378)**
ALP (U/L)			0.799	
Median (IQR)	222 (100-360)	192 (97-366)		n.r.
Missing (%)	18	11		
PSA (ug/L)			0.711	
Median (IQR)	200 (65-567)	209 (79-500)		144
Missing (%)	12	8		1
Hemoglobin (mmol/L)			0.029	
Median (IQR)	7.1 (6.3-7.8)	7.7 (6.7-8.1)		n.r.
Missing (%)	17	11		
LDH (U/L)			0.010	
Median (IQR)	328 (252-504)	268 (209-397		n.r.
Missing (%)	26	14		
ECOG performance (%)			0.186	
0	16	23		ECOG 0-1: 93%
1	49	56		
>1	9	3		n.r.
Missing	27	17		n.r.
Visceral disease (%)				
No	29	45		n.r.
Yes	19	11		25%
Missing	52	44	0.038	n.r.
Opioid use (%)			0.140	
No	23	41		n.r.
Yes	28	27		
Missing	50	33		
Symptoms (%)			0.033	
No	6	17		n.r.
Yes	78	72		
Missing	16	11		

Total percentages may not equal 100 because of rounding. N.r. = not reported; IQR, interquartile range; SOC, standard of care; ADT, androgen deprivation therapy; ALP, alkaline phosphatase; PSA, prostate specific antigen; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group

Table 1b. Treatment characteristics pre-docetaxel, docetaxel and post-cabazitaxel. Life prolonging drug treatments: docetaxel, abiraterone, cabazitaxel, enzalutamide, radium-223; LPD, life prolonging drug; DOC, docetaxel; mo, months; IQR, interquartile range; SOC, standard of care

	Cabazitaxel 2nd line (n=173)			**TROPIC**
	SOC (n=109)	**Trial (n=64)**	**p-value**	**cabazitaxel arm (n=378)**
Pre-docetaxel therapy (%)				
Abiraterone	10	2	0.099	n.r.
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	
Docetaxel cycles				
Median (IQR)	7 (5-10)	10 (7-10)	0.002	n.r.
Missing (%)	1	3		
Time last DOC dose 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 month (valid %)	48	33		
Missing (%)	8	9		
Time since last DOC dose (mo)				
Median (IQR)	2.2 (0.9-4.7)	3.9 (2.0-6.0)	0.001	n.r.
<6 months (valid %)	86	74		
Missing (%)	5	5		
Type of progression on DOC (%)				
PSA	84	91	0.095	n.r.
missing	6	6	0.761	
Radiologic	37	44	0.704	
missing	53	42		
Clinical	58	53		
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	n.r.

Table 1b. (Continued)

	Cabazitaxel 2nd line (n=173)			TROPIC
	SOC (n=109)	**Trial (n=64)**	**p-value**	**cabazitaxel arm (n=378)**
Total LPD treatment duration in days (median, IQR)				
ART	185 (113-273)	152 (91-253)	0.156	n.r.
Taxane	218 (134-305)	268 (217-357)		
Radium	102 (52-148)	143 (72-217)		
Total	328 (221-508)	365 (269-534)		
Number of LPD treatments (%)				
2	26	27	0.672	n.r.
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	n.r.
range	2-8	2-7		

Treatment outcomes

Treatment intensity of cabazitaxel was numerically higher in trials as compared to SOC, expressed by both median number of cabazitaxel cycles (5 versus 4, respectively; p=0.051), proportion of patients reaching 10 cycles (24 vs 14%, respectively) and cumulative dose (228mg versus 165mg; p=0.026) (see Table 2).

Serious adverse events (hospitalization and death) did not differ significantly between trial and SOC patients (see Table 2). 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 vs 12%, respectively (p=0.209). In patients receiving cabazitaxel directly post-docetaxel, median OS was 13.6 vs 9.6 months for trial patients and SOC, respectively (HR 0.732, 95% CI 0.524-1.022, p=0.067), see Table 3 and Figure 1. The patients who were treated with at least an additional LPD post-cabazitaxel had a median OS from the first cabazitaxel treatment of 15.1 months, versus 4.6 months for patients who only received best-supportive care after cabazitaxel treatment. Only 42 of 173 patients had no missing data for multivariate cox regression analysis. After imputation of missing values in all patients, in multivariate analysis trial participation was not prognostic for survival in the pooled data (HR 1.00, 95% CI 0.69-1.45, p=0.999). Longer time on ADT, lower PSA and lower LDH were prognostic for longer OS, and visceral disease had a trend for shorter survival (see Table 4).

Table 2. Treatment characteristics of cabazitaxel treatment.

	Cabazitaxel 2nd line (n=173)			TROPIC
	SOC (n=104; 5 pts censored)	**Trial (n=64)**	**p-value**	**cabazitaxel arm (n=378)**
Cycles (n)				
Median (IQR)	4 (3-6)	5 (3-9)	0.051	6 (3-10)
≥10 cycles (%)	14	24		28
Range	1-11	1-12		n.r.
Missing (%)	4	3		2
Dose adjustment (%)				
No dose reduction or delay	36	42	0.743	n.r.
Dose mitigation	33	44		9%
Dose reduction	15	20		
Dose delay	26	38		
Missing	31	9		
G-CSF support (%)				
None	80	81	0.534	n.r.
Pegfilgastrim	3	5		
Missing	17	14		
Cumulative dose (mg)				
Median (IQR)	165 (126-300)	228 (144-422)	0.026	n.r.
Missing (%)	36	28		
Severe adverse events (%)				
None	30	33	0.967	n.r.
Any	44	48		5
Hospital admission	44	48		
Death	8	3		
Missing	26	19		
Reason of discontinuation (%)				
PD	72	50	0.011	48
Patient preference	2	0		2
Toxicity	4	14		18
Death	5	2		28
Treatment completed	8	19		
Other	2	2		
Missing	8	14		

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 less than 30 days. 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. IQR, interquartile range; CI, confidence interval; SOC, standard of care; G-CSF, Granulocyte-colony stimulating factor; PD, progressive disease

Table 3. Treatment outcomes. IQR, interquartile range; CI, confidence interval; SOC, standard of care

	Cabazitaxel 2nd line (n=173)			TROPIC
	SOC (n=109)	**Trial (n=64)**	**p-value**	**cabazitaxel arm (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)

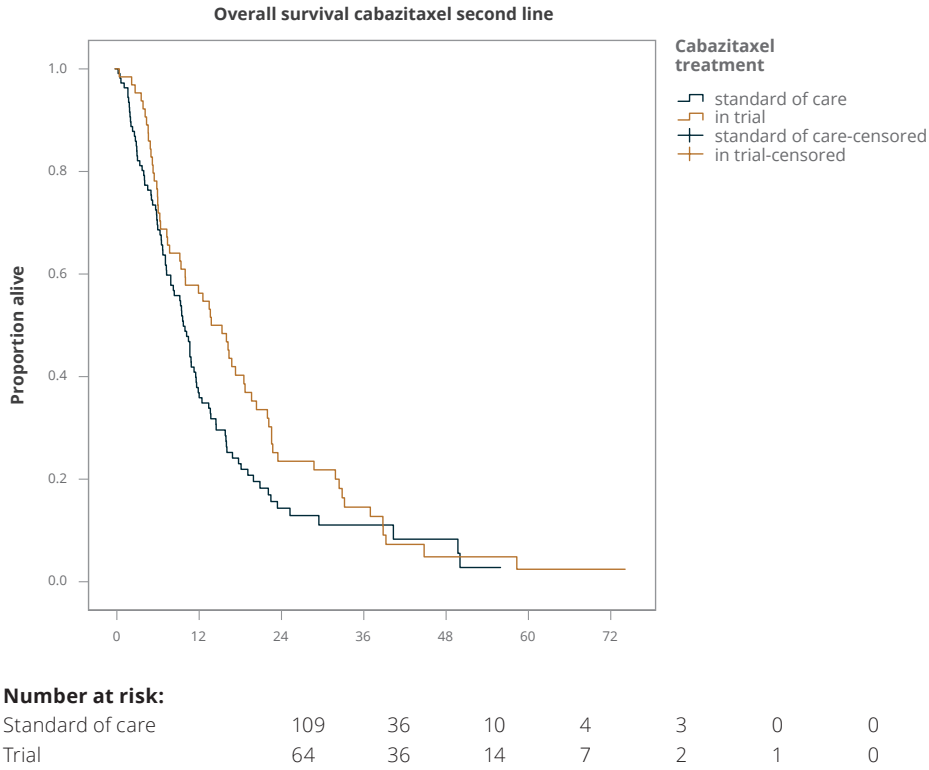

Figure 1. Overall survival second line cabazitaxel treatment (univariate)

Table 4. Univariate and multivariate Cox-proportional hazard analysis for overall survival (multivariate analysis after multiple imputation (pooled data)); HR, hazard ratio; CI, confidence interval; ADT, androgen deprivation therapy; cont., continuous; ALP, alkaline phosphatase; PSA, prostate specific antigen; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group

		Cabazitaxel 2nd line				Cabazitaxel 2nd line		
		actual data				**pooled imputed data**		
		(n=173, 149 events)				(n=173, 149 events)		
		univariate				multivariate		
		events/cases	HR	95% CI interval	P value	HR	95% CI interval	P value
Age		149/173	1.011	0.985-1.011	0.414	1.015	0,984-1,047	0,349
Charlson comorbidity index (%)		149/173						
	7-8 vs 6		0.974	0.681-1.392	0.884			
	9-10 vs 6		0.800	0.253-2.528	0.704			
	>10 vs 6		2.540	0.350-18.407	0.356			
Gleason sumscore								
	8-10 vs ≤7	138/161	1.278	0.892-1.830	0.181	1.102	0.720-1.687	0.654
Time on ADT (months, cont.)		149/173	0.984	0.975-0.994	0.001	0.988	0.976-0.999	0.033
ALP (U/L, cont.)		129/146	1.000	1.000-1.001	0.241	1.000	0.999-1.001	0.589
PSA (ug/L, cont.)		134/155	1.000	1.000-1.000	0.027	1.000	1.000-1.000	0.046
Hemoglobin (mmol/L, cont.)		131/147	0.782	0.659-0.928	0.005	1.006	0.819-1.235	0.957
LDH (U/L, cont.)		121/136	1.001	1.000-1.001	<0.001	1.001	1.000-1.001	0.039
ECOG performance score		118/133						
	1 vs 0		1.568	1.005-2.444	0.047	1.040	0.627-1.725	0.878

Table 4. (Continued)

		Cabazitaxel 2nd line				Cabazitaxel 2nd line		
		actual data				**pooled imputed data**		
		(n=173, 149 events)				(n=173, 149 events)		
		univariate				multivariate		
		events/cases	HR	95% CI interval	P value	HR	95% CI interval	P value
	>1 vs 0		2.228	1.028-4.825	0.042	1.031	0.427-2.489	0.945
Visceral disease (%)		76/88						
	Yes vs No		3.102	1.869-5.150	<0.001	2.143	0.875-5.249	0.086
Opioid use (%)		88/98						
	Yes vs No		1.973	1.253-3.108	0.003	1.505	0.763-2.968	0.215
Symptoms (%)		132/149						
	Yes vs No		1.931	1.138-3.277	0.015	1.524	0.812-2.860	0.187
Time since last docetaxel (months, cont.)		143/166	0.901	0.849-0.956	0.001	0.958	0.887-1.035	0.275
Docetaxel cycles (n, cont.)		146/170	0.937	0.880-0.998	0.044	0.969	0.898-1.045	0.409
Trial		149/173						
	Yes vs No		0.732	0.524-1.022	0.067	1.000	0.688-1.453	0.999

DISCUSSION

Differential outcomes

To our knowledge, this is the first study comparing trial patients and SOC patients treated with cabazitaxel after docetaxel in one of the largest contemporary observational studies. 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 to the mOS of patients in the TROPIC trial (13.4 months vs 15.1 months)[3]. The eligibility criteria of these trial patients (enrolled in the PROSELICA, Re-Cab, CABARESC and CABENZA trials) were similar to the TROPIC trial, with minor differences with respect to ECOG performance score and estimated life expectancy (see Table 5)[9,22]. Although the median OS in trial patients confirms the survival outcome of the TROPIC trial, the SOC patients had a trend to shorter OS in first-line post-docetaxel (9.6 vs 13.4 months).

Table 5. Key eligibility criteria in trials; References: www.clinicaltrials.gov (NCT identifier) and www.trialregister.nl (NTR number); published results: 3,9,22. CNS, central nervous system; N.a., not available; mo, months.

Trial	TROPIC	PROSELICA	CABARESC	Re-Cab	CABENZA
Reference nr	NCT00417079	NCT01308580	NTR2991	NTR3233	NTR5164
Study type	Phase III, open-label randomised	Phase III, open-label randomised	Phase II, open-label randomised	Phase I/II, open-label randomised	Single-arm crossover study
Inclusion					
Life expectancy	>2 mo	>6 mo	any	>3 mo	any
ECOG	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
Outcomes Cabazitaxel 25mg/m2 arm					
Overall survival median	15.1	14.5	n.a.	n.a.	n.a.

Reasons for the observed difference between trial and SOC patients

Possible reasons for the differential survival of patients in the trial and SOC subgroup include differential prognostic baseline characteristics (introduced by strict eligibility criteria of trials), cabazitaxel treatment adherence (influenced by a trial protocol), exposure to other life prolonging drugs and the Hawthorne effect (changes in behavior or outlook associated with being under observation)[23,24].

After correction for baseline differences, time on 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 prevent enrollment of sicker patients and subsequently limit early cancer deaths[17]. Indeed, trial patients had significantly higher hemoglobin, lower LDH, less visceral metastases, and less symptoms compared to SOC patients. At a closer look, the cabazitaxel OS curves in 1st line post-docetaxel separate directly from the start of treatment, possibly reflecting the difference in prognostic baseline parameters.

PSA response was numerical lower, but not 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 trial (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 suggest that premature discontinuation is associated with shorter OS and 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[25-27]. 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, less than 10 cycles was shown to have a negative impact in patients without progressive disease[28]. In a post-hoc analysis of the MAINSAIL trial, an independent effect on OS by the number of docetaxel cycles administered has been shown[29]. It has 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[30]. 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 hemoglobin, may play a role. It remains unclear whether treatment adherence affects outcomes including survival. This is difficult to analyze, mainly because of methodological reasons such as immortal time bias. But we acknowledge the possibility that the low number of cycles may have negatively influenced survival outcomes.

Although infrequent, patients in the SOC subgroup were numerical more often treated with LPD pre-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.

Table 6. Overview of published observational studies on second line cabazitaxel treatment. Ref, reference; D, docetaxel; C or CAB, cabazitaxel, A, abiraterone; X, any treatment; QoL, quality of life

Study (first author, ref, year)	Population (n); sequence (if reported)	Type of study, period	Median cycles cabazitaxel (n)	Median overall survival (months)
Wissing ([14], 2015)	63 DCA	Multi center retrospective 2009-2012	7	19.1 DCA
Sonpavde ([11], 2015)	54 DC, 77 DCA	Multicenter retrospective 2011-2012	5 / 6	7.0 DC / 18.2 DCA
Moriceau ([36]; 2016)	24 DC, 17 DAC	Single center retrospective 2011-2014	5	11.9 DC / 12.5 DAC
Hofheinz ([30], 2016)	527	Multi center prospective QoL study 2011-2014	6	16.8
Cicero ([37],2017)	30	Single center retrospective 2013-2016	8	14.8
Zschäbitz ([38]; 2017)	18 DC, 5 XXC	2 centers retrospective 2011-2016	5	10.0 (all patients, n=69; no difference between groups based on line of CAB treatment)
Suner ([13]; 2016)	103	Multi center retrospective 2012-2014	5	10.6
Carles ([39], 2018)	160 DC, 23 XXC	Multi center prospective QoL study 2012-2016	6	13.2 (all patients n=189)
Delanoy ([15], 2018)	158 DCX	Multicenter retrospective 2012-2016	7	21.0 DCX
Angelergues ([16], 2018)	267 DC, 124 DCX	Multicenter retrospective 2012-2016	6 / 7	12.7 DC / 22.7 DCX
CAPRI (this report)	55 DC, 118 DCX	Multicenter retrospective 2010-2018	3 / 5	4.6 DC / 15.1 DCX

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 did still apply and therefore reports on these programs still have limited external validity on real world patients[31-34]. Published reports on real world cabazitaxel outcomes are summarized in Table 6. In retrospective studies, differential mOS is observed with regards to the registration trials (10.0-12.1 months versus 13.4-15.1 months, respectively)[3,10,35]. Direct comparisons between trial patients and real world patients are lacking, and 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 a better mOS than patients treated with 2 LPD lines (docetaxel and cabazitaxel). In our study, the patients who were treated with LPD post-cabazitaxel had a median OS from the first cabazitaxel treatment of 15.1 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 and previous and subsequent treatments.

Limitations

Because of the retrospective database that is available in our registry, the sample size was not based on power calculations, but on patients available matching 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 non-randomized subgroups, reflecting trial availability and the choices of patients and physicians in real world practice. Our results are therefore hypothesis generating.

CONCLUSION

This paper emphasizes 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.

REFERENCES

1. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.
2. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65(2):467-479.
3. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.
4. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
5. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
6. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
7. Maines F, Caffo O, Veccia A, et al. Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer. *Crit Rev Oncol Hematol*. 2015;96(3):498-506.
8. Sekine I, Takada M, Nokihara H, Yamamoto S, Tamura T. Knowledge of efficacy of treatments in lung cancer is not enough, their clinical effectiveness should also be known. *J Thorac Oncol*. 2006;1(5):398-402.
9. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m(2)) and the currently approved dose (25 mg/m(2)) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. *J Clin Oncol*. 2017;35(28):3198-3206.
10. Beer TM, Hotte SJ, Saad F, et al. Custirsen (OGX-011) combined with cabazitaxel and prednisone versus cabazitaxel and prednisone alone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (AFFINITY): A randomised, open-label, international, phase 3 trial. *Lancet Oncol*. 2017;18(11):1532-1542.
11. Sonpavde G, Bhor M, Hennessy D, et al. Sequencing of cabazitaxel and abiraterone acetate after docetaxel in metastatic castration-resistant prostate cancer: Treatment patterns and clinical outcomes in multicenter community-based US oncology practices. *Clin Genitourin Cancer*. 2015;13(4):309-318.
12. Moriceau G, Guillot A, Pacaut C, et al. Translating clinical evidence-based medicine into the real world: Single-center experience with cabazitaxel in metastatic prostate cancer patients. *Chemotherapy*. 2016;61(3):127-133.
13. Suner A, Aydin D, Hacioglu MB, et al. Effectiveness and safety of cabazitaxel chemotherapy for metastatic castration-resistant prostatic carcinoma on turkish patients (the anatolian society of medical oncology). *Eur Rev Med Pharmacol Sci*. 2016;20(7):1238-1243.

14. Wissing MD, Coenen JL, van den Berg P, et al. CAST: A retrospective analysis of cabazitaxel and abiraterone acetate sequential treatment in patients with metastatic castrate-resistant prostate cancer previously treated with docetaxel. *Int J Cancer*. 2015;136(6):E760-72.
15. Delanoy N, Hardy-Bessard A, Efstathiou E, et al. Sequencing of taxanes and new androgen-targeted therapies in metastatic castration-resistant prostate cancer: Results of the international multicentre retrospective CATS database. *European Urology Oncology*. 2018;Accepted 16 May 2018, Available online 8 June 2018.
16. Angelergues A, Efstathiou E, Gyftaki R, et al. Results of the FLAC european database of metastatic castration-resistant prostate cancer patients treated with docetaxel, cabazitaxel, and androgen receptor-targeted agents. *Clin Genitourin Cancer*. 2018;16(4):e777-e784.
17. Unger JM, Barlow WE, Martin DP, et al. Comparison of survival outcomes among cancer patients treated in and out of clinical trials. *J Natl Cancer Inst*. 2014;106(3):dju002.
18. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in trial and real-world populations in the dutch castration-resistant prostate cancer registry. *Eur Urol Focus*. 2016.
19. Templeton AJ, Vera-Badillo FE, Wang L, et al. Translating clinical trials to clinical practice: Outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials. *Ann Oncol*. 2013;24(12):2972-2977.
20. Goyal J, Nuhn P, Huang P, et al. The effect of clinical trial participation versus non-participation on overall survival in men receiving first-line docetaxel-containing chemotherapy for metastatic castration-resistant prostate cancer. *BJU Int*. 2012;110(11 Pt B):E575-82.
21. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol*. 2016;34(12):1402-1418.
22. Bins S, Nieuweboer AJM, De Graan AM, et al. A randomized phase II multicenter trial on the effects of budesonide on cabazitaxel-induced diarrhea: CABARESC. *J Clin Oncol*. 2016;34.
23. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: A systematic review of rigorous evaluations. *Lancet*. 1993;342(8883):1317-1322.
24. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? evidence for a "trial effect". *J Clin Epidemiol*. 2001;54(3):217-224.
25. Poon DM, Ng J, Chan K. Importance of cycles of chemotherapy and postdocetaxel novel therapies in metastatic castration-resistant prostate cancer. *Prostate Int*. 2015;3(2):51-55.
26. Park SC, Lee JW, Seo IY, Rim JS. Predictive factors for premature discontinuation of docetaxel-based systemic chemotherapy in men with castration-resistant prostate cancer. *Korean J Urol*. 2013;54(3):157-162.
27. Kawahara T, Miyoshi Y, Sekiguchi Z, et al. Risk factors for metastatic castration-resistant prostate cancer (CRPC) predict long-term treatment with docetaxel. *PLoS One*. 2012;7(10):e48186.
28. Pond GR, Armstrong AJ, Wood BA, et al. Evaluating the value of number of cycles of docetaxel and prednisone in men with metastatic castration-resistant prostate cancer. *Eur Urol*. 2012;61(2):363-369.

29. de Morree ES, Vogelzang NJ, Petrylak DP, et al. Association of survival benefit with docetaxel in prostate cancer and total number of cycles administered: A post hoc analysis of the mainsail study. *JAMA Oncol*. 2017;3(1):68-75.
30. Hofheinz R-, Lange C, Ecke T, et al. Quality of life and pain relief in men with metastatic castration-resistant prostate cancer on cabazitaxel: The non-interventional 'QoLiTime' study. *BJU Int*. 2016.
31. Castellano D, AntÃ³n Aparicio LM, Esteban E, et al. Cabazitaxel for metastatic castration-resistant prostate cancer: Safety data from the spanish expanded access program. *Expert Opin Drug Saf*. 2014;13(9):1165-1173.
32. Wissing MD, Van Oort IM, Gerritsen WR, et al. Cabazitaxel in patients with metastatic castration-resistant prostate cancer: Results of a compassionate use program in the netherlands. *Clin Genitourin Cancer*. 2013;11(3):238-250e.1.
33. Heidenreich A, Scholz H-, Rogenhofer S, et al. Cabazitaxel plus prednisone for metastatic castration-resistant prostate cancer progressing after docetaxel: Results from the german compassionate-use programme. *Eur Urol*. 2013;63(6):977-982.
34. Bracarda S, Gernone A, Gasparro D, et al. Real-world cabazitaxel safety: The italian early-access program in metastatic castration-resistant prostate cancer. *Future Oncol*. 2014;10(6):975-983.
35. De Bono JS, Hardy-Bessard A, Kim C-, et al. Phase III non-inferiority study of cabazitaxel (C) 20 mg/m2 (C20) versus 25 mg/m2 (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D). *J Clin Oncol*. 2016;34.
36. Moriceau G, Guillot A, Pacaut C, et al. Translating clinical evidence-based medicine into the real world: Single-center experience with cabazitaxel in metastatic prostate cancer patients. *Chemotherapy*. 2016;61(3):127-133.
37. Cicero G, De Luca R, Dorangricchia P, et al. Cabazitaxel in metastatic castration-resistant prostate cancer patients progressing after docetaxel: A prospective single-center study. *Oncology*. 2017;92(2):94-100.
38. Zschäbitz S, Vallet S, Hadaschik B, et al. Efficacy of cabazitaxel treatment in metastatic castration resistant prostate cancer in second and later lines. an experience from two german centers. *J Cancer*. 2017;8(4):507-512.
39. Carles J, Pichler A, Korunkova H, et al. An observational, multicentre study of cabazitaxel in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (CAPRISTANA). *BJU Int*. 2018.

PART 2

Real-world outcomes in mCRPC

CHAPTER 5

The effects of new life prolonging drugs for metastatic castration-resistant prostate cancer (mCRPC) patients in a real-world population

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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 introduction of new LPDs on treatment patterns and overall survival (OS) over time.

Patients and methods

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 analyzed: 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% to 29% and 20% to 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 imputation 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).

Conclusion(s)

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[1]. 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)[2,3]. Five-year survival is different per stage group in prostate cancer, ranging from 100% for stage I to 51% for stage IV (TNM 7th edition) in the period 2010-2015 in the Netherlands[4]. Cancer survival may be increased by improved early detection and/or more effective therapy; however, several forms of bias may influence survival results, including length-time and lead-time bias[1-3].

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 for mCRPC, with a significant increase of median OS (mOS)[5]. Between 2011 and 2014 new life-prolonging drugs (LPD) for mCRPC (cabazitaxel[6], abiraterone[7,8], enzalutamide[9,10] and radium-223[11]) were introduced in the Netherlands. Sipuleucel-T was not available in these years in the Netherlands. The reimbursement of new oncolytics follows published positive treatment outcomes, regulatory drug approval and market authorization. In the Netherlands, the use of these oncolytics is generally conditional on positive guidance by the Dutch Society of Medical Oncology (NVMO) Committee 'Beoordeling van Oncologische Middelen (Appraisal of oncolytics)' (CieBOM). The publication dates of the positive guidance by the European Medicines Agency and CieBOM on the aforementioned LPD are shown in Table 1.

Registration is based on 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[12,13]. 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[14,15]. 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 introduction of new LPD treatments on treatment patterns and OS over time in a real world population.

Table 1. Dates of positive cieBOM guidance per LPD

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

* guidances are published in Dutch on https://www.nvmo.org/bom-type/bom/?order=disease;
** 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.

METHODS

The study design, setting, participants, follow up and data collection of the CAPRI registry has been described in more detail[12]. In short: CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multi-center cohort study in 20 hospitals in the Netherlands. Data collection started after approval by the local medical ethics committee and hospital board. Data has 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 PSA and metastatic pattern), and had disease progression despite ADT. Disease progression was defined as in the EAU CRPC definition[16] 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 in 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 analyzed 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 in groups based on 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 Dec 31, 2010 and before January 1, 2017. Year groups were created on docetaxel-progression date (2011-2012, 2013-2014, 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 Chi-square test or Kruskall-Wallis test. OS from CRPC diagnosis and progression on docetaxel to database cut off was analyzed 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 imputation by Monte Carlo Markov Chain method was applied: the distribution of the observed data was used to estimate a set of plausible values for the missing data. The outcome variables overall survival time and end of follow up state were included and used as indicator. 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, ALP and 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[17]. 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 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.

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 analyzed 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), see Supplementary Table S1a and Figure 1a. The use of docetaxel as 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).

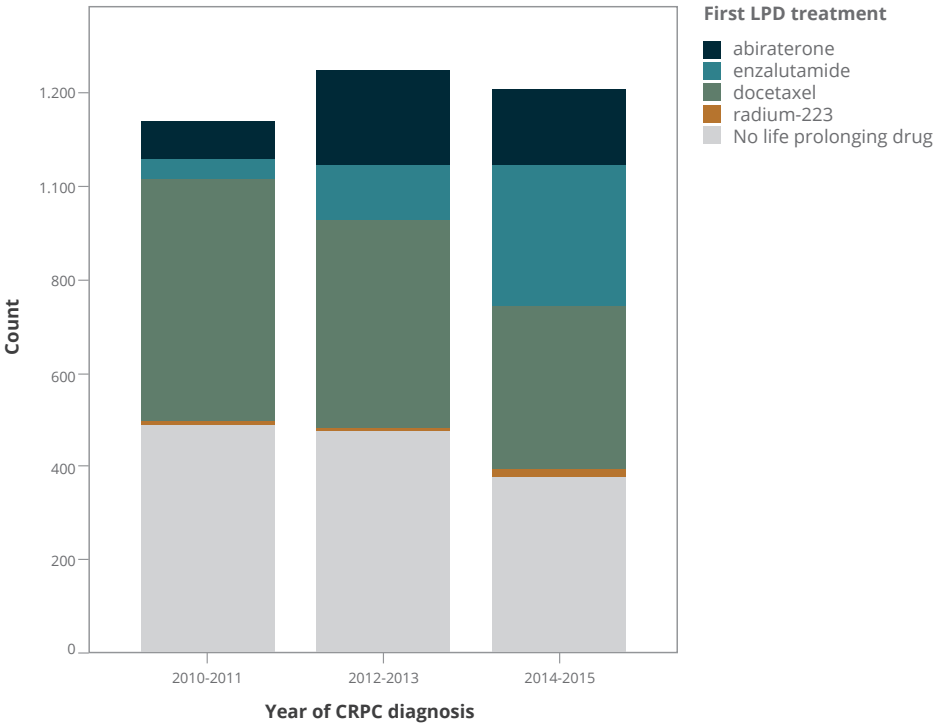


Figure 1a. Treatment patterns. First LPD treatment after CRPC-diagnosis (subgroup 1). Abbreviations: LPD, life-prolonging drug; CRPC, castration resistant prostate cancer.

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 S1b and Figure 1b).

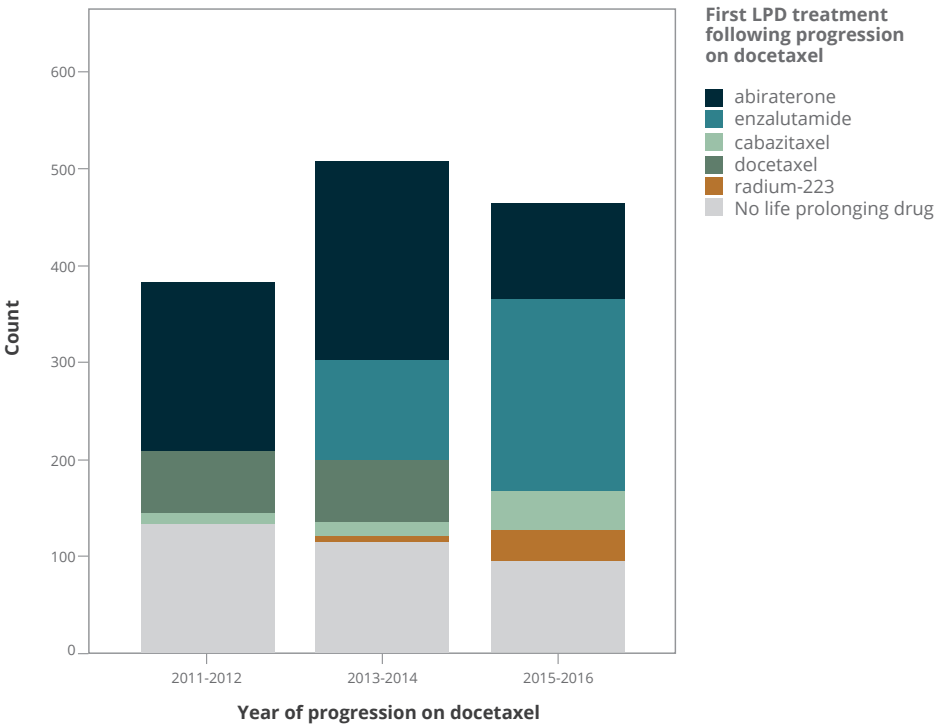


Figure 1b. First LPD treatment after progression on docetaxel (subgroup 2). Abbreviations: LPD, life-prolonging drug; CRPC, castration resistant prostate cancer.

Baseline characteristics

In subgroup 1 during the CRPC-diagnosis years, CRPC patients showed a significant and gradual increase in age, Gleason sumscore 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 2a).

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, hemoglobin and patients with clinical progression during treatment periods (Table 2b). A gradual and significant decrease was shown in ALP, LDH and PSA. Missing data was especially frequent (sometimes >50%) in ECOG PS, LDH and visceral disease in both subgroups.

Table 2a. Baseline characteristics at CRPC-diagnosis (subgroup 1)

	Year of CRPC diagnosis			
	2010-2011	**2012-2013**	**2014-2015**	*p*-value
Number of patients	1,140	1,249	1,211	
Age (years)				<0.001
Median (IQR)	74 (68-81)	75 (68-81)	76 (70-82)	
>75 (%)	49	51	56	
Charlson comorbidity index (%)				0.794
6	60	61	63	
7-8	33	32	30	
9-10	5	5	5	
>10	2	2	2	
Missing	0	0	<1	
Gleason sumscore (%)				<0.001
<8	39	33	31	
8-10	47	51	55	
Missing	15	16	14	
Time from castration to CRPC (months)				0.011
Median (IQR)	15.9 (8.9-30.8)	15.2 (8.4-30.1)	14.2 (7.9-27.6)	
Missing (%)	1	<1	0	
ECOG performance score (%)				<0.001
0	24	20	11	
1	22	17	13	
2	3	4	4	
>2	1	1	1	
Missing	50	58	70	
ALP (U/L)				0.878
Median (IQR)	105 (77-187)	105 (79-193)	108 (78-198)	
Missing (%)	40	41	31	
Hemoglobin (mmol/L)				0.247
Median (IQR)	8.1 (7.4-7.3)	8.0 (7.3-8.6)	8.0 (7.3-8.6)	
Missing (%)	36	36	31	
PSA (µg/L)				0.137
Median (IQR)	18 (6-67)	15 (6-55)	17 (5-63)	
Missing (%)	4	3	2	
Visceral disease (%)				0.047
Yes	4	3	4	
No	18	16	12	
Missing (%)	78	81	85	

Table 2a. (Continued)

	Year of CRPC diagnosis			
	2010-2011	**2012-2013**	**2014-2015**	*p*-value
Pain and/or opioid use				0.089
Yes	25	23	21	
No	42	33	16	
Missing (%)	33	44	63	
LDH (U/L)				
Median (IQR)	226 (188-329)	230 (191-313)	217 (186-268)	0.001
Missing (%)	63	61	52	

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

Table 2b. Baseline characteristics at progression date of docetaxel (subgroup 2)

	Year of progression on docetaxel			
	2011-2012	2013-2014	2015-2016	*p*-value
Number of patients	384	508	463	
Age at progression on docetaxel (years)				0.005
Median (IQR)	71 (65-76)	72 (66-77)	72 (68-78)	
>75 (%)	30%	37%	38%	
Charlson comorbidity index at start docetaxel (%)				0.197
6	66	70	66	
7-8	30	26	29	
9-10	4	4	3	
>10	<1	<1	2	
Missing	0	0	0	
Gleason sumscore (%)				0.514
<8	35	34	32	
8-10	54	56	59	
Missing	12	11	10	
Time from castration to progression on docetaxel (months)				<0.001
Median (IQR)	24 (16-34)	28 (18-44)	30 (20-50)	
Missing (%)	1	<1	0	
Time from last docetaxel to progression on docetaxel (months)				<0.001
Median (IQR)	1.5 (0.6-3.7)	2.0 (0.7-4.3)	2.3 (0.7-5.1)	
≤ 0 months (%)	11	9	4	

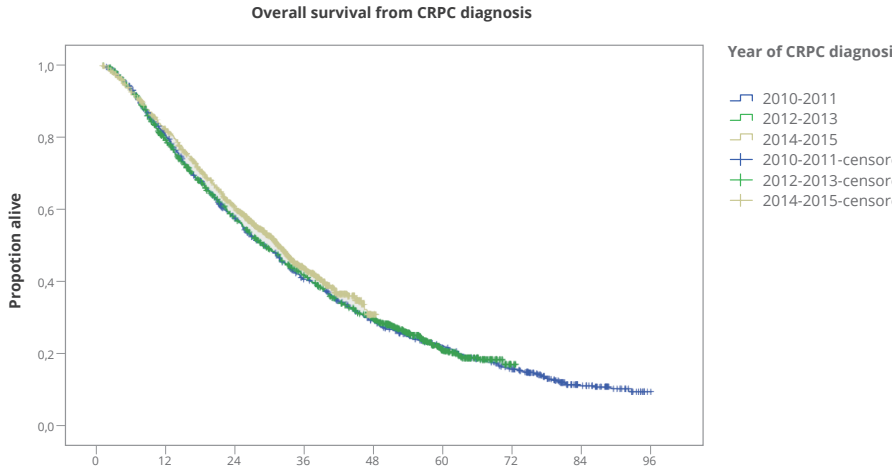
Table 2b. (Continued)

	Year of progression on docetaxel			
	2011-2012	2013-2014	2015-2016	*p*-value
≤ 6 months (%)	91	86	81	
Missing (%)	4	3	1	
Docetaxel cycles				
Median (IQR)	6 (4-9)	7 (5-10)	7 (5-10)	0.001
≥10 (%)	21	27	25	
Missing (%)	1	1	0	
ECOG performance score (%)				0.310
0	10	12	10	
1	31	26	25	
2	12	13	8	
>2	5	4	2	
Missing	43	46	56	
ALP (U/L)				<0.001
Median (IQR)	161 (89-311)	144 (86-311)	120 (76-225)	
Missing (%)	34	30	19	
Hemoglobin (mmol/L)				0.039
Median (IQR)	7.1 (6.4-7.9)	7.2 (6.6-8.0)	7.5 (6.6-8.1)	
Missing (%)	30	35	41	
PSA (µg/L)				<0.001
Median (IQR)	128 (37-391)	108 (33-296)	73 (24-225)	
Missing (%)	18	19	13	
LDH (U/L)				0.001
Median (IQR)	304 (228-493)	276 (217-435)	255 (209-334)	
Missing (%)	43	50	51	
Visceral disease (%)				0.165
Yes	13	19	17	
No	34	33	37	
Missing (%)	53	47	47	
Clinical progression (%)				0.013
Yes	60	62	60	
No	21	22	32	
Missing (%)	19	16	8	

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

Overall survival

For all patients (n=3,600) the mOS was 29.6 months. In subgroup 1, the median OS was 28.5, 28.5 and 31.0 months for the CRPC-diagnosis 2010-2011, 2012-2013 and 2014-2015, respectively (p=0.196). 12-months and 24-months survival increased from 79% to 81% and 57% to 60%, respectively (see Figure 2a). Overall survival in patients treated with LPD was 32.7 months versus 20.8 months for patients not treated with LPD (p<0.0001). Univariate prognostic factors for survival were age, Charlson comorbidity score, Gleason sumscore, time from ADT tot CRPC, ALP, PSA, hemoglobin, LDH, ECOG PS, visceral disease and pain and/or opioid use (see Table 3a). Because only 223 patients had complete data, multiple imputation of missing baseline values was performed to allow for multivariate analysis with prognostic factors. After multiple imputation, 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, hemoglobin, LDH, ECOG PS, visceral disease and pain and/or opioid use remained independent prognostic factors (see Table 3a).

