Original Article

Lost opportunities: the underutilization of castrate-resistant prostate cancer treatment in real-world settings

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Background: Various treatment regimens are now available for metastatic castrate-resistant prostate cancer (CRPC). This work evaluates the real-world prescription patterns of CRPC in a large tertiary care center and the factors influencing them.

Methods: Health records of 330 patients with *de novo* metastatic hormone-sensitive prostate cancer (HSPC), treated and progressed to CRPC between 2016 and 2020, were reviewed from a prospective uro-oncological database. We studied their demographics, medical co-morbidities, treatment utilization patterns before and after progression to CRPC, and survival outcomes.

Results: The median age was 74 years [interquartile range (IQR), 67–80 years] at diagnosis of CRPC. At CRPC, beyond androgen deprivation therapy (ADT) monotherapy, 70.3% (n=232) of patients received at least one additional line, 21.5% (n=71) received two lines, and 5.5% (n=18) received three lines of systemic treatments. As first-line treatment, novel hormonal agents (NHAs) were the most prescribed at 57.6% (n=190). The likelihood of receiving treatment was associated with age <65 years [odds ratio (OR) 2.08, P=0.01, 95% confidence interval (CI): 1.22–3.57] and lower Charlson Comorbidity Index (CCI) score (OR: 2.62, P=0.04, 95% CI: 1.07–6.45), treatment intensification for HSPC (OR 2.45, P=0.04, 95% CI: 1.07–5.62) and primary physician being an oncologist (OR 1.59, P=0.04, 95% CI: 1.04–2.48). Patients who received additional treatment lines at CRPC had longer survival (median: 23 *vs.* 17 months, OR 1.72, P<0.01, 95% CI: 1.23–2.38).

Conclusions: More than one in four patients do not receive any additional treatment line beyond ADT monotherapy and have worse survival outcomes. Health status, prescribing physician, and treatment at HSPC appear to affect prescription patterns at the CRPC stage.

Keywords: Metastatic prostate cancer; prostate cancer; real-world prescription patterns; prescription patterns; treatment underutilization

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Introduction

Prostate cancer is the second most common malignancy in men and the fourth most common globally (1). In recent years, an increased incidence of the metastatic form of the disease has been observed in the United States (US), partly due to the controversy in prostate-specific antigen (PSA) testing (2). Traditionally, metastatic prostate cancer (mPCa) is treated with androgen deprivation therapy (ADT), but in the past decade, there has been a rapidly emerging role of complementary adjuncts (3-5). Unfortunately, almost without exception, these patients eventually develop castrate-resistant prostate cancer (CRPC) (6,7), the terminal stage of the disease. The treatment landscape for CRPC has evolved significantly since the turn of the century. Because of the inherent castration resistance, various additional treatment lines have been encouraged. These comprise novel agents targeting the androgen receptor axis (abiraterone, apalutamide, and enzalutamide) (8-10); other chemotherapeutic agents like docetaxel and cabazitaxel (11,12); radiopharmaceuticals like lutetium-177 (13,14) and radium-223 (15); immunotherapy like sipuleucel-T (16); and poly(ADP-ribose) polymerase inhibitors (PARPi), which were introduced into clinical practice more recently (16-20).

However, patients at this terminal stage often have concurrent morbidities, which may affect treatment choices (21). Formal clinical trials are susceptible to selection biases (22) and may consequently tend to recruit fitter participants. Such results may not always apply to actual population demographics with this terminal illness. Real-world findings may be more pertinent in such conditions but remain underreported (23,24). Recent evidence suggests that many CRPC patients do not receive the approved therapies (23,24). In this work, we study the real-world prescription patterns and survival outcomes for patients with CRPC treated at a high-volume tertiary care center. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-130/rc).

Highlight box

Key findings

- Approximately 70.3% of patients with castrate-resistant prostate cancer (CRPC) received at least one additional line of therapy beyond androgen deprivation therapy, with novel hormonal agents being the most commonly prescribed.
- Younger patients and those with fewer comorbidities were more likely to receive additional treatment lines.
- Patients who received at least one additional line of treatment for CRPC had improved cancer-specific survival outcomes.

What is known and what is new?

- Many patients in real-world settings do not receive approved therapies for CRPC, despite proven survival benefits.
- This study provides new real-world data on prescription patterns and survival outcomes for CRPC patients from a large tertiary care center in Asia, which has been underreported in existing literature.
- This study also identifies factors such as patient age, and comorbidities that influence the likelihood of receiving additional treatment lines for CRPC.

What is the implication, and what should change now?

