

## Predictors for progression of metastatic prostate cancer to castration-resistant prostate cancer in Indians

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**Background & objectives:** There is lack of data on natural history and progression of prostate cancer (PC) which have implications in the management of the disease. We undertook this retrospective study to analyze factors predicting progression of metastatic PC to castration-resistant prostate cancer (CRPC) in Indian men.

**Methods:** Complete records of 223 of the 489 patients with metastatic PC were obtained from computerized data based system in a tertiary care hospital in north India between January 2000 to June 2012. Patients with follow up of < 6 months were excluded. Age ( $\leq$  and  $>$  65 yr), baseline PSA ( $<$  and  $\geq$  50 ng/ml), bone scan and Gleason score ( $\leq 7$  and  $> 7$ ) were recorded. Extent of bone disease (EOD) was stratified according to the number of bone lesions *i.e.*,  $<$  5, 5-10,  $>$  10. CRPC was defined as two consecutive PSA rise of  $>$  50 per cent from nadir or an absolute value of  $>$  5 ng/ml.

**Results:** Mean age of patients was  $61.5 \pm 12.45$  yr and their PSA level was  $325.6 \pm 631.35$  ng/dl. Of the 223 patients, 193 (86%) progressed to CRPC at median time of 10.7 (4-124) months. Median follow up was 24 (6-137) months. On univariate and multivariate analyses EOD on bone scan was found to be a significant predictor ( $P=0.006$ ) for time to CRPC. Median time to CRPC was 10 months (CI 95%, 7.5-12.48) with  $> 10$  lesions or super scan versus 16 months (CI 95%, 10.3-21.6) with  $< 10$  bone lesion ( $P=0.01$ ). Ninety (46.6 %) patients of CRPC died with median time to death from time of CRPC 21 (10-120) months.

**Interpretation & conclusions:** Median time for progression of metastatic PC to CRPC ranged from 10-16 months depending on the extent of the bone involvement. In Indians, the aggressive course of advanced prostate cancer warrants further clinical trials to explore the need for additional treatment along with initial castration.

**Key words** Castration-resistant prostate cancer (CRPC) - metastatic prostate cancer - predictors - progression

Prostate cancer (PC) is globally the most common non-cutaneous cancer and second leading cause of cancer related deaths in men<sup>1</sup>. Natural history of PC encompasses certain definite clinical endpoints like

hormone responsive state, androgen independent (AI) state and the castration-resistant prostate cancer (CRPC) status before progressing to death. Despite known factors predicting survival, our understanding of

natural history of PC is far from complete. This is partly because the disease is heterogeneous in morphology, clinical behaviour and geographical variation<sup>2</sup>.

In India, PC has not been perceived as a problem of serious magnitude. There is a lack of data regarding natural history and character of disease which may have profound implications regarding management protocols for our population. Some reports have indicated a rising trend of PC in Indian population<sup>3-5</sup>. Moreover, PC in our population is usually of higher grade and more likely to be metastatic at diagnosis as compared to western counterparts<sup>6</sup>. In this retrospective analysis, we tried to find out factors predicting progression of metastatic PC (D2) to CRPC and overall survival.

### Material & Methods

A retrospective study was conducted in the department of Urology at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, between January 2000 to June 2012 after obtaining the institutional ethical clearance from the committee. Medical records of 489 patients with biopsy proven metastatic (bone scan positive) PC were retrieved from computer based Hospital Information System (HIS). Patients with follow up of less than six months were excluded from the analysis. Complete data with required follow up were available in 223 patients, which formed the study group. Data regarding the age at presentation, baseline prostate specific antigen (PSA), biopsy Gleason scores and bone scan at presentation were obtained. Significance of each of these parameters was analysed in relation to the attainment of CRPC status.

