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ORIGINAL RESEARCH

Real-World Treatment Patterns and Overall Survival (OS) of Patients with Metastatic Castration-Resistant Prostate Cancer in Italy

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Purpose: This real-world analysis described the characteristics and therapeutic management of patients with metastatic castration-resistant prostate cancer (mCRPC) in Italy before and after 2015, when androgen receptor signalling inhibitors (ARPI) entered clinical practice.

Patients and Methods: An observational retrospective analysis was conducted using administrative healthcare databases from a pool of Italian Local Health Units, covering ~6.2 million residents. Adult men with ≥1 prescription of androgen deprivation therapy (ADT) from January 2011 to June 2022 were identified. mCRPC was proxied by treatment patterns—addition of docetaxel/cabazitaxel or ARPI to ADT—and confirmed by hospital discharge for metastasis. Patients were stratified according to their inclusion (date of the last inclusion criterion met): pre-2015 (2011–2014) and post-2015 (2015–2020).

Results: Among 1890 mCRPC patients identified, 551 (29%) received ≥2 treatment lines. Chemotherapy (CHT) was the predominant first-line (1L) therapy in both cohorts [97.2% vs 82.9%], followed by ARPI [2.8% vs 17.1%]. In a 2020 sensitivity analysis (n=406), 1L therapy was ARPI in 76% and CHT in 24%. Among pre- and post-2015 patients, 29.4% and 31.6% received second-line (2L) therapy, mostly ARPI. Median OS from ADT initiation was 46.4 months (pre-2015) and 53.9 months (post-2015). In post-2015 patients, median OS from mCRPC index-date—reflecting the proxy-based diagnosis—was 14.2 months.

Conclusion: In Italian clinical practice, CHT remains the most common 1L therapy though ARPI use has increased since 2015. While OS from ADT initiation has improved, survival from mCRPC diagnosis—based on proxies in administrative data—remains poor, underscoring an unmet clinical need. Differences in OS estimates depending on the starting point (ADT initiation vs mCRPC diagnosis) should be considered when interpreting results.

Keywords: chemotherapy, new hormone therapy, oncological drugs, real-world evidence, therapeutic sequences

Introduction

Prostate cancer (PC) is the most common neoplasm in the male population in 112 countries,[1] occurring in around one-third of men during their lifetime.[2,3] It has been estimated that the number of new PC annual cases diagnosed globally will rise from 1,4 million in 2020 to 2,9 million by 2040.[1,4]

According to the latest available estimates of the AIOM-AIRTUM (Italian Association of Medical Oncology and Italian Association of Tumor Registries), 41,100 new case of PC were reported in Italy during 2023, accounting for PC for 19.8% of all male cancers.[5]

While prostate-specific antigen (PSA)–based screening can reduce PC mortality, results from large randomized trials remain conflicting.[6–9] Concerns about biopsy-related complications, false positives, and overdiagnosis have limited its widespread adoption.[10–12]

Even though early-stage localized PC can be successfully managed by local curative treatments like radical prostatectomy or external radiotherapy,[13–15] an estimated 10% to 50% of cases progress to metastatic disease.[16] The

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initial phase, when metastatic PC is still responsive to androgen deprivation therapy (ADT), referred to as hormone-sensitive prostate cancer (mHSPC), evolves to metastatic castration-resistant prostate cancer (mCRPC) in the majority of patients within 2–3 years, resulting in poorer prognosis and a median survival of 13.2 months.[16–19]

Since 2004, docetaxel-based chemotherapy (CHT) has represented the standard of care as frontline therapy of mCRPC.[20,21] Over the last decade, the portfolio of treatment options for mCRPC has broadened thanks to the introduction of new innovative agents with different mechanisms of action, such as novel chemotherapies, radiopharmaceuticals and androgen receptor signalling inhibitors (ARPI),[3,22–26] including abiraterone (an androgen synthesis inhibitor) and enzalutamide (an androgen receptor antagonist), approved by the European Medicines Agency (EMA) in 2011 and 2013, respectively.[27–29] These drugs were originally recommended as second-line (2L) treatments, but later they have been progressively introduced earlier in the event of failure of conventional ADT.[2,30] European guidelines now recommend ARPI in combination with ADT or chemotherapy in selected mHSPC and mCRPC patients, reflecting evolving treatment paradigms.[30]

In Italy, abiraterone and enzalutamide received indications in March 2013[31] and November 2014,[32] respectively, for 2L treatment of adult men with mCRPC whose disease had progressed on or after docetaxel-based CHT. Later, in September 2014[33] and April 2016,[34] abiraterone and enzalutamide were approved for reimbursement as first-line (1L) treatments of mCRPC in adult men who are asymptomatic or mildly symptomatic after failing ADT, and for whom CHT is not yet clinically indicated.

