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Research Article

Oral chemotherapeutic agents in metastatic hormone-sensitive prostate cancer: A network meta-analysis of randomized controlled trials

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ABSTRACT

Background: Multiple oral chemotherapeutic agents for metastatic hormone-sensitive prostate cancer (mHSPC) have been developed for conjugated use with conventional androgen deprivation therapy (ADT). Several randomized controlled trials (RCTs) report significant benefits in mHSPC patients. Therefore, we compared overall survival (OS) and progression-free survival (PFS) benefits among considerable mHSPC oral chemotherapeutic agents.

Materials and methods: We investigated mHSPC treatment efficacy through a systematic RCT-trial literature review (PubMed, Embase, Web of Science, the Cochrane Library, and Scopus). Two reviewers independently screened, extracted data, and assessed bias risk in duplicate.

Results: We identified 18 RCTs (n = 13,509). Concerning OS, ADT + abiraterone, ADT + abiraterone + docetaxel, ADT + apalutamide, ADT + bicalutamide, ADT + darolutamide + docetaxel, ADT + enzalutamide, ADT + orteronel, and ADT + rezvilutamide were more effective than the standard of care (SOC). Comparing PFS, most treatments were more effective than SOC, excluding ADT + bicalutamide, nilutamide, flutamide, ADT + bicalutamide + palbociclib, and ADT + nilutamide. ADT + docetaxel with androgen receptor targeted agent (ARTA) triplet therapy was not among the top three treatments determined through ranking analysis.

Conclusions: Novel oral chemotherapeutic agent combination therapies must replace current ADT monotherapy and ADT + docetaxel SOC. Even so, ADT + docetaxel with ARTA triplet therapy still is not the best mHSPC treatment and requires further study.

1. Introduction

Globally, more than 1.4 million new prostate cancer cases and 375,000 related deaths were reported in 2020.[1] Approximately, 9% of all men diagnosed with prostate cancer will have metastatic disease at the time of their diagnosis (*de novo*) in the USA.[2] Furthermore, about 27% of localized prostate cancer patients will eventually develop metastatic disease depending on the

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higher Gleason score or stage after radical prostatectomy.[3] Metastatic hormone-sensitive prostate cancer (mHSPC) includes synchronous (*de novo*) and metachronous disease. Eventually, mHSPC can lead to castrate-resistant prostate cancer (CRPC) and mortality.[4]

Androgen-suppressing strategies were the mHSPC standard of care (SOC) when Huggins and Hodges showcased how responsive prostate cancer is to androgen deprivation therapy (ADT) over 70 years ago.[5] However, the mHSPC treatment landscape has severely changed over the last 10 years, with novel agents expressing mCRPC survival benefits. Randomized control trials (RCTs) CHAARTED and STAMPEDE revealed a higher overall survival (OS) compared to ADT monotherapy, establishing docetaxel and ADT combinations as new mHSPC SOC.[6,7] Androgen receptor targeted agent (ARTA) is a prostate cancer treatment that targets the androgen receptor by blocking androgen activity and production. Novel ARTA medications are orally administered, making hospitalization unnecessary as patients prefer it to intravenous treatment.[8] Recent PEACE-1 and ARASENS ADT, docetaxel, and ARTA triplet therapy trials confirmed superior OS than previous SOC.[9,10] Continuously, new medicines using other pathways have been developed.[11,12]

With these dramatically changing mHSPC treatment options, clinicians are spoilt for choice. Therefore, we aimed to determine which oral chemotherapeutic agents with ADT combination therapy could most benefit mHSPC patients.

2. Materials and methods

2.1. Ethics statement

This meta-analysis did not require ethical approval because the data were synthesized from previously published studies.

2.2. Protocol and registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. In addition, this review was registered in the PROSPERO International Prospective Registry of Systematic Reviews.

