Original Article

Estimation of the burden of high-volume disease among metastatic hormone-sensitive prostate cancer patients presenting to urologists in Pakistan

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Abstract

Introduction: There is a scarcity of data in Pakistan, describing the extent of metastases in men with hormone-sensitive prostate cancer (HSPC). We aimed first to determine the proportion of high-volume/extensive disease among metastatic HSPC patients, presenting to urologists. Secondly, to evaluate the profile of these patients and their adherence to the treatment plan.

Materials and Methods: This prospective observational study recruited consenting men with metastatic HSPC between October 2016 and September 2018. The high-volume disease was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis. Adherence to the treatment plan was observed during a period of three and six months. Descriptive statistics were used for the analysis of categorical and continuous variables.

Results: The study included 100 patients from five cities in Pakistan. Their mean and standard deviation (SD) of age was 69.2 ± 9.9 years. Performance status 2 was reported in 45% (n=45/100) patients, and Gleason score 8-10 in 69% (n=69/100). High-volume disease was prevalent in 68% (n=68/100) of patients, with bone metastases positive in 91% (n=91/100). Visceral metastases were identified in 26% (n=26/100) of patients with 10% reported in the lungs. At three and six months, physicians reported that 90% (n=85/94) and 91% (n=81/89) of patients adhered to the planned treatment, with hormonal manipulation in 86% (n=81/94) and 88% (n=78/89) respectively.

Conclusion: Our first nationwide study in Pakistan demonstrated a high metastatic burden among HSPC patients presenting to a urologist. A multidisciplinary team approach, with the early involvement of oncologists, is imperative for the most appropriate management.

Keywords: Prostatic Neoplasms, Carcinoma, Metastasis, Urologists, Pakistan.

Introduction

Globally, prostate cancer (PCa) is the second most common malignancy among men. The annual incidence of PCa was 7.3% in 2020 and it was responsible for 3.8% of all cancer-related deaths among men.[1] The overall prevalence of PCa in Pakistan is 5-8% as reported in original studies and meta-analyses. However, information about the epidemiological characteristics of this malignancy in Pakistan is still scarce.[2,3]

The growth of PCa cells is driven by androgens, and androgen deprivation therapy (ADT) remains the mainstay of therapy in hormone-sensitive diseases.[4] However, resistance to ADT is not only common in these patients but is also associated with cardiovascular morbidity and cognitive dysfunction.[5] Docetaxel, a chemotherapeutic agent approved in 2004, was the first medical therapy to demonstrate an overall survival benefit for metastatic castration-resistant PCa.[6,7] Previously, docetaxel was reserved for patients who did not respond to ADT. However, recent investigations and robust clinical evidence have shown an increased median survival and delayed progression with a combination of ADT and docetaxel.[5] The CHAARTED (Chemo Hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial reported that a combination of standard ADT and six cycles of docetaxel resulted in significantly longer overall survival than with standard ADT alone in men with metastatic HSPC, with a 16.8-month survival advantage in patients with high-volume/extensive disease. The high-volume disease was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral column and pelvis.[8]

Traditionally, newly diagnosed metastatic PCa patients are initially managed by urologists. However, there have been inconsistencies in the management approaches to advanced PCa as it remains a complicated decision for urologists.[9] In light of new findings, a multi-disciplinary team (MDT) approach, with the early involvement of oncologists, is important for the optimum management of metastatic HSPC.[10] European Association of Urology (EAU) also recommended the MDT approach for patients with advanced and metastatic PCa.[11]

The need to establish MDTs in oncology has been repeatedly pressed in the literature. The phenomenon is deep-rooted in high-income developed countries; however, in developing countries like Pakistan, MDTs are still an uncommon practice due to a lack of resources. Some tertiary care hospitals in Pakistan have managed to establish site-specific MDT tumor boards and have seen significant advancements in their management.[12,13] In Pakistan, the burden of high-volume metastatic disease among men with PCa may be high due to a relative lack of MDT approach. However, there exists no data to support this premise. Thus, it is important to document the magnitude of this burden and understand the disease characteristics of these patients. The main objective of this study was to determine the proportion of high-volume disease amongst metastatic HSPC patients presenting to urologists. The study also aimed to describe the profile of these patients and evaluate their adherence to the treatment plan.