Considering the clinical heterogeneity of the disease and the possible cross-resistance between the drugs currently available for mCRPC, it is of important to understand how treatment patterns have evolved following the introduction of ARPIs. While some RWE studies have explored these trends internationally, evidence from large Italian populations is still limited. Analyses using administrative healthcare data can provide a valuable overview of real-world management, offering insights that may inform both clinical decisions and healthcare planning.

Thus, this real-world analysis conducted in Italy was undertaken to describe the therapeutic management and survival in patients with mCRPC, before and after 2015, which represents the year of spread of ARPI in the routine clinical Italian practice.

Materials and Methods

Study Design and Data Source

An observational retrospective analysis was conducted on the administrative databases of a pool of Italian healthcare entities (Local Health Units, LHUs), covering nearly 6.2 million health-assisted residents. Administrative databases are large data warehouses of healthcare resources reimbursed by the NHS. For the analysis purposes, data were extracted from the following databases: beneficiaries' database, for patients' demographic data; pharmaceuticals database, for information on drug prescriptions, including the anatomical therapeutic code (ATC), prescription date, and number of packages; hospitalization database, for data related to hospital admissions, like the date of hospitalization, main and secondary diagnosis identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and Diagnosis Related Group (DRG); outpatient specialist service (OSS) database for information on specialist visits, diagnostic tests and laboratory determinations with type and date of provision.

All the results of the analyses were produced and presented as aggregated summaries. The dataset used consists solely of anonymized data. Approval has been obtained from the ethics committees of the involved LHUs, as follows: authorization of the Ethics Committee "Comitato Etico per le province di L'Aquila e Teramo" (protocol number 11, approval date 24/03/2021); authorization of the Ethics Committee "BAT (Barletta-Andria-Trani) Comitato etico inter-provinciale Area I" (protocol number 68/CE/20, approval date 3/12/2020); authorization of the Ethics Committee "Frosinone Comitato Etico Lazio 2" (protocol number 0179046/2020, approval date 28/10/2020); authorization of the Ethics Committee "Genova Comitato Etico Regionale Liguria" (protocol number 0179046/2020, approval date 14/06/2021); authorization of the Ethics Committee "Napoli 3 Comitato Etico Interaziendale Campania Sud" (protocol number 51, approval date 02/09/2020); authorization of the Ethics Committee of Roma 3 "Comitato Etico Lazio 2" (protocol number 0031200/2021, approval date 10/02/2021); authorization of the Ethics Committee "Roma 4 Comitato Etico Lazio 1" (protocol number 1079/CE Lazio 1, approval date 23/09/2020); authorization of the Ethics Committee "Roma 6

Comitato Etico Lazio 2" (protocol number 0216084/2020, approval date 16/12/2020); authorization of the Ethics Committee "Taranto Comitato Indipendente di Etica Medica" (protocol number 48144, approval date 28/05/2021); authorization of the Ethics Committee "Vercelli Comitato Etico Interaziendale A.O. SS. Antonio e Biagio e Cesare Arrigo – Alessandria" (protocol number 0008668, approva-l date 20/04/2021).

Study Population and Study Design

Between January 2011 and June 2022, PC patients were firstly identified by the presence of at least one prescription of ADT, using the ATC codes (Table S1 of the Supplementary materials) as a proxy for diagnosis. Among them, mCRPC patients were then selected through: (i) treatment with ADT plus chemotherapy (CHT), including docetaxel and cabazitaxel or ARPI, and (ii) at least one hospital discharge diagnosis for metastatic disease. In order to evaluate CHT, we considered both prescriptions of antineoplastic agents and procedure or diagnosis codes (Table S1 of the supplementary materials). Patients with no continuous data availability during the study period (eg those who moved to another healthcare institution or to another region), patients aged <18 years, and female subjects were excluded from the analysis. The codes used to identify therapies and metastasis hospitalization diagnoses in the databases are provided in Table S1 of the Supplementary materials. This combined approach, previously adopted in Italian and European real-world studies,[17–19] offers high specificity for advanced prostate cancer in the absence of biochemical progression data. Sensitivity in similar claims datasets has been reported at 75–90%, depending on coding completeness for metastases and systemic treatments. Potential misclassification may occur, particularly for patients managed exclusively in the outpatient setting without hospital-coded metastases. Variability in coding practices and treatment indications may also influence case identification and baseline characteristics.