2.3. Search strategy

A comprehensive literature search was conducted using several databases: PubMed, Embase, Web of Science, the Cochrane Library, and Scopus. The date was restricted to articles published on or before November 12, 2022, as the search transpired on November 13, 2022. The search specifics were as follows: (Prostate cancer OR prostate carcinoma OR prostatic cancer OR prostatic cancer disease) AND (metastatic OR M1 OR high volume disease OR low volume disease OR advanced) AND (hormone-sensitive OR hormone naïve OR castration sensitive) AND (randomized). The search criteria were used to identify all potentially relevant articles. After combining the results, two authors (S.Y.C. and M.S.H.) independently selected the relevant studies. The Kappa value (κ) was assessed for interrater validity. Any conflicts between the two reviewers were resolved through discussion.

2.4. Eligibility criteria

The inclusion criteria were as follows: (1) mHSPC patients; (2) oral chemotherapeutic agent use; (3) control group comparisons; (4) OS or progression-free survival (PFS) outcomes; and (5) only RCTs. The exclusion criteria were review articles, basic studies, non-English articles, and duplicated studies.

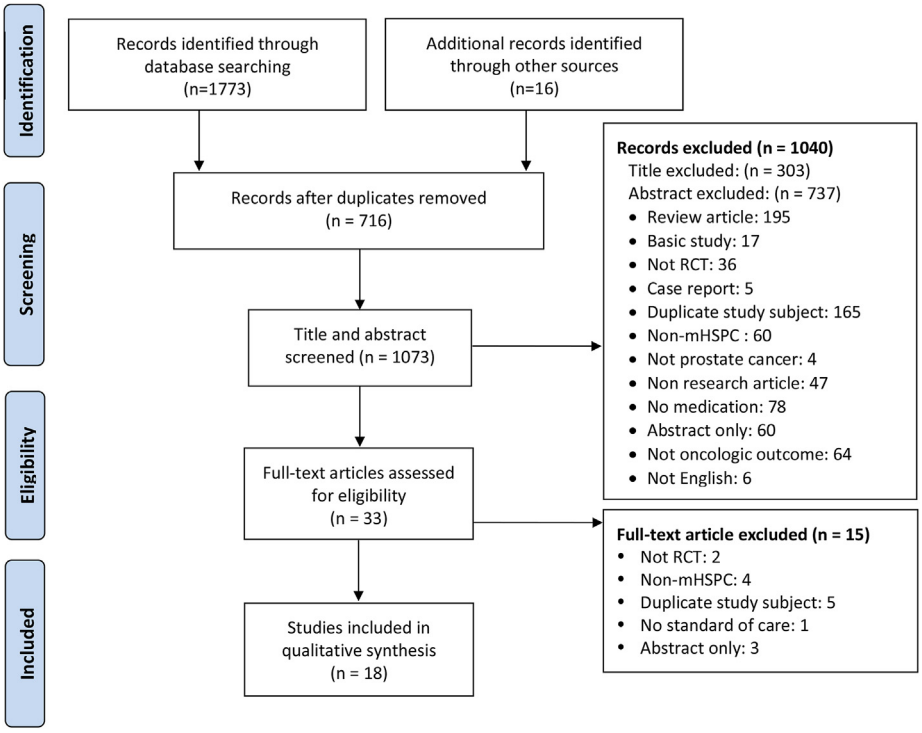

Fig. 1. Study design flow chart. RCT, randomized control trial; mHSPC, metastatic hormone-sensitive prostate cancer.

2.5. Data extraction and collection

Two authors (S.Y.C. and M.S.H.) independently reviewed each eligible article and extracted: (1) publication (first author name and publication year); (2) population (each group's sample size); (3) tumor (high and low volumes); (4) treatment (oral chemotherapeutic agents); and (5) outcome (OS, and PFS) data.

2.6. Risk of bias assessment

Randomization process, intended intervention deviation, missing outcome data, outcome measurement, reported result selection, and overall biases were assessed. Any disagreements were resolved through discussion.

2.7. Statistical analysis

Network meta-analysis (NMA) determined the relative treatment effect correlations.[13] Hazard ratio (HR) and confidence intervals (CIs) estimated OS and PFS differences.[13] Relative rankings were assessed through surface under the cumulative ranking curve (SUCRA) probabilities. NMAs were applied by high- and low-mHSPC volumes.[6] All statistical analyses were performed with R software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study selection

We identified 1,773 articles through the initial database search and 16 from other sources; thus, 716 were duplicate publications. Among these, title and abstract reviews eliminated 1,040 articles; full-text reviews excluded another 33. Finally, 18 articles were selected for the meta-analysis ($\kappa = 0.84$, almost perfect agreement). The flow diagram in Fig. 1 illustrates this selection process.

3.2. Study characteristics

The 18 eligible studies, published between 1997 and 2022, involved 13,509 patients (treatment group: 6,753 and control group: 6,756; Table 1). Ten studies focused on high-volume disease patients, and 14 treatment types were used, including SOC. The SOC included PEACE-1 and ARASENS ADT monotherapy and ADT + docetaxel. Supplementary Table 1 summarizes the assessment results for bias risk in the included studies.

3.3. Network meta-analysis

Fig. 2 displays the network plot. The mHSPC OS analysis evaluated and ranked 12 treatments: SOC had the highest patient number ($n = 4{,}623$; related studies = 10), ADT + bicalutamide the second ($n = 1{,}510$; related studies = 5), and ADT + flutamide the third ($n = 1{,}259$; related studies = 3). Similarly, mHSPC PFS analysis evaluated and ranked 14 treatments: SOC the highest ($n = 3{,}783$; related studies = 8), ADT + bicalutamide the second ($n = 1{,}569$; related studies = 7), and ADT + enzalutamide the third ($n = 1{,}173$; related studies = 3). Finally, high- and low-volume mHSPC OS analysis assessed six treatments.

3.4. Network comparison

Fig. 3 denotes the forest plots. In the total mHPSC OS comparison, ADT + abiraterone, ADT + abiraterone + docetaxel, ADT + apalutamide, ADT + bicalutamide, ADT + darolutamide

Table 1
Randomized controlled trials included in network meta-analysis

Study	Year	Name	Medicine		No. of patients		Age		High volume (%)		Outcomes
			Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	
Smith[10]	2022	ARASENS	ADT + Darolutamide + Docetaxel	ADT + Docetaxel	651	654	67 (41–89)	67 (42–86)			OS, PFS
Armstrong[22]	2022	ARCHES	ADT + Enzalutamide	ADT	574	576	70 (46–92)	70 (42–92)	61.7	64.8	OS, PFS
Akaza[14]	2009		ADT + Bicalutamide	ADT	102	101	≥75: 48%	≥75: 50.5%			OS
Usami[15]	2007		ADT + Bicalutamide	ADT	102	101	≥75: 48%	≥75: 50.5%			PFS
Vaishampayan[23]	2021		ADT + Enzalutamide	ADT + Bicalutamide	36	35	66 (54–86)	63 (51–84)	56	49	OS, PFS
Davis[24]	2019	ENZAMET	ADT + Enzalutamide	ADT + Bicalutamide, Nilutamide, Flutamide	563	562	69 (64–73)	69 (63–75)	51.7	52.8	OS, PFS
Tyrrell[16]	2000		ADT + Flutamide	ADT	152	151	73 (47–91)	73 (50–90)			OS
Fizazi[25]	2019	LATITUDE	ADT + Abiraterone	ADT	597	602	67.3	66.8	81.6	77.7	OS
Fizazi[9]	2022	PEACE-1	ADT + Abiraterone + Docetaxel	ADT + Docetaxel	583	589	67 (61–72)	66 (59–72)	57	57	OS, PFS
Gu[26]	2022	CHART	ADT + Rezvilutamide	ADT + Bicalutamide	326	328	69 (64–74)	69 (64–75)	100	100	OS, PFS
Chi[27]	2021	TITAN	ADT + Apalutamide	ADT	525	527	69 (45–94)	68 (43–90)	61.9	63.6	OS, PFS
Schellhammer[17]	1997		ADT + Bicalutamide	ADT + Flutamide	404	409	70 (43–91)	70 (42–93)			OS, PFS
Eisenberger[18]	1998		ADT + Flutamide	ADT	698	687	71 (65–76)	71 (65–76)			OS
Alghandour[21]	2021	MANSMED	ADT + Metformin + Bicalutamide	ADT + Bicalutamide	36	39	67 (46–81)	69 (46–87)	50	59	PFS
Reijke[19]	2002		ADT + Nilutamide	ADT	225	232	71 (50–85)	72 (46–86)			OS, PFS
Agarwal[28]	2022		ADT + Orteronel	ADT + Bicalutamide	638	641	68 (46–90)	68 (19–92)	49	49	OS, PFS
Palmbos[20]	2021		ADT + Bicalutamide + Palbociclib	ADT + Bicalutamide	40	20	68	66			PFS
James[29]	2022	STAMPEDE	ADT + Abiraterone	ADT	501	502	67 (62–71)	67 (62–72)	48.7	51.3	OS, PFS

