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Original article

Metastatic burden in newly diagnosed hormone-naive metastatic prostate cancer: Comparing definitions of CHAARTED and LATITUDE trial

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Abstract

Objectives: No uniformity exists in the definition of metastatic burden in metastatic hormone-naive prostate cancer (mHNPC) across clinical trials making their comparison challenging. We explored definition agreement and prognostic significance of bulky mHNPC according to the CHAARTED and LATITUDE trial.

Materials and methods: Since 2014, 95 patients with newly diagnosed mHNPC were prospectively registered. For this study, they were categorized as having high-volume (HVD) vs. low-volume (LVD) and high-risk (HRD) vs. low-risk disease (LRD) according to the definition of CHAARTED and LATITUDE, respectively. Agreement was tested using Cohen's κ coefficient. The Kaplan-Meier method was used to compare castration-resistant prostate cancer-free survival (CRPC-FS) and overall survival (OS). Prognostic significance was analyzed using Cox regression models.

Results: In total, 44 (46%) and 46 (48%) patients showed HVD and HRD, respectively. Cohen's κ coefficient was 0.83 indicating "almost perfect" agreement ($P < 0.001$).

Median CRPC-FS was 40 (95% CI: 25–55) vs. 11 months (95% CI: 8–14) for LVD and HVD ($P = 0.001$); 40 (95% CI: 27–53) vs. 11 months (95% CI: 8–14) for LRD and HRD ($P < 0.001$), respectively. Median OS was not reached vs. 51 months (95% CI: 0–102) for LVD and HVD ($P = 0.001$); not reached vs. 51 months (95% CI: 2–100) for LRD and HRD ($P = 0.003$), respectively. The prognostic significance of both definitions remained significant in the multivariate model for CRPC-FS ($P = 0.012$ and $P = 0.003$).

Conclusions: There is an excellent agreement between the definitions of bulky mHNPC in the CHAARTED and LATITUDE trial. Both definitions have significant prognostic value for predicting worse CRPC-FS and OS.

Keywords: Prostate cancer; Metastatic load; Hormone sensitive; CHAARTED; LATITUDE; Outcome

1. Introduction

Since 1940, androgen deprivation therapy (ADT) has been the cornerstone in the treatment of newly diagnosed metastatic hormone-naive prostate cancer (mHNPC) [1,2].

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Considering the rather disappointing outcomes under ADT only for patients with mHNPC (median overall survival [OS] of 42 months) [3], interest emerged in concomitant administration of systemic treatments. Combined therapy with ADT and docetaxel has been studied in 3 randomized controlled phase 3 trials (GETUG-AFU 15 [4], CHAARTED [5], and STAMPEDE [6]). Meta-analyses have demonstrated a survival benefit for combined docetaxel and ADT relative to ADT alone in mHNPC [7,8]. This led to docetaxel becoming part of the standard of care treatment for suitable patients with mHNPC.

The GETUG-AFU 15 [4] and CHAARTED [5] trial evaluated the impact of the metastatic burden. The GETUG-AFU 15 trial showed no survival benefit in the total cohort nor in the subgroup analysis according to Glass risk groups [9] making this risk stratification not directly relevant for further implementation. The subgroup analysis from the CHAARTED trial suggested that patients with high-volume disease (HVD) will have a larger benefit from upfront combination therapy compared to patients with a low-volume metastatic burden [5].

Subsequently, the concomitant administration of ADT and abiraterone acetate also showed a survival benefit in two randomized controlled phase 3 trials (STAMPEDE [10] and LATITUDE [11]). In the STAMPEDE trial, these result were consistent when performing a subanalysis regarding the metastatic status [10]. The LATITUDE trial on the other hand, only included patients with high-risk disease (HRD) anticipating their poor prognosis [11]. Table 1 shows an overview of the OS of trials combining ADT to other systemic treatments in patients with mHNPC.

To describe the metastatic burden in prostate cancer, no uniformly accepted definition exists. There are several prognostic nomograms in metastatic prostate cancer to predict the prognosis in mHNPC [9] and CRPC [12–14] but in practice these are rarely applied to guide therapy. Furthermore, having multiple definitions might cause confusion in terms of utilization of these risk stratification factors in the real world clinical use.

The primary objectives of this study were firstly to explore whether the definitions of bulky mHNPC used in the CHAARTED and LATITUDE trial are compatible (definition agreement). Secondly, the prognostic significance of HVD and HRD was tested in a daily practice cohort of patients with mHNPC.

2. Material and methods

2.1. Trial design and patients

Between May 2014 and July 2017, all patients with newly diagnosed mHNPC at Ghent University Hospital were offered to sign an informed consent for prospective registration (Belgian registration number B670201420709; EC 2014-0328). Metastatic prostate cancer was defined as histologically confirmed prostate cancer and the presence of at least 1 metastatic lesion after staging using thoraco-abdominopelvic computed tomography and bone scintigraphy. Exclusion criteria were patients with metastatic recurrence after prior local curative treatment, previous local or systemic therapy for prostate cancer or patients with regional lymph node metastasis only (N1M0). Digital rectal examination, transrectal ultrasound, and/or multiparametric-magnetic resonance imaging of the prostate were used for local staging (T-stage). Tumor grade group was assessed using the 2014 International Society of Urologic Pathology (ISUP) grading system [15]. Systemic treatment was offered according to multidisciplinary oncologic discussion and in concordance with contemporary guidelines of the European Association of Urology (EAU) [16]. Starting 2016, docetaxel was added to ADT in high-volume patients. Available systemic therapies from the moment castration-resistance occurred, were secondary anti-hormonal agents (abiraterone

Table 1
Overview median overall survival in months of trials combining ADT with other systemic treatments in patients with mHNPC

	n	TOTAL		Hazard ratio (95% CI)	HVD/HRD		Hazard ratio (95% CI)	LVD/LRD		Hazard ratio (95% CI)
		ADT + systemic treatment	ADT only		ADT + systemic treatment	ADT only		ADT + systemic treatment	ADT only	
ADT ± DOCETAXEL										
GETUG-AFU 15	385	62	49	0.88 (0.68–1.14)	40	35	0.78 (0.56–1.09)	NR	83	(0.67–1.55)
STAMPEDE[a]	1,086	60	45	0.76 (0.62–0.92)*	NA	NA	NA	NA	NA	NA
CHAARTED	790	58	44	0.61 (0.47–0.80)*	49	32	0.60 (0.45–0.81)*	NR	NR	0.60 (0.32–1.13)
ADT ± ABIRATERONE										
STAMPEDE[b]	1,002	NR	46	0.61 (0.49–0.75)*	NA	NA	NA	NA	NA	NA
LATITUDE	1,199	NA	NA	NA	NR	35	0.62 (0.51–0.76)*	NA	NA	NA

NR = not reached; NA = not applicable.
*$P < 0.05$.
[a]Only metastatic patients included and exclusion of patients concomitantly treated with zolendronic acid.
[b]Only metastatic patients included.