Comparison of effectiveness and safety outcomes of abiraterone versus enzalutamide in patients with metastatic castration-resistant prostate cancer: a systematic review and meta-analysis

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ABSTRACT- Purpose: To compare the effectiveness and safety between abiraterone and enzalutamide in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** We systematically searched for relevant articles from PubMed, Cochrane, Embase from their inception through November 4, 2019. Available articles from conferences were searched. The endpoints were prostate-specific antigen (PSA) response, overall survival (OS), progression-free survival (PFS), number of patients with any adverse event (AE). **Results:** 15 cohort studies involving 3546 participants were included in this meta-analysis. Pooled result showed that PSA response rate in the enzalutamide group was significantly greater than that in the abiraterone group (867 patients, risk ratio (RR) 0.69, 95% confidence interval (CI) 0.61-0.79, $p < 0.00001$, I^2=29%). There was no significant difference in the total incidence of AEs between two groups (730 patients, RR 0.42, 95% CI 0.14-1.31, $p = 0.14$, I^2=84%). The common adverse events observed in the published articles were fatigue and perceived cognitive impairments. Patients who received enzalutamide had the higher risk to have the feeling of fatigue compared with abiraterone group (2555 patients, RR 0.45, 95% CI 0.24-0.85, p=0.01, I^2=92%). And there was no statistical difference between two groups respect to the side effect of perceived cognitive impairments (1856 patients, RR 0.94, 95% CI 0.47-1.88, p=0.85, I^2=15%). **Conclusions:** Our results demonstrated that enzalutamide was associated with higher PSA response rate compared to abiraterone in patients with mCRPC, and no significant difference was found between two groups in the overall AE. But enzalutamide use induced higher risk of the AE of fatigue.

INTRODUCTION

Prostate cancer (PCa) is currently the most common male neoplasm worldwide and is the second leading cause of cancer-related deaths after lung cancer in men (1). Androgen deprivation therapies (ADT) is considered the mainstay treatment for PCa. ADT therapy is effective in most PCa, but as treatment continues, most patients eventually experience resistant to ADT and disease progression (2). Metastatic castration resistant prostate cancer (mCRPC) was known as a lethal stage which is characterized by poor prognosis and high lethality, despite the maintenance of a serum testosterone level within the castration range (3, 4).

The United States' Food and Drug Administration (FDA) approved of several new treatment agents for mCRPC during the pastdecade, including abiraterone (the androgen synthesis inhibitor) and enzalutamide (potent androgen receptor antagonist) (5). Several key phase III randomized controlled trials (RCTs) have proved that these two agents were associated with favorable clinical activities, characterized by a high PSA response rate, prolonged overall survival (OS) of patients in treatment of pre-or post-chemotherapeutic mCRPC (6-9). A meta-analysis published in 2019 has demonstrated that, relative to placebo, both abiraterone and enzalutamide significantly improved clinical efficacy in men with CRPC (10). While the two drugs have distinct mechanisms of action and may have different toxicity profile, Moreira et al demonstrated that abiraterone was associated with an increased risk of

cardiovascular events, while enzalutamide induced increased risk of fatigue (11). Currently, studies of comparative assessment of clinical outcomes between abiraterone and enzalutamide in patients with mCRPC have been published (12-26). The aim of this systematic review was to conduct a meta-analysis of studies to assess the impact of these two drugs on effectiveness and safety outcomes in patients with mCRPC.

ABBREVIATIONS. metastatic castration-resistant prostate cancer (mCRPC); prostate-specific antigen, (PSA); overall survival, (OS); progression-free survival, (PFS); adverse event, (AE); risk ratio, (RR); confidence interval, (CI); prostate cancer, (PCa); androgen deprivation therapies, (ADT); androgen receptor, (AR); Food and Drug Administration, (FDA); randomized controlled trial, (RCT); American Society of Clinical Oncology, (ASCO); European Society of Medical Oncology, (ESMO); Newcastle-Ottawa Scales, (NOS); central nervous system, (CNS); hazard ratio, (HR); Common Terminology Criteria for Adverse Events, (CTCAE)

MATERIALS AND METHODS

Search strategy. We systematically searched for articles from PubMed, Cochrane, Embase from their inception through November 4, 2019, with no language restrictions. References of the retrieved articles were also searched for additional studies. In addition, American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) relevant abstracts were manually searched. The MeSH terms used for searching PubMed and the Cochrane Library were 'abiraterone' and 'enzalutamide'. The following search terms were utilized: ((abiraterone) OR (abiraterone acetate) OR-(17-(3-pyridyl)-5, 16-androstadien-3beta-acetate) OR (Zytiga) OR (CB 7630)) AND ((enzalutamide) OR (MDV3100)).