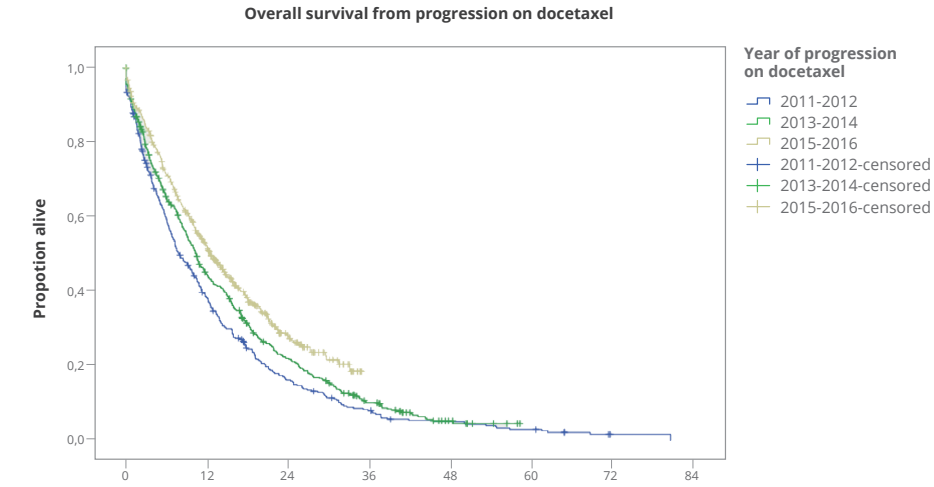


Patients at risk (*n*)									
2010-2011	1140	874	608	421	280	202	132	43	0
2012-2013	1249	941	653	451	291	91	0		
2014-2015	1211	939	634	220	0				

Estimated cumulative survival (%)							
2010-2011	100	79	57	41	28	22	16
2012-2013	100	78	57	41	29	21	
2014-2015	100	81	60	43			

Figure 2a. Overall survival from CRPC diagnosis (subgroup 1). Abbreviations: CRPC, castration resistant prostate cancer.

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 (see Figure 2b). Overall survival 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, Hb, LDH, ECOG PS, visceral disease, clinical progression, time since last docetaxel and number of docetaxel cycles, and also the treatment period (see Table 3b). 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 last period vs first period, p=0.037; see Table 3b). Time since start castration, ALP, Hb, ECOG PS, visceral disease, clinical progression, time since last docetaxel and number of docetaxel cycles were all associated with increased survival.



Patients at risk (*n*)								
2011-2012	384	138	55	26	15	9	1	0
2013-2014	508	213	100	39	9	0		
2015-2016	463	209	55	0				

Estimated cumulative survival (%)							
2011-2012	100	38	16	8	5	3	2
2013-2014	100	45	22	10	5		
2015-2016	100	52	28				

Figure 2b. Overall survival from progression on docetaxel (subgroup 2). Abbreviations: CRPC, castration resistant prostate cancer.

Table 3a. Cox-regression analysis of OS from CRPC-diagnosis (subgroup 1)

	Univariable analysis of actual data				Multivariable analysis of pooled imputed data		
	events/cases	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age	2,432/3,600	1.018	1.013-1.022	<0.001	1.021	1.015-1.026	<0.001
Charlson comorbidity index	2,431/3,598						
7-8 vs 6		1.196	1.097-1.303	<0.001	1.096	0.987-1.217	0.086
9-10 vs 6		1.315	1.104-1.566	0.002	1.238	0.957-1.602	0.099
>10 vs 6		2.605	1.953-3.475	<0.001	2.173	1.564-3.020	<0.001
Gleason sumscore	2,055/3,078						
8-10 vs ≤7		1.145	1.048-1.251	0.003	1.041	0.927-1.169	0.483
Period ADT to CRPC (months, cont.)	2,426/3,588	0.986	0.984-0.988	<0.001	0.987	0.985-0.989	<0.001
ALP (U/L, cont.)	1,617/2,254	1.001	1.001-1.001	<0.001	1.001	1.001-1.001	<0.001
PSA (ug/L, cont.)	2,359/3,491	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	<0.001
Hemoglobin (mmol/L, cont.)	1,701/2,361	0.608	0.579-0.638	<0.001	0.731	0.698-0.766	<0.001
LDH (U/L, cont.)	1,091/1,481		1.001-1.001	<0.001	1.000	1.000-1.001	0.016
LOG(LDH)		1.001		<0.001			
ECOG performance score	1,066/1,452						<0.001
1 vs 0		1.794	1.574-2.044	<0.001	1.336	1.175-1.520	<0.001
>1 vs 0		4.686	3.876-5.665	<0.001	2.844	2.191-3.692	
Visceral disease	500/672						
Yes vs No		1.563	1.257-1.943	<0.001	1.224	1.004-1.494	0.047
Pain and/or opioid use							
Yes vs No	1,432/1,916	2.013	1.811-2.239	<0.001	1.375	1.188-1.592	<0.001
Year of CRPC diagnosis	2,432/3,600		0.905-1.092				0.022
2012-2013 vs 2010-2011		0.994		0.899	0.893	0.810-0.983	<0.001
2014-2015 vs 2010-2011		0.915	0.823-1.106	0.098	0.749	0.670-0.838	

Abbreviations: OS, overall survival; CRPC, castration resistant prostate cancer; HR, hazard ratio, CI, confidence interval; ADT, androgen deprivation therapy; ALP, alkaline phosphatase; PSA, prostate specific antigen; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

Table 3b. Cox-regression analysis of OS from progression on docetaxel (subgroup 2)

	Univariable analysis of actual data				Multivariable analysis of pooled imputed data (n=1,355)		
	events/cases	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age	1,096/1,355	1.009	1.001-1.017	0.037	1.002	0.993-1.012	0.622
Charlson comorbidity index	1,096/1,355						
7-8 vs 6		1.071	0.938-1.222	0.311	1.028	0.897-1.179	0.690
9-10 vs 6		1.362	1.019-1.819	0.037	1.068	0.762-1.499	0.699
>10 vs 6		1.834	0.913-3.685	0.088	1.856	0.802-4.294	0.146
Gleason sumscore							
8-10 vs ≤7	9,81/1,211	1.075	0.945-1.224	0.272	0.895	0.772-1.038	0.140
Period on ADT (months, cont.)	1,091/1,350	0.988	0.985-0.991	<0.001	0.992	0.989-0.995	<0.001
ALP (U/L, cont.)	795/983	1.001	1.001-1.002	<0.001	1.001	1.000-1.001	<0.001
PSA (ug/L, cont.)	904/1,131	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	0.055
Hemoglobin (mmol/L, cont.)	726/875	0.618	0.574-0.666	<0.001	0.748	0.695-0.804	<0.001
LDH (U/L, cont.)	584/702	1.000	1.000-1.001	<0.001	1.000	1.000-1.000	0.067
ECOG performance score	582/698						0.307
1 vs 0		1.454	1.160-1.822	0.001	1.113	0.903-1.373	0.022
>1 vs 0		3.619	2.826-4.635	<0.001	1.517	1.074-2.145	
Visceral disease	552/695						
Yes vs No		1.650	1.383-1.970	<0.001	1.478	1.235-1.768	<0.001
Clinical progression	942/1,167						
Yes vs No		1.807	1.562-2.091	<0.001	1.245	1.036-1.497	0.021
Time since last docetaxel and	1,070/1,321						0.005
progression (months, cont.)		0.926	0.909-0.944	<0.001	0.971	0.952-0.991	
Docetaxel cycles (n, cont.)	1,089/1,346	0.899	0.880-0.919	<0.001	0.951	0.929-0.974	<0.001
Year of progression on docetaxel	1096/1,355						0.160
2011-2012		ref					0.037
2013-2014		0.849	0.738-0.978	0.023	0.887	0.749-1.050	
2015-2016		0.686	0.587-0.802	<0.001	0.811	0.667-0.987	

Abbreviations: OS, overall survival; CRPC, castration resistant prostate cancer; HR, hazard ratio, CI, confidence interval; ADT, androgen deprivation therapy; ALP, alkaline phosphatase; PSA, prostate specific antigen; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

DISCUSSION

In this large contemporary outcomes registry of CRPC patients in the Netherlands, we observed an increased survival in multivariate analyses of newly diagnosed CRPC patients and post-docetaxel patients during the years 2010-2018. In these years, several new life prolonging drugs 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 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 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 sumscore 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 differential diagnostic and therapeutic behavior 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 strict because of the availability of more treatment options leading to shorter time to CRPC. Interestingly, the same shift in age and Gleason sumscore was seen in a recent single-center analysis[18]. 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,

higher number of docetaxel cycles, higher hemoglobin 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, hemoglobin 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[19,20]. 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 favorably to previous reports. Previously reported mOS from mCRPC diagnosis in observational studies in different periods ranges from 9-15 months (before 2004)[21-23], 11-26 months (2004-2010)[18,24,25] to 33-34 months (from 2010)[18,25], 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 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 (see supplementary Table S2), this would lead to invalid (non-representative) outcomes. 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 preferences and experience of physicians. However, we did not have insight in 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.

REFERENCES

1. Siesling S, Visser O, Aarts MJ, et al. Fight against cancer in the netherlands: Current state of affairs. *Ned Tijdschr Geneeskd*. 2019;163.
2. Trama A, Foschi R, Larranaga N, et al. Survival of male genital cancers (prostate, testis and penis) in europe 1999-2007: Results from the EUROCARE-5 study. *Eur J Cancer*. 2015;51(15):2206-2216.
3. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in europe 1999-2007 by country and age: Results of EUROCARE--5-a population-based study. *Lancet Oncol*. 2014;15(1):23-34.
4. Netherlands cancer registry (NCR) - NKR cijfers/IKNL. www.cijfersoverkanker.nl. Accessed January, 23th, 2020.
5. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.
6. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.
7. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: Final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992.
8. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.
9. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
10. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
11. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
12. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in trial and real-world populations in the dutch castration-resistant prostate cancer registry. *Eur Urol Focus*. 2018;4(5):694-701.
13. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. Second-line cabazitaxel treatment in castration-resistant prostate cancer clinical trials compared to standard of care in CAPRI: Observational study in the netherlands. *Clin Genitourin Cancer*. 2019;17(5):e946-e956.
14. Flaig TW, Potluri RC, Ng Y, Todd MB, Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer (mCRPC) with recent introduction of new oral agents: Retrospective analysis of real world data. *J Clin Oncol*. 2014;32(15).

15. Kwan EM, Semira MC, Bergin ART, et al. Impact of access to novel therapies on the initial management of castrate-resistant prostate cancer: An australian multicentre study. *Intern Med J*. 2019;49(11):1378-1385.
16. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65(2):467-479.
17. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399.
18. Francini E, Gray KP, Shaw GK, et al. Impact of new systemic therapies on overall survival of patients with metastatic castration-resistant prostate cancer in a hospital-based registry. *Prostate Cancer Prostatic Dis*. 2019;22(3):420-427.
19. Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol*. 2003;21(7):1232-1237.
20. Halabi S, Lin CY, Small EJ, et al. Prognostic model predicting metastatic castration-resistant prostate cancer survival in men treated with second-line chemotherapy. *J Natl Cancer Inst*. 2013;105(22):1729-1737.
21. Soerdjbalie-Maikoe V, Pelger RC, Lycklama a Nijeholt GA, et al. Bone scintigraphy predicts the risk of spinal cord compression in hormone-refractory prostate cancer. *Eur J Nucl Med Mol Imaging*. 2004;31(7):958-963.
22. Hwang SS, Chang VT, Alejandro Y, et al. Study of hormone refractory prostate cancer: Hospital care and palliative care resource use at a VA medical center. *Cancer Invest*. 2004;22(6):849-857.
23. Berruti A, Tucci M, Mosca A, et al. Predictive factors for skeletal complications in hormone-refractory prostate cancer patients with metastatic bone disease. *Br J Cancer*. 2005;93(6):633-638.
24. Chin SN, Wang L, Moore M, Sridhar SS. A review of the patterns of docetaxel use for hormone-resistant prostate cancer at the princess margaret hospital. *Curr Oncol*. 2010;17(2):24-29.
25. Chaumard-Billotey N., Chabaud S., Boyle H.J., Favier B., Devaux Y., Droz J.-P., Flechon A. Impact of news drugs in the median overall survival of patients with metastatic castration resistant prostate cancer (mCRPC). *Journal of Clinical Oncology*. 2013;31(15 SUPPL. 1).

Supplementary Table S1a. First LPD treatment for CRPC (subgroup 1)

	Year of CRPC-diagnosis		
	2010-2011 N=1,140	2012-2013 N=1,249	2014-2015 N=1,211
Type of treatment, n (%)			
No LPD	491 (43)	475 (38)	379 (31)
Docetaxel	522 (46)	448 (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.

Supplementary Table S1b. First LPD treatment after docetaxel progression (subgroup 2)

	Year of progression on docetaxel		
	2011-2012 N=384	2013-2014 N=508	2015-2016 N=463
Type of treatment, n (%)			
No LPD	134 (35)	115 (23)	95 (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.

Supplementary Table S2. Baseline characteristics of patients with complete data versus patients with any missing data.

	Data complete		
	yes	**no**	*p*-value
Number of patients	223	3,377	
Age (years)			<0.001
Median (IQR)	70 (65-77)	75 (69-82)	
>75 (%)	34	53	
Missing (%)	0	0	
Charlson comorbidity index (%)			n.s.
6	65	61	
7-8	27	32	
9-10	7	5	

Supplementary Table S2. (Continued)

	Data complete		
	yes	**no**	*p*-value
>10	2	2	
Missing	0	<1	
Gleason sumscore (%)			
<8	40	34 (40)*	0.009
8-10	60	51 (60)*	
Missing	0	16	
Time from castration to CRPC (months)			<0.001
Median (IQR)	10.3 (6.1-19.1)	15.4 (8.6-30.2)	
Missing (%)	0	<1	
ECOG performance score (%)			0.004
0	34	17 (47)*	
1	50	15 (42)*	
2	12	3 (9)*	
>2	4	1 (2)*	
Missing	0	64	
ALP (U/L)			<0.001
Median (IQR)	132 (84-289)	104 (77-184)	
Missing (%)	0	40	
Hemoglobin (mmol/L)			<0.001
Median (IQR)	7.9 (7.1-8.4)	8.1 (7.3-8.6)	
Missing (%)	0	37	
PSA (µg/L)			<0.001
Median (IQR)	42 (13-140)	16 (5-57)	
Missing (%)	0	3	
Visceral disease (%)			n.s.
Yes	22	2 (17)*	
No	78	11 (83)*	
Missing (%)	0	87	
Pain and/or opioid use			<0.001
Yes	53	31 (62)	
No	47	19 (39)	
Missing (%)	0	50	
LDH (U/L)			n.s.
Median (IQR)	227 (190-320)	222 (188-288)	
Missing (%)	0	65	

* valid percentage is shown between brackets

CHAPTER 6

Health-related quality of life and pain in a real-world castration resistant prostate cancer population: results from the PRO-CAPRI-study in the Netherlands

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ABSTRACT

In castration-resistant prostate cancer (CRPC), several life-prolonging drugs have been registered, but patient- reported outcomes in daily practice are scare. In our study, 151 patients with CRPC completed quality of life (QoL) questionnaires. Although the majority received life-prolonging drugs, QoL deteriorated during the course of CRPC. Supportive care should be timely thought of to maintain QoL as long as possible.

Background

The purpose of this study was to determine generic, cancer-specific, and prostate cancer-specific health-related quality of life (HRQoL), pain and changes over time in patients with metastatic castration-resistant prostate cancer (mCRPC) in daily practice.

Patients and Methods

PRO-CAPRI is an observational, prospective study in 10 hospitals in the Netherlands. Patients with mCRPC completed the EQ-5D, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and Brief Pain Inventory-Short Form (BPI-SF) every 3 months and European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module (EORTC QLQ-PR25) every 6 months for a maximum of 2 years. Subgroups were identified based on chemotherapy pretreatment. 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. The median follow-up from the start of the study was 19.5 months, and 84% were treated with at least 1 life-prolonging agent. Overall, patients were in good clinical condition (Eastern Cooperative Oncology Group performance status 0-1 in 78%) with normal baseline hemoglobin, lactate dehydrogenase, and alkaline phosphatase. At inclusion, generic HRQoL was high with a mean EQ visual analog score of 73.2 out of 100. The lowest scores were reported on role and physical functioning (mean scores of 69 and 76 of 100, respectively), and 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.[1] Several life-prolonging drugs (LPDs), such as chemotherapy (ie, docetaxel, cabazitaxel), androgen-receptor targeting treatments (ie, abiraterone, enzalutamide), and radionuclide therapy (ie, radium-223), have shown a survival benefit compared with placebo.[2-8] In a contemporary cohort with access to these new LPDs, we observed a median overall survival of 26 months.[9]

mCRPC has a negative impact on health-related quality of life (HRQoL) with a decline in HRQoL over time.[1,10-17] Deterioration occurs in general domains as well as specific symptoms such as pain, fatigue, and appetite loss.[12] However, these results are derived from trials performed in the era before the registration of new LPDs.[1,12,15,16] In the pivotal phase III trials, the LPDs showed a delay in HRQoL deterioration and pain progression in both chemotherapy-naive (CTx-naive) and post- chemotherapy (post-CTx) disease phases,[18-21] 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 toward the fact that trials utilize highly selected populations with significantly better outcomes that are commonly not generalizable to an oncology practice.[9] 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.[22]

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 previously.[9]

Objectives

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.[9] Patients were eligible for the PRO- CAPRI study from diagnosis of CRPC to 4 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-naive state (CTx-naive [ie, no prior docetaxel treatment]) and (post-) chemotherapy state (post-CTx [ie, 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 4 participating hospitals, but because of slow accrual, the protocol was amended after 1 year to include an additional 6 hospitals and prolong the inclusion period for 6 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 4 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 [EORTC QLQ-PR25], and after the amendment, BPI-SF) and commonly used demographic items, namely age, socio-economic status, marital status, and educational level. After baseline measurement, EQ-5D, EORTC QLQ-C30, and BPI-SF were repeated every 3 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 2 years from the start of the study or December 31, 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 5-dimensional questionnaire on a 5-point Likert scale, which was transformed into utility or EQ-5D index value based on Dutch population norms.[23] The second part is a visual analogue scale (VAS).[24]

The secondary outcomes were cancer-specific HRQoL, 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 4-point Likert-type response scale was used. Exception is the global health status, where a 7-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.[25,26] 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."[27] Clinically relevant pain was defined as a score of ≥ 4 on pain severity. Supplemental Table 1 shows an overview of the used questionnaires.

Both the primary and secondary outcomes are measured at baseline (ie, inclusion) and over time. A minimally important difference (MID) was used to assess clinically relevant changes.[27-30] The thresholds for MIDs are also shown in Supplemental Table 1. Time to first MID deterioration was calculated in months from the date of first questionnaire to the date of 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.[24] 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.[25-27]

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 3 months prior to 3 months after inclusion. 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 c2 test were used to compare parametric continuous, nonparametric continuous, and categorical variables, respectively, between CTx-naive 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) 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 1).

In total, 873 questionnaires were completed, and the median number of questionnaires per patient was 6 (range, 1-9). The median follow-up from the first questionnaire was 19.5 months (IQR, 13-25 months). Thirty-eight (25%) patients completed all 9 questionnaires. Termination of the study before the maximum follow-up of 2 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 cutoff (n = 26; 17%). The compliance rate ranged from 94% to 100% per questionnaire, except for BPI-SF, which was added during the study after a protocol amendment (see Supplemental Table 2).

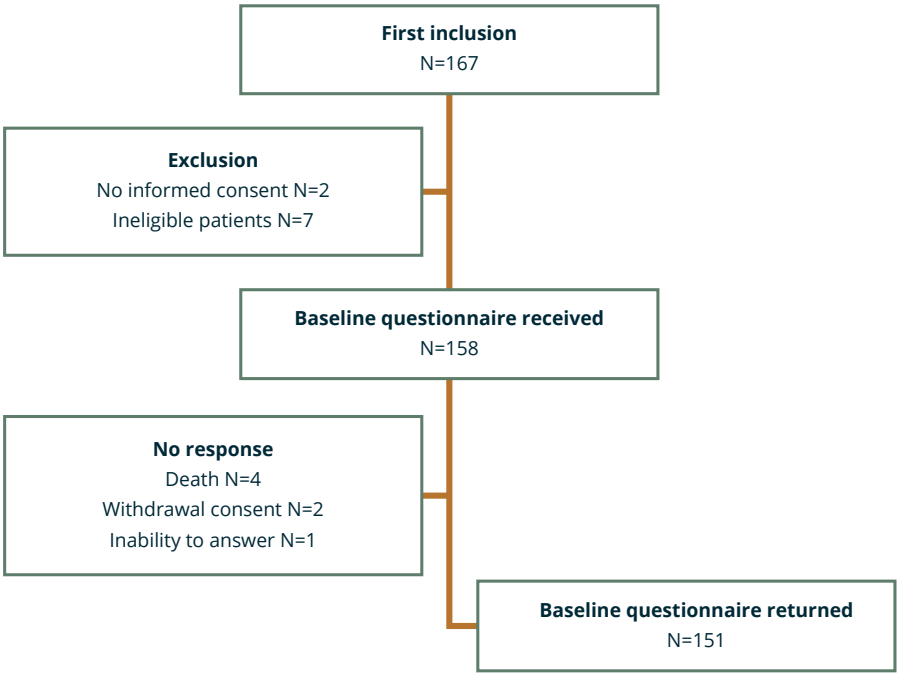


Figure 1. Flowchart of patient inclusion

Treatment Characteristics

At inclusion, 112 (74%) patients were in the CTx-naive state, and 39 (26%) patients were in the post-CTx state. At the time of the first questionnaire, 37 (33%) patients in the CTx-naive 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 1 LPD, mainly enzalutamide (n = 89; 59%) or docetaxel (n = 65; 43%) (Table 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 (see Supplemental Table 3).

CTx-naive 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 1). PSA tended to be lower in CTx-naive patients (median, 36 vs. 86 mg/L; $p = 0.06$).

Table 1. Patient and disease characteristics per disease state

		Total N=151	**CTx-naïve N=112**	**Post-CTx N=39**	**p-value**
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	
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	

Table 1. (Continued)

		Total N=151	CTx-naïve N=112	Post-CTx N=39	p-value
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	-
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 of 100 and EQ-5D index value of 0.82 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 2A, Supplemental Table 4).

Table 2. Proportion of patients with a clinically relevant deterioration in HRQoL at month 6 and month 12

		Month 6	Month 12	p-value
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*

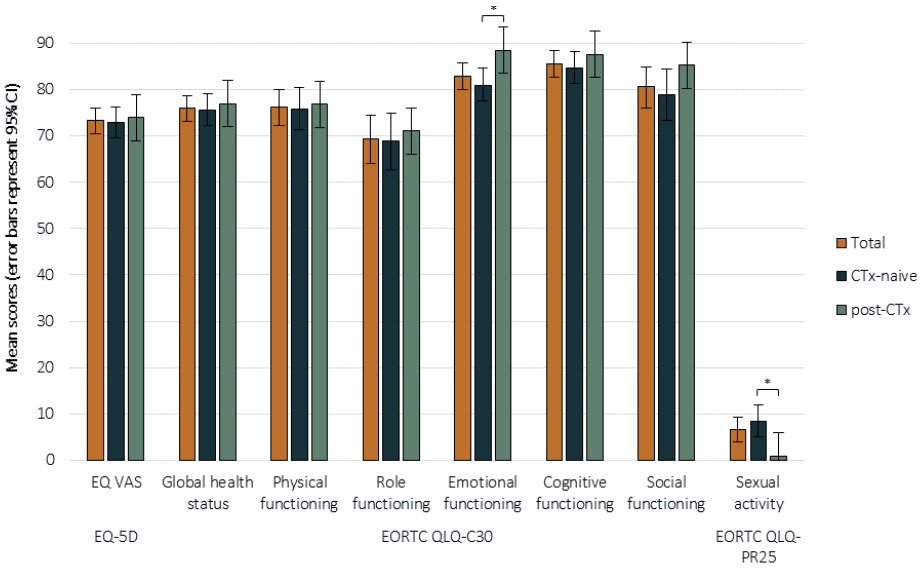
Data are presented as n/N (%) for total population (N=151). p-values calculated for differences percentage of patients with MID at month 6 and month 12; * significant at p-value<0.05.
Abbreviations: HRQOL, health-related quality of life; MID, minimal important difference; CTx-naive, no or no prior docetaxel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

EQ VAS deteriorated over time, but changes were small, and the mean change did not reach MID during 24 months of follow-up (Figure 3A). There were no differences in proportion with MID deterioration at 6 and 12 months (Table 2, Supplemental Table 5 [in the online version]). The median time to MID deterioration on generic HRQoL was 10.8 months for EQ VAS, without differences between CTx-naive and post-CTx patients (Table 3, Supplemental Table 6).

Cancer-specific HRQoL (EORTC QLQ-C30)

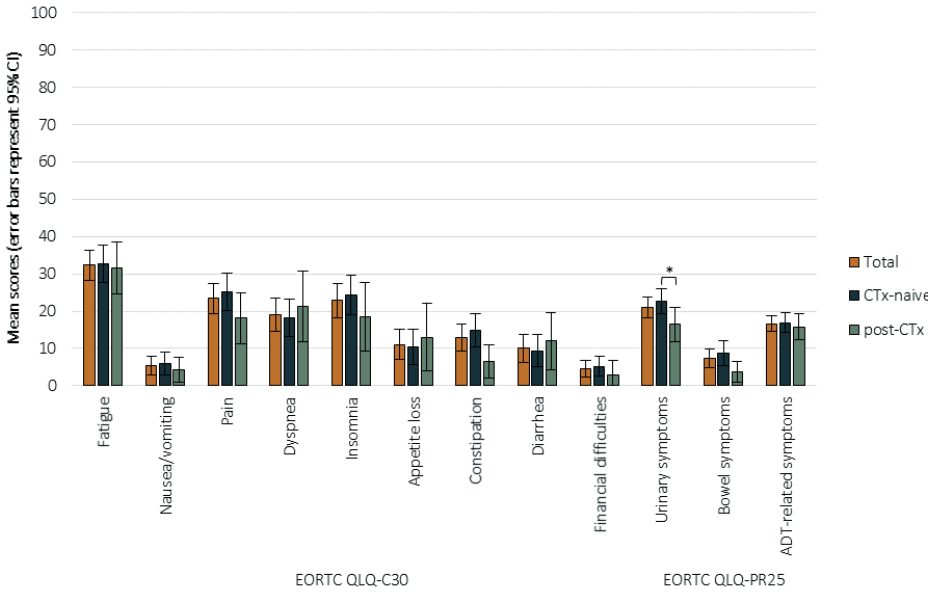
Figure 2A and B show cancer-specific HRQoL at inclusion. Role (ie, patient's ability to perform daily activities, leisure time activities, and/or work) and physical functioning were most affected in cancer- specific HRQoL (mean scores of 69 and 76 of 100, respectively). CTx-naive patients had significant but not relevant lower levels of emotional functioning compared with post-CTx patients (mean scores of 81 vs. 88; p = 0.02). Most symptoms were measured on scales of fatigue, pain, and insomnia, without differences in sub-groups per disease state (Figure 2A and B).

Figure 2A. Health-related quality of life measured at study inclusion; mean scores of functioning scales



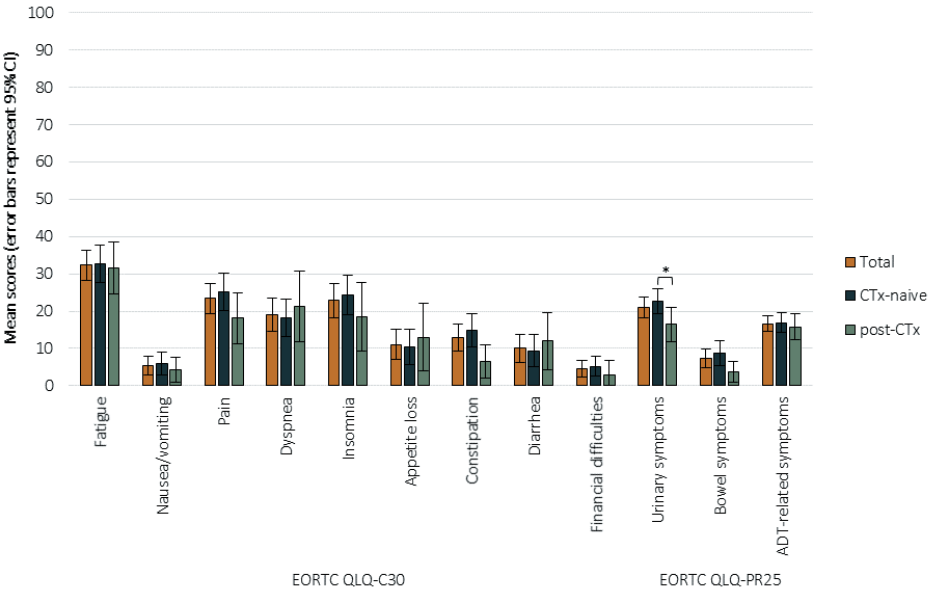
High scores indicate high level of functioning. Error bars represent 95% confidence intervals. * significant at p-value <0.05. Abbreviations: CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy.

Figure 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 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.

Deterioration was seen on all functioning domains of EORTC QLQ-C30, except for emotional functioning (Figures 3B-G). The proportion of CTx-naive patients with MID after 12 months was higher compared with after 6 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 6 and 12 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 12 months was higher than after 6 months for pain (22% vs. 36%; p < 0.01), which was only present in the CTx-naive subgroup (see Supplemental Table 5).

All functioning domains of EORTC QLQ-C30 deteriorated approximately 1 year after inclusion, except for emotional functioning (median, 26.6 months) (Table 3). The median time to deterioration of the symptoms fatigue and pain were, respectively, 8.2 and 15.3 months.

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-naive 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-naive patients reported more bowel symptoms than post-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.

Table 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)

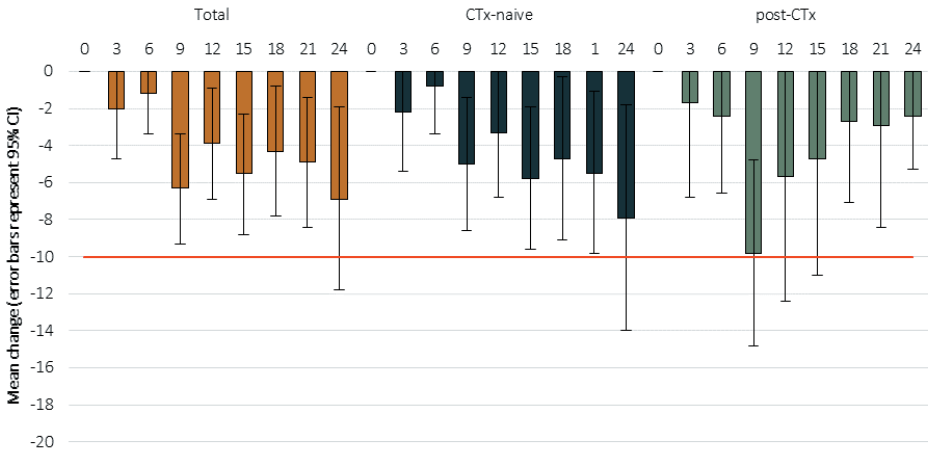
Data are presented as percentages for number of events (i.e. number of patients with MID) and median (IQR) for time to first MID in total population (N=151); a only patients with BPI-SF measurement at inclusion (N=111). *Abbreviations*: HRQoL, health-related quality of life; CTx-naive, no or no prior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

Pain (BPI-SF)

The mean pain severity and interference were low at inclusion, without differences between subgroups (Figure 2C). Sixteen percent (17 of 108 patients with baseline BPI-SF) reported clinically relevant pain at inclusion.

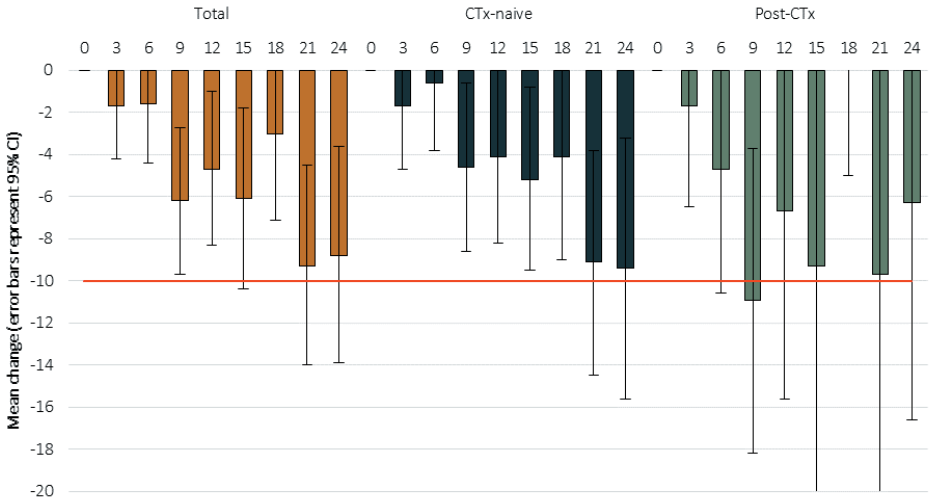
Thirty-six percent of patients without clinical meaningful pain at inclusion had MID deterioration during follow-up. Eight (47.1%) of 17 patients with clinical meaningful pain at inclusion had evaluable follow-up questionnaires, with 4 (23.5%) reporting MID improvement of pain. In CTx-naive patients, the proportion of patients with MID after 12 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 6 months (see Supplemental Table 5a). No differences between CTx-naive and post-CTx patients were found in time to deterioration except for "worst" pain (see Supplemental Table 6). CTx-naive 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).

