Real-world data on the outcomes of upfront docetaxel in hormone-sensitive metastatic prostate cancer

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Abstract. The present retrospective, single-centre study investigated the efficacy and toxicity of upfront docetaxel chemotherapy in patients with hormone-sensitive metastatic prostate cancer and evaluated the impact in high and low-volume disease. Data from 167 patients with hormone-sensitive metastatic prostate cancer treated between January 2016 and December 2019 were analysed. The data cut-off was February 2024; the median follow-up time was 37 months and the median age was 66 years. The cohort consisted of varying Gleason scores, with the majority scoring 9 (n=86; 51.1%). Surgical castration was performed in the majority of cases (n=136; 81.4%). Overall, 66 (39.5 %) of the patients had low-volume disease (≤5 sites of metastasis, no visceral metastasis), while 101 (60.5%) patients had high-volume disease. Disease progression occurred in 100 patients (59.9%), with a median progression-free survival (PFS) of 47 months (95% CI, 37.503-56.497). The median overall survival (OS) was 71 months. In the comparison of low-volume vs. high-volume disease groups, the median PFS was 57 vs. 47 months respectively (P=0.276) and the corresponding median OS was not reached vs. 57 months respectively (P=0.192). Among the 100 patients with disease progression, 20 received second-line therapy. The median OS for untreated patients was 9.88 months, while those treated with antiandrogens was 15.14 months and those with re-challenge chemotherapy was 12.46 months (P=0.496; 95% CI, -6.47-11.83). Grade 3-4 treatment-related toxicities were observed in ~37.8% of patients, while one death was associated with chemotherapy-related neutropenic sepsis. The most common toxicities were mucositis (n=53; 31.7%), febrile neutropenia (n=44; 26.3%) and sepsis (n=29; 17.4%). The present study demonstrated that upfront docetaxel chemotherapy may be an effective and tolerable treatment for hormone-sensitive metastatic prostate cancer, particularly in settings where access to novel antiandrogens is limited, thus potentially offering a viable management strategy amidst resource constraints.

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Introduction

Prostate cancer is the second most prevalent cancer among males (1) and accounts for a notable proportion of cancer-related fatalities, ranking fifth worldwide (2) in this regard. Approximately 8% of patients present with *de novo* metastatic disease (3), while one-third of localized prostate cancer cases progress to metastatic disease during the clinical course (4). The definition of disease volume has continued to evolve among patients with metastatic disease, since disease volume plays a crucial role in determining prognosis. Prior to the findings of the CHAARTED (5) and STAMPEDE (6) trials in 2015 and 2016 respectively, conventional treatment for metastatic hormone-sensitive prostate cancer relied primarily on androgen deprivation therapy (ADT) with median progression-free survival (PFS) time typically ranging from 24 to 36 months (7), resulting in an early transition to metastatic castrate-resistant prostate cancer.

Historically, the role of chemotherapy was confined to cases of castrate-resistant metastatic prostate cancer (8,9). Yet, the emergence of key data (5,6) indicated that the integration of upfront chemotherapy demonstrates prolonged PFS and overall survival (OS) compared with ADT alone (5,6). The CHAARTED and STAMPEDE trials demonstrated that the combination of upfront chemotherapy and ADT leads to improvements in OS time of 1.1 and 1.8 years, respectively, for hormone-sensitive metastatic prostate cancer (3,4). These results led to the rapid incorporation of combination therapy with ADT and docetaxel into international guidelines, including those from the National Comprehensive Cancer Network (10) and European Society for Medical Oncology (11) in 2015, establishing the new standard of care for metastatic

hormone-sensitive prostate cancer. Consequently, Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH and RC), based in Lahore and Peshawar, Pakistan, aligned its practices with this paradigm shift, and adopted the use of upfront chemotherapy with docetaxel alongside ADT in the treatment of patients presenting with hormone-sensitive metastatic prostate cancer.