Study selection. Inclusion criteria: We have searched for articles including men with histologically or cytologically proven mCRPC. The articles evaluating the effectiveness or safety of abiraterone and enzalutamide in patients with mCRPC were included, and the type of studies included cohort study and RCT. Exclusion criteria: studies without control group, no confidence intervals or bounds were reported for the median estimates, studies without available clinical outcomes, results of studies with >1 publication were considered once.

Data extraction. Data extraction and assessment were made independently by two different authors (X.W and H.Y) and the disagreements were solved by discussion with another author (X.P.H). The data included the characteristics of each study (the first author's name, study design, year of publication, country), population demographics (sample size, age, length of follow up, treatment setting), description of interventions (the name, duration of medication therapy).

Outcomes. The primary outcomes were PSA response rate (The PSA response was defined as a PSA decline of ≥ 50% from the baseline) and the incidence of AE. The second outcomes were OS and progression-free survival (PFS).

Quality assessment. Two reviewers (X.W and H.Y) independently evaluated methodological quality. A third review author (W.W) resolved any disagreements, and a final consensus was reached by all the authors. RCTs were appraised for methodological quality using the criteria developed by the Cochrane risk of bias tool. Observational studies assessed the quality using the Newcastle-Ottawa Scales (NOS) (27). Publication bias assessed by the funnel plot.

Statistical analysis. The meta-analysis was performed using Review Manager for Windows (version 5.3). Risk Ratio (RR) and 95% confidence interval (CI) were calculated for each outcome. All comparisons were based on two-tailed tests, and p-values lower than 0.05 were considered significant. Heterogeneity was assessed using the Q statistic and the I^2 method. Mantel-Haenszel fixed effects model was used when there was no significant heterogeneity between studies; otherwise, a random effects model was chosen. In order to evaluate the stability of results without estimation bias from individual study, sensitivity analysis was performed by exclusion of each study one by one. Egger regression was used to evaluate publication bias (28).

RESULTS

Literature search. The search for literature identified in a total of 880 records. A total of 818 articles were excluded after the review of abstracts, and 62 articles remained for full-text analysis. 47 articles without available clinical outcomes were excluded after full-text review. Overall, 15 studies with 3546 patients were eligible for the meta-analysis (12-26). The literature search process was summarized in Figure 1.

As there was no RCT evaluating the effectiveness or safety of abiraterone and enzalutamide in patients with mCRPC compared retrospective cohort studies (Table 1, Supplement). All together, 15 studies involving 3546 participants were included (12-26).

Table 1. The characteristics of included studies

Source	Study design, years, region	Patients enrolled	Median age, years (range)	Follow up (months)	Abiraterone (n)	Enzalutamide (n)	Treatment stage
Miyake, 2017 [12]	Cohort, 2014.8 - 2015.12, Japan	280	76.9 (47-96)	24	113	167	Pre-chemotherapy
Norris, 2017 [13]	Cohort, 2011.9 - 2015.11, UK	198	NR	NR	98	100	Pre-chemotherapy and post-chemotherapy
Salem, 2017 [14]	Cohort, 2011.9 - 2015.6, Canada	189	76.5	12	76	113	Pre-chemotherapy
Pilon, 2017 [15]	Cohort, 2005.1 - 2014.12, NR	1659	NR	12	1067	592	NR
Al-Ali, 2018 [16]	Cohort, 2013.9 - 2016.8, Austria	334	74.4	30	195	139	Pre-chemotherapy and post-chemotherapy
Antoine, 2018 [17]	Cohort, 2016.3-2018.3, Europe	105	74.5 (53-92)	3	46	59	NR
Richter, 2016 [18]	Cohort, NR, Czech	32	NR	6.5	9	23	Post-chemotherapy
Lista, 2016 [19]	Cohort, 2014.1 - 2015.9, NR	42	74.02	NR	22	20	NR
Heo, 2017 [20]	Cohort, 2013 – 2014, NR	54	70 (45-86)	15	25	29	Post-chemotherapy
Selvi, 2018 [21]	Cohort, 2013.1 - 2017.6, NR	74	76	12	59	15	Pre-chemotherapy and post-chemotherapy
García, 2018 [22]	Cohort, 2015.1 - 2017.7, Spain	48	75.8 (56-92)	NR	26	22	Pre-chemotherapy and post-chemotherapy
Khalaf, 2018 [23]	Cohort, 2009.7 - 2016.9, NR	210	85 (83-88)	NR	106	104	Pre-chemotherapy
Shore, 2018 [24]	Cohort, 2015.12-2017-1, US	92	75	2	46	46	NR
Dearden, 2019 [25]	Cohort, 2011 - 2015, France, Germany and the UK	152	NR	NR	78	74	Pre-chemotherapy and post-chemotherapy
Chang, 2019 [26]	Cohort, 2012.4-2018.1, China	77	68.1	18.2(abiraterone) vs. 14.5(enzalutamide)	64	13	Prior treatment-failure with docetaxel

