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GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

# A Systematic Review and a Meta-analysis of Randomized Controlled Trials' Control Groups in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

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## Abstract

**Purpose of Review** Determining the risk for progression or survival after standard androgen deprivation treatment (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC) is essential for stratifying patients according to expected outcomes in future studies of treatment combination. This systematic review and meta-analysis aims to estimate the progression-free survival (PFS) and overall survival (OS) probabilities in the control group of randomized controlled trials (RCTs) of different regimens of standard androgen deprivation treatment (ADT) in mHSPC and to identify possible predictors of outcomes.

**Recent Findings** Studies reporting time-dependent outcomes (progression or death) after standard ADT treatment of mHSPC were searched in MEDLINE, CANCERLIT, the Cochrane Controlled Trials Register, and the Cochrane Library from inception through June 2021. Data on patient populations and outcomes were extracted from each study by three independent observers and combined using a distribution-free summary survival curve. Primary outcomes were actuarial probabilities of disease progression and survival. Fifteen studies met the inclusion criteria. The pooled estimate of the actuarial PFS rate was 35.2% at two years. The pooled actuarial OS rate was 62.5% at three years. Heterogeneity among studies was highly significant for all outcomes. By univariate meta-regression analyses, high-volume disease and the presence of visceral metastases were associated with shorter survival.

**Summary** Our findings show that PFS and OS are highly variable in patients with mHSPC treated with ADT, providing a helpful benchmark for indirect comparisons of the benefits of the combination of chemotherapy and second-generation hormonotherapy.

**Keywords** mHSPC and ADT · Deprivation Therapy · Metastatic Hormone-Sensitive Prostate Cancer

## Abbreviations

| | |
|---|---|
| ADT | Androgen deprivation treatment |
| mHSPC | Metastatic hormone-sensitive prostate cancer |
| ARTA | Androgen receptor-targeted agents |
| RCT | Randomized controlled trial |
| PFS | Progression-free survival |
| OS | Overall survival |

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## Introduction

Prostate cancer is the most common cancer in males, with an estimated new case incidence of 248,530 and an estimated mortality of 34,130 expected in 2021 [1]. Despite an overall 5-year survival rate of 97.5%, metastatic prostate cancer has a dismal 30.6% 5-year survival rate.

Since Huggins and Hodges [2], in 1941, demonstrated the androgen sensitivity of prostate cancer, ADT alone had been the standard of care for mHSPC. Analyzing 917 mHSPC patients enrolled in the control arm of the STAMPEDE trial, James et al. [3] reported a median OS of 42 months, a 2-year OS of 72%, and a median failure-free survival (FFS) of 11 months, with a 2-year FFS of 29%. In the last twenty years, several efforts have been made to improve metastatic prostate cancer patient outcomes using maximum androgen blockade [4] and chemotherapy [5]. Tannok IH et al. [6] demonstrated a 2.5-month increase in the median survival by treating patients with a castration-resistant disease with docetaxel (every three weeks).

A better knowledge of prostate cancer biology and the underlying mechanisms of resistance to ADT led to the development of new hormone therapies that have improved the survival of patients with castration-resistant disease [7].

Furthermore, hormone-sensitive prostate cancer patients may benefit from the association of chemotherapy with ADT [8]. Three randomized controlled trials [9, 10, 11] and two subsequent meta-analyses [8, 12] demonstrated the activity of ADT combined with docetaxel in improving OS. More recently, the addition of androgen receptor-targeted agents (ARTA) to ADT also improved the OS of mHSPC patients compared to ADT alone. The rationale for combining ARTA with ADT relies on the adaptation theory. According to this theory, prostate cancer cells initially susceptible to ADT would acquire drug escape mechanisms that would allow them to proliferate even at low androgens levels. Finally, also local radiotherapy improved OS in patients with mHSPC [13, 14]. However, all these novel therapeutic opportunities have made the treatment's selection and sequencing challenges, as no comparative data are currently available to guide treatment choice between the different available regimens. Therefore, a customized strategy based on an indirect comparison of the outcomes in the control group of multiple phase-3 studies might help clinicians tailor the decision-making process. An accurate estimate of PFS and OS rates in this group is essential for evaluating the natural history of the disease, assessing the treatment's effect size, and thus translating the results into clinical practice.

To increase the statistical power, we performed a meta-analysis of a single control arm of phase 3 studies of mHSPC patients who have received an intensification of ADT with other active systemic treatments (Docetaxel, ARTA, Zoledronic acid) or radiotherapy.

The aims of this research were as follows: (1) to estimate the pooled actuarial probabilities of PFS and OS among mHSPC patients who received ADT as a single treatment modality, (2) to analyze variation in PFS and OS across the studies (heterogeneity), and (3) to identify the factors associated with disease progression and survival in this population.

