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**Review Article**

# Current landscape in first-line treatment of metastatic hormone sensitive prostate cancer: a cost-effectiveness focused review

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## Abstract

Contemporary treatment of metastatic hormone-sensitive prostate cancer (mHSPC) has evolved significantly over the past decade with the introduction of upfront combination therapies (ie, ADT plus androgen receptor pathway inhibitors (ARPIs), with or without docetaxel), previously reserved for more advanced stages of the disease. However, the evidence is still controversial regarding the benefit of triple combinations beyond high volume disease (HVD) compared to double combinations, particularly those consisting of ADT + ARPIs. In addition, financial considerations regarding net benefits make these treatment regimens an unfavorable option from a cost-effectiveness standpoint, an element that becomes even more relevant in resource-limited contexts. Considering the lack of head-to-head trials for the direct comparison of triplets vs. ADT + ARPIs in different subgroups (as most evidence of specific combination superiority comes from indirect comparison in meta-analyses and the questionable cost-effectiveness profile triplets have shown), we propose that the current role of triplets is reserved for synchronous, HVD mHSPC in a resource-rich setting. Consequently, our work proposes a treatment algorithm that weighs the OS benefit according to the clinical risk of each patient subgroup and the availability of clinical resources. In this current scenario of abundant options, future research will focus on clarifying the selection of the most appropriate treatment for each patient according to their clinical characteristics and re-evaluating the cost-effectiveness of treatments as new drugs and generics emerge.

**Key words:** metastatic hormone-sensitive prostate cancer; androgen receptor pathway inhibitors; docetaxel; first-line combination therapy; standard of care; real-world treatment patterns; cost-effectiveness.

### Implications for practice

We present a narrative review of landmark trials that have changed a half-century-old paradigm and shaped the contemporary management of mHCSPC, as reflected by current international guidelines. This work provides a critical analysis and indirect comparison of upfront combination treatment regimens based on meta-analyses, real-world prescription data and cost-effectiveness studies. The findings of this review have been translated into a proposed resource-adjusted algorithm based on the current therapeutic landscape for the first-line treatment of mHSPC.

## Introduction

Prostate cancer (PCa) is the second most common neoplastic disease.[1] Most PCa cases are diagnosed in asymptomatic patients with early-stage disease: 69% have localized disease, 13% have regional lymph node involvement, and 8% have distant metastasis (U.S. SEER data).[2] However, stage distribution at diagnosis may differ in developing countries, possibly due to reduced access to mass screening compared to developed countries.[3,4]

Metastatic PCa (mPCa) is a critical stage given its incurable nature and association with morbidity (eg, complications such as skeletal related events and urethral obstruction)[5] and mortality (metastasis-free survival is used as a surrogate outcome for overall survival (OS) in localized PCa).[6] mPCa is initially responsive to androgen deprivation therapy (ADT), a stage referred to as metastatic hormone-sensitive prostate cancer (mHSPC). Consequently, ADT has been the cornerstone of mPCa treatment for decades. However, despite an initial response to ADT, progression typically occurs within 1-2 years of ADT initiation.[7] Progression despite ADT is a hallmark of metastatic androgen deprivation-resistant

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prostate cancer (mARPC), from which most PCa deaths result.[8]

The mCSPC therapeutic landscape has changed significantly over the past decade with the introduction of combination therapies (ie, ADT plus androgen receptor pathway inhibitors (ARPIs), with or without docetaxel). Combination strategies have consistently shown benefit in OS over ADT, and guidelines have been updated accordingly, recommending combination therapy as the standard of care (SoC). However, head-to-head comparisons are lacking, and indirect meta-analyses are conflicting, with uncertainties about the optimal treatment for specific subgroups based on disease presentation and volume. Additionally, combination therapies increase treatment costs, posing challenges for clinicians, patients, and healthcare systems.

The present narrative review analyzes landmark trials that reshaped the contemporary management of mHSPC, as reflected by current guidelines. We provide a critical analysis and indirect comparison of upfront combination treatment regimens based on meta-analyses, real-world prescription data and cost-effectiveness studies. The findings are used to propose a resource-adjusted algorithm for first-line mHSPC treatment.

## Upfront systemic therapy combinations

### ADT plus docetaxel

The CHAARTED study was the first trial to show compelling evidence in favor of upfront systemic therapy combinations for mHSPC after decades of ADT as the sole SoC. Patients ($n$ = 790) with mHSPC were randomized to receive either ADT + docetaxel or ADT alone. Median OS was 13.6 months longer with docetaxel than ADT alone (57.6 months vs. 44.0 months; hazard ratio (HR) 0.61, 95% confidence interval (CI, ) 0.47–0.80, $P$ < 0.001). Results also showed a benefit in progression-free survival (PFS) favoring the docetaxel group (20.2 months vs. 11.7 months, HR 0.61, 95% CI, 0.51–0.72, $P$ < 0.001).[9]