ADT, Androgen deprivation therapy; OS, overall survival; PFS, progression-free survival.

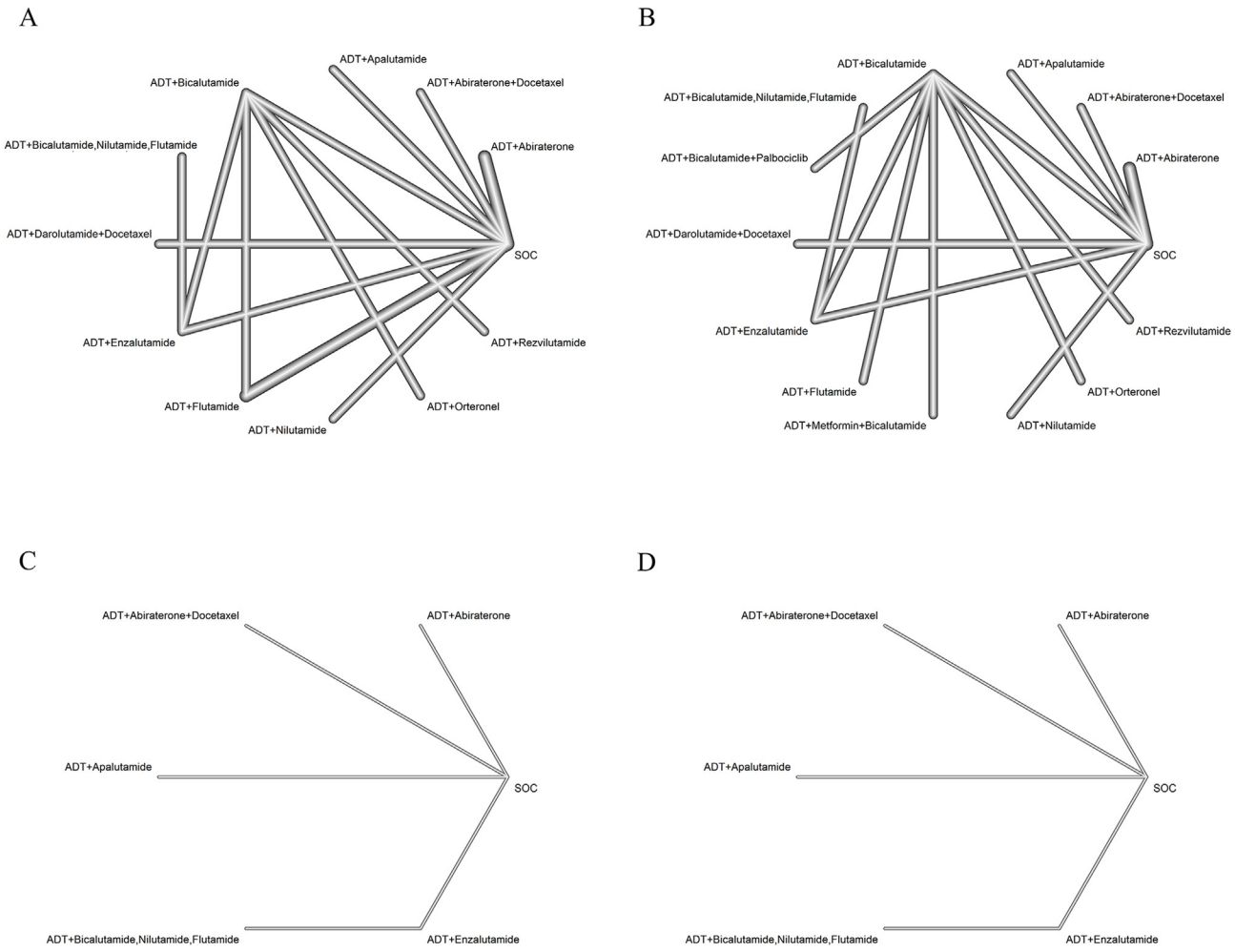

Fig. 2. Network plot (A) Overall and **(B)** progression-free survival in total metastatic hormone-sensitive prostate cancer. Overall survival in **(C)** high- and **(D)** low-volume metastatic hormone-sensitive prostate cancer.

+ docetaxel, ADT + enzalutamide, ADT + orteronel, and ADT + rezvilutamide were more effective than SOC. In the total mHPSC OS comparison, ADT + abiraterone was more effective than ADT + abiraterone + docetaxel, ADT + bicalutamide, ADT + bicalutamide, nilutamide, flutamide, ADT + flutamide, and SOC. In the total mHPSC PFS comparison, most treatments were more effective than SOC, except ADT + bicalutamide, nilutamide, flutamide, ADT + bicalutamide + palbociclib and ADT + nilutamide. In the total mHPSC PFS comparison, ADT + apalutamide, ADT + darolutamide + docetaxel, ADT + orteronel, and ADT + rezvilutamide were more effective than ADT + abiraterone. In the high-volume mHSPC OS comparison, ADT + abiraterone, ADT + abiraterone + docetaxel, ADT + apalutamide, and ADT + enzalutamide were more effective than SOC. In the low-volume mHSPC OS comparison, ADT + apalutamide was more effective than SOC.

3.5. Treatment ranking

Total mHSPC OS SUCRA value rankings were ADT + rezvilutamide (98%), ADT + enzalutamide (77%), and ADT + abiraterone (76%). Total mHSPC PFS SUCRA value rankings were ADT + rezvilutamide (95%), ADT + metformin + bicalutamide (88%), and ADT + orteronel (81%). High-volume mHSPC OS SUCRA value rankings were ADT + abiraterone (84%), ADT + enzalutamide (70%), and ADT + apalutamide (58%). Low-volume mHSPC OS SUCRA value rankings were ADT + apalutamide (91%), ADT + enzalutamide (70%), and ADT + abiraterone (62%) (Fig. 4).

3.6. Publication bias

The funnel plot does not suggest a publication bias in eligible studies (Supplementary Fig. 1). In addition, the funnel plot shape does not convey any evidence of pronounced asymmetry.

4. Discussion

Effective mHSPC treatment is imperative for managing advanced prostate cancer, improving survival, delaying disease progression, and improving patient quality of life. Traditionally, maximum androgen blockade involves medical or surgical castration and anti-androgen medications to reduce androgen levels.[14–19] However, some maximum androgen blockade trials with additional medicine utilized alternative pathways to inhibit prostate cancer growth.[20,21] Additionally, several clinical trials have signified that earlier ARTA uses with conventional ADT considerably improve oncologic outcomes.[22–29] For instance, two recent RCTs garnered increased interest in ARTA and ADT + docetaxel triplet therapy.[9,10] Although these trials could represent a patient survival

