

1 Differences in trial and real world populations in the Dutch castration-resistant prostate cancer
 2 registry (CAPRI).

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15

16

17 Abstract

18

19 Background

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

23

24 Objective

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

27

28 Design, setting and participants

29 A population based sample is registered in the observational, retrospective CAPRI registry.
30 CRPC patients from 20 hospitals in the Netherlands have been included from 2010 to 2013.

31

32 Outcome measurements and statistical analysis

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

36

37 Results and limitation

38 Of the total 1,524 patients, 203 patients had been enrolled in trials at any time during a
39 median follow up period of 23 months. Patients in the trial subgroup were significantly
40 younger and had less comorbidity. Docetaxel treatment was more frequent in trial patients
41 (85% vs 40%). Despite an observed unadjusted median OS difference of 35 versus 24 months
42 between the trial and standard care subgroup, this difference was not retained after adjustment
43 for baseline differences and treatment effect.

44

45 Conclusions

46 At CRPC diagnosis, baseline characteristics of patients who are enrolled in trials notably
47 differ from patients who receive standard treatment options only. The survival difference
48 between the trial and standard care subgroup could be explained by baseline differences and
49 treatment effect. These results indicate that trial results cannot easily be translated to real
50 world practice.

51

52 Patient summary

53 We observed that patients treated in clinical trials differ from patients who are not. We
54 conclude that this may lead to differential treatment and survival. This warrants caution when
55 comparing real world outcomes to trial results.

56 Introduction

57

58 Prostate cancer is a common cause of cancer in men[1]. The incidence and mortality in the
59 Netherlands in 2010 were 104 and 25 per 100,000 (European Standardized Rate), respectively
60 [2]. Relative survival for patients with prostate cancer in the Netherlands and Europe is
61 comparable [3].

62

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

69

70 Treatment recommendations depend mainly on the presence of metastases and the presence of
71 symptoms, and include (year of introduction in the Netherlands in brackets): secondary
72 hormonal manipulations (including abiraterone (post-docetaxel 2012, chemotherapy naïve
73 2013) and enzalutamide (post-docetaxel 2013, chemotherapy naïve 2014)), chemotherapy
74 (including docetaxel (2005) and cabazitaxel (2011)), bone directed therapy (including radium-
75 223 (2014)), immune therapy (sipuleucel-T, not available in the Netherlands during the study
76 period) and treatment in clinical trials [4-7].

77

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

85

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

89

90

91 Methods

92

93 Study design and setting

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

103

104 Objective

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

107

108 Participants

109 Patients were screened for inclusion in both the urology and medical oncology departments of
110 each hospital, and were identified by the diagnosis code prostate cancer from the hospital
111 information systems based on encoded “Diagnosis Treatment Combinations”, a nationwide
112 coding and reimbursement system providing information about the type of care, diagnosis and
113 all treatment modalities. Eligible patients had to be diagnosed with prostate cancer (defined as
114 histologic confirmation of prostate cancer or as concluded by the treating doctor based on
115 elevated PSA and metastatic pattern), and had disease progression despite ADT. Disease
116 progression was defined as in the EAU CRPC definition [6], or as progression according to
117 the treating doctor. Anti-androgen therapy following progression on ADT was considered first
118 line systemic therapy for CRPC. In addition, patients had to be diagnosed with CRPC in years
119 2010, 2011 or 2012 and have more than two outpatient clinic visits. Eligible patients treated in
120 more than 1 hospital were included only once.

121

122 If a patient was enrolled in a phase 1, 2 or 3 trial during the follow up period, the patient was
123 assigned to the “trial” subgroup, otherwise the patient was assigned to the “standard care”
124 subgroup.

125

126 Follow up and data collection

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

130

131 Study size

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

133

134 Statistics

135 Descriptive statistics were used. Differences in subgroups were tested for significance by
136 either Chi-square test (categorical variables) or Mann-Whitney U (continuous variables).

137 Survival analyses were done by Kaplan-Meier methods and Cox regression analyses.

138 Differences were considered of statistical significance at a p-value of 0.05 or less.

139 For imputation of missing baseline characteristics, multiple imputation by Monte Carlo

140 Markov Chain method was used as described before [10]. For statistical analyses, IBM SPSS

141 Statistics version 22 was used.

142 Results

143

144 At the time of this analysis (March 2015), 29,565 prostate cancer patients were identified in
145 20 hospitals (11 large teaching hospitals, 5 general hospitals and 4 academic hospitals). A
146 flow diagram of the screened population, exclusion and inclusion of patients is shown in
147 Figure 1.