Figure 3A. Changes in HRQoL over time per disease state; mean changes of EQ VAS (generic HRQoL)



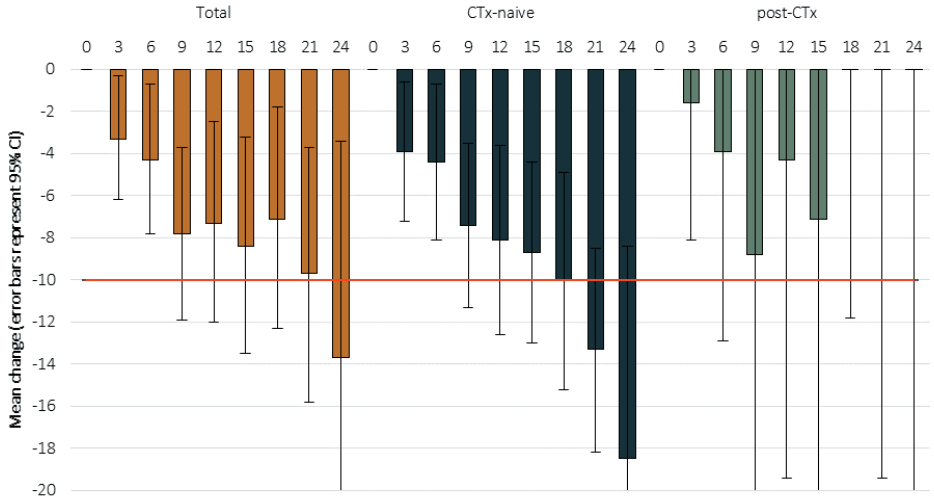
Mean changes from inclusion. Error bars represent 95% CI, red line is MID. Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

Figure 3B. Changes in HRQoL over time per disease state; mean changes in global health status (cancer-specific HRQoL)



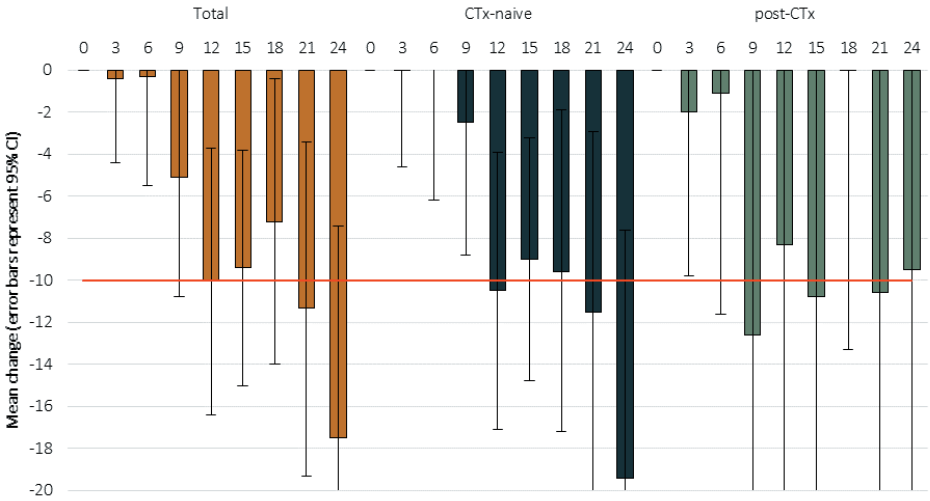
Mean changes from inclusion. Error bars represent 95% CI, red line is MID. Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

Figure 3C. Changes in HRQoL over time per disease state; mean changes in physical functioning (cancer-specific HRQoL)



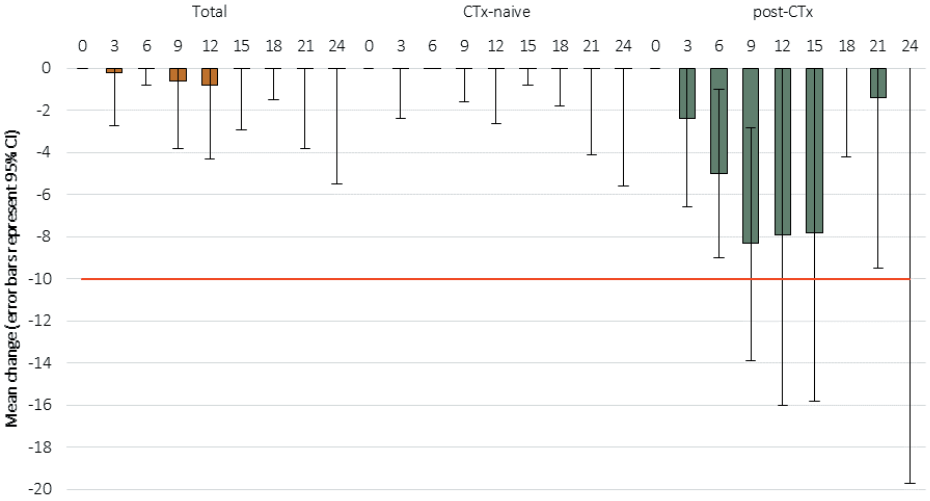
Mean changes from inclusion. Error bars represent 95% CI, red line is MID. Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

Figure 3D. Changes in HRQoL over time per disease state; mean changes in role functioning (cancer-specific HRQoL)



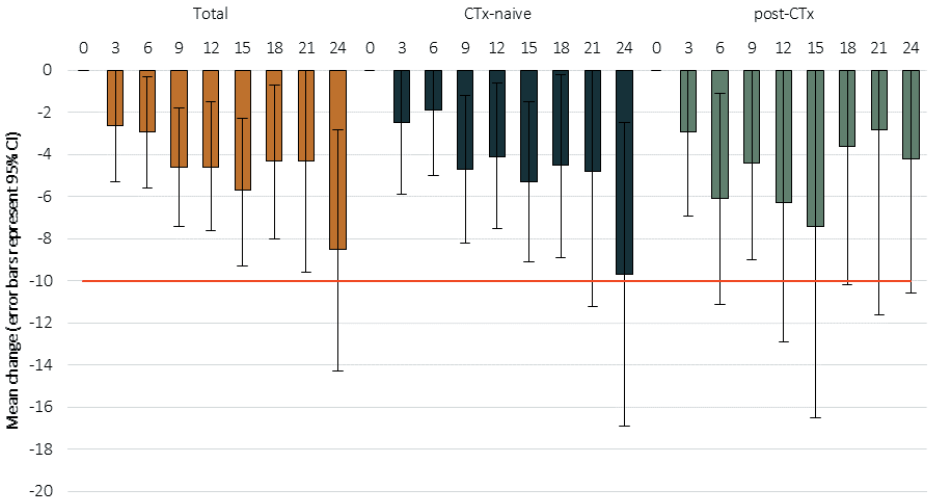
Mean changes from inclusion. Error bars represent 95% CI, red line is MID. Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

Figure 3E. Changes in HRQoL over time per disease state; mean changes in emotional functioning (cancer-specific HRQoL)



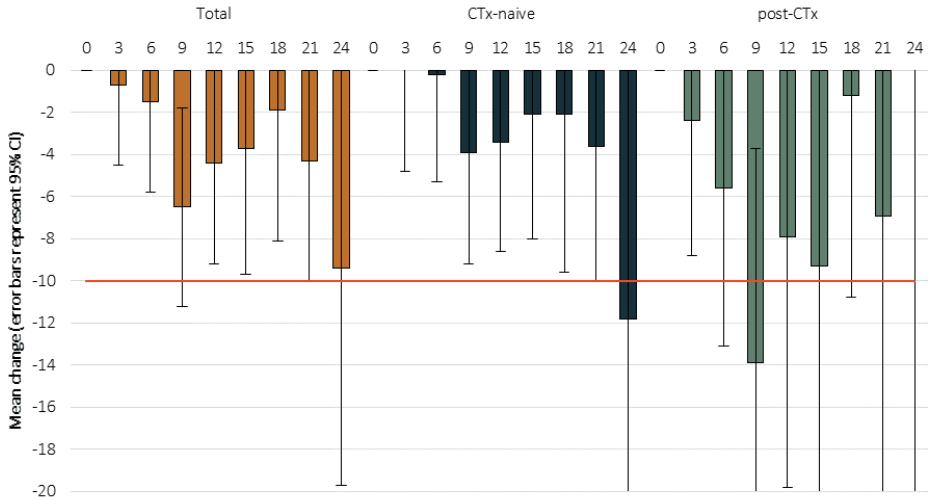
Mean changes from inclusion. Error bars represent 95% CI, red line is MID. Abbreviations: HRQoL, health-related quality of life; CTx-naive, no or no prior docetaxel chemotherapy at inclusion; post-CTx, current or post-docetaxel chemotherapy at inclusion; MID, minimally important difference.

Figure 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 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.

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.[9] 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 pretreatment and a short interval from diagnosis of castrate-resistance to inclusion into the study. Previously published mCRPC cohorts reported lower HRQoL.[12,32] For example, the mean EQ-5D index value was 0.82 in our study, compared with 0.64 to 0.74 in other reports.[12,32] 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.[33,34] This contemporary cohort indicates that in Dutch daily practice, generic HRQoL is high in the early mCRPC state.[12,14,15,32] Most baseline symptoms were identified in role (ie, 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).[35] However, we found low scores on role and physical functioning at inclusion, probably showing the impact of mCRPC on these domains.35 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.[18-21] 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 CTX-naive and 9.9 months in post-CTX patients. This time to progression on "worst" pain is in agreement with the chemotherapy- naive COU-AA-302 treatment arm (25.8 months)[36] and in the post-chemotherapy COU-AA-301 treatment arm (7.4 months).[37] 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.[38] 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.38 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.[14] 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 4 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 LPDs, 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.

REFERENCES

1. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract 2011; 65:1180-92.
2. Tannock IF, de Wit R, Berry WR, et al, TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351:1502-12.
3. de Bono JS, Oudard S, Ozguroglu M, et al, TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376:1147-54.
4. Fizazi K, Scher HI, Molina A, et al, COU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo- controlled phase 3 study. Lancet Oncol 2012; 13:983-92.
5. Ryan CJ, Smith MR, de Bono JS, et al, COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368:138-48.
6. Scher HI, Fizazi K, Saad F, et al, AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187-97.
7. Beer TM, Armstrong AJ, Rathkopf DE, et al, PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371:424-33.
8. Parker C, Nilsson S, Heinrich D, et al, ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213-23.
9. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in trial and real-world populations in the Dutch Castration-resistant Prostate Cancer Registry. Eur Urol Focus 2018; 4:694-701.
10. Payne H, Pearcy R. Symptoms and health-related quality of life in castration- resistant prostate cancer: the patient's perspective. J Mens Health 2012; 9:9-16.
11. Sandblom G, Carlsson P, Sennfält K, Varenhorst E. A population-based study of pain and quality of life during the year before death in men with prostate cancer. Br J Cancer 2004; 90:1163-8.
12. Sullivan PW, Mulani PM, Fishman M, Sleep D. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. Qual Life Res 2007; 16:571-5.
13. James N, Eisenberger M, Fizazi K, et al. EQ-5D utility index in patients with metastatic castration-resistant prostate cancer (mCRPC) with progression during or after first-line docetaxel therapy. Value Health 2011; 14:A457-8.
14. Lloyd AJ, Kerr C, Penton J, Knerer G. Health-related quality of life and health utilities in metastatic castrate-resistant prostate cancer: a survey capturing experiences from a diverse sample of UK patients. Value Health 2015; 18:1152-7.
15. Melmed GY, Kwan L, Reid K, Litwin MS. Quality of life at the end of life: trends in patients with metastatic prostate cancer. Urology 2002; 59:103-9.

16. Litwin MS, Lubeck DP, Stoddard ML, Pasta DJ, Flanders SC, Henning JM. Quality of life before death for men with prostate cancer: results from the CaP- SURE database. J Urol 2001; 165:871-5.
17. Beer TM, Miller K, Tombal B, et al. The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant pros- tate cancer patients: exploratory analyses of AFFIRM and PREVAIL studies. Eur J Cancer 2017; 87:21-9.
18. Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol 2013; 14:1193-9.
19. Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol 2015; 16:509-21.
20. Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal- related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol 2014; 15:1147-56.
21. Bahl A, Oudard S, Tombal B, et al, TROPIC Investigators. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol 2013; 24:2402-8.
22. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol 2014; 32:1480-501.
23. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. Value Health 2016; 19:343-52.
24. EuroQol Research Foundation. EQ-5D-5L User Guide 2019, Available at: https:// euroqol.org/publications/user-guides. Accessed: April 1, 2018.
25. Scott NW, Fayers P, Aaronson NK, et al. EORTC QLQ-C30 Reference Values Manual. 2nd ed. Brussels, Belgium: EORTC Quality of Life Group; 2008.
26. van Andel G, Bottomley A, Fosså SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008; 44:2418-24.
27. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994; 23:129-38.
28. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007; 5:70.
29. Nussbaum N, George D, Abernethy A, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. Prostate Cancer Prostatic Dis 2016; 19:111-21.

30. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16:139-44.
31. Central Bureauof Statistics (CBS). Standaard Onderwijsindeling 2016, Available at: https://www.cbs.nl/nl-nl/onze-diensten/methoden/classificaties/onderwijs-en- beroepen/standaard-onderwijsindeling–soi–/standaard-onderwijsindeling-2016. Accessed: February 22, 2018.
32. Torvinen S, Färkkilä N, Sintonen H, Saarto T, Roine RP, Taari K. Health-related quality of life in prostate cancer. Acta Oncol (Madr) 2013; 52:1094-101.
33. Feng Y, Herdman M, van Nooten F, et al. An exploration of differences between Japan and two European countries in the self-reporting and valuation of pain and discomfort on the EQ-5D. Qual Life Res 2017; 26:2067-78.
34. Bernert S, Fernández A, Haro JM, et al, ESEMeD/MHEDEA 2000 In- vestigators. Comparison of different valuation methods for population health status measured by the EQ-5D in three European countries. Value Health 2009; 12:750-8.
35. Hinz A, Singer S, Brähler E. European reference values for the quality of life questionnaire EORTC QLQ-C30: results of a German investigation and a sum- marizing analysis of six European general population normative studies. Acta Oncol (Madr) 2014; 53:958-65.
36. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol 2014; 66: 815-25.
37. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and pred- nisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol 2012; 13: 1210-7.
38. Downing A, Wright P, Hounsome L, et al. Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. Lancet Oncol 2019; 20:436-47.

SUPPLEMENTARY MATERIAL

Table S1. 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 S2. 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 S3. Representativeness of PRO-CAPRI population based on baseline characteristics

		PRO-CAPRI	CAPRI	p-value
		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	

Table S3. (Continued)

		PRO-CAPRI	CAPRI	p-value
		N=151	N=3,616	
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	
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. Assessment of HRQoL with subgroups per disease state at inclusion

		Total	CTx-naïve	Post-CTx	p-value
		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
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 S5A. 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-value
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 S5B. 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-value
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 S6. Time to clinical relevant deterioration in months of HRQoL per disease state

		CTx-naive		Post-CTx		p-value
		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.

CHAPTER 7

High-intensity care in the end-of-life phase of castration-resistant prostate cancer (CRPC) patients: results from the Dutch CAPRI-registry

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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 (end-of-life [EOL]) in castration-resistant prostate cancer (CRPC).

Methods

Castration-resistant prostate cancer registry (CAPRI) is an investigator-initiated, observational multicenter 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 (LPDs) in the last month, continuation of LPD in last 14 days, >1 admission, admission duration ≥14 days, and/or intensive care admission in last three months of life. Descriptive and binary logistic regression analyses were performed.

Results

High-intensity care was experienced by 41% of 2,429 patients in the EOL period. Multivariable analysis showed that age (odds ratio [OR] 0.98, 95% confidence interval [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[1]. In a contemporary real world cohort we previously reported a median overall survival (OS) of 26 months[2]. Several prognostic models and individual factors have been studied to aid in the identification of the beginning of the end-of-life (EOL)[3–5]. However, the overestimation of survival by clinicians shows that identification of EOL remains challenging[6–8]. 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[7].

The focus of EOL-care should shift from active LPD treatment to symptom management and meeting the subjective needs of patients[9]. In EOL, patients are less willing to accept treatment complications and want a dignified end of life, as comfortable as possible[10–13]. 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[14–16].

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[14,15]. 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[2]. 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[17] 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 31, 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 1). In the last 3 months of life TAX was prescribed in 6%, ART in 9% and radium-223 rarely (1%).

Table 1. Treatment characteristics during the course of CRPC

	CRPC-6 mo	6-3 mo	EOL phase	Adjusted p-value[a]
Total systemic treatment utilization, no. (%)				
No	315 (13)	736 (30)	992 (41)	
Yes	1,821 (75)	1,590 (66)	1,437 (59)	
Missing	293 (12)	103 (4)	0 (0)	<0.001
Type of utilized therapy, no. (%)				
Non-LPD	565 (23)	516 (21)	486 (20)	
LPD	1,256 (52)	1,074 (44)	951 (39)	<0.001
Docetaxel	969 (40)	319 (13)	230 (10)	<0.001
Cabazitaxel	224 (9)	171 (7)	133 (6)	<0.001
Abiraterone	603 (25)	426 (18)	384 (16)	<0.001
Enzalutamide	395 (16)	275 (11)	253 (10)	<0.001
Radium-223	104 (4)	83 (3)	69 (3)	0.001
New therapy initiated, no. (%)				
No	315 (13)	1,637 (67)	1,953 (80)	
Yes	1,821 (75)	689 (28)	476 (20)	
Missing	293 (12)	103 (4)	0 (0)	<0.001
Type of new initiated therapy, no. (%)				
Non-LPD	565 (23)	187 (8)	103 (4)	
LPD	1,256 (52)	502 (21)	373 (15)	0.001
Docetaxel	969 (40)	134 (6)	86 (4)	<0.001
Cabazitaxel	224 (9)	90 (4)	51 (2)	<0.001
Abiraterone	603 (25)	152 (6)	132 (5)	<0.001
Enzalutamide	395 (16)	104 (4)	91 (4)	<0.001
Radium-223	104 (4)	37 (2)	21 (1)	<0.001

[a] adjusted for multiple testing using Bonferroni correction.
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).

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 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 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 2).

Table 2. Baseline characteristics at start of EOL based on LPD treatment

	No LPD treatment N=1,327	**LPD continuation N=729**	**LPD initiation N=373**	**Adjusted p-value[a]**
Age, years				
Median (range)	80 (51-99)	74 (46-96)	74 (50-93)	
≥ 75 years (no, %)	956 (72)	346 (48)	180 (48)	<0.001
ECOG PS, no. (%)				
0	30 (2)	31 (4)	21 (6)	
1	161 (12)	175 (24)	139 (37)	
> 1	219 (17)	172 (24)	103 (28)	
unknown	917 (69)	351 (48)	110 (30)	0.007
Charlson score, no. (%)				
6	629 (47)	453 (62)	217 (58)	
7-8	508 (38)	218 (30)	120 (32)	
9-10	122 (9)	50 (7)	29 (8)	
>10	67 (5)	8 (1)	7 (2)	
Unknown	1 (<1)	0 (0)	0 (0)	<0.001
Bone metastases, no. (%)				
Yes	868 (65)	644 (88)	305 (82)	
No	90 (7)	21 (3)	17 (5)	
unknown	369 (28)	64 (9)	51 (14)	<0.001
Visceral metastases, no. (%)				
Yes	103 (8)	115 (16)	58 (16)	
No	284 (21)	259 (36)	113 (30)	
Unknown	940 (71)	355 (49)	202 (54)	0.181
Opioid use, no. (%)				
Yes	207 (16)	199 (27)	140 (38)	
No	138 (10)	90 (12)	54 (15)	
Unknown	982 (74)	440 (60)	179 (48)	0.007
PSA, ng/ml				
Median (IQR)	96 (25-307)	200 (65-607)	160 (61-365)	
unknown (no, %)	1,058 (80)	423 (58)	35 (9)	<0.001
Hemoglobin, mmol/L				
Median (IQR)	6.8 (5.9-7.6)	6.6 (5.9-7.4)	6.9 (6.1-7.5)	
unknown (no, %)	717 (54)	239 (33)	59 (16)	0.049

Table 2. (Continued)

	No LPD treatment N=1,327	LPD continuation N=729	LPD initiation N=373	Adjusted p-value[a]
Alkaline phosphatase, U/L				
Median (IQR)	170 (100-371)	213 (113-457)	216 (125-381)	
unknown (no, %)	762 (57)	181 (25)	62 (17)	0.001
Lactate dehydrogenase, U/L				
Median (IQR)	299 (224-450)	342 (230-530)	328 (248-536)	
unknown (no, %)	933 (70)	322 (44)	108 (29)	0.021
Referred to medical oncologist, no. (%)				
Yes	784 (59)	671 (92)	352 (94)	
No	523 (39)	54 (7)	21 (6)	
Unknown	20 (2)	4 (1)	0 (0)	<0.001
Prior LPD treatment lines, no. (%)				
0	899 (68)	238 (33)	124 (33)	
1	193 (15)	214 (29)	125 (34)	
2	134 (10)	183 (25)	71 (19)	
≥3	101 (8)	94 (13)	53 (14)	<0.001
Prior treatment, no. (%)				
Docetaxel	296 (22)	439 (60)	217 (58)	<0.001
Cabazitaxel	75 (6)	84 (12)	49 (13)	<0.001
Abiraterone acetate	212 (16)	203 (28)	98 (26)	<0.001
Enzalutamide	161 (12)	107 (15)	47 (13)	0.252
Radium-223	17 (5)	36 (5)	17 (5)	0.109

[a] adjusted for multiple testing using Bonferroni correction.
Characteristics measured in period of one month prior or after the start of last 3 months of life.
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); ECOG PS, Eastern Cooperative Oncology Group performance score; PSA, prostate specific antigen; IQR, interquartile range.

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 6-3mo 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 3).

Table 3. Hospital admissions during the course of CRPC

	CRPC-6 mo	6-3 mo	EOL phase	Adjusted p-value[a]
Hospital admission, no. (%)				
0	891 (37)	1,331 (55)	935 (39)	
1	989 (41)	468 (19)	773 (32)	
≥2	121 (5)	276 (11)	592 (24)	
Missing	428 (9)	354 (15)	129 (5)	<0.001
Admission duration[b], valid median	1.5	7	9	
IQR	1-3	3-13	4-16	
missing (no, %)	3 (<1)	5 (<1)	22 (1)	
< 14 days, no. (%)	1,056 (43)	567 (23)	920 (38)	<0.001
≥ 14 days, no. (%)	41 (2)	172 (7)	423 (17)	<0.001
Admission reason, no. (%)				
diagnostic evaluation	232 (10)	104 (4)	177 (7)	0.178
therapeutic	299 (12)	155 (6)	234 (10)	0.001
complication of therapy	251 (10)	94 (4)	112 (5)	<0.001
complication of CRPC	317 (13)	242 (10)	582 (24)	0.049
blood transfusion	70 (3)	86 (4)	183 (8)	<0.001
other	237 (10)	103 (4)	223 (9)	<0.001
ICU admission, no. (%)				
Yes	32 (1)	13 (1)	39 (2)	
No	1,969 (81)	2,062 (85)	2,261 (93)	
Missing	428 (18)	354 (15)	129 (5)	0.006

[a] adjusted for multiple testing using Bonferroni correction;

[b] number of admissions and admission duration calculated per 3 months.

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 4).

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%).

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 5).

Table 4. Hospital admission in EOL based on LPD treatment

	No LPD treatment N=1,327	**LPD continuation N=729**	**LPD initiation N=373**	**Adjusted p-value[a]**
Hospital admission, no. (%)				
0	569 (43)	277 (38)	89 (24)	
1	400 (30)	241 (33)	132 (35)	
≥2	255 (19)	188 (26)	149 (40)	
Missing	103 (8)	23 (3)	3 (1)	<0.001
Admission duration, valid				
median	9	9	11	
IQR	4-16	4-15	5-18	
missing (no, %)	10 (2)	6 (1)	6 (2)	
< 14 days, no. (%)	451 (34)	298 (41)	171 (46)	0.021
≥ 14 days, no. (%)	194 (15)	125 (17)	104 (28)	0.040
Admission reason, no. (%)				
diagnostic evaluation	77 (6)	59 (8)	41 (11)	0.418
therapeutic	108 (8)	80 (11)	46 (12)	0.607
complication of therapy	19 (1)	42 (6)	51 (14)	<0.001
complication of CRPC	220 (17)	212 (29)	150 (40)	<0.001
blood transfusion	61 (5)	83 (11)	39 (11)	<0.001
other	112 (8)	65 (9)	46 (12)	0.698
ICU admission, no. (%)				
Yes	12 (1)	16 (2)	11 (3)	
No	1,212 (91)	690 (95)	359 (96)	
Missing	103 (8)	23 (3)	3 (1)	0.013
Total number of high intensity care indicators, no. (%)				
0	1,005 (76)	352 (48)	80 (21)	
1	190 (14)	246 (34)	120 (32)	
> 1	132 (10)	131 (18)	173 (46)	<0.001

[a] adjusted for multiple testing using Bonferroni correction.

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.

Table 5. Univariable and multivariable logistic regression predicting any high intensity care in EOL

			Univariable analysis of original data			Multivariable analysis of pooled data after imputation		
		N	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (years), cont.		2,429	0.958	0.949-0.967	<0.001	0.980	0.968-0.993	0.002
ECOG PS	0	82	REF	-	-	REF	-	-
	1	475	0.870	0.542-1.394	0.562	0.832	0.487-1.422	0.487
	≥2	494	0.687	0.429-1.100	0.118	0.569	0.334-0.968	0.038
State, visceral	No	656	REF	-	-	REF	-	-
	Yes	276	1.119	0.844-1.484	0.433	0.960	0.669-1.379	0.819
Hemoglobin (mmol/L), cont.		1,414	0.907	0.827-0.994	0.037	0.901	0.797-1.019	0.093
LDH (U/L), cont.		1,066	1.000	1.000-1.000	0.209	1.000	0.999-1.000	0.106
ALP (U/L), cont.		1,424	1.000	0.999-1.000	0.043	1.000	0.999-1.000	0.121
PSA (U/L), cont.		913	1.000	1.000-1.000	0.902	1.000	1.000-1.000	0.320
Opioid use	No	282	REF	-	-	REF	-	-
	Yes	546	1.540	1.153-2.058	0.004	1.453	1.083-1.951	0.015
Time from CRPC diagnosis to EOL phase (months), cont.		2,429	0.988	0.983-0.993	<0.001	0.977	0.970-0.984	<0.001
LPD started prior to EOL phase	0	1,023	REF	-	-	REF	-	-
	1	556	1.942	1.570-2.401	<0.001	1.527	1.192-1.957	0.001
	≥2	850	1.936	1.604-2.337	<0.001	1.723	1.305-2.275	<0.001
Referral to medical oncologist	No	598	REF	-	-	REF	-	-
	Yes	1,807	2.612	2.123-3.214	<0.001	1.988	1.551-2.547	<0.001
Year of death	2010-2011	226	REF	-	-	REF	-	-
	2012-2013	684	0.962	0.708-1.306	0.802	1.048	0.751-1.462	0.782
	2014-2015	837	1.132	0.840-1.525	0.416	1.178	0.839-1.654	0.343
	2016-2017	682	0.909	0.668-1.235	0.541	1.080	0.743-1.571	0.686

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; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; CRPC, castration-resistant prostate cancer;); LPD, life-prolonging drugs (i.e. docetaxel, cabazitaxel, abiraterone acetate, enzalutamide or radium-223).

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%)[16,18,19], 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[6–8]. 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[3–5].

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[13]. 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[20]. 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[21]. 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[22]. 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[23].

Moreover, the indicators for high intensity care in our analysis is commonly used[24] (REF: Earle, Identifying potential indicators of the quality of end-of-life cancer care from administrative data). 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. The overuse of these 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[25–28], 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.

REFERENCES

1. Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. BMJ. 2005 Apr 30;330(7498):1007–11.
2. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry. Eur Urol Focus. 2018 Sep 13;4(5):694–701.
3. Guinney J, Wang T, Laajala TD, et al. Prediction of overall survival for patients with metastatic castration-resistant prostate cancer: development of a prognostic model through a crowdsourced challenge with open clinical trial data. Lancet Oncol. 2017 Jan 1;18(1):132–42.
4. Halabi S, Lin C-Y, Small EJ, et al. Prognostic Model Predicting Metastatic Castration-Resistant Prostate Cancer Survival in Men Treated With Second-Line Chemotherapy. JNCI J Natl Cancer Inst. 2013 Nov 20;105(22):1729–37.
5. Halabi S, Lin C-Y, Kelly WK, et al. Updated Prognostic Model for Predicting Overall Survival in First-Line Chemotherapy for Patients With Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2014 Mar 1;32(7):671–7.
6. World Palliative Care Alliance; WHO. Global atlas of palliative care at the end of life [Internet]. Geneva: World Health Organization; 2014. Available from: https://www.who.int/nmh/Global_Atlas_of_Palliative_Care.pdf
7. Glare P, Virik K, Jones M, et al. A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ. 2003 Jul 26;327(7408):195–8.
8. Cheon S, Agarwal A, Popovic M, et al. The accuracy of clinicians' predictions of survival in advanced cancer: a review. Ann Palliat Med. 2016 Jan;5(1):22–9.
9. Dy SM, Shugarman LR, Lorenz KA, Mularski RA, Lynn J. A Systematic Review of Satisfaction with Care at the End of Life. J Am Geriatr Soc. 2008 Jan;56(1):124–9.
10. Smith R. A good death. An important aim for health services and for us all. BMJ. 2000 Jan 15;320(7228):129–30.
11. Steinhauser KE, Christakis NA, Clipp EC, et al. Factors Considered Important at the End of Life by Patients, Family, Physicians, and Other Care Providers. JAMA. 2000 Nov 15;284(19):2476.
12. Heyland DK, Dodek P, Rocker G, et al. What matters most in end-of-life care: perceptions of seriously ill patients and their family members. CMAJ. 2006 Feb 28;174(5):627–33.
13. Voogt E, van der Heide A, Rietjens JAC, et al. Attitudes of patients with incurable cancer toward medical treatment in the last phase of life. J Clin Oncol. 2005 Mar 20;23(9):2012–9.
14. Earle CC, Neville BA, Landrum MB, et al. Evaluating claims-based indicators of the intensity of end-of-life cancer care. Int J Qual Heal care J Int Soc Qual Heal Care. 2005 Dec 1;17(6):505–9.
15. Earle CC, Landrum MB, Souza JM, et al. Aggressiveness of Cancer Care Near the End of Life: Is It a Quality-of-Care Issue? J Clin Oncol. 2008 Aug 10;26(23):3860–6.

16. Pataky RE, Cheung WY, De Oliveira C, et al. Population-based trends in systemic therapy use and cost for cancer patients in the last year of life. Curr Oncol. 2016 Feb 29;23(Suppl 1):S32–41.
17. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017 Apr;71(4).
18. Zaghloul HA, Murillo JR. Treatment Given Near the End of Life in Castration-Resistant Prostate Cancer. Am J Hosp Palliat Med. 2012 Nov 4;29(7):536–40.
19. Earle CC, Neville BA, Landrum MB, et al. Trends in the Aggressiveness of Cancer Care Near the End of Life. J Clin Oncol. 2004 Jan 15;22(2):315–21.
20. Meeussen K, Van den Block L, Echteld MA, et al. End-of-life care and circumstances of death in patients dying as a result of cancer in Belgium and the Netherlands: a retrospective comparative study. J Clin Oncol. 2011;29(32):4327–34.
21. Hearn J, Higginson IJ. Do specialist palliative care teams improve outcomes for cancer patients? A systematic literature review. Palliat Med. 1998 Sep;12(5):317–32.
22. Brinkman-Stoppelenburg A, Boddaert M, Douma J, van der Heide A. Palliative care in Dutch hospitals: a rapid increase in the number of expert teams, a limited number of referrals. BMC Health Serv Res. 2016 Sep 23;16(1):518.
23. Henson LA, Gomes B, Koffman J, et al. Factors associated with aggressive end of life cancer care. Support Care Cancer. 2016 Mar 8;24(3):1079–89.
24. Earle CC, Park ER, Lai B, et al. Identifying potential indicators of quality of end-of-life cancer care from administrative data. J Clin Oncol. 2003 Mar 15;12(6):1133-8.
25. Temel JS, Greer JA, Muzikansky A, et al. Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer. N Engl J Med. 2010 Aug 19;363(8):733–42.
26. Bakitas MA, Tosteson TD, Li Z, et al. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. J Clin Oncol. 2015 May 1;33(13):1438–45.
27. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet. 2014 May 17;383(9930):1721–30.
28. Greer JA, Pirl WF, Jackson VA, et al. Effect of Early Palliative Care on Chemotherapy Use and End-of-Life Care in Patients With Metastatic Non–Small-Cell Lung Cancer. J Clin Oncol. 2012 Feb 1;30(4):394–400.

Supplementary Table 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 (no. %)	1,320 (54)	1,479 (61)
ECOG PS, no. (%)		
0	432 (18)	82 (3)
1	481 (20)	470 (20)
> 1	152 (6)	494 (20)
unknown	1,364 (56)	1,377 (57)
Charlson score, no. (%)		
6	1,430 (59)	1,296 (54)
7-8	812 (33)	843 (35)
9-10	138 (6)	201 (8)
>10	48 (2)	82 (3)
unknown	1 (<1)	1 (<1)
Bone metastases, %		
Yes	1,418 (58)	1,817 (75)
No	191 (8)	128 (5)
unknown	820 (34)	484 (20)
Visceral metastases, %		
Yes	103 (4)	276 (11)
No	397 (16)	656 (27)
unknown	1,929 (79)	1,497 (62)
Opioid use, no. (%)		
Yes	230 (10)	544 (23)
No	551 (23)	282 (12)
unknown	1,648 (68)	1,597 (66)
PSA, ng/ml		
Median (IQR)	22.7 (8-79)	159 (44-410)
unknown (no, %)	72 (3)	1,516 (62)
Hemoglobin, mmol/L		
Median (IQR)	7.9 (7.2-8.5)	6.7 (5.9-7.5)
unknown (no, %)	730 (30)	1,015 (42)
Alkaline phosphatase, U/L		
Median (IQR)	116 (81-224)	192 (108-404)
unknown (no, %)	812 (33)	1,005 (41)
Lactate dehydrogenase, U/L		
Median (IQR)	232 (192-330)	321 (230-506)
unknown (no, %)	1,340 (55)	1,363 (56)
Referred to medical oncologist, no. (%)		
Yes	339 (14)	1,801 (74)
No	2,046 (84)	598 (25)
Unknown	44 (2)	24 (1)

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; IQR, interquartile range.

PART 3

Towards improvement of routine care: lessons learned from real world data

CHAPTER 8

Real-world outcomes of sequential androgen-receptor targeting therapies with or without interposed life-prolonging drugs in metastatic castration-resistant prostate cancer: Results from the Dutch Castration-resistant Prostate Cancer Registry

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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 (LPDs; ie, docetaxel, cabazitaxel, or radium-223) between ART1 and ART2.

Design, setting, and participants

Castration-resistant prostate cancer 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 limitations

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 favorable 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 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 randomized 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[1]. 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 signaling 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[2]. 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[3–6]. A short interval between both ARTs and progression on ART1 are related to low PSA responses[7,8].

The European Association of Urology advises the use of DOC after first-line ART because of concerns about cross resistance[9], 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[10].

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 programs 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 (LPDs) such as TAX or Ra-223.

PATIENTS AND METHODS

Study design and setting

Castration-resistant Prostate Cancer Registry (CAPRI) is an investigator-initiated, observational, multicenter 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[11]. Castration-resistant prostate cancer patients were included retrospectively from January 1, 2010 until December 31, 2015, with regular updates of all data until December 31, 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 July 1, 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" (ie, ART1 treatment duration ≥12 weeks according to the Prostate Cancer Clinical Trials Working Group 3 [PCWG 3] criteria [12]) or "short ART1 treatment" (ie, ART1 treatment duration <12 weeks)
3. Interval between ART1 and ART2: interval between ART1 and ART2 calculated as the time between stop of ART1 and start of ART2, with a cut-off of 40 d based on previous published work [7]

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 6 weeks before to 1 week after the start of ART2. All patients were followed until death, loss to follow-up, or December 31, 2017. Follow-up duration was calculated from the start date of ART2 to the last recorded date.

Outcome

The 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 week s(according to the PCWG 3 criteria for response measurement[12]) or, if treatment was for <12 weeks, at the end of treatment or start of next treatment. PSA response was defined as a ≥50% PSA decline from baseline[12].

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.

