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Time of Metastatic Disease Presentation and Volume of Disease are Prognostic for Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

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Abstract

Background—Currently, there is no universally accepted prognostic classification for patients (pts) with metastatic hormone sensitive prostate cancer (mHSPC) treated with androgen deprivation therapy (ADT). Subgroup analyses demonstrated that pts with low volume (LV), per CHAARTED trial definition, mHSPC and those who relapse after prior local therapy (PLT) have longer overall survival (OS) compared to high volume (HV) and *de-novo* (DN), respectively. Using a hospital-based registry, we aimed to assess whether a classification based on time of metastatic disease (PLT vs. DN) and disease volume (LV vs. HV) are prognostic for mHSPC pts treated with ADT.

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Disclosure statement

Dr. Francini reports travel, accommodations, and expenses from Janssen.

Dr. Albiges reports consulting and advisory role with compensation for Novartis, Pfizer, Amgen, Bayer, BMS, Roche, Ipsen, Astellas, Janssen.

Prof. Kantoff received compensation for scientific advisory board/consulting for Astellas, Bayer, Bellicum, BIND Biosciences, BN Immunotherapeutics, DRGT, Ipsen Pharmaceuticals, Janssen, Metamark, Merck, MTG Therapeutics, New England Research Institutes, Omnitura, OncoCellMDX, Progenity, Sanofi, Tarveda Therapeutics, Thermo Fisher Scientific; he has investment interests in Bellicum, DRGT, Metamark, Tarveda Therapeutics; and he is on data safety monitoring board of Genetech/Roche, Merck, Oncogenex. LCH reports compensation for consulting/advisory role at Dendreon, Genentech, KEW Group, Medivation/Astellas, Pfizer, Theragene; and institutional research funding from Bayer, Dendreon, Genentech/Roche, Medivation/Astellas, Sotio, Takeda, BMS; travel, accommodations, and expenses from Sanofi. Prof. Taplin reports personal fees for attending advisory boards for Janssen and Medivation; and receives research funding from Janssen and Medivation.

Prof. Sweeney reports consulting with compensation for Astellas, Bayer, Genentech, Janssen, Pfizer, Sanofi; and received research funding from Astellas, Janssen, Sotio, Sanofi. All remaining authors have declared no conflicts of interest.

Methods—A retrospective cohort of consecutive patients with mHSPC treated with ADT between 1990 and 2013 was selected from the prospectively collected Dana-Farber Cancer Institute database and categorized as DN or PLT and HV or LV, at time of ADT start. Primary and secondary endpoints were OS and time to castration-resistant prostate cancer (CRPC), respectively, which were measured from date of ADT start using Kaplan-Meier method. Multivariable Cox proportional hazards models using known prognostic factors was used.

Results—The analytical cohort consisted of 436 patients. The median OS and time to CRPC for PLT/LV were 92.4 (95% CI: 80.4 – 127.2) and 25.6 (95% CI: 21 – 35.7) months and 43.2 (95% CI: 37.2 – 56.4) and 12.2 (95% CI: 9.8 – 14.8) months for DN/HV, respectively, whereas intermediate values were observed for PLT/HV and DN/LV. A robust gradient for both outcomes was observed (Trend test $P < 0.0001$) in the 4 groups. In a multivariable analysis, DN presentation, HV, and cancer-related pain were independent prognostic factors.

Conclusions—In our hospital-based registry, time of metastatic presentation and disease volume were prognostic for mHSPC pts treated with ADT. This simple prognostic classification system can aid patient counseling and future trial design.

Introduction

Androgen deprivation therapy (ADT) has been the standard of care for mHSPC for almost 80 years and generally results in a prompt decrease of tumor burden, palliation of pain, and fall of serum levels of prostate specific antigen (PSA) [1]. However, the efficacy of ADT substantially varies, with some patients dying within 2 years and others living longer than 10 years [2] and a small minority showing primary resistance to ADT [1,3,4]. The mechanisms underlying this variability have been extensively investigated in the past and an array of factors including biological ones, such steroid receptor expression and androgens levels, as well as clinical factors, such as metastatic burden and cancer-related pain, have been correlated with clinical outcome in several studies [5–10]. Nonetheless, to date no prognostic classification is universally accepted for use in clinical practice or clinical trial conduct.