CRPC, castration resistant prostate cancer; mCRPC' metastatic castration resistant prostate cancer; NR, not report.

Quality of included studies. Since there was no RCT comparing the two regimens, risk of bias was assessed using the NOS for all studies. Eight factors were used to assess study quality according to NOS. All included observational studies were high quality, 6 studies (14-17, 22-23) were missed one indicator, 6 studies (13, 18-21, 24) were missed two indicators. The results presented in Table 2 showed that all observational studies were high quality.

Prostate-specific antigen response rate. Six studies enrolling 867 patients evaluated the PSA response rate in mCRPC settings (12, 13, 20, 22-23, 26). Pooled results showed PSA response rate in the enzalutamide group was significantly greater than that in the abiraterone group (RR 0.69, 95% CI 0.61-0.79, $p < 0.00001$, I^2=29%; Figure 2). The funnel plot did not show obvious asymmetry (Figure 1), and there was no publication bias presented by Egger's test (p=0.998). The sensitivity analysis showed that the above result was reliable after exclusion of individual study one by one.

Adverse event rate. A total of four studies evaluated the total rate of AEs (12, 13, 19, 23), and there was no statistical difference in the total incidence of AEs in the enzalutamide group compared to that in the abiraterone group (730 patients, RR 0.42, 95% CI 0.14-1.31, p = 0.14, I^2=84%; Figure 3). Obvious asymmetry was not found in the funnel plot (Figure 2), and no significant publication bias was detected by Egger test (p=0.230). The results of sensitivity analysis showed no substantial modification of the estimates after exclusion of individual study one by one which showed that the result was reliable.

The most common adverse reaction reported for the two drugs was central nervous system (CNS). Fatigue and perceived cognitive impairments were the most common CNS events affecting patients during treatment. Seven articles reported the rate of fatigue (12, 14, 15, 17, 24-26) and three articles reported the rate of perceived cognitive impairments (15, 17, 24). Patients who received enzalutamide had the higher risk to have the feeling of fatigue compared with abiraterone group (2555 patients, RR 0.45, 95% CI 0.24-0.85, p=0.01, I^2=92%; Figure 4). And there was no statistical difference between two groups respect to the side effect of perceived cognitive impairments (1856 patients, RR 0.94, 95% CI 0.47-1.88, p=0.85, I^2=15%; Figure 4). Obvious asymmetry was not found in the funnel plot (Figure 3). No significant publication bias was detected by an Egger regression (p=0.509). The sensitivity analysis showed the results were reliable.

Table 2. Quality of observational studies (indicators from New-Castle-Ottawa scale)

Study	1[a]	2[b]	3[c]	4[d]	5A[e]	5B[f]	6[g]	7[h]	8[i]	Total quality scores
Miyake, 2017 (12)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Norris, 2017 (13)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Salem, 2017 (14)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Pilon, 2017 (15)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Al-Ali, 2018 (16)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Antoine, 2018 (17)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Richter, 2016 (18)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Lista, 2016 (19)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Heo, 2017 (20)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
Selvi, 2018 (21)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
García, 2018(22)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
Khalaf, 2018 (23)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Shore, 2018 (24)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7
Dearden, 2018 (25)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9
Chang, 2019 (26)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9

[a] Indicates exposed cohort truly representative; [b] Non-exposed cohort drawn from the same community; [c] Ascertainment of exposure from the same community; [d] Outcome of interest not present at start of study; [e] Cohorts comparable on basis of site and etiology of infection; [f] Cohorts comparable on others factors; [g] Assessment of outcome of record linkage or independent blind assessment; [h] Follow-up long enough for outcomes to occur; [I] Complete accounting for cohorts

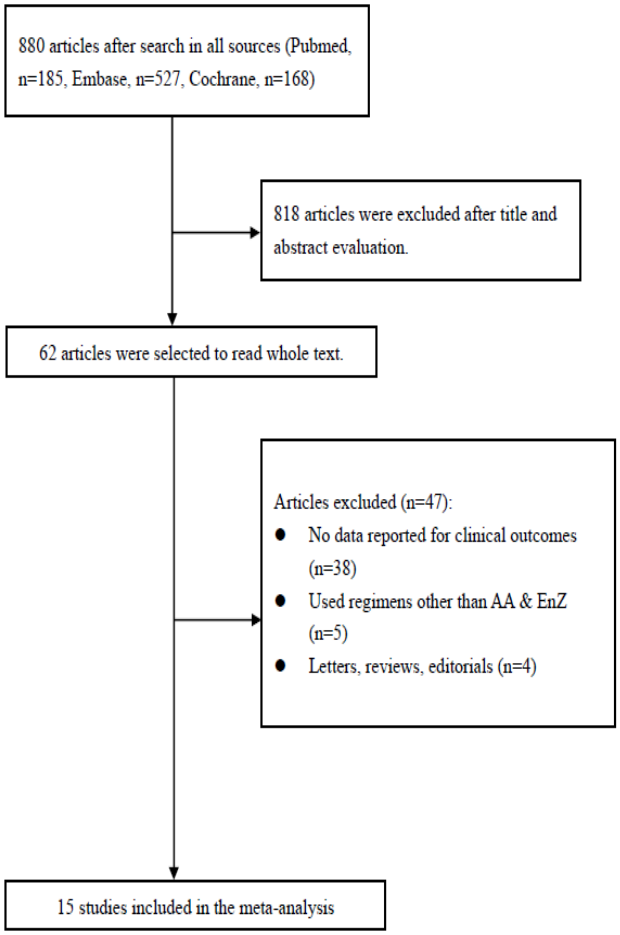

Figure 1. The search strategy of the meta-analysis

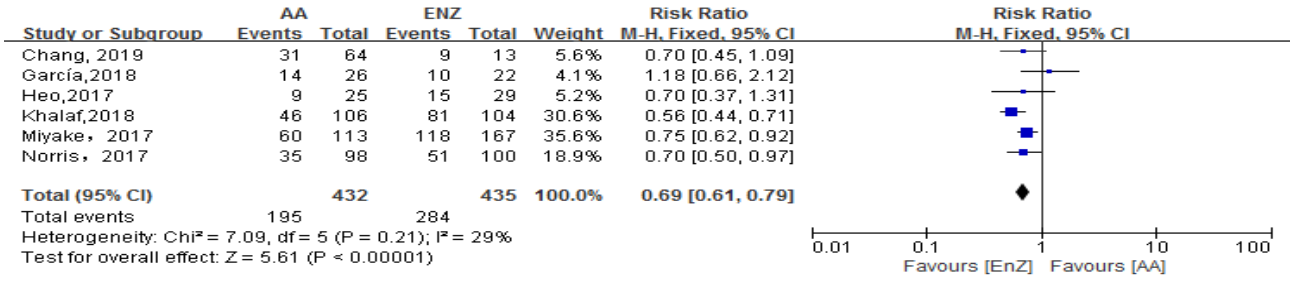

Figure 2. Meta-analysis of studies investigating association of PSA response with abiraterone versus enzalutamide

Overall survival. Five articles enrolling 851 patients evaluated the OS between abiraterone group and enzalutamide group, statistical analysis was not applied due to limited available data. Four articles reported that statistical difference was not observed in OS between the groups (13, 18, 23, 26). And another one article reported the median OS but p value was not reported (16.7 ± 0.8 months vs 19.7 ± 1.1 months) (16).