Materials and Methods

This multicenter, prospective, observational study was conducted across the country. For this study, a center was defined as any urologist associated with a tertiary care hospital in a major city in Pakistan. Ten centers were selected after simple random sampling from a list of qualified urologists. The study was conducted in accordance with Helsinki principles[14] and Good Epidemiology Practice guidelines.[15] Before study initiation, approvals were sought from ethics review committees of respective study centers.

The study included male patients with histologically confirmed prostate adenocarcinoma, evidence of metastatic disease, and intention to treat with long-term ADT. Patients who had a history of any other cancer in the past 5 years (except basal-cell or squamous-cell skin cancer), patients taking prior hormone therapy in the metastatic setting, and patients with Eastern Cooperative Oncology Group (ECOG) [16] performance status >2 were excluded. All patients who fulfilled the inclusion criteria were included in the study after attaining written informed consent.

Based on the findings reported by Sweeney CJ et al.[8] the proportion of high-volume disease among metastatic HSPC patients was assumed to be 65%. With a 95% confidence level and a margin of error of 10%, the sample size required for this study was 88. A sample of 100 patients was proposed on account of missing information and patients lost to follow-up (LTF). All patients were followed for at least six months. The study included three visits; first at baseline; second at three months (+/- two weeks), and

the third follow-up visit at six months (+/- two weeks).

At baseline, patient age, height, weight, living status (urban/rural), level of education, occupation, family history for prostate cancer, co-morbidity status, cancer-related symptoms (fatigue, weight loss, hematuria, or anorexia), and cancer-related pain were evaluated. All patients completed the International Prostate Symptom Score (I-PSS) [17] to assess their lower urinary tract symptoms (LUTS). The Gleason score[18] was utilized to assess the aggressiveness of cancer. ECOG status, biochemical and radiological investigations, Tumor Nodes Metastases (TNM) classification, and extent of metastases (high-volume/low-volume) were also recorded.

Planned treatments were recorded at the baseline visit. On the subsequent visits at three and six months, patient status – alive / LTF / dead was recorded, and the subsequent treatments administered were assessed. The information was collected from the patient's charts/records. The adherence to the treatment plan was evaluated by the investigators and reported as a categorical variable.

All the analyses were conducted using SPSS (Statistical Package for the Social Sciences) software, version 22. Statistical analysis was mainly based on descriptive statistics. For categorical data, frequencies and percentages were calculated. Whereas for continuous data, mean and SD were calculated.

Operational Definitions:

- High-volume /extensive disease was defined as: Visceral metastases (extra-nodal) AND/OR bone metastases in at least four or more bone lesions, one of which must be outside of the vertebral column and pelvis.[8]
- The low-volume disease was defined as any metastatic disease that was not extensive.

Results

From October 2016 to September 2018, information was gathered for 100 eligible patients recruited from five major cities in Pakistan. Their mean (SD) age was 69.2 (±9.9) years. Sixty percent of patients had a body mass index (BMI) between 18.5- 24.9 kg/m2. More than half of the participants (57%) belonged to urban areas. Thirty-five percent of the participants acquired secondary education and 15% (n=15/100) were engaged in a highly skilled occupation. (Table 1)

Table 1: Socio-demographic characteristics of the study population (n=100)

Characteristics	*Values*	*Characteristics*	*Values*
Age (years), mean ± SD	69.2±9.9	***Educational Level, n (%)***	
Weight (kg), mean ± SD	66.1 ±12.7	Illiterate	22 (22%)
Height (cm), mean ± SD	162.7 ± 17.2	Primary	26 (26%)
Waist circumference (cm), mean± SD	81.8 ± 15.4	Secondary	12 (12%)
BMI (kg/m²), n (%)		Intermediated	17 (17%)
<18.5	04 (4%)	University/Higher Education	23 (23%)
18.5-24.9	60 (60%)	***Occupation, n (%)***	
25.0-29.9	19 (19%)	Highly skilled	15 (15%)
≥30.0	17 (17%)	Skilled	32 (32%)
Living Status, n (%)		Semi-skilled	35 (35%)
Urban area	57 (57%)	Unskilled	18 (18%)
Rural area	35 (35%)	***Family history of Prostate Cancer, n (%)***	
Sub-urban area	08 (8%)	In first degree relatives	04 (4%)

-Values are calculated as n (%) or means (SD). BMI, body mass index.