*Androgen deprivation therapy (ADT) and biochemical measurements:* PSA was measured in the departmental laboratory using CanAg PSA EIA kit (Fugirabio Diagnostics Inc., Goteborg, Sweden). All the patients had either bilateral orchiectomy (N=168, 75.3%) or on luteinizing hormone-releasing hormone (LHRH) agonists (N=55, 24.7%) to begin with and with rising PSA after an achievement of nadir level, antiandrogen (bicalutamide, 50 mg daily) was started. CRPC was defined as two consecutive PSA rise of > 50 per cent from nadir or an absolute value > 5 ng/ml with no response to antiandrogen drugs<sup>7</sup>.

*Biopsy findings:* As per the departmental protocol, 6-12 core, transrectal ultrasound guided biopsies were taken. Patients with hard palpable disease on digital rectal examination (DRE) had six cores (N=95,

42.6%). The specimens were processed and evaluated for histopathology.

*Bone scan:* Bone scan was done at the initial diagnosis and repeated as clinically indicated. Evaluation of bone metastasis was based on the stratification of the extent of disease (EOD) score; 1 as less than 5 lesions, each of which is < 50 per cent the size of the vertebral body; 2 as lesions between 5 and 10, each of which < 50 per cent the size of the vertebral body; 3 as more than 10 or "super scan" or its equivalent, namely > 75 per cent of the ribs, vertebrae, and pelvic bones. A super scan refers to observation of a diffuse increase in radioactivity throughout skeletal system with faint visualization of the kidneys with normal renal function tests<sup>8</sup>.

*Statistical analysis:* Statistical analysis was done by applying Cox univariate and multivariate regression model and Kaplan-Meier survival curve. Comparison between groups was done by Mantel-Cox log rank test. Multivariate Cox proportional hazard models were developed to estimate the effect of each covariate. "Kruskal-Wallis one-way analysis of variance (ANOVA) was used to compare the median time to CRPC in various strata of predictors with more than two groups. Statistical software, SPSS 20 (SPSS Inc., Chicago, IL) was used.

### Results

A total of 223 men with biopsy proven metastatic (bone scan positive) adenocarcinoma of the prostate were evaluated, with respect to age at presentation, baseline PSA, Gleason score and baseline bone scan reports ( Tables I, II) The mean age was 61.5 ± 12.45 yr. Mean serum PSA at presentation was 325.6 ± 631.35 ng/ml. One hundred and ninety three patients (86%) progressed to CRPC at median time of 11 (4-124) months. Total median follow up was 24 (6-137) months.

The patients were classified by age as ≤ 65 yr (n=104, 46.6%) and more than 65 yr (n=119, 53.4%). In < 65 yr of age group, 85 (44%) patients progressed to CRPC while 108 (56%) of patients >65 yr progressed to CRPC. Calculated hazard ratio (HR) for age > 65 yr was 1.113 (95% CI 0.85 - 1.471) as compared to age ≤65 (P=0.071). Median time to progression in the two groups was 10 and 13 months, respectively (P=0.04) (Tables I, II).

Patients were analysed according to their PSA levels at presentation as < 50 or ≥ 50 ng/ml. Fifty eight patients (30%) of the first group progressed to

**Table I.** Demographic profile of total patients (n=233), comprising 193 patients with castration resistant prostate cancer (CRPC) and 30 without CRPC

Characters	Strata	Total patients n (%)	CRPC (%)#	No CRPC (%)#
Age (yr)	<65	104 (46.6)	85 (81.7)	19 (18.3)
	>65	119 (53.4)	108 (90.8)	11 (9.2)
PSA (ng/ml)	<50	70 (31.4)	58 (82.9)	12 (17.1)
	≥50	153 (68.6)	135 (88.2)	18 (11.8)
Bone scan (No. of lesions)	<5	73 (32.7)	57 (78)	16 (22)
	5-10	40 (18)	33 (82.5)	7 (17.5)
	>10	110 (47.3)	103 (93.6)	7 (6.4)
Gleason grade	≤7	114 (51.1)	103 (90.3)	11 (9.7)
	>7	109 (48.9)	90 (82.5)	19 (17.5)

