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ARTICLE

Clinical

Impact of new systemic therapies on overall survival of patients with metastatic castration-resistant prostate cancer in a hospital-based registry

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Abstract

Background In 2004, docetaxel was shown to prolong the overall survival (OS) of patients with metastatic castration-resistance prostate cancer (mCRPC). Since 2010, five new systemic therapies have been shown to prolong OS in men with mCRPC. We sought to evaluate the aggregate impact of these newer therapies on the OS of patients with mCRPC.

Methods Two cohorts of patients diagnosed with mCRPC between 2004 and 2007, treated with drugs used in the limited treatment era only (A), and between 2010 and 2013, treated also with newer therapies (B), were identified from the Dana-Farber Cancer Institute database. The analysis endpoint was OS within 5 years after mCRPC diagnosis. Kaplan–Meier method assessed time-to-event distributions with median (95% confidence interval (CI)). A piece-wise regression model assessed the association between endpoint and treatment cohorts with estimate of hazard ratio (HR) with 95% CI within two time segments in univariate and multivariable analyses adjusting for relevant covariates.

Results Compared to cohort A ($n = 318$), cohort B ($n = 272$) patients in newer therapy era demonstrated an OS advantage (2.8 vs. 2.2 years) with a 41% decreased risk of death (HR = 0.59; 95% CI, 0.47–0.74; $P < 0.0001$), and a 3-year OS rate of 46% vs. 33%. This benefit was accentuated (median OS 2.7 vs. 2.1 years; HR = 0.46; 95% CI, 0.32–0.67; $P < 0.0001$) in patients who initially presented with de-novo metastatic disease (de-novo). On multivariable analysis, longer OS was associated with cohort B vs. A and performance status 0 vs. 1.

Conclusions Using a single-institution registry, mCRPC patients treated since 2010 had a significant survival improvement vs. those treated before 2010. Although the median survival was only modestly improved and less than predicted when simply adding each newer drug survival advantage, the cumulative benefit from the new therapies was more pronounced in longer-term survivors and de-novo patients.

Introduction

In 2018, prostate cancer is estimated to be the third most commonly diagnosed cancer (164,690 cases) and the cause of cancer death for an estimated 29,430 men in the United States [1]. Most deaths occur when the disease is metastatic castration resistant, an advanced clinical state associated with poor prognosis [2]. To date, metastatic castration-resistance prostate cancer (mCRPC) is a lethal disease and the primary aim of treatment is extending survival while maintaining quality of life. From 2004 to 2009, the treatment options for patients with mCRPC were limited to docetaxel, mitoxantrone, ketoconazole, antiandrogens, estrogens, and corticosteroids. Of these agents, only docetaxel was approved on the basis of a survival benefit, albeit marginal, shown in two randomized phase 3 trials, while the others were used with symptom palliation intent [3, 4]. Since 2010, a growing knowledge of prostate cancer biology led to an increase in therapeutic options for mCRPC with the advent of five new systemic therapies (newer therapies): the

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dendritic cell-based vaccine sipuleucel-T, the taxane-based chemotherapy cabazitaxel, the two novel hormonal agents abiraterone acetate and enzalutamide, and the bone-targeting radiopharmaceutical radium-223 dichloride. Each of these drugs was approved for mCRPC on the basis of an overall survival (OS) advantage demonstrated in large randomized clinical trials, albeit with the limitation of placebo being the comparator for radium, enzalutamide, and sipuleucel-T [5–11]. However, there are limited data in the literature concerning the aggregate impact of these new systemic approaches on the OS of patients with mCRPC and, to our knowledge, no analysis included all five newer therapies [12–15]. Given the non-curative intent, toxicity, and costs of the newer therapies, there is a need to determine whether their introduction in routine clinical care cumulatively resulted in meaningful clinical benefit in the management of mCRPC, compared with the period when these therapies were not available. Although a clear survival benefit was shown individually for each newer therapy in clinical trials, several factors including the lack of an optimal sequence of use, the potential for cross-resistance mechanisms, and the clinical unfitness of many patients to receive all five newer therapies may limit the cumulative benefit [16–19]. Therefore, we aimed to evaluate the aggregate impact of the newer therapies comparing the survival outcomes of two historical cohorts of men selected according to whether they developed mCRPC prior to or during the newer therapies era, from a single-institution database. Furthermore, we conducted a subgroup analysis to determine the clinical effects of the newer therapies on mCRPC patients who presented with poorer prognosis de-novo metastatic disease (de-novo) or developed metastatic disease after prior local therapy with curative intent (prior local therapy) [20–22].