Between 2014 and 2017 docetaxel and abiraterone acetate were shown to increase the longevity of men commencing ADT for mHSPC [11–14]. In particular, the CHAARTED trial showed a clear benefit for patients with a high burden of disease. The E3805 investigators defined high volume (HV) disease as the presence of visceral metastases and/or 4 or more osseous metastases of which at least 1 extra-axial with the remainder being low volume (LV) [13]. Subgroup analyses of patients treated with ADT alone demonstrated that the prospectively defined LV patients and those relapsing with metastases after prior local therapy with curative intent (PLT) had a longer overall survival (OS) compared to patients with HV disease and men with newly diagnosed with mHSPC (*de-novo*, DN) [15–17].

Identification and use of simple and reliable clinical factors prognostic of survival with ADT would facilitate treatment decision making, clinical trial design, biological interrogations, and personalized therapy. This study aimed to assess whether a classification system based on time of metastatic disease occurrence (PLT or DN) and volume of disease (LV or HV) is

prognostic for patients with mHSPC treated with ADT in a prospectively collected hospital-based registry.

Materials and Methods

From the Dana-Farber Cancer Institute prospectively collected and institutional review board (IRB) approved database we retrospectively identified consecutive patients with histologically confirmed and radiologically evaluable mHSPC who were commencing ADT (orchiectomy or luteinizing hormone-release hormone analogues) between 1990 and 2013. Sixty-six patients who at the time of ADT start had received prior systemic therapy or previous ADT or had no disease volume data or no notation of PLT versus (vs.) DN were excluded from the analysis. The resultant cohort was stratified by time of metastatic disease presentation (PLT or DN) and volume of disease (LV or HV) at time of ADT start, into 4 groups: PLT/LV, PLT/HV, DN/LV, DN/HV (Fig. 1). The primary endpoint of the study was overall survival (OS), defined as time from ADT start to death from any cause or censored at last follow-up date, and secondary endpoint was time to castration-resistance prostate cancer (CRPC), defined per Prostate Cancer Working Group 3 definition [18]. For those patients who, despite PSA not having increased ≥ 1 ng/mL above nadir level and the absence of radiographic or symptomatic progression, were given a secondary hormonal manipulation as combined androgen blockade, CRPC was deemed when PSA ≥ 1 ng/mL on the secondary manipulation. Data on metastatic burden and sites were gathered from bone or CT or MRI scans performed within 6 months prior to start of ADT. The volume of disease was determined per E3805 investigators' definition of LV vs. HV [13]. Serum PSA and alkaline phosphatase (ALP) levels were collected from routine laboratory tests carried out within 4 months prior to ADT initiation. Patients' age, race, biopsy Gleason score (GS), year of diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and cancer-related pain (pain), and follow up data were assembled from clinical records. Year of diagnosis was classified by whether < 2004, 2004–2009, or > 2009 considering the time frames where new agents were introduced in the therapeutic paradigm of prostate cancer. ECOG PS was categorized in = 0 and ≥ 1 and pain was evaluated whether present or absent at ADT start. Finally, the extent of disease was classified as node only, bone plus/minus node, or viscera plus any.

The distribution of the outcome measures was estimated using the Kaplan-Meier method, including median time to event and its 95% confidence interval (CI). Cox proportional hazards model assessed disease outcomes according to the composite prognostic risk groups defined by time of metastatic disease presentation and disease volume groups and provided estimates of hazard ratio (HR) (95% CI) for the comparison by groups. In addition, cox proportional hazards model was used to evaluate the associations between disease outcomes and potential baseline covariates such as biopsy GS, median PSA, ECOG PS, extent of disease, pain, age, and year of diagnosis [9,10]. A multivariable Cox proportional hazards model assessed the relationship between outcomes and risk groups after adjusting for the putatively prognostic covariates which were significant in the univariate analysis - median PSA, year of diagnosis, extent of disease, and pain [9,10]. This was conducted in a subset of 335 patients with data of all covariates available.