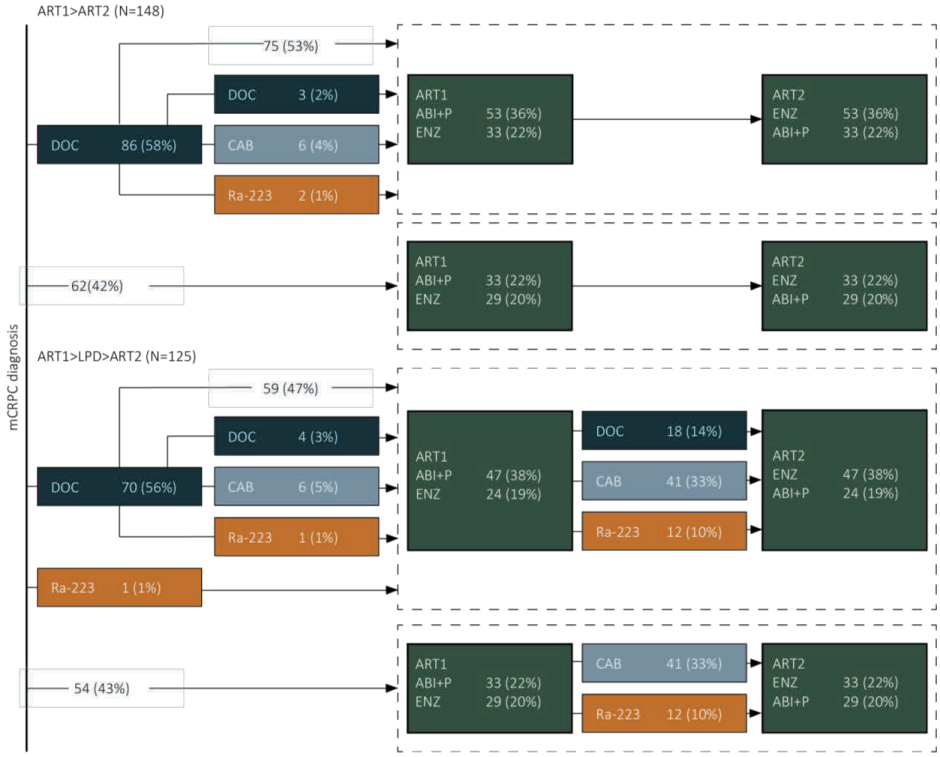
RESULTS

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 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 (Fig. 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 (31%) with ENZ > ABI + P in ART1 > LPD > ART2 (Fig. 1).

Median follow-up from ART2 was 8.4 months (range 0.3–35.8 months). At the end of the study, 202 all-cause deaths (74%) 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).

Figure 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.

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 1). ART1 > ART2 patients had favorable prognostic characteristics: less visceral metastases (12% vs 22%, $p = 0.04$),

higher hemoglobin 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 mg/l, p = 0.03).

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 1).

Table 1. Baseline characteristics at the start of second AR-targeting therapy (ART2)

		ART1>ART2	**ART1>LPD>ART2**	**p-value**
		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	

Table 1. (Continued)

		ART1>ART2	ART1>LPD>ART2	p-value
		N=148	**N=125**	
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	
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.

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 2 and Fig. 2). PSA response of ART2 in ART1 > ART2 was similar to PSA response of LPD in ART1 > LPD > ART2 (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 3).

Table 2. PSA response and treatment duration of second AR-targeting therapy (ART2)

		ART1>ART2	ART1>LPD>ART2	p-value
		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	

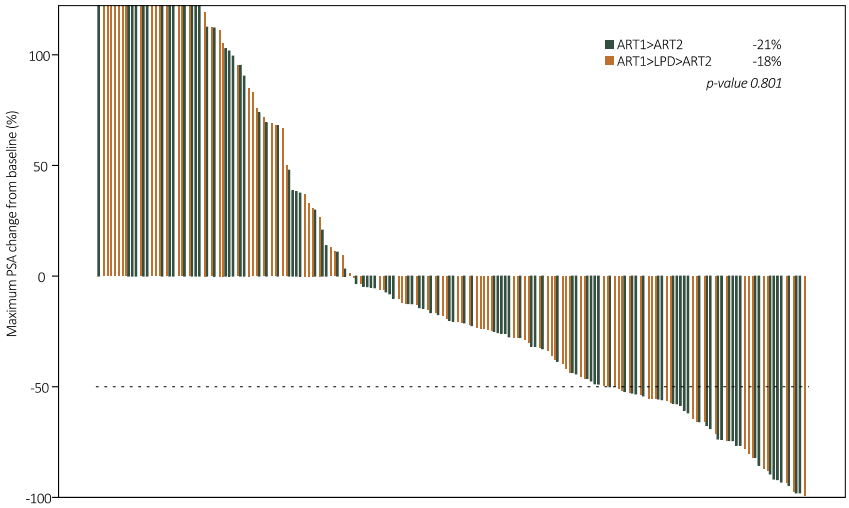
* significant at p-value<0.05; [a] measured as relative change from baseline value (negative values indicate a PSA decline, positive values a PSA increase); [b] still on treatment at end of follow-up; [c] PSA response rate of ART2 in ART1>ART2 and of interposed LPD in ART1>LPD>ART2. *Abbreviations*: PSA, prostate-specific antigen; ART2, second AR-targeting therapy; ART1, first AR-targeting therapy; LPD, life-prolonging drug; IQR, interquartile range; mo, months.

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. Fig. 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 to ART2 had a median treatment duration of 7.3 months (IQR 4.1–13.0 months).

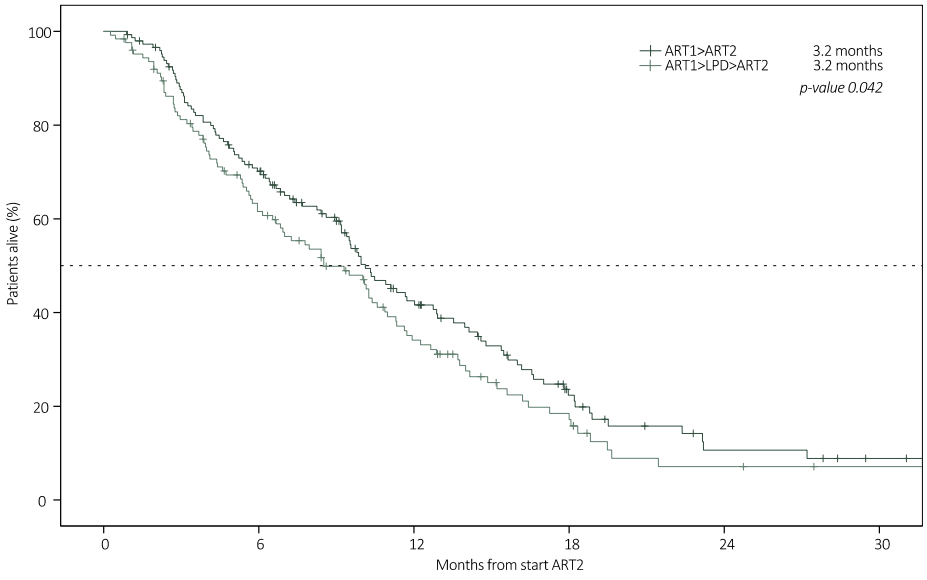
No differences were observed in ART2 treatment duration between ABI + P and ENZ sequence, ART1 treatment duration, and interval between ART1 and ART2 (Table 3).

Figure 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).

Figure 3. Treatment duration (months) during second AR-targeting therapy (ART2)



Abbreviations: ART2, second AR-targeting therapy; ART1, first AR-targeting therapy; LPD, other life prolonging drug (docetaxel, cabazitaxel or radium-223).

Table 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-value**	≥ 12 weeks	< 12 weeks	**p-value**	< 40 days	≥ 40 days	**p-value**
		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.

Multivariate analyses

Eighty-three patients (30%) were excluded from multivariate binary logistic regression due to missing PSA response of ART2 (Table 4). There was no difference in PSA response of ART2 between ART1 > ART2 and ART1 > LPD > ART2 (odds 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 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).

Table 4. Univariable and multivariable binary logistic regression for PSA-responset

		Univariable analysis of original data				Multivariable analysis of pooled data after imputation		
		N	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
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*

Table 4. (Continued)

		Univariable analysis of original data				Multivariable analysis of pooled data after imputation		
		N	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
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.

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 multicenter population in which patients are treated according to the views and opinions of their medical oncologists and urologists. Outcomes therefore reflect current daily practice.

Patients with ART1 > ART2 had better prognostic factors at the start of ART2 (less visceral disease, higher hemoglobin, 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 mo. PSA response is in line with previously published reports on ART2 (4–30%[4–6,13–16]), 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[17–20]). 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 mechanisms (eg, AR aberrations, including amplification, genomic structural variants, or splice variants such as AR-V7) and AR-independent mechanisms (eg, neuroendocrine transformation or glucocorticoid receptor overexpression)[2]. 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 multicenter study showed that the biochemical response rates decreased to 38%, 24%, and 16%, respectively, on second, third, and fourth lines irrespective of the treatment sequence[21].

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 rapid time to castration resistance are known prognostic factors for overall survival[22,23], but can possibly impact PSA response due to a correlation between survival and PSA response rate[24,25].

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 of <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 favorable effects for ABI + P > ENZ than for ENZ > ABI + P[4–7,13,26,27]. 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[24,25].

Although the PSA response rate of ART2 is fairly low and 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 AR-V7[2].

Monitoring treatment efficacy in mCRPC is complex[28]. The decision to discontinue treatment should not be based on a single indicator for progression, but on the association between different outcome measures (eg, clinical, biochemical, patient-reported outcomes, and imaging)[12]. 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[12].

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 noninvasive 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 (eg, CARD study [ClinicalTrials.gov identifier NCT02485691] and phase 2 randomized cross-over trial of ART [NCT02125357]).

CONCLUSIONS

In conclusion, our study suggests that PSA response 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 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.

REFERENCES

1 Commissie Farmaceutische Hulp. Kostenprognose van Opname van Cabazitaxel (Jevtana1) in de Beleidsregel Dure Geneesmiddelen. 2011.

2 Buttigliero C, Tucci M, Bertaglia V, et al. Understanding and over- coming the mechanisms of primary and acquired resistance to abiraterone and enzalutamide in castration resistant prostate cancer. Cancer Treat Rev 2015;41:884–92.

3 Khalaf D, Annala M, Finch DL, et al. Phase 2 randomized cross-over trial of abiraterone + prednisone (ABI+P) vs enzalutamide (ENZ) for patients (pts) with metastatic castration resistant prostate cancer (mCRPC): results for 2nd-line therapy. J Clin Oncol 2018;36 (15_suppl):5015.

4 Matsubara N, Yamada Y, Tabata K-I, et al. Abiraterone followed by enzalutamide versus enzalutamide followed by abiraterone in chemotherapy-naive patients with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2018;16:142–8.

5 Nadal R, Tsai H-L, Sinibaldi VJ, et al. Prognostic factors for clinical outcomes in patients with metastatic castration resistant prostate cancer treated with sequential novel androgen receptor-directed therapies. Prostate 2016;76:512–20.

6 Terada N, Maughan BL, Akamatsu S, et al. Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemo- therapy-naïve castration-resistant prostate cancer: the Kyoto-Baltimore collaboration. Int J Urol 2017;24:441–8.

7 Badrising SK, van der Noort V, van den Eertwegh AJM, et al. Prognostic parameters for response to enzalutamide after docetaxel and abiraterone treatment in metastatic castration-resistant prostate cancer patients; a possible time relation. Prostate 2016;76:32–40.

8 Petrelli F, Coinu A, Borgonovo K, et al. Enzalutamide after docetaxel and abiraterone acetate treatment in prostate cancer: a pooled analysis of 10 case series. Clin Genitourin Cancer 2015;13:193–8.

9 Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 2017;71:630–42.

10 Miyake H, Hara T, Ozono S, Fujisawa M. Impact of prior use of an androgen receptor-axis-targeted (ARAT) agent with or without subsequent taxane therapy on the efficacy of another ARAT agent in patients with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2017;15:e217–22.

11 Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in trial and real-world populations in the Dutch castration-resistant prostate Cancer registry. Eur Urol Focus 2018;4:694–701.

12 Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials working Group 3. J Clin Oncol 2016;34:1402–18.

13 Miyake H, Sugiyama T, Aki R, et al. Comparison of alternative androgen receptor-axis-targeted agent (ARATA) and docetaxel as second-line therapy for patients with metastatic castration-resis- tant prostate cancer with progression after initial ARATA in real- world clinical practice in Japan. Clin Genitourin Cancer 2018;16:219–25.

14 Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013;24:1802–7.
15 Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013;24:1807–12.
16 Cheng HH, Nadal R, Gulati R, et al. The effect of prior abiraterone (Abi) use on the activity of enzalutamide (Enza) in men with mCRPC. J Clin Oncol 2014;32(4_suppl):18.
17 Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
18 Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in meta- static prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33. 19 de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995– 2005.
20 Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
21 Caffo O, De Giorgi U, Fratino L, et al. Clinical outcomes of castration- resistant prostate cancer treatments administered as third or fourth line following failure of docetaxel and other second-line treatment: results of an Italian multicentre study. Eur Urol 2015;68:147–53.
22 Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration- resistant prostate cancer. J Clin Oncol 2016;34:1652–9.
23 Hung J, Taylor AR, Divine GW, Hafron JM, Hwang C. The effect of time to castration resistance on outcomes with abiraterone and enzalutamide in metastatic prostate cancer. Clin Genitourin Cancer 2016;14:381–8.
24 Armstrong AJ, Saad F, Phung D, et al. Clinical outcomes and survival surrogacy studies of prostate-specific antigen declines following enzalutamide in men with metastatic castration-resistant prostate cancer previously treated with docetaxel. Cancer 2017;123:2303–11.
25 Xu XS, Ryan CJ, Stuyckens K, et al. Clinical correlation between prostate-specific antigen kinetics and overall survival in abiraterone acetate-treated castration-resistant prostate cancer patients. Clin Cancer Res 2015;21:3170–7.
26 de Bono JS, Chowdhury S, Feyerabend S, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for 2:24 weeks in Europe. Eur Urol 2018;74:37–45.
27 Brasso K, Thomsen FB, Schrader AJ, et al. Enzalutamide antitumour activity against metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone: a multicentre analysis. Eur Urol 2015;68:317–24.
28 Scher HI, Morris MJ, Basch E, Heller G. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. J Clin Oncol 2011;29(27):3695–704.

CHAPTER 9

Third-line life prolonging drug treatment in a real-world metastatic castration resistant prostate cancer (mCRPC) population: results from the Dutch CAPRI-registry

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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 favorable 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, $p < 0.001$), hemoglobin < 0.002), prostate-specific antigen ≥130 mg/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[1]. Part of these patients will eventually progress and develop metastatic castration-resistant prostate cancer (mCRPC)[2]. In 2004, docetaxel, a member of the taxane drug class, was the first treatment to improve overall survival (OS) of mCRPC patients[3]. In the last years, several new therapeutic agents, including cabazitaxel, abiraterone acetate, enzalutamide and radium-233, have also been registered for 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[4-9].

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[10]. To date, randomized controlled trials of third-line LPD in mCRPC patients are scarce[11]. The reports on third-line LPD are particularly retrospective and based on small cohorts of patients receiving one specific third-line LPD[12-16]. mCRPC patients on third-line LPD may have worse outcomes, compared to first- and second-line LPD treatment, due to the in general more advanced stages, decreased performance status, worse tolerance to treatments[17] and possible cross-resistance[18].

Thus, third-line LPD 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[19]. Prediction of treatment outcome may allow for better patient selection. Nevertheless, current prognostic models for survival using clinical- and laboratory baseline variables in mCRPC patients have only been described in first- or second-line LPD[20-23].

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

CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multi-center cohort study in 20 hospitals in the Netherlands. The study design has been described before[24]. Patients with mCRPC were included retrospectively from January 1, 2010 until December 31, 2015. mCRPC was either defined by the criteria set by the EAU[25] or by the treating physician. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Objectives

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

Participants

mCRPC 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 three weeks prior to three weeks after the progression date after a second-line LPD. All patients were followed until death, lost-to-follow-up or December 31, 2017. Follow-up duration was calculated as time from date of progression on a second-line LPD to 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 last recorded date.

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

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 PCWG 3 criteria for response measurement[26]) 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.

Statistical analysis

Descriptive statistics were performed. The T test (or Mann-Whitney 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 were based on clinical applicability (routinely collected and used by clinicians), previous research and expert opinion[27]. Continuous variables were categorized using median cut off or clinical 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 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. 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 2nd LPD treatment and were included in the analysis. At database cutoff, 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 either, 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 patients (60%) received a third-line LPD. 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 1.

Baseline characteristics

Baseline characteristics of mCRPC patients at the progression date of a second-line LPD, according to subsequent third-line LPD or not, are shown in Table 1. Patients receiving a third-line LPD had a more favorable prognostic profile (significantly younger, better ECOG PS, less opioid use, less visceral metastases, higher hemoglobin (Hb), lower ALP and lower LDH) compared to patients who received BSC.

Table 1. Baseline characteristics at time of progression on a second-line LPD in mCRPC patients

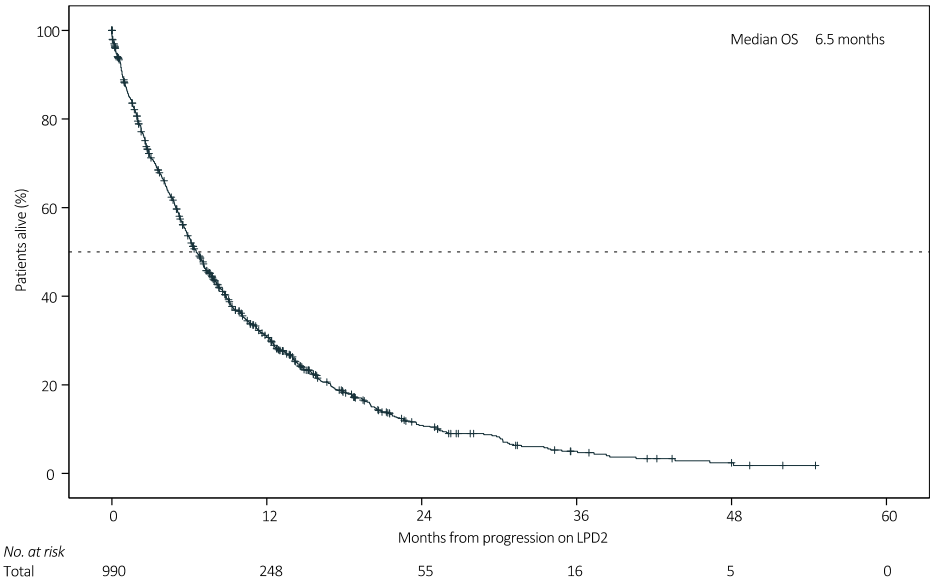
		Total group[a]	BSC	Third-line LPD	p-value
		N=1,011	N=409	N=602	
Age (years)	mean ± SD	71.6 ± 7.5	73.0 ± 7.8	71.0 ± 7.3	0.032*
	unknown, n (%)	21 (2)	0 (0)	21 (3)	
ECOG PS, n (%)	0	93 (9)	15 (4)	78 (13)	<0.001*
	1	280 (28)	67 (16)	213 (35)	
	≥2	130 (13)	98 (24)	32 (5)	
	unknown	508 (50)	229 (56)	279 (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)	

Table 1. (Continued)

		Total group[a]	BSC	Third-line LPD	p-value
		N=1,011	**N=409**	**N=602**	
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)	

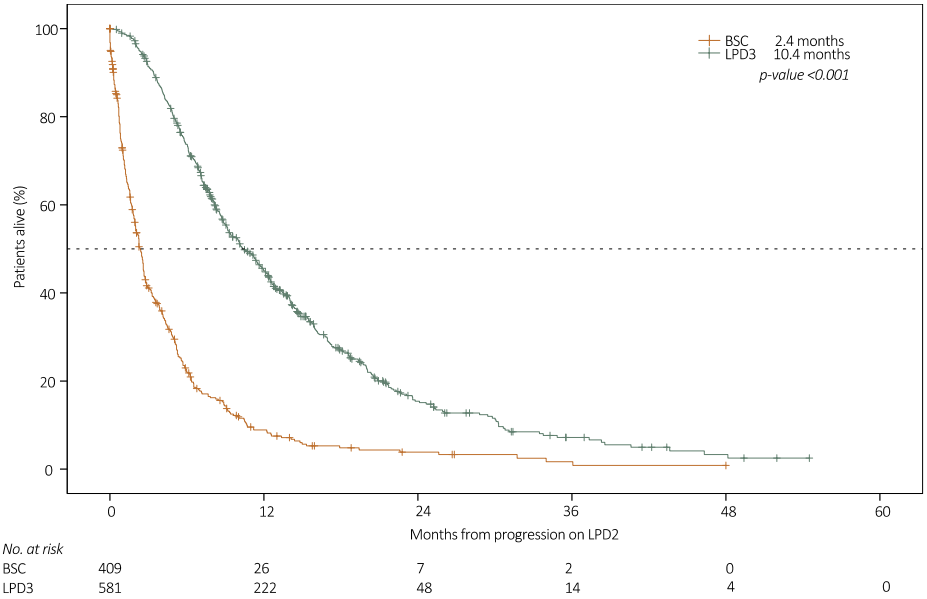
* significant at p-value <0.05. [a] total group of patients progressive on or after a second-line LPD. *Abbreviations*: mCRPC, metastatic castration-resistant prostate Cancer; LPD, life prolonging drug; BSC, best supportive care; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group Performance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

Figure 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 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.

Table 2. Univariable and multivariable analysis of different prognostic variables for overall survival

		Univariable analysis			Multivariable analysis				
	n/N[a]	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**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						

Table 2. (Continued)

		Univariable analysis			Multivariable analysis				
	n/N[a]	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**β[b]**	**pt**
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 constant (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.

Overall survival and risk-scoring system

The median OS (mOS) from progression on a second-line LPD was 6.5 months (95% CI 5.9-7.2). mOS was longer for patients receiving a third-line LPD (10.4 months, 95% CI 9.2-11.6) compared to patients who received BSC (2.4 months, 95% CI 2.1-2.7; Figure 1).

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 2).

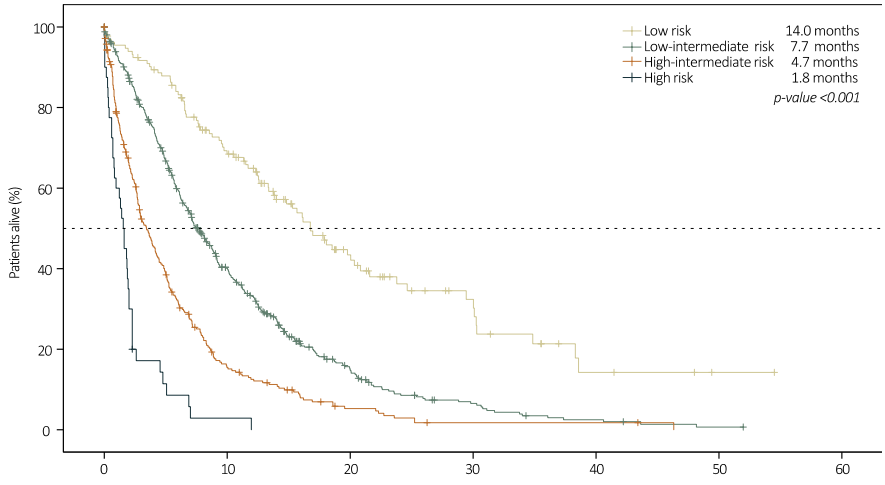
The multivariable Cox regression analysis of pooled data identified seven variables independently associated with OS: : ECOG PS of 1 and ≥2 (HR 1.51, 95% CI 1.13-2.00, p = 0.007 and HR 3.08, 95% CI 2.31-4.10, p < 0.001, respectively), opioid use (HR 1.55, 95% CI 1.10-2.19, p = 0.019), visceral metastases (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 µg/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) were related to worse survival.

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 µg/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 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 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 months (95% CI 10.7-17.3), 7.7 months (95% CI 6.6-8.9), 4.7 months (95% CI 4.0-5.4) and 1.8 months (95% CI 1.4-2.2), respectively (p < 0.001; Figure 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. mOS for these risk groups, according to whether or not treated with a third-line LPD, are depicted in Figure 2.

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

Figure 2A. Overall survival from progression after LPD2 according to risk groups: total (N=1,011)

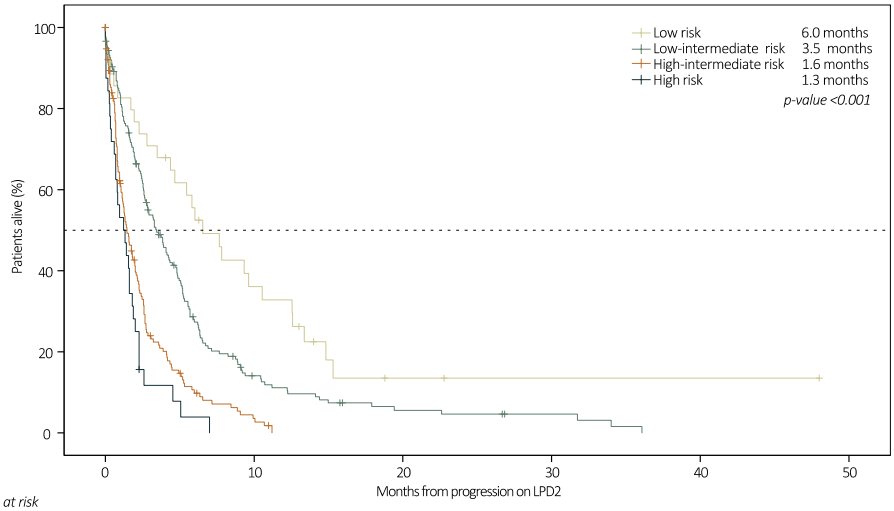


No. at risk

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			

Dotted line indicates the median overall survival. *Abbreviations*: LPD2, second-line life-prolonging drug; BSC, best supportive care; LPD3, third-line life prolonging drug.

Figure 2B. Overall survival from progression after LPD2 according to risk groups: LPD3 (N=602)

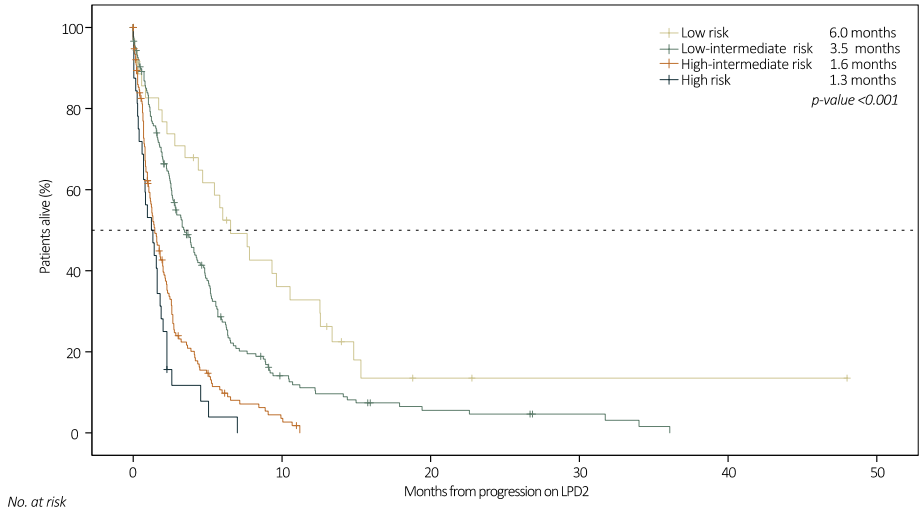


No. at risk

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

Dotted line indicates the median overall survival. Abbreviations: LPD2, second-line life-prolonging drug; third-line life prolonging drug.

Figure 2C. Overall survival from progression after LPD2 according to risk groups: BSC (N=409)

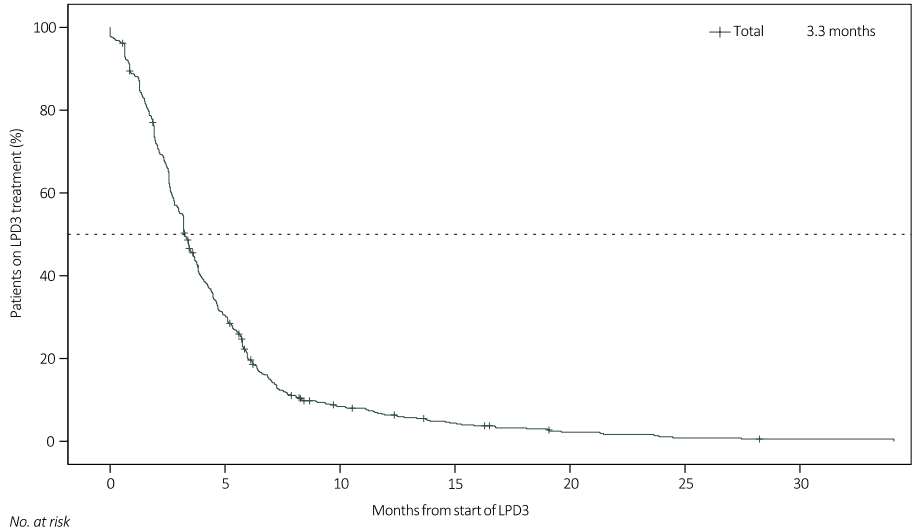


No. at risk

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

Dotted line indicates the median overall survival. *Abbreviations*: LPD2, second-line life-prolonging drug; BSC, best supportive care.

Figure 3A. Treatment duration of LPD3: all patients (n=602)

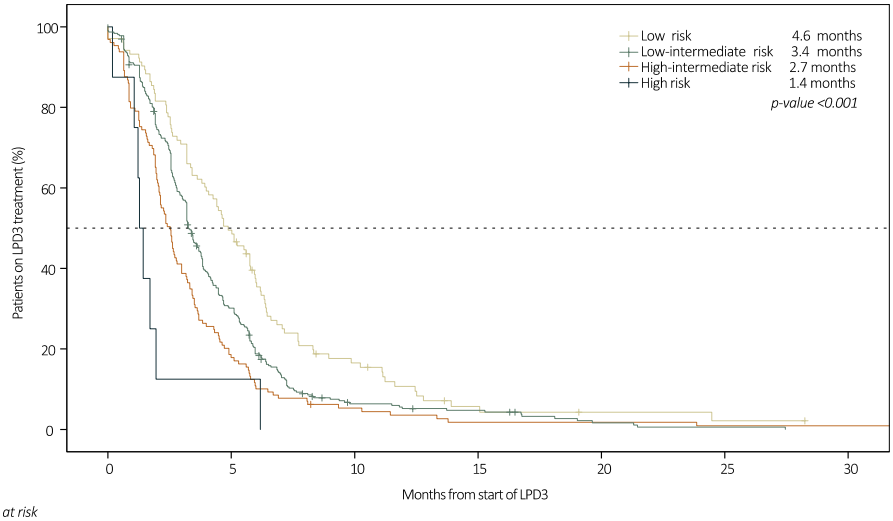


No. at risk

Total	364	80	11	6	4	0

Abbreviations: LPD3, third-line life prolonging drug.

Figure 3B. Treatment duration of LPD3 according to the risk groups: all patients (n=602)



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				

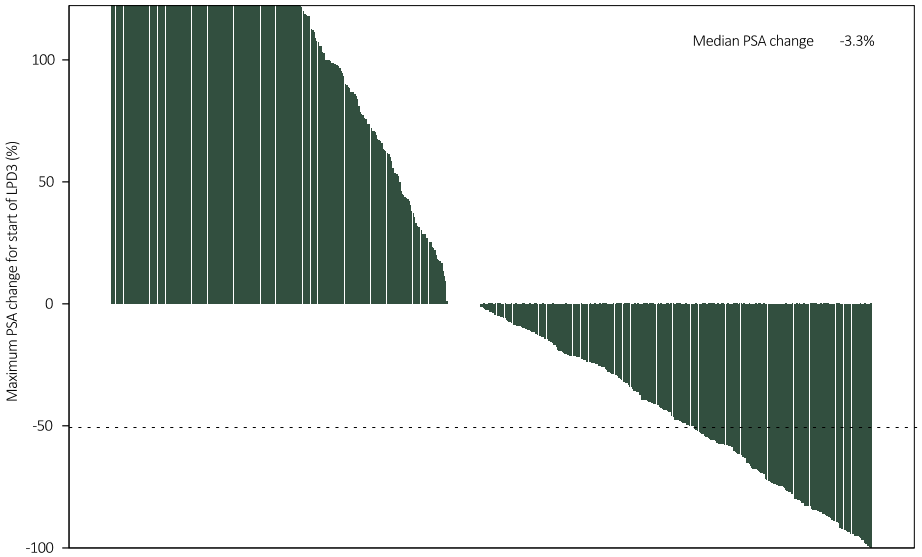
Abbreviations: LPD3, third-line life prolonging drug.

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. Median TD (mTD) for third-line LPD was 3.3 months (95% CI 3.0-3.5). PSA decline on third-line LPD was assessable in 560 (93%) patients and observed in 130 (22%) patients.

mTD for the four risk groups (low-, low-intermediate-, high-intermediate- and high-risk groups) were 4.6 months (95% CI 3.8-5.4), 3.4 months (95% CI 3.2-3.6), 2.7 (95% CI 2.4-3.0) and 1.4 months (95% CI 1.1-1.7), respectively ($p < 0.001$; Figure 3). PSA response rates (>50% PSA response) were 24% (18 out of 76 patients), 22% (66 out of 301), 23% (41 out of 181 patients) and 6% (1 out of 17 patients), respectively. Waterfall plot of the PSA responses are shown in Figure 4.

Figure 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 multicenter 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 a mOS of 6.5 months from progression of second-line LPD. mOS was longer in patients with a third-line LPD compared to patients receiving BSC (10.4 vs. 2.4 months), but TD was short (3.3 months) 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[13-15].

Pivotal phase III trials on first- and second-line LPD treatment in mCRPC patients reported a mOS of 14.0-34.7 months. 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[24] 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[28]. Possible cross-resistance with previous treatments can further

decrease treatment effect[18]. Moreover, tolerability to new systemic treatments can be worse[17] 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[10,17,29]. This is recently prospectively confirmed by a study of de Wit et al.[11], which reported an increased mOS in patients receiving cabazitaxel compared to ART (13.6 vs. 11.0 months) after prior docetaxel and the other ART. Since all patients had progression on an alternative ART within 12 months, 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 months, respectively ($p < 0.001$).

Especially, high-risk patients had remarkable short mOS. Moreover, high-risk patients treated with 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 LPD 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 LPD and 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. Moreover, careful consideration is also warranted considering possible low cost-effectiveness.

This study is not without limitations. Firstly, our results are limited by the absence of previously identified risk factors such as albumin level[27]. 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[30]. Second, the effect of third-line LPD in other outcomes such as QoL and cost-effectiveness could not be included in this analyses. 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 easily calculated. 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.

Conclusions

Third-line LPD 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.

REFERENCES

1. Zhou, C.K., et al., *Prostate cancer incidence in 43 populations worldwide: An analysis of time trends overall and by age group.* Int J Cancer, 2016. **138**(6): p. 1388-400.
2. Karantanos, T., P.G. Corn, and T.C. Thompson, *Prostate cancer progression after androgen deprivation therapy: mechanisms of castrate resistance and novel therapeutic approaches.* Oncogene, 2013. **32**(49): p. 5501-11.
3. Tannock, I.F., et al., *Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer.* N Engl J Med, 2004. **351**(15): p. 1502-12.
4. Fizazi, K., et al., *Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study.* Lancet Oncol, 2012. **13**(10): p. 983-92.
5. Scher, H.I., et al., *Increased survival with enzalutamide in prostate cancer after chemotherapy.* N Engl J Med, 2012. **367**(13): p. 1187-97.
6. de Bono, J.S., et al., *Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial.* Lancet, 2010. **376**(9747): p. 1147-54.
7. Parker, C., et al., *Alpha emitter radium-223 and survival in metastatic prostate cancer.* N Engl J Med, 2013. **369**(3): p. 213-23.
8. Ryan, C.J., et al., *Abiraterone in metastatic prostate cancer without previous chemotherapy.* N Engl J Med, 2013. **368**(2): p. 138-48.
9. Beer, T.M. and B. Tombal, *Enzalutamide in metastatic prostate cancer before chemotherapy.* N Engl J Med, 2014. **371**(18): p. 1755-6.
10. Maines, F., et al., *Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer.* Crit Rev Oncol Hematol, 2015. **96**(3): p. 498-506.
11. de Wit, R., et al., *Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer.* N Engl J Med, 2019.
12. Badrising, S., et al., *Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment.* Cancer, 2014. **120**(7): p. 968-75.
13. Brasso, K., et al., *Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis.* Eur Urol, 2015. **68**(2): p. 317-24.
14. Pezaro, C.J., et al., *Activity of cabazitaxel in castration-resistant prostate cancer progressing after docetaxel and next-generation endocrine agents.* Eur Urol, 2014. **66**(3): p. 459-65.
15. Schrader, A.J., et al., *Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone.* Eur Urol, 2014. **65**(1): p. 30-6.
16. Caffo, O., et al., *Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study.* Eur Urol, 2015. **68**(1): p. 147-53.