Subsequently, the treatment landscape underwent further transformation with the advent of the role of novel antiandrogens in hormone-sensitive metastatic prostate cancer, which improved survival rates and enhanced the quality of life for patients with metastatic prostate cancer (5,6,12). Data from STAMPEDE trial suggested superior efficacy outcomes and a more favourable toxicity profile with upfront novel antiandrogens, particularly for those with low-volume disease (13,14). However, despite these advancements, cost constraints have hindered the widespread adoption of antiandrogen therapy, especially in resource-limited settings such as in the present study (15). Currently, limited data exists on the efficacy of combination therapy for metastatic castration-sensitive prostate cancer in Pakistan. Notable trials (5,6,12) establishing chemohormonal therapy as the standard of care predominantly involved Caucasian populations, with minimal representation from South Asian groups. There is a lack of trial and real-world data specific to the present patient population, which may have poorer performance status and factors not typically accounted for in clinical trials, such as elderly patients, and patients from ethnic minorities and lower socioeconomic groups. In addition, standard guidelines (16,17) for treating low-volume disease with antiandrogens are also based on data from settings where access to these medications is not as limited. Therefore, it was crucial to evaluate the impact of chemohormonal therapy in low-volume disease, while considering the broader effects of financial limitations on tailoring therapy in resource-limited settings. Therefore, the present retrospective study was conducted with a focus on patients with hormone-sensitive metastatic prostate cancer, irrespective of disease volume, who underwent upfront chemohormonal therapy within the Pakistani patient population, offering insights into its efficacy and relevance in the present setting. The objective was to assess the efficacy and tolerability of this approach and explore the impact of disease volume on these outcomes. Furthermore, analysis was conducted to assess the impact of subsequent lines of treatment on overall disease outcomes. The aim of present study was to investigate the efficacy and toxicity of the upfront docetaxel in patients with hormone-sensitive metastatic prostate cancer and assess the impact in patients with low- and high-volume disease.

Materials and methods

Study design and population. The present analysis was a retrospective, longitudinal, observational and single-centre study conducted on patients with hormone-sensitive metastatic prostate cancer who were treated with upfront chemotherapy. The patients registered at SKMCH and RC in Lahore and Peshawar between January 2016 and December 2019 were included in the present study. The inclusion criteria were as follows: Patients with newly diagnosed *de novo* hormone-sensitive metastatic prostate cancer with a confirmed diagnosis of prostate cancer on histopathology, who were treated with upfront chemotherapy with docetaxel within 6 months of diagnosis were included in the present study. The exclusion criteria were as follows: i) Patients with prostate cancer without a histopathological diagnosis; ii) patients with localized disease only; iii) patients with castrate resistant metastatic prostate cancer; iv) patients with hormone-sensitive metastatic prostate cancer who were not started on chemotherapy within 6 months of diagnosis; and v) patients treated with upfront antiandrogens (for example abiraterone and enzalutamide) were excluded from the present study.

Procedure. After selecting the patients appropriate to the aforementioned criteria, data was retrieved from the hospital information system (HIS) database of SKMCH and RC. Patients had been treated with docetaxel at a dose of 75 mg/m^2 every 3 weeks and doses were reduced in the event of toxicity to 60 mg/m^2. For patients that developed febrile neutropenia, granulocyte colony-stimulating factor was used as a secondary prophylaxis. Patients with osseous metastasis were treated with zoledronic acid to prevent fractures. HIS records were reviewed to collect data for baseline characteristics including age, Gleason score, mode of ADT (surgical or pharmacological) and disease burden (low-volume vs. high-volume). The records were reviewed for the number of cycles of chemotherapy, and the type and grade of toxicity. Toxicity grading was performed according to the Common Toxicity Criteria for Adverse Events (version 5) guidelines (18). The data-cut off for the present study was 20 February 2024.

Study definitions. Low-volume disease was defined as: Metastatic hormone-sensitive prostate cancer with ≤5 sites of metastasis in bones or lymph nodes with no visceral metastasis. High-volume disease (19) was defined as: Metastatic hormone-sensitive prostate cancer with >5 sites of metastasis in bones or lymph nodes with or without visceral metastasis. OS was defined as the duration between diagnosis and death. PFS was defined as the duration between the start of chemotherapy to biochemical or radiological progression.