Results

Overall, of 502 patients with mHSPC, 436 were evaluable for this analysis (Fig. 1), 192 with PLT and 244 were DN at time of ADT initiation. Patients' baseline demographic and clinical characteristics are summarized in Table 1. Most patients were white, < 65 years, did not have cancer-related pain, and had ECOG PS = 0, at ADT commencement. Biopsy GS was ≥ 8 in 72% of DN patients while in PLT cohort it was 34% of men. Patients who were considered having developed CRPC when PSA ≥ 1 ng/mL on a secondary hormonal manipulation were 82 (19%) and they were quite evenly distributed across the study cohorts (Supplementary Table 1). The distributions of the 4 risk groups were as follows: 29% PLT/LV, 15% PLT/HV, 22% DN/LV, 34% DN/HV (Table 2). A statistically significant (Trend test $P < 0.0001$) gradient was noted in both median OS and time to CRPC within the 4 groups in favor of PLT/LV. Namely, patients with PLT/LV showed longer median OS and time to CRPC at 92.4 (95% CI: 80.4 – 127.2) and 25.6 (95% CI: 21 – 35.7) months, respectively. Intermediate results were observed in PLT/HV and DN/LV which yielded a similar OS, 55.2 (95% CI: 44.4 – 80.4) and 51.6 (95% CI: 48 – 78) months, and time to CRPC, 15 (95% CI: 12.2 – 23.9) and 17.9 (95% CI: 12.8 – 21.1) months. DN/HV cohort showed the shortest OS and time to CRPC, which were 43.2 (95% CI: 37.2 – 56.4) and 12.2 (95% CI: 9.8 – 14.8) months, respectively. Compared to patients with PLT/LV (reference group), those in the other 3 cohorts had a statistically significant higher risk of developing CRPC or dying. Particularly, DN/HV patients showed a robust greater than two-fold higher risk of developing CRPC (HR=2.09; 95% CI: 1.63 – 2.66) or death (HR = 2.48; 95% CI: 1.83 – 3.36) (Table 2). Median OS and time to CRPC Kaplan-Meier curves further highlight the existence of 3 distinct categories: a good prognosis group represented by PLT/LV, an intermediate prognosis group with either PLT/HV or DN/LV, and a poor prognosis group corresponding to DN/HV (Fig. 2).

In univariate analysis, while covariates median PSA and pain showed a robust association with both OS and time to CRPC, year of diagnosis < 2004 vs. > 2009 was shown to be associated with a shorter time to CRPC but not to death (Table 3). Furthermore, patients with node only metastases had a significantly longer OS and time to CRPC compared to bone plus/minus node metastases. Therefore, we further assessed the prognostic properties of the composite risk groups with a multivariable Cox model, adjusted for median PSA, pain, year of diagnosis and extent of disease (Table 4). Consistently with the results of the univariate model, PLT/LV was shown to be the group with the significantly lowest risk of CRPC or death compared with the other covariates. This suggests that time of metastatic disease presentation and volume of disease are independent prognostic factors. In addition, while presence of cancer-related pain was confirmed to be a significant predictive factor of shorter survival (HR = 1.4, 95% CI: 1.04 – 1.89; P = 0.029) and time to CRPC (HR = 1.3, 95% CI: 1 – 1.7; P = 0.054), median PSA and year of diagnosis < 2004 vs. > 2009 were associated with a shorter time to CRPC but not OS (Table 4).

Discussion

High metastatic burden and DN presentation are known to be associated with poor prognosis for mHSPC patients treated with ADT [15–17]. The present study showed that time of

metastatic disease occurrence (PLT vs. DN) and volume of disease (LV vs. HV) of mHSPC patients in a hospital-based registry are significantly independent prognostic factors and that a classification based on these 2 factors is prognostic for survival and time to CRPC as it identifies 3 distinct categories of patients with good, intermediate, and poor outcomes (Fig. 2). Particularly, patients with PLT/LV seemed to benefit the most from ADT with a prolonged median OS of 92.4 months and time to CRPC of 25.6 months, respectively, whereas, patients with DN/HV characteristics had less than half the survival and time to CRPC, 43.2 and 12.2 months, respectively, and their risk of shorter survival and time to CRPC was more than double (Table 2).