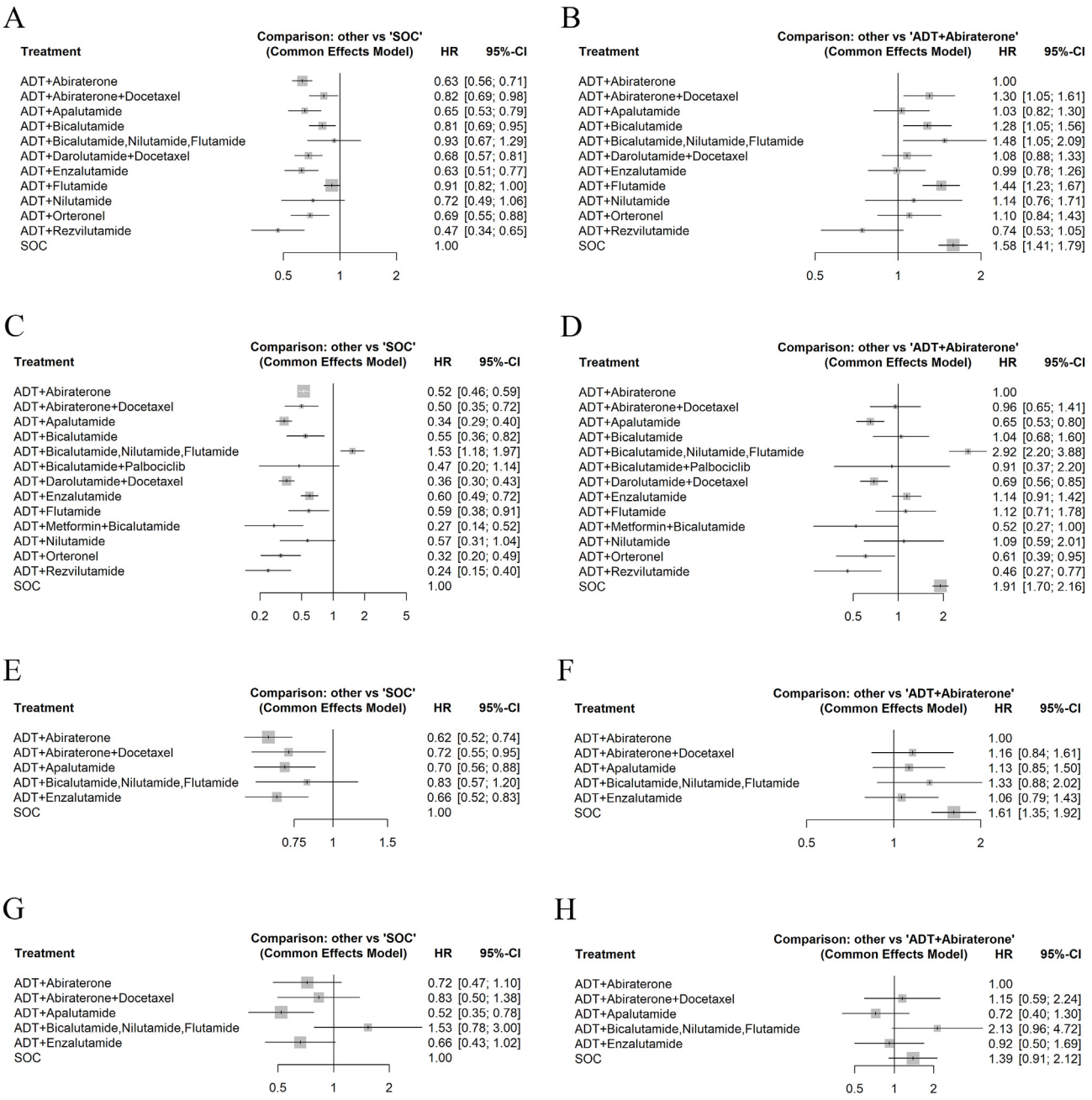

Fig. 3. Forest plot Overall survival compared to **(A)** standard of care (SOC) and **(B)** ADT + abiraterone in total metastatic hormone-sensitive prostate cancer. Progression-free survival compared to **(C)** SOC and **(D)** ADT + abiraterone in total metastatic hormone-sensitive prostate cancer. Overall survival compared to **(E)** SOC and **(F)** ADT + abiraterone in high-volume metastatic hormone-sensitive prostate cancer. Overall survival compared to **(G)** SOC and **(H)** ADT + abiraterone in low-volume metastatic hormone-sensitive prostate cancer.

breakthrough, dramatic mHSPC treatment changes challenge physicians' decision-making.