The index-date was that of the last match of an inclusion criterion. The patients were investigated for at least 12 months before the index-date (characterization period) and followed-up for all the period of available data after the index-date (follow-up period).

Patients were identified between January 2011 and June 2022 to define the mCRPC population and describe its characteristics. However, to ensure sufficient follow-up for clinical outcomes (at least 12 months), only those with a diagnosis up to December 2020 were included in the subsequent analysis.

Based on their index-date, patients were then stratified into pre-2015 (included from January 2011 up to December 2014) cohort and post-2015 (included from January 2015 up to December 2020) cohort. Baseline characteristics (age and age class distribution) were assessed at index-date. To have an overall evaluation of baseline clinical status, a modified version of the Charlson Comorbidity Index (CCI) not accounting for the score of cancer was used.[35]

Metastatic sites were investigated during the characterization period (at least 12 months preceding the index-date) and during follow-up. Treatment patterns, lines (L) of therapy, treatment sequences, and overall survival (OS) were described during follow-up. Survival analysis was performed using Kaplan-Meier curves. OS was defined as time (in months) from index-date to the date of death for any cause. For alive patients, OS was censored at the date of database availability. Because hospital discharge diagnosis for metastasis represents an inclusion criterion, there may have been a delay in identifying mCRPC patients (index-date delaying effect), a factor to be considered in the analysis of baseline characteristics, treatment patterns, and outcomes assessed during follow-up. A sensitivity analysis of therapeutic patterns was carried out in mCRPC patients treated with ARPI (abiraterone or enzalutamide) during 2020: these patients, based on Italian Medicines Agency (AIFA) reimbursement criteria valid during 2020, were defined as mCRPC. Among them, those starting with ARPI in 2020 and those with CHT preceding ARPI (by considering 12 months before ARPI start) were identified.

Statistical Analysis

All the statistical analyses are descriptive. Continuous variables are given as mean ± standard deviation (SD), and categorical variables as numbers and percentages. Overall survival was investigated using Kaplan-Meier curves. According to the "Opinion 05/2014 on Anonymization Techniques" drafted by the European Commission Article 29 Working Party, the analyses involving less than ≤3 patients were not reported, as potentially traceable to single individuals. All analyses have been conducted using STATA SE version 17.0.

Results

From a catchment area of 6,162,507 residents, of whom 2,499,981 adult males, 42,512 (1.7% of males) patients with PC were selected through ADT prescriptions between January 2011 and June 2022. Among them, 1890 patients with mCRPC were identified as those treated with either CHT or ARPI plus ADT, along with a hospitalization discharge diagnosis for metastasis. To investigate the impact of ARPI on clinical practice, a further analysis was conducted on mCRPC patients diagnosed between 2011 and 2014 (pre-2015, n=428) and those diagnosed between 2015 and 2020 (post-2015, n=1207), totalling 1635 out of the initial 1890 identified. The average age at inclusion was 73.6 years (71.9 years for patients included before 2015 and 73.9 years for those included after 2015), with nearly 68% of patients aged between 60 and 79 years (Table 1A). The patients included before 2015 showed a slightly worse average CCI than those included after 2015 (0.6 and 0.5, respectively), and were more represented in the cluster with CCI above 1 (12.6% and 8.9%, respectively) (Table 1B).

Given that all the patients identified with mCRPC had at least one hospital discharge related to metastatic disease, the sites of metastases were traced according to their specific hospital discharge diagnosis codes (Table S1 of the Supplementary materials). Considering both characterization and follow-up periods, 73% of overall patients were hospitalized for bone metastasis, 42.5% for lymph node metastasis and 34% for visceral metastasis (Table 1C).

Figure 1 represents the analysis of the number of treatment lines received by the 1890 patients with mCRPC identified between January 2011 and June 2022: 551 (29%) were treated with ≥2 lines (L) of therapy after the diagnosis of mCRPC, and 9.7% received ≥3L therapy).