Patients and methods

Study cohorts

Institutional review board approval was achieved prior to commencing this study. The Dana-Farber Cancer Institute prospectively collected registry of consecutively consented and enrolled patients was interrogated to select two cohorts of consecutive patients who developed radiographic evidence of mCRPC, defined per Prostate Cancer Working Group 3 criteria [23], between 2004 and 2007 (cohort A) and between 2010 and 2013 (cohort B). The cohort time frames were determined to identify patients treated with limited therapies alone in cohort A and treated also with the newer therapies in cohort B and with sufficient follow-up to limit bias. Use of limited therapies and newer therapies in each cohort was annotated. Patients who had been administered drugs approved for mCRPC when their disease was still hormone sensitive and patients of cohort A who had received any of the newer therapies as part of clinical trials were excluded. Demographic, pathologic, and clinical data such as age at baseline, race, biopsy Gleason score, time of metastatic disease presentation, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at baseline, and number and type of treatments received for mCRPC were collected from clinical records.

Statistical analyses

In light of the expected discrepancy in median follow-up between the two cohorts, the analysis endpoint OS was defined as the time from mCRPC diagnosis to death from any cause or last follow-up visit within 5 years. Two subgroups were identified by time of metastatic disease presentation (de-novo vs. prior local therapy). The distributions of OS within 5 years for the overall population and subgroups were evaluated using the Kaplan–Meier method, including median time to event and its 95% confidence interval (CI). To overcome the non-proportional hazard issue illustrated by the Kaplan–Meier curves overlapping or crossing within 1–2 years from mCRPC diagnosis and assessed using scaled Schoenfeld residuals [24], a piecewise regression model was used to estimate the hazard ratio (HR) with 95% CI within the two time periods and assess the association between OS and treatment cohorts in univariate (UVA) and multivariable (MVA) analyses after adjusting for relevant clinical covariates including baseline age, Gleason score, ECOG PS, and time of metastatic disease presentation, in the overall population as well as subsets (except for time of metastatic disease presentation). The relationship between the number of treatments received for mCRPC and cohorts was described as proportion, absolute difference, and odds ratio, with 95% CI.

For the overall analytic cohort of 590 subjects, with an OS event rate of 84% (497 of 590 patients) and 54% of patients in cohort A, there is a statistical power of 85% (two-sided type I error of 0.05) to detect a HR of 0.76 comparing the hazard of cohort B vs. cohort A.

Results

Patient characteristics

Overall, 590 patients were eligible for this analysis: 318 (54%) in cohort A and 272 (46%) in cohort B. The median age at baseline was 68 years (interquartile range (IQR), 61–74) and a majority of the patients were Caucasians (89%; 525 of 590 patients). Prior local therapy was received by 374 (63%) patients and 216 (37%) men had de-novo metastatic disease. Cohorts A and B were well balanced in