- This study highlights the low adoption rates of CRPC treatment in an Asian center and identifies some of the factors influencing that.
- Multidisciplinary management of CRPC patients may allow for a more wholesome assessment of their health status and tailoring their treatment regime accordingly, which may consequently increase adoption rates.

Methods

Data source

This retrospective observational cohort study uses real-world data from a prospectively maintained database in a tertiary academic medical institution. Ethics approval was obtained from the institutional ethics board of SingHealth Duke-NUS Academic Medical Center (CIRB Ref 2009/1053/D), and the study was conducted according to the principles of the Helsinki Declaration (as revised in 2013) and Good Clinical Practice Guidelines. Informed consent was taken from all the patients. We included men diagnosed with *de novo* metastatic HSPC who had progressed to CRPC between January 2016 and December 2020. Participants were followed up every three months by either a medical oncologist, a urologist subspecialised in oncology (uro-oncologist), or a urologist not subspecialized in oncology (general urologist). Patients who received any form of local therapy to the prostate and patients who were part of clinical trials were excluded from the study. Progression to CRPC was defined according to the European Association of Urology guidelines (25). Data extraction was divided into three categories: patient characteristics (age and baseline health status), disease characteristics (Gleason score, PSA, burden of initial metastatic disease as defined by the CHAARTED criteria (4), time to CRPC, overall survival); and treatment characteristics [treating physician, treatment at hormone-sensitive prostate cancer (HSPC), type and number of therapy lines prescribed at CRPC].

Prescription patterns and survival data

We examined how life-prolonging therapies were used for CRPC. We defined a first 'additional line' as the use of a treatment agent for at least three consecutive months, alongside ADT, after progression to CRPC. If a change of agent occurred due to biochemical or radiological disease progression after using it for at least 3 months, it was classified as a second or third line. The approved additional lines of therapy for CRPC were divided into novel hormonal agents [NHAs; abiraterone, apalutamide, and enzalutamide (8-10)], chemotherapy (docetaxel and cabazitaxel) (11,12), and others such as PARP-inhibitors; prostate-specific membrane antigen (PSMA)-targeted therapy [lutetium-177 (14,25)] and radium-223 (15,16). While these patients typically receive care from a multidisciplinary team of doctors, the primary physician refers to the healthcare provider who prescribes treatment, monitors treatment response, adverse events, and overall survival on a regular basis. Cancer-specific survival (CSS) was defined as the time from CRPC diagnosis to death from prostate cancer, censoring deaths from other causes. Participants who survived until the end of the study were censored. The time of censoring was noted at their most recent contact in the database, which could include a clinic visit, hospital discharge, or remote medication order.

Statistical analysis

We used standard descriptive statistics to summarise the data. Categorical variables were summarized as frequencies (n) and proportions (%), and continuous variables were summarized as median and interquartile range (IQR). Binomial logistic regression models were used to identify factors associated with the use of additional treatment lines. Proportional hazard models were used to compare survival outcomes across treatment groups. Listwise deletion was used to handle missing data. Statistical significance was determined at a P value of <0.05. R software version 4.2.1 was used to compute statistical analyses and generate graphic illustrations (26).

Results

Patient and disease characteristics

A total of 585 patients with *de novo* metastatic HSPC were identified; 330 progressed to CRPC during the follow-up period and were included in the study. Among the participants, 216 (65.5%) had high-volume disease at the initial HSPC stage; 106 (32%) had local urinary complications from the disease, and 70 (21%) had systemic complications (*Table 1*). All 330 patients had received ADT at the HSPC stage, and 88 (26.7%) had received additional treatment intensification. The median time of progression to CRPC was 18 months (IQR, 11–28 months). The median age at CRPC progression was 76 years old, with a majority having an age-adjusted Charlson Comorbidity Index (CCI) score of 0–2 (n=284, 85.9%).

Prescription patterns

At the HSPC stage, 214 (36.6%) of the 585 eligible received treatment intensification. Among the 330 participants who eventually progressed to CRPC, 88 (26.7%) had received HSPC treatment intensification. At the CRPC stage, as shown in *Figure 1*, 232 (70.3%) participants received at least one additional line: the majority received NHA (n=190; 57.6%), fewer received chemotherapy (n=30; 9.1%), and a small number (n=5, 1.5%) received other forms of treatment.

Seventy-one patients received a second line of treatment: 39 (11.8%) received NHA, 20 (6.1%) received chemotherapy, and 12 (3.6%) received other forms of treatment.

Eighteen participants received a third line of treatment: 9 (50%) received chemotherapy, 3 (16.7%) received NHA, and 6 (33.3%) received other forms of treatment.