These results are consistent with those of the post-hoc analysis of the CHAARTED trial and of the CHAARTED – GETUG-AFU15 combined study [16,17]. Similarly to our report, in both these analyses, patients were classified by time of metastatic disease occurrence and extent of disease burden and the OS of each of the 4 groups was evaluated. Consistently with our study, the PLT/LV cohort experienced the best prognosis with ADT, while DN/HV had the worst outcomes and a halving of survival compared to PLT/LV in the GETUG-AFU15 dataset [34.0 (28.5 – 43.6) vs. NR (69.8 – NR) months] [17]. Collectively, these results suggest that DN/HV disease is a biologically distinct entity which is less androgen dependent and has a more aggressive phenotype. In our study, some biological evidence is provided by the observation that DN patients have a two-fold higher rate of biopsy GS ≥ 8 (72%) compared to PLT (34%). Besides, absence of pain and ECOG PS = 0 were more common among patients with PLT than DN, 70% and 78% vs. 51% and 65%, respectively, and median PSA at ADT start was notably higher in DN compared to PLT (Table 1). Furthermore, in both above-mentioned post-hoc trial-based analyses, DN/HV was shown to be the only group to benefit from the chemohormonal regimen. While the survival improvement was only numerical in the GETUG-AFU15 analysis, it was statistically significant in the CHAARTED study (HR = 0.63; P = 0.0004) [16,17]. These data further corroborate the hypothesis that DN/HV may be a less testosterone dependent disease for which the addition of chemotherapy to ADT can be more beneficial. Conversely, there appears to be no benefit of chemotherapy in PLT/LV patients who have a prolonged response to ADT [16,17]. The intermediate prognostic group, PLT/HV or DN/LV, represents a greyer area as some of these patients may profit from the addition of docetaxel to hormone therapy, which highlights the need of accurate biomarkers for identification, whereas other subjects would probably benefit more from a different treatment. In this respect, while recent data from the early analysis of the large phase III randomized LATITUDE trial support the validity of the addition of abiraterone acetate plus prednisone to ADT as a new option for mHSPC patients with DN disease and poor prognostic features (HR = 0.62, 95% CI: 0.51 – 0.76; P < 0.001), the latest results of the multiarm STAMPEDE trial show that this combination is more effective than ADT alone for mHSPC patients (HR = 0.61; 95% CI: 0.49 – 0.75) [11–12]. Notably, 94% of the STAMPEDE metastatic population had DN disease but, since disease burden in this subgroup was not defined, the classification in LV vs. HV cannot be done. In addition, more research focusing on pts with PLT and/or LV disease would be needed to confidently state that the upfront combination of ADT and abiraterone is better than sequential treatment in these unique patient cohorts.

The 3 prognostic groups identified in the present study may predict distinct outcomes with different therapies and this classification could ultimately be an efficient tool to personalize treatment and avoid unnecessary toxicity. A definitive confirmation could come from future prospective studies which should stratify patients using this prognostic system based on history of prior local therapy and volume of metastases.