In the 1890 mCRPC patients, treatment sequences were then analyzed using Sankey plots (Figure 2A). The main 1L treatment class was CHT found in 85.4% of the patients (1615 out of 1890), followed by ARPI given to 14.6% (275 out of 1890). Of the 1615 patients who received CHT in 1L, 430 (27%) progressed to 2L, while among 275 patients who received ARPI in 1L, 121 (44%) moved to 2L. The mean duration of therapy was 9.1 months (median 3.4 months) for CHT and 6.4 months (median 2.4 months) for ARPI. Among 551 patients who started a 2L treatment, 67% (369/551) received ARPI, 31% (171/551) received CHT, and 2% (11/551) radium-223. In 2L, the mean duration of therapy was 12.2 months (median: 8 months) for ARPI and 7 months (median 3.8 months) for CHT. Among 184 patients who started a 3L treatment, 66.3% (122/184) received ARPI, 29.4% (54/184) received CHT and 4.3% (8/184) radium-223. In 3L, the

Table 1 Baseline Characteristics (A), Charlson Index (B) and Metastatic Sites (C) of the Overall mCRPC Population Included Between January 2011 and June 2022 and in Patients Stratified by Inclusion Period: 2011–2014 (Pre-2015) and 2015–2020 (Post-2015)

	Total mCRPC (n=1890)	mCRPC Pre-2015 (n=428)	mCRPC Post-2015 (N=1207)
A. Demographic variables			
Age (years) at index-date, mean ± SD	73.6 ± 8.4	71.9 ± 8.3	73.9 ± 8.2
<60 years, n (%)	111 (5.9%)	29 (6.8%)	65 (5.4%)
60–69 years, n (%)	461 (24.4%)	128 (29.9%)	284 (23.5%)
70–79 years, n (%)	817 (43.2%)	190 (44.4%)	530 (43.9%)
80–89 years, n (%)	467 (24.7%)	77 (18.0%)	304 (25.2%)
≥ 90 years, n (%)	34 (1.8%)	4 (0.9%)	24 (2.0%)
B. Charlson index, mean ± SD	0.5 ± 0.7	0.6 ± 0.8	0.5 ± 0.7
Charlson index = 0, n (%)	1144 (60.5%)	232 (54.2%)	750 (62.1%)
Charlson index = 1, n (%)	566 (29.9%)	142 (33.2%)	350 (29.0%)
Charlson index ≥ 1, n (%)	180 (9.5%)	54 (12.6%)	107 (8.9%)
C. Metastatic sites			
Bone (%)	73.0%	78.3%	73.7%
Lymph nodes (%)	42.5%	43.5%	42.6%
Respiratory and digestive systems (%)	34.0%	35.0%	34.7%

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; SD, standard deviation.

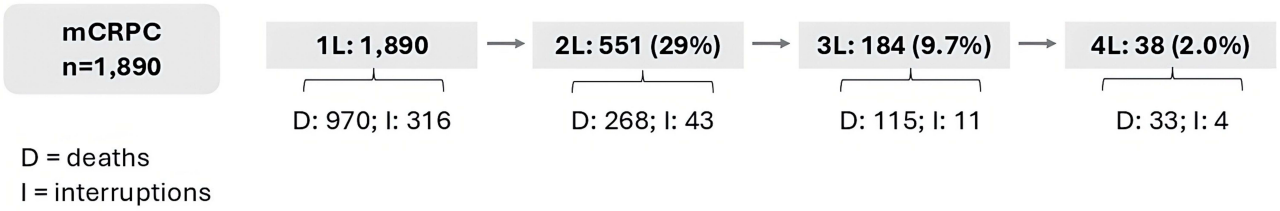
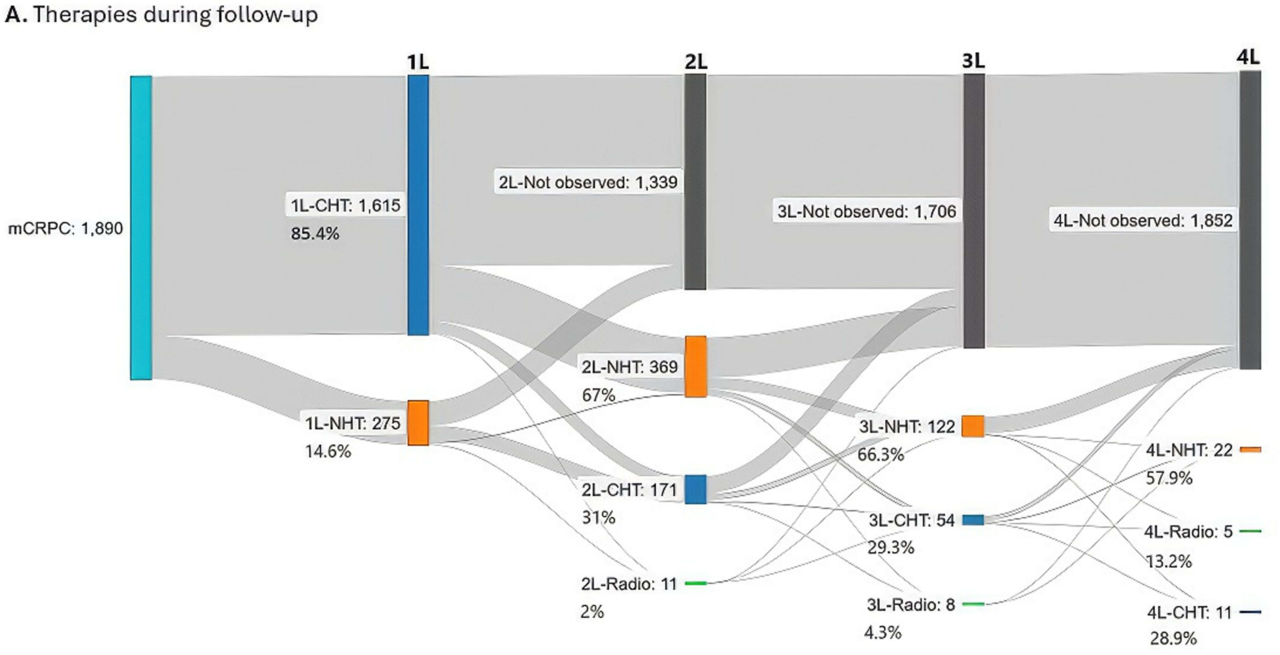