148

149 1,524 CRPC patients were included, diagnosed with CRPC in 2010 (30%), 2011 (37%) or
150 2012 (33%). Of all patients, 203 (13%) had been treated in at least one trial (range 1-4; 48
151 patients participated in more than 1 trial) during the course of disease (trial subgroup). The
152 remaining 87% patients had not been treated in a trial (standard care subgroup). The most
153 common trials are shown in supplementary Table S4. Life prolonging drugs have been given
154 to patients in the trial subgroup in both trials and as standard care: docetaxel 46/173 (27%) in
155 trials, cabazitaxel 69/94 (73%) in trials, abiraterone 3/114 (3%) in trials, enzalutamide 0/46
156 (0%) in trials and radium-223 4/7 (57%) in trials. Life-prolonging drugs have been given as
157 study drug in randomized placebo-controlled trials in a minority of cases (abiraterone/placebo
158 n=5, enzalutamide/placebo n=18).

159

160 The median follow up period from CRPC diagnosis was 23 months (Inter quartile range
161 (IQR) 11 to 34 months). At the time of the database cutoff, 983 deaths (65%) had occurred,
162 180 patients (12%) were lost to follow up and 361 patients (24%) were still in follow up with
163 a median follow up period of 39 months (range 26 – 62 months).

164

165 *Baseline characteristics*

166 Baseline characteristics of the patients at CRPC diagnosis, and differences between the two
167 subgroups, are shown in Table 1. Distribution of CRPC criteria are provided in supplementary
168 Table S5. The population includes 6% of patients without a histologic diagnosis of prostate
169 cancer and 4% with unknown histologic status, thus included on the basis of PSA and clinical
170 characteristics alone. Testosterone was not measured in 51% at baseline, however in 10% of
171 patients testosterone was measured later in the course of CRPC. Patients in the trial subgroup
172 were significantly younger (67 vs 76 years, $p<0.001$) and had less comorbidity (No
173 comorbidity 76% vs 54%, $p<0.001$). At CRPC diagnosis, patients in the trial subgroup had
174 higher hemoglobin (8.4 vs. 8.0 mmol/L, $p<0.001$), lower LDH (215 vs 228 U/L, $p=0.033$),
175 and better clinical performance score (ECOG ≥ 2 2% vs 7%, $p=0.015$).

176

177 *Treatment*

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

179

180 During the follow up period, 46% of all patients had been treated with docetaxel. In the trial
181 subgroup, 85% of patients were treated with docetaxel as compared to 40% of patients in the
182 standard care subgroup ($p<0.001$). In the trial subgroup, cabazitaxel (46% vs 7%, $p<0.001$),
183 abiraterone post-docetaxel (50% vs 22%, $p<0.001$), enzalutamide post-docetaxel (20% vs
184 15%, $p<0.001$), enzalutamide chemo-naïve (5% vs 1%, $p<0.001$) and radium-223 post-
185 docetaxel (3% vs 1%, $p=0.003$) were initiated more often, whereas prescription of abiraterone
186 (6% vs 8%, $p=0.419$) and radium-223 (0% vs <1%, $p=0.377$) in chemotherapy-naïve patients
187 was more equally spread.

188

189 *Survival*

190 Median overall survival (OS) of all patients was 26 months (IQR 12 – 48 months). Median
191 OS was 35 months (IQR 21 – 60 months) for the trial subgroup, as compared to 24 months

192 (IQR 12 – 48 months) for the standard care subgroup ($p < 0.001$), and is shown in Figure 2.
193 Univariate analysis of baseline variables, trial enrollment and treatment strategy were done:
194 the variables were dichotomized and patients with missing values were separately analyzed
195 (see supplementary Table S6). After multiple imputation of missing values, we performed
196 multivariate analysis of the pooled imputed data. After correction for baseline differences,
197 independent significant prognostic factors for survival were Gleason score, period on ADT,
198 hemoglobin, alkaline phosphatase (ALP), PSA and ECOG performance status (see Table 3).
199 Treatment with abiraterone, enzalutamide and radium-223 in chemotherapy-naïve patients, as
200 well as treatment with cabazitaxel, abiraterone, enzalutamide and radium-223 post-docetaxel
201 was associated with longer survival (Hazard ratio (HR) 0.53; $p < 0.0001$ and HR 0.46;
202 $p < 0.0001$, respectively). However, trial enrollment was no longer significant for OS (HR
203 0.95, $p = 0.658$).
204
205

206 Discussion

207

208 To our knowledge, this is the first registry of this size in which outcomes are registered
209 independent of the treating doctors. The design of the registry allowed the inclusion of
210 patients without histologic confirmation of prostate cancer or not meeting the CRPC
211 definition by the EAU but regarded as CRPC by the treating doctor. Therefore, the outcomes
212 in this study truly reflect daily practice.

213

214 The population includes 6% of patients without a histologic diagnosis of prostate cancer and
215 41% without measurement of testosterone during the course of disease. It is unlikely that
216 patients are enrolled in trials without histological diagnosis or without an objective CRPC
217 status, however the baseline period in our study (90 days before to 90 days after CRPC
218 diagnosis) differs from the date of trial enrollment. This explains missing or unknown data on
219 CRPC status in the trial subgroup.