Our NMAs confirmed that even though some portion of SOC included ADT + docetaxel, SOC was still inferior to most new ARTA. Similar NMA studies comparing ARTA and docetaxel in mHSPC reported that enzalutamide, apalutamide, and abiraterone expressed more efficacy in PFS,[30] possibly from each medicine's duration. ARTA was continuously used until CRPC progression, but docetaxel was only used for six cycles. Considering adverse effects, docetaxel exhibited the highest risk among new drugs,[31] provoking fatigue, neuropathy, neutropenia, anemia, and thrombocytopenia.[30] In addition, efficacy, safety, and administration method influence treatment preference.[8] Docetaxel administration is age-limited, so only highly selected patients with favorable health status are considered intravenous chemotherapy candidates.[32] Therefore, we focused on oral chemotherapeutic agents in mHSPC.

In our ranking analysis, triplet therapy did not offer more pronounced OS or PFS benefits than current doublet therapy, such as rezvilutamide, orteronel, enzalutamide, or abiraterone. Rezvilutamide is a novel androgen-receptor inhibitor with a low blood-brain barrier penetration rate, reducing seizure risk.[26] Although all CHART trial patients with high-volume mHSPC and previous docetaxel were excluded, the rezvilutamide treatment group demonstrated improved OS and PFS compared to

