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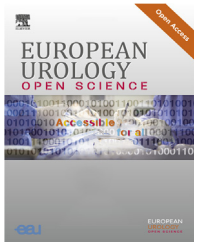

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Opinion: Open Science

Treatment Intensification for Low-risk Metastatic Hormone-sensitive Prostate Cancer: The Time Is Now

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The treatment landscape for metastatic hormone-sensitive prostate (mHSPC) has undergone dramatic changes within the past decade. Historically, androgen deprivation therapy (ADT) with or without a first-generation antiandrogen was the standard of care for patients with mHSPC, with treatment intensification including chemotherapy and androgen receptor signaling inhibitors (ARSIs) reserved for individuals with metastatic castration-resistant prostate cancer (mCRPC). In 2015, results from the landmark phase 3 CHAARTED [1] and STAMPEDE [2] trials catapulted us into the modern era of treatment intensification for patients with mHSPC. These two studies tested the simple question of whether addition of docetaxel to ADT would improve overall survival (OS) for patients with mHSPC. The trials were resoundingly positive. Subsequently, a series of phase 3 trials were reported that tested the addition of ARSIs including abiraterone (LATITUDE [3], STAMPEDE [4]), apalutamide (TITAN [5]), and enzalutamide (ARCHES [6], ENZAMET [7]) to ADT for men with mHSPC. The addition of each of these agents to ADT led to an improvement in OS for patients with mHSPC in the overall intent-to-treat (ITT) populations of these studies.

The CHAARTED trial integrated an a priori analysis of outcomes by volume of disease, setting in motion a shift in the field to more accurate assessment of patient risk to better inform therapy selection. CHAARTED included a stratification factor at enrollment that was based on the presence of high- or low-volume disease [1]. While the LATITUDE trial only accrued patients with high-risk disease [3], STAMPEDE [4], TITAN [5], ARCHES [6], and ENZAMET [7] enrolled all-comer patient populations. As detailed in the Open Horizon paper by Jazayeri and colleagues [8], in aggregate, data from these studies provide overwhelming evidence to support the earlier use of ARSIs for patients with mHSPC, including those with low-volume/low-risk disease (Table 1). Focusing on patients with low-volume/low-risk disease, it is important to understand the traditional definitions, the evolution of these definitions with integration of more sensitive prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging, additional clinical factors that inform risk assessment, application of triple-therapy strategies in this population, and real-world utilization of treatment intensification strategies for patients with mHSPC.

The CHAARTED trial defined high-volume disease as the presence of visceral metastases and/or four or more bone lesions of which one or more were outside the vertebra or pelvic bones [1]. This definition evolved from prior studies testing chemotherapy and first-generation antiandrogens for men with mHSPC [9]. While this may not fully capture disease burden, as individuals with bulky diffuse adenopathy would have been classified as having low-volume disease and individuals with an isolated pulmonary metastasis as having high-volume disease, the definition is prognostic, with consistently better OS for patients with low-volume disease across the phase 3 mHSPC studies. Furthermore, although the CHAARTED definition of high-volume disease does not fully overlap with the LATITUDE definition of high risk (defined as two of the following three criteria: Gleason score $\geq$8, three or more bone lesions, and the presence of visceral metastases), there is substantial overlap and both definitions are prognostic. An analysis from the STAMPEDE trial evaluating the benefit of abiraterone in both low-risk and low-volume cases demonstrated that 78% of patients defined as having low-risk disease according to LATITUDE had low-volume disease

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Table 1 – Randomized controlled trials in metastatic hormone-sensitive prostate cancer for patients with low-volume disease

Trial	Experimental arm	Control arm	Patients with LVD	HR for OS for LVD
LATITUDE	Abiraterone + PDN + ADT	ADT	243	0.72
STAMPEDE Arm G	Abiraterone + PDN + ADT	ADT	428	0.66
TITAN	Apalutamide + ADT	ADT[a]	392	0.67
ARCHES	Enzalutamide + ADT	ADT[a]	423	0.66
ENZAMET	Enzalutamide + ADT	ADT + NSAA (± DOC)	537	0.43