## Materials and Methods

### Selection of Trials

This meta-analysis was performed following the PRISMA statement [15]. The primary sources of the reviewed studies were MEDLINE, CANCERLIT, the Cochrane Controlled Trials Register, and the Cochrane Library, with the following medical subject headings (MeSH): "metastatic hormone-sensitive prostate cancer," "metastatic castration sensitive prostate cancer," "docetaxel," "chemotherapy," "abiraterone," "enzalutamide," "apalutamide," "darolutamide," "randomized trial," and "clinical trial." The search included literature published through June 2021 with no lower date limit. The computer search was supplemented with manual searches of the reference lists of all retrieved review articles and primary studies to identify additional studies. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the meta-analysis.

Studies were included in the analysis if (1) they included patients with mHSPC, (2) they were phase 3 RCTs comparing ADT alone versus other active treatments, and (3) they assessed PFS and OS as time-dependent outcomes.

Among the 4325 studies identified, the inclusion criteria were met by 15 studies (Fig. 1). Studies were excluded if they were published without survival data.

### Review of Studies

The trials were first reviewed using a list of predefined pertinent issues that concerned the characteristics of patients and treatments. Study- and patient-level variables were extracted from all studies and entered into a database. Study-level variables included the study name, the first author's last name, publication year, location, number of subjects, number of centers (single vs. multiple), outcomes measured, and study validity. Patient-level variables included mean age, percentage of patients with ECOG 0, percentage of patients with

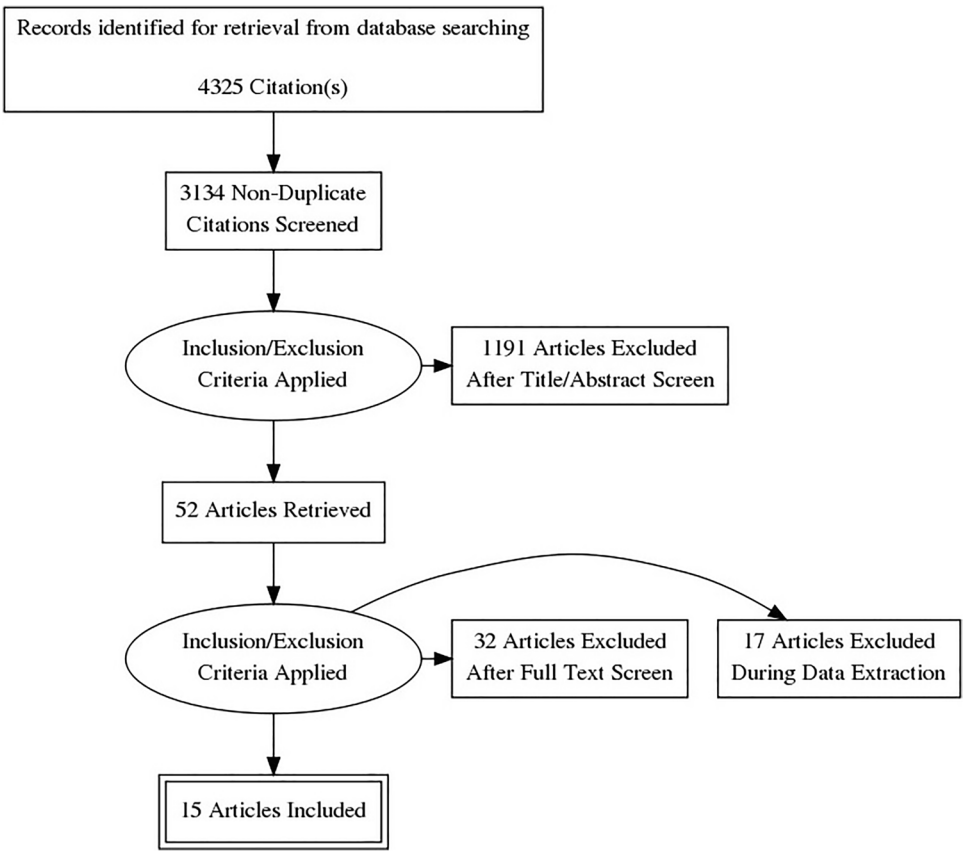


**Fig. 1** Study flow-chart

Gleason score ≥ 8, the ratio of patients with bone metastases, and high-volume disease (defined as the presence of visceral metastasis or ≥ 4 bone lesions [7].

Each RCT was evaluated and classified by three independent investigators (NG, FM, BF). Discrepancies among reviewers were infrequent (overall interobserver variations < 10%) and were resolved by discussion.

## Statistical Analyses

Crude rates of 3-year PFS and 3-year OS were extracted as outcome measures. Pooled estimates of 3-year PFS and 3-year OS rates were calculated using random-effects logistic regression analysis after applying sample weights according to the sample size. The Pearson $\chi^2$ test and the $I^2$ statistic assessed heterogeneity across studies.

Only univariate logistic meta-regression analyses examined associations between patient- or study-level covariates and 3-year OS rates. We did not consider multivariate meta-regression analysis due to the lack of individual patient data to identify candidate variables that could explain the heterogeneity. Begg's funnel plots were generated, and Egger's regression asymmetry test was used to examine potential publication bias related to 3-year PFS and OS, respectively.