- Used WHO general population BMI classification

Regarding cancer-related symptoms, fatigue was most reported (n=67/100; 67%). The three most frequently reported co-morbidities at baseline were hypertension (n=40; 40%), active smoking (n= 26; 26%), and diabetes mellitus (n= 21; 21%). The mean (SD) I-PSS score of the study sample was 16.63 (± 6.4) and 60% (n=60/100) patients were moderately symptomatic (score: 8-19). Quality of life due to urinary symptoms scores were reported as mixed (neither satisfied nor happy) by 36% (n=36/100) of patients. Forty-five percent (n=45/100) of patients had an ECOG performance status of 2. The median (range) prostate-specific antigen (PSA) was 80.5 (2-2552) ng/ml. A Gleason score of 8-10 was reported in 69% (n=69/100) of patients. In addition, 32% (n=32/100) of the cases were reported as T2 (Table 2).

Table 2: Clinical Characteristics at baseline (n=100)

Clinical Characteristics	*Frequency (%)*	*Clinical Characteristics*	*Frequency (%)*
Cancer-related symptoms		***Other Investigations***	
Fatigue	67 (67%)	Bone Scan	96 (96%)
Weight loss	49 (49%)	Chest X-ray	76 (76%)
Anorexia	48 (48%)	CT Scan	26 (26%)
Gross Hematuria	19 (19%)	MRI	22 (22%)
Tingling or numbness in arms or legs	13 (13%)	***Year of Diagnosis***	
Swelling in one or both legs	7 (7%)	<2016	6 (6%)
Pain related to cancer		2016	27 (27%)
No pain	60 (60%)	2017	65 (65%)
Mild pain	4 (4%)	2018	2 (2%)
Moderate pain	17 (17%)	***Gleason Score at diagnosis***	
Severe pain	19 (19%)	4-6	7 (7%)
Co-morbidities		7	20 (20%)
Hypertension	43 (43%)	8-10	69 (69%)
Current smokers	26 (26%)	Unknown	4 (4%)
Diabetes Mellitus	21 (21%)	***TNM Classification at diagnosis***	
Coronary artery disease	13 (13%)	***T (Primary Tumor)***	
COPD	7 (7%)	Tx	6 (6%)
Chronic renal failure	7 (7%)	T1a	1 (1%)
Hyperlipidemia	4 (4%)	T1b	7 (7%)
Chronic liver failure	1 (1%)	T1c	5 (5%)
Others	4 (4%)	T2a	16 (16%)
I-PSS score		T2b	9 (9%)
Mildly symptomatic	6 (6%)	T2c	7 (7%)
Moderately symptomatic	60 (60%)	T3a	13 (13%)
Severely symptomatic	34 (34%)	T3b	13 (13%)
Quality of life regarding urinary symptoms score		T4	18 (18%)
Mostly satisfied	13 (13%)	***N (lymph nodes)***	
Mixed (neither satisfied nor happy)	36 (26%)	Nx	24 (24%)
Mostly unhappy	25 (25%)	No	29 (29%)
Unhappy	18 (18%)	N1	41 (41%)
Terrible	8 (8%)	***M (Distant Metastasis)***	
ECOG performance status		M1a	24 (24%)
0	27 (27%)	M1b	59 (59%)
1	28 (28%)	M1c	15 (15%)
2	45 (45%)		
Laboratory Investigations, median (range)			
PSA value (ng/ml)	80.5 (1-2553)		
Testosterone (ng/dl)	20 (2-1354)		

-Values are calculated as n (%) or median (range).
-The sum may not add up to the total
- COPD, chronic obstructive pulmonary disease
-I-PSS score, International Prostate Symptom Score (7), ECOG, Eastern Cooperative Oncology Group (16)
- PSA, Prostate Specific Antigen

High-volume of disease was present in 68% (n=68/100) of patients. Bone metastases were positive in 91% (n=91/100) patients. Visceral metastases (extra nodular) were identified in 26% (n=26/100) of patients with 10% (n=10/100) documented in the lungs (Table 3).