The specific primary objectives investigated were as follows: OS and PFS. The secondary objectives were as follows: Toxicity, impact of disease burden on the OS and PFS, and impact of further lines of treatment on PFS and OS.

Statistical analysis. IBM SPSS Statistics 29.0 was used to conduct the analysis. Counts and percentages were computed for the categorical variables and descriptive statistics were used for age. The survival analysis was conducted using the Kaplan-Meier method and the log-rank test was applied to evaluate the survival distributions. OS and PFS were estimated and each were subsequently stratified by the disease burden (low-volume vs. high-volume). Death was the outcome used for OS and for PFS, both disease progression and death were used as endpoints. The log-rank test in survival analysis reported a χ^2 value and a P-value was computed. The analysis of variance (ANOVA) test was used to compare the difference in the mean survival time between the three groups following the second-line of treatment (no treatment, antiandrogens and rechallenge therapy). The interval computed for the patients on second-line therapy began at progression

and finished at death or last encounter. An a-level of 0.05 or P≤0.05 was considered to indicate a statistically significant difference.

Results

The present study included 167 male patients with hormone-sensitive metastatic prostate cancer. The baseline characteristics of included patients are shown in Table I. The median age was 66 years with an age range of 45-80 years. Among the patients, 63 (37.7%) were aged 45 to 64 years, while 104 (62.3%) were in the 65 to 80-year age group. In the present study, 2 patients (1.2%) had a Gleason score of 6, 30 patients (18.0%) scored 7, 28 patients (16.8%) scored 8, 86 patients (51.1%) scored 9 and 9 patients (5.4%) scored 10. Overall, 123 patients (73.7%) had a Gleason score between 8 and 10. The Gleason score was unknown for 12 patients (7.2%). Prostate-specific antigen was low (≤10) in 16 (9.6%), while it was high (>10) in 151 (90.4%) patients. All patients underwent castration, predominantly through surgical means (n=136; 81.4%). In remaining patients pharmacological castration with leuprolide was performed (castration with bicalutamide/flutamide only was not done). Additionally, 66 patients (39.5%) had low-volume disease, while 101 patients (60.5%) presented with high-volume disease (Table I).

There were 100 (59.9%) patients who had disease progression (Table II). The median PFS was 47 months (95% CI, 37.503-56.497; Fig. 1). There were 101 (60.5%) patients still alive at the time of data cut off (Table II), with a median OS of 71 months (Fig. 2). Out of 66 deaths, 62 (93.9%) were related to cancer, predominantly disease progression, while 4 (6%) were related to comorbidities. The cause of death in these 4 patients was either a cardiovascular event or ischemic heart disease.

There was no statistically significant difference in the OS or PFS distributions by age group (45-64 vs. 65-80 years; P>0.05; data not shown). Gleason score (≤6, low-risk; 7, intermediate-risk; and ≥8, high risk) had no impact on the PFS; however, was notably associated with OS. The median OS for patients with high-risk Gleason score was 71 months vs. not reached for intermediate-risk group (P=0.046; data not shown). In the low-risk group there were two cases and both were censored; therefore, no statistics were computed.

The median PFS for low-volume vs. high-volume disease was 57 vs. 47 months, respectively (P=0.276; Fig. 3). The median OS for low- and high-volume disease was not reached vs. 57 months, respectively (P=0.192; Fig. 4). The comparison of the survival curves by disease volume using the log-rank test was not statistically significant either for the PFS [χ^2=1.18; degrees of freedom (df)=1; P=0.276] or the OS (χ^2=1.70; df=1; P=0.192).

