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ORIGINAL ARTICLE

Prostate Cancer

Androgen-deprivation therapy alone versus combined with radiation therapy or chemotherapy for nonlocalized prostate cancer: a systematic review and meta-analysis

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In this paper, we reviewed the long-term survival outcomes, safety, and quality-of-life of androgen-deprivation therapy (ADT) alone versus combined with radiation therapy (RT) or chemotherapy for locally advanced and metastatic prostate cancer (PCa). A literature search was performed using OvidSP. Randomized controlled trials (RCTs) that met the following criteria were included: including locally advanced or metastatic PCa, comparing ADT alone versus combined with any treatment method and reporting quantitative data of disease control or survival outcomes. Finally, eight RCTs met the inclusion criteria. Among these, three compared ADT versus ADT plus RT (n = 2344) and one compared ADT versus ADT plus docetaxel–estramustine (n = 413) in locally advanced PCa; two compared ADT versus ADT plus docetaxel (n = 1175) and two compared ADT versus ADT plus estramustine (n = 114) in metastatic PCa. For locally advanced PCa, the addition of RT to long-term ADT can improve the outcomes of survival and tumor control with fully acceptable adverse effects. Specially, the pooled odds ratio (OR) of overall survival (OS) was 1.43 (95% confidence interval 1.20–1.71) when compared ADT plus RT with ADT alone (P < 0.0001). For metