Effect of adjuvant hormone therapy in patients with prostate cancer
A meta-analysis of randomized controlled trials

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Abstract
Objectives: To summarize the evidence regarding the treatment effect of adjuvant hormone therapy (AHT) in patients with prostate cancer (PCa). AHT following radiotherapy, chemotherapy, or surgery is widely used in patients with PCa. However, the treatment effect is inconsistent in individual trials.

Methods: The electronic databases including PubMed, EmBase, and Cochrane Library were searched to identify randomized controlled trials (RCTs) in September 2016. RCTs that evaluated the effects of AHT in patients with PCa were included. Hazard ratio (HR) and relative risks (RR) were used to measure the treatment effects of AHT using a random effects model. The analyses were further stratified by factors that could affect the treatment efficacy.

Results: A total of 14,594 potential studies were identified, and 27 RCTs were included. Compared with the control group, patients who received AHT were associated with a significant improvement in overall survival (OS) (HR: 0.78; 95% confidence interval [CI]: 0.71–0.85; P < .001), disease-free survival (DFS) (HR: 0.50; 95% CI: 0.39–0.65; P < 0.001), total mortality (RR: 0.90; 95% CI: 0.85–0.96; P = .001), recurrence (RR: 0.70; 95% CI: 0.60–0.81; P < .001), and disease-specific mortality (RR: 0.70; 95% CI: 0.56–0.87; P < 0.001). However, no significant difference was observed between AHT and control for response rate (RR: 1.75; 95% CI: 0.91–3.37; P = .095).

Conclusions: The findings of this meta-analysis confirmed that patients who received AHT had a significant improvement in OS, DFS, total mortality, recurrence, and disease-specific mortality. Further, large-scale RCTs are required to evaluate the treatment effect in specific subpopulations.

Abbreviations: ADT = androgen deprivation therapy, AHT = adjuvant hormone therapy, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, PCa = prostate cancer, PSA = prostate-specific antigen, RCTs = randomized controlled trials, RRs = relative risk.

Keywords: adjuvant hormone therapy (AHT), meta-analysis, prostate cancer (PCa)

1. Introduction
Prostate cancer (PCa) has become a major health problem with 913,000 cases in 2008 around the world.[1] With the development of diagnostic techniques, the morbidity of PCa has been increasing in Asian countries, especially in developed cities.[2] Similarly, approximately 241,000 men are diagnosed with PCa each year in America; 82% of them have localized PCa and 11% have regional or locally advanced disease.[3] However, around 20% to 30% of men with PCa present with high-risk tumor characteristics.[4]

In the last decades, hormone therapy, alongside surgery and external beam radiotherapy as the most common approaches, was applied for PCa treatment.[5] For patients with locally advanced PCa, hormone therapy alone and radiotherapy alone have become acceptable methods. Moreover, compared with radiation alone, the combined treatment with hormonal therapy and radiotherapy can increase survival benefits.[6–9] However, the effect of this multimodal treatment is still unclear.[10] Furthermore, according to different risk classifications, patients with PCa having prostate-specific antigen (PSA) levels ≥20ng/mL, stage T3–T4 disease, or Gleason scores ≥7 are most commonly defined as patients with high-risk PCa.[11] For patients with high-risk PCa, radiation therapy (RT) plus androgen deprivation therapy (ADT) or radical prostatectomy have been the main therapy options.[11] However, the number of neoplasm recurrence for patients with high-risk PCa are more significant.[12]

As high-risk PCa is prone to recurrence and metastasis after treatment, an increasing number of studies have focused on this issue. Unfortunately, no consensus is reported regarding the
optimal treatment choice. A meta-analysis and systematic review of the literature were performed in the present study to evaluate the efficacy and safety of endocrine therapy in treating patients with high-risk PCa. Furthermore, a subgroup analysis was also performed to compare treatment effects among patients with different baseline characteristics.

2. Materials and methods

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.1. Search strategy and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1). A comprehensive and systematic search of the literature was performed from 3 electronic databases (PubMed, EMBASE, and Cochrane library), which were last updated in September 2016 (The details of PubMed search strategy was shown in supplemental 1, http://links.lww.com/MD/C651). Relevant English-language articles were searched using the following Key words: PCa; hormone therapy; and randomized controlled trials (RCTs). The reference lists of the published articles were hand-searched for any additional studies.