Table 1 Patient characteristics

Characteristic	All patients ($N = 590$)	Cohort A ($N = 318$)	Cohort B ($N = 272$)
Median age at baseline, years (IQR)	68 (61–74)	68 (60–74)	69 (63–74)
Race			
Caucasian	525 (89)	273 (86)	252 (93)
Others/unknown	65 (11)	45 (14)	20 (7)
Biopsy Gleason Score			
≤6	85 (14)	57 (18)	28 (10)
7	151 (26)	82 (26)	69 (25)
≥8	287 (49)	146 (46)	141 (52)
Missing	67 (11)	33 (10)	34 (13)
De-novo	216 (37)	121 (38)	95 (35)
Prior local therapy	374 (63)	197 (62)	177 (65)
ECOG PS at baseline			
0	420 (71)	246 (77)	174 (64)
≥1	57 (10)	29 (9)	28 (10)
Missing	113 (19)	43 (14)	70 (26)
Number of treatments received			
Median (IQR)	4 (2–5)	4 (3–5)	3 (2–5)
≤3	285 (48)	142 (45)	143 (53)
4–5	209 (35)	133 (42)	76 (28)
6–12	96 (16)	43 (14)	53 (19)
Type of treatments received			
Antiandrogens	216 (37)	161 (51)	55 (20)
Ketoconazole	261 (44)	213 (67)	48 (18)
Other 2nd hormone manipulations	71 (12)	68 (21)	3 (1)
Sipuleucel-T	68 (12)	0	68 (25)
Abiraterone	167 (28)	0	167 (61)
Enzalutamide	119 (20)	0	119 (44)
Radium-223	52 (9)	0	52 (19)
Docetaxel	435 (74)	270 (85)	165 (61)
Cabazitaxel	80 (14)	0	80 (29)
Mitoxantrone	93 (16)	87 (27)	6 (2)
Other chemo-/immunotherapies	211 (36)	149 (47)	62 (23)
Median follow-up, years (95% CI)	5.5 (5.2 to 6.5)	10.6 (10.2 to NA)	4.6 (4.4 to 5.1)

Data are expressed as numbers (%) except where otherwise noted

Abiraterone abiraterone acetate, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *IQR* interquartile range, *N* number, *NA* not available, *PS* performance status

terms of demographic and pathologic characteristics and most patients had a baseline ECOG PS of 0 (Table 1). In the limited treatment era (cohort A), docetaxel was the most commonly administered drug (85%; 270 of 318 patients), followed by ketoconazole (67%; 213 of 318 patients). In contrast, in the newer therapies era (cohort B), docetaxel administration declined to 61% (165 of 272 patients) and abiraterone acetate was given to an equal proportion of patients (61%, 167 of 272), while ketoconazole use was drastically reduced (18%; 48 of 272 patients). Because of the selected time frames of enrollment, the median follow-up in cohort A was more than twofold that of cohort B, 10.6 years (95% CI, 10.2 to NA years) vs. 4.6 years (95% CI, 4.4 to 5.1 years), respectively.

Efficacy

The Kaplan–Meier curves for the overall, de-novo, and prior local therapy populations start separating after 1.5, 1.2, and 1.9 years since mCRPC diagnosis, respectively (Fig. 1). For the overall population, the median OS was 2.8 years (95% CI, 2.5 to 3.1 years) in cohort B and 2.2 years (95% CI, 2 to 2.4 years) in cohort A (Table 2). Additionally, the 3-year OS rate was 46% (standard error (SE), 3.1) in cohort B vs. 33% (SE, 2.7) in cohort A. Patients in the newer treatment era had a 41% decreased risk of death (HR = 0.59; 95% CI, 0.47 to 0.74; $P < 0.0001$, post initial 1.5 years of follow-up) compared with patients treated in the limited treatment era (Table 3). Of the potential clinical factors (time of metastatic disease presentation, age, Gleason score, and ECOG PS), only ECOG PS was found to correlate with OS on UVA. The MVA, adjusting for the above-mentioned covariates in a subset of 427 patients with all covariates data available, indicated that longer OS was strongly associated with cohort B vs. cohort A beyond >1.5 years ($P < 0.0001$), and ECOG PS = 0 vs. ≥1 ($P < 0.0001$; Table 4).

The interaction test of cohorts A and B by the time of metastatic disease presentation (de-novo vs. prior local therapy) indicates a differential effect in the subsets ($P = 0.048$). In subgroup analysis, an OS benefit in favor of cohort B was maintained in both those with de-novo disease or prior local therapy metastatic disease (Table 2). The subgroup with de-novo metastatic disease showed the greater survival improvement, with a median OS of 2.7 years (95% CI, 2.2 to 3.7 years) in cohort B vs. 2.1 years (95% CI, 1.8 to 2.4 years) in cohort A. The OS advantage was less pronounced in the subgroup with prior local therapy, in which median OS was 2.8 years (95% CI, 2.3 to 3.2 years) in cohort B and 2.3 years (95% CI, 2.1 to 2.5 years) in cohort A. In the de-novo metastatic subset, patients in cohort B had a more than halved risk of death (HR = 0.46; 95% CI, 0.32 to 0.67; $P < 0.0001$, post initial 1.2 years of follow-up) compared to cohort A. Patients in cohort B who had prior local therapy also demonstrated a lower risk of death (HR = 0.61; 95% CI, 0.44 to 0.84; $P = 0.003$, post initial 1.9 years of follow-up) compared to their cohort A counterparts (Table 3). Similarly, on MVA of both the de-novo and prior local therapy subgroups, cohort B was associated with improved OS, compared to cohort A, when follow-up was