In the past, several studies proposed different prognostic classifications for mHSPC treated with ADT. Most of them took into consideration the disease burden, often defined according to the number of metastases on the bone scan [9,19] or whether axial or extra-axial [8,9]. While identifying the correct number of metastases can be challenging, especially when confluent, a selection based solely on location may be misleading, especially in case of a solitary appendicular lesion. The Glass prognostic system was based on the latter and other factors, such as ECOG PS, PSA levels, and biopsy GS, validated from a large randomized clinical trial dataset [9]. As in our study, this classification would allow identifying 3 prognostic groups predictive of survival. However, a statistical limitation of the Glass classification study was the low R^2 values for the test and validation model (13% and 12%, respectively). Besides, while this classification based on 4 factors identifies prognostic groups with significantly different outcomes, segregation is not intuitive and lacks the reproducibility necessary for routine clinical use which was observed with our easily applicable model of stratification based on 2 clinically meaningful factors. Furthermore, in our univariate analysis, ECOG PS and biopsy GS did not result in being independent prognostic factors (Table 3). It could be postulated that both these covariates were trumped by the more potent prognostic factors of time of metastatic disease presentation and volume of disease as these are clinical variables that presumably represent disease biology more accurately. Namely, DN/HV disease is usually rapidly progressive and thus probably represents a more aggressive multiclonal entity compared to PLT/LV.

Conversely, in multivariate analysis, the absence of cancer-related pain at time of start of ADT was confirmed an independent predictive factor of longer survival and time to CRPC for mHSPC patients (Table 3). However, this association was not as statistically robust as for PLT/LV and data regarding pain were extracted from clinical chart notations rather than from standardized pain assessments, which may limit the validity of this finding. Nevertheless, it should be noted that the absence of cancer-related pain has been found to be significantly related to survival in several studies in the past [20,21].

The retrospective nature of the present study, the small size of the cohorts, and the wide accrual time window during which several new life-extending agents emerged, admittedly represent limitations which prevent us from drawing general conclusions. Additionally, further work for a complete evaluation of this simple prognostic classification requires assessment in different ethnic and socio-economic populations as well as part of a prospective validation study. However, our prognostic classification based on the volume of metastases and time of metastatic presentation provides an easy and intuitive model of stratification which would aid in the design of large-scale clinical trials allowing more accurate identification of the study population and more balanced randomization. In addition, a validated classification system would improve understanding of findings from phase II studies of novel treatments and guide subsequent larger trials. Finally, as also shown

in the CHAARTED and CHAARTED-GETUG-AFU15 combined analyses, it would also help in treatment-decision making process. Nevertheless, there remains an unmet need for molecular prognostic and predictive biomarkers of treatment in this setting to further advance personalized treatment.

Conclusions

The prognostic system based on time of metastatic presentation and E3805 defined volume of disease can be easily applied as a prognostic tool for counseling patients with mHSPC treated with ADT and can be a simple and reproducible stratification system for future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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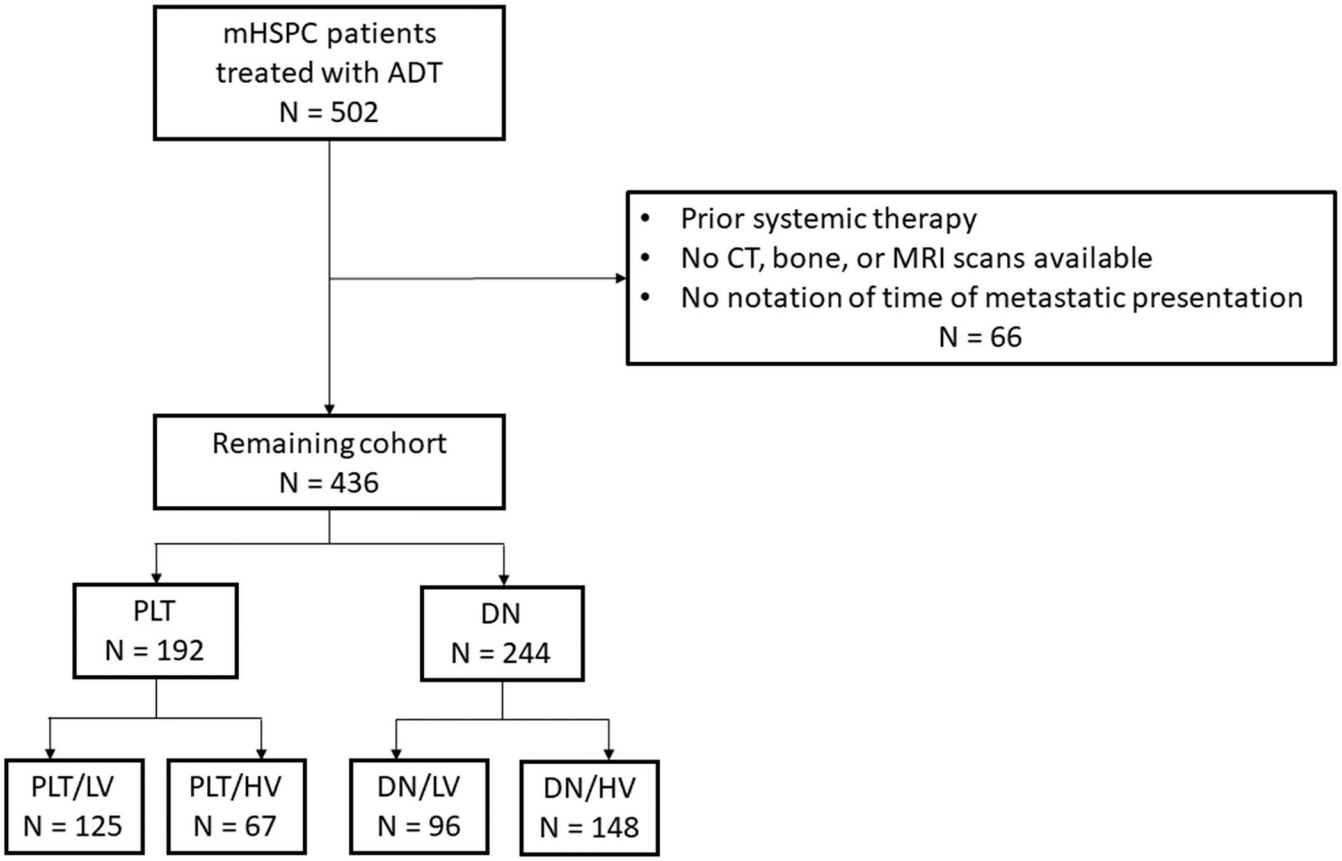

Figure 1 -
Study Flowchart
Legend: ADT = androgen deprivation therapy; DN = *de-novo*; HV = high volume; LV = low volume; mHSPC = metastatic hormone sensitive prostate cancer; PLT = prior local therapy

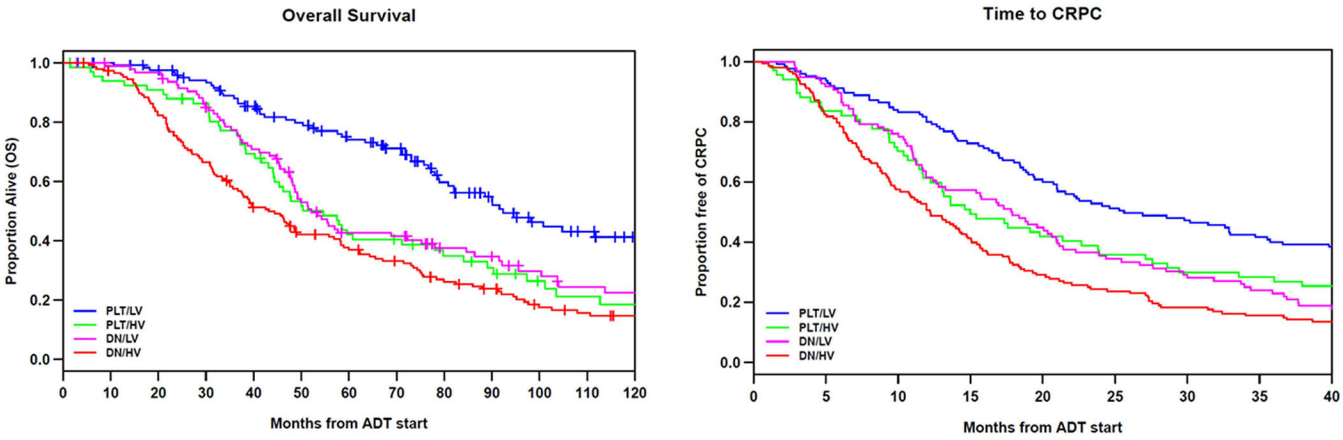

Figure 2 -

Overall Survival and Time to CRPC

Legend: ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; DN = *de-novo*; HV = high volume; LV = low volume; OS = overall survival; PLT = prior local therapy

Table 1.