In clinical trials with a time-dependent outcome (death or disease progression), survival curves were used to describe the risk of the event over time. The most informative finding was a summary survival curve in meta-analyses of studies reporting a survival curve. We used the nonparametric approach reported by Combescure et al. [16] to assess pooled survival probabilities from several single-arm studies. This approach uses random effects to model between-study heterogeneity. The between-study covariance matrix was estimated using the multivariate extension of DerSimonian and Laird's method [17, 18]. Compared to meta-analyses of survival probabilities at a single point [19], this approach has several advantages. First, estimating the pooled survival probability at time $t$ also involves all studies ending before $t$ because these studies contribute to the estimated conditional survival probabilities for time intervals prior to $t$. Second, this approach does not require assumptions about the shape of survival curves. Finally, the pooled survival probabilities are guaranteed not to increase over time. For all analyses, a $p$-value < 0.05 was considered statistically significant. All analyses and graphics were completed with the R Statistical Computing Environment (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Description of Studies

Fifteen RCTs, all published since 2004, fulfilled the inclusion criteria and were selected for review. Thirteen were multicentric. All reported PFS and OS curves. Three RCTs analyzed ADT versus ADT plus Docetaxel [9, 10, 11, 11] in treating patients with a high metastatic burden or a rapid kinetic of disease. Three trials, instead, compared ADT versus ADT plus an inhibitor of the enzymatic activity of steroid 17alpha-monooxygenase such as abiraterone [21, 22, 23] and orteronel [24]. Other four studies analyzed ADT versus ADT and ARTA, namely enzalutamide [25•, 26, 27•] and apalutamide [28, 29•]. Three trials compared ADT versus ADT plus zoledronic acid [30, 31, 32]. Finally, two RCTs compared ADT versus ADT and radiotherapy [13, 14]. Table 1 reports the distributions of the main study- and patient-level characteristics of the single arms of the 15 studies. Control arms of these 15 RCTs included 7032 patients. The size of the single arm in each study ranged from 35 to 1184 patients. The mean patients' age was 67.3 years, ranging from 62 years [23] to 72 years [30]. The performance status defined with the ECOG scale went from 45% [26] to 84% [13]. The percentage of patients with a Gleason score ≥ 8 differed greatly among trials, from 56.1% [9] to 97.6% [21]. The rate of patients with bone metastases varied from 53% [11] to 100% [23, 23, 31]. The percentage of patients with high-volume disease ranged from 28.8% [30] to 79.6% [21].

#### PFS

Pooled estimates of 2-year PFS actuarial probabilities were 35.2% (95% confidence interval [CI], 27.6–43.6%). There was statistically significant heterogeneity across the studies for the 2-year PFS ($p < 0.0001$) with $I^2 = 96.4\%$ (Fig. 2a).

The subgroup analysis (Table 2) showed that 2-year PFS changed according to the experimental combination used in RCTs. Analyzing the control arm of the studies where ADT was intensified with chemotherapy (control arm C) [9, 10, 11, 20] involving 1770 patients and 1014 disease progression, the pooled two-year PFS was 37.1% (95%CI, 17–63.1%) with a high heterogeneity $I^2 = 93.7\%$. In the control arm of RCTs using ARTA, there were 1665 patients and 1011 disease progressions [25•, 27•, 28, 29•] (control arm A), with a pooled two-year PFS of 38.1% (95%CI, 10–77%) and a very high heterogeneity $I^2 = 98.6\%$. While there were 1745 patients and 1003 disease progression in the control group of the trials investigating two inhibitors of the enzymatic activity of steroid 17alpha-monooxygenase abiraterone [21, 22, 23] and orteronel [24] (control arm I), with a two-year PFS of 42.5% (95%CI, 28.2–58.2%) and a high heterogeneity $I^2 = 92.5\%$. With 432 patients and 104 disease progression, the same feature in the control arm of the study where zoledronic acid was used (control arm Z) [30, 32] was 21.7% (95%CI, 11–87%) with a high heterogeneity $I^2 = 93.7\%$. Finally, in the control arm of two phase-3 trials where ADT was combined with radiotherapy [14] (control arm R), there were 1029 patients and 309 disease progression, resulting in a 2-year PFS of 30% (95%CI, 27.3–32.9%) with no heterogeneity.

No statistical difference was found between pooled rates of control arm C vs. control arm A ($p = 0.186$), of control arm C vs. control arm I ($p = 0.942$), of control arm A vs. control arm I ($p = 0.213$), and between control arm R and control arm Z ($p = 0.081$).

Instead, a statistical difference in 2-year PFS was obtained in all other comparisons.

Univariate logistic meta-regression analysis was used to identify potential sources of heterogeneity among studies. Among the variables assessed, none was associated with an increase in the 2-year PFS (Table 3).

mHSPC progression curves extracted from the studies and a summary mHSPC progression curve, respectively, are shown in Fig. 2b. At a median time of 48 months, we observed a PFS rate of 26.5% (range 21.7–32.3%).

#### OS

Pooled estimate of 3-year OS actuarial probability was 62.5% (95%CI, 57–67.7%) (Fig. 3a). There was statistically significant heterogeneity across the studies at three years ($p < 0.001$) with an $I^2 = 93.3\%$.