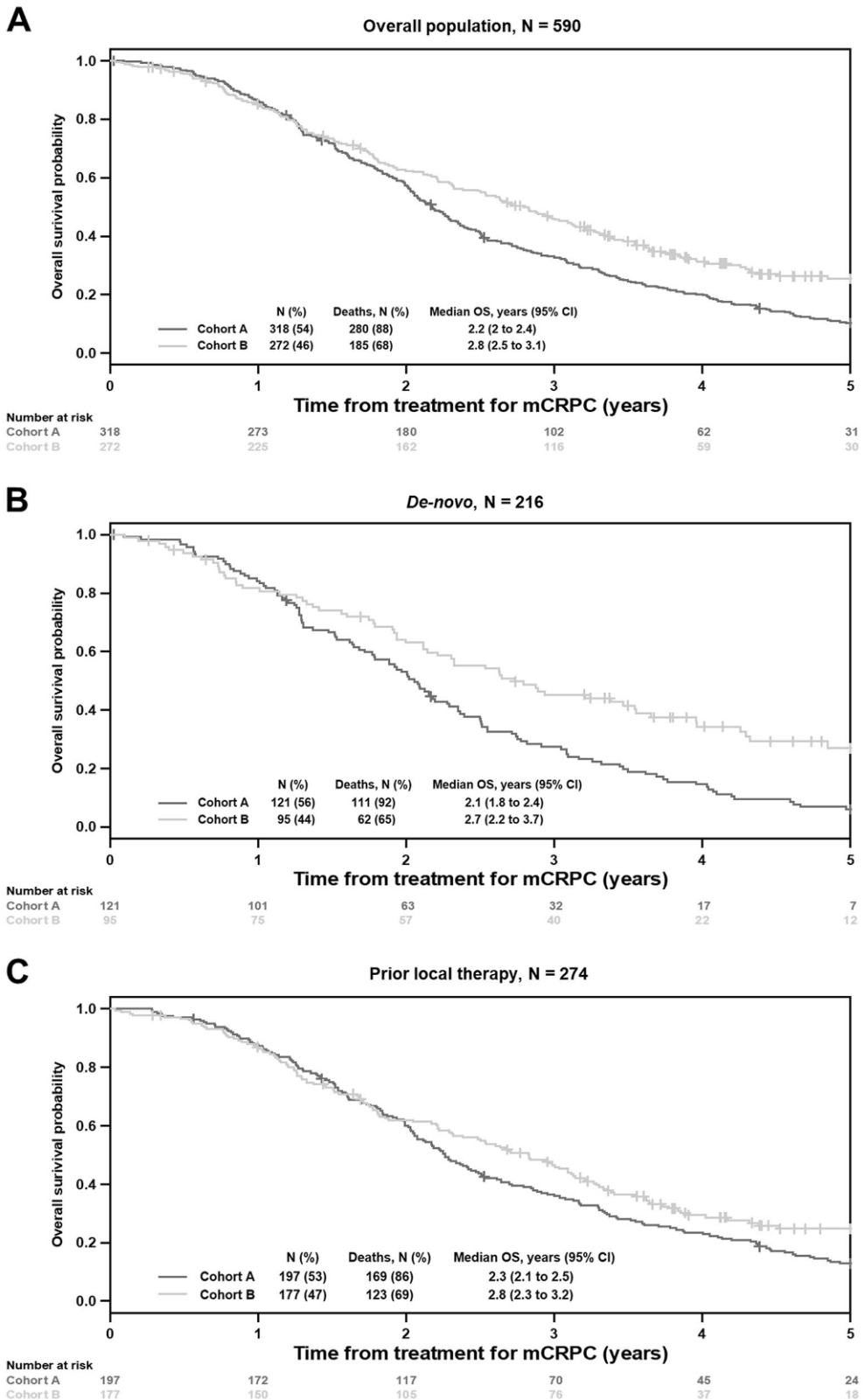

Fig. 1 Kaplan–Meier analyses of overall survival (OS) within 5 years by use of new systemic therapies for metastatic castration-resistant prostate cancer (mCRPC) in: **a** the overall population and **b** patients with de-novo and **c** prior local therapy metastatic disease presentation. CI confidence interval

Table 2 Empirical estimates of overall survival according to the era of mCRPC therapy

	Cohorts	*N* (%)	Deaths, *N* (%)	Median OS, years (95% CI)	3-Year OS, % (SE)
Overall population	A	318 (54)	280 (88)	2.2 (2 to 2.4)	33 (2.7)
	B	272 (46)	185 (68)	2.8 (2.5 to 3.1)	46 (3.1)
De-novo	A	121 (56)	111 (92)	2.1 (1.8 to 2.4)	27 (4.1)
	B	95 (44)	62 (65)	2.7 (2.2 to 3.7)	45 (5.2)
Prior local therapy	A	197 (53)	169 (86)	2.3 (2.1 to 2.5)	36 (3.5)
	B	177 (47)	123 (69)	2.8 (2.3 to 3.2)	46 (3.8)

CI confidence interval, *mCRPC* metastatic castration-resistant prostate cancer, *N* number, *OS* overall survival, *SE* standard error

Table 3 Univariate analysis piece-wise regression model of overall survival according to the era of mCRPC therapy

	HR (95% CI)	*P*
Overall population ($N = 590$)		
FU >1.5 years: cohort B vs. cohort A (ref)	0.59 (0.47 to 0.74)	<0.0001
FU ≤1.5 years: cohort B vs. cohort A (ref)	0.95 (0.7 to 1.3)	0.76
De-novo ($N = 216$)		
FU >1.2 years: cohort B vs. cohort A (ref)	0.46 (0.32 to 0.67)	<0.0001
FU ≤1.2 years: cohort B vs. cohort A (ref)	0.94 (0.52 to 1.68)	0.83