17. Loriot, Y., et al., *Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100).* Ann Oncol, 2013. **24**(7): p. 1807-12.
18. van Soest, R.J., et al., *Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer.* Eur J Cancer, 2013. **49**(18): p. 3821-30.
19. Chanez, B., et al., *A scoring system to guide the decision for a new systemic treatment after at least two lines of palliative chemotherapy for metastatic cancers: a prospective study.* Support Care Cancer, 2017. **25**(9): p. 2715-2722.
20. Halabi, S., et al., *Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer.* J Clin Oncol, 2003. **21**(7): p. 1232-7.
21. Halabi, S., et al., *Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer.* J Clin Oncol, 2014. **32**(7): p. 671-7.
22. Armstrong, A.J., et al., *The development of risk groups in men with metastatic castration-resistant prostate cancer based on risk factors for PSA decline and survival.* Eur J Cancer, 2010. **46**(3): p. 517-25.
23. Chi, K.N., et al., *A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel.* Ann Oncol, 2016. **27**(3): p. 454-60.
24. Westgeest, H.M., et al., *Differences in Trial and Real-world Populations in the Dutch Castration-resistant Prostate Cancer Registry.* Eur Urol Focus, 2018. **4**(5): p. 694-701.
25. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. 2017;7–1. .
26. Scher, H.I., et al., *Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3.* J Clin Oncol, 2016. **34**(12): p. 1402-18.
27. Pinart, M., et al., *Prognostic models for predicting overall survival in metastatic castration-resistant prostate cancer: a systematic review.* World J Urol, 2018.
28. Frieling, J.S., D. Basanta, and C.C. Lynch, *Current and emerging therapies for bone metastatic castration-resistant prostate cancer.* Cancer Control, 2015. **22**(1): p. 109-20.
29. Attard, G., et al., *Abiraterone Alone or in Combination With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer With Rising Prostate-Specific Antigen During Enzalutamide Treatment.* J Clin Oncol, 2018. **36**(25): p. 2639-2646.
30. Jakobsen, J.C., et al., *When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts.* BMC Med Res Methodol, 2017. **17**(1): p. 162.

SUPPLEMENTARY TABLES

Supplementary Table 1. Overview of treatment lines

First-line (n=1,011)		**Second-line** (n=1,011)		**Third-line** (n=602)	
Drug	**No. of patients (%)**	**Drug**	**No. of patients (%)**	**Drug**	**No. of patients (%)**
DOC	872 (86.3)	DOC	170 (16.8)	DOC	45 (8.0)
CAB	0	CAB	155 (15.3)	CAB	213 (35.4)
ABI	89 (8.8)	ABI	436 (43.1)	ABI	137 (22.8)
ENZ	49 (4.8)	ENZ	233 (23.0)	ENZ	129 (21.4)
RA-223	1 (0.1)	RA-223	17 (1.7)	RA-223	78 (13.0)

Abbreviations: DOC, docetaxel; CAB, cabazitaxel; ABI, abiraterone acetate; ENZ, enzalutamide; RA-223, radium-223

Supplementary Table 2A. Risk factors to calculate risk score

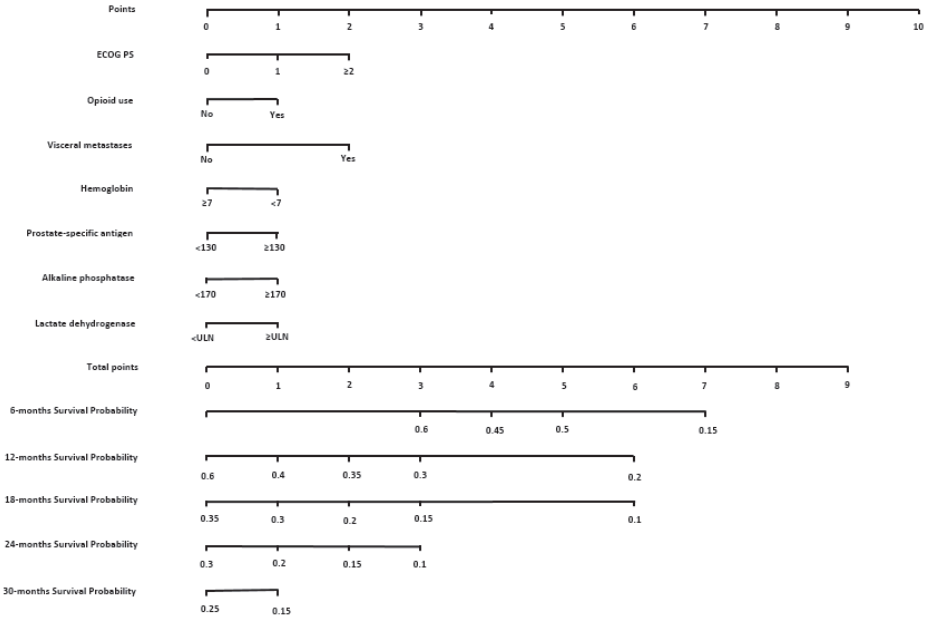
Risk variables	**Points***
ECOG PS 1	1
ECOG PS ≥2	2
Opioid use	1
Visceral metastases	2
Hemoglobin	1
Prostate-specific antigen	1
Alkaline phosphatase	1
Lactate dehydrogenase	1

Abbreviation: ECOG PS, eastern cooperative oncology group performance status.
Note: * points assigned to the risk variables are based on their regression coefficients.

Supplementary table 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

Supplementary Figure 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 'point' line. The total sum of points for seven risk variables is plotted on the 'total points' line. A line is drawn down to the corresponding predictions of 6-, 12-, 18-, 24- and 30-months survival probability.



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ULN, Upper Limit of Normal.

CHAPTER 10

A clinician's guide for developing a prediction model: a case study using real-world data of patients with castration-resistant prostate cancer

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ABSTRACT

Purpose

With the increasing interest in treatment decision-making based on risk prediction models, it is essential for clinicians to understand the steps in developing and interpreting such models.

Methods

A retrospective registry of 20 Dutch hospitals with data on patients treated for castration-resistant prostate cancer was used to guide clinicians through the steps of developing a prediction model. The model of choice was the Cox proportional hazard model.

Results

Using the exemplary dataset several essential steps in prediction modelling are discussed including: coding of predictors, missing values, interaction, model specification and performance. An advanced method for appropriate selection of main effects, e.g. Least Absolute Shrinkage and Selection Operator (LASSO) regression, is described. Furthermore, the assumptions of Cox proportional hazard model are discussed, and how to handle violations of the proportional hazard assumption using time-varying coefficients.

Conclusion

This study provides a comprehensive detailed guide to bridge the gap between the statistician and clinician, based on a large dataset of real-world patients treated for castration-resistant prostate cancer

INTRODUCTION

As an urologist or oncologist it is not rare to encounter a 77 year old prostate cancer patient treated with androgen deprivation therapy, whose PSA rises consecutively at castrate serum levels of testosterone and who develops new bone lesions on imaging studies. According to the European Association of Urology guidelines, this patient meets the criteria for metastatic Castration-Resistant Prostate Cancer (CRPC) (Cornford et al. 2017). The patient has a medical history of chronic obstructive pulmonary disease (COPD) and diabetes mellitus. He has no prostate cancer related symptoms but due to his comorbidities he has a performance status of 1. We have previously shown that based on these factors Dutch clinicians are more likely to opt for watchful waiting or hormone targeted drugs, instead of docetaxel/prednisolone or radium-223 (Angst et al. 2019). In absence of clear recommendations for a preferred treatment option and sequence, clinicians may benefit from support of a clinical prediction model that is able to predict survival per treatment option based on patients' clinical baseline characteristics.

Recently, a significant amount of work has been published concerning risk prediction in prostate cancer (Kearns and Lin 2017). Risk prediction models evolved to indispensable tools to aid clinicians in making evidence-based decisions. In the urology field clinical risk prediction models for different disease states of prostate cancer exist, to predict for example the probability of biopsy-detectable aggressive prostate cancer, lymph node involvement, or overall survival (OS) in first-line chemotherapy. Nevertheless, despite existing general guidelines for reporting of a multivariable prediction model for individual prognosis or diagnosis (Collins et al. 2015), the process of developing and validating such models is still shrouded in mystery for most clinicians. The aim of this paper is to provide a comprehensive detailed guide to help clinicians understand the (sometimes complex) steps in developing a useful prediction model for CRPC patients, based on a real-life case, using a retrospective dataset of real-world patients treated for CRPC. We aim to both assist the clinician in understanding the development of a prediction model and to support the clinician in recognizing common shortcomings in existing prediction models. Of course, it is of highly importance to involve a statistician in the preparatory phase as well as constructing and validating the model.

METHODOLOGY

Research question and statistical model choice

First and foremost, one needs to formulate a clear research question. Additionally, before delving into the process of developing a prediction model it should first be checked if a similar model exists. In this case it may sometimes be more appropriate to update or adapt these previous models. In this study we aimed to develop a model to predict mortality in patients with CRPC treated in first-line with either abiraterone, enzalutamide, docetaxel, watchful waiting (defined as best supportive care using systemic treatment without proven life prolonging benefits, such as anti-androgens and ketoconazole) or radium-223, with the goal to use the model for treatment decision-making and to incorporate the model into a decision aid. Based on the type of outcome an appropriate model should be chosen, because different models should be used for different types of data (Supplementary Table 1). In our case we are dealing with survival data. Hence, a non-parametric Cox proportional hazard model was chosen. It should be noted that for very long-term predictions a parametric model (e.g. Weibull) may be preferred, since these provide more stable predictions at the end of follow up (Carroll 2003). A summary of all considerations in model development is presented in Table 1.

Data inspection

In our case we used a retrospective registry called the CAstration-resistant Prostate cancer RegIstry (CAPRI), which is an investigator-initiated, observational multi-center registry in 20 hospitals in the Netherlands. In the subset of the data we used, with first line treatment only, 3,588 patients and 2,335 deaths were recorded (Westgeest et al. 2018). The patients were treated according to clinical practice with a variety of first-line treatments including abiraterone, enzalutamide, docetaxel, or watchful waiting. Radium-223 was excluded from analyses due to the fact that only ten patients received Radium-223 as first line treatment in this dataset. Baseline variables are presented in Table 2. Furthermore, this dataset contained sixteen potential predictors. In general, it is recommended to have at least ten events (deaths in our case) to investigate one predictor. If a predictor has multiple categories you need 10*(number of categories − 1) events for that predictor.

Table 1. Summary of considering in prediction modelling (adapted from original version Steyerberg et all. ref)

Step	Specific Issues	CAPRI-dataset
General considerations		
Research question	Aim: predictors/prediction?	Prediction
Intended application	Clinical practice/research?	Clinical practice
Outcome	Clinically relevant?	Mortality
Predictors	Reliable measurement? Comprehensiveness	Oncological clinical work-up and literature; extensive set of candidate predictors
Study design	Retrospective/prospective? Cohort; case-control	Registry study: retrospective cohort
Statistical model	Appropriate for research question and outcome?	Non-parametric cox proportional hazard
Sample size	Sufficient for aim?	3584 patients; 2335 events
5 modelling steps		
Data inspection	Data distribution Missing values	Table 2 (baseline table) Multiple imputation
Coding of predictors	Continuous predictors	Extensive checks of transformations for continues predictors
	Combining categorical predictors	Comorbidity score was collapsed to 3 categories instead of 8
	Combining predictors with similar effects	Pain and opioid use
Model specification	Appropriate selection of main effects?	LASSO regression
	Assessment of assumptions	Additivity checked with interaction terms, interaction with treatment was checked, 3 included Proportional hazard assumption checked -> relaxed by time varying coefficients
Model performance	Appropriate measures used?	Discrimination
Model validation	Internal validation? External validation?	Bootstrap and k-fold cross-validation No, external dataset was available to us

Table 2. Baseline characteristics of patients with CRPC treated with abiraterone, enzalutamide, docetaxel or watchful waiting.

Treatment	abiraterone	enzalutamide	docetaxel	Watchful waiting
n	249	184	1006	2149
Antiandrogens before CRPC (%)	114 (46.0)	81 (44.0)	397 (39.5)	788 (36.8)
Comorbidity score (%)				
0	168 (67.5)	107 (58.2)	703 (70.0)	1227 (57.1)
1	43 (17.3)	38 (20.7)	185 (18.4)	496 (23.1)
2	24 (9.6)	23 (12.5)	80 (8.0)	252 (11.7)
3	6 (2.4)	6 (3.3)	22 (2.2)	86 (4.0)
4	5 (2.0)	4 (2.2)	8 (0.8)	46 (2.1)
5	0 (0.0)	2 (1.1)	3 (0.3)	13 (0.6)
6	3 (1.2)	2 (1.1)	4 (0.4)	17 (0.8)
7	0 (0.0)	1 (0.5)	0 (0.0)	5 (0.2)
8	0 (0.0)	1 (0.5)	0 (0.0)	5 (0.2)
Bone metastases (%)	142 (87.7)	103 (87.3)	703 (91.1)	929 (81.7)
Lymph node metastases (%)	66 (80.5)	41 (83.7)	373 (82.5)	507 (76.6)
Visceral metastases (%)	8 (16.7)	8 (24.2)	57 (21.7)	52 (16.1)
WHO (%)				
1	37 (40.2)	26 (43.3)	222 (42.0)	360 (47.1)
2	41 (44.6)	21 (35.0)	245 (46.3)	317 (41.5)
3	14 (15.2)	13 (21.7)	62 (11.7)	87 (11.4)
Pain (%)	47 (42.0)	28 (37.8)	317 (49.2)	323 (31.0)
opioid use (%)	22 (32.8)	9 (24.3)	120 (29.3)	113 (22.7)
Gleason >7 (%)	143 (67.8)	105 (65.2)	591 (65.9)	998 (55.5)
Time to castration (median [range])	11.17 [1.4, 192]	13.34 [1, 196]	10.12 [0.2, 172.7]	20.47 [0.3, 248.4]
Age (median [range])	76.00 [46, 95]	77.00 [50, 94]	70.00 [46, 93]	78.00 [49, 99]
Weight (median [range])	83.00 [52, 120]	86.00 [60, 120]	84.50 [48, 150]	81.00 [44, 118]
Hemoglobulin (median [range])	8.00 [5.1, 9.6]	8.00 [4.7, 10.3]	8.00 [4.3, 10.2]	8.10 [3.9, 10.5]
Platelets (median [range])	234.00 [37, 569]	228.50 [54, 473]	243.00 [0.4, 749]	233.00 [0.3, 714]
Lactate dehydrogenase (median [range])	218.00 [72, 3179]	216.00 [98, 730]	232.00 [21, 4100]	218.00 [79, 4329]
Alkaline phosphatase(median [range])	122.00 [41, 1673]	109.00 [38, 1263]	136.00 [34.8, 3457]	93.00 [21, 4315]
PSA (median [range])	34.00 [0.1, 8730]	24.40 [0.1, 4150]	40.00 [0.0, 8700]	9.70 [0.1, 4034]

Missing values and coding of predictors

In an ideal world the predictors in a dataset are all clinically relevant (Cornford et al. 20172), comprehensible (Angst et al. 2019), measured reliably (Kearns and Lin 2017), without missing data (Collins et al. 2015), and not correlated with each other (Carroll 2003). Unfortunately, datasets fulfilling all these criteria are the exception rather than the rule. Regarding the first three criteria it is recommended that clinician's perspectives are taken into account. Several authors mentioned to perform systematic reviews in order to find suitable candidate predictors (Steyerberg 2008). In the sections below we will address the latter two criteria (missing values and correlation between predictors). Additionally, we will give special attention on how to handle continuous predictors (e.g. age and hemoglobin).

Missing values

Various approaches are described to handle missing data, each with its own limitations and benefits (Papageorgiou et al. 2018). In our case we used multiple imputation using the MICE statistical package of R (Buuren and Groothuis-Oudshoorn 2011). "Imputation" in the context of missing baseline variables basically means that missing values are predicted upon other baseline values and/or outcome. Alike almost every statistical manipulation, certain assumptions must be made about the missing data, especially the mechanism of missing data (missing completely at random, missing at random, missing not at random) should be addressed (Papageorgiou et al. 2018). Following the latest consensus we incorporated the outcome in the imputation model using the Nelson-Aalen estimator, a non-parametric estimator of the cumulative hazard rate function (Moons et al. 2006). Using multiple imputation one creates multiple datasets in which the missing values are imputed, resulting in multiple completed datasets. The formal rules state that the analyses need to be conducted on all datasets separately and the obtained estimated must be pooled thereafter (Rubin 2004). Nevertheless, in case of a few missing values some authors proposed to develop the model on one dataset and test the model on the other datasets (Steyerberg 2008). Controversy remains on the cut-off of how much missing values is "too much" missing (Papageorgiou et al. 2018).

Correlation between predictors

In medicine many variables roughly describe the same phenomena and are therefore correlated with each other. One should avoid putting highly correlated variables in the same model. Firstly, the aim of a prediction model is to be as simple as possible, and incorporating similar variables is considered redundant. Secondly, in case of correlated variables a phenomena called "multicollinearity" can occur, characterized by extremely high/low estimates or standard errors (Multicollinearity 2020). Therefore, it is advisable to investigate all the correlations between the predictors by means of Pearson's R or

Spearman's rho, and high correlation should be addressed. This can either be done by excluding one of the two correlated variable or recoding the variables into one new variable. In our case the variables "pain" and "opioid use" were correlated (Spearman's rho: 0.36). Clinically this makes perfect sense, as opioids are prescribed when a patient is in pain. We recoded opioid and pain in several variables and a combined variable consisting out of 3 categories proved to be the best predictor (Supplementary Table 3).

Continuous predictors

Continuous predictors are variables that can take an infinite number of values (e.g. age and lactate dehydrogenase), and contain a lot of information. Hence, simply dichotomizing continuous predictors is paired with significant information loss (Royston et al. 2006). Nevertheless, incorporating continuous predictors into a statistical model comes along with the assumption the continuous predictors is associated with the outcome in a linear way. While a linear association can also be applied for some non-linear associations, this may not always be the case (Fig. 1). Thus, we recommend firstly to explore the association of the continuous predictor with the outcome in a univariable model. In order to explore the best fitting association with the outcome and a continuous predictor one can use: transformation (like logarithmic transformation), categorization, splines and fractional polynomials, as is explained in Table 3 and Fig. 2 (Steyerberg 2008).

Figure 1. Example of a continuous outcome (y axis) and continuous predictor (x axis). As is shown: with the assumption the relation is linear the model (red line) does not fit the observed data well (black dots).

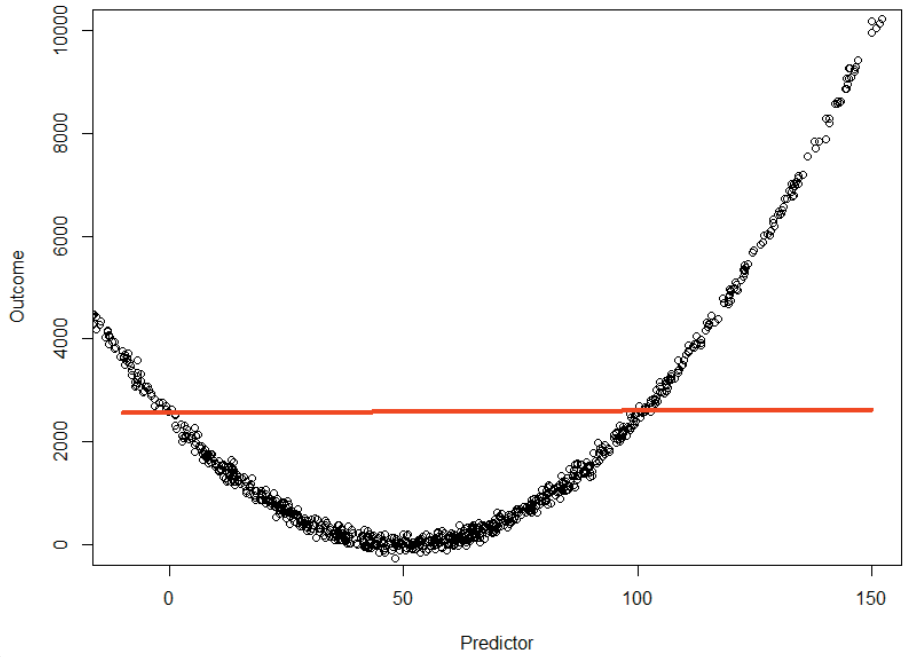
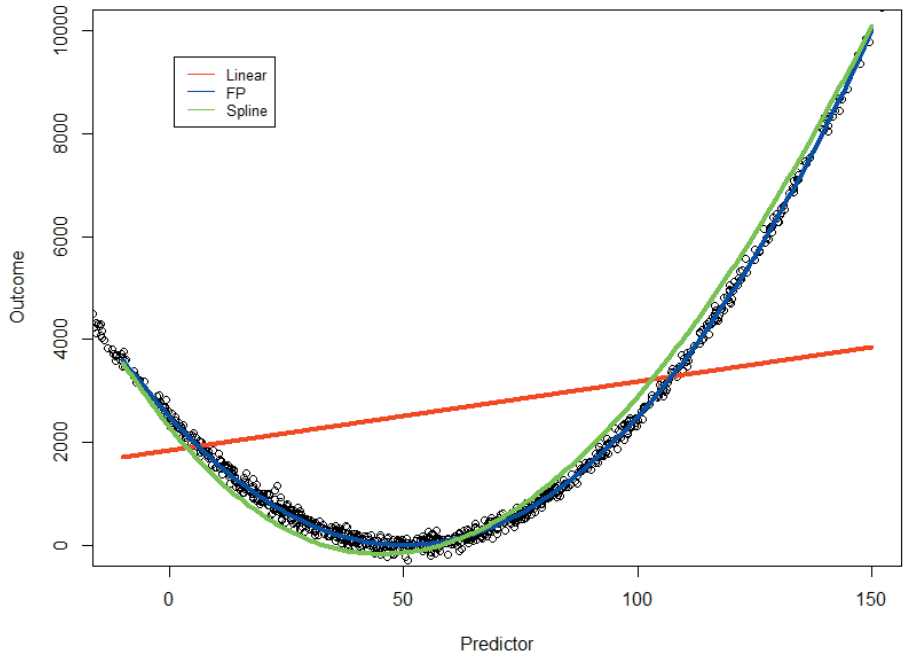


Table 3. Performance of a linear model by adding flexibility to assumed linear association with the outcome. *R-squared is measure of how close the model fits the data, 1 indicates the model explains all the variability of the data, whereas with 0 the model does not explain any variability. For other types of models similar measurements are available.

Variable	R-squared*
Predictor linear	0.00938
Predictor with splines with 1 knot	0.9853
Predictor with fractional polynomial	0.9992

Figure 2. Example of relaxation of the linear assumed association (red line) of a continuous outcome and predictor. This can be done either with natural splines (green line) or fractional polynomials (blue line). Using splines the data is divided in separate sections, and each section has its own estimate of the line. Using fractional polynomials the relationship is described as multiple polynomials, which can produce a very flexible line.



Interaction

Let us consider two predictors. Separately, they have no association with the outcome, however, when they are both present, a significant association with the outcome is observed (or vice versa). Such a phenomena is called "interaction" (Steyerberg 2008). For example these interactions are quite common in gene studies: Only when gene X and gene Y are turned on a certain chemical reaction will start. When either one

of the genes is turned off, the reaction will not begin. Naturally, these interactions can also be present in epidemiology studies. However, especially when one considers many predictors, constructing interaction terms can be an overwhelming task. There are so many possibilities one cannot see the wood for the trees. In this case it is advisable to avert to the clinicians and a priori select a number of possible interactions, which make clinical sense. In our study, we tested the interaction term "watchful waiting" and "opioid use or pain", which turned out to be highly significant. This corresponds to the clinic; a patient with watchful waiting and opioid use or pain indicates a palliative setting, in which the patient is expected to die soon. Hence, watchful waiting and opioid use together have a stronger association with the outcome than watchful waiting and opioid use separately.

Model specification

As mentioned earlier, the first step of predictor selection should be together with subject-specific experts. Predictor selection is arguably the hardest part of model building (Ratner 2010). Multiple methods exist to address the selection process of the a priori selected set of predictors. The most widely used methods include stepwise selection and best subset regression, and these are previously described (Miller 2002; Harrell 2015). In our case we had a lot of variables due to the interaction terms and non-linear continuous predictors. One always wants the most parsimonious model and does not want to exceed the one predictor per ten events rule of thumb. Therefore, it is reasonable to drop predictors that do not add much to the performance of the model. We employed a lesser known selection method using Least Absolute Shrinkage and Selection Operator (LASSO) regression (Tibshirani 1996). This is a penalized machine learning technique that shrinks the estimate of unimportant predictors to zero (Supplementary Fig. 1). An estimate of zero equals no association with the outcome and, therefore a predictor is excluded. This method also can handle correlation within predictors to some extent, as the algorithm will "see" that in case of high correlation of predictor A and B, shrinking predictor B to zero will not influence performance of the model (Tibshirani 1996). Nevertheless, an algorithm cannot judge which predictor is more comprehensible or measured reliably. Therefore, one should never skip the step of looking for correlations between predictors. A package to run LASSO regression in R is the "glmnet" package (Friedman et al. 2010), with an elaborate vignette to code this in R (Hastie and Qian 2016). However, in our case we had multiple polynomials describing the relation of a continuous predictor with the outcome (see "Continuous predictors"). One wants either include all the polynomials in the model or none at all. Hence, we need to "tell" the LASSO algorithm they belong together as a group. The statistical R package "grpreg" has implemented such a function (Breheny and Huang 2015). We opted for a two-step approach. Firstly, we ran the LASSO regression and thereafter we incorporated all the non-zero predictors in a Cox-model. The final model is shown in Table 4.

Table 4. Final cox model for predicting mortality in patients with CRPC. The model contains fractional polynomials and splines to address non-linear associations of a continues variable with the outcome and a stepwise time-varying coefficient function; e.g. some covariates have a hazard ratio for below 10 months of follow-up and above ten months of follow-up.

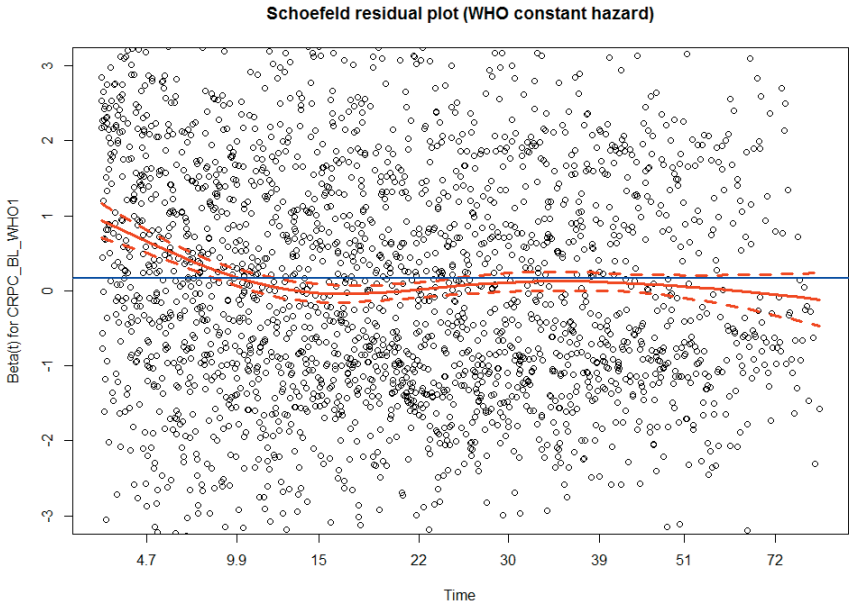
Characteristic	Hazard ratio (95% CI)	P-value
Age	1.07 (1.04 to 1.09)	>0.001
Antiandrogens before CRPC	0.87 (0.8 to 0.95)	0.001
Bone metastases	1.16 (1.03 to 1.32)	0.016
AF polynomial 1[1]	1.02 (0.9 to 1.16)	0.75
AF polynomial 2[2]	0.75 (0.57 to 0.99)	0.044
Enzalutamide vs abiraterone	1.17 (0.64 to 2.15)	0.60
Docetaxel vs abiraterone	1.85 (1.23 to 2.77)	0.003
Watchful waiting vs abiraterone	0.45 (0.31 to 0.67)	>0.001
Time to start castration spline 1 $_{\text{HR for <10 months}}$	0.2 (0.1 to 0.39)	>0.001
Time to start castration spline 2 $_{\text{HR for <10 months}}$	0.19 (0.13 to 0.26)	>0.001
Time to start castration spline 1 $_{\text{HR for >10 months}}$	1.45 (0.75 to 2.8)	0.27
Time to start castration spline 2 $_{\text{HR for >10 months}}$	0.71 (0.51 to 1)	0.048
WHO $_{\text{HR for <10 months}}$	1.64 (1.44 to 1.87)	>0.001
WHO $_{\text{HR for >10 months}}$	1.07 (0.99 to 1.15)	0.11
PSA polynomial 1[3] $_{\text{HR for <10 months}}$	1.34 (1.15 to 1.56)	>0.001
PSA polynomial 1[3] $_{\text{HR for >10 months}}$	1.02 (0.88 to 1.17)	0.82
PSA polynomial 2[4] $_{\text{HR for <10 months}}$	1.27 (1.16 to 1.4)	>0.001
PSA polynomial 2[4] $_{\text{HR for >10 months}}$	1.11 (1.01 to 1.21)	0.023
HB $_{\text{HR for <10 months}}$	0.82 (0.76 to 0.89)	>0.001
HB $_{\text{HR for >10 months}}$	0.92 (0.87 to 0.97)	0.003
Platelets polynomial 1[5] $_{\text{HR for <10 months}}$	0.97 (0.95 to 0.99)	0.001
Platelets polynomial 1[5] $_{\text{HR for >10 months}}$	1.01 (0.99 to 1.02)	0.42
Platelets polynomial 2[6] $_{\text{HR for <10 months}}$	1 (1 to 1.01)	0.001
Platelets polynomial 2[6] $_{\text{HR for <10 months}}$	1 (1 to 1)	0.46
LDH $_{\text{HR for <10 months}}$	1.66 (1.42 to 1.94)	>0.001
LDH $_{\text{HR for >10 months}}$	1.09 (0.96 to 1.23)	0.18
Opioid or pain vs none $_{\text{HR for <10 months}}$	1.09 (0.97 to 1.22)	0.16
Opioid or pain vs none $_{\text{HR for >10 months}}$	1.02 (0.94 to 1.09)	0.67
Age*Enzalutamide vs abiraterone[7]	0.94 (0.9 to 0.97)	0.001
Age*Docetaxel vs abiraterone[7]	0.96 (0.93 to 0.99)	0.003
Age*Watchful waiting vs abiraterone[7]	0.99 (0.96 to 1.01)	0.25
Log(PSA)*Enzalutamide vs abiraterone[7]	1.08 (0.92 to 1.26)	0.35
Log(PSA)*Docetaxel vs abiraterone[7]	0.91 (0.83 to 1)	0.057
Log(PSA)*Watchful waiting vs abiraterone[7]	1.23 (1.12 to 1.35)	>0.001

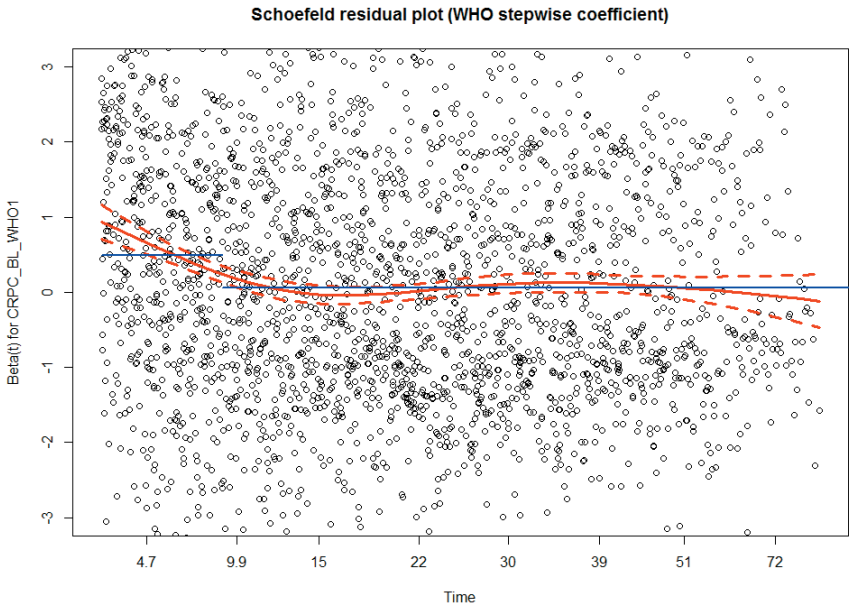
1:(AF/100)^-2), 2: (AF/100)^-1, 3: PSA^-1, 4: log(PSA), 5: Platelets*1,6: Platelets * log(Platelets), 7: interaction term

Assessment of assumptions

Every statistical model comes along with certain assumptions (Freedman 2009). If these assumptions are not met, the model is not or less valid (Freedman 2009). Each model family has its own specific assumptions. A key assumption in the cox model we used is the proportional hazard (PH) assumption. This basically means that ratio of hazards (the output of a Cox model) is constant over time. Two approaches are commonly used to test whether this assumption is violated: plotting Kaplan–Meier curves or plotting the residuals. Both methods are implemented in most statistical programs or packages. The Schoenfeld residuals should be used to test the PH assumption. Schoenfeld residuals represent the difference between the observed covariate and the expected given the risk set at that time. If one draws an average line through the residuals, this line should be straight (Schoenfeld 1982). A formal test has also been developed (Schoenfeld F test) (Grambsch and Therneau 1994). In our model certain variables did not meet the PH assumption. Fortunately, this is not the end of the world. One can avert to parametric models, since some of these models do not rely on the PH assumption, however you need to start all over again. Another approach is to use an extension of the Cox model called time-varying coefficients, not to be confused with time-varying covariates (Hastie and Tibshirani 1993; Fisher and Lin 1999). Time-varying coefficients can be applied if the effect of a predictor is not constant over time, or in other words if the PH assumption is violated. In our case the effect predictor WHO performance status was not constant over time. As is shown in the Schoenfeld residual plot the effect of the performance status was higher in the first months compared to later in follow-up (Fig. 3a). Therefore, we decided to use a stepwise time varying coefficient function; we made a separate hazard ratio for the first ten months and for the following months thereafter. As presented in Fig. 3b, the PH assumption as not violated anymore. A vignette to implement time-varying coefficients in R has been published previously (Therneau et al. 2013).

Figure 3ab. Example of a Schoenfeld residuals plot in order to check the proportional hazard assumption. When the hazard of WHO is assumed constant over time (blue line in part A), the assumption is violated, especially in the first 10 months the blue line deviates from the red line. In part B we have two coefficients for WHO, one for the first 10 months and one for more than ten months. Proportional hazards assumption is not violated anymore.





Model performance

Two related terms are important in model performance: discrimination and calibration (Alba et al. 2017). Discrimination describes how well a model discriminates a high risk patient from a low risk patient or, in other words: Does the model estimate higher probabilities for patients that have an event compared to patients that do not have an event? Discrimination of binary outcomes is measured with the c-statistic or with ROC-curves (Pencina and D'Agostino 2015). In our study, the overall c-statistic of the model was 0.74, which indicates a good discrimination of the model. Calibration or goodness-of-fit conveys to which extent the predicted probability agrees with the observed probability. For example a high risk patient had a sevenfold higher probability of an event compared to a low risk patient and predicted risks are 7% vs 1%. The observed probabilities of a high risk patient and a low risk patient were 70% vs 10%. In this case discrimination is satisfactory, as the model discriminates well between a high and low risk patient. Nevertheless, calibration is extremely off; the observed risks are not even close to the predicted risks. Several methods exist to assess calibration and are described previously (Calster et al. 2016).