The proportion of patients receiving additional treatment lines yearly remained relatively consistent throughout the study period.

It is noteworthy that many patients received NHA after disease progression despite prior treatment with a different type of NHA. Among the 71 patients initially treated with NHA as the first-line agent for CRPC, 27 (14%) had previously undergone treatment intensification with a different type of NHA during the HSPC stage. Similarly, among the 39 patients treated with NHA as a second-line therapy for CRPC, 16 (41%) had previously received a different type of NHA as their first-line treatment.

Associated factors

Factors affecting the prescription patterns were evaluated (*Table 2*). On multivariate analysis, patients aged 65 years or less (OR 2.08, P=0.01, 95% CI: 1.22–3.57) with fewer comorbidities (CCI 0–2) (OR 2.62, P=0.04, 95% CI:

Table 1 Cohort characteristics

Characteristics	Did not receive additional CRPC treatment	Received additional CRPC treatment
Age (years)	76 [68–82]	73 [67–79]
Age-adjusted CCI		
0	23 (23.7)	74 (76.3)
1	15 (30.6)	34 (69.4)
2	8 (36.4)	14 (63.6)
3 or more	13 (54.2)	11 (45.8)
ECOG at diagnosis		
0–1	26 (20.8)	99 (79.2)
2 or more	16 (32.0)	34 (68.0)
Missing	56 (36.1)	99 (63.9)
PSA at diagnosis (ng/mL)	210 [56–547]	152 [47–837]
Gleason sum		
7	11 (42.3)	15 (57.7)
8	10 (20.0)	40 (80.0)
9	28 (25.9)	80 (74.1)
10	15 (37.5)	25 (62.5)
Missing	33 (31.4)	72 (68.6)
Presence of bone metastasis		
Yes	51 (25.5)	149 (74.5)
No	47 (36.2)	83 (63.8)
Presence of visceral metastasis		
Yes	20 (41.7)	28 (58.3)
No	56 (26.4)	156 (73.6)
Missing	22 (31.4)	48 (68.6)
High disease volume*		
Yes	63 (29.2)	153 (70.8)
No	35 (30.7)	79 (69.3)
Local complications		
Yes	32 (30.2)	74 (69.8)
No	66 (29.5)	158 (70.5)
Distal complications		
Yes	21 (30.0)	49 (70.0)
No	77 (29.6)	183 (70.4)
Treating physician		
Non-oncologist urologist	38 (65.5)	20 (34.5)
Urological oncologist	14 (19.2)	59 (80.8)
Medical oncologist	47 (23.6)	152 (76.4)
Received HSPC intensification		
Yes	18 (20.5)	70 (79.5)
No	80 (33.1)	162 (66.9)

Data are presented as N (%) or median [IQR]. *, high disease volume defined according to CHAARTED criteria. CRPC, castrate-resistant prostate cancer; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; HSPC, hormone-sensitive prostate cancer; N, number of patients; IQR, interquartile range.

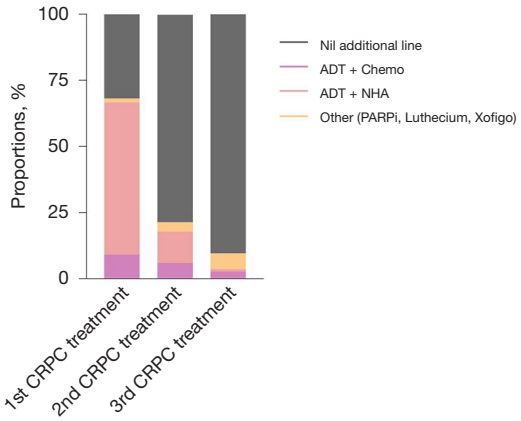

Figure 1 Proportions of patients who received additional treatment after CRPC progression. Only 70.3% of patients received an additional line of treatment after progressing to CRPC, 21.5%, received two lines, and 5.5% received a third line. ADT, androgen deprivation therapy; NHA, novel hormonal agent; PARPi, poly(ADP-ribose) polymerase inhibitors; CRPC, castrate-resistant prostate cancer.

1.07–6.45) were more likely to receive additional treatment lines. Physician-related factors also played a role: treatment intensification at HSPC (OR 2.45, P=0.04, 95% CI: 1.07–5.62) and primary physicians being oncologists (OR 1.59, P=0.04, 95% CI: 1.04–2.48) demonstrated a greater likelihood of receiving additional treatment lines. Disease characteristics were not shown to affect the prescribing decisions.