Figure 1 Treatment lines during follow-up in total patients with mCRPC.



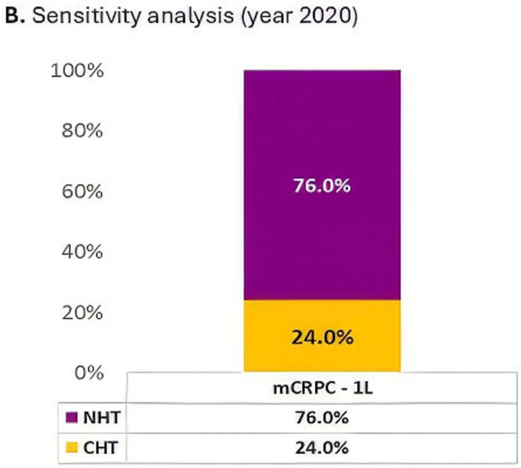


Figure 2 (**A**) Treatment patterns and lines of therapy during follow-up in patients with mCRPC included from January 2011 to June 2022); (**B**) sensitivity analysis focused on year 2020.

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mean duration of therapy was 7.3 months (median: 4.6 months) for ARPI and 6.6 months (median 4.8 months) for CHT. Lastly, 38 patients received a 4L treatment; with a mean duration of therapy of 7.3 months (median: 3.3 months) for ARPI and 4.5 months (median 2.5 months) for CHT. The short median durations observed for both chemotherapy and ARPI in 1L and subsequent lines largely reflect high rates of early therapy discontinuation, mainly due to mortality or clinical deterioration, rather than primary drug inefficacy.

To represent a more recent treatment scenario and to evaluate the possible delaying effect of index-date, a sensitivity analysis was conducted on patients mCRPC treated with ARPI during 2020. Total 406 patients were included in the sensitivity analysis. Considering the 12-month period before the start of ARPI during 2020, 76% of patients started 1L of treatment with ARPI and 24% with CHT (Figure 2B).

In mCRPC patients stratified by index-date (2011–2014 and 2015–2020), the median overall survival (mOS) from the start of ADT was 46.4 months in those included before 2015 and 53.9 months in those included after 2015, respectively (Figure 3A). Among patients included in the survival analysis, about one-fifth were censored due to loss to follow-up or end of data availability before the study cut-off. Considering only the patients included after 2015, the mOS from date-index was 14.2 months (Figure 3B).