Notably, docetaxel showed a more robust OS response in patients with high-volume disease (HVD), compared with ADT-alone group (49.2 months vs. 32.2 months, respectively; HR 0.60, 95% CI, 0.45–0.81, $P$ < 0.001).[9] HVD was defined as visceral metastases and/or ≥ 4 bone metastases with at least one metastasis outside of the spine/pelvis.[10] An update of the CHAARTED trial was published in 2018, showing that, at a median follow-up of 53.7 months, the median OS was 57.6 months for the docetaxel arm vs. 47.2 months for ADT alone (HR 0.72, 95% CI, 0.59–0.89, $P$ = 0.0018). For patients with HVD ($n$ = 513), the median OS was 51.2 months with docetaxel vs. 34.4 months with ADT alone (HR 0.63, 95% CI, 0.50–0.79, $P$ < 0.001). For those with low-volume disease (LVD) ($n$ = 277), no OS benefit was observed (HR 1.04, 95% CI, 0.70–1.55, $P$ = 0.86).[11]

Before CHAARTED, GETUG-AFU15 randomized 385 patients to receive either ADT + docetaxel or ADT alone. Median OS was 58.9 months (95% CI, , 50.8–69.1) in the intensification group and 54.2 months (42.2-not reached) in the ADT group (HR 1.01, 95% CI, 0.75–1.36), suggesting no benefit of docetaxel in first-line mHSPC treatment..[12] An updated analysis (median follow-up: 83.9 months) showed a nonsignificant 20% reduction in mortality risk in the HVD intensification subgroup. Patients with LVD had no survival improvement with docetaxel. Limitations of this study include retrospective analysis of metastatic extent and lack of statistical power to detect a significant difference in subgroups.[13]

Data from the open-label STAMPEDE trial (arm C) supported the CHAARTED results by showing an OS benefit of intensification vs. ADT alone. A critical weakness of this trial lies in the heterogeneity of its population: 1817 (61%) men had M + disease, 448 (15%) had N+/X M0, and 697 (24%) had N0M0.[14] Despite this, a post hoc analysis of M1 patients stratified by CHAARTED disease volume criteria showed evidence of the benefit of docetaxel over SoC on OS (HR 0.81, 95% CI, 0.69–0.95, $P$ = 0.009), with a similar benefit of docetaxel for patients with HVD (OS HR 0.81, 95% CI, 0.64–1.02, $P$ = 0.064), and LVD (OS HR 0.76, 95% 0.54–1.07, $P$ = 0.107).[15]

A 2018 Cochrane systematic review and meta-analysis that included 2261 patients from the GETUG-AFU15, CHAARTED, and STAMPEDE trials indicated that early treatment with ADT + docetaxel likely reduces overall mortality compared with ADT alone (HR 0.77, 95% CI, 0.68–0.87; moderate-certainty evidence). For HVD, the OS HR was 0.67 (95% CI, 0.56–0.82), and for LVD, the HR was 1.03 (95% CI, 0.77–1.38). The treatment effect may be greater for participants with HVD than for those with LVD, but the included trials were not designed nor powered to assess subgroup effects.[16]

A 2023 meta-analysis of the aforementioned trials endorsed the use of ADT + docetaxel, confirming clear benefits on OS (HR 0.79, 95% CI, 0.70–0.88, $P$ < 0.0001), PFS (HR 0.70, 95% CI, 0.63–0.77, $P$ < .0001), and failure-free survival (FFS) (HR 0.64, 95% CI, 0.58–0.71, $P$ < .0001), representing five-year absolute survival improvements of approximately 9%–11%. Notably, it showed no evidence of improved absolute OS at five years for patients with metachronous LVD compared to ADT alone (0%, 95% CI, –10% to 12%).[17]

### ADT plus abiraterone

In 2017, results from the double-blind, placebo-controlled LATITUDE trial, comparing ADT + abiraterone acetate + prednisone vs. ADT + placebo, showed significant improvement in median OS in the abiraterone group vs. the placebo group (not reached vs. 34.7 months) (HR 0.62, 95% CI, 0.51–0.76, $P$ < 0.001).[18] All patients had synchronous, high-risk disease (ie, at least two of the following: Gleason score ≥ 8, ≥ 3 bone lesions, or visceral metastases).

The STAMPEDE trial (arm G) randomized 1917 patients to ADT + abiraterone acetate + prednisolone or ADT + placebo, with a 52% rate of metastatic disease. The OS was superior in the combination group (HR, 0.63, 95% CI, 0.52–0.76, $P$ < .001) and the metastatic combination subgroup (HR 0.61, 95% CI, 0.49–0.75).[19] Interestingly, a post hoc analysis of STAMPEDE comparing 901 M1 patients stratified to high-risk and low-risk subgroups per LATITUDE criteria showed no heterogeneity of effect between both groups for OS or FFS.[20]