The literature search was independently undertaken by 2 authors using a standardized approach. Any inconsistencies between these 2 authors were settled by the primary author until a consensus was reached. Studies were included if they fulfilled all of the following criteria:

(1) the study had an RCT design;
(2) patients included in trials with PCa;
(3) patients received adjuvant hormone therapy (AHT), and the control group did not receive AHT or delayed AHT; and
(4) the trial reported at least 1 of the following outcomes: overall survival (OS), disease-free survival (DFS), total mortality, disease-specific mortality, disease progression, and response rate. The studies were excluded if Studies were excluded if studies that used the same population or overlapping database and studies on animal models. Disagreements were resolved through discussions.

2.2. Data collection and quality assessment

The relevant data were extracted and the accuracy was checked for all eligible studies. The extracted data of studies included the name of the first author or study group, publication year, country, sample size, mean age, type of intervention, type of control, disease status, serum PSA, duration of the follow-up, and reported endpoints. If the same population was reported in more than 1 study, the study comprising the more detailed information was chosen. The quality of included RCTs was assessed using the Jadad score, ranging from 0 to 5, on the basis of parameters including randomization, blinding, allocation concealment, withdrawals and dropouts, and use of intention-to-treat analysis.

2.3. Statistical analysis

The meta-analysis was conducted using the STATA software (version 10.0; StataCorp, TX). Compared with the control group, the effect of AHT on OS and PFS [defined as hazard ratio (HR)] and on total mortality, disease-specific mortality, disease progression, and response rate [defined as relative risk (RR)] were assessed. The pooled HR or RR with corresponding 95% CIs of AHT and control were compared using the random effects model (DerSimonian-Laird method). Heterogeneity was evaluated using Cochran Q test and I² statistic. A P value <.05 or I² value >50% was considered significant. In addition, subgroup analyses were conducted to investigate whether substantial heterogeneity existed between RCTs. The RR and the corresponding 95% confidence intervals (CIs) were estimated using specific HRs or RRs and 95% CIs after considering the influence of each study on the overall effect size. Funnel plots and Egger and Begg tests were used to assess the potential publication bias. All reported P values were 2 sided, and P values <.05 were considered statistically significant for all included studies.

3. Results

A total of 14,594 articles were studied from PubMed, Embase, and Cochrane Library. After reviewing the titles and abstracts, 14,549 articles were removed. Further, 45 full-text articles were assessed for eligibility, and 2 records without appropriate control, 5 trials without any desirable outcomes, and 11 trials that reported same populations in multiple studies were excluded. Finally, 27 trials were included in this meta-analysis. The flow diagram is shown in Figure 1.

Among the 27 studies, a worldwide distribution was displayed, including 14 trials of South-American population, 8 European studies, 3 Asian studies, and 2 studies mixed of South-American and European population. The sample size ranged from 85 to 1979, and the duration of the follow-up ranged from 1.2 to 9.1 years. Fifteen studies reported OS, 15 reported DFS, 23 reported total mortality, 17 reported recurrence, 11 reported disease-specific mortality, and 6 reported the response rate. The descriptive data of the included studies are summarized in Table 1. In the quality assessment, 9 studies had a score of 4, 8 had a score of 3, 7 had a score of 2, and the remaining 3 had a score of 1 (Table 1).
| Study            | Publication years | Country            | Sample size | Mean age | Type of intervention                | Type of control | Disease status        | Serum PSA | Follow-up duration (year) | Reported endpoints                                      | Jadad score |
|------------------|-------------------|--------------------|-------------|----------|------------------------------------|-----------------|-----------------------|-----------|--------------------------|---------------------------------------------------------|-------------|
| Manni et al 1999 | USA               | 85 67              | Androgen priming | None     | Advanced PCa                       | NA             | 3.6                   | Total mortality, response rate | 2           |
| Resnick et al 2012 | USA and Canada   | 302 68             | Dutasteride   | Placebo  | Localized PCa                      | NA             | 5.7                   | Total mortality, response rate | 4           |
| Jones et al 2011 | USA               | 1979 71            | Androgen deprivation therapy | None     | Localized PCa                       | NA             | <0.2                  | Total mortality, response rate | 3           |
| Iversen et al 2002 | Nordic countries | 1218 69            | Bicalutamide  | Standard care | Early non-metastatic PCa | 17.2           | 3.0                   | Total mortality, recurrence; DSM | 3           |
| Meising et al 1999 | USA              | 98 66              | Androgen therapy, with either goserelin, a synthetic agonist of gonadotropin-releasing hormone, LHRH-A | None     | Node-positive PCa                   | NA             | 7.1                   | Total mortality, recurrence; DSM | 2           |
| Akaza et al 2003 | Japan             | 151 76             | LHRH agonist and chlormadinone acetate | LHRH agonist | Locally advanced PCa | 22.5           | 6.5                   | Total mortality, recurrence; DSM | 2           |
| Berry et al 2004 | US                | 163 71             | Estramustine   | None     | Progressive, metastatic, hormone-refractory PCa | NA             | 136.5                 | Total mortality, response rate | 1           |
| Mottet et al 2012 | Europe            | 169 69             | Continuous androgen deprivation therapy | Intermittent androgen deprivation therapy | Metastatic PCa | 610.8          | Total mortality, response rate | 2           |
| Crawford et al 1999 | USA              | 603 69             | Leuprolide plus flutamide | Leuprolide plus placebo | Disseminated, untreated PCa | NA             | 3.5                   | Total mortality, recurrence; response rate | 3           |
| Pleij et al 2001 | USA               | 456 NA             | Goserelin and flutamide | None     | Locally advanced PCa | NA             | 6.7                   | Total mortality, recurrence; DSM | 1           |
| Hudes et al 1999 | USA               | 201 70             | Estramustine Phosphate plus Vinblastine | None     | Hormone-refractory PCa | 166.7          | 3.5                   | Total mortality, recurrence; response rate | 4           |
| See and Tyrrell 1999 | Japan            | 1370 69            | Goserelin acetate plus either androgen or estrogen agonist | Goserelin acetate | Advanced PCa | 3.5             | 7.2                   | Total mortality, response rate | 3           |
| Bolla et al 2009 | Europe            | 1113 69            | Lutetium hormone-releasing hormone agonist | None     | Locally advanced PCa | 18.4           | 6.4                   | OS, DFS; total mortality, response rate | 4           |
| Irani et al 2002 | France            | 129 73             | Androgen blockade | None     | PCa | 56.4           | 5.0                   | OS, DFS; total mortality | 2           |
| Schroder et al 2009 | Europe            | 234 66             | Immediate LHRH | Delayed LHRH | PCa and nodal metastases (gP1–3) | NA             | 4.8                   | OS, total mortality, DSM | 3           |
| McDermott et al 2014 | Europe         | 1195 69            | Abiraterone acetate | Placebo plus prednisone | Metastatic castration-resistant PCa | 29.9           | 2.0                   | OS, DFS; total mortality, recurrence | 4           |
| Ryan et al 2015 | USA               | 1088 NA            | Abiraterone acetate plus prednisone | Placebo plus prednisone | Metastatic castration-resistant PCa | NA             | 4.1                   | OS, total mortality | 4           |
| Bolla et al 2007 | Europe            | 401 71             | Goserelin | None     | Locally advanced PCa | NA             | 3.8                   | DFS, recurrence | 3           |
| Carducci et al 2007 | Western countries | 809 73             | Abiraterone | Placebo | Metastatic hormone-refractory PCa | 74.7           | 1.5                   | OS          | 4           |
| Beer et al 2014 | USA               | 1717 NA            | Enzalutamide | Placebo | Metastatic castration-resistant PCa | NA             | 1.8                   | OS, DFS; total mortality, recurrence | 4           |
| Scher et al 2012 | Western countries | 1190 NA            | Enzalutamide | Placebo | Metastatic castration-resistant PCa | NA             | 1.2                   | OS, DFS; total mortality | 4           |
| Usmani et al 2007 | Japan             | 203 NA             | Bicalutamide plus LHRH-A | LHRH-A | Advanced PCa | NA             | 2.4                   | DFS, total mortality, recurrence; DSM | 2           |
| Quinn et al 2013 | USA               | 994 69             | Docetaxel and abiraterone | Docetaxel and Placebo | Metastatic castration-resistant PCa | 68.4           | 2.5                   | OS, DFS; total mortality, response rate | 4           |
| Eisenberger et al 1998 | USA            | 1387 70            | Flutamide | Placebo | Metastatic PCa | 161           | 4.1                   | OS          | 3           |
| Wirth et al 2004 | Germany           | 309 NA             | Flutamide | None     | Locally advanced, lymph node-negative PCa | NA             | 6.1                   | OS, DFS | 2           |
| Pleij et al 2005 | USA               | 945 NA             | Goserelin | None     | PCa (clinical stage T3) | NA             | 7.6                   | Total mortality, recurrence; DSM | 3           |

DFS = disease-free survival, DSM = disease-specific mortality, LHRH = luteinizing hormone-releasing hormone, LHRH-A = luteinizing hormone-releasing hormone agonist, OS = overall survival, PSA = prostate cancer.
The summary HRs for comparing OS between AHT and control were available in 15 trials. Compared with the control group, the AHT group was associated with a statistically significant improvement in OS (HR: 0.78; 95% CI: 0.71–0.85; \(P<.001\); Fig. 2), and a substantial heterogeneity was observed (\(I^2=60.3\%\); \(P=.001\)). In a sensitivity analysis that excluded the selected studies one by one, the result was not affected by any individual study. Subgroup analyses were performed based on several important confounding factors to identify the sources of heterogeneity. Overall, it was noted that patients who received immediate AHT were not associated with a significant improvement in OS compared with those who received delayed AHT (HR: 0.82; 95% CI: 0.62–1.09; Table 2). No evidence of a factor-specific difference was observed in the HR for PCa among participants who received AHT compared with the control group.

The summary HRs for comparing DFS between AHT and control groups were available in 15 trials. The pooled results showed that patients with PCa on AHT had a significant improvement in DFS compared with those in the control group (HR: 0.50; 95% CI: 0.39–0.65; \(P<.001\); Fig. 3). The heterogeneity was at a significantly high level (\(I^2=94.4\%\); \(P<.001\)). In the sensitivity analysis, no significant variation in the pooled HR was revealed from the exclusion of any of included studies. The subgroup analyses suggested that AHT played a beneficial effect on DFS in patients of all subsets, and no significant factor-specific difference was noted for DFS (Table 2).

The effect of AHT on the incidence of total mortality was available in 23 trials. The summary RR showed that the risk of total mortality was significantly reduced in patients who received AHT compared with the control group (RR: 0.90; 95% CI: 0.85–0.96; \(P=.001\); Fig. 4), but potential evidence of significant heterogeneity was observed (\(P<.001\)). As a result, a sensitivity analysis was conducted, and the conclusion was not affected by the exclusion of any specific study after the sequential exclusion of each study from all of the pooled analyses. The subgroup analysis indicated that AHT significantly reduced the risk of total mortality when the study was conducted in Western countries, the mean age of the participants was less than 70, the study was compared with placebo, the duration of follow-up was less than 5 years, and the study was of a high quality (Table 2). No evidence of a factor-specific difference was reported for total mortality.

The effect of AHT on the incidence of recurrence was available in 17 trials. The summary RR showed that AHT was associated with a reduced risk of recurrence compared with control (RR: 0.70; 95% CI: 0.60–0.81; \(P<.001\); Fig. 5). Although substantial heterogeneity was observed in the magnitude of the effect across the studies (\(I^2<.001\)), the conclusion was not affected by the exclusion of any specific study after the sequential exclusion of each study from all of the pooled analyses. The subgroup analyses suggested that AHT had no significant effect on the risk of recurrence if the mean age of patients was greater than 70, or when compared with delayed AHT (Table 2). The summary RR (placebo to delayed AHT) of AHT was associated with a greater beneficial effect on recurrence (RR: 0.69; 95% CI: 0.55–0.85).

The effect of AHT on the incidence of disease-specific mortality was available in 11 trials. The pooled analysis results for disease-specific mortality indicated that the comparison of AHT versus control showed a beneficial effect (RR: 0.70; 95% CI: 0.56–0.87; \(P=.001\); Fig. 6). Heterogeneity was observed in the magnitude of the effect across the trials (\(I^2=62.5\%\); \(P=.003\)); however, the conclusion was not affected by the exclusion of any specific trial after the sequential exclusion of each trial from all of the pooled analyses. The subgroup analyses indicated that patients who received AHT were associated with a significantly reduced risk of disease-specific mortality when the study was conducted in Western countries, compared with placebo, duration of follow-up was greater than 5 years, and study was with a lower Jadad...
| Outcomes | Group | HR/RR and 95% CI | P value | Heterogeneity (%) and P value | RR and 95% CI |
|----------|-------|------------------|---------|------------------|--------------|
| OS       | Country |               |         |                   |              |
|          | Eastern | 0.78 (0.71–0.85) | <.001   | 60.3 (0.001) |              |
|          | Western | 0.84 (0.73–0.96) | .023    | 59.0 (0.045) | 1.11 (0.90–1.38) |
| Mean age | <70 | 0.76 (0.66–0.88) | <.001   | 52.7 (0.048) |              |
|          | Control group | 0.77 (0.71–0.85) | <.001   | 62.9 (0.001) | 0.94 (0.70–1.26) |
|          | Placebo or none | 0.82 (0.62–1.09) | .168    | —                |              |
| Duration of the follow-up periods | 5 years or more | 0.77 (0.67–0.88) | <.001   | 8.9 (0.35) | 0.97 (0.82–1.16) |
|          | <5 years | 0.79 (0.71–0.88) | <.001   | 71.7 (0.000) | 1.00 (0.83–1.20) |
| Jadad score | 4 | 0.78 (0.69–0.87) | <.001   | 70.0 (0.001) | 1.00 (0.83–1.20) |
|          | <4 | 0.79 (0.68–0.90) | .001    | 46.2 (0.072) |              |
| DFS      | Country |               |         |                   |              |
|          | Eastern | 0.40 (0.26–0.62) | <.001   | —                | 0.78 (0.47–1.31) |
|          | Western | 0.51 (0.39–0.67) | <.001   | 94.7 (0.000) |              |
| Mean age | 70 or more | 0.55 (0.33–0.94) | .029    | 92.2 (0.000) | 0.93 (0.52–1.68) |
|          | <70 | 0.59 (0.45–0.77) | <.001   | 88.7 (0.000) |              |
| Control group | Placebo or none | 0.50 (0.39–0.65) | <.001   | 94.4 (0.000) |              |
|          | Delayed AHT | —               |         | —                |              |
| Duration of the follow-up periods | 5 years or more | 0.56 (0.41–0.76) | <.001   | 60.2 (0.040) | 1.17 (0.83–1.64) |
|          | <5 years | 0.48 (0.35–0.67) | <.001   | 94.1 (0.000) |              |
| Jadad score | 4 | 0.56 (0.37–0.85) | .007    | 97.3 (0.000) | 1.24 (0.76–2.03) |
|          | <4 | 0.45 (0.35–0.59) | <.001   | 74.2 (0.000) |              |
| Total mortality | Country |               |         |                   |              |
|          | Eastern | 1.00 (0.78–1.28) | .993    | 0.0 (0.540) | 1.11 (0.86–1.44) |
|          | Western | 0.90 (0.84–0.96) | .001    | 74.1 (0.000) |              |
| Mean age | 70 or more | 0.91 (0.81–1.02) | .104    | 44.2 (0.067) | 0.99 (0.86–1.14) |
|          | <70 | 0.92 (0.85–0.99) | .034    | 66.7 (0.001) |              |
| Control group | Placebo or none | 0.90 (0.84–0.96) | .001    | 73.1 (0.000) | 0.94 (0.83–1.08) |
|          | Delayed AHT | 0.90 (0.86–1.06) | .411    | 0.0 (0.970) |              |
| Duration of the follow-up periods | 5 years or more | 0.90 (0.77–1.05) | .197    | 75.2 (0.000) | 1.00 (0.84–1.18) |
|          | <5 years | 0.90 (0.84–0.96) | .002    | 70.9 (0.000) |              |
| Jadad score | 4 | 0.86 (0.79–0.95) | .002    | 80.8 (0.000) | 0.92 (0.82–1.05) |
|          | <4 | 0.93 (0.86–1.02) | .127    | 63.6 (0.000) |              |
| Recurrence | Country |               |         |                   |              |
|          | Eastern | 0.55 (0.37–0.83) | .004    | —                | 0.79 (0.51–1.21) |
|          | Western | 0.70 (0.60–0.82) | <.001   | 96.7 (0.000) |              |
| Mean age | 70 or more | 0.60 (0.36–1.02) | .057    | 98.1 (0.000) | 0.71 (0.41–1.20) |
|          | <70 | 0.85 (0.76–0.96) | .006    | 88.9 (0.000) |              |
| Control group | Placebo or none | 0.68 (0.58–0.80) | <.001   | 96.8 (0.000) | 0.69 (0.55–0.85) |
|          | Delayed AHT | 0.99 (0.86–1.15) | .911    | —                |              |
| Duration of the follow-up periods | 5 years or more | 0.68 (0.53–0.86) | .002    | 84.7 (0.000) | 0.96 (0.70–1.30) |
|          | <5 years | 0.71 (0.59–0.86) | <.001   | 97.5 (0.000) |              |
| Jadad score | 4 | 0.76 (0.59–0.97) | .027    | 97.7 (0.000) | 1.15 (0.84–1.58) |
|          | <4 | 0.66 (0.54–0.80) | <.001   | 93.9 (0.000) |              |
| Disease-specific mortality | Country |               |         |                   |              |
|          | Eastern | 1.06 (0.74–1.58) | .692    | 0.0 (0.658) | 1.69 (1.08–2.64) |
|          | Western | 0.64 (0.51–0.83) | <.001   | 65.4 (0.003) |              |
| Mean age | 70 or more | 0.64 (0.40–1.01) | .054    | 71.3 (0.008) | 0.90 (0.42–1.91) |
|          | <70 | 0.71 (0.39–1.28) | .252    | 72.3 (0.027) |              |
| Control group | Placebo or none | 0.66 (0.53–0.83) | <.001   | 52.8 (0.025) | 0.69 (0.51–0.95) |
|          | Delayed AHT | 0.95 (0.77–1.18) | .653    | —                |              |
| Duration of the follow-up periods | 5 years or more | 0.65 (0.50–0.84) | .001    | 43.4 (0.132) | 0.89 (0.58–1.36) |
|          | <5 years | 0.73 (0.52–1.02) | .066    | 67.0 (0.018) |              |
| Jadad score | 4 | 0.61 (0.26–1.41) | .246    | —                | 0.87 (0.36–2.09) |
|          | <4 | 0.70 (0.56–0.88) | .002    | 65.9 (0.002) |              |

AHT = adjuvant hormone therapy, CI = confidence interval, DFS = disease-free survival, HR = hazard ratios, OS = overall survival, RR = relative risk, RR = relative risks.
score. Furthermore, the pooled RR showed a statistically significant effect between AHT and control for disease-specific mortality in Eastern countries compared with Western countries (RR: 1.69; 95% CI: 1.08–2.64), and the control group was placebo compared with delayed AHT (RR: 0.69; 95% CI: 0.51–0.95).

The effect of AHT on the incidence of response rate was available in 6 trials. No significant effect was observed on the HR.

![Figure 3. Forest plot of studies showing hazard ratios for comparing DFS between AHT and control groups. AHT = adjuvant hormone therapy, DFS = disease-free survival.](image)

| Study             | HR (95% CI) | % Weight |
|-------------------|-------------|----------|
| REDEEM            | 0.62 (0.43, 0.89) | 6.2     |
| Christopher U. Jones | 0.69 (0.49, 0.97) | 6.2     |
| P Iversen         | 0.63 (0.34, 0.55) | 6.6     |
| William A. See    | 0.56 (0.40, 0.78) | 6.3     |
| Jacques Irani     | 0.91 (0.56, 1.67) | 5.4     |
| Peter F.A. Mulders(a) | 0.66 (0.51, 0.86) | 6.5     |
| Peter F.A. Mulders(b) | 0.66 (0.56, 0.78) | 6.8     |
| Michel Bolla      | 0.42 (0.28, 0.64) | 5.9     |
| EM Messing        | 0.29 (0.17, 0.51) | 5.3     |
| MICHELBOLLA      | 0.22 (0.15, 0.32) | 6.1     |
| Michael A. Carducci | 0.89 (0.76, 1.04) | 6.8     |
| PREVAIL           | 0.19 (0.15, 0.23) | 6.7     |
| AFFIRM            | 0.40 (0.35, 0.47) | 6.8     |
| M Usami           | 0.40 (0.26, 0.63) | 5.8     |
| SWOG S0421        | 0.98 (0.86, 1.12) | 6.9     |
| Manfred P. Wirth  | 0.51 (0.32, 0.81) | 5.7     |
| Overall           | 0.50 (0.39, 0.65); P<0.001 | 100.0   |

(I-square: 94.4%; P<0.001)

![Figure 4. Forest plot of studies showing relative risks for comparing total mortality between AHT and control groups. AHT = adjuvant hormone therapy.](image)

| Study             | Risk ratio (95% CI) | % Weight |
|-------------------|---------------------|----------|
| By Andrea Manni   | 1.17 (0.98, 1.38)   | 4.7     |
| Christopher U. Jones | 0.98 (0.91, 1.05) | 6.8     |
| P Iversen         | 0.99 (0.73, 1.36)   | 2.5     |
| EM Messing        | 0.42 (0.19, 0.92)   | 0.6     |
| Prostate Cancer Study Group | 1.01 (0.64, 1.60) | 1.5     |
| William R. Berry  | 0.89 (0.75, 1.06)   | 4.7     |
| Nicolas Mottet   | 0.95 (0.73, 1.25)   | 3.1     |
| ED Crawford       | 0.82 (0.71, 0.95)   | 5.3     |
| MILJENKO V. PILEPICH | 0.84 (0.71, 0.99) | 4.8     |
| By Gary Hudes     | 0.94 (0.80, 1.12)   | 4.8     |
| William A. See    | 0.89 (0.75, 1.05)   | 4.9     |
| Toshikiko Kotake  | 1.08 (0.78, 1.51)   | 2.3     |
| Michel Bolla      | 0.74 (0.59, 0.93)   | 3.7     |
| Jacques Irani     | 0.62 (0.37, 1.06)   | 1.1     |
| Fritz H. Schroeder | 0.96 (0.85, 1.08) | 5.9     |
| Peter F.A. Mulders(a) | 0.86 (0.75, 1.00) | 5.4     |
| Peter F.A. Mulders(b) | 0.88 (0.81, 0.97) | 6.5     |
| CDU-AA–302        | 0.91 (0.84, 0.99)   | 6.7     |
| MICHELBOLLA      | 0.59 (0.41, 0.85)   | 2.0     |
| PREVAIL           | 0.78 (0.68, 0.90)   | 5.4     |
| AFFIRM            | 0.72 (0.64, 0.82)   | 5.7     |
| M Usami           | 0.72 (0.37, 1.38)   | 0.8     |
| SWOG S0421        | 1.02 (0.95, 1.09)   | 6.9     |
| RT0G 85–31        | 1.41 (1.14, 1.74)   | 4.0     |
| Overall           | 0.90 (0.85, 0.96); P<0.001 | 100.0   |

(I-square: 70.8%; P<0.001)
The incidence of response rate (RR, 1.75; 95% CI, 0.91–3.37; \( P = 0.095 \); Fig. 7). Although substantial heterogeneity was observed in the magnitude of the effect across the studies \( (P < 0.001) \), the conclusion was not affected by the exclusion of any specific study after sequential exclusion of each study from all of the pooled analyses.

The review of funnel plots could not rule out the potential for publication bias for OS and DFS (Figs. 8 and 9). The Egger and Begg tests results showed no evidence of publication bias for DFS. Although the Begg test showed no evidence of publication bias for OS, the Egger test showed the potential evidence of publication bias for OS \( (P = 0.039) \). The conclusions were not
changed after adjustment for publication bias by using the trim and fill method.

4. Discussion

The present study was based on RCTs and explored the effect of AHT on the risk of OS, DFS, total mortality, recurrence, disease-specific mortality, and response rate when treating PCa. This large quantitative study included 18,889 individuals from 27 RCTs with a broad range of populations. The findings from the present meta-analysis suggest that AHT versus control produced a significant beneficial effect on OS, DFS, total mortality, recurrence, and disease-specific mortality. However, patients who received AHT had no effect on the incidence of response rate. Furthermore, a significant difference in the RR for PCa between AHT and control was observed for country and placebo.

The source of heterogeneity was explored carefully. In the sensitivity analysis, no substantial change was revealed when any individual study was excluded, suggesting the homogeneity of the pooled effect estimates. In the subgroup analyses, a factor difference in the RR for PCa between AHT and control was observed for country and control. However, the number of eligible studies was rather small to draw firm conclusions. Thus, these differences might be due to changes and needed a further study to verify the treatment effect on specific subpopulations.

A previous meta-analysis suggested that AHT following radiotherapy improved OS, disease-specific survival, and DFS. Furthermore, another important meta-analysis suggested

| Study                      | Risk ratio (95% CI) | % Weight |
|----------------------------|---------------------|-----------|
| By Andrea Manni            | 0.76 (0.50, 1.13)   | 17.7      |
| William R. Berry           | 1.10 (0.93, 1.30)   | 18.7      |
| ED Crawford                | 1.27 (1.02, 1.58)   | 18.6      |
| By Gary Hudes              | 3.03 (0.63, 14.66)  | 9.0       |
| Toshihiko Kotake           | 1.09 (0.90, 1.32)   | 18.7      |
| PREVAIL                    | 11.88 (7.52, 18.79) | 17.3      |
| Overall                    | 1.75 (0.91, 3.37); P=0.095 | 100.0 (I-square: 96.9%; P<0.001) |

Figure 7. Forest plot of studies showing relative risks for comparing response rate between AHT and control groups. AHT = adjuvant hormone therapy.

Figure 8. Funnel plot of included studies for OS. OS = overall survival.

Figure 9. Funnel plot of included studies for DFS. DFS = disease-free survival.
that longer duration of androgen deprivation combined with radiotherapy prolongs OS, DFS, and disease-specific survival (DSS) in patients with intermediate and high-risk nonmetastatic PCa. However, this evidence is based on trials using older radiation techniques, and further research on combination of androgen deprivation, and new RT technologies may be warranted. The inherent limitation of the previous review is that the effect of AHT in several specific subpopulations was not evaluated, and the treatment effect among patients with different baseline characteristics was not compared. Therefore, a meta-analysis of RCTs was conducted to evaluate the effect of AHT in treating PCa.

Most of the findings of the present study were in agreement with the included trials. REDEEM trials indicated that dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk PCa. CU Jones suggested that the use of short-term ADT for 4 months before and during radiotherapy was associated with significantly decreased disease-specific mortality and increased OS among patients with stage T1b, T1c, T2a, or T2b prostate adenocarcinoma and a PSA level of 20 ng/mL or less. The post hoc study indicated that the benefit was observed mainly in intermediate-risk patients, whereas no significant benefit was observed in low-risk patients. Finally, Messing et al indicated that immediate androgen therapy after radical prostatectomy and pelvic lymphadenectomy improves survival and reduces the risk of recurrence in patients with node-positive PCa. The present study also indicated that patients who received AHT showed a significant improvement in OS, DFS, recurrence, and disease-specific mortality. However, no significant difference was observed between immediate AHT and delayed AHT for OS, DFS, total mortality, recurrence, and disease-specific mortality. The reason for this could be that only a few studies compared immediate AHT with delayed AHT, which always acquired broad CIs, that is, no statistically significant difference.

This study suggested that AHT was associated with a significant improvement in survival outcomes. However, several studies included in the present study reported inconsistent results. Carducci et al indicated no delay in disease progression in patients with metastatic HRPC who received atrasentan despite evidence of biologic effects of HRPC on PSA and BAP as markers of disease burden. Furthermore, SWOG S0421 suggested that atrasentan when added to docetaxel, does not improve OS or PFS in men with castration-resistant PCa and bone metastases. The possible reasons could be that these 2 studies reported the effect of atrasentan on PCa, and the disease status might play an important role, which biased these treatment effects.

The findings of subgroup analysis suggested that AHT had a beneficial impact on patients with PCa in multiple subsets. Previous studies indicated that country, mean age, control group, follow-up duration, and study quality contributed significantly to the progression of PCa. The present study compared the treatment effect in groups of trials categorized by these factors. It was concluded that the pooled RR (Eastern to Western countries) of AHT was significantly increased, and the summary RR (AHT vs placebo to immediate AHT vs delayed AHT) of AHT was associated with a lower risk of disease-specific mortality. These differences could be explained by few trials that reported Eastern countries and compared with delayed AHT. These findings might be due to chance and required further verification. Therefore, herein only a relative result and synthetic and comprehensive review are described.

Three strengths of this study are as follows: First, only RCTs were included, eliminating selection, recall, and confounder biases, which could be of concern in observational studies. Second, the large sample size facilitated quantitative assessment of the effect of AHT on treatment of patients with PCa, and thus the findings of this study are potentially more robust than those of any individual study. Third, a summary RR to compare the treatment effect in groups of patients categorized by several confounders were conducted.

The limitations of this study are as follows:

1. different baseline characteristics might play an important role in the progression of PCa;
2. substantial heterogeneity was detected but the confounders were not detected;
3. in a meta-analysis of published studies, publication bias is an inevitable problem; and
4. the analysis used pooled data (individual data were not available), which caused hindrance in performing a more detailed relevant analysis and obtaining more comprehensive results.

In conclusion, the results of this study suggested that patients with AHT might play a beneficial impact on OS, DFS, total mortality, recurrence, and disease-specific mortality, especially in Western countries. However, no significant difference was observed between AHT and control for response rate. Future studies should focus on specific populations and different modes of AHT to analyze the treatment in subpopulations.

Author contributions

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