# Percentage of each group was calculated from the total no. of patients in the respective strata

**Table II.** Variables influencing median and mean time from metastatic prostate cancer (PC) of progression to castration-resistant prostate cancer (CRPC)

Variable	Strata	Median time (months)	95% CI	Mean time (months)	95% CI
Age (yr)	<65	9	5.66-12.33	12.85	10.344-15.36
	>65	11	8.62-13.375	15.46	12.54-18.37
PSA (ng/ml)	<50	13	9.73-16.26	17.6	12.84-22.35
	>50	10	8.06-11.93	12.71	10.92-14.50
Bone scan (No. of lesions)	<5	14	12.15-15.84	18.561	14.74-22.38
	5-10	16	10.37-21.62	20.818	15.484-26.15
	>10	10	7.516-12.484	13.90	11.16-16.64
Gleason grade	≤7	11	7.92-14.07	14.6	11.73-17.51
	>7	10	7.27-12.72	13.8	11.23-16.46

CRPC against 135 (70%) of second group ( $P=0.01$ ). Calculated HR was 1.367 (95% CI 0.98 - 2.01) for PSA ≥ 50 ng/ml as compared to PSA of <50. Median time to progression was 13 and 10 months, respectively ( $P=0.08$ ) (Tables I, II).

Of the 193 patients in the three groups of bone metastasis (with bone lesions <5, 5-10 and >10), 57 (29.5%), 33 (17%) and 103 (52.5%) patients progressed to CRPC, respectively. Calculated HRs for

5-10 and >10 bone lesions were 0.648 (0.433-0.970) and 1.74 (0.948-2.33) when compared with < 5 lesions. The median time to progression was 14, 16, and 10 months, respectively ( $P<0.006$ ) (Figs 1, 2 and Tables I, II).

Amongst the Gleason scores of <7 and >7, 103 (53.4%) and 90 (46.6.3%) of 193 patients progressed to CRPC ( $P=0.4$ ). HR was 0.903 (95% CI 0.678-1.202) for Gleason's score >7 as compared to ≤7. In

two categories, median time to progression was 11 and 10 months, respectively ( $P=0.09$ ) (Tables I, II).

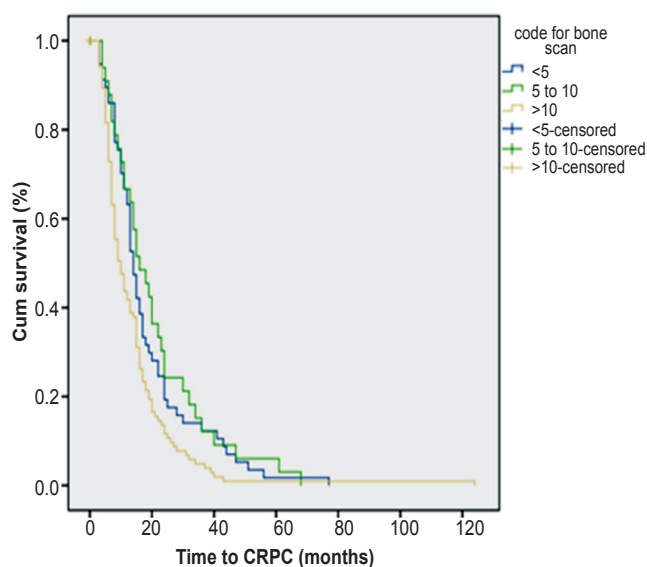
On univariate and multivariate analyses, only patients with bone lesions of  $> 10$  were found to have significant correlation with time to progression to CRPC ( $P=0.006$ ). Ninety (46.4%) patients with CRPC died with median follow up period of 24 (6-137) months and median time to death from time of CRPC was 21 (10-120 months) (Fig. 3).