The subgroup analysis (Table 2) showed that 3-year survival actuarial probability changed according to the experimental combination used in RCTs. Analyzing the control arm of the studies where ADT was intensified with chemotherapy (control arm C) [9, 10, 11, 20], involving a total of 1770 patients and 561 deaths, the pooled three years OS was 65.4% (95%CI, 50.2–78%) with a high heterogeneity $I^2 = 91.4\%$. In the control arm of RCTs using ARTA, there were 1700 patients and 553 deaths (control arm A) [25•, 26, 27•, 28, 29•], with a pooled three-year OS of 67.2% (95%CI, 58.9–74.6%) and a high heterogeneity $I^2 = 81.3\%$. While there were 1745 patients and 670 deaths in the control group of the trials investigating abiraterone [21, 22, 23] and orteronel [24] (control arm I), with a 3-year OS of 61.8% (95%CI, 36.9–81.7%) and a very high heterogeneity $I^2 = 97.1\%$. With 572 patients and 275 deaths, the same feature in the study's control arm where zoledronic acid was used (control arm Z) [30, 32] was 55.5% (95%CI, 18.9–86.9%), and a high heterogeneity $I^2 = 94\%$. Finally, in the control arm of two phase-3 trials where ADT was combined

**Table 1** Study- and patient-level characteristics of the studies in the meta-analysis

| | Experimental arm | Control arm sample Size | Inclusion criteria | Median F-up months | Mean age | Gleason score ≥ 8 (%) | ECOG 0 (%) | High volume disease (%) | Bone metastasis (%) | Visceral metastasis (%) | De novo metastasis (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ARCHES [27•] | Antiandrogen (A) | 576 | mHSPC | 14.4 | 70 | 66 | 77.5 | 63.2 | 84.4 | 4.9 | 72 |
| CALGB 90,202 [32] | Zoledronic acid (Z) | 322 | mHSPC (bone metastases whose androgen deprivation therapy was initiated within 6 months of study) | 13.6 | 71 | 57.8 | 63.6 | NR | 96.4 | NR | NR |
| CHARTEED [10, 10] | Chemotherapy (C) | 393 | mHSPC | 53.7 | 63 | 61.3 | 69.5 | 64.9 | 69.5 | 16.8 | 73 |
| ENZAMET [25•] | Antiandrogen (A) | 562 | mHSPC (previous adjuvant testosterone suppression for up to 24 months was allowed if the treatment had been completed at least 12 months earlier) | 34 | 69.2 | 58.3 | 72 | 52.3 | 80.7 | 12 | 58 |
| GETUG-AFU15 [9] | Chemotherapy (C) | 193 | mHSPC | 83.9 | 63 | 56.1 | 100 | NR | 80.8 | 12.9 | 66 |
| HORRAD Trial [13] | Radiotherapy (R) | 216 | Patients were eligible if they had a previously untreated, histologically confirmed diagnosis of adenocarcinoma of the prostate with any number of bone metastases on bone scintigraphy<br>Tumors could be of any grade (Gleason score 6–10) and T stage (cT1-cT4; cN0-cN1; M1) | 47 | 67 | 66.6 | 84 | 62.9 | 100 | NR | NR |
| LATITUDE [21, 22] | Enzimatic inhibitor (I) | 602 | High risk:<br>-GS ≥ 8<br>-Bone lesions 3<br>-Measurable visceral metastasis<br>-ADT exposure < 3 months | 30.4 | 67.3 | 97.6 | NR | 79.6 | 97.2 | 21.6 | 100 |
| MRC PR04 & PR05 [31] | Zoledronic acid (Z) | 140 | mHSPC (bone metastases) | 138 | 69 | NR | 65.6 | NR | 100 | NR | NR |
| SWOG S1216 [24] | Enzimatic inhibitor (I) | 641 | mHSPC | 59 | 68 | 58.9 | 67.1 | 51.3 | 67 | NR | NR |

**Table 1** (continued)

| | Experimental arm | Control arm sample Size | Inclusion criteria | Median F-up months | Mean age | Gleason score ≥ 8 (%) | ECOG 0 (%) | High volume disease (%) | Bone metastasis (%) | Visceral metastasis (%) | De novo metastasis (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| STAMPEDE C [11] | Chemotherapy (C) | 1184 | Newly diagnosed as metastatic node-positive- or high-risk locally advanced | 48 | 66 | 79.1 | 71.1 | 54.3 | 89.1 | 9.7 | 100 |
| STAMPEDE G [23] | Enzimatic inhibitor (I) | 502 | Newly diagnosed as metastatic node-positive- or high-risk locally advanced | 40 | 62 | 74.9 | 77.7 | NR | 88 | 5.7 | 96 |
| STAMPEDE H [14] | Radiotherapy (R) | 1029 | Newly diagnosed, with no previous radical treatment, and had metastatic disease confirmed on a scintigraphic bone scan and soft-tissue imaging done within 12 weeks of starting androgen deprivation therapy | 37 | 68 | 70.2 | 82.9 | NR | 53 | 7.9 | 95 |
| TITAN [28, 29•] | Antiandrogen (A) | 527 | mHSPC EXCLUDED if visceral met is the only site of metastasis | 22.9 | 69 | 67.4 | 64.3 | 62.7 | 100 | 13.6 | 85 |
| Vaishampayan et al. [26] | Antiandrogen (A) | 35 | mHSPC | 39 | 65 | 73 | 45 | 54 | 83 | 5 | 56 |
| ZAPCA Trial [30] | Zoledronic acid (Z) | 110 | mHSPC (bone metastases) | 41.5 | 72 | 82.2 | 68.9 | 28.8 | 100 | NR | NR |

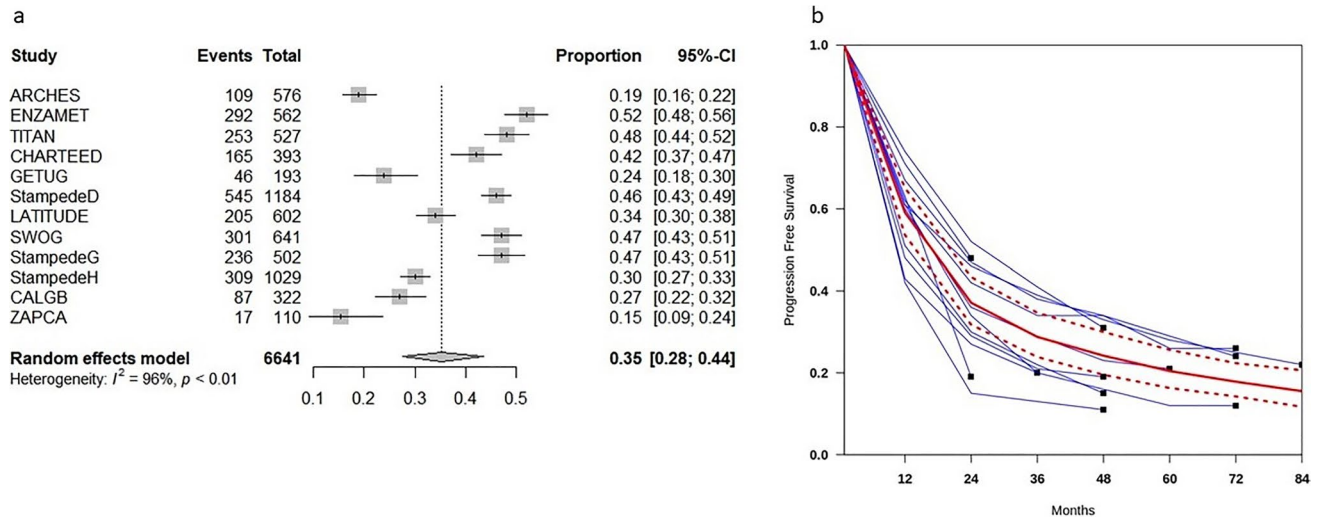


**Fig. 2** Forest plot of (**A**) 2-year progression-free survival and (**B**) curve of prostate cancer progression-free survival. Black squares indicate the end of the follow-up. Thick lines represent the summarized recurrence curves with the 95% confidence bands (dashed lines) obtained using the approach of Combescure et al. with random effects

with radiotherapy [13, 14] (control arm R), there were 1245 patients and 485 deaths, resulting in a 3-year OS of 61.1% (95%CI, 42.8–76.6%), and no heterogeneity ($I^2 = 0$).

No statistical difference was found between pooled rates of control arm C vs. control arm A ($p = 0.903$) and between control arm R and control arm I ($p = 0.836$).

Instead, a statistical difference in 3-year OS was obtained between control arm C vs. control arm I ($p = 0.004$) vs. control arm Z ($p < 0.001$) and control arm R ($p = 0.004$). Similarly, a statistical difference was observed between control arm A and control arm I ($p = 0.013$) and vs. control arm R ($p = 0.013$) and control arm Z ($p < 0.001$). Finally, a statistical difference between control arm R and control arm Z ($p = 0.004$) was found. Univariate logistic regression analysis was used to identify potential sources of heterogeneity. Among the variables assessed, four patient-level covariates were associated with a decrease in the 3-year survival rate: Gleason ≥ 8 ($p = 0.028$), high-volume disease ($p = 0.028$), metastatic bone lesions ($p = 0.028$), and

**Table 2** Subgroup analysis for 2-year PFS and 3-year OS

| | Estimated effect | 95% CI | $I^2$ |
|---|---|---|---|
| 2-year progression-free survival | | | |
| Control arm of RCTs intensified with CT | 37.1 | 16.7–63.1 | 93.7 |
| Control arm of RCTs intensified with ARTA | 38.1 | 10–77.3 | 98.6 |
| Control arm of RCTs intensified with enzymatic inhibitors | 42.5 | 28.2–58.2 | 92.5 |
| Control arm of RCTs intensified with zoledronic acid | 21.7 | 11.3–87.1 | 82.9 |
| Control arm of RCTs intensified with CT | 30 | 27.3–32.9 | 0 |
| 3-year overall survival | | | |
| Control arm of RCTs intensified with CT | 65.4 | 50.2–78 | 91.4 |
| Control arm of RCTs intensified with ARTA | 67.2 | 58.9–74.6 | 81.3 |
| Control arm of RCTs intensified with enzymatic inhibitors | 61.8 | 36.9–81.7 | 97.1 |
| Control arm of RCTs intensified with zoledronic acid | 55.5 | 18.9–86.9 | 94 |
| Control arm of RCTs intensified with CT | 61.1 | 42.8–76.6 | 0 |

**Table 3** Predictors of 2-year progression-free survival and 3-year overall survival among all studies

| Study characteristics | No. of studies | No. of patients | *B* | SE | *p* |
|---|---|---|---|---|---|
| Outcome: 2-year progression-free survival | | | | | |
| Age (years) | | | −0.691 | 0.048 | 0.183 |
| ECOG 0 (%) | 14 | 4740 | −1.187 | 1.743 | 0.513 |
| Gleason ≥ 8 (%) | 14 | 4672 | −1.623 | 1.045 | 0.151 |
| High volume disease (%) | 10 | 2880 | −1.623 | 1.044 | 0.150 |
| Bone metastases (%) | 15 | 5758 | −1.623 | 1.045 | 0.151 |
| Visceral metastases (%) | 10 | 615 | 0.013 | 0.033 | 0.697 |
| De novo metastases (%) | 10 | 4868 | 0.291 | 1.111 | 0.801 |
| Outcome: 3-year overall survival | | | | | |
| Age (years) | | | 0.010 | 0.037 | 0.792 |
| ECOG 0 (%) | 14 | 4740 | 0.636 | 0.942 | 0.513 |
| Gleason ≥ 8 (%) | 14 | 4672 | −1.545 | 0.623 | 0.028 |
| High volume disease (%) | 10 | 2880 | −1.545 | 0.623 | 0.028 |
| Bone metastases (%) | 15 | 5758 | −1.545 | 0.623 | 0.028 |
| Visceral metastases (%) | 10 | 615 | −0.036 | 0.014 | 0.030 |
| De novo metastases (%) | 10 | 4868 | −0.809 | 0.539 | 0.172 |

visceral metastasis ($p = 0.030$) (Table 3). Figure 3b shows the OS curves extracted from the studies and summary survival curves. At a median time of 48 months, we observed an overall survival rate of 52.96% (range 47.7–58.8%).

## Publication Bias

The funnel publication bias plot for the 2-year progression-free survival (Fig. 4a) and the Egger test for publication bias showed that the risk of having missed or overlooked trials was not significant ($p = 0.099$). The funnel publication bias plot for 3-year survival rates (Fig. 4b) and the Egger test for publication bias showed that the risk of having missed or overlooked trials was not significant ($p = 0.321$).

## Discussion

Over the past years, the advent of different treatment options for men with mHSPC has resulted in clinically meaningful survival improvements that have generated

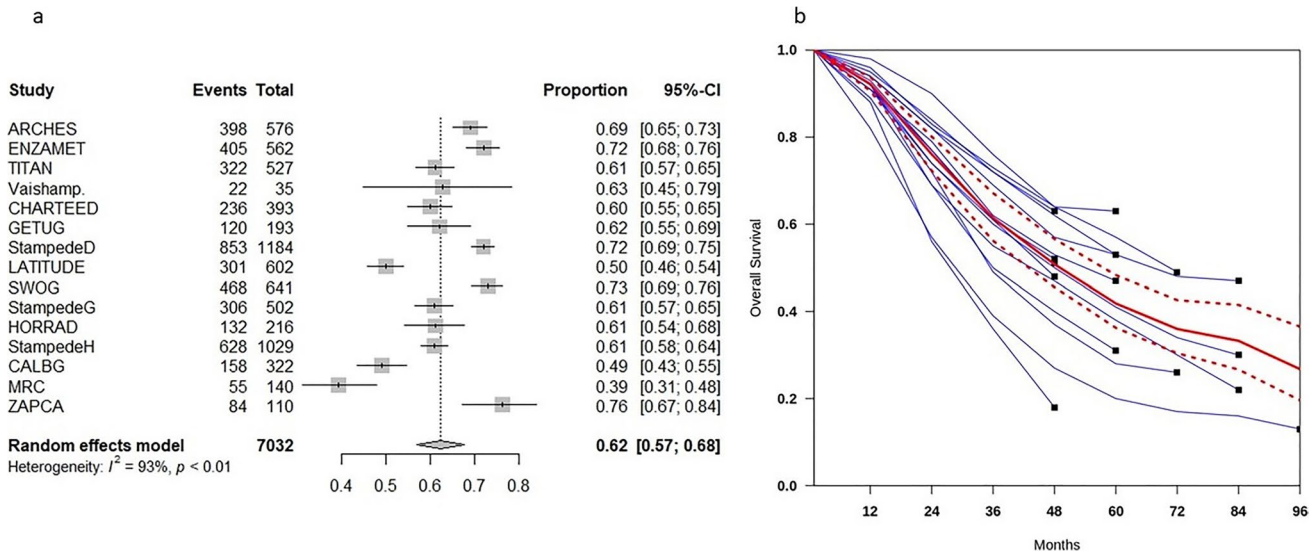


**Fig. 3** Forest plot of (**A**) 3-year overall survival and (**B**) curve of prostate cancer overall survival. Black squares indicate the end of the follow-up. Thick lines represent the summarized recurrence curves with the 95% confidence bands (dashed lines) obtained using the approach of Combescure et al. with random effects

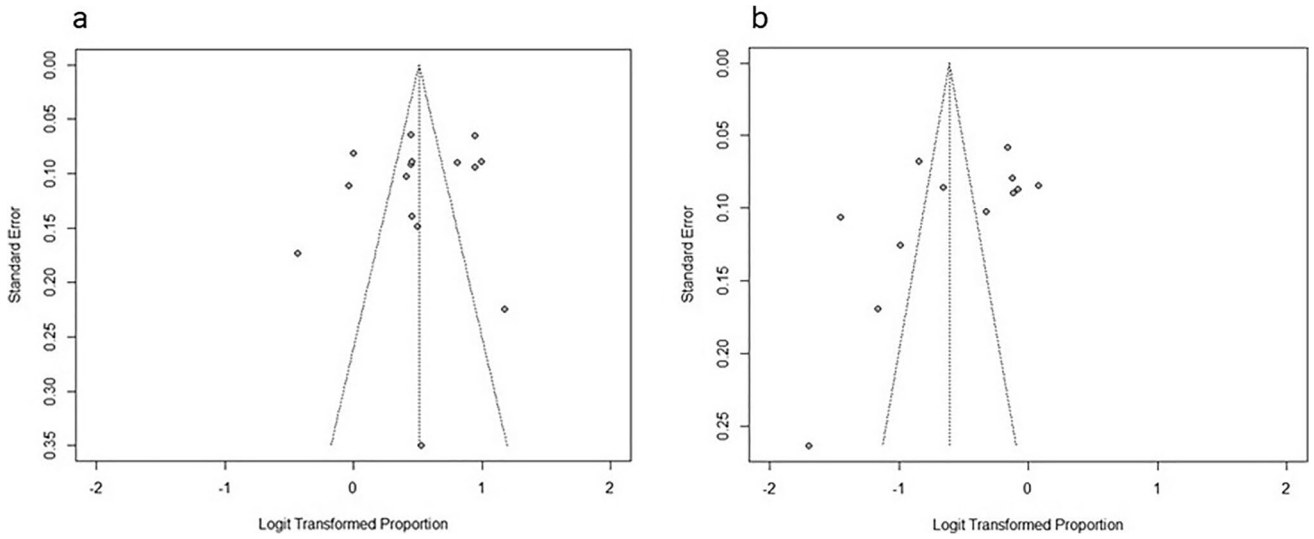


**Fig. 4** Funnel plot of (**A**) 2-year progression-free survival and (**B**) 3-year overall survival. A symmetry in these graphs does not indicate publication bias

hopes of prolonging the hormone-sensitive phase and, ultimately, the natural history of the disease. On the other hand, this practice-changing scenario has challenged clinicians to select the optimal strategy for the appropriate patient. In this context of substantial evidence, what commonly guides the treatment selection heavily relies on the inclusion criteria of published RCTs. For example, in the CHAARTED trial [10, 20], patients with high-volume disease gained a significant OS when chemotherapy was added to ADT alone; the treatment with upfront docetaxel has become the standard of care for those with high-volume disease if they are fit enough to receive it. The recent EAU-EANM-ESTRO-ESUR-SIOG guidelines [33••] replicate such an approach. To support inclusion criteria among the factors that may influence the treatment's selection, it is mandatory to unveil outcomes' differences in patients who met similar inclusion criteria in the RCTs.

For this reason, we performed a meta-analysis of individual and aggregated data from the control arm of 15 RCTs enrolling mHSPC patients for treatment intensification. All these patients were treated with the standard ADT. Evaluating the PFS and OS rates in the control groups and analyzing these results in light of the apparent differences in inclusion criteria can ameliorate the quality of treatment of mHSPC and help choose the appropriate therapy for each patient in the clinical practice.