Survival outcomes

The median follow-up time after progression to CRPC was 20 months, during which 165 (50%) had died. Patients who received at least one additional treatment line at CRPC had better survival outcomes, with improved median CSS of 17 *vs.* 23 months (OR 1.72, P<0.01, 95% CI: 1.23–2.38). The Kaplan-Meier curve is depicted in *Figure 2*.

Discussion

In this study, we report the prescription patterns of CRPC patients in a large tertiary academic institution. To our knowledge, this is the first such study in an Asian demographic. We found that most (70%) patients receive at least one additional treatment line beyond ADT for CRPC. The decision to prescribe additional treatment lines appears to be more influenced by patient health and functional status, as well as physician-related factors like specialty and previous prescriptions, rather than by disease-specific factors. Prescription of additional lines was associated with better survival outcomes.

Despite the proven oncological benefits of prescribing additional treatment lines beyond ADT monotherapy, adoption rates in real-world settings remain low. In a recent study in the US, George *et al.* reported that close to a quarter of their cohort did not receive such therapy (27). Similarly, in a recent real-world survey, Wen *et al.* reported that just over half of the patients were prescribed additional lines of treatment for CRPC (23). Our findings confirmed similar tendencies in a large Asian tertiary care center.

The complexity of CRPC treatment partly contributes to this variability in practice patterns. With multiple therapies available and no consensus on a straightforward algorithmic approach, treatment decisions can vary widely (16). Given the rapidly evolving array of treatment options, physicians may struggle to stay current with the latest therapies. Therefore, these patients are best managed by a specialized medical team that is well-versed and continuously updated. Our study illustrated this, with a mix of general urologists and oncologists as primary physicians. Additional lines of treatment were prescribed to 34.5% of patients treated by general urologists, compared to 76.4% and 80.8% of those managed by medical oncologists and urological oncologists, respectively. This pattern was also seen at the HSPC stage, where oncology specialists are more likely to prescribe treatment intensification (28).

In this cohort, younger age and fewer comorbidities predicted a higher likelihood of receiving an additional treatment line for CRPC. This is expected, as many CRPC therapies are associated with significant toxicity, potentially diminishing quality of life or exacerbating comorbid conditions, thereby limiting their use (21). This fact may also explain the discrepancy observed in prescription patterns between different specialists. The vast majority of prostate cancers are initially diagnosed and managed by urologists, who are not necessarily subspecialized in oncology. As the first point of contact, urologists may decide not to refer patients they deem unsuitable for further treatment lines. Along with age and comorbidities, such decisions are likely guided by the clinical impression of the patient's overall health and functional status. This may be measured with specialized tools like the Eastern Cooperative Oncology Group (ECOG) performance scores (29), Clinical Frailty Score (30), and the G8

Table 2 Factors associated with prescription patterns

Factors affecting treatment patterns	Received additional line (n)	Nil additional line (n)	Univariate P value	Multivariate P value	OR (95% CI)
Age (years)					
≤65	50	19	<0.01*	0.01*	2.08 (1.22–3.57)
>65	79	189			
CCI score					
0–2	207	77	0.02*	0.04*	2.62 (1.07–6.45)
>2	25	21			Ref
Disease volume[#]					
High	153	63	0.8	0.58	
Low	79	35			
Visceral metastasis					
Yes	28	20	0.04*	0.60	
No	156	56			
Complications (local and systemic combined)					
Yes	98	42	0.9	0.15	
No	134	56			
Time to CRPC					
≤12 months	69	31	0.79	0.78	
>12 months	163	67			
Intensification at HSPC					
Yes	70	18	0.03*	0.04*	2.45 (1.07–5.62)
No	162	80			Ref
Prescribing physician					
General urologist	20	20			Ref
Urological or medical oncologist	206	46	<0.01*	0.04*	1.59 (1.04–2.48)

[#], according to CHAARTED criteria; *, a statistically significant correlation. OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; CRPC, castrate-resistant prostate cancer; HSPC, hormone-sensitive prostate cancer.

Geriatric Screening tool (31). We could not detect a statistically significant correlation with the ECOG scores at diagnosis. Clinical frailty score and G8 data were regrettably not available.

The proportion of eligible patients who received intensification at the HSPC stage at our center was 36.6%, which is low but congruent with adoption rates of HSPC treatment intensification in other regions (32,33). Interestingly, our study finds that patients who receive treatment intensification at the HSPC stage are more likely to receive additional therapy lines upon progressing to CRPC. This may be because patients with more health issues and poorer functional status—who are less 'fit' for additional CRPC treatments—were likely not good candidates for treatment intensification at the HSPC stage either.