Patient characteristics at time of presentation with metastatic disease

Characteristics	Total N = 436	Prior Local Therapy, N = 192	De-novo, N = 244
Age, years			
Median	62	61	63
Range	56 – 68	57 – 66	55 – 70
Race, N (%)			
White	373 (86)	174 (91)	199 (82)
Unknown	63 (14)	18 (9)	45 (18)
Biopsy Gleason Score, N (%)			
≤ 6	74 (17)	53 (28)	21 (9)
7	103 (24)	65 (34)	38 (15)
8–10	216 (49)	62 (32)	154 (63)
Unknown	43 (10)	12 (6)	31 (13)
Year of diagnosis, N (%)			
< 2004	200 (46)	114 (60)	86 (35)
2004 – 2009	193 (44)	64 (33)	129 (53)
> 2009	27 (6)	4 (2)	23 (9)
Unknown	16 (4)	10 (5)	6 (3)
Extent of disease, N (%)			
Node only	78 (18)	44 (23)	34 (14)
Bone plus/minus node	333 (76)	133 (69)	200 (82)
Viscera plus any	25 (6)	15 (8)	10 (4)
Cancer related pain, N (%)			
No pain	259 (59)	134 (70)	125 (51)
Pain	98 (23)	32 (16)	66 (27)
Unknown	79 (18)	26 (14)	53 (22)
ECOG performance status, N (%)			
0	308 (71)	150 (78)	158 (65)
≥ 1	45 (10)	15 (8)	30 (12)
Unknown	83 (19)	27 (14)	56 (23)
Median PSA, ng/mL (IQR)	31 (12 – 140)	14 (6 – 39)	75 (21 – 325)
Unknown, N (%)	11 (3)	5 (3)	6 (2)
Alkaline Phosphatase, N (%)			
Normal	130 (30)	86 (45)	44 (18)
Abnormal	45 (10)	18 (9)	27 (11)
Unknown	261 (60)	88 (46)	173 (71)
Median Follow-up, years (95% CI)	9.6 (8.9 – 10.5)	8.9 (7.9 – 10.2)	10.5 (9.6 – 15)

Table 2.

Overall survival and time to CRPC

Groups	N (% events)	N = 436 (%)	5-yr OS-free, (%) (SE)	Median OS, months (95% CI)	HR (95% CI)	P-trend	Log-rank P-value
PLT/LV	125 (50)	125 (29)	74 (4.2)	92.4 (80.4 – 127.2)	1	<0.0001	<0.0001
PLT/HV	67 (75)	67 (15)	42 (6.2)	55.2 (44.4 – 80.4)	1.9 (1.31 – 2.75)		
DN/LV	96 (70)	96 (22)	43 (5.2)	51.6 (48 – 78)	1.64 (1.16 – 2.31)		
DN/HV	148 (84)	148 (34)	37 (4)	43.2 (37.2 – 56.4)	2.48 (1.83 – 3.36)		
Groups	N (% events)	N =436 (%)	10-mos CRPC-free, (%) (SE)	Median CRPC, months (95%CI)	HR (95% CI)	P-trend	Log-rank P-value
PLT/LV	125 (100)	125 (29)	83 (3.3)	25.6 (21 – 35.7)	1	<0.0001	<0.0001
PLT/HV	67 (100)	67 (15)	70 (5.6)	15 (12.2 – 23.9)	1.62 (1.2 – 2.19)		
DN/LV	96 (100)	96 (22)	76 (4.4)	17.9 (12.8 – 21.1)	1.61 (1.23 – 2.11)		
DN/HV	148 (100)	148 (34)	57 (4.1)	12.2 (9.8 – 14.8)	2.09 (1.63 – 2.66)		

P-trend: 1 degree of freedom (df) Wald test p-value to indicate the (trend) association

Log-rank test (score test) P-value: to assess the heterogeneity of the risk groups

DN = *de-novo*; HV = high volume; LV = low volume; PLT = prior local therapy; SE = standard error

Table 3.