Table 3: Pattern and Extent of Metastases at baseline (n=100)

Pattern of metastases	*Values*
Lymph nodes metastases, *n (%)*	44 (44%)
Bone metastases, n (%)	91 (91%)
Bone lesions, mean ± SD	5.84 ± 1.1
Bone lesions outside vertebral column and pelvis, mean ± SD	3.44 ± 2.8
Sites of visceral metastases (extra nodular), n (%)	
Lungs	10 (10%)
Liver	5 (5%)
Others	11 (11%)
Extent of metastases, n (%)	
High-volume	68 (68%)
Low volume	32 (32%)

-Values are calculated as n (%) or mean (SD).
-The sum may not add up to the total

At baseline, treatment was planned for 100 patients. Subsequent treatment-related information was recorded for 94 patients at visit 2 and 89 patients at visit 3 (Figure 1).

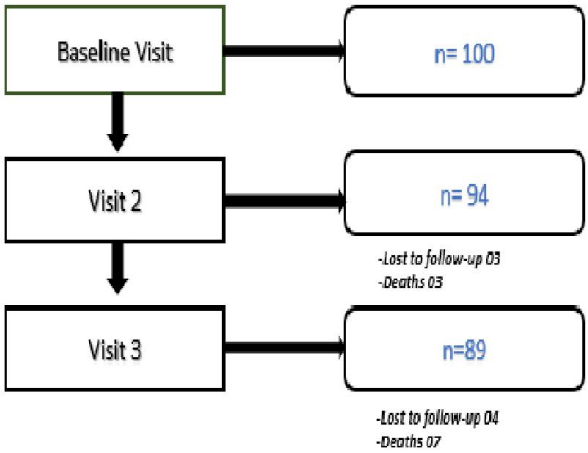

Figure1: Patient Flow Chart

All treatment-related characteristics are summarized in Table 4. At baseline, hormonal manipulation was planned in 81% (81/100) of patients. Subsequently at visit 2 and visit 3, hormonal manipulation was recorded for 86% (n=81/94) and 88% (n=78/89) patients respectively. At the second and third visits, regarding adherence to planned treatment, physicians reported that 90% (n=85/94) and 91% (n=81/89) of patients were administered subsequent treatment in line with the planned treatment, respectively. (Table 4)

Table 4: Characteristics of treatment planned v/s treatments actually administered

Treatment plan	*Treatment planned (n=100)*	*Treatment at second visit (n=94)*	*Treatment at third visit (n=89)*
Hormonal manipulation			
Bilateral orchiectomy	43 (43%)	40 (42.5%)	35 (39.3%)
CAB	39 (39%)	50 (53.2%)	50 (56.2%)
Antiandrogen	29 (29%)	25 (26.5%)	22 (24.7%)
LHRH agonist	24 (24%)	21 (22.3%)	12 (13.5%)
Antiandrogen + Orchiectomy	22 (22%)	32 (34.0%)	31 (34.8%)
Antiandrogen +LHRH agonist	17 (17%)	18 (19.1%)	19 (21.3%)
LHRH antagonist	4 (4%)	3 (3.2%)	1 (1.1%)
5-alpha –reductase inhibitor	3 (3%)	--	--
Estrogen	1 (1%)	--	--
Surgery			
Transurethral resection of prostate	23 (23%)	27 (28.7%)	27 (30.3%)
Others	9 (9%)	10 (10.6%)	14 (15.7%)
Radiation therapy			
External beam radiation therapy	7 (7%)	7 (7.4%)	7 (7.8%)
Bisphosphonates	5 (5%)	4 (4.3%)	3 (3.4%)
Palliative therapy	3 (3%)	1 (1.1%)	4 (4.5%)
Best supportive care	18 (18%)	11 (11.7%)	11 (12.4%)
Chemotherapy with Taxane	1 (1%)	1 (1.1%)	1 (1.1%)

-Values are calculated as n (%), The sum may not add up to the total, CAB, complete androgen blockade, LHRH agonist/antagonist, Luteinizing hormone-releasing hormone

Discussion

The present study showed that around two-thirds of the metastatic HSPC patients (68%) presenting to urologists in Pakistan have the high-volume disease as defined in the CHAARTED trial. The trial itself reported approximately 65% of patients with high-volume of metastases at baseline.[8] In a study conducted in Belgium in 2017, high-volume disease was reported among 46% of newly diagnosed hormone-naïve patients [19] as compared to an Italian study where 76% of patients had the high-volume disease.[20] In an observational study conducted in Egypt, the burden of high-volume disease was 62%).[21] All results are comparable to our study.