We reported relatively high rates of treatment crossover from one type of NHA to another after disease progression, 14.2% at progression to CRPC and 41% at progression to second-line therapy due to biochemical or radiological progression. Despite multiple reports documenting an increased risk of resistance to NHA in such circumstances

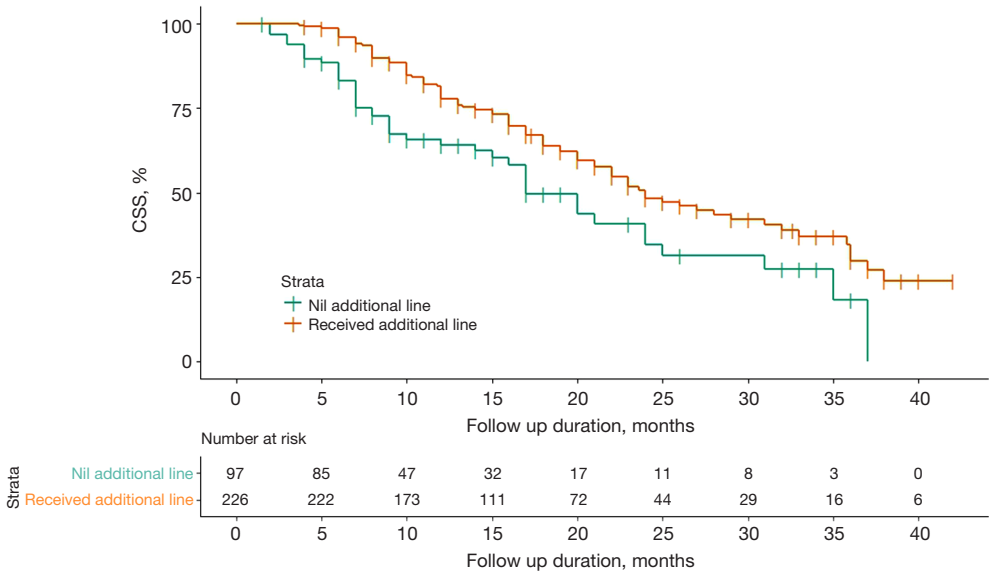

Figure 2 Survival after CRPC progression. Patients who received additional lines of treatment had significantly longer CSS. CSS, cancer-specific survival; CRPC, castrate-resistant prostate cancer.

(29,30), this practice remains curiously prevalent and was reported by contemporary real-world studies in other parts of the world (23,24).

None of the traditional disease-specific characteristics (PSA, Gleason score, disease volume, site of metastasis) were significantly associated with the likelihood of receiving additional treatment lines for CRPC. This may be because progression to CRPC inherently indicates aggressive disease with a poor prognosis, regardless of disease burden. Unlike in HSPC, many trials assessing CRPC therapies do not stratify patients based on disease burden (14,19,34,35). In current practice, where chemotherapy and NHA have been brought forward to the HSPC stage, patients are even more likely to have a different, refractory biology. A newer biomarker, the androgen receptor splice variant AR-V7, has demonstrated the ability to predict NHA resistance (36). Patients with this variant, which can be tested from prostatic tissue or on circulating tumor cells in peripheral blood vessels, have been proven to have better survival outcomes when treated with chemotherapy (37,38). Unfortunately, this assay is not routinely available in our center and was not used in this cohort.

This study has some limitations. The duration of each treatment line was not captured. While we obtained pertinent findings by analyzing treatment sequences, further studies delving into these patterns in more detail may uncover additional valuable insight. The study could access data on quality of life and the use of palliative care services. For further work, more robust health status assessments such as the ECOG, G8, and the clinical frailty scores obtained at various points throughout the illness trajectory would be crucial, as they often impact clinical decisions and could explain real-world prescription pattern variations.

Conclusions

These findings highlight a phenomenon in mPCa practice that had not previously been documented in this region of the world. In real-world settings, most patients with CRPC receive at least one additional line of treatment beyond ADT; however, a significant portion does not and has worse survival outcomes. The likelihood of receiving additional treatment lines appears to be associated with the treating physician's characteristics and the patient's comorbidities. Still, other factors might influence these patterns, which have yet to be identified. This work prompted the establishment of a dedicated multidisciplinary clinic for mPCa patients treated at the study center. Further research is warranted to identify and address the barriers to guideline-adherent treatment in real-world settings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-130/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-130/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethics approval was obtained from the institutional ethics board of SingHealth Duke-NUS Academic Medical Center (CIRB Ref 2009/1053/D), and the study was conducted according to the principles of the Helsinki Declaration (as revised in 2013) and Good Clinical Practice Guidelines. Informed consent was taken from all the patients.

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