220

221 We observed a median OS in the total population of 26 months, and a significant longer OS in
222 the trial subgroup compared to standard care (35 vs 24 months, $p < 0.001$). This difference may
223 at least partly be explained by confounding factors, including baseline differences or
224 differences in treatment. After correction for baseline prognostic factors and treatment effect,
225 trial participation was not associated with a significantly lower risk of death (HR 0.95,
226 $p = 0.658$).

227

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

231

232 Baseline characteristics of recent clinical trials in docetaxel-naïve populations are relatively
233 similar to this study, particularly to the trial subgroup [11-13]. The median OS in the trial
234 subgroup of 35 months compares slightly favorably to the median OS of the trial comparator
235 arms in chemotherapy-naïve CRPC trials of 21.7 to 30.2 months [11-13]. We observed
236 subsequent docetaxel therapy in the trial subgroup in 85% of patients, whereas subsequent
237 therapy with docetaxel in the comparator arms of the trials ranged from 50 to 57% [11-13]. In
238 a single-center analysis of trial participants only, chemotherapy-naïve CRPC patients (median
239 age 67 years) had a median OS of 30.6 months and subsequent docetaxel treatment was given
240 in 64% [14]. In conclusion, the baseline characteristics, systemic treatment and outcomes of
241 our trial subgroup are representative for known trial populations.

242

243 Missing values are a limitation of our study. This is inherent to the retrospective method of
244 the study. For this analysis, we have analyzed baseline differences at the moment of CRPC
245 diagnosis, not at the start of each subsequent treatment. In the baseline period, evaluation of
246 disease stage (CT-scan and bone scintigraphy) and laboratory parameters (hemoglobin, ALP,
247 LDH), as well as performance status registration, were frequently incomplete. LDH and
248 visceral disease status were missing in $>50\%$ of cases, but were included because of known
249 prognostic relevance. Missing values were less frequent at the start of subsequent treatment,
250 especially in life-prolonging drugs (data not shown), reflecting daily practice and the absence
251 of direct need of documentation of these parameters at progression on ADT. Gleason scores
252 may be missing if no histologic biopsy was taken, or if the biopsy dates from the period prior
253 to the introduction of the Gleason scoring system in 2004 [15]. However, we adapted tumor
254 grades to Gleason scores if possible (see Appendix 1). When excluding all patients with
255 missing values in prognostic factors, only 113 patients were available for multivariate

256 analysis, which consequently lacked statistical power. Imputation of missing data provides a
257 valid and reproducible solution for this problem, allowing multivariate analysis on the
258 complete study population [10].
259

260 Known predictors of survival in metastatic CRPC include disease site (visceral disease),
261 Gleason score, performance status, ALP, hemoglobin, PSA and LDH [16]. After imputation
262 of missing values, we confirmed these predictors of survival in our population (see
263 supplementary Table S7). Moreover, after correction for baseline differences, independent
264 significant prognostic factors for survival did also include period on ADT.
265

266 The treatment effect is difficult to assess in this analysis. Treatments were given sequentially
267 with differential sequences in a non-protocolled manner. Therefore we analyzed the
268 prescription of life-prolonging drugs (abiraterone, enzalutamide, radium-223, docetaxel and
269 cabazitaxel) as a proxy for treatment effect. We observed that patients in the trial subgroup
270 were treated with more treatment lines and more life-prolonging drugs. Treatment with life-
271 prolonging drugs was associated with increased survival in multivariate analysis.
272

273 Trial patients were enrolled in more than 15 different trials. A total of 264 trial treatments
274 were registered, with a substantial number of treatments in a trial with survival benefit but
275 placebo-controlled (n=28), a trial with no difference in outcome between the study arms
276 (n=96) or a trial that has no results yet (n=93). Although we did not aim to answer the
277 question if trial participation is an independent prognostic factor for survival, we hypothesize
278 that placebo treatment or treatment in trials without proven survival benefit over standard
279 treatment may have diluted a positive effect of trial treatment on survival, if present.
280

281 Based on a systematic review in 2001, it was concluded that there is weak evidence to suggest
282 that clinical trials have a positive effect on the outcome of participants, possibly through
283 enhancing quality of care, stringent patient selection criteria, and adapting aggressive
284 measures for treating patients in trials [17]. Two recent reports on patients treated with
285 docetaxel for metastatic CRPC either in a trial or outside a trial resulted in improved OS for
286 trial participants [18;19]. In our study participation in trials does not yield survival benefit
287 after adjusting for baseline characteristics and treatments received. We hypothesize that this
288 may reflect the high availability of novel treatment options and mandatory health care
289 insurance in the Netherlands. A limitation may therefore be the lack of external validity to
290 populations outside the Netherlands, especially those populations with different access to
291 healthcare.
292

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