Progression-free survival. Four articles enrolling 463 patients evaluated the PFS between abiraterone group and enzalutamide group, statistical analysis was not applied due to limited available data. The conclusions of the four articles were not consistent. Three articles reported that there was no statistical difference in PFS between enzalutamide group and abiraterone group (18, 21, 26), but Miyake et al (12) reported that the median PFS was longer in the enzalutamide group than abiraterone group (11.6 months vs 9.0 months, p=0.014).

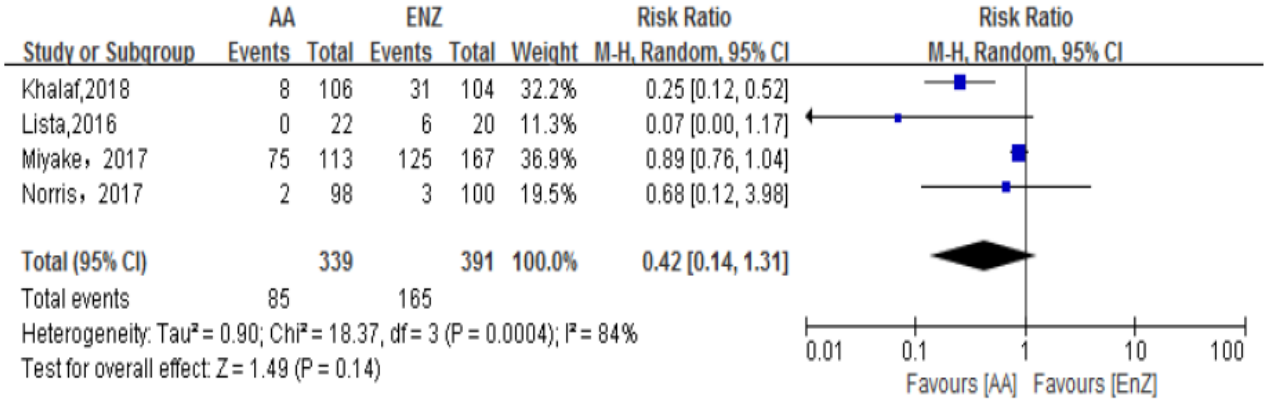

Figure 3. Meta-analysis of studies investigating association of AEs with abiraterone versus enzalutamide