ADT = androgen deprivation therapy; DOC = docetaxel; HR = hazard ratio; LVD = low-volume disease; NSAA = nonsteroidal antiandrogen; PDN = prednisone; OS = overall survival.
[a] Allowed prior DOC.

according to CHAARTED, and 83% of patient defined as having low-volume disease according to CHAARTED had low-risk disease according to LATITUDE [10]. In addition, both low-volume and low-risk groups had relatively longer survival than the groups with high-volume/high-risk disease.

As PSMA PET imaging becomes more common, it is important to note that the CHAARTED and LATITUDE low-volume/low-risk disease definitions have only been validated using conventional imaging (computed tomography, magnetic resonance imaging, and ^{99m}Tc bone scans). Application to PSMA PET has not yet been established and prospective clinical trials are warranted to define low-volume/low-risk and even oligometastatic disease that could be amendable to focal therapy using PSMA PET.

Additional clinical parameters have emerged that impact outcomes, including the presence of metachronous or synchronous distant metastases [11]. A growing body of evidence has demonstrated that patients with metachronous disease appear to have more favorable outcomes. While the classic definitions of low-volume/low-risk disease do not account for this clinical feature, given the potential for therapeutic implications, it is an important clinical factor to consider. Data from STAMPEDE support the role of prostate radiation for patients with synchronous low-volume mHPSC.

While data support doublet therapy with ADT and an ARSI for patients with low-volume/low-risk mHSPC, the role of triple therapy with ADT, docetaxel, and ARSI is still evolving for patients with low-volume/low-risk disease. The PEACE-1 trial investigated the role of ADT and docetaxel ± abiraterone for patients with mHSPC [12]. While there was a clear benefit for triple therapy in the overall study population and those with high-volume disease, the benefit was not observed for patients with low-volume disease (hazard ratio 0.83, 95.1% confidence interval 0.50–1.39; p = 0.66). Inspection of the Kaplan-Meier OS curves for docetaxel-treated patients with low-volume disease, with median follow-up of 3.8 yr, reveals that the curves initially overlap, with a low number of events. Although longer follow-up is warranted, demonstration of an OS benefit in this setting may be elusive given the low number of patients, low number of events, and effective subsequent therapies. The ARASENS trial also evaluated the role of triple therapy with ADT, docetaxel, and darolutamide compared to placebo; however, subset analyses by disease volume/risk are not yet available [13].

Lastly, while several large phase 3 trials have now provided level 1 evidence to support the role of treatment intensification with either chemotherapy or an ARSI for patients with mHSPC, the sobering statistics are that treatment escalation is underutilized. A study of real-world evidence involving more than 66 000 men newly diagnosed with mHSPC since 2015 demonstrated that on average only 25% received an ARSI and 12% received chemotherapy [14]. While these data are not broken down by disease volume and risk, there is a clear need to understand barriers to therapy intensification in clinical practice and to implement measures to promote evidence-based practice for men with mHSPC.

In conclusion, there has been tremendous improvement in outcomes for patients with advanced prostate cancer given strategies to intensify therapy early on. The development of strategies to improve education and increase application to clinical practice is warranted so that men can reap the long-term survival benefit of treatment. Many trials are testing treatment intensification for patients with localized disease (PROTEUS, NCT03767244; PREDICT-RT, NCT04513717) and biochemically recurrent disease (PRESTO, NCT03767244; EMBARK NCT02319837) and these will further shape the treatment landscape for patients with prostate cancer.

Conflicts of interest: Rana R. McKay serves as an advisory board member/consultant for Aveo, AstraZeneca, Bayer, Bristol-Myers Squib, Calithera, Caris, Dendreon, Exelixis, Eli Lilly, Janssen, Merck, Myovant, Novartis, Pfizer, Sanofi, Sorrento Therapeutics, Tempus, and Telix, and has received research funding from Bayer and Tempus.

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