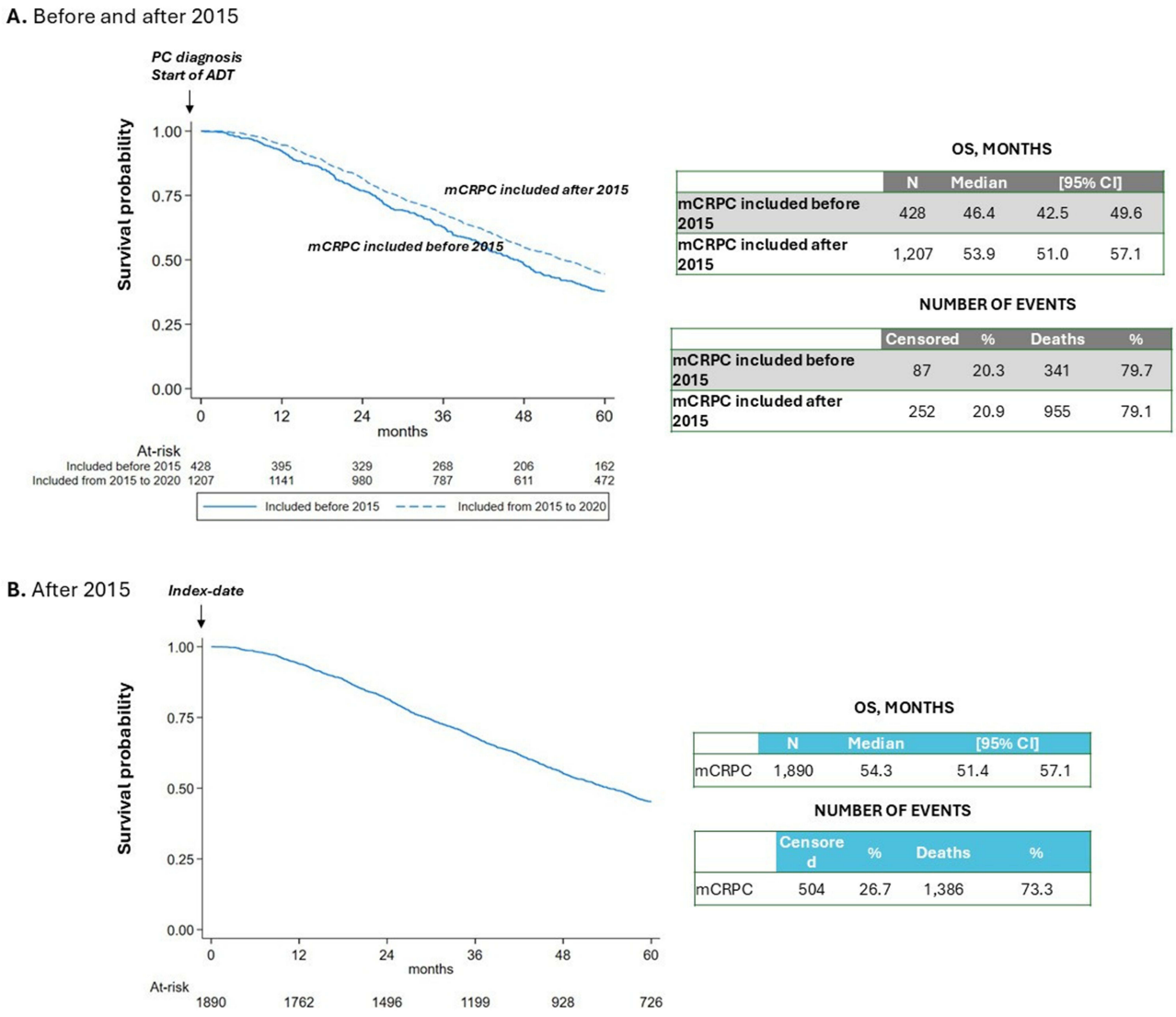

Figure 3 Analysis of treatment patterns during follow-up in patients with mCRPC: (**A**) included before 2015; (**B**) included after 2015.

Discussion

The present analysis, conducted in a setting of Italian clinical practice, provided real-world data on the main characteristics, treatment schedules and overall survival of patients with mCRPC. The study design was based on a stratification of patients according to the time of inclusion to have an overview of the repercussions occurred after 2015 with the widespread utilization of ARPI in the standard clinical practice in Italy.

Here, we identified 1.7% of males with a diagnosis of PC proxied by the presence of ADT prescriptions, a proportion slightly higher compared with previously published data by Spandonaro et al, who reported a total number of 450,000 PC cases in Italy during year 2018 (about 1.5% of the Italian male population).[36] This difference could be explained by the study design adopted in the current analysis, as our population was selected using ADT therapy as proxy of diagnosis.

Although a large percentage of newly diagnosed PC men have a localized or locally advanced disease with a generally favourable prognosis, there is still a minor portion of patients who develop the metastatic form, and after an initial response to ADT, they inexorably progress to mCRPC with worse outcomes and increased mortality.[22]

Here, we focused on patients with mCRPC, identified in the administrative databases from January 2011 to June 2022 through the presence of treatment with CHT or ARPI (plus ADT) and hospitalization discharge diagnosis for metastasis. The analysis of the therapeutic journey of these patients confirmed the clinical complexity and the challenging management of this tumor form. Among the 1890 patients with mCRPC, only 29% initially treated in 1L with CHT or ARPI, could progress to a 2L or further, because of the elevated rates of deaths or interruptions. When analysing the type of 1L therapy received, we noticed that CHT was the most common choice as entry therapy for metastatic disease, in front of 14.6% of patients who received ARPI. However, among those receiving CHT in 1L, only 27% progressed to 2L, while those treated with ARPI in 1L, 44% could move to a 2L therapy.