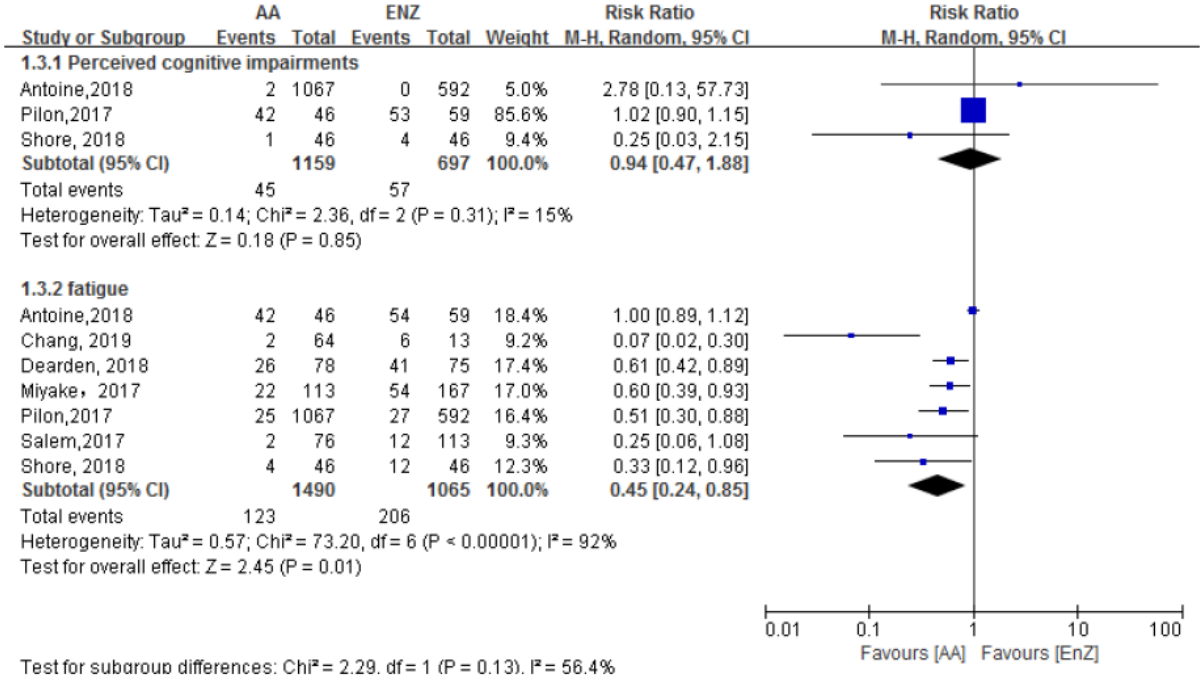

Figure 4. Meta-analysis of studies investigating association of CNS events with abiraterone versus enzalutamide

DISCUSSION

Abiraterone and enzalutamide have shown promising clinical efficacy for mCRPC patients in multicenter Phase III RCTs (6-9). However, there was a paucity of evidence regarding the comparative outcomes of treatment with the two agents, making it difficult to select the first-line treatment of choice in patients with mCRPC. Therefore, we performed a meta-analysis to assess the impact of these two drugs. To the best of our knowledge, this was the first systematic review and meta-analysis to directly compare the clinical outcomes of abiraterone and enzalutamide in mCRPC patients. In our meta-analysis, we found that PSA response rate in the enzalutamide group was significantly greater than that in the abiraterone group. And there was no statistical difference between two groups respect to the total incidence of AEs. However, patients who received enzalutamide had the higher risk to have the feeling of fatigue compared with abiraterone group.

Our meta-analysis found that the PSA response rate in the enzalutamide group was significantly greater than that in the abiraterone group. The statistical analysis for both OS and PFS were not applied due to limited available data. But a network meta-analysis published by Kang et al reported that enzalutamide was more efficacious than abiraterone in OS and PFS (29). We speculated that the two drugs'

different mechanisms of action might result in different response outcomes. In terms of the modes underlying drug actions, abiraterone is known to inhibit two specific enzymes (17α-hydroxylase and C17, 20-lyase) that are needed for testosterone synthesis from cholesterol precursors. In contrast, enzalutamide selectively inhibits AR activities by interfering with different portions of the AR pathway, including cell nuclear translocation, impeding DNA binding to androgen response elements, andinterplay with co-activators (30). Therefore, as compared with abiraterone, enzalutamide may have
more selective actions on the AR signaling pathway in prostate cancer cells.

Fatigue was one of the most common symptoms experienced by patients with mCRPC, occurring as a consequence of the cancer itself and/or as a side effect of medication, and can significantly interfere with daily functioning (31, 32). Our meta-analyses demonstrated that there was no statistical difference in the total incidence of AEs in the enzalutamide group compared to abiraterone group. However, patients who received enzalutamide had the higher risk to have the AE of fatigue. This result was consistent with the findings of the recent indirect meta-analysis by Moreira et al (11). Another indirect meta-analysis suggested that mCRPC patients treated with enzalutamide had a higher risk of developing neurological and psychiatric disorders than the patients treated with abiraterone (33). Enzalutamide was acknowledged to penetrate the blood-brain barrier, which may at least in part explain its effect on the CNS (34). Furthermore, the affinity of enzalutamide for GABA receptor may play a role in the toxicities related to the feeling of fatigue (33). Conversely, a phase 3 clinical trial reported a meaningful improvement in fatigue for patients receiving abiraterone plus prednisone compared with those receiving prednisone alone in patients with mCRPC progressing after docetaxel chemotherapy treatment (35).

Some limitations of this study should be noted. First, all included studies were cohort designs not RCT, the potential drawbacks of the study designs included inadequate time of follow up, heterogeneous disease statuses. Second, different sample sizes also brought some estimates bias. Third, the included studies adopted different versions of the Common Terminology Criteria for Adverse Events (CTCAE), which could bring some bias.

CONCLUSIONS

This was the first study to directly compare the clinical effectiveness and safety of abiraterone and enzalutamide in mCRPC patients. Our results demonstrated that enzalutamide was associated with higher PSA response rate compared to abiraterone in patients with mCRPC, and no significant difference was found between two groups in the overall AE. But enzalutamide use induced higher risk of the AE of fatigue. Prospective or randomized controlled trials compared the clinical outcomes of these agents is needed.