A 2020 Cochrane systematic review and meta-analysis included both aforementioned studies to evaluate the benefit of adding abiraterone to ADT in mHSPC, showing a reduction in the probability of overall mortality compared to ADT alone (HR 0.64, 95% CI, 0.56–0.73; two randomized controlled trials (RCTs), $n$ = 2201; high certainty of evidence).[21]

### ADT plus enzalutamide

The ARCHES trial randomized 1150 patients including both synchronous and metachronous disease to ADT + placebo vs. ADT + enzalutamide.[22] Patients were stratified by disease volume per CHAARTED criteria, and prior docetaxel chemotherapy for PCa. After adjustment for crossover effects (ARCHES was unblinded after the analysis showed the benefit of ADT + enzalutamide in radiographic PFS, which was the primary endpoint of the study), the authors reported a 43% reduction in mortality risk with ADT + enzalutamide vs.ADT + placebo (HR 0.57, 95% CI, 0.45–0.70, $P < .001$), which was consistent across prespecified subgroups.[23]

ENZAMET compared ADT + enzalutamide vs. ADT plus a first-generation antiandrogen in 1125 patients. Interim analysis showed OS improvement in the enzalutamide group (HR 0.67, 95% CI, 0.52–0.86, $P = .002$), independently of disease volume.[24] In a later analysis, with a median follow-up of 68 months (IQR 67–69), the median OS was not reached (HR 0.70, 95% CI, 0.58–0.84, $P < .0001$), with a five-year OS of 57% (0.53–0.61) in the control group and 67% (0.63–0.70) in the enzalutamide group. The OS benefits with enzalutamide were consistent across predefined prognostic subgroups and planned use of concurrent docetaxel.[25]

### ADT plus apalutamide

The TITAN trial randomized mHSPC patients to receive either ADT + apalutamide or ADT + placebo, ($n = 1052$, 62.7% HVD, 37.3% LVD). At 24 months, OS was greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; HR 0.67, 95% CI, 0.51–0.89, $P = .005$). After the first interim analysis, the trial was unblinded in January 2019, allowing placebo patients to crossover.[26] In a subsequent survival analysis, 208 placebo-treated patients (39.5%) had crossed over to apalutamide at a median follow-up of 44.0 months. Compared with placebo, apalutamide significantly reduced the risk of death by 48% after adjustment for crossover (HR 0.52, 95% CI, , 0.42–0.64, $P < .0001$).[27]

### ADT plus darolutamide

ARANOTE is the latest reported ARPI plus ADT trial for mHSPC, with 669 patients (71% HVD) randomized (2:1) to darolutamide plus ADT vs. placebo plus ADT.[28] Darolutamide + ADT showed significantly improved rPFS at 46% versus placebo (HR 0.54 95% CI, 0.41-0.71, $P < .0001$). Said benefit was consistent across subgroups, including HVD and LVD. Nevertheless, at the primary analysis cutoff date, OS benefit was not significant for darolutamide (HR 0.81 95% CI, 0.59-1.12). Additionally, incidence of adverse events was similar between treatment groups.

Notably, this study has received criticism due to the use of a control arm considered inferior to mHSPC SoC by the time of enrollment (March 2021—August 2022).[29] Authors of the study argue that given the geographic diversity of the study's patient population, combination treatment is not generally available and therefore not considered SoC at a local level.[30] Given the immaturity of present data, additional follow-up will help clarify the potential OS benefit of darolutamide.[31]

### Primary tumor-targeted therapy in mHSPC: ADT plus ERBT

HORRAD randomized 432 mHSPC patients to receive either ADT with external beam radiotherapy (EBRT) to the primary tumor or ADT alone (control group). The median follow-up was 47 months. No significant difference was found in the OS between groups (HR 0.90, 95% CI, 0.70–1.14, $P = .4$).[32]

The STAMPEDE (arm H) protocol randomized 2061 synchronous mHSPC patients to receive either ADT+/-docetaxel (once the CHAARTED protocol became the SoC, 18% of patients in each group received docetaxel) or ADT+/-docetaxel + EBRT. Patients were followed for a median of 61.3 months and stratified by disease volume per CHAARTED criteria. EBRT improved OS in patients with a low (HR 0.64, 95% CI, 0.52–0.79, $P < .001$), but not high (HR 1.11, 95% CI, 0.96–1.28, $P = .164$) metastatic burden. Interestingly, long-term urinary toxicity of grade 3 or worse was reported for 10 patients in each group. Long-term bowel toxicity of grade 3 or worse was reported for 15 and 11, respectively, showing no significant detriment in quality of life (QoL).[33]

A 2019 systematic review and meta-analysis pooled the HORRAD and STAMPEDE (H) trials (2126 men; 90% of those eligible), showing no improvement in OS (HR 0.92, 95% CI, 0.81–1.04, $P = .195$) or PFS (HR 0.94, 95% CI, 0.84–1.05, $P = .238$) with ERBT in unselected mHSPC. Nevertheless, the effect of prostate radiotherapy varied by metastatic burden, a pattern consistent across trials and outcome measures, including survival ($< 5, \geq 5$ bone metastases; interaction HR = 1.47, 95% CI, 1.11–1.94, $P = .007$). There was an OS benefit for men with less than 5 bone metastases (HR 0.73, 95% CI, 0.58–0.92, $P = .0071$), which translated into a 7% improvement in the 3-year survival rate.[34]

Conversely, recent data on subgroup data from PEACE-1 on the use of EBRT, shows that adding radiotherapy improved radiographic progression-free survival in patients with low-volume disease treated with abiraterone plus ADT ± docetaxel (HR 0.65, 99.9% CI, 0.36-1.19, $P = .019$), but not in patients not treated with abiraterone. No benefit was seen on OS.[35]

### ADT plus abiraterone and docetaxel

PEACE-1 is an open-label, randomized, phase 3 study with a 2 × 2 factorial design. The study enrolled 1172 synchronous mHSPC patients and assigned them to receive the SoC (ADT+/-docetaxel; $n = 296$), SoC + EBRT ($n = 293$), SoC + abiraterone ($n = 292$), or SoC + ERBT + abiraterone ($n = 291$). Patients receiving abiraterone ($n = 583$) had longer radiographic PFS (HR 0.54, 99.9% CI, 0.41–0.71, $P < .0001$) and OS (HR 0.82, 95.1% CI, 0.69–0.98, $P = .030$) vs. patients not receiving abiraterone ($n = 589$). Adjusted Cox regression modeling revealed no interaction between abiraterone and radiotherapy, enabling a pooled analysis of abiraterone efficacy. Moreover, in the population receiving ADT with docetaxel ($n = 355$ in both with and without abiraterone groups), the HRs were consistent (radiographic PFS HR 0.50, 99.9% CI, 0.34–0.71, $P < .0001$; OS HR 0.75, 95.1% CI, 0.59–0.95, $P = .017$). Notably, the survival benefit was significant for patients with HVD (HR 0.72, 95% CI, 0.55–0.95, $P = .019$) but not for those with LVD (HR 0.83, 95% CI, 0.5–1.38, $P = .66$).[36]

### ADT plus darolutamide and docetaxel

The ARASENS trial randomized 1306 mHSPC patients (86.1% synchronous) to receive darolutamide ($n = 651$) or placebo ($n = 655$), both in combination with ADT and docetaxel. The mortality risk was significantly lower (by 32.5%) in the darolutamide group than in the placebo group (HR 0.68, 95% CI, 0.57–0.80, $P < .001$).[37] Later analyses reported results in this cohort by prespecified subgroups according to disease volume (per CHAARTED) and risk (per LATITUDE). Of 1305 patients, 1005 (77%) had HVD, and 912 (70%) had high-risk disease. Darolutamide increased OS vs. placebo in patients with HVD (HR, 0.69, 95% CI, 0.57–0.82), high-risk (HR, 0.71, 95% CI, 0.58–0.86), and low-risk disease (HR, 0.62, 95% CI, 0.42–0.90). In the LVD subgroup, the results were suggestive of a survival benefit, although inconclusive, likely due to the small sample size in this subgroup (HR, 0.68, 95% CI, 0.41–1.13).[38]

## Selection of systemic therapy combinations

Timing of metastatic disease and disease volume are key in assessing progression and death risk in mHSPC patients, guiding inclusion criteria and subgroup analyses in landmark upfront combination studies. Consequently, proper categorization is crucial for selecting the optimal combination in personalized practice (see **Table 1** for a summary of landmark trials).

Triplet systemic therapy has found its place at the forefront of HVD mHSPC management, as it has been shown to effectively improve OS and other relevant outcomes in phase III trials.[40] Conversely, in LVD, triplets have failed to demonstrate a substantial benefit in OS in at least three meta-analyses.[41-43] Furthermore, a network meta-analysis by Roy *et al*. that included data from 11 RCTs (including PEACE-1 and ARASENS; $n = 11\,546$) showed that triplets did not confer a statistically significant OS benefit over ADT + ARPIs (HR 0.89, 95% CI, 0.68–1.16).[44] Another meta-analysis by Riaz *et al*. that included 10 RCTs ($n = 11043$) demonstrated the benefits of the darolutamide triplet (HR 0.68, 95% CI, 0.57–0.81) and abiraterone triplet (HR 0.75, 95% CI, 0.59–0.95) compared to ADT + docetaxel (but not to ADT + ARPIs) in the overall population. Moreover, in LVD, the abiraterone triplet may not provide an OS benefit over doublets.[43] Currently, head-to-head trials for the direct comparison of triplets vs. ADT + ARPIs in different subgroups are lacking, and most evidence of specific combination superiority comes from indirect comparisons in meta-analyses.

## Practical considerations: real-world treatment patterns and cost-effectiveness analyses

Phase III trial results supporting upfront combinatorial therapy have led medical organizations to update their guidelines (see **Table 2**). However, real-world data on mHSPC treatment patterns differs significantly from these evidence-based recommendations.

A retrospective study by Ryan et al analyzed insurance claim data from 19 841 mHSPC patients (2014-2019), showing 2%-13% used abiraterone acetate or docetaxel, 45%-46% used only ADT, and 38%-48% remained untreated or

**Table 1.** Trials on systemic therapy combinations for mHSPC. Trials on systemic therapy combinations for mHSPC.

| Trial | First report | *n* | Synchronous % | Intervention (Comparator) | OS: HR (CI, 95%) | PFS: HR (CI, 95%) |
|---|---|---|---|---|---|---|
| CHAARTED[9,11] | 2015 | 790 | 72.8 | DOC + ADT (ADT) | 0.61 (0.47-0.8), $P < 0.001$ | 0.61 (0.51-0.72), $P < 0.001$ |
| STAMPEDE (C)[14,15] | 2016 | 1086 | 95 | DOC + ADT (ADT) | 0.78 (0.66-0.93), $P = 0.006$ | *0.61 (0.53-0.70), $P = 0{\cdot}413 \times 10^{-13}$ |
| LATITUDE[18] | 2017 | 1199 | 100 | AAP + ADT (placebo + ADT) | 0.62 (0.51-0.76), $P < 0.001$ | 0.47 (0.39-0.55), $P < 0.001$ |
| STAMPEDE (G)[19,20] | 2017 | 1003 | 93.8 | AAP + ADT (ADT) | 0.63 (0.52-0.76), $P < 0.001$ | 0.29 (0.25-0.34) $P < 0.001$ |
| STAMPEDE (H)[33,39] | 2018 | 2061 | 100 | ERBT + ADT+/-DOC (ADT+/-DOC) | #0.68 (0.52-0.90), $P = 0.001$ | #0.78 (0.63-0.98) |
| ARCHES[22] | 2019 | 1150 | 73.4 | ENZ + ADT (placebo + ADT) | 0.57 (0.45-0.70), $P < 0.001$) | 0.39 (0.30-0.50), $P < 0.001$ |
| ENZAMET[24,25] | 2019 | 1125 | 58.0 | ENZ + ADT (NSAA + ADT) | 0.67 (0.52—0.86), $P = 0.002$ | 0.40 (0.33-0.49), $P < 0.001$ |
| TITAN[26,27] | 2019 | 1052 | 83.6 | APA + ADT (placebo + ADT) | 0.67 (0.51-0.89), $P = 0.005$ | 0.48 (0.39-0.60), $P < 0.001$ |
| PEACE-1[36] | 2022 | 1173 | 100 | AAP + DOC + ADT (DOC + ADT) | 0.75 (0.59–0.95), $P = 0.017$ | 0.50 (0.34-0.71), $P < 0{\cdot}0001$ |
| ARASENS[37,38] | 2022 | 1306 | 86.1 | DAR + DOC + ADT (placebo + DOC + ADT) | 0.68 (0.57–0.80), $P < 0.001$ | Not described among secondary endpoints |
| ARANOTE | 2024 | 669 | 71 | DAR + ADT (placebo + ADT) | 0.81 (0.59-1.12) | 0.54 (0.41-0.71), $P < 0.0001$ |

Abbreviations: ADT, androgen deprivation therapy; DOC, docetaxel; AAP, abiraterone acetate plus prednisone; ENZ, enzalutamide; APA, apalutamide; ERBT, external beam radiotherapy; NSAA, first-generation nonsteroidal antiandrogen (flutamide, nilutamide, bicalutamide, etc.); DAR, darolutamide. Specified OS and PFS at first report. *Failure-free survival, #: low volume disease subgroup.

**Table 2.** Recommendation summary of relevant clinical practice guidelines.

| Treatment (including ADT) | AUA/SUO[8] | CUA/CUOG[45] | EAU[46] | NCCN[47] | ASCO[48] | ESMO[49] | NICE[50] |
|---|---|---|---|---|---|---|---|
| Docetaxel | Strong (High) | Strong (High)[b]& Weak (Moderate)[c] | Strong (High) | Strong (Moderate, only as adjuvant to ERBT)[bd,ac] | Strong (High)[b] | Strong (High) | Strong (High)[a] |
| External Beam Radiotherapy | Conditional (Low)[c] | Strong (Moderate)[c] | Strong (Moderate)[ac] | Strong (High)[ac] | - | Strong (High)[c] | - |
| Abiraterone | Strong (High) | Strong (High)[e] Weak (Low)[c] | Strong (High) | Strong (High)[ab, bd,ac,cd] | Strong (High)[e] | Strong (High) | - |
| Enzalutamide | Strong (High) | Strong (High) | Strong (High) | Strong (High)[ab, bd,ac,cd] | Strong (High)[d] | Strong (High) | - |
| Apalutamide | Strong (High) | Strong (High) | Strong (High) | Strong (High)[ab, bd,ac,cd] | Strong (High)[d] | Strong (High) | - |
| Docetaxel + Abiraterone | Strong (High)[a] | Strong (High)[b] Weak (Low)[c] | Strong (High)[a] | Strong (High)[ab, bd,ac] | Strong (High)[a,b] | Strong (Moderate)[ab] | - |
| Docetaxel + Darolutamide | Strong (Moderate)[a] | Strong (Moderate) | Strong (High)[a] | Strong (High)[ab, bd,ac] | Strong (High)[a] | Strong (Moderate)[ab] | - |