Successively, to further elucidate the effects of the spread of ARPI in the clinical practice, a comparative analysis was conducted between 428 mCRPC patients included before 2015, and 1207 after 2015 (up to 2020). In general, the baseline characteristics of patients in the two groups were similar, the patients included after 2015 were tendentially older and more represented among the age classes above 80 years. This might partly explain the unexpectedly shorter duration of 1L therapy with ARPI (median: 2.4 months) compared to CHT (3.4 months), considering that around 7 of 10 patients died or interrupted the therapy without progressing to 2L. These aspects, not directly measurable in administrative datasets, may have contributed to early discontinuations. However, there might also have been a treatment selection bias, where older and/or more comorbid patients, potentially deemed unfit for chemotherapy, were preferentially initiated on ARPI in 1L. Indeed, in the post-2015 cohort, patients were older on average (73.9 vs 71.9 years) and had a slightly higher proportion with CCI ≥1 compared with the pre-2015 cohort, supporting this interpretation. Moreover, there was a larger proportion of patients with bone metastases in patients included before 2015, which remain the most common type of metastasis in this neoplasm and are associated with the worse outcome and prognosis.[37]

Among patients included before 2015, from the index-date, 97.2% started CHT as 1L therapy, while in 2L, 83.3% of patients were in ARPI and 17% in CHT. On the other hand, among patients included after 2015, 83% of cases had CHT as 1L and 17% ARPI; in 2L, 62% of patients were in ARPI and 35% in CHT. This trend reflects the progressive shift of attitude in using ARPI earlier in patients' therapeutic pathways.[2,18,22,30] Recent data from for a single oncological center in the Czech Republic of patients described a substantial survival benefit from 1L treatment with abiraterone or enzalutamide in mCRPC patients. The study reported a favourable prognostic effect on both PFS and OS mCRPC patients, more marked in younger subjects (<74 years) and those with early reduction of PSA ≥50% within 3 months from therapy initiation.[30]

In our analysis, the inclusion criteria (the addition of ARPI or CHT to ADT treatment and the presence of a hospital admission related to metastatic disease) used to proxy mCRPC diagnosis might have delayed the index-date. To overcome the problem and to depict a more recent scenario of mCRPC therapeutic management, a sensitivity analysis was performed on mCRPC patients who started ARPI during 2020. The analysis showed that for 76% of these patients, the ARPI treatment represented the 1L of treatment, as reported in a recent RWE analysis based on physician-reported data stating that 42% of mCRPC patients were in 1L with abiraterone, 28% with enzalutamide, 24% with docetaxel and 5% with cabazitaxel.[17]

As mentioned, our findings indicate also that, despite the progressive shift toward the use of ARPI as 1L therapy for mCRPC patients, the duration of ARPI 1L therapy was unexpectedly shorter with respect to CHT 1L therapy, but also to ARPI 2L therapy, suggesting a patient selection bias toward less fit patients for the use of ARPI in 1L rather than a true real-world difference in efficacy. Consistently, a literature review on RWE of abiraterone or enzalutamide in 1L treatment of mCRPC patients recently showed highly heterogenous outcomes in terms of effectiveness, safety, economic and/or health-related quality of life across the selected studies, together with a moderate-to-high risk of bias.[18] Despite this possible bias, altogether these results highlight an unmet medical need and significant room for improvement in the treatment of mCRPC. Consistently with our data on the very high rate of patients' loss (due to death or interruptions) from 1L to 2L, RWE outcomes in 1L for mCRPC remain poor despite treatment, emphasizing how the "best choice" of 1L therapy might have the most significant impact on individual patient's prognosis.

In the present analysis, the median OS calculated starting from the first ADT prescription was 46.4 and 53.9 months in patients included before and after 2015, respectively. The increase of OS observed may reflects a general improvement of PC patient's management, considering that this type of analysis includes patients initially diagnosed with a non-metastatic disease and then progressed, or those with a hormone-sensitive metastatic disease. Such observation seems to be also substantiated by the general evaluation of patients' clinical complexity through the CCI: the patients included before 2015 showed a slightly worse CCI compared to those included after 2015 (0.6 and 0.5, respectively) and had more commonly a CCI $\geq$1. Focusing only on patients included after 2015 who received a 1L of therapy for metastatic disease, the median OS from the index-date (which corresponded to either ADT prescription or metastatic diagnosis) was 14.2 months. While this value is low as compared to OS data of clinical trials with ARPIs,[38] it reflects reported data of patients with metastatic castration-resistant prostate receiving only chemotherapy.[38] Moreover, in our population there might be an underestimation of OS due to index-date delaying effect, due to the use of hospital discharge diagnosis for metastasis as an inclusion criterion.