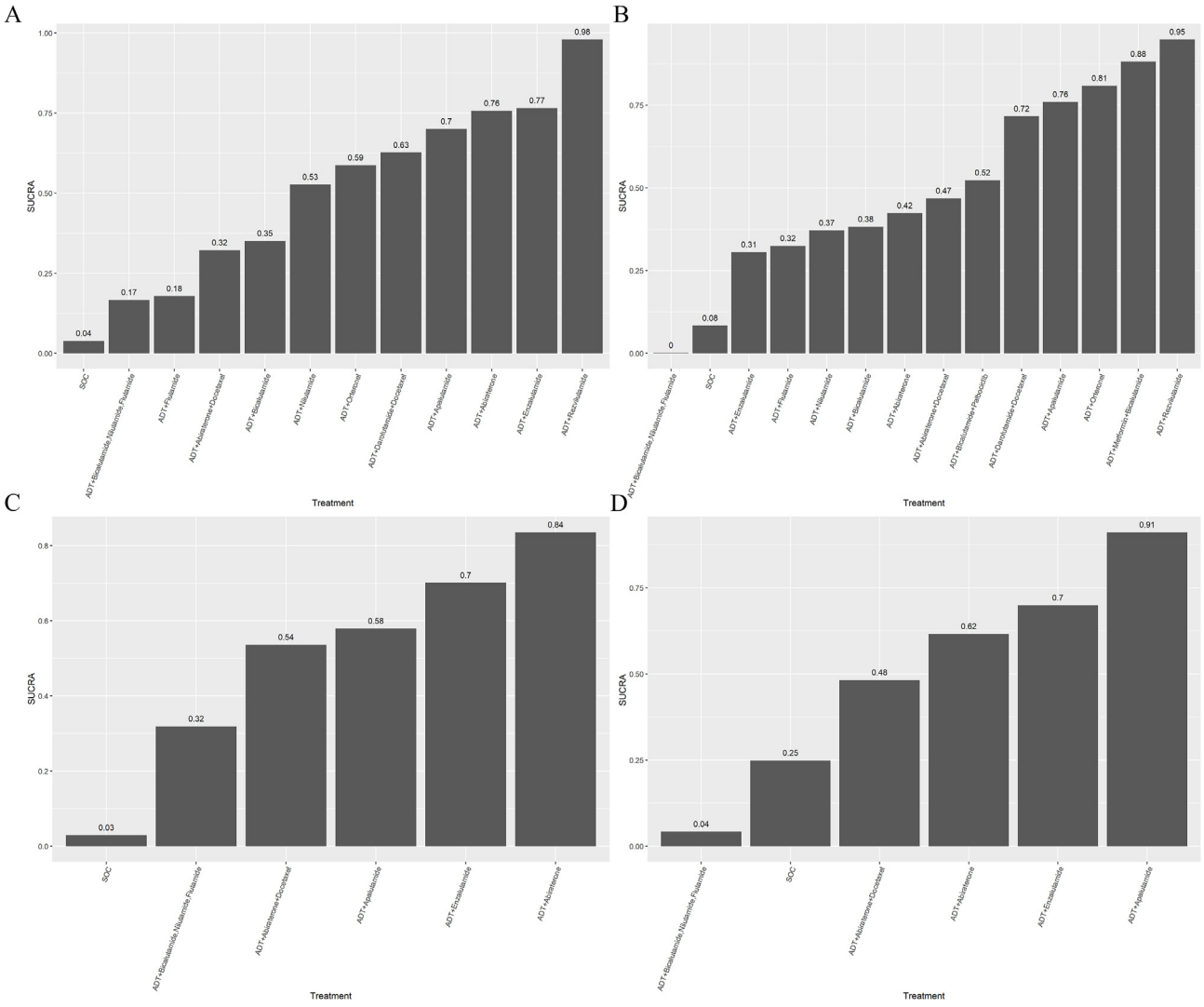

Fig. 4. Ranking analysis (A) Overall and **(B)** progression-free survival in total metastatic hormone-sensitive prostate cancer. Overall survival in **(C)** high- and **(D)** low-volume metastatic hormone-sensitive prostate cancer.

ADT + bicalutamide. Orteronel is a novel CYP17 inhibitor with a higher CYP17,20-lyase specificity and reduces secondary mineralocorticoid excess syndrome risks.[28] In other NMA triplet therapy studies, ADT + darolutamide + docetaxel ranked first, and ADT + abiraterone + docetaxel second compared to ARTA doublet therapy[33]; however, the triplet therapies failed to demonstrate more significant OS benefits.[33] In addition, we used more RCTs, including maximum androgen blockade and novel oral chemotherapeutic agents. In the PEACE-1 trial, triplet therapy showed an 11% higher rate of grade 3 or more adverse effects than doublet therapy.[9] In the ENZAMET trial, planned early docetaxel use (almost triplet therapy) increased adverse effects during the first six months, possibly related to a drug–drug interaction between enzalutamide and docetaxel.[24] Therefore, mHSPC triplet therapies need further grounding to be considered SOC.

In high-volume mHSPC subgroup analysis, ARTA doublet or triplet therapies were superior to SOC, but maximum androgen blockade was not. In low-volume mHSPC, only apalutamide revealed significantly better OS than SOC. Apalutamide's maximal efficacy at lower steady-state plasma may have a higher therapeutic effect than enzalutamide.[34] However, the low-volume subgroup might be underpowered to confirm differences between experimental and SOC groups. In addition, favorable low-volume OS between groups might mature results during follow-up periods.