Overall median survival of metastatic PC was 51 months (CI 95%, 42.91-59.08) and it varied from 42

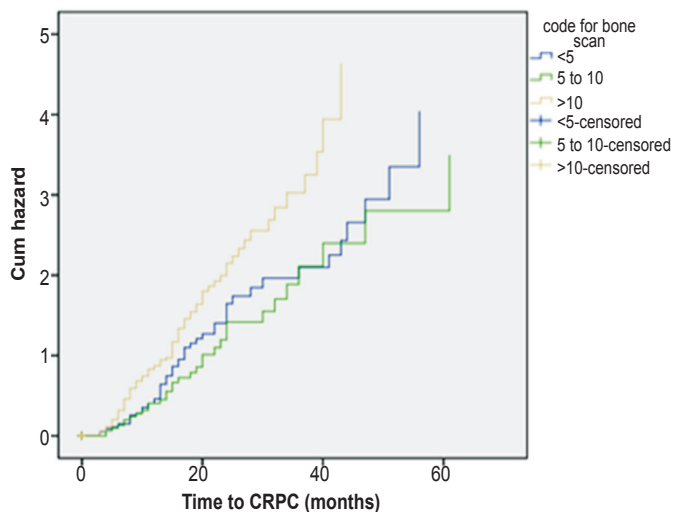
(CI-95%, 31.2-52.8) to 86 months (CI 95%,53.3-118.6) with bone lesions of  $>10$  vs. $<5$ , respectively ( $P=0.001$ ) (Fig. 4). Five year survival in patients with metastatic PC was 41.2 per cent whereas it was only 13 per cent in CRPC group.

### Discussion

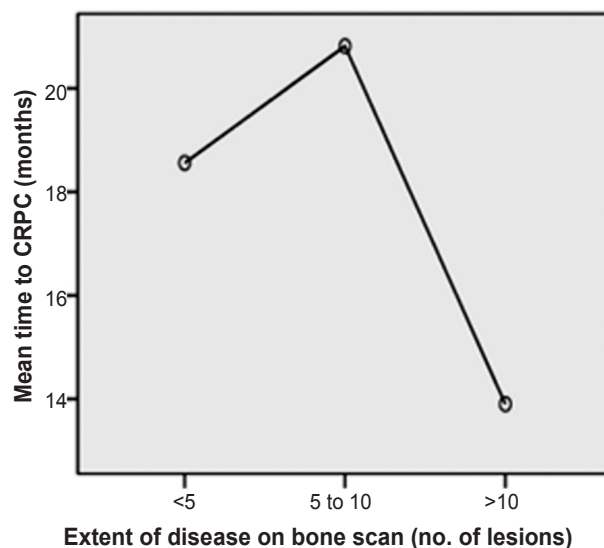
Prognostic factors are clinically relevant and routinely used by clinicians to inform patients about various treatment options and prognosis. In the pre-PSA era, severe bone pain, poor performance status,



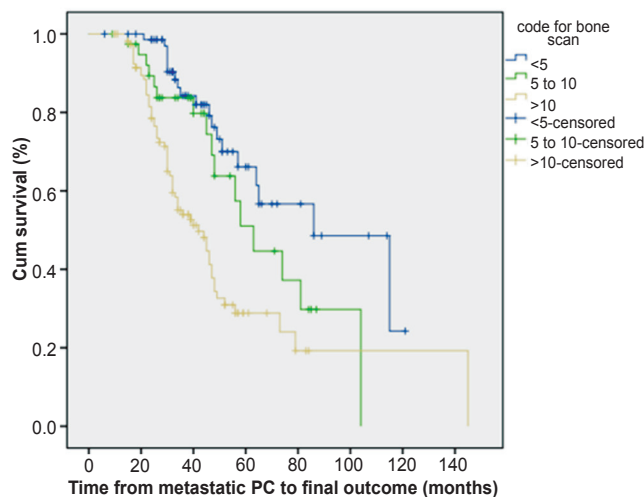
**Fig. 1.** Kaplan Meier survival for time to castration-resistant prostate cancer (CRPC) in various strata of bone involvement.