Prior local therapy ($N = 374$)		
FU >1.9 years: cohort B vs. cohort A (ref)	0.61 (0.44 to 0.84)	0.003
FU ≤1.9 years: cohort B vs. cohort A (ref)	1.05 (0.75 to 1.47)	0.76

The interaction test of cohorts A and B by the time of metastatic disease presentation (de-novo vs. prior local therapy) indicates a statistically significant difference ($P = 0.048$).

CI confidence interval, *FU* median follow-up, *HR* hazard ratio, *mCRPC* metastatic castration-resistant prostate cancer, *N* number, *ref* reference

greater than 1.2 ($P < 0.0001$) and 1.9 years ($P = 0.001$), respectively (Table 4).

Number of treatments

The median number of treatments received was 4 (IQR, 2–5) for all patients, 4 (IQR, 3–5) for cohort A, and 3 (IQR, 2–5) for cohort B. In the overall population, a higher proportion of patients in cohort B vs. cohort A received at least 5 treatments for mCRPC (33.5% vs. 30.8%, respectively; absolute difference = 2.6%; Supplementary material). A greater difference was observed in the de-novo subgroup, where 42.1% (95% CI, 32.2% to 52.0%) of patients in cohort B received ≥5 treatments for mCRPC vs. 29.8% (95% CI, 21.6% to 37.9%) in cohort A. In contrast, in cohort B among those who received prior local therapy, the proportion of patients receiving 5 or more therapies was lower than in cohort A (28.8% vs. 31.5%). As previously specified, these differences were only numerical.