Model validation

Testing model performance on the dataset on which is developed is most of the time overly optimistic (Babyak 2004). After all, the model "learned" the estimates out of the correlations/associations derived from that specific dataset. To assess the possibly overly optimistic performance a statistical model should be validated. Preferably, this should be done internally and externally. During internal validation the model is validated with the original dataset. Historically, this is done by randomly splitting the original dataset into two datasets. One training dataset and one validation dataset. Nevertheless, this approach is not recommended, because this inherently implies one cannot train the model on all the patients. In small datasets the amount of data is reduced, possibly leading to overfitting, and in very large datasets randomly splitting results in very comparable datasets. Therefore, we recommend to employ either bootstrapping techniques or k-fold cross validation. Using k-cross validation one uses the whole dataset as training dataset for the model, and thereafter splits the dataset in k groups (usually ten groups). One group is the validation set and the others are the training sets. This process is repeated k times with each a different group for the validation set (Supplementary Fig. 3) (Harrell 2015). Using bootstrapping the model is also trained on the whole dataset and thereafter random samples are drawn from the original data. Herein a patient can be drawn multiple times and the drawn sample is usually of the same size of the original dataset (Supplementary Fig. 4) (Efron and Tibshirani 1994). Notwithstanding, the ultimate test for a model is external validation. This means that the performance of the model is still satisfactory if it is tested on a different dataset. For example this dataset could be

derived from another center, or geographical area. A model that calibrates poorly on external data can be recalibrated, whereas a model that discriminates poorly cannot. In this case a new model is required (Su et al. 2018). There is another highly important form of validity called "face validity". Yet, again the expert clinician comes into play here, as there are no formal ways to test face validity. Face validity says something about whether the test or model measures what it is supposed to measure. For instance face validity may be impaired when key predictors are not included in the model because they were not collected. Or when the dataset is old and does not represent clinical practice anymore. In our case, the patients in the CAPRI dataset were included from January 1, 2010 until December 31, 2017. Our aim was to develop a model to predict mortality in patients with CRPC treated with either abiraterone, enzalutamide, docetaxel, or watchful waiting in first line, to support adequate decision making. However, due to the retrospective nature of this dataset, strong selection bias is present for treatment, especially since abiraterone and enzalutamide were not available as first-line treatment in the Netherlands from 2010–2013. So patients that were eligible for those treatments, received watchful waiting or docetaxel in this period. Of course, a multivariable model will adjust to some extend for this, and one can include intervention year as covariate to assess/and adjust for this phenomena. However, for future predictions, intervention year as covariate implies that a certain trend will continue in the future. This does not make (clinical) sense at all. Hence, this model failed the face validity.

CONCLUSION

Risk prediction is becoming increasingly more important in medical practice. In this article, we discuss several steps in developing a prediction model including missing data, predictor encoding and selection using LASSO, testing model assumptions, performance and validation, using an example from uro-oncology. Prediction model development is not a futile task and both the input of the clinician and statistician are essential. This article may be used to bridge the gap between the two disciplines.

SUPPLEMENTARY DATA

Supplementary Table 1. Types of data and their associated models

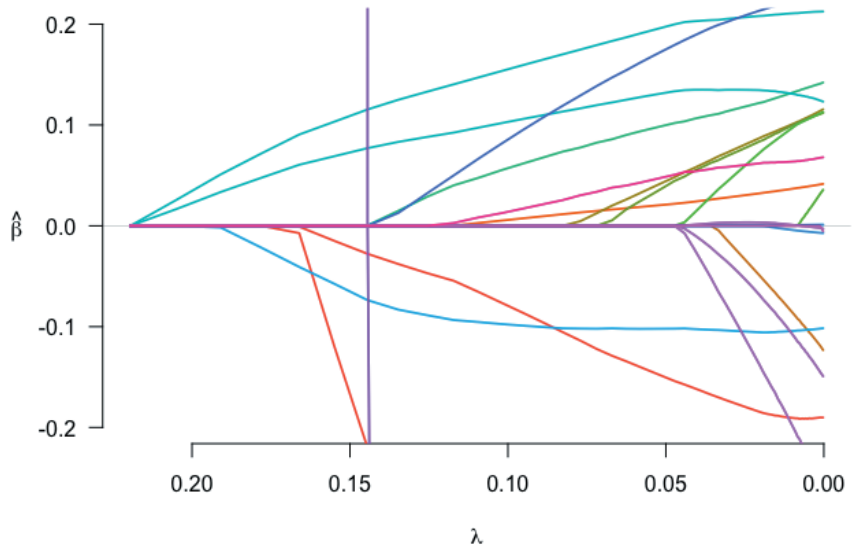
Type of data	Example	Regression model
Continuous	Blood pressure, age	Linear regression
Discrete	Yes/no variables	Logistic regression
Count data (special case of continuous data)	Hospital stay	Poisson regression Negative binomial regression
Ordinal data	WHO class	Ordinal regression
Survival data	Mortality	Cox regression (non-parametric) Accelerated time failure models (parametric)

Supplementary Table 2. The variables opioid and pain were highly correlated. Hence, these variables was combined in several ways and it was tested which variable had the best prediction. 1 is if the characteristics is present and 0 when not.

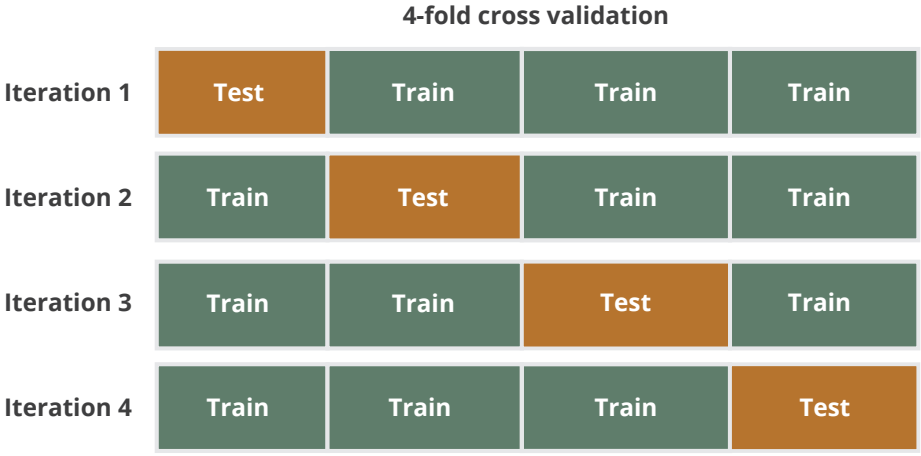
Name recoded variable	Recoding scheme	AIC	BIC
Opioid and pain	If opioid = 1 AND pain = 1 -> Opioid and pain = 1 Else: Opioid and pain = 0	35954.57	35960.37
Opioid or pain	If opioid=1 OR pain = 1 -> Opioid or pain = 1 Else: Opioid or pain = 0	35962.20	35968.00
Ordered opioid and pain_3 (3 levels)	If opioid =1 OR pain = 1 -> Ordered opioid and pain_3 = 1 If opioid =1 AND pain = 1 -> Ordered opioid and pain_3 = 2 Else: Ordered opioid and pain_3 = 0	35910.92	3596.72
Ordered opioid and pain_4 (4 levels)	If pain = 1 -> Ordered opioid and pain_4 = 1 If opioid = 1 -> Ordered opioid and pain_4 = 2 If opioid =1 AND pain = 1 -> Ordered opioid and pain_4 = 3 Else: Ordered opioid and pain_4 = 0	35911.34	35922.93

AIC =Akaike information criterion and BIC =Bayesian information criterion, both are comparative measurements of the fit of a model, penalized for the number of fitted covariates. A lower AIC and BIC indicate a better model.

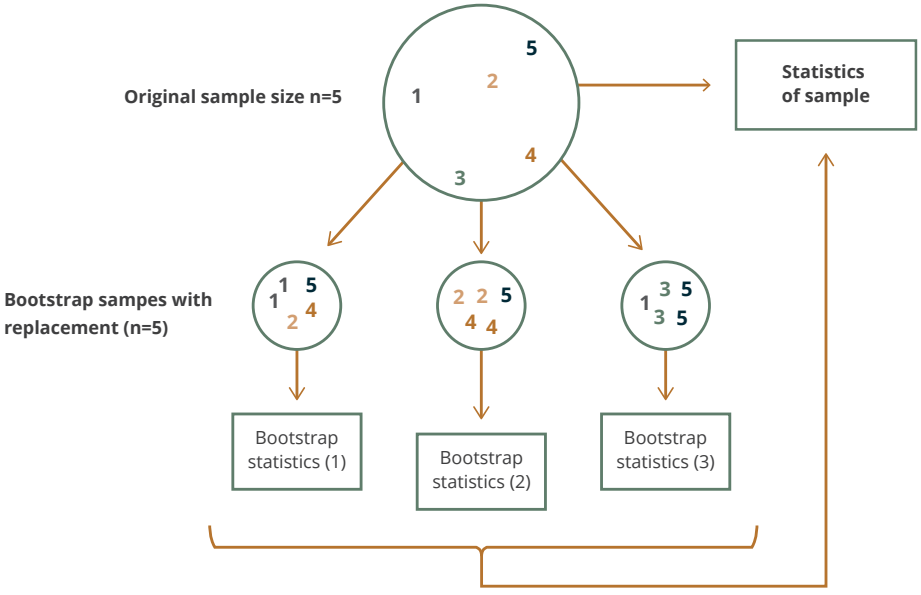
Supplementary figure 1. Shrinkage of predictors to zero using LASSO regression



Supplementary Figure 2. Schematic of k-fold cross validation in which k=4.



Supplementary figure 3. Schematic of bootstrapping. The general idea behind bootstrapping is that of the original sample several bootstrap samples can be drawn with the same sample size as the original sample. In the bootstrap sample *replacement* is possible (e.g. the same subject can be drawn multiple times and at every step every subject has equal probability to be selected). Bootstrapping can be used to test model performance.



REFERENCES

Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ et al (2017) Discrimination and calibration of clinical predic- tion models: users' guides to the medical literature. JAMA 318(14):1377–1384

Babyak MA (2004) What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med 66(3):411–421

Breheny P, Huang J (2015) Group descent algorithms for nonconvex penalized linear and logistic regression models with grouped pre- dictors. Stat Comput 25(2):173–187

Carroll KJ (2003) On the use and utility of the Weibull model in the analysis of survival data. Control Clin Trials 24(6):682–701

Collins GS, Reitsma JB, Altman DG, Moons KG (2015) Transpar- ent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. J Clin Epidemiol 68(2):134–143

Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T et al (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 71(4):630–642

de Angst IB, Kil PJM, Bangma CH, Takkenberg JJM (2019) Should we involve patients more actively? Perspectives of the multidis- ciplinary team on shared decision-making for older patients with metastatic castration-resistant prostate cancer. J Geriatr Oncol 10(4):653–658

Efron B, Tibshirani RJ (1994) An introduction to the bootstrap. CRC Press, London

Fisher LD, Lin DY (1999) Time-dependent covariates in the Cox proportional-hazards regression model. Annu Rev Public Health 20(1):145–157

Freedman DA (2009) Statistical models: theory and practice. Cam- bridge University Press, Cambridge

Friedman JH, Hastie T, Tibshirani R (2010) Regularization paths for generalized linear models via coordinate descent 33(1):22

Grambsch PM, Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81(3):515–526

Harrell FE Jr (2015) Regression modeling strategies: with applica- tions to linear models, logistic and ordinal regression, and survival analysis. Springer, New York

Hastie T, Tibshirani R (1993) Varying-coefficient models. J Roy Stat Soc Ser B (Methodol) 55(4):757–779 Hastie T, Qian J (2016) Glmnet Vignette. https://web.stanford. edu/~hastie/Papers/Glmnet_Vignette.pdf. Accessed 5 Jan 2020

Kearns JT, Lin DW (2017) Prediction models for prostate cancer outcomes: what is the state of the art in 2017? Curr Opin Urol 27(5):469–474

Miller A (2002) Subset selection in regression. Chapman and Hall/ CRC, London

Moons KG, Donders RA, Stijnen T, Harrell FE Jr (2006) Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 59(10):1092–1101

Franke, GR (2010) Multicollinearity part 2. Marketing Research. Wiley International Encyclopedia of Marketing

Papageorgiou G, Grant SW, Takkenberg JJM, Mokhles MM (2018) Statistical primer: how to deal with missing data in scientific research? Interact Cardiovasc Thorac Surg 27(2):153–158

Pencina MJ, D'Agostino RB Sr (2015) Evaluating discrimination of risk prediction models: the C statistic. JAMA 314(10):1063–1064 Ratner B (2010) Variable selection methods in regression: Ignorable problem, outing notable solution. J Target Meas Anal Market 18(1):65–75

Royston P, Altman DG, Sauerbrei W (2006) Dichotomizing con- tinuous predictors in multiple regression: a bad idea. Stat Med 25(1):127–141

Rubin DB (2004) Multiple imputation for nonresponse in surveys. Wiley, Hoboken

Schoenfeld D (1982) Partial residuals for the proportional hazards regression model. Biometrika 69(1):239–241

Steyerberg EW (2008) Clinical prediction models: a practical approach to development, validation, and updating. Springer, New York

Su T-L, Jaki T, Hickey GL, Buchan I, Sperrin M (2018) A review of statistical updating methods for clinical prediction models. Stat Methods Med Res 27(1):185–197

Therneau T, Crowson C, Atkinson E (2013) Using time dependent covariates and time dependent coefficients in the Cox model. Red 2:1

Tibshirani R (1996) Regression shrinkage and selection via the lasso. J Roy Stat Soc Ser B (Methodol) 58(1):267–288

Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, de Wit R, van den Bergh ACM, Coenen J et al (2018) Differences in trial and real-world populations in the Dutch castration-resistant prostate cancer registry. Eur Urol Focus 4(5):694–701

van Buuren S, Groothuis-Oudshoorn K (2011) Mice: Multivariate Imputation by Chained Equations in R 45(3):67.

Van Calster B, Nieboer D, Vergouwe Y, De Cock B, Pencina MJ, Steyerberg EW (2016) A calibration hierarchy for risk models was defined: from utopia to empirical data. J Clin Epidemiol 74:167–176

CHAPTER 11

Discussion

SHORT SUMMARY

The CAstration-resistant Prostate cancer RegIstry (CAPRI) has provided evidence on differences between trial and real world populations (Part 1). Based on strict selection criteria at baseline, outcomes in trial populations are more favorable compared to the real world. Trials have provided efficacy data on new life prolonging drugs (LPDs) but effectiveness in CAPRI was lower in patients with differential baseline characteristics. To ensure optimal outcomes, the importance of an adequate estimation of the trial eligibility and health status of metastatic castration-resistant prostate cancer (CRPC) patients in daily practice is important to ensure optimal treatment outcomes.

In CAPRI, real world outcomes in CRPC were studied (Part 2). LPDs have led to increased treatment options in CRPC patients, which was related to increased overall survival in the period 2010-2018. Over time the course of disease still has a negative impact on health-related quality of life (HRQoL), with deterioration in all domains, especially with respect to 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. In the end of life phase, we observed a high intensity care in 41% of CRPC patients. This high intensity care is not easily justifiable due to high economic cost and little effect on life span or improvement of quality of life.

Lessons from real world data may help to improve routine care (Part 3). We observed no differences in outcomes of patients treated with sequential abiraterone acetate plus prednisone and enzalutamide with or without interposed chemotherapy or radium-223, with low response rates (around 20% PSA responses) of the second treatment. The additional effect of a second treatment with abiraterone or enzalutamide in daily practice is therefore questioned. Prospective trials have confirmed this observation[1,2]. In the next chapter, we developed a prognostic model and identified a subgroup of patients in whom third-line LPD treatment has no meaningful benefit, although this has to be confirmed in prospective trials. In the last chapter, we presented a detailed guide for clinicians through the (sometimes complex) steps in developing a useful prediction model for CRPC patients.

The set-up of CAPRI

Real world data are used to inform decision making in health care by providing effectiveness data. In Chapter 2 we provided practical guidance in setting up patient registries to facilitate real-world data collection for health care decision making, based on our experiences and involvement in setting up patient registries in oncology in the Netherlands.

CAPRI was set up as a retrospective observational registry using a population-based sample to provide real world data on patients, treatments and outcomes in CRPC. The registry is an investigator-initiated study and a broad collaboration was sought in a period that more than one industrial company needed intervention-based outcome data. Therefore, the registry was set up as a disease-based registry rather than a drug-based registry. Pharmaceutical industry parties and governmental subsidy parties were sought to jointly finance the registry. This resulted in the financial support of four pharmaceutical companies, and a ZonMW grant for the Patient Reported Outcomes in CAPRI (PRO-CAPRI) study. Twenty Dutch hospitals were invited to participate, based on both geographical spread and type of hospitals: 4 academic centers, 11 large teaching hospitals and 5 general hospitals. All invited hospitals agreed to participate. We focused on the CRPC population, and eligibility was met if CRPC was diagnosed either by the EAU[3] or by the treating physician (regardless of the CRPC definition, but based on CRPC treatment initiated; addition of antiandrogen therapy following progression on ADT was considered first line systemic therapy for CRPC). Prostate cancer was defined as histologic confirmation of prostate cancer or as concluded by the treating doctor based on elevated PSA and metastatic pattern. Because CRPC patients are difficult to capture, we retrospectively screened all prostate cancer patients (N=41,724) in both urology and internal medicine departments in 20 hospitals, based on the diagnosis code in the defined study period. We identified 3,616 eligible patients (see Figure 1). The frequencies of patients in the subsequent diagnosis years and per hospital of inclusion are shown in Figures 2 and 3.

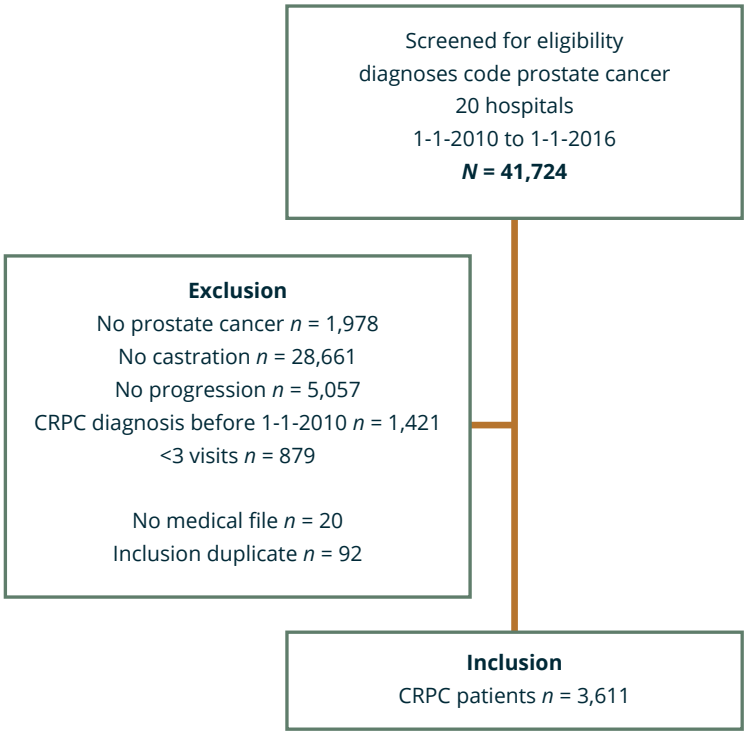


Figure 1. Flow diagram of the study population. Inclusion duplicate means a patient was screened and found eligible in more than one participating center and was subsequently registered in only one center. CRPC = castration-resistant prostate cancer.

Strengths and limitations

Strengths

Our study had several strengths. All stakeholders were involved in the design, analyses and scientific output of the study. In the steering committee active involvement of clinicians (from urology, medical oncology and radiotherapy), health economists, patient advocates and representatives from the Dutch Uro-Oncology Studygroup (DUOS) was accomplished, and representatives from the relevant pharmaceutical industry were passively involved. The steering committee had meetings every 6 months to discuss registry data, analyses and future directions.

The long lead-time from prostate cancer diagnosis to CRPC is a challenge in finding the CRPC patients. Our method of finding eligible patients, by screening all prostate cancer patients by datamanagers, provided a solution for this challenge. In Sweden, a large

registry also captures patients in different disease states including non-metastatic CRPC (nmCRPC) and metastatic CRPC (mCRPC), based on prostate cancer diagnosis, start of ADT and imaging, clinical assessment and PSA kinetics[4]. Other retrospective CRPC registries with published results from databases such as SEER/Medicare found patients based on CRPC treatment [5-9]. Prospective enrolment of mCRPC patients provides a solution in prospective registries[10-12].

We were able to include a unique multicenter real world CRPC cohort that reflected daily practice. Distinct to other cohorts, our cohort was independent of histologic confirmation or type of treatment[5-12]. To illustrate this, we included 474 (13%) patients without known histology, of whom 111 (3%) patients did not have a histologic confirmed diagnosis of prostate cancer. These patients have been diagnosed based on PSA, metastatic pattern and response on androgen deprivation therapy. Also, 1,346 (37%) patients were included without life prolonging drug treatment (of whom 424 (12%) patients without any systemic treatment for CRPC), leading to a sample of patients that closely reflects daily practice, including specific subgroups of patients that are normally not included in studies.

The eligibility criteria anticipated the new definition of CRPC by the European Association of Urology (EAU) from 2014[13]. Patients were defined as castration-resistant at the moment of progression on androgen deprivation therapy. Thus, the addition of anti-androgen treatment to androgen deprivation therapy was considered the first line therapy for CRPC.

To increase external validity, we captured an estimated 20% sample of all Dutch CRPC patients, from different types of hospitals spread over the country (n=20) (Figure 2). A comparison between patients in the participating hospitals to all prostate cancer patients in the Netherlands with data from the Dutch Cancer Registry, showed no differences in criteria available (age, disease stage, initial treatment, Gleason score and initial performance status (PS)), supporting external validity.

Moreover, the large population size provided good statistical power for the analyses, and allowed for subgroup analyses. CAPRI captured a cohort over a time period of 6 years inclusion (2010-2016) and 8 years of follow up (2010-2018), see Figure 3. At the end of the study, it was a mature cohort with 2,442 (68%) death events.

We captured detailed longitudinal patient level data, including important factors that are often not reported in clinical trials, such as comorbidity. Outcomes of treatments in different lines could be analyzed separately or as sequential treatment.

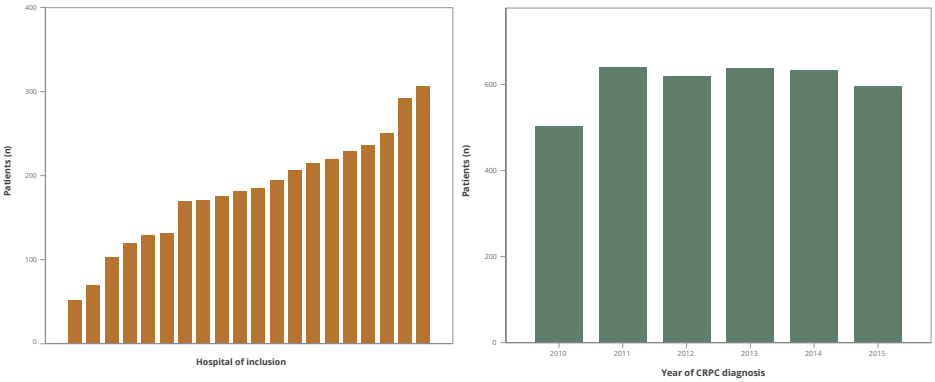


Figure 2. Distribution of CRPC patients in CAPRI by hospital of inclusion (anonymized).
Figure 3. Distribution of CRPC patients in CAPRI by year of CRPC diagnosis

Limitations
The eligibility criteria excluded patients not treated in hospitals. It is unknown how many patients diagnosed with CRPC are treated only by general practitioners or in nursing homes or hospices. Furthermore, we did not collect data outside the hospitals and missing death date was a common problem (21% of patients was lost to follow up), that was solved by censoring at the last visit date.

The retrospective nature of the study minimized the Hawthorne effect (the change in behavior while being studied), but has led to significant missing data. Missing data were particularly common in laboratory parameters (mainly LDH) and clinical parameters (including ECOG/WHO clinical PS), but also in visceral dissemination status. Multiple imputation provided a solution for missing data. The retrospective nature also led to the limitation that only data that had been recorded in the medical file was available for registration. Furthermore, due to choices made in the study design phase, not all relevant variables were captured (e.g. albumin) and only hospital data were collected (for example leading to restriction on analyses on the terminal phase in hospices or at home).

Given the large number of treatment options and sequences, the study population is still small for a part of subgroup analyses.

Head to head comparisons are not easily justified because of the retrospective nature. Because treatment decisions were not randomized, treatment selection (confounding by indication) may bias the results. For example, older patients with more comorbidity may have a worse prognosis irrespective of treatment and may often not be treated

with chemotherapy. Although propensity score matching might provide a potential solution, the relatively short follow up and temporal effects of subsequent market access of new LPD increase the probability of bias in the results.

We assumed all deaths were CRPC-related. Although patients with CRPC will likely die from the disease, competing risks such as cardiovascular death, may have occurred. However, we assume this influence was small, if present.

The study reflects the Dutch situation and may not be generalizable to other countries. In the Netherlands, health insurance is mandatory for everyone and everyone has access to reimbursed medical oncology and urology care in hospitals. New treatments are widely available in clinical trials. In addition, use of new oncolytic drugs is generally conditional on positive guidance by the Dutch society of medical oncology (NVMO) committee "beoordeling van oncologische middelen (appraisal of oncolytics)" (CieBOM). Only after positive appraisal by CieBOM treatment will become widespread and standard available. Dutch oncologists may be generally conservative in selecting patients for treatment. Treatment restrictions in resuscitation and intensive care admission are common. All aforementioned factors are more or less specific for the Dutch situation.

IMPLICATIONS OF THIS THESIS: A ROADMAP TO BETTER CARE

This thesis on real world evidence in castration-resistant prostate cancer may contribute to improvement of treatment outcomes, the most important being survival, quality of life and efficiency. This could be done by using a roadmap to enhance the quality of care in metastatic (prostate) cancer patients, focusing on the following 5 statements:

1. Increase trial participation and increase generalizability and applicability of trial results
2. Continue the registry prospectively with the relevant population, efficient data management and analyses, and relevant objectives
3. Increase effectiveness of LPD: optimize sequencing, treat the right patient with LPD and stop further LPD treatment at the right moment (and off course continue palliative care!)
4. Determine the value of Patient Reported Outcome Measurements (PROMs) in clinical practice and solve barriers.
5. Optimize end-of-life care by decreasing high-intensity care in the last 3 months

1. INCREASE TRIAL PARTICIPATION

Clinical trials are imperative for testing novel cancer therapies, advancing the science of cancer care, and determining the best treatment strategies to enhance outcomes for patients with cancer[14]. We analyzed the differences of trial populations and real world populations in Chapter 3 and 4. Trial populations are subject to clinical trial accrual. This accrual is dependent on trial availability, trial awareness, and trial acceptance[15,16]. Barriers can be categorized in structural barriers (availability of trials), clinical barriers (patient eligibility), and attitudinal barriers (physician barriers: is the trial discussed and is the trial offered to a patient or are trials published on websites. Further there can be patient barriers: does the patient agree to participate?). In addition demographic and socio-economic factors play a role in disparities and barriers [17].

Trial availability

Clinical trials focus on specific disease states. For a specific disease state, such as metastatic symptomatic CRPC, a clinical trial has to be available for a patient. Barriers are usually limitations in availability (many trials in the Netherlands are only started in few selected hospitals), and this can be improved or limited by communication between hospitals and clinicians, clinician's knowledge about available trials and willingness to refer (clinician) or travel (patient) for clinical trial participation.

Patient eligibility

Eligibility criteria of clinical trials may limit trial participation. For example, patients may be excluded based on impaired clinical performance status, laboratory results (such as renal function or bone marrow reserve) and comorbidity (such as auto-immune disease in immunotherapy trials or cardiovascular disease in ART).

Trial discussion and trial offer

If a trial is available and the patient is eligible, reasons may exist why clinicians do not discuss or offer trial participation with patients. Factors to deter clinician recommendation include strong inclinations toward a specific treatment, interference of the clinician-patient relationship, or subversion of patient confidence due to randomisation[17]. In addition, clinicians often lack incentives for recruitment and may find trial enrolment, participation and administrative burden too time consuming.

Patient agreement

Patients have differential concerns including finding the best possible treatment of their disease. This may affect their consent to participate in experimental treatment. Mistrust in research or dislike of randomization are among the reasons to decline participation

in trials. Another reason is that patients may already have a strong sense of the new treatment they wish to receive after discussion with their physicians[17]. Although the patient will sign the consent form, participation is usually discussed within family members, who may influence patient agreement.

Demographic and socio-economic factors

Age accounts for the most consistent disparity. Gender and race disparities also exist. Race is not routinely registered in cancer research in the Netherlands and race disparities are therefore understudied and largely unknown in the Netherlands. In other countries such as the United States race is often registered and studied. Socio-economic status may be important, although not routinely registered in trials and therefore the impact is not documented[17]. However, financial barriers are acknowledged as meaningful in the United States[14]. This is different in the Netherlands, because of the imperative and collective healthcare insurance for all citizens that includes hospital care and cancer drugs.

External validity of clinical trials

Barriers in trial participation will impair external validity of clinical trials. External validity consists of two unique underlining concepts, generalizability and applicability[18].

Generalizability can be evaluated by both the size and representativeness of the study sample. It has been reported that the generalizability of clinical trials in oncology is questionable, because fewer than 5% of cancer patients participate[19]. The trial participation rate is dependent on the population studied, with higher participation observed at populations in specialized academic centers and lower participation in general hospitals. In contrast to the aforementioned percentage, in a large retrospective single center cohort from 1990 to 1997 in a specialized cancer clinic the trial participation was 33%[19]. However, the higher participation rate in a specialized clinic does not improve representativeness by the selection of patients seeking treatment in a specialized clinic.

In our registry, 388 patients (11%) were enrolled in at least one of the 79 different clinical trials in the 20 participating hospitals of CAPRI during the study period. For specific treatments the participation in clinical trials was even higher (to illustrate this, participation in trials was 37% for cabazitaxel in 2nd line, and 23% for cabazitaxel in 3rd line)[20]. In addition, trial participation differed between hospitals, ranging from 1% to 47%. When comparing types of hospitals, trial participation in 4 academic hospitals (748 patients) was 29% (range 10%-47%) and in 16 non-academic hospitals (2,868 patients) trial participation was 6% (range 1%-26%). Please notice that despite the difference

in trial participation, the ranges do overlap between academic and non-academic hospitals.

Trial participants in cancer trials are not randomly sampled from the total population; as mentioned above, structural, medical, attitudinal, demographic and socioeconomic factors lead to selection. Indeed, we observed that patients with better prognostic features were selected for trials. When analyzing the prognostic characteristics at CRPC diagnosis, the patients who would participate in any trial during the course of CRPC were already significantly different at baseline with regards to age, comorbidity and clinical parameters (Chapter 3)[21]. The same was observed when focusing on cabazitaxel treatment in 2nd line (Chapter 4)[20].

The consequence of this selection is that *applicability* of clinical trial evidence is a struggle for clinicians. Applicability concerns the question: "are trial results applicable for my patient?". The clinician has to decide whether the treatment effects (benefits and harms) are expected to be similar to the treatment effect observed in the trial[18]. This is affected by the degree of selection, but also other factors that negatively affect the quality of evidence, such as other forms of bias and imprecision. Bias is systematic error that distorts study findings, caused by flaws in study design, data collection or analysis. Common types of bias beside selection bias detection bias, observer bias, recall bias, response bias, publication bias, regression to the mean, Hawthorne effect and treatment selection bias[22]. Imprecision is the amount or degree of random error in a study.

We observed significant longer overall survival for CRPC patients enrolling in any trial over patients who did not (35 months versus 24 months) and we observed the same for cabazitaxel treated patients in 2nd line (13.6 vs 9.6 months)[20,21]. In multivariate analyses, the difference in overall survival was not retained. Therefore we assume it is most likely explained by differential prognosis at baseline, thus selection bias applies. In treatment decisions, patients should therefore be counselled accordingly. If clinicians counsel patients based on reported outcomes from landmark clinical trials, prognosis and treatment effects will often be estimated too optimistic. This has been demonstrated recently in a real world analysis in metastatic colorectal cancer patients [23].

Generalizability and applicability should be improved to better inform treatment decisions in daily practice. I therefore suggest that trial participation, both in intervention trials and observational studies, should be optimized. Solutions that may help include the following items:

- Structural barriers (Trial availability): Oncology practices should obligatory participate in clinical trials and actively recruit patients or refer patients to other clinics for trial participation. Cooperation of clinics in regional or (inter-) national cancer networks should facilitate increased recruitment in trials. Known 'best practices' in the Netherlands are in hematology (Hemato-Oncologie voor Volwassenen Nederland (HOVON – the Heamato Oncology Foundation for Adults in the Netherlands)) and the Win-O (Working group Immunotherapy in the Netherlands) melanoma group.

- Clinical barriers (Patient eligibility): Trial designs should allow for a broader eligible population (by applying less strict eligibility criteria). Observational research may complete the lacunas in knowledge from clinical trials. Participation in patient registries should be encouraged.

- Attitudinal barriers (Physician and patient): Clinician and patient information and education and will improve trial recruitment.

- Effectiveness should be studied routinely in clinical practice, with special interest on the population that is not eligible for the clinical registration trial of new treatment. Ideally, this should be monitored in a nation-wide disease registry.

- Financial barriers: trial procedures are not considered routine care and therefore are not reimbursed to hospitals by healthcare insurances. This leads to financial barriers in hospitals to build an infrastructure for trial participation, especially in non-academic hospitals where the majority of cancer patients is treated. In investigator initiated research, often funded by public resources, reimbursement is often limited to study procedures and tariffs are generally insufficient to compensate for infrastructure (such as research staff and facilities). This is an important barrier. Since research is considered more and more as morally obligatory and as an integral part of expert-level oncology care by patient advocates, and which is adopted by other stakeholders, it is important to recognize this financial barrier and include research reimbursement for infrastructure in standard care.

2. CONTINUE THE REGISTRY PROSPECTIVELY WITH THE RELEVANT POPULATION, EFFICIENT DATA MANAGEMENT AND ANALYSES, AND RELEVANT OBJECTIVES

The CAPRI registry is being continued in the CAPRI 3.0 project. Given the evolution of treatment and new options for hormone-sensitive prostate cancer (HSPC), the population studied should include HSPC patients as well. Important progress could be made by turning the registry in a prospective registry that not only captures clinical outcomes and resource use but also PROMs and patient reported experiences (PREMs), and molecular characteristics (biobanking). Using the continuously improving ICT solutions, data management should be minimized and data quality and completeness should be maximized, with shorter data handling times. To increase efficiency of the registry, I would suggest to collect clinical data on patient- and disease characteristics and treatment outcomes on a national level, and collect PROMs, PREMs, resource use and biomaterials for subgroups based on specific scientific questions. Governance should be in a separate entity led by a steering board endorsed by all relevant medical professional organizations (including the Dutch Urological Society (NVU) and NVMO), research organizations (including DUOS) and patient advocate organizations (including the Dutch Federation of Cancer Patients (NFK) and ProstaatKankerStichting), with representatives from the stakeholders in a scientific steering committee. To optimize all efforts to start and continue the registry, the registry should not only be financed by commercial pharmaceutical companies, but ideally for a substantial part by other stakeholders such as the government, healthcare insurance companies and perhaps even hospitals. We are facing increasing strain on the healthcare budget that increases the need for efficient delivery of healthcare. Efficiency research is pivotal. All stakeholders must therefore take their responsibility and their involvement should also be financial. The CAPRI registry is a good example that all stakeholders supported such a registry and experienced collaboration as valuable for the future of patient care.

3. INCREASE EFFECTIVENESS OF LPD: OPTIMIZE SEQUENCING, TREAT THE RIGHT PATIENT WITH LPD AND STOP FURTHER TREATMENT AT THE RIGHT MOMENT

An important question is whether the availability of new LPD increase survival and quality of life in real world treatment of CRPC.

In Chapter 5, we analyzed the overall survival over time, which improved numerically but not significantly: the median overall survival (OS) was 28.5, 28.5 and 31.0 months for patients with CRPC-diagnosis in the years 2010-2011, 2012-2013 and 2014-2015,

respectively (p=0.196). The use of LPD increased from 57% to 69% in this period. When adjusting for baseline prognostic factors in multivariable cox-regression analysis, the treatment period was independent significant for OS (2014-2015 vs 2010-2011 with HR 0.749, p<0.001).