Recommendation summary of relevant clinical practice guidelines. Cells contain strength of recommendation and (evidence quality assessment). Outlier recommendations are highlighted. [a] In select, synchronous mHSPC patients. [b] In select, high volume mHSPC patients. [c] In select, low volume mHSPC patients. [d] In select, metachronic mHSPC patients. [e] In select, high risk mHSPC patients.

deferred treatment.[51] Since this study predated the approval and inclusion of apalutamide and enzalutamide in mHSPC guidelines, these were not assessed.

Goebell et al performed a retrospective, cross-sectional data study using the Ipsos Global Oncology Monitor database (2018–2020), showing that 76.1% of reported mHSPC patients from the United States, Europe, and Asia received non-guideline-concordant care (predominantly ADT or ADT plus first-generation ARPIs).[52] Similar results have been reported in other studies.[53,54]

A 2024 meta-analysis of 13 studies carried out in five countries including 166 876 patients sought to determine the use of docetaxel and ARPIs in mHSPC patients in routine practice. The utilization rate of treatment intensification with either docetaxel or ARPIs (enzalutamide, apalutamide, or abiraterone) plus ADT ranged from 9.3% to 38.1% across the studies. The authors hypothesized that the underutilization of treatment intensification in mHSPC could include patient preference, prescribing restrictions (including financial barriers or access to certain drug treatments), geographic access, educational access, and other patient determinants (eg, patient frailty).[55] These results are aligned with several, recent studies and systematic reviews.[56-58–]

Indeed, PCa imposes a significant financial burden due to direct and indirect care costs, expected to rise with new therapies (anticancer drugs could account for 70% of total cancer care costs by 2025),[59] increasing cancer prevalence and survivorship.[60] mHSPC is particularly costly, using 4–5 times more healthcare resources than localized PCa.[51]

This burden correlates with declines in QoL, treatment nonadherence,[59,60] psychological symptoms,[61] and increased mortality.[62] Therefore, debates about triplets as the SoC for mHSPC go beyond clinical outcomes, raising concerns about cost-effectiveness due to the increased financial burden on patients and healthcare systems. This is reflected in ASCO and ESMO guidelines, which incorporate value considerations into clinical trial design.[63,64]

Drug availability depends on factors like regulatory approval, socioeconomic conditions, insurance policies, and healthcare system structures.[65] In health economics, an intervention's cost-effectiveness is assessed based on its willingness-to-pay (WTP) threshold, estimating what consumers might pay for a QALY.[66] WHO guidelines recommend a WTP threshold of <3 times GDP per capita (GDPpc), which varies by country and time.[67] A 2024 review by Nu Vu et al found a median WTP/QALY of $16,647.6 and a WTP/QALY per GDPpc ratio of 0.53.[68] Another review by Iino et al suggested 0.5–1.5 times GDPpc as appropriate.[69] Incremental cost-effectiveness ratio (ICER), defined as the difference in cost between two possible interventions divided by the difference in their effect, is used to compare interventions.

Regarding the cost-effectiveness of ERBT, Lester-Coll et al conducted a microsimulation modeling study based on clinical data from the STAMPEDE H arm trial, showing its addition was a dominant strategy compared with ADT alone, with a gain of 0.16 QALYs (95% CI, , 0.15–0.17 QALYs) and a reduction in net costs by $19 472 (95% CI, $16 333–$22 611) at 37 months of follow-up (to mirror the STAMPEDE-H follow-up) and a gain of 0.81 QALYs (95% CI, 0.73–0.89 QALYs) and savings of $30,229 (95% CI, $23 096–$37 362) with a lifetime follow-up.[70] These results suggest that the added up-front cost of radiotherapy may be associated with reduced net costs by improving PFS in a non-curable setting.

In the case of systemic therapy combinations, the cost-effectiveness data is more extensive. In 2022, Barbier et al studied mHSPC treatment cost-effectiveness by comparing doublets through a Markov cohort model with states of progression-free disease, progressive disease, and mortality in men with newly diagnosed mHSPC (with a 30-year time horizon) based on survival and adverse events data from RCT results from the Swiss healthcare payer perspective. Results estimated an ICER of ADT + docetaxel vs. ADT at EUR 10 205 per QALY gained, showing the cost-effectiveness of ADT + docetaxel over ADT.[71] These results are in line with

**Table 3.** Comparison of several Cost Effectiveness Analysis (CEA) on systemic therapy for mHSPC. Comparison of several Cost Effectiveness Analysis (CEA) on systemic therapy for mHSPC. All CEA were based on a Markov state-transition model. All ICER were calculated on cost increments per QALY based on ADT alone unless otherwise specified.