Discussion

In this study, we reported the OS of nearly 600 men with mCRPC according to whether they were treated during or prior to the newer therapies era, using a single-institution dataset. Compared to when only the limited therapies were available, treatment in the newer therapies era was associated with a significant survival gain of 7.2 months (0.6 years; $P < 0.0001$). Of note, the OS advantage of the newer therapies in clinical trials ranged from 2.4 months with cabazitaxel vs. mitoxantrone to 4.8 months with enzalutamide vs. placebo, for patients progressing on docetaxel [6–9], and more than half of the patients (53%) in the newer therapies era cohort received only 3 treatments or less. Interestingly, nearly half of patients in cohort B lived for at least 3 years after mCRPC diagnosis compared to one-third of patients in cohort A (46% vs. 33%), which indicates that the newer therapies were even more beneficial for a specific subset of patients.

In the subgroup analysis, an OS improvement in favor of cohort B was confirmed irrespective of the time of metastatic disease presentation. However, while the OS advantage of men with de-novo metastatic disease was the same as observed in the overall population (7.2 months), that of patients with prior local therapy was slightly smaller (6 months). Notably, the therapies used in the limited treatment era showed the least efficacy on the de-novo metastatic subgroup (2.1 years) and the greatest efficacy on the prior local therapy subgroup (median OS = 2.3 years), and hence the impact of the newer therapies was more limited here (median OS = 6 months) than in the de-novo subgroup or the overall population (median OS = 7.2 months). Additionally, while the 3-year OS proportion of either subgroup in cohort B was nearly the same as documented in the overall population (46%), the rates of patients in cohort A who survived at least 3 years were lower in the de-novo subgroup (27%) and higher in the prior local therapy subgroup (36%), respectively, compared to the overall population (33%; Table 2). It could be postulated that de-novo metastatic disease identifies a more aggressive phenotype of prostate cancer that is less sensitive to the therapies used in the limited treatment era and benefits more from the use of the newer therapies, whereas prior local therapy metastatic disease is the phenotypic manifestation of a more indolent disease which responds better to the traditional therapies. This hypothesis could be

Table 4 Multivariate analysis in subsets with all covariates data available

	HR (95% CI)	*P*
Overall population ($N = 427$)		
FU >1.5 years: cohort B vs. cohort A (ref)	0.49 (0.37 to 0.65)	<0.0001
FU ≤1.5 years: cohort B vs. cohort A (ref)	1 (0.69 to 1.46)	0.99
Age (years)	1 (0.99 to 1.01)	0.63
Gleason score 7 vs. ≤6 (ref)	0.86 (0.61 to 1.2)	0.37
Gleason score ≥8 vs. ≤6 (ref)	1.33 (0.97 to 1.83)	0.08
De-novo vs. Prior local therapy (ref)	1 (0.79 to 1.26)	1
ECOG PS ≥1 vs. 0 (ref)	2.26 (1.63 to 3.12)	<0.0001
De-novo ($N = 143$)		
FU >1.2 years: cohort B vs. cohort A (ref)	0.32 (0.19 to 0.52)	<0.0001
FU ≤1.2 years: cohort B vs. cohort A (ref)	0.69 (0.31 to 1.55)	0.37
Age (years)	0.99 (0.98 to 1.01)	0.45
Gleason score 7 vs. ≤6 (ref)	0.84 (0.38 to 1.9)	0.68
Gleason score ≥8 vs. ≤6 (ref)	1.59 (0.77 to 3.32)	0.21
ECOG PS ≥1 vs. 0 (ref)	2.42 (1.35 to 4.34)	0.003
Prior local therapy ($N = 284$)		
FU >1.9 years: cohort B vs. cohort A (ref)	0.53 (0.36 to 0.78)	0.001
FU ≤1.9 years: cohort B vs. cohort A (ref)	1.14 (0.77 to 1.69)	0.52
Age (years)	1.01 (0.99 to 1.02)	0.29
Gleason score 7 vs. ≤6 (ref)	0.86 (0.59 to 1.24)	0.41
Gleason score≥8 vs. ≤6 (ref)	1.28 (0.89 to 1.83)	0.18
ECOG PS ≥1 vs. 0 (ref)	2.44 (1.64 to 3.63)	<0.0001