Associations of potential baseline covariates with CRPC and OS

Covariates	CRPC, HR (95%CI)	P-value	OS, HR (95%CI)	P-value
Gleason score = 7 vs. ≤ 6 (ref)	0.9 (0.67 – 1.22)	0.508	0.85 (0.58 – 1.24)	0.398
Gleason score ≥ 8 vs. ≤ 6 (ref)	1.25 (0.96 – 1.63)	0.093	1.26 (0.91 – 1.74)	0.166
Median PSA (one log10 unit change)	1.33 (1.19 – 1.48)	< 0.001	1.23 (1.09 – 1.4)	0.001
Median Age > 62 vs. ≤ 62 years (ref)	1.04 (0.85 – 1.26)	0.721	1.19 (0.94 – 1.49)	0.142
ECOG PS ≥ 1 vs. = 0 (ref)	1.22 (0.89 – 1.67)	0.217	1.23 (0.86 – 1.77)	0.257
Pain vs. No pain (ref)	1.47 (1.17 – 1.86)	0.001	1.56 (1.19 – 2.04)	0.001
Year of diagnosis < 2004 vs. > 2009 (ref)	0.49 (0.32 – 0.73)	< 0.001	0.74 (0.4 – 1.37)	0.337
Year of diagnosis 2004 – 2009 vs. > 2009 (ref)	0.92 (0.62 – 1.38)	0.694	1.32 (0.71 – 2.44)	0.377
Extent of disease Bone plus/minus node vs. Node only (ref)	1.28 (1 – 1.65)	0.048	1.58 (1.14 – 2.19)	0.006
Extent of disease Viscera plus any vs. Node only (ref)	0.92 (0.59 – 1.45)	0.722	1.12 (0.63 – 2)	0.698

Trend-test = test of trend effect (Bone only vs. Node only vs. Bone plus node vs. Viscera plus any)

CRPC = castration-resistant prostate cancer; OS = overall survival; ref = reference

Table 4.

Multivariate analysis adjusted for potentially significant covariates in a subset of N=335 with all available covariates data

Groups	Time to CRPC, HR (95%CI)	P-value	OS, HR (95%CI)	P-value
PLT/HV vs. PLT/LV (ref)	1.71 (1.19 – 2.45)	0.004	1.95 (1.24 – 3.06)	0.004
DN/LV vs. PLT/LV (ref)	1.12 (0.78 – 1.62)	0.541	1.4 (0.88 – 2.22)	0.151
DN/HV vs. PLT/LV (ref)	1.47 (1.04 – 2.07)	0.028	1.79 (1.16 – 2.76)	0.009
Median PSA (one log10 unit change)	1.24 (1.07 – 1.44)	0.004	1.05 (0.88 – 1.26)	0.585
Pain vs. No pain (ref)	1.3 (1 – 1.7)	0.054	1.4 (1.04 – 1.89)	0.029
Year of diagnosis < 2004 vs. > 2009 (ref)	0.82 (0.53 – 1.28)	0.386	1.03 (0.54 – 1.96)	0.932
Year of diagnosis 2004 – 2009 vs. > 2009 (ref)	0.4 (0.25 – 0.64)	< 0.001	0.59 (0.3 – 1.15)	0.123
Extent of disease Bone plus/minus node vs. Node only (ref)	0.93 (0.68 – 1.28)	0.672	1.19 (0.79 – 1.8)	0.398
Extent of disease Viscera plus any vs. Node only (ref)	0.73 (0.42 – 1.26)	0.254	0.81 (0.39 – 1.68)	0.568

DN: de novo; HV: high volume; LV: low volume; PLT: prior local therapy; ref: reference.