The incidence of metastatic HSPC has risen in the past few years mainly because of the increased utilization of advanced imaging modalities.[22] Precise and intricate imaging techniques have enabled sensitivity to minute tumor foci. This has allowed earlier detection of metastatic disease. Early diagnosis of metastasized disease enables the healthcare providers to intervene at an earlier stage and hence, improves the chances of a favorable outcome and prolonged survival.[22] In Alhanafy et al. all patients were managed with hormonal manipulation and other therapies were indicated as per individual patient needs. They concluded that the volume of disease and disease progression essentially predicted survival in patients with metastatic HSPC. The median survival without disease progression was 19 months for patients with high-volume disease as compared to 48 months for patients with low-volume disease.[21] In a retrospective cohort from the United States, the median overall survival for patients with the high-volume disease was 43 months. De-novo presentation, high-volume, and cancer-associated pain independently predicted the prognosis.[23] Along with these factors, the choice of treatment also critically impacts the disease outcome, overall survival, and prognosis.[22] Current guidelines recommend ADT combined with either chemotherapy (docetaxel) or androgen pathway-directed therapy in patients with metastatic HSPC.[24,25]

Gleason score is important in correlating the histological advancement of PCa with its clinical aggressiveness and prognosis. It is also crucial in choosing therapy for patients with prostatic adenocarcinoma.[18] In our study, as many as 69% of patients had a high Gleason score (≥8) at baseline. In Alhanafy et al.[21] 68% of patients with metastatic HSPC had Gleason score ≥8.[21] Similarly, in the CHAARTED trial, there were approximately 60% of such patients at baseline.[8] A higher Gleason score predicts an adverse prognosis; however, it alone holds no value in risk prediction.[21] Prognostic factors include high-volume disease, high initial PSA level, high or unknown Gleason score, bone metastases with or without soft tissue metastases, and worse performance status.[21-26]

In our study, there were 91% of patients with bone lesions at baseline, and 26% with visceral metastases, including 10% in the lungs, which is a critically high burden. In the CHAARTED trial[8], 15.5% of patients had visceral metastases at the start of the study[8], while Buelens S et al.[19] reported 25% of patients with visceral disease. Similarly, Iacovelli R et al.[20] identified 22% of patients with visceral metastases, with 16.7% in the lungs. Visceral diseases have been identified as a predictor of poor prognosis.[19,20]

This study is the first of its kind in establishing the burden of high-volume disease among metastatic HSPC patients presenting to urologists in Pakistan. Thus, the MDT approach with the early involvement of oncologists is imperative for the most appropriate management of these patients.[10,12,13] In a report from a multidisciplinary genitourinary clinic, improved quality of care for patients at all stages of prostate cancer was observed along with improved adherence to National Comprehensive Cancer Network guidelines.[27] Approach to malignancies through MDT empowers the patients and their caregivers by allowing them to gain more insight into the disease progression, gain more knowledge about the treatments administered, learn about the potential future treatments their safety and efficacy and make more informed decisions regarding their treatment choices. It plays an important role in ensuring patient adherence to the treatments.[27]

To the best of our knowledge, there was no previously published data in Pakistan regarding the burden of high-volume disease in metastatic HSPC. We attribute our results to readily available advanced imaging modalities helping in the early recognition of metastasized disease. The study was conducted in both public and private tertiary care hospitals in Pakistan. Most cancer patients in Pakistan tend to consult urban tertiary care hospitals, due to the availability of advanced medical treatment. Moreover, the study data were representative of urban (57%), rural (35%), and sub-urban (8%) populations. Hence, its results can be generalized for the entire population. However, the study has its limitations too. It was exclusively planned for metastatic HSPC patients presenting to a urologist. As the study was observational, the patient's medical records were

utilized for investigational purposes. With regards to adherence, we reported that 90% and 91% of patients adhered to their treatment plans at three and six months follow up. However, only the physicians' perspectives were captured.

To understand the real-life burden of prostate cancer in Pakistan establishing nationwide registries has become essential. Furthermore, the utilization of advanced imaging modalities and genomic testing along with the integration of multidisciplinary tumor boards remains a more efficient and inclusive approach to the management of prostate cancer. The main aim must be to collaboratively utilize all medical and surgical expertise in deciding the best treatment modalities through a tumor board of multidisciplinary experts.

Conclusion

The results of the study demonstrate a high metastatic burden among prostate cancer patients presenting to urologists.

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