| CEA study (year) | Setting | WTP/QALY threshold | ICER for ADT + DOC | ICER for optimal CE per threshold | ICER for optimal OS |
|---|---|---|---|---|---|
| Zheng et al (2017)[72] | China | USD 20 301 | USD 12 816 | *See previous column* | - |
| Woods *et al.* (2018)[77] | UK | GBP 30 000 | GBP 5514 | *See previous column* | - |
| Sathianathen et al (2019)[78] | USA | USD 100 000 | USD 34 723 | *See previous column* | USD 295,212 (ADT + AAP) |
| Liu et al (2019)[74] | China | CNY 179 800 | CNY 67 758 | *See previous column* | CNY 137,487 (ADT + AAP) |
| Ramamurthy *et al.* (2019)[79] | USA | USD 150 000 | USD 50 500 | *See previous column* | USD 1,010,000 (ADT + AAP) |
| Chiang et al. (2019)[75] | Hong-Kong | USD 138 649 | USD 14 397 | *See previous column* | USD 361,439 (ADT + AAP) |
| Sung et al (2021)[82] | USA | USD 100 000 | USD 12 870 | USD 38,897 (ADT + AAP)* | USD 509,813 (ADT + ENZ) |
| Barbier et al (2022)[71] | Switzerland | EUR 70 400 | EUR 10 205 | EUR 39,814 (ADT + AAP vs. ADT + DOC)* | *See previous column* |
| Sathianathen et al (2024)[84] | USA | USD 150 000 | USD 13 647 | *See previous column* | USD 287,722 (ADT + DOC + AAP) (USD 4,243*) |
| Sathianathen et al (2024)[84] | UK | GBP 30 000 | GBP 19 938 | *See previous column* | GBP 83,235 (ADT + DOC + AAP) |
| Sathianathen et al (2024)[84] | Australia | AUD 28 033 | AUD 19 543 | *see previous column* | AUD 107,083 (ADT + DOC + AAP) |

Abbreviations: AAP, abiraterone acetate plus prednisone; APA, apalutamide; ADT, androgen deprivation therapy; DAR, darolutamide; DOC, docetaxel; ENZ, enzalutamide. *CEA using generic-price abiraterone.

previous cost-effectiveness studies favoring ADT + docetaxel over ADT from the perspectives of China,[72-74] Hong Kong,[75] France,[76] the United Kingdom[77] and the United States.[78,79]

These studies have been endorsed by both a systematic review of economic evaluations[80] and a network meta-analysis[81] favoring docetaxel as the most cost-effective of all available treatments as a first-line strategy for mHSPC, especially at lower WTP thresholds.

In the context of the recent availability of generic abiraterone at the time of publication, Barbier et al showed ADT + abiraterone to be the preferred treatment option with an ICER of EUR 39 814—below an assumed WTP threshold of EUR 70 400 per QALY gained. These results are consistent with previous cost-effectiveness analyses from a United States payer perspective.[82,83] Both ADT + enzalutamide and ADT + apalutamide resulted in higher costs and lower QALYs.

In 2024, Sathianathen et al published the first study to examine the cost-effectiveness of treatment intensification including triplet therapy in men with mHSPC through a Markov state-transition model to simulate outcomes. Treatment intensification with doublet and triplet therapy resulted in an improvement in quality-adjusted survival for all strategies in comparison to ADT monotherapy. However, only docetaxel doublet therapy was cost-effective at standard thresholds, with an ICER of USD 13 647. The cost of ARSIs needed to be discounted by 47%–70% before they were cost-effective. Since quality-adjusted survival is improved with ARSIs, the cost of these medications is prohibitive to high-value healthcare. Results have indicated that docetaxel doublet therapy is the best-value treatment strategy across the United States, United Kingdom, and Australian healthcare systems.[84]

Results of discussed cost-effectiveness studies (see **Table 3**) are broadly consistent with the Global Prostate Cancer Consensus Conference for Developing Countries statement.[85] Cost-effectiveness studies require careful extrapolation, as results vary by country/year based on drug costs and WTP thresholds, which impact treatment cost-effectiveness. However, they offer valuable insights for countries with similar pricing and medical practices. These studies also highlight the situation in low- to middle-income countries, where the WTP threshold is lower due to lower GDP per capita.

## Conclusions

Modern treatment of metastatic hormone-sensitive prostate cancer (mHSPC) has advanced with the introduction of therapies once reserved for more advanced stages, such as ADT + docetaxel + ARPIs combinations. However, evidence on their benefit beyond high-volume disease (HVD) remains controversial, particularly compared to doublets like ADT + ARPIs. These triplet regimens are also costly, raising concerns about cost-effectiveness, especially in resource-limited settings. Due to the lack of head-to-head trials and the unfavorable cost-effectiveness profile of triplets, we suggest their use should be limited to synchronous, HVD mHSPC in resource-rich settings.