Our findings revealed a 2-year PFS of 35.2% and a 3-year OS actuarial probability of 62.5%. There was high heterogeneity across the studies in both PFS and OS rates. Although the number of patients included was quite large, suggesting the robustness of the estimated rates, the 95% CIs of 2-year PFS (27.6–43.6%) and 3-year OS (56.9–67.7%) highlight that the distributions were broad. Clinical heterogeneity of progression and survival was a common feature in these studies, with 2-year PFS and 3-year OS rates ranging from 15% [30] to 52% [25•] and from 39% [31] to 73% [24], respectively. A possible reason for this wide variability in the treatment of mHSPC patients with ADT alone is the accrual's time. In fact, excluding studies with the accrual period before 2005, an improvement in OS of about 12% (i.e., 3-year mortality before 2005: 46.6%, after 2005: 34.7%) with a statistically significant difference ($p < 0.001$) was found. This data resembles the mortality rate of 41.3% ($p = 0.160$) gathered from 917 patients in the control arm of the STAMPEDE Trial [3]. These large different outcomes might be related to some prognostic features determined throughout the treatment while others established at diagnosis, namely due to the distinct staging procedures therein employed. Our analysis has stratified the studies into five subgroups according to the type of combined treatment used in the experimental arm. It is immediately apparent that there are no differences in the survival between the control arm A and C ($p = 0.903$) and between the control arm R and I ($p = 0.836$). The first conclusion that can be drawn is that the survival outcomes in the control groups are similar regardless of the differences in the inclusion criteria between the RCTs, which also allows for comparing the results in the experimental groups more appropriately. Furthermore, we stratified RCTs according to patient- and study-level covariates identified by meta-regression analyses. The percentage of patients with high-volume disease and visceral

metastasis was significantly predictive of 3-year OS, confirming that cancer-related factors strongly impact survival in mHSPC patients. When RCTs were stratified according to the percentage of high-volume disease, the 3-year OS was far higher in studies including patients with a percentage of high-volume disease of < 54% (1955 patients with 293 deaths) than in those with a percentage of > 54% (2314 patients with 925 deaths) ($p < 0.001$). The heterogeneity of survival rates among RCTs could reflect variability in the prostate tumors' molecular characteristics and biological behavior. However, there is currently insufficient evidence to suggest that a clinical feature-based scoring system might account for the molecular features and pathobiology of the tumor (invasiveness, angiogenesis, microvascular invasion, and microenvironment) [34] [35], or those genetic markers could guide treatment in this setting.

Our analyses were unable to explain the observed heterogeneity in disease progression fully. Indeed, no patient-level covariate was significantly associated with 2-year PFS.

Clinicians are often presented with the dilemma of choosing which of several competing interventions is likely to be most effective, which becomes especially challenging when the interventions have not been directly evaluated in RCTs. We believe that our meta-analysis can be considered a valuable benchmark for obtaining indirect comparisons among different uncontrolled studies estimating the benefit of combined treatment modalities. As for all meta-analyses, a limitation of the current work is that it might not yield relevant information about the treatment effects outside the population directly targeted by the RCTs, which raises the issue of the generalizability of its results in some other target populations. The included studies were performed by enrolling "healthier" patients. This choice limits the broad application of the results to the "sickest" patients, who could have potentially benefited from active treatments.

Notwithstanding, this study highlights relevant issues: a median OS of 49.9 months, while a PFS was slightly more than a third (18.7 months). This finding demonstrates that mHSPC patients can still be successfully treated after the progression. Furthermore, these patients now spend most of their remaining life in a state of castration-resistant relapse. This phase drives most of the survival time rather than a short-term phase with limited treatment options. It is, therefore, no longer acceptable to manage mHSPC patients with only a palliative intent, and efforts should be made to promote the attitude of offering them active treatments aimed at improving survival and reducing morbidity. The long time for the evolution of the clinical scenario reinforces the hypothesis of a metastasis-to-metastasis spread [36] in prostate cancer. In this regard, the integration of systemic therapies with local treatment, not only to the primary tumor [14] but also to all metastatic sites using a metastasis-directed treatment, should be considered to reduce the tumor burden and slow down the selective pressure on cancer cells [37••, 38]. It becomes mandatory to stage patients with the most advanced and accurate diagnostic tools to pursue this aim.

Although the overall sample size analyzed exceeded 7000 patients, it was not large enough to draw conclusive evidence. Differences in baseline severity of illness (bone metastasis, node metastasis, visceral metastasis, or a combination), the different appearance of metastases (de novo or relapsed metastasis), and different treatment strategies after the failure of androgen suppression (chemotherapy, ARTA, supportive care) may limit the accuracy of this meta-analysis. We attempted to control these differences by including covariates that described patient- and study-level features. Unfortunately, our study is limited by the patient-level covariates reported in each study, which were not consistent across trials. Therefore, our summary findings describe only between-study, not between-patient, variations because they reflect group averages rather than individual data. Moreover, there were likely other potentially important confounders that might not have been accounted for, which might have affected the results.

## Conclusions

The available evidence from this meta-analysis is sufficient to conclude that in patients with mHSPC.

(1) The 2-year PFS of 35.2% and 3-year survival of 64.5% pooled actuarial probabilities are highly variable, and no single patient or study characteristic can fully explain this heterogeneity.
(2) Percentage of high-volume disease and presence of visceral metastases are associated with shorter survival.

These pooled reported actuarial PFS and overall OS probabilities provide a helpful tool for indirect comparisons of clinical benefit in the comparative effectiveness of various combinatorial regimens of ADT in the mHSPC setting and a correct design of RCTs of novel treatment approaches.

## Declarations

**Conflict of Interest** The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


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