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CONFLICTS OF INTEREST.

The authors declare no conflicts of interest.

Authors' contributions. The experiments were designed by X.W, H.Y, L.H.L and performed by X.W, H.Y. The data were collected and analyzed by X.W, H.Y, S.H.W, X.P.H. The manuscript was written by X.W, H.Y and revised by X.J.Y, W.W, X.D.Z and L.H.L. The submission was approved by all authors. XW and HY contributed equally to this work and should be considered co-first authors.

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Supplementary pertaining to: The clinical outcomes of included studies

Author, year, reference	PSA response（≥50%）			PFS（months）				OS (months)				AEs			CNS events			Perceived cognitive impairments			Fatigue		
	Abiraterone, n/N (%)	Enzalutamide, n/N (%)	P	Abiraterone	Enzalutamide	P	HR (95%CI)	Abiraterone	Enzalutamide	P	HR (95%CI)	Abiraterone, n/N (%)	Enzalutamide, n/N (%)	P	Abiraterone, n/N (%)	Enzalutamide, n/N (%)	P	Abiraterone, n/N (%)	Enzalutamide, n/N (%)	p	Abiraterone, n/N (%)	Enzalutamide, n/N (%)	P
Miyake, 2017 [12]	60/113, (53.1%)	118/167, (70.7%)	NR	9	11.6	0.014	NR	NR	NR	NR	NR	75/113, (66.4%)	125/167, (74.9%)	0.12	NR	NR	NR	NR	NR	NR	22/113, (19.4%)	54/167, (32.3%)	0.018
Norris, 2017 [13]	35/98, (35.7%)	51/100, (51.0%)	0.031	NR	NR	NR	NR	15.3	22.2	0.913	NR	2/98, (2.04%)	3/100, (3.00%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Salem, 2017 [14]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2/76, (2.6%) [A]	12/113, (10.6%) [A]	0.04
Pilon, 2017 [15]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	78/1067, (7.3%) [A]	54/592, (9.1%) [A]	NR	2/1067, (0.19%) [A]	0/592, (0.0%) [A]	NR	25/1067(2.3%) [A]	27/592(4.6%) [A]	NR
Al-Ali, 2018 [16]	NR	NR	NR	NR	NR	NR	NR	15	24	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Antoine, 2018 [17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	42/46, (91.3)% [B]	53/59, (89.8)% [B]	NR	42/46, (91.3)% [B]	54/59, (91.5)% [B]	NR

Richter, 2016 [18]	NR	NR	NR	NR	NR	0.939	0.985(0.293-3.308)	NR	NR	0.102	0.236(0.029-1.894)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lista, 2016 [19]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0/22, (0.0 %)	6/20, (30. 0%)	0.006	NR	NR	NR	NR	NR	NR	NR	NR
Heo, 2017 [20]	9/25, (36. 0%)	15/29, (51. 7%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Selvi, 2018 [21]	NR	NR	NR	12.4	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
García, 2018 [22]	14/26, (53. 9%)	10/22, (58. 9%)	0.579	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Khalaf, 2018 [23]	46/106, (43. 4%)	81/104, (77. 9%)	< 0.001	NR	NR	NR	NR	13.2	18.7	NR	1.2 (0.89-1.63)	8/106, (7.5 %)	31/104, (29. 8%)	P<0.001	NR	NR	NR	NR	NR	NR	NR	NR
Shore, 2018 [24]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	17/46, (37. 0%)	24/46, (52. 2%)	NR	1/46, (2.2 %)	4/46, (8.7 %)	NR	4/46, (8.7 %)	12/46, (26. 1%)	NR
Dearden, 2019 [25]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	26/78, (33. 3%)	41/75, (54. 7%)	0.006
Chang, 2019 [26]	31/64(48.44 %)	9/13 (69. 23%)	0.171	7.3	9.5	0.766	NR	30.2	16.2	0.734	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2/64 (3.1 3%)	6/13 (46. 15%)	NR

PSA: prostate-specific antigen, PFS: progression-free survival, OS: overall survival, AEs: adverse events, CNS: central nervous system, NR: not report; A: Patients with 3 months of exposure; B: Patients were observed at months 1.