Consequently, our work proposes a treatment algorithm (see **Figure 1**) that weighs the OS benefit according to the clinical risk of each patient subgroup and the availability of clinical resources. In this current scenario of abundant options, future research will focus on clarifying the selection of the most appropriate treatment for each

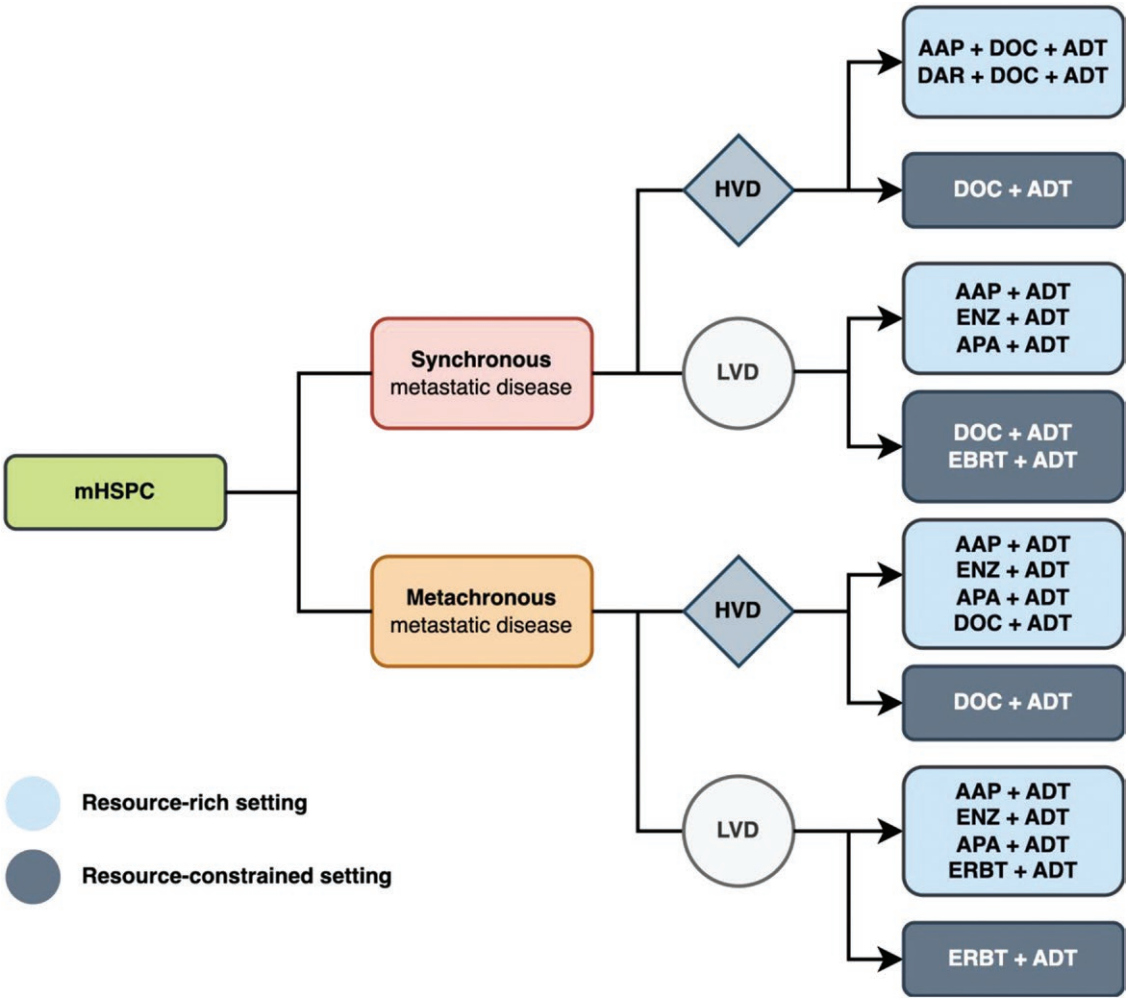


**Figure 1.** Resource-adjusted mHSPC management algorithm. ADT: androgen deprivation therapy. DOC: docetaxel. Abbreviations: AAP, abiraterone acetate plus prednisone; APA, apalutamide; ERBT, external beam radiotherapyENZ, enzalutamide; DAR, darolutamide; High-volume (HVD) and low-volume disease (LVD) are defined according to CHAARTED criteria.[9]

patient according to their clinical characteristics and re-evaluating the cost-effectiveness of treatments as new drugs and generics emerge.

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## Author contributions

Conception/design: C.A; M.B.

Data analysis and interpretation: C.A; R.M; M.B.

Manuscript writing: C.A; J.G-M.; M.B.

Editing, review and final approval of manuscript: C.A; J.G-M.; C.R.; R.M; M.B.

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## Conflicts of interest

Cristóbal Ávila: No conflicts of interest to declare.

Jaime González-Montero: No conflicts of interest to declare.

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## Data availability

No new data were generated or analyzed in this study.

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