There were 100 patients who had disease progression. However, only 20 patients received second-line therapy (Table III). The impact of second-line therapy was not statistically significant (P=0.496). The mean survival time following the second line of treatment for the antiandrogens group (n=7) was 15.14±8.84 months and that of the rechallenge therapy group (n=13) was 12.46±9.51 months (t=0.616; df=20; two-sided P=0.546), with a mean difference of 2.68 months (95% CI, -6.47-11.83) between the groups. The difference in median OS in the second-line therapy groups was 9.88 months for patients without treatment, 15.14 months for those treated with antiandrogens and 12.46 months for those with rechallenge chemotherapy.

In the present study, 131 patients (78.4%) completed 6 cycles of chemotherapy. There were 8 patients (7.8%) who completed 8 cycles of chemotherapy. Grade 3-4 treatment-related toxicities were observed in ~37.8% of patients. Moreover, one death was associated with neutropenic sepsis and colitis; a 69-year-old patient who was diagnosed with metastatic and locally advanced prostate cancer, and presented with low BMI (BMI, 19), bowel obstruction and right obstructive uropathy. The patient was managed with a right percutaneous nephrostomy and loop colostomy. Postoperatively, the patient experienced high stoma output. After receiving the first cycle of docetaxel with a 20% dose reduction, the patient developed neutropenic sepsis and colitis. The patient succumbed to sepsis

Table I. Baseline characteristics.

Clinicopathological variables	No. of patients (%)
Age, years	
Median	66
Range	45-80
Gleason score	
6	2 (1.2)
7	30 (18.0)
8	28 (16.8)
9	86 (51.5)
10	9 (5.4)
Unknown	12 (7.2)
Prostate-specific antigen	
Normal (≤10)	16 (9.6)
High (>10)	151 (90.4)
Castration	
Pharmacological	31 (18.6)
Surgical	136 (81.4)
Disease volume	
Low-volume	66 (39.5)
High-volume	101 (60.5)

Table II. Clinical outcomes.

Disease progression	No. of patients (%)
No	66 (39.5)
Yes	101 (60.5)
Patient status	
Alive	101 (60.5)
Dead	66 (39.5)
Cause of death	
Cancer-related	62 (93.9)
Comorbidities-related	4 (6.0)

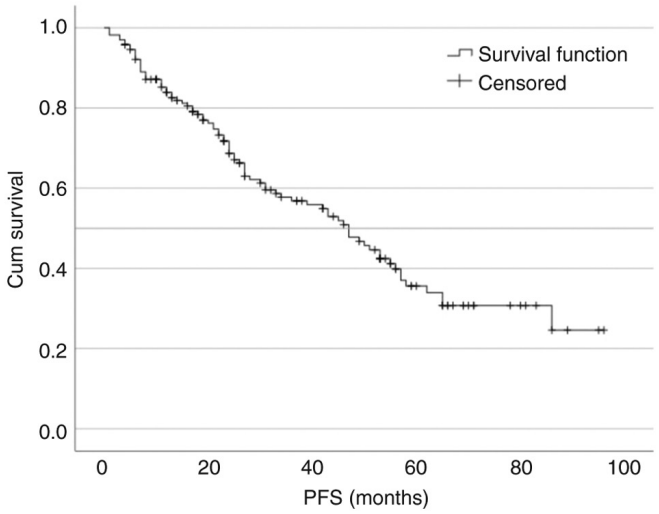

Figure 1. Kaplan-Meier curve illustrating the PFS. The x-axis represents the PFS in months, while the y-axis represents cumulative survival. The median PFS is 47 months with a 95% confidence interval of 37.503 to 56.497 months. Censored data points are indicated by crosses on the curve. PFS, progression-free survival; cum, cumulative.