The question whether survival improves on a population basis improved with the availability of new LPD in a specified population (such as CRPC patients) remains difficult to answer and requires long follow up. This can be illustrated by examples from cancer treatment outcomes in the Netherlands.

In 2020, the Dutch Comprehensive Cancer Center (Integraal Kankercentrum Nederland, IKNL) published a report on metastatic cancer (Uitgezaaide Kanker in Beeld)[24]. In this report, median survival of synchronous metastatic cancer (that is, metastases are present from the moment of diagnosis) improved marginally from 5.1 months (2004-2008) to 6.3 months (2014-2018). In contrast, synchronous metastatic prostate cancer showed an impressive improvement of median survival from 26.5 months (2004-2008: limited LPD options) to 37.2 months (2014-2018: several new LPD available). Metachronous metastatic cancer (that is, subsequent dissemination after treatment of the primary tumor and locoregional metastases (if present)) is not represented in the Dutch Cancer Registration of IKNL.

Another example comes from the Dutch Melanoma Treatment Registry (DMTR). Recent analyses showed a marked improvement of survival in advanced melanoma patients alongside with the introduction of new LPD (immunotherapy and targeted therapy). Subsequent reports showed an increase in survival in unresectable stage III/stage IV melanoma from 10.7 months (2012) to 13.8 months (2015)[25]; recent data show that the 2016 cohort had a median survival of 17.7 months[26].

These positive findings were not observed in an interesting analysis in colorectal cancer (CRC). In contrast to the wide belief based on trial data that overall survival of metastatic CRC patients receiving systemic therapy has improved substantially, improvement could not be demonstrated in a large real-life population in the period 2008-2016[23]. However, improvement of survival in subgroups could be demonstrated. According to the authors, "This indicates that only a minority of patients benefits from the availability of more effective treatment strategies, and emphasizes the importance of real–life data in determining the impact of treatments on the outcome of the total patient population". In the period 2008-2016 limited new drugs for colorectal cancer received positive CieBom guidance: in 2008, eGFR inhibition (panitumumab or cetuximab) was

the only new LPD. This may be another explanation of the contrasting findings with prostate cancer and melanoma.

Besides efficacy of new LPD, other factors may contribute to improved survival. First, differences in diagnosis may contribute; for example, when new treatment becomes available for a certain disease state, patients and clinicians may be more eager to diagnose the disease state. If metastatic disease is diagnosed earlier (lead time), the perceived survival from that point in time is longer. This is called lead time bias or length time bias. Second, other determinants of palliative treatment besides new drugs may have improved and may lead to longer survival. These effects are not studied in CRPC.

On the contrary, ineffective use of LPD may decrease survival benefit. When LPD are used off-label or in subgroups that are not studied well (for example in patients who are unfit for treatment), the survival benefit may turn in a survival detriment: in case of toxicity, survival may even shorten compared to placebo or best supportive care. It is insufficiently studied to what extent this ineffective use of LPD is present in real world practice, and what the consequences are with respect to outcomes. We analyzed treatment with docetaxel in mCRPC patients in CAPRI in the cohort 2010-2012 (n=1,524)[27]. In total, 46% of the patients was treated with docetaxel. Based on symptoms, metastases and clinical WHO performance score the indication for docetaxel was defined as present or absent. Patients having an indication for docetaxel (n=1,083; 73%) were treated with docetaxel in 60% (n=646); Patients without an indication for docetaxel (n=441; 29%) were not treated with docetaxel in 88% (n=388). Consequently, a substantial number of patients were not treated by indication. However, in this report we did not study potential explanations such as the use of alternative treatment options or the preference of patients. Unfortunately, this analysis did also not allow for studying the effect on outcomes such as survival. Still, it is important to have more insight in effective use of LPD. The same conclusion was drawn by the PERCEPTION researchers, a population-based registry of metastatic renal cell carcinoma patients in the Netherlands[28]. In this study approximately one-third of patients eligible for sunitinib (based on trial criteria), the standard first-line option, was not treated in the period 2008-2013. In patients treated, 30% were ineligible for treatment based on trial criteria. The overall survival for ineligible patients was not significantly shorter than the OS of eligible patients treated with sunitinib in this study.

Treatment sequencing

A specific problem in the treatment of CRPC patients is the sequencing of treatments: can we extrapolate results from trials in the past to patients in the present, who may have been treated with previous treatment lines? Furthermore, trials study

direct treatment comparisons in specified populations, often regardless of type and outcomes of previous and subsequent treatment. This leads to heterogeneity in treatment sequencing of the population studied (although the extent of heterogeneity is conditional on the specific trial eligibility criteria). For example, how do we deal with the TROPIC trial data (all patients were treated with cabazitaxel directly post-docetaxel) in an era that patients may also have been treated with one or two androgen-receptor targeting drugs (abiraterone or enzalutamide). The CARD trial has provided some answers[1]. In this randomized study, patients who had previously received docetaxel and an androgen-signaling-targeted inhibitor (ART; abiraterone or enzalutamide) to receive cabazitaxel or the other ART. Cabazitaxel was superior in the primary endpoint imaging-based progression free survival (PFS), but also OS and PSA response (36% vs 14%). However, in this study only a specific population with early failure of the first ART was selected. Sequencing studies are needed to inform treatment decisions in later treatment lines.

In CAPRI, we studied sequencing of two different ART (Chapter 8). We observed no differences in PSA response or treatment duration of patients treated with sequential abiraterone and enzalutamide with or without interposed chemotherapy or radium-223. In general, outcomes were lower than those in randomized trials, questioning the additional effect of second treatment with abiraterone or enzalutamide in daily practice. PSA response was more likely with abiraterone before enzalutamide. In patients with abiraterone and enzalutamide directly sequenced (n=148), PSA response was seen in 20%. In a prospective study of 220 patients in patients treated with abiraterone and enzalutamide in a randomized sequence, enzalutamide showed some activity (PSA response 36%), whereas abiraterone acetate did not (PSA response 4%), leading to a longer time to second PSA progression for the sequence of abiraterone followed by enzalutamide than with the opposite treatment sequence[29]. In conclusion, both the CARD data and our analysis do not support the use of a second ART in mCRPC patients.

Treating the right patient with the right drug

Precision medicine is very popular these days. Hormonal therapy in prostate cancer and breast cancer can be seen as early examples of targeted therapy. In breast cancer, tumors with Her2 overexpression are treated with Her2-targeting drugs (for example trastuzumab, pertuzumab and antibody-drug conjugates such as trastuzumab-emtansin)[30]; in melanoma, tumors harboring an oncogenic BRAF-mutation are treated with BRAF- and MEK-inhibitors (for example dabrafenib and trametinib)[31]; patients with tumors that are mismatch-repair deficient (dMMR) or microsatellite-instability-high (MSI-H) benefit from checkpoint-inhibition[32]. These examples are particularly interesting, because a predictive marker is available, guiding the choice of treatment. Precision

medicine in prostate cancer has been moving slowly[33]. However, it is now reaching clinical practice. In the PROFOUND trial, patients with mCRPC who had qualifying alterations in homologous recombination repair genes and who progressed during previous ART treatment were randomized between olaparib and either enzalutamide or abiraterone. In patients with at least one alteration in *BRCA1*, *BRCA2*, or *ATM* and who were treated with olaparib, OS was significantly longer[2]. PSA response was confirmed in 30% in the olaparib group and 10% in the control group.

In the Netherlands, whole genome sequencing (WGS) in metastatic cancer has been studied in the CPCT-02 trial (NCT01855477) and genomic sequencing is now studied in the mCRPC specific PROMPT trial (NCT04746300). Patients with specific targetable (druggable) mutations can be treated in the Drug Rediscovery Protocol (DRUP). This is a prospective, non-randomized clinical trial that aims to describe the efficacy and toxicity of commercially available, targeted anticancer drugs prescribed for treatment of patients with advanced cancer with a potentially actionable variant as revealed by a genomic or protein expression test (NCT02925234). In the report of the large CPCT-02 cohort (n=2,520), 62% of patients had genetic variants that may be used to stratify patients towards therapies that either have been approved or are in clinical trials[34]. However, clinical benefit in the DRUP analysis was limited to 34% of 215 treated patients (defined as an overall rate of clinical benefit-defined as complete or partial response, or as stable disease beyond 16 weeks). These patients comprised 136 patients who received targeted therapies and 79 patients who received immunotherapy[35]. In prostate cancer, precision medicine has limited benefit for the whole patient population, as illustrated by the CPCT-02 analysis on metastatic prostate cancer. In this analysis, successful WGS after biopsy was achieved in 63% (n=197); of these patients, 18% (n=35) had a druggable mutation (7% had high tumor mutational burden that is targetable by immune checkpoint inhibition and 11% had homologous recombination deficiency (HRD) that is targetable by PARP-inhibitors)[36].

Stop further treatment at the right time

In systemic palliative treatment of mCRPC, 63% of all patients was treated with at least one LPD in CAPRI. When analyzing these 2270 LPD treated patients, only part of the patients received a subsequent treatment line (see Figure 4). 61% of the patients got a second LPD; 50% a third LPD and 37% received a fourth LPD. Of all treated patients, only 31% received a third LPD and 11% a fourth LPD. Identifying the patients with both an indication for a next LPD treatment line and the patients with benefit of this treatment in real world is a challenge. We observed that 61% of LPD treated patients received two LPD lines (mostly chemotherapy and ART or vice versa (n=980, 70%), two

lines of chemotherapy (n=199, 14%), or two lines of ART (n=80, 6%) or any combination including radium-223 (n=132, 9%).

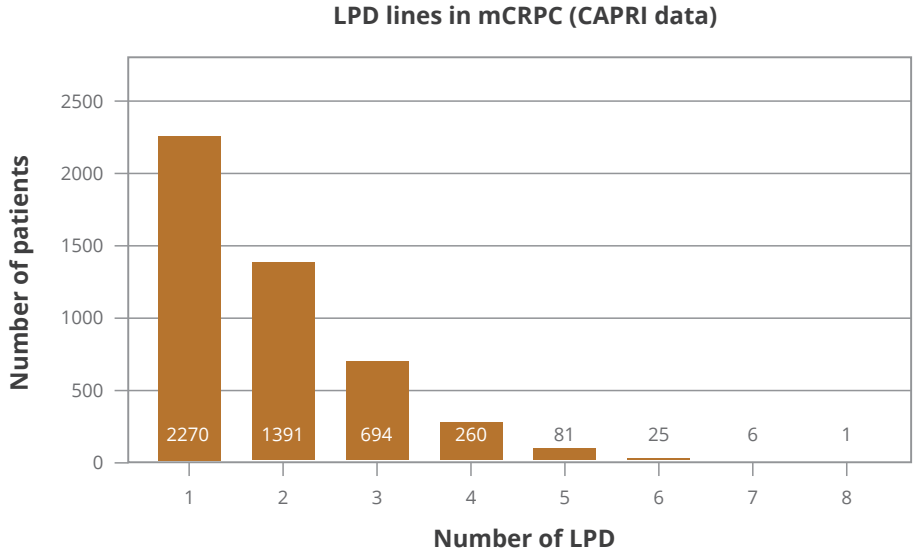


Figure 4. LPD treated mCRPC patients in CAPRI, by number of LPD lines.

After two lines of LPDs, prospective data on third-line treatment is scarce, and therefore it is justified to study the outcomes of a third LPD in real world. In Chapter 9 we identified four risk groups based on prognostic parameters (ECOG performance status 0 vs 1 vs 2 or higher, opioid use no vs yes, , hemoglobin ≥7.0 mmol/L vs <7.0 mmol/L , alkaline phosphatase <170 U/L vs ≥170 U/L, and lactate dehydrogenase ≤250 U/L vs >250 U/L. The median OS values for low-, low-intermediate-, high-intermediate-, and high-risk groups were 14, 7.7, 4.7, and 1.8 months, respectively. 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 median treatment duration and low PSA responses. Therefore, high-risk patients should not be treated with third-line LPDs; instead, they should be treated with best supportive care (BSC). These results may support an intervention after two LPD lines by a palliative care team to limit treatments without expected benefit.

4. DETERMINE THE VALUE OF PROMS IN CLINICAL PRACTICE AND SOLVE BARRIERS.

Patient reported outcomes

In CRPC, PROMs are well studied in clinical trials. The Prostate Cancer Clinical Trials Working Group (PCWG3) recognizes the importance of patient-centered drug development and reporting the patient experience on study[37]. LPD treatment results in a delay of HRQOL deterioration and pain progression in clinical trials[38-41]. However, HRQOL is often a secondary endpoint and studies may be underpowered to draw strong conclusions. For example, quality of life in CARD has been studied but was underpowered[42].

Real world data on PROMs are scarce. In Chapter 6 we studied PROMs in CRPC and reported results of the PRO-CAPRI study. The study was limited by a small sample size: accrual was slow, the study had to be amended from 4 to 10 participating hospitals to increase accrual and still the included patients (n=151) did not reach our initial target of n=400. Also, the interpretation and translation of results to daily practice was difficult. Although most patients were treated with new treatments during follow-up, mCRPC had 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[43].

PROMs are still not routinely assessed in the daily oncology practice. Because of the debate about the value of using PROMS in daily clinical follow-up, a systematic review of the literature was recently reported that identified 22 studies out of 8,341 references[44]. The authors concluded that "predominantly positive findings were found in the use of a PROM in daily cancer care. Additionally, more positive effects were seen when feedback is provided to patient and/or health care professionals, and it is thus highly recommended that this is always done". Potential benefits have been identified: it empowers patients to actively participate in their health care, facilitates early detection and monitoring of patient symptoms, and enables clinicians to better understand and act on patients' needs; it helps communication between patient and clinician by raising specific issues on symptoms and functioning; assessing PROs itself may already improve treatment outcomes; and it may improve safety and quality of health care delivery[45].

Barriers to implement PROMs exist on different levels, as reported in a recent review: At the patient level, patient time, incapacity and difficulty using electronic devices to

complete PROMs were prominent barriers. At the health professional level, major barriers included health professionals' lack of time and knowledge to meaningfully interpret and integrate PRO data into their clinical practice and the inability for PRO data to be acted upon. Prominent barriers at the service level included difficulties integrating PROs and PROMs into clinical workflows and inadequate information technology (IT) infrastructures for easy PRO collection [45]. Structured interviews with Dutch oncological health care providers showed that adequately functioning IT technology, sufficient knowledge on PROMs, and dedicated time during the consultation are essential for successful implementation of PROMs in oncological care[46]. It can be anticipated that in the near future, barriers will be solved and the use of PROMs will become part of standard care. To derive optimal benefit from PROMs, feedback to patients and health care providers should be implemented. Today, this is almost never the case.

5. OPTIMIZE END-OF-LIFE CARE BY DECREASING HIGH-INTENSITY CARE IN THE LAST 3 MONTHS

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 of our study in Chapter 7 was to investigate the care in last three months of life (EOL) in CRPC. In conclusion, high intensity care in EOL in CRPC occurred in 41%. While Dutch clinicians seemed reserved to start LPD in EOL, hospital admissions were frequent especially in patients starting a new LPD. Younger patients and patients in better condition were more likely to have high intensity care in EOL. A limitation is that we only captured in-hospital data. 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 have been overestimated. High intensity care is not easily justifiable from both patient and economic perspective, but the effect on quality of life is largely unknown[48].

Although few studies on high-intensity care has been done in the end-of-life phase, knowledge to optimize end-of-life care is still lacking. An important factor is that recognition of the last 3 months of life is difficult: clinicians often overestimate when predicting a patients' survival[47]. Further research on prognostic models may improve estimation of survival and may identify useful markers to recognize the EOL phase.

In daily practice clinicians recognize the importance of avoiding high-intensity care. This includes but is not limited to avoid intensive care unit (ICU) admissions before death in metastatic cancer patients, to not start new treatment in the last 3 months before death, to die in the right place (preferably not the hospital, but at home or in

a hospice) and to give patients time to accept the near death and to say farewell to their relatives. It can be hypothesized that reduction of high-intensity care in EOL may improve effectiveness and reduce healthcare costs of EOL care. However, it is unclear what the goals should be; because we cannot reliably mark the last 3 months before death, high-intensity care should not be zero. Cyclic feedback on EOL high-intensity care indicators in daily practice, for instance by dashboards, may facilitate multidisciplinary discussions and improve awareness in clinicians which may reduce high-intensity care and costs, and may improve quality of life.

IMPLEMENTATION OF CAPRI RESULTS AND LESSONS LEARNED TURNED INTO POLICY

This thesis on real world evidence in castration-resistant prostate cancer already contributed to improving daily practice in the Netherlands, and especially my hospital (Amphia, Breda, the Netherlands) and in our regional cancer network EMBRAZE. This is based on the following lessons learnt and recommendations:

1. Increase trial participation and increase generalizability and applicability of trial results
   In EMBRAZE, we started to discuss trial feasibility regionally and we use the network to improve accrual of trials.
2. Continue the registry prospectively with the relevant population, efficient data management and analyses, and relevant objectives
   Lessons learned from CAPRI have been used in the setting up of patients registries including CAPRI 3.0 (metastatic prostate cancer), ProRCC (renal cancer) and ProBCI (bladder cancer).
3. Increase effectiveness of LPD: optimize sequencing, treat the right patient with LPD and stop further LPD treatment at the right moment (and off course continue palliative care!)
   Effectiveness is now a major theme in the oncologic strategy in Amphia. Dashboards on LPD use and outcomes have been developed. The transmural palliative care team started an outpatient clinic for patients progressive on two lines of palliative treatment (for any cancer type)
4. Determine the value of PROMS in clinical practice and solve barriers.
   PROMs are part of the oncologic strategy in Amphia, and many other hospitals. Projects on PROMs that already started are in prostate cancer (EMBRAZE), breast cancer and multiple myeloma (in cooperation with ErasmusMC)
5. Optimize end-of-life care by decreasing high-intensity care in the last 3 months
   Amphia developed End-of-life-dashboards for different cancer types to promote awareness and facilitate multidisciplinary discussions in clinical practice.

REFERENCES

1. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381(26):2506-2518.
2. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;383(24):2345-2357.
3. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65(2):467-479.
4. Svensson J, Lissbrant IF, Gauffin O, et al. Time spent in hormone-sensitive and castration-resistant disease states in men with advanced prostate cancer, and its health economic impact: Registry-based study in sweden. *Scand J Urol*. 2021;55(1):1-8.
5. Fallara G, Lissbrant IF, Styrke J, Montorsi F, Garmo H, Stattin P. Observational study on time on treatment with abiraterone and enzalutamide. *PLoS One*. 2020;15(12):e0244462.
6. Delanoy N, Hardy-Bessard AC, Efstathiou E, et al. Clinical progression is associated with poor prognosis whatever the treatment line in metastatic castration resistant prostate cancer: The CATS international database. *Eur J Cancer*. 2020;125:153-163.
7. Akaza H, Procopio G, Pripatnanont C, et al. Metastatic castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy: Treatment patterns from the PROXIMA prospective registry. *J Glob Oncol*. 2018;4:1-12.
8. Stenner F, Rothschild SI, Betticher D, et al. Quality of life in second-line treatment of metastatic castration-resistant prostate cancer using cabazitaxel or other therapies after previous docetaxel chemotherapy: Swiss observational treatment registry. *Clin Genitourin Cancer*. 2017.
9. Unger JM, Hershman DL, Martin D, et al. The diffusion of docetaxel in patients with metastatic prostate cancer. *J Natl Cancer Inst*. 2014;107(2):10.1093/jnci/dju412. Print 2015 Feb.
10. Chowdhury S, Bjartell A, Lumen N, et al. Real-world outcomes in first-line treatment of metastatic castration-resistant prostate cancer: The prostate cancer registry. *Target Oncol*. 2020;15(3):301-315.
11. Penson DF, Lin DW, Karsh L, et al. Treatment registry for outcomes in patients with castration-resistant prostate cancer (TRUMPET): A methodology for real-world evidence and research. *Future Oncol*. 2016;12(23):2689-2699.
12. Droz JP, Efstathiou E, Yildirim A, et al. First-line treatment in senior adults with metastatic castration-resistant prostate cancer: A prospective international registry. *Urol Oncol*. 2016;34(5):234.e21-234.e29.
13. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65(2):467-479.
14. Nipp RD, Hong K, Paskett ED. Overcoming barriers to clinical trial enrollment. *Am Soc Clin Oncol Educ Book*. 2019;39:105-114.

15. Lara PN,Jr, Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: Identifying potential barriers to enrollment. *J Clin Oncol*. 2001;19(6):1728-1733.
16. Denicoff AM, McCaskill-Stevens W, Grubbs SS, et al. The national cancer institute-american society of clinical oncology cancer trial accrual symposium: Summary and recommendations. *J Oncol Pract*. 2013;9(6):267-276.
17. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: Barriers, evidence, and strategies. *Am Soc Clin Oncol Educ Book*. 2016;35:185-198.
18. Murad MH, Katabi A, Benkhadra R, Montori VM. External validity, generalisability, applicability and directness: A brief primer. *BMJ Evid Based Med*. 2018;23(1):17-19.
19. Elting LS, Cooksley C, Bekele BN, et al. Generalizability of cancer clinical trial results: Prognostic differences between participants and nonparticipants. *Cancer*. 2006;106(11):2452-2458.
20. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. Second-line cabazitaxel treatment in castration-resistant prostate cancer clinical trials compared to standard of care in CAPRI: Observational study in the netherlands. *Clin Genitourin Cancer*. 2019;17(5):e946-e956.
21. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in trial and real-world populations in the dutch castration-resistant prostate cancer registry. *Eur Urol Focus*. 2018;4(5):694-701.
22. Higgins JPT, Thomas J, Chandler J, et al, eds. *Cochrane handbook for systematic reviews of interventions*. 6.1st ed. Cochrane; 2020. http://handbook.cochrane.org/chapter_8/8_4_introduction_to_sources_of_bias_in_clinical_trials.htm.
23. Hamers PAH, Elferink MAG, Stellato RK, et al. Informing metastatic colorectal cancer patients by quantifying multiple scenarios for survival time based on real-life data. *Int J Cancer*. 2020.
24. Fransen H, Aarts M, Brom L, et al. Uitgezaaide kanker in beeld. . 2020;ISBN 9789072175502.
25. van Zeijl MCT, van den Eertwegh AJM, Wouters MWJM, et al. Recent treatment results for metastatic melanoma: Data from the dutch melanoma treatment registry. *Ned Tijdschr Geneeskd*. 2018;162.
26. van Zeijl MCT, de Wreede LC, van den Eertwegh AJM, et al. Survival outcomes of patients with advanced melanoma from 2013 to 2017: Results of a nationwide population-based registry. *Eur J Cancer*. 2021;144:242-251.
27. Verbetersignalement: Zinnig gebruik van geneesmiddelen bij patiënten met castratie refractair prostaatcarcinoom. . 2016;volgnummer: 2016018485.
28. De Groot S, Sleijfer S, Redekop WK, et al. Variation in use of targeted therapies for metastatic renal cell carcinoma: Results from a dutch population-based registry. *BMC Cancer*. 2016;16:364-016-2395-x.
29. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: A multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol*. 2019;20(12):1730-1739.
30. Kunte S, Abraham J, Montero AJ. Novel HER2-targeted therapies for HER2-positive metastatic breast cancer. *Cancer*. 2020;126(19):4278-4288.

31. Tetu P, Baroudjian B, Lebbe C. Targeting BRAF and MEK inhibitors in melanoma in the metastatic, neoadjuvant and adjuvant setting. *Curr Opin Oncol*. 2020;32(2):85-90.
32. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207-2218.
33. Ku SY, Gleave ME, Beltran H. Towards precision oncology in advanced prostate cancer. *Nat Rev Urol*. 2019;16(11):645-654.
34. Priestley P, Baber J, Lolkema MP, et al. Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature*. 2019;575(7781):210-216.
35. van der Velden DL, Hoes LR, van der Wijngaart H, et al. The drug rediscovery protocol facilitates the expanded use of existing anticancer drugs. *Nature*. 2019;574(7776):127-131.
36. van Dessel LF, van Riet J, Smits M, et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. *Nat Commun*. 2019;10(1):5251-019-13084-7.
37. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol*. 2016;34(12):1402-1418.
38. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol*. 2013;24(9):2402-2408.
39. Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: Patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol*. 2013;14(12):1193-1199.
40. Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: Results from the randomised, phase 3 AFFIRM trial. *Lancet Oncol*. 2014;15(10):1147-1156.
41. Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): Results from a randomised, phase 3 trial. *Lancet Oncol*. 2015;16(5):509-521.
42. Fizazi K, Kramer G, Eymard JC, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): An analysis of a randomised, multicentre, open-label, phase 4 study. *Lancet Oncol*. 2020;21(11):1513-1525.
43. Kuppen MCP, Westgeest HM, van den Eertwegh AJM, et al. Health-related quality of life and pain in a real-world castration-resistant prostate cancer population: Results from the PRO-CAPRI study in the netherlands. *Clin Genitourin Cancer*. 2019.
44. Graupner C, Kimman ML, Mul S, et al. Patient outcomes, patient experiences and process indicators associated with the routine use of patient-reported outcome measures (PROMs) in cancer care: A systematic review. *Support Care Cancer*. 2021;29(2):573-593.

45. Nguyen H, Butow P, Dhillon H, Sundaresan P. A review of the barriers to using patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs) in routine cancer care. *J Med Radiat Sci*. 2020.
46. Graupner C, Breukink SO, Mul S, Claessens D, Slok AHM, Kimman ML. Patient-reported outcome measures in oncology: A qualitative study of the healthcare professional's perspective. *Support Care Cancer*. 2021.
47. Cheon S, Agarwal A, Popovic M, et al. The accuracy of clinicians' predictions of survival in advanced cancer: A review. *Ann Palliat Med*. 2016;5(1):22-29.
48. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. 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 Aug 19. Online ahead of print.

APPENDICES

SUMMARY

This thesis concerns real world outcomes of systemic treatment in metastatic CRPC patients. Prostate cancer is the second most commonly diagnosed cancer and the sixth leading cause of cancer death among men worldwide. Prostate cancer that progresses despite androgen deprivation therapy, either metastatic (m) or non-metastatic (nm), is defined as castration-resistant prostate cancer (CRPC). Until 2004, no survival benefit over best supportive care was observed in clinical trials on systemic treatment. In 2004 docetaxel was the first available life-prolonging drug for mCRPC[1]. Between 2011 and 2014 new life-prolonging drugs (LPD) for mCRPC (cabazitaxel[2], abiraterone[3,4], enzalutamide[5,6] and radium-223[7]) were introduced in the Netherlands. In 2021, olaparib was also introduced[8].

A general introduction and outline of the thesis is presented in **chapter 1**.

Real world data are used to inform decision making in health care by providing effectiveness data. In **chapter 2** we provided practical guidance in setting up patient registries to facilitate real-world data collection for health care decision making, based on our experiences and involvement in setting up patient registries in oncology in the Netherlands. It can be expected that patient registries will become the new standard alongside randomized controlled trials due to their unique value[9].

CAPRI was set up as a retrospective observational registry using a population-based sample to provide real world data on patients, treatment and outcomes in castration-resistant prostate cancer. The registry is investigator-initiated and a broad collaboration was sought in a period that more than one industrial company needed intervention-based outcome data. Therefore, the registry was set up as a disease-based registry. Twenty hospitals in the Netherlands were invited to participate, based on both geographical spread and type of hospitals: 4 academic centers, 11 large teaching hospitals and 5 general hospitals. All invited hospitals agreed to participate. We focused on the CRPC population, and eligibility was met if CRPC was diagnosed either by the EAU criteria[10] or by the treating physician (regardless of the CRPC definition, but based on CRPC treatment initiated; addition of antiandrogen therapy following progression on ADT was considered first line systemic therapy for CRPC). Prostate cancer was defined as histologic confirmation of prostate cancer or as concluded by the treating doctor based on elevated PSA and metastatic pattern. Because CRPC patients are difficult to capture, we retrospectively screened all prostate cancer patients (n=41,714) in both urology and internal medicine departments in 20 hospitals in the Netherlands, based on the diagnosis code in the defined study period (2010-2016). We identified 3,616 CRPC

patients that met the eligibility criteria, an estimated sample of 20% of the total Dutch CRPC population in the study period, with follow up to 2018.

PART 1

In part 1 of this thesis, we focused on differences in clinical trial populations and real world populations. Clinical trials are designed to maximize the internal validity and these trials eliminate factors such as doctor-patient relationship, placebo effects and patient preference (by blinding, placebo-control and exclusion of patients and clinicians with strong treatment preferences)[11]. This leads to increased internal validity and will provide evidence on efficacy. However, this also leads to decreased external validity and therefore clinical trials are often not informative on effectiveness.

In **chapter 3** we assessed the baseline differences at CRPC diagnosis in patients who did participate in one or more clinical trials (trial group, 13%), versus patients who did not (standard care group, 87%), in the first cohort of CAPRI (n=1,564). Patients in the trial group were significantly younger and had less comorbidities. Despite an observed unadjusted median overall survival difference of 35 months versus 24 months between the trial and standard care group, this difference was not retained after adjustment for baseline characteristics and treatment effect. The survival difference between the trial and standard care group could be explained by baseline differences and treatment effects. These results indicate that trial results cannot easily be translated to real-world practice[12].

We assessed differences between trial patients and standard care patients in more detail in **chapter 4**. Cabazitaxel treatment as second line chemotherapy in 173 mCRPC patients was analyzed, in both standard care (63%) and in trial patients (37%). Trial patients had favorable prognostic factors: fewer symptoms, less visceral disease, lower lactate dehydrogenase, higher hemoglobin, 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 standard care, 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). To conclude, 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[13].

PART 2

In part 2 we focused on the real world outcomes in mCRPC. In **chapter 5**, we assessed the impact of introduction of new LPDs on treatment patterns and overall survival over time. Two subgroups were analysed: treatment-naïve patients (subgroup 1, n=3,600) and post-docetaxel patients (subgroup 2, n=1,355). 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% to 29% and 20% to 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 imputation 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). In conclusion, between 2010-2018, a larger proportion of mCRPC patients was treated with LPDs, which was related to an increased median overall survival[14].

The PRO-CAPRI study was a side study of the CAPRI study. Patients who were eligible for CAPRI were prospectively included for patient-reported outcome measurement in 10 CAPRI hospitals. The purpose of this study was to determine generic, cancer-specific, and prostate cancer-specific health-related quality of life (HRQoL), pain and changes over time in patients with metastatic castration-resistant prostate cancer (mCRPC) in daily practice. In **chapter 6** we reported this study, with 151 CRPC patients who completed quality of life (QoL) questionnaires. Although patients were generally in good clinical condition and the majority (84%) received life-prolonging drugs, QoL deteriorated during the course of CRPC. At inclusion, the generic HRQoL was high with a mean EQ visual analog score of 73.2 out of 100. The lowest scores were reported on role and physical functioning (mean scores of 69 and 76 of 100, respectively), and fatigue, pain, and insomnia were the most impaired domains. These domains deteriorated in > 50% of patients. Therefore, timely started supportive care management, especially focused on role and physical functioning, needs specific attention during follow-up to maintain HRQoL as long as possible[15].

In **chapter 7** we investigated high-intensity care in the end of life phase of CRPC patients. Intensive end-of-life care (EOL) defined as the overuse of treatments and

hospital resources in the last three months of life, is undesirable since it has a minimal clinical benefit with a substantial financial burden. Fifteen percent of 2,429 patients with a known date of death in CAPRI started a new LPD in EOL and 56% had at least one hospital admission. High intensity care was experienced by 41%. Multivariable analyses showed that older patients (OR 0.98, 95% CI 0.97-0.99), patients with worse performance status (OR 0.57, 95% CI 0.33-0.97) and longer time from CRPC diagnosis to EOL (OR 0.98, 95% CI 0.97-0.98) were significant less likely to experience high intensity care, while referral to a medical oncologist (OR 1.99, 95% CI 1.55-2.55,), prior LPD treatment (1 line OR 1.53, 95% CI 1.19-1.96 and >1 line OR 1.72, 95% CI 1.31-2.28) and opioid use (OR 1.45, 95% CI 1.08-1.95) were associated with significant high intensity care. In EOL, Dutch clinicians were not likely to start a new LPD treatment, but hospital admissions were frequent. High intensity care 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'[16]

PART 3

In part 3 we describe the lessons learned from real-world data. Many questions on sequencing of therapy are not answered in clinical trials. In **chapter 8**, we reported real-world outcomes (treatment duration and PSA response) of sequential androgen-receptor targeting therapies (ART) with or without interposed life-prolonging drugs in mCRPC patients. A total of 273 patients were included with a median follow-up of 8.4 mo from ART2. Patients with ART1 > ART2 were older and had favorable 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). In conclusion, 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 short time on castration, visceral disease, and enzalutamide before abiraterone[17].

Another issue in treatment sequencing is when to start best supportive care over a next line of systemic treatment. In **chapter 9** we assessed outcomes of third-line LPD in mCRPC patients, and identified variables associated with overall survival to establish a prognostic model. Of 1,011 mCRPC patients progressive on second-line LPD, 602 patients (60%) received third-line LPD. Patients receiving third-line LPD had a more favorable prognostic profile at baseline and longer median OS than patients with best

supportive care (10.4 vs. 2.4 months, p <0.001). ECOG PS 1 and ≥2 (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), hemoglobin <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. Median OS for low-, low-intermediate-, high-intermediate- and high-risk groups were 14, 7.7, 4.7 and 1.8 months, respectively. Thus, 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[18].

In the last **chapter 10**, we report a case study using our real-world data of CRPC patients to develop a prediction model. We aim to both assist the clinician in developing a prediction model and to support the clinician in recognizing common shortcomings in existing prediction models. Risk prediction is becoming increasingly more important in medical practice. In this article we discuss several steps in developing a prediction model including missing data, predictor encoding and selection using LASSO, testing model assumptions, performance and validation. Prediction model development is not a futile task and both the input of the clinician and statistician are essential. This article may be used to bridge the gap between the two disciplines[19].

REFERENCES

1. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.
2. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.
3. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: Final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13(10):983-992.
4. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.
5. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
6. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
7. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
8. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22):2091-2102.
9. de Groot S, van der Linden N, Franken MG, et al. Balancing the optimal and the feasible: A practical guide for setting up patient registries for the collection of real-world data for health care decision making based on dutch experiences. *Value Health*. 2017;20(4):627-636.
10. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65(2):467-479.
11. Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?". *Lancet*. 2005;365(9453):82-93.
12. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al. Differences in trial and real-world populations in the dutch castration-resistant prostate cancer registry. *Eur Urol Focus*. 2018;4(5):694-701.
13. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. Second-line cabazitaxel treatment in castration-resistant prostate cancer clinical trials compared to standard of care in CAPRI: Observational study in the netherlands. *Clin Genitourin Cancer*. 2019;17(5):e946-e956.
14. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. 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.

15. Kuppen MCP, Westgeest HM, van den Eertwegh AJM, et al. Health-related quality of life and pain in a real-world castration-resistant prostate cancer population: Results from the PRO-CAPRI study in the netherlands. *Clin Genitourin Cancer*. 2019.
16. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. 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 Aug 19. Online ahead of print.
17. Kuppen MCP, Westgeest HM, van den Eertwegh AJM, et al. Real-world outcomes of sequential androgen-receptor targeting therapies with or without interposed life-prolonging drugs in metastatic castration-resistant prostate cancer: Results from the dutch castration-resistant prostate cancer registry. *Eur Urol Oncol*. 2019.
18. Notohardjo JCL, Kuppen MCP, Westgeest HM, et al. Third-line life-prolonging drug treatment in a real-world metastatic castration-resistant prostate cancer population: Results from the dutch castration-resistant prostate cancer registry. *Eur Urol Focus*. 2020.
19. Veen KM, de Angst IB, Mokhles MM, et al. A clinician's guide for developing a prediction model: A case study using real-world data of patients with castration-resistant prostate cancer. *J Cancer Res Clin Oncol*. 2020;146(8):2067-2075.