**Fig. 2.** Hazard plots for time to castration-resistant prostate cancer (CRPC) in various strata of bone involvement.



**Fig. 3.** Plot showing time to castration-resistant prostate cancer (CRPC) related to extent of disease (EOD) on bone scan.



**Fig. 4.** Survival curve showing survival of metastatic PC with different extent of bone disease.

anaemia, elevation of serum lactate dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), alkaline and acid phosphatases, hypoalbuminaemia and prolactin were described as predicting short survival<sup>9-10</sup>. Several studies have described factors predicting survival following CRPC status<sup>9-12</sup> based on a number of variables like baseline PSA levels, PSA nadir, PSA doubling time (PSADT), PSA velocity, baseline Gleason score, bone scan at presentation and so forth. Due to a different spectrum of disease in Indians<sup>3-5</sup>, information of prognostic factors is necessary for judicious use of newer additional therapies.

In our study, the higher age (>65 yr) was associated with delayed progression to CRPC. Smaletz *et al*<sup>11</sup> have also reported higher age as a predictor of better survival. However, other reports<sup>9-11</sup> prognosticate higher age as a marker of poor survival while there are also studies, which have not found age as a predictive variable for survival.

Baseline PSA level has been a predictor of shortened survival<sup>13-15</sup>. But in our study as most of the patients had advanced disease, PSA *per se* did not predict the time to CRPC. Similarly, Gleason score at diagnosis, a portent indicating an aggressive nature of the disease with early clinical endpoints, did not influence the time to CRPC on Cox multivariate hazard regression analysis.

Bone pain and higher EOD score at diagnosis of CRPC have significant bearing on the prognosis<sup>16</sup>. In this study, EOD score at presentation was an independent prognostic factor of early CRPC on multivariate analysis. Though time to CRPC was marginally higher in 5-10 bone lesions than <5 bone lesions, but was not significant. It may be, to some extent, related to biological behaviour of the cancer and other factors such as co-morbidity, performance status and nutritional status. Unfortunately, consideration of such factors was not possible in our study.

In one study the median time to CRPC was reported in the range between 33.9 and 45 months depending on whether PSADT was < 45/ > 45 days<sup>17</sup>. Better response could be attributed to lesser disease load in terms of bony metastasis at the time of presentation. In our patients, the median time to CRPC ranged from 10-16 months which, indirectly reflected the late presentation in the course of the disease and high disease load. A group of patients with more than 10 metastases had a median time to CRPC of 10 months. Therefore, predicting the

aggressiveness of disease at presentation, may guide us for initiating multi-institutional trial with an additional therapy along with ADT in the form of abiraterone acetate, chemotherapy or radioisotope therapy. As reported by Sarkar *et al*<sup>18</sup>, role of other potential marker like plasma chromogranin A needs to be evaluated further in context of variable extent of bone lesions; which may guide us better to individualize treatment policy of CRPC in Indian population.

Our study had certain limitations. The patient population was heterogeneous. Since clinical data were retrospectively collected, careful control and monitoring of data acquisition were not possible. Retrospective acquisition of data resulted in incomplete retrieval of some information. Finally, our model did not include many of the well recognized prognostic variables such as performance status, LDH, alkaline phosphatase and serum albumin.

In conclusion, the current study showed that the median time to CRPC in Indian patients with metastatic PC varied from 10-16 months depending on the number of lesions on the bone scan. Age at presentation, PSA and Gleason score did not influence the time to CRPC and survival in presence of bone metastasis. Patients with bone scan having more than 10 hotspots were found to have a very early progression to CRPC. Multicentre prospective studies are needed to further delineate the natural history of PC in Indian population so that optimal therapies could be devised for maximum benefit.

**Conflicts of Interest:** None.

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