CI confidence interval, *ECOG* Eastern Cooperative Oncology Group, *FU* median follow-up, *HR* hazard ratio, *N* number, *PS* performance status, *ref* reference

partly confirmed by the observation that the rate of patients treated with at least 5 therapies in the newer therapies era was the highest in the de-novo subset (42.1%) and the lowest in the prior local therapy subset (28.8%); vice versa, the proportion of men receiving 5 or more drugs when the newer therapies were not available was the lowest in the de-novo subgroup (29.8%) and the highest in the prior local therapy subgroup (31.5%; Supplementary material). Furthermore, in the overall population, treatment of mCRPC in the newer therapies vs. pre-newer therapies era is strongly associated with longer OS after a follow-up of 1.5 years, both on UVA and MVA ($P < 0.0001$). This association is confirmed as statistically significant and at an earlier follow-up (1.2 years) for the *de-novo* subgroup and at a later follow-up (1.9 years) for the prior local therapy subgroup. Among the limitations of this analysis are its retrospective design and the inherent difference in median follow-up between the two cohorts (10.6 vs. 4.6 years). However, the choice of an OS truncated at 5 years as endpoint of this study allowed for comparable times to observe death events. Furthermore, these data represent a single academic medical center and may not necessarily reflect the outcomes of the patients treated in community centers.

To our knowledge, this is the first analysis to provide data on the aggregate clinical effect of all five newer therapies for patients with mCRPC. In recent years, two small retrospective studies also documented robust OS benefits ($P < 0.0001$) for patients with mCRPC treated with the newer therapies. However, both reports evaluated only three agents—cabazitaxel, abiraterone acetate, and enzalutamide—and the setting was post docetaxel, per inclusion criteria [12, 13]. In addition, a small contemporary study reported a conspicuous survival gain (16.4 months; $P < 0.0001$) for patients treated with the newer therapies vs. those used in the limited treatment era. However, no patient received sipuleucel-T in this analysis and men who received less than two treatments for mCRPC were excluded per protocol [14]. The above-mentioned differences in study design limit comparisons with our analysis and may explain the discordant results attained in these reports. It is worth noting that an OS advantage (6 months; $P < 0.0001$) similar to that observed in our de-novo subset was shown in a contemporary Surveillance Epidemiology and End Results (SEER) dataset-based analysis of de-novo metastatic castration-sensitive prostate cancer patients diagnosed within 2004–2008 vs. 2009–2014 [15].

Conclusions

The five new systemic agents approved for mCRPC since 2010 produced in aggregate a median survival advantage of approximately 7 months for patients with mCRPC, in a hospital-based registry. A more substantial benefit was observed in 3-year survivors and patients who presented with de-novo metastatic disease compared to men who had prior local therapy. In this regard, future prospective clinical studies should evaluate the role of time of metastatic disease presentation as a potential clinical feature impacting the efficacy of the newer therapies for patients with mCRPC.

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Author contributions Conception and design: EF, KPG, and CJS; collection and assembly of data: EF, GKS, CPE, AAH, and CEP; data analysis and interpretation: EF, KPG, PWK, M-ET, and CJS; manuscript writing: all authors; final approval of the manuscript: all authors; accountable for all aspects of the work: all authors.

Compliance with ethical standards

Conflict of interest EF has been sponsored for travel, accommodations, and expenses by Janssen-Cilag. AAH has participated in advisory boards for Roche and received compensation. PWK has consulted or participated in advisory boards for Astellas, Bayer, Genentech, Janssen-Cilag, Merck, Sanofi, Dendreon, Medivation/Astellas, and Pfizer and received compensation; he also received grants or funding from Bayer, Dendreon, Genentech/Roche, and Medivation/Astellas, and has been sponsored for travel, accommodations, expenses by Sanofi. M-ET has consulted or participated in advisory boards for Janssen-Cilag and Medivation and received compensation: she also received grants or funding by Janssen-Cilag and Medivation, Travel, and has been sponsored for travel, accommodations, expenses by Sanofi. CJS has consulted or participated in advisory boards for Astellas, Bayer, Genentech, Janssen-Cilag, Pfizer, and Sanofi, and received compensation: he also received grants or funding by Astellas, Janssen-Cilag, Sotio, and Sanofi. KPG, GKS, CPE, and CEP declare that they have no conflict of interest.

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