Indeed, most of the patients were treated with a CHT-only regimen considering that 85% of them received it in 1L and that only 29% of patients received a 2L therapy. Although it is conceivable that OS data would improve including more recent patients, these findings corroborate the view that the prognosis in patients with mCRPC is still unsatisfying. Recent RWE data from the US MEDICARE population reported a median survival from mCRPC diagnosis of 25.6 months, highlighting a still significant undertreatment for this cancer type, either for therapies beyond ARPI or for the sequential ARPI.[39] Indeed, despite the growing availability of next-generation hormonal agents, abiraterone, enzalutamide and other therapies for the treatment of mCRPC [eg, radium-223, sipuleucel-T (Sip-T) immunooncology, cabazitaxel],[23,40,41] treatment response is mostly short-term, and tumor resistance ultimately develops,[42,43] pointing to the need of new therapeutic approaches with a different mechanisms of action.[44] Among them, promising results are coming from the recently approved polyadenosine diphosphate–ribose polymerase inhibitors (PARPi), including olaparib and rucaparib, alone or in combination with ARPIs, in either the entire mCRPC population or in carriers of gene alterations involved in homologous recombination repair[45–49] and other therapeutic agents including the radiotherapeutic 177-lutetium-prostate-specific membrane antigen (PSMA)-617 targeting PSMA-expressing prostate cancer.[50,51]

The main strength of this analysis lies in the large sample size generated from the real clinical practice of a sample corresponding to about 10% of the Italian population. This approach, based on data from unselected study populations, can facilitate the generalisability of the results. On the other hand, there are some limitations to be acknowledged. First, there might be incompleteness or limited accuracy in some information that is not traceable in databases, like the severity of comorbidities, clinical variables, reasons beyond therapy discontinuation and other potential confounding factors. Moreover, PC patients were identified by the presence of ADT prescriptions as a proxy of diagnosis, so the actual epidemiological burden of the disease might have been underestimated, as patients managed with active surveillance, watchful waiting or surgery were missed. Specifically, a key limitation of this study is the methodology used to identify mCRPC patients, which relied on administrative databases without access to clinical variables typically used in clinical practice to define mCRPC. As a result, the identification process and, in particular, the "index date" may be less precise compared with definitions based on clinical records. Furthermore, the requirement for a hospital admission for metastatic disease could have introduced selection bias, potentially excluding patients managed entirely in the outpatient setting, as well as those whose metastatic disease was miscoded or under-

reported. These factors may have led to an underestimation of the number of eligible patients and could affect the generalisability of the findings. In addition, our definition of mCRPC was based on treatment proxies and administrative data, without histologic confirmation or PSA progression information, which limits the precision of disease classification. We also lacked access to important clinical covariates such as ECOG performance status, Gleason score, and other prognostic biomarkers, which precluded adjustment for potential confounders. Finally, no multivariate survival analysis or subgroup comparisons by specific ARPI agents were performed, which limits the ability to draw conclusions on differential treatment effects.

Conclusion

This real-world analysis conducted in Italy on mCRPC patients confirmed that CHT is still the most common 1L therapy, although after 2015 and in more recent years, an increasing trend in the use of ARPI, also as entry therapy, has been observed. The most common therapeutic sequence was CHT in 1L, followed by ARPI in 2L, but other treatment sequences have also been found. Our findings, corroborated by literature data, revealed that a significant proportion of patients do not reach 2L therapy, confirming that mCRPC outcomes in 1L are still poor. These results highlight the importance of selecting the most appropriate and effective treatment for 1L—particularly in fit patients who may derive greater benefit from early use of potent agents. Despite the improving trend of mOS after 2015, mOS from mCRPC diagnosis is still suboptimal, highlighting an unmet clinical need and the requirement of alternative therapeutic approaches possibly targeting different tumor pathways. These insights may support clinicians and policymakers in optimizing treatment strategies, resource allocation, and guideline updates to improve patient outcomes in mCRPC. Future research combining administrative data with clinical registries or electronic health records would allow more granular analyses, enabling better adjustment for patient and disease characteristics and supporting the development of more tailored treatment strategies.

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Disclosure

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