SAMENVATTING (DUTCH)

Dit proefschrift gaat over 'real world' (echte wereld, dagelijkse praktijk) uitkomsten van systemische (medicamenteuze) behandelingen in patiënten met gemetastaseerd castratie-resistent prostaatcarcinoom (CRPC). Prostaatcarcinoom is bij mannen wereldwijd de tweede meest-gediagnosticeerde kankersoort en de zesde oorzaak van overlijden door kanker. CRPC wordt gedefinieerd als prostaatcarcinoom dat progressie vertoont ondanks androgeen deprivatie therapie, ofwel gemetastaseerd (mCRPC) ofwel niet-gemetastaseerd (nmCRPC). Tot 2004 was er geen systemische behandeling met in klinisch onderzoek aangetoond overlevingsvoordeel boven ondersteunende zorg. Docetaxel chemotherapie was in 2004 de eerste beschikbare behandeling met overlevingsvoordeel voor mCRPC. Tussen 2011 en 2014 werden nieuwe levensverlengende behandelingen geïntroduceerd in Nederland: cabazitaxel, abiraterone, enzalutamide en radium-223. In 2021 werd olaparib ook toegevoegd.

In **Hoofdstuk 1** werd een algemene inleiding en overzicht van het proefschrift gepresenteerd.

'Real world' data worden door data over doelmatigheid (efficiëntie) te genereren gebruikt om besluitvorming in gezondheidszorg te ondersteunen. In **Hoofdstuk 2** gaven we praktische aanwijzingen om patiënt-registers op te zetten om deze 'real world' data, geschikt voor besluitvorming in de gezondheidszorg, te verzamelen. Deze praktische aanwijzingen zijn gebaseerd op onze ervaringen en betrokkenheid bij het opzetten van oncologische patiënt-registers in Nederland. Het is aannemelijk dat door hun unieke toegevoegde waarde patiënt-registers de nieuwe standaard worden naast gerandomiseerde gecontroleerde onderzoeken.

CAPRI (een acroniem voor CAstration resistant Prostate cancer Reglstry) is opgezet als een retrospectief observationeel register waarin een populatie-steekproef wordt gebruikt om 'real world' data te verzamelen over patiënten, behandelingen en uitkomsten van mCRPC. Het register is geïnitieerd door onderzoekers. Toen bleek dat meerdere farmaceutische bedrijven interventie-gebaseerde uitkomstendata nodig hadden werd een brede samenwerking nagestreefd. Daarom werd CAPRI als een ziekte-register opgezet (en niet als behandelingsregister). Twintig ziekenhuizen in Nederland werden uitgenodigd om te participeren. Deze ziekenhuizen werden uitgenodigd op basis van geografische spreiding en type ziekenhuis: 4 academische ziekenhuizen, 11 'Samenwerkende Topklinische opleidingsZiekenhuizen' (STZ), en 5 algemene ziekenhuizen. Alle uitgenodigde ziekenhuizen stemden in met deelname. De studiepopulatie betrof CRPC-patiënten, en patiënten werden in het register opgenomen

als de CRPC diagnose op basis van de 'European Association of Urology' (EAU) criteria kon worden gesteld, of op basis van de diagnose CRPC door de behandelaar (ongeacht de EAU definitie van CRPC, maar gebaseerd op geïnitieerde behandeling van CRPC: toevoegen van een anti-androgeen behandeling volgende op progressie op androgeen deprivatie therapie werd beschouwd als de eerste lijn systemische therapie voor CRPC). Prostaatkanker werd gedefinieerd als histologisch bewezen/bevestigde prostaatcarcinoom, of op basis van de concluderende diagnose van de behandellaar gebaseerd op een verhoogd PSA en metastaseringspatroon. Omdat CRPC patiënten niet direct in ziekenhuisregistraties gevonden kunnen worden, hebben we retrospectief alle prostaatkanker patiënten gescreend (n=41,714), in zowel de urologie als interne geneeskunde afdelingen van de twintig deelnemende ziekenhuizen, op basis van de diagnosecode 'prostaatkanker' in de gedefinieerde studieperiode (2010-2016). We identificeerden 3,616 CRPC patiënten die aan onze criteria voldeden, en we schatten dat deze steekproef ongeveer 20% van de totale Nederlandse CRPC-populatie in de studieperiode besloeg. De patiënten werden retrospectief gevolgd tot 2018.

DEEL 1

In deel 1 van dit proefschrift bestudeerden we de verschillen in de populatie patiënten die meedoet aan klinische onderzoeken en de 'real world' populatie. Klinische onderzoeken zijn opgezet om de interne validiteit te maximaliseren. Deze onderzoeken elimineren factoren die de uitkomst beïnvloeden zoals de arts-patiënt relatie, placebo effecten en specifieke patiënt-voorkeuren (door respectievelijk blindering, placebo-controle en exclusie van patiënten en behandelaren met sterke behandelvoorkeuren). Dit verhoogt de interne validiteit en genereert bewijs over de werkzaamheid van de behandeling. Dit gaat echter ten koste van externe validiteit en daarom zijn klinische onderzoeken vaak niet informatief over de doelmatigheid van behandeling.

In **Hoofdstuk 3** onderzochten we in het eerste cohort van CAPRI (2010-2013, n=1,564) de verschillen op het moment van CRPC diagnose tussen patiënten die meededen aan één of meer klinische onderzoeken (de 'trial groep', 13% van de populatie) en de patiënten die niet meededen aan klinische onderzoeken (de 'standaard zorg groep', 87%). Het bleek dat patiënten in de 'trial groep' significant jonger waren en minder bijkomende ziektes (co-morbiditeit) hadden. We observeerden ongecorrigeerd een mediaan overlevingsverschil van 35 maanden versus 24 maanden tussen respectievelijk de 'trial groep' en 'standaard zorg groep', maar dit verschil verdween na correctie voor factoren op moment van diagnose en behandeleffect. Het verschil in overleving zou daarom verklaard kunnen worden door verschillen bij diagnose en behandeleffecten.

Deze resultaten tonen dat resultaten uit klinische onderzoeken niet zonder meer naar de dagelijkse praktijk vertaald kunnen worden.

We onderzochten de verschillen tussen patiënten in klinisch onderzoek en de 'real world' populatie meer in detail in **Hoofdstuk 4**. Cabazitaxel behandeling als tweedelijns chemotherapie werd onderzocht bij 173 mCRPC patiënten, zowel in 'standaard zorg' patiënten (63%) als bij 'trial' patiënten (37%). 'Trial' patiënten hadden gunstiger prognostische factoren: minder symptomen, minder viscerale metastasen, lager lactaatdehydrogenase, hoger hemoglobine, meer docetaxel cycli gehad en een langer behandelvrij-interval sinds de docetaxel behandeling. PSA respons (>50% afname) was 28% versus 12%, respectievelijk (p=0.209). De mediane overleving was 13.6 versus 9.6 maanden voor 'trial' en 'standaard zorg' patiënten (Hazard ratio 0.73, p=0.067). Na correctie voor prognostische factoren was er geen verschil meer in overleving (Hazard ratio 1.00, p=0.999). Concluderend waren patiënten die met cabazitaxel in klinische onderzoeken werden behandeld fitter en hadden zij uitkomsten vergelijkbaar met de registratie onderzoeken. Daarentegen hadden patienten die cabazitaxel als standaard zorg kregen meer agressieve ziekte en een slechtere uitkomst. Dit kan verklaard worden door een slechtere prognose al op het moment van starten van cabazitaxel.

DEEL 2

In deel 2 hebben we 'real world' uitkomsten van mCRPC onderzocht. In **Hoofdstuk 5** onderzochten we het effect van introductie van nieuwe levensverlengende medicijnen (LPD) op behandelpatronen en de ontwikkeling van overleving in de tijd. We onderzochten twee subgroepen: behandel-naïeve patiënten (subgroep 1, n=3,600) en post-docetaxel patiënten (subgroep 2, n=1,355). In beide subgroepen nam het gebruik van LPD toe: van 57% (2010-2011) naar 69% (2014-2015) in subgroep 1, en van 65% (2011-2012) naar 79% (2015-2016) in subgroep 2. Het aandeel chemotherapie als eerste mCRPC-behandeling (docetaxel) nam af van 46% naar 29%, en chemotherapie als eerste post-docetaxel behandeling (cabazitaxel of herbehandeling met docetaxel) nam af van 20% naar 9%. Het aandeel androgeen-receptor gerichte behandeling (ART; enzalutamide of abiraterone) nam echter toe van 11% naar 39% in subgroep 1 en van 46% naar 64% in subgroep 2. In subgroep 1 nam de mediane overleving vanaf CRPC diagnose toe van 28.5 maanden naar 31.0 maanden (p=0.196). In subgroep 2 nam de mediane overleving vanaf progressie op docetaxel toe van 7.9 maanden naar 12.5 maanden (p<0.001). Na multipele imputatie van missende waarden, zagen we in multivariabele Cox-regressie analyse dat de behandelperiode onafhankelijk en significant voorspellend was voor overleving in subgroep 1 (2014-2015 vs 2010-2011 met HR 0.749, p<0.001) en in subgroep 2 (2015-2016 vs 2011-2012 met HR 0.811, p=0.037).

Concluderend werd tussen 2010 en 2018 een groter deel van de mCRPC patiënten behandeld met LPD, en dat was gerelateerd aan een toegenomen overleving.

De PROCAPRI studie was een zelfstandig onderdeel van de CAPRI studie. In tien CAPRI ziekenhuizen werden patiënten, die ook in de CAPRI studie opgenomen zouden worden, gevraagd om prospectief patiënt-gerapporteerde uitkomsten (PROMs) te rapporteren. Het doel van deze studie was om de generieke, kanker-specifieke en prostaatkanker-specifieke gezondheid-gerelateerde kwaliteit van leven (HRQoL), pijn en veranderingen in de tijd te bepalen bij patiënten met mCRPC in de dagelijkse praktijk. In **Hoofdstuk 6** wordt deze studie gerapporteerd, waarin 151 patiënten kwaliteit van leven vragenlijsten hebben ingevuld. Ondanks dat de patiënten overwegend in goede conditie waren en de meerderheid (84%) behandeld werd met LPD, ging de HRQoL achteruit gedurende het verloop van CRPC. Bij inclusie was de generieke HRQoL hoog met een gemiddelde EQ visueel analoge score van 73.2 van 100. De laagste scores werden gerapporteerd bij rol-functioneren en fysiek functioneren (gemiddelde scores van 69 en 76 van 100, respectievelijk), en vermoeidheid, pijn en slapeloosheid waren de meest aangedane domeinen. Deze domeinen verslechterden in >50% van de patiënten. Daarvoor is specifieke aandacht nodig voor tijdige ondersteunende zorg, met name gericht op rol- en fysiek functioneren, om HRQoL zo lang mogelijk te behouden.

In **Hoofdstuk 7** onderzochten we hoog-intensieve zorg in de laatste levensfase van CRPC patiënten. Intensieve zorg in de laatste levensfase (EOL zorg) is gedefinieerd als overbehandeling en overmatig gebruik van ziekenhuiszorg in de laatste drie maanden voor overlijden. Dit is onwenselijk omdat het minimaal klinisch voordeel geeft met substantiële financiële kosten. Vijftien procent van 2,249 patiënten met een bekende overlijdensdatum in CAPRI begonnen nog met een nieuwe LPD in EOL en 56% werd tenminste één keer opgenomen in het ziekenhuis. In totaal kreeg 41% van de patiënten hoog intensieve zorg. Multivariabele analyses toonden dat oudere patiënten (Odds Ratio (OR) 0.98, 95% betrouwbaarheidsinterval (BI) 0.97-0.99), patiënten met een minder goede conditie (OR 0.57, 95% BI 0.33-0.97) en patiënten met een langere tijd van CRPC diagnose tot EOL (OR 0.98, 95% BI 0.97-0.98) significant minder kans op hoog intensieve zorg hadden, terwijl verwijzing naar een medisch oncoloog (OR 1.99, 95% BI 1.55-2.55), eerdere LPD behandeling (1 lijn OR 1.53, 95% BI 1.19-1.96 en >1 lijn OR 1.72, 95% BI 1.31-2.28) en opiaat gebruik (OR 1.45, 95% BI 1.08-1.95) geassocieerd waren met significant meer hoog intensieve zorg. In de laatste levensfase werden door Nederlandse artsen weinig nieuwe LPD behandelingen opgestart, maar er waren veel ziekenhuisopnames. Hoog-intensieve zorg in de laatste levensfase is onwenselijk gezien de hoge kosten en beperkte effecten op levensduur, maar meer onderzoek is noodzakelijk naar het effect op de kwaliteit van leven van patiënten en hun verzorgers.

DEEL 3

In deel 3 beschrijven we de geleerde lessen van de 'real world' data. Veel vragen over de volgorde van behandelingen worden niet beantwoord in klinische onderzoeken. In **Hoofdstuk 8** rapporteerden we de 'real world' uitkomsten (behandelduur en PSA respons) van sequentiele ART behandelingen met of zonder tussenliggende andere LPD behandelingen bij mCRPC patiënten. In totaal 273 patienten werden geincludeerd met een mediane opvolging van 8.4 maanden vanaf de tweede ART (ART2). Patienten met ART1 > ART2 waren ouder en hadden gunstiger prognostische factoren bij start van ART2 in vergelijking met patienten met ART1 > LPD > ART2. Er werden geen verschillen gevonden in de PSA respons en behandelduur tussen de groepen ART1 > ART2 en ART1 > LPD > ART2. Multivariabele analyse suggereerde dat de PSA respons op ART2 minder voorkomt bij patiënten met viscerale metastasen (OR 0.143, p=0.04) en meer voorkomt bij patiënten met een relatief langere duur van androgeen deprivatie therapie (OR 1.028, p=0.01), en als abiraterone voor enzalutamide wordt gegeven (OR 3.192, p=0.02). Concluderend is de effectiviteit van ART2 laag, met een lage PSA responskans en een korte behandelduur ongeacht eventuele tussenliggende behandeling met chemotherapie of radium-223. Dit geldt met name in patiënten met een korte tijd sinds castratie, viscerale metastasen en als enzalutamide voor abiraterone werd gegeven.

Een ander probleem in de behandeling is wanneer ondersteunende zorg zonder systemische therapie gestart moet worden, in plaats van een nieuwe lijn systemische therapie. In **Hoofdstuk 9** onderzochten we de uitkomsten van derdelijns behandeling met LPD in mCRPC patiënten, en identificeerden we variabelen die zijn geassocieerd met overleving om een prognostisch model te maken. Van 1,011 mCRPC patiënten die progressief waren na tweedelijns LPD, kregen 602 patiënten (60%) een derdelijns LPD. Patiënten die een derdelijns LPD kregen hadden een gunstiger prognostisch profiel bij start en een langere mediane overleving dan patiënten die ondersteunde zorg kregen zonder LPD (10.4 versus 2.4 maanden, p<0.001). Conditie (ECOG PS 1 en ≥2 (HR 1.51, p<0.007 en HR 3.08, p<0.001, respectievelijk), opiaatgebruik (HR 1.55, p=0.019), viscerale metastasen (HR 2.09, p<0.001), hemoglobine <7 mmol/l (HR 1.44, p<0.002), prostaat-specifiek antigeen ≥130 µg/l (HR 1.48, p=0.001), alkalisch fosfatase ≥170 U/l (HR 1.52, p<0.001) en lactaat dehydrogenase ≥250 U/l (HR 1.44, p=0.015) waren geassocieerd met kortere overleving. Mediane overleving voor laag-, laag-intermediair-, hoog-intermediair- en hoog-risico groepen waren 14, 7.7, 4.7 en 1.8 maanden, respectievelijk. Aldus ontwikkelden we een prognostisch model en we identificeerden een subgroep patiënten bij wie derdelijns LPD behandeling geen betekenisvol voordeel biedt. Onze resultaten zullen moeten worden bevestigd in prospectieve klinische onderzoeken.

In het laatste **Hoofdstuk 10** rapporteerden we een casus onderzoek waarbij we onze 'real world' data van CRPC patiënten hebben gebruikt om een predictiemodel te maken. We hadden als doel om zowel de clinicus mee te nemen in het ontwikkelen van een predictiemodel en om de clinicus de veel voorkomende tekortkomingen te laten herkennen in bestaande predictiemodellen. Risico voorspelling wordt steeds belangrijker in de medische dagelijkse praktijk. In dit artikel bespreken we verschillende stappen in het ontwikkelen van een predictiemodel waaronder missende waardes, coderen van voorspellers en selectie middels LASSO, het testen van de aannames in het model, de prestatie van het model en de validatie. Predictiemodel ontwikkeling is belangrijk en de inbreng van zowel de clinicus als de statisticus is essentieel. Dit artikel kan de kloof tussen de beide disciplines overbruggen.

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ABOUT THE AUTHOR

Hans Westgeest (1980) was born in Amstelveen, The Netherlands. He obtained his high school graduation at the Ignatius Gymnasium in Amsterdam in 1998 and started medical school at VU university in Amsterdam. After finishing his bachelor's degree *cum laude* in 1999, he obtained his master's degree in 2003 and his medical degree in 2005. He started working at the internal medicine department of Spaarne Ziekenhuis in Hoofddorp as resident not-in-training, and after nine months he started his training in internal medicine in 2006 in VU Medical Center in Amsterdam (under supervision of prof. S.A. Danner and from 2007 prof. M.H.H. Kramer). He did part of his training in Sint Lucas Andreas Ziekenhuis in Amsterdam (supervision: C.E.H. Siegert). During his training he is a board member and vice-chair of the JNIV (junior department of the Dutch Internal Medicine association). In 2010 he starts his medical oncology training at the medical oncology department in VU Medical Center in Amsterdam (supervision: prof. E. Boven). From 2011 he starts his PhD research at VU Medical Center in Amsterdam and Erasmus University in Rotterdam, on real world outcomes in castration-resistant prostate cancer. He has been involved in the CAPRI and PRO-CAPRI studies from the start (supervisors: prof. C.A. Uyl-de Groot, prof. W.R. Gerritsen and prof. A.J.M. van den Eertwegh). After finishing his training as medical oncologist in 2013, he works fulltime in his PhD research for almost two years. In 2015 he starts as medical oncologist in Amphia hospital in Breda, the Netherlands. He has been involved in the organization of oncology care in Amphia (as member and later chair of the Regieraad Oncologie) and regional in the cancer care network EMBRAZE. He is dedicated to urogenital oncology and melanoma. From 2019 he is ambassador for Stichting Fight Cancer.

Hans is married to Mieke and they have two children: Julia (2011) and Laurens (2015). They live in Breda.

CURRICULUM VITAE

Hans Westgeest werd geboren op 16 mei 1980 te Amstelveen en groeide op in Ouderkerk aan de Amstel. Na afronding van het gymnasium aan het Ignatius Gymnasium in Amsterdam in 1998 is hij gestart met de studie geneeskunde aan de Vrije Universiteit te Amsterdam. De propedeuse behaalde hij cum laude in 1999, in 2003 behaalde hij zijn doctoraal geneeskunde en in 2005 zijn arts-examen. Na negen maanden als ANIOS in het Spaarne Ziekenhuis te Hoofddorp, werd hij in 2006 aangenomen voor de opleiding interne geneeskunde aan het VU Medisch Centrum te Amsterdam (opleiders prof.dr. S.A. Danner en vanaf 2007 prof.dr. M.H.H. Kramer). Gedurende zijn opleiding is hij actief in het JNIV bestuur (junior afdeling van de Nederlandse Internisten Vereniging), onder meer als vice-voorzitter. In 2009-2010 heeft hij een deel van zijn opleiding in het Sint Lucas Andreas Ziekenhuis gevolgd (opleider dr. C.E.H. Siegert). In 2010 start hij met zijn aandachtsgebied oncologie bij de afdeling medische oncologie in het VU Medisch Centrum (opleider prof.dr. E. Boven). Vanaf 2011 start hij met promotieonderzoek naar uitkomsten in de dagelijkse praktijk bij CRPC behandeling (en is vanaf het begin betrokken bij de opzet van de CAPRI en PRO-CAPRI studies) bij de afdeling medische oncologie in het VU Medisch Centrum en het instituut for Medical Technology Assessment van de Erasmus Universiteit te Rotterdam (thans: ESHPM) (promotoren prof.dr. C.A. Uyl-de Groot, prof.dr. W.R. Gerritsen en prof.dr. A.J.M. van den Eertwegh). Hij onderbreekt hiervoor zijn opleiding voor een korte periode, en combineert nadien zijn opleiding met onderzoek. Na het afronden van zijn opleiding tot internist-oncoloog in 2013 werkt hij bijna 2 jaar voltijds aan dit promotie-onderzoek alvorens hij in 2015 start als internist-oncoloog in het Amphia ziekenhuis te Breda. Vanaf 2019 raakt hij betrokken bij de organisatie van de oncologische zorg in Amphia (als lid en later voorzitter van de regieraad oncologie) en hij is nauw betrokken bij de regionale organisatie in het oncologisch netwerk EMBRAZE. Hij ontwikkelt zich als expert op het gebied van urogenitale tumoren en melanoom. Vanaf 2019 zet hij zich in als ambassadeur voor Stichting Fight Cancer.

Hans is getrouwd met Mieke en samen hebben zij twee kinderen: Julia (2011) en Laurens (2015). Zij wonen in Breda.

LIST OF PUBLICATIONS

1. Symptomatic Skeletal Events and the Use of Bone Health Agents in a Real-World Treated Metastatic Castration Resistant Prostate Cancer Population: Results From the CAPRI-Study in the Netherlands. Kuppen MCP, **Westgeest HM**, van den Eertwegh AJM, van Moorselaar RJA, van Oort IM, Tascilar M, Mehra N, Lavalaye J, Somford DM, Aben KKH, Bergman AM, de Wit R, van den Bergh ACMF, de Groot CAU, Gerritsen WR. Clin Genitourin Cancer. 2021 Nov 2:S1558-7673(21)00200-7. doi: 10.1016/j.clgc.2021.10.008. Online ahead of print. PMID: 34848157

2. Life-prolonging treatment restrictions and outcomes in patients with cancer and COVID-19: an update from the Dutch Oncology COVID-19 Consortium. de Joode K, Tol J, Hamberg P, Cloos M, Kastelijn EA, Borgers JSW, Nuij VJAA, Klaver Y, Herder GJM, Mutsaers PGNJ, Dumoulin DW, Oomen-de Hoop E, van Diemen NGJ, Libourel EJ, Geraedts EJ, Bootsma GP, van der Leest CH, Peerdeman AL, Herbschleb KH, Visser OJ, Bloemendal HJ, van Laarhoven HWM, de Vries EGE, Hendriks LEL, Beerepoot LV, **Westgeest HM**, van den Berkmortel FWPJ, Haanen JBAG, Dingemans AC, van der Veldt AAM; DOCC investigators. Eur J Cancer. 2021 Oct 25:S0959-8049(21)01162-X. doi: 10.1016/j.ejca.2021.10.009. Online ahead of print. PMID: 34799210 Free PMC article.

3. Anti-PD-1 Efficacy in Patients with Metastatic Urothelial Cancer Associates with Intratumoral Juxtaposition of T Helper-Type 1 and CD8+ T cells. Rijnders M, Balcioglu HE, Robbrecht DGJ, Oostvogels AAM, Wijers R, Aarts MJB, Hamberg P, van Leenders GJLH, Nakauma-González JA, Voortman J, **Westgeest HM**, Boormans JL, de Wit R, Lolkema MP, van der Veldt AAM, Debets R. Clin Cancer Res. 2021 Oct 6. doi: 10.1158/1078-0432.CCR-20-3319. Online ahead of print. PMID: 34615720

4. Adjuvant treatment for melanoma in clinical practice - Trial versus reality. de Meza MM, Ismail RK, Rauwerdink D, van Not OJ, van Breeschoten J, Blokx WAM, de Boer A, van Dartel M, Hilarius DL, Ellebaek E, Bonenkamp HJ, Blank CU, Aarts MJB, van Akkooi ACJ, van den Berkmortel FWPJ, Boers-Sonderen MJ, de Groot JWB, Haanen JB, Hospers GAP, Kapiteijn EW, Piersma D, van Rijn RS, van der Veldt AAM, Vreugdenhil A, **Westgeest HM**, van den Eertwegh AJM, Suijkerbuijk KPM, Wouters MWJM. Eur J Cancer. 2021 Nov;158:234-245. doi: 10.1016/j.ejca.2021.08.044. Epub 2021 Sep 29. PMID: 34600790

5. Sex-Based Differences in Treatment with Immune Checkpoint Inhibition and Targeted Therapy for Advanced Melanoma: A Nationwide Cohort Study. van der

Kooij MK, Dekkers OM, Aarts MJB, van den Berkmortel FWPJ, Boers-Sonderen MJ, de Groot JWB, Hospers GAP, Piersma D, van Rijn RS, Suijkerbuijk KPM, **Westgeest HM**, van der Veldt AAM, Vreugdenhil G, Wilgenhof S, Wouters MWJM, Haanen JBAG, van den Eertwegh AJM, Kapiteijn E. Cancers (Basel). 2021 Sep 16;13(18):4639. doi: 10.3390/cancers13184639. PMID: 34572865 Free PMC article.

6. Survival of stage IV melanoma in Belgium and the Netherlands. Suijkerbuijk KPM, Haanen JBAG, Boers-Sonderen MJ, Hospers GAP, Blank CU, van den Berkmortel FWPJ, de Groot JWB, Piersma D, Aarts MJB, van Rijn RS, Vreugdenhil G, **Westgeest HM**, Kapiteijn E, van der Veldt AAM, van den Eertwegh AJM. J Eur Acad Dermatol Venereol. 2021 Sep 18. doi: 10.1111/jdv.17668. Online ahead of print. PMID: 34536304 No abstract available.

7. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. Choueiri TK, Tomczak P, Park SH, Venugopal B, Ferguson T, Chang YH, Hajek J, Symeonides SN, Lee JL, Sarwar N, Thiery-Vuillemin A, Gross-Goupil M, Mahave M, Haas NB, Sawrycki P, Gurney H, Chevreau C, Melichar B, Kopyltsov E, Alva A, Burke JM, Doshi G, Topart D, Oudard S, Hammers H, Kitamura H, Bedke J, Perini RF, Zhang P, Imai K, Willemann-Rogerio J, Quinn DI, Powles T; **KEYNOTE-564 Investigators.** N Engl J Med. 2021 Aug 19;385(8):683-694. doi: 10.1056/NEJMoa2106391. PMID: 34407342 Clinical Trial.

8. The effectiveness of monotherapy with PI3K/AKT/mTOR pathway inhibitors in ovarian cancer: A meta-analysis. van der Ploeg P, Uittenboogaard A, Thijs AMJ, **Westgeest HM**, Boere IA, Lambrechts S, van de Stolpe A, Bekkers RLM, Piek JMJ. Gynecol Oncol. 2021 Nov;163(2):433-444. doi: 10.1016/j.ygyno.2021.07.008. Epub 2021 Jul 10. PMID: 34253390 Review.

9. Validation of the updated renal graded prognostic assessment (GPA) for patients with renal cancer brain metastases treated with gamma knife radiosurgery. van Ruitenbeek NJ, Ho VKY, **Westgeest HM**, Beerepoot LV, Hanssens PEJ. J Neurooncol. 2021 Jul;153(3):527-536. doi: 10.1007/s11060-021-03793-9. Epub 2021 Jun 25. PMID: 34170460

10. Dutch Oncology COVID-19 consortium: Outcome of COVID-19 in patients with cancer in a nationwide cohort study. de Joode K, Dumoulin DW, Tol J, **Westgeest HM**, Beerepoot LV, van den Berkmortel FWPJ, Mutsaers PGNJ, van Diemen NGJ, Visser OJ, Oomen-de Hoop E, Bloemendal HJ, van Laarhoven HWM, Hendriks LEL, Haanen JBAG, de Vries EGE, Dingemans AC, van der Veldt AAM; DOCC Investigators.

Eur J Cancer. 2020 Dec;141:171-184. doi: 10.1016/j.ejca.2020.09.027. Epub 2020 Oct 7. PMID: 33161241 Free PMC article.

11. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, Ogawa O, Park SH, Lee JL, De Giorgi U, Bögemann M, Bamias A, Eigl BJ, Gurney H, Mukherjee SD, Fradet Y, Skoneczna I, Tsiatas M, Novikov A, Suárez C, Fay AP, Duran I, Necchi A, Wildsmith S, He P, Angra N, Gupta AK, Levin W, Bellmunt J; **DANUBE study investigators**. Lancet Oncol. 2020 Dec;21(12):1574-1588. doi: 10.1016/S1470-2045(20)30541-6. Epub 2020 Sep 21. PMID: 32971005 Clinical Trial.

12. Impact of DNA damage repair defects and aggressive variant features on response to carboplatin-based chemotherapy in metastatic castration-resistant prostate cancer. Slootbeek PHJ, Duizer ML, van der Doelen MJ, Kloots ISH, Kuppen MCP, **Westgeest HM**, Uyl-de Groot CA, Pamidimarri Naga S, Ligtenberg MJL, van Oort IM, Gerritsen WR, Schalken JA, Kroeze LI, Bloemendal HJ, Mehra N. Int J Cancer. 2021 Jan 15;148(2):385-395. doi: 10.1002/ijc.33306. Epub 2020 Oct 3. PMID: 32965028 Free PMC article.

13. [As series of success stories; the pitfall of preoperative chemotherapy in unresectable carcinoma of the colon]. Geijteman ECT, Eskens FALM, **Westgeest HM**. Ned Tijdschr Geneeskd. 2020 Jun 25;164:D4948. PMID: 32749820 Dutch.

14. Real-world outcomes of radium-223 dichloride for metastatic castration resistant prostate cancer. Kuppen MC, **Westgeest HM**, van der Doelen MJ, van den Eertwegh AJ, Coenen JL, Aben KK, van den Bergh AC, Bergman AM, den Bosch JV, Celik F, Hendriks MP, Lavalaye J, der Meer SV, Polee MB, Somford DM, van Oort IM, Uyl-de Groot CA, Gerritsen WR. Future Oncol. 2020 Jul;16(19):1371-1384. doi: 10.2217/fon-2020-0039. Epub 2020 May 29. PMID: 32469606

15. Targeted Therapy in Advanced Melanoma With Rare BRAF Mutations. Menzer C, Menzies AM, Carlino MS, Reijers I, Groen EJ, Eigentler T, de Groot JWB, van der Veldt AAM, Johnson DB, Meiss F, Schlaak M, Schilling B, **Westgeest HM**, Gutzmer R, Pföhler C, Meier F, Zimmer L, Suijkerbuijk KPM, Haalck T, Thoms KM, Herbschleb K, Leichsenring J, Menzer A, Kopp-Schneider A, Long GV, Kefford R, Enk A, Blank CU, Hassel JC. J Clin Oncol. 2019 Nov 20;37(33):3142-3151. doi: 10.1200/JCO.19.00489. Epub 2019 Oct 3. PMID: 31580757

16. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, Kramer G, Eymard JC, Bamias A, Carles J, Iacovelli R, Melichar B, Sverrisdóttir Á, Theodore C, Feyerabend S, Helissey C, Ozatilgan A, Geffriaud-Ricouard C, Castellano D; **CARD Investigators**. N Engl J Med. 2019 Dec 26;381(26):2506-2518. doi: 10.1056/NEJMoa1911206. Epub 2019 Sep 30. PMID: 31566937 Clinical Trial.

17. Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting. Aluwini SS, Mehra N, Lolkema MP, Oprea-Lager DE, Yakar D, Stoevelaar H, van der Poel H; Dutch Oligometastatic Prostate Cancer Working Group, Busstra M, de Jong IJ, de Reijke T, de Vries K, Heijmink S, Jenster G, Klaver S, Kneppers J, Lavalaye J, Leyten G, Moonen L, Nagaraj J, Noordzij W, Osanto S, Oving I, Schaake E, Scheenen T, Schoots I, Sedelaar M, Somford D, van den Berkmortel F, van der Hulle T, van der Voort van Zyp J, van Leeuwen P, van Moorselaar J, van Oort I, Vogel W, **Westgeest H**. Eur Urol Oncol. 2020 Apr;3(2):231-238. doi: 10.1016/j.euo.2019.07.010. Epub 2019 Aug 8. PMID: 31401014

18. An In-Depth Evaluation of the Validity and Logistics Surrounding the Testing of AR-V7 mRNA Expression in Circulating Tumor Cells. Sieuwerts AM, Mostert B, van der Vlugt-Daane M, Kraan J, Beaufort CM, Van M, Prager WJC, De Laere B, Beije N, Hamberg P, **Westgeest HM**, Tascilar M, Dirix LY, Onstenk W, de Wit R, Lolkema MP, Mathijssen RHJ, Martens JWM, Sleijfer S. J Mol Diagn. 2018 May;20(3):316-325. doi: 10.1016/j.jmoldx.2018.01.008. Epub 2018 Feb 21. PMID: 29474983

19. CAST: A retrospective analysis of cabazitaxel and abiraterone acetate sequential treatment in patients with metastatic castrate-resistant prostate cancer previously treated with docetaxel. Wissing MD, Coenen JL, van den Berg P, **Westgeest HM**, van den Eertwegh AJ, van Oort IM, Bos MM, Bergman AM, Hamberg P, Ten Tije AJ, Los M, Lolkema MP, de Wit R, Gelderblom H. Int J Cancer. 2015 Mar 15;136(6):E760-72. doi: 10.1002/ijc.29231. Epub 2014 Oct 3. PMID: 25242736

20. Recurrent dyspnea following a swollen leg in a 46-year-old man. Post JP, **Westgeest HM**, Blankensteijn JD, van der Meijs B, Klaassen RJL, Nossent E, Grünberg K, Buter J, Serné EH. Chest. 2013 Oct;144(4):1402-1405. doi: 10.1378/chest.13-0390. PMID: 24081354 No abstract available.

21. Successful treatment of renal cell carcinoma with sorafenib after effective but hepatotoxic sunitinib exposure. **Westgeest HM**, van Erp NP, Honeywell RJ, Hoekstra

R, Peters GJ, Verheul HM. J Clin Oncol. 2013 Feb 20;31(6):e83-6. doi: 10.1200/JCO.2012.43.6485. Epub 2012 Nov 26. PMID: 23182994 No abstract available.

22. Bone pain and extremely low bone mineral density due to severe vitamin D deficiency in celiac disease. Rabelink NM, **Westgeest HM**, Bravenboer N, Jacobs MA, Lips P. Arch Osteoporos. 2011;6(1):209-13. doi: 10.1007/s11657-011-0059-7. Epub 2011 Jun 15. PMID: 22207878 Free PMC article.

23. European School of Internal Medicine (ESIM) in Brighton: experiences and reflections. Hewitt S, Weidanz F, **Westgeest H**, Ruza I, Ciferska H, Pasquet F, Salomäki S, Olsen E. Eur J Intern Med. 2011 Jun;22(3):238-40. doi: 10.1016/j.ejim.2011.01.006. Epub 2011 Feb 22. PMID: 21570640

24. Pure naratriptan-induced ischemic colitis: a case report. **Westgeest HM**, Akol H, Schreuder TC. Turk J Gastroenterol. 2010 Mar;21(1):42-4. doi: 10.4318/tjg.2010.0047. PMID: 20533112

PhD Portfolio	Year	Workload (ECTS)
Training		
General courses		
Teach the teacher (VUMC Amsterdam)	1-11-2011	0.5
Basic course rules and organization for clinical researchers (BROK)	18-11-2013	1.5
Training in medical oncology	2010-2013	120
Specific courses		
ISPOR short courses		
Use of propensity scores in observational studies of treatment effects	8-11-2014	0.1
Discrete event simulation for economic analyses – concepts and applications	4-11-2012	0.2
Decision analytic modelling for economic evaluation (University of Glasgow)	7-10-2013	1
Developing a cochrane systematic review of interventions	21-5-2013	0.5
Presentations		
ISPOR workshop 'use of real world data'	8-11-2014	0.25
Bossche urologie avond	10-11-2016	0.1
Prostaatkanker masterclass	10-1-2017	0.1
DUOS jaarsymposium	3-12-2021	0.1
(Inter)national conferences		
ISPOR European Annual Congress		
Berlin	2012	1
Amsterdam (workshop)	2014	1
EAU Annual congress		
Copenhagen (poster)	2018	1
ESMO Annual Congress		
Stockholm	2011	1
Amsterdam	2013	1
Copenhagen	2016	1
Madrid	2017	1

Munich (poster and poster discussant)	2018	1
EMUC Annual Congress		
Barcelona (poster)	2015	1
ASCO Genitourinary symposium		
San Francisco	2016	1
San Francisco	2020	1

Teaching

Supervising bachelor's thesis (iBMG/ESHPM)

Jonathan Windster	2013	4
Jeanine Los	2015	4

Lecturing

General introduction lectures on prostate cancer for iBMG students	2013-2014	0.25