This study has some limitations. First, indirect comparison cannot replace direct, well-designed RCT. However, NMA was used for our indirect comparison because no direct data existed. Second, heterogeneous patient characteristics and study designs were included. Surgical orchiectomy was regarded as SOC ADT.[18] Previous or early docetaxel was allowed in some studies.[22,24,27] Third, ADT + docetaxel was used as SOC. ADT + docetaxel offered better OS than ADT monotherapy and became the new SOC. During the PEACE-1 trial, a new docetaxel trend had a heterogenous SOC composition.[9] Lastly, the ARASENS trial recently reported their subgroup analysis by disease volume[35] but was excluded because of search date restrictions.

5. Conclusions

In this mHSPC patient study, we indirectly compared OS and PFS data from RCTs employing oral chemotherapeutic agents. We determined that new oral chemotherapeutic agents with ADT are effective treatment options. Combination therapies with new oral chemotherapeutic agents must replace previous mHSPC SOC,

including ADT monotherapy and ADT + docetaxel. However, ADT + docetaxel with ARTA triplet therapy is still not the best mHSPC treatment option, and further triplet therapy studies are essential.

Authors' contributions

Conception and design: Se Young Choi and Seong Hwan Kim. Acquisition of data: Se Young Choi, Jong Hyun Tae, Joongwon Choi, Jung Hoon Kim, and Jin Wook Kim. Analysis and interpretation of data: Myoungsuk Kim, Se Young Choi, and Yong Seong Lee. Drafting of the manuscript: Yong Seong Lee and Seong Hwan Kim. Critical revision of the manuscript: In Ho Chang, Tae-Hyoung Kim, Soon Chul Myung, Tuan Thanh Nguyen, and Yong Seong Lee. Obtaining funding: Se Young Choi. Supervision: Se Young Choi.

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Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2023.06.003.

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