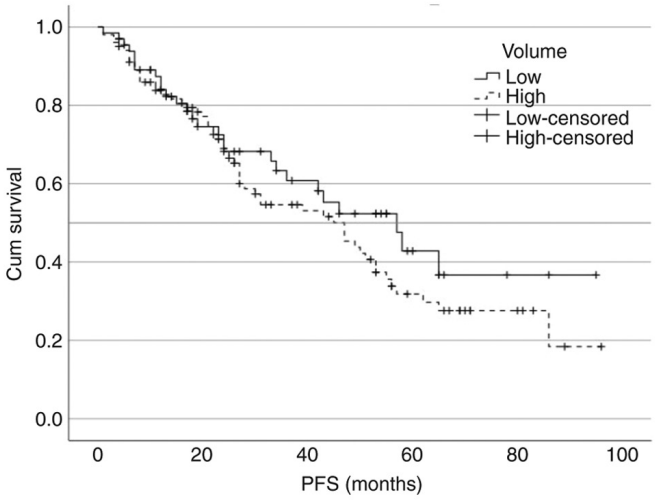

Figure 3. Kaplan-Meier curves illustrating the impact of disease volume on PFS. The x-axis represents PFS in months, while the y-axis represents cumulative survival. The dashed line represents the high-volume disease, and the solid line represents the low-volume disease. Censored data points are indicated by crosses. The P-value for the comparison between low- and high-volume groups is 0.276. PFS, progression-free survival; cum, cumulative.

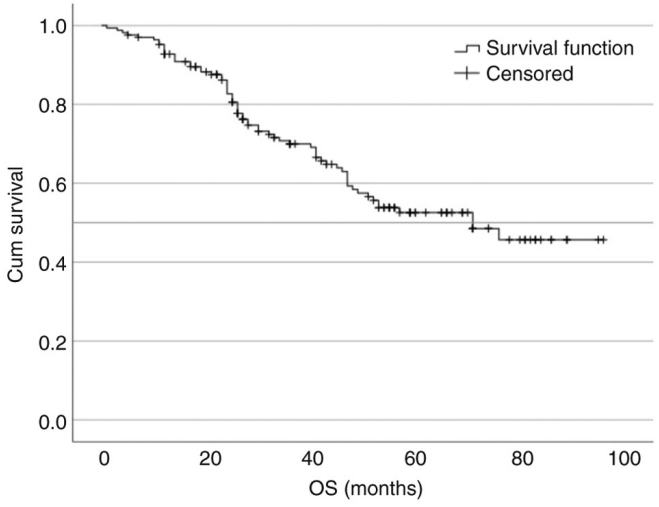

Figure 2. Kaplan-Meier curve illustrating the OS. The x-axis represents the OS in months and the y-axis represents cumulative survival. The median OS is 71 months. Censored data points are indicated by crosses on the curve. OS, overall survival; cum, cumulative.

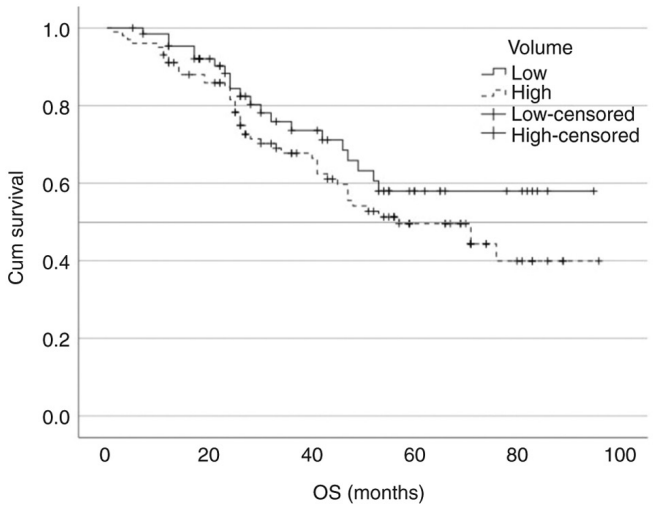

Figure 4. Kaplan-Meier survival curves depicting the impact of disease volume on OS. The curves represent cumulative survival over time (in months) for patients with different levels of disease burden, categorized as low-(solid line) and high-volume (dashed line) groups. Censored data points are indicated by crosses. The P-value for the comparison of OS between low- and high-volume groups is 0.192. OS, overall survival; cum, cumulative.

despite all supportive measures. The most common toxicities were mucositis with 53 (31.7%) patients, febrile neutropenia with 44 (26.3%) patients and sepsis with 29 (17.4%) patients. Overall, 116 (69.4%) patients required dose reduction mainly due to neutropenia, sepsis, mucositis and performance status (Table IV).

Discussion

The findings of the present study provided insight on the characteristics of metastatic prostate cancer within the Pakistani population and treatment efficacy and outcomes, particularly in the context of limited economic resources and access to advanced therapies. The health economics of cancer treatments cannot be underestimated. Within the constraints of limited resources, in a low-income country with the majority of patients having a poor socioeconomic status, free access to docetaxel due to its low cost makes this treatment relatively affordable.

It was demonstrated that the median age of presentation for upfront metastatic prostate cancer in the present study population aligned closely with international (5,6,12) and national (20-22) data, underscoring the consistency of disease characteristics across different demographics and corroborates findings from aforementioned studies, emphasizing the universality of prostate cancer demographics.

Table III. Impact of second-line therapy on OS.

Second-line therapy in patients with progression	No. of patients (%)	OS, months	P-value
Total	100 (100)		0.496
None	80 (80.0)	9.88	
Antiandrogens (abiraterone or enzalutamide)	7 (7.0)	15.14	
Chemotherapy rechallenge with docetaxel	13 (13.0)	12.46	

OS, overall survival.

Table IV. Tolerance and toxicities.

Parameter	No. of patients (%)
No. of cycles of docetaxel	
1	1 (0.6)
2	0 (0.0)
3	5 (3.0)
4	6 (3.6)
5	5 (3.0)
6	131 (78.4)
7	1 (0.6)
8	13 (7.8)
9	2 (1.2)
10	2 (1.2)
11	0 (0.0)
12	1 (0.6)
Toxicity, grade	
1	16 (9.6)
2	85 (50.9)
3	35 (21.0)
4	28 (16.8)
5	1 (0.6)
Type of toxicity	
Diarrhoea and vomiting	2 (1.2)
Peripheral neuropathy	8 (4.8)
Mucositis	53 (31.7)
Febrile neutropenia	44 (26.3)
COVID-19	3 (1.8)
Mixed	28 (16.8)
Sepsis	29 (17.4)
Dose reduction	116 (69.4)

In terms of treatment modalities for metastatic prostate cancer, while pharmacological castration is predominantly used in developed countries (6), the present study highlighted the prevalence of surgical castration in the present population due to socioeconomic factors and challenges with treatment compliance. This underscores the significance of tailored approaches to therapy based on resource availability and patient demographics. Moreover, the present study demonstrated a high proportion of patients with high Gleason scores, mirroring findings from published data (6,23). This underscores the aggressive nature of the disease in the present population, necessitating robust treatment strategies.

Regarding chemotherapy protocols, the approach of the present study, which offered 6-10 cycles of docetaxel, aligns with how the guidelines (16,17) on the management of prostate cancer have evolved. In the initial trials >6 cycles of chemotherapy were given (12), Therefore, initially, the present centre adopted the approach of 6-10 cycles; however, as further data emerged (5,6) the approach was switched to 6 cycles of chemotherapy.

Recent advancements (16,24) have delineated distinct standards of care based on disease volume, with novel antiandrogens established as the preferred option for low-volume disease, whereas chemotherapy remains a key treatment strategy for high-volume disease. The present retrospective analysis provided insights on the treatment patterns and outcomes observed in a cohort of patients with prostate cancer, some of whom were managed prior to the crystallization of explicit guidelines (25,26) regarding treatment stratification by disease volume (27). Notably, the present patient cohort received upfront chemohormonal therapy, irrespective of disease volume, reflecting the prevailing guidelines and economic considerations at the time. This approach, though divergent from contemporary standards (28,29), yielded a median OS of 71 months, comparable to outcomes reported in landmark trials such as STAMPEDE (6), where docetaxel and ADT conferred a median OS of 81 months. By contrast, the median OS observed in the GETUG-AFU-15 trial (12), where treatment modalities may not have mirrored current standards, was notably lower at 58.9 months. Despite limitations such as the lack of access to subsequent lines of therapy upon disease progression, the present findings underscore the reasonable survival outcomes achieved with the adopted treatment strategy. The present study suggested that the efficacy of this approach could transcend the availability of advanced therapies, as evidenced by outcomes superior to those reported in previous studies such as the GETUG-AFU-15 trial, which was conducted during a period when novel antiandrogens were less accessible. Notably, despite constraints on access to novel agents, these data reflect improved PFS and OS rates, suggesting the efficacy of the upfront chemotherapy approach within resource limitations. The present data provided evidence that could support the use of this treatment within the constraints within low-medium income countries where access to certain cancer treatments is dependent on affordability.

The finding that there were no significant differences in PFS or OS between low- and high-volume disease demonstrates the efficacy of the upfront chemotherapy approach across disease burdens; the cost-effectiveness of the present approach potentially makes it a valuable and equitable option, particularly in resource-limited settings.

Limited use of second-line therapy post-progression was observed, primarily due to cost constraints and patient frailty, which highlighted the challenges in accessing advanced treatments. Despite this, patients showed comparable survival outcomes to international data (6,12), indicating the clinical impact of the present approach. However, the small sample size of the present study limits the ability to control for confounding factors such as age, comorbidities, performance status, disease burden or severity which could independently affect outcomes. Further multicentre studies are warranted to enhance statistical power and provide a more representative patient population.

In terms of treatment tolerability, the present study demonstrated comparable completion rates of chemotherapy cycles to international benchmarks (5,6,12), albeit with higher incidences of toxicities, particularly neutropenic sepsis. However, despite these challenges, overall treatment-related mortality was low, highlighting the importance of diligent monitoring and supportive care in resource-limited settings. Additionally, 19 patients received >6 cycles of chemotherapy. When docetaxel was first introduced for metastatic hormone-sensitive prostate cancer, guidelines regarding the optimal number of cycles were not well defined (12). As a result, a number of patients in the present study who initiated treatment before precise guidelines were established continued therapy >6 cycles at the discretion of their oncologists if good tolerance was demonstrated.

Incorporating existing treatment guidelines into low-income countries presents challenges, particularly when tailoring therapies to financial constraints. The present findings offer supporting evidence to physicians in such settings regarding the efficacy of this approach. While abiraterone is preferred for low-volume disease due to its quality-of-life benefits (16,24), the present study highlighted the feasibility of docetaxel with acceptable toxicity, thereby reducing financial burden.

Moreover, the present study addresses a key research gap by including South Asian patients, who are often underrepresented in notable clinical trials. This inclusion provides key insights into disease behaviour within this population, supporting the need for more diverse representation in future studies. Limitations of present study are that it was a retrospective, single institution study with only a small proportion of patients who went on to receive second line therapy and head-to-head comparison with novel antiandrogens was not possible.

In conclusion, the present study underscored the importance of tailored management strategies in the context of limited resources and access to advanced therapies. While challenges exist, it was demonstrated that effective treatment outcomes may be achieved through utilization of available resources and adaptation of international guidelines to local contexts. Further research is warranted to optimize treatment protocols and improve outcomes for patients with prostate cancer in similar resource-constrained settings. Future work includes the continued collection of prospective data, as reporting outcomes such as toxicity and efficacy in the real-world setting remains key in the changing landscape of cancer management. To combat the cost constraints at the policy-making level, the use of biosimilars and access programs for novel therapies is warranted.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MQ, YI and SAH contributed to the conception and study design. Data collection was conducted by SR and AA. Statistical analysis was performed by FB. YI and MQ completed the manuscript writing, with manuscript review provided by SAH. MQ and SAH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Based on its retrospective nature, with information in existence being recorded without subject identification and without contact with the study subjects, the present study was granted waiver by the Institutional Review Board of Shaukat Khanum Memorial Trust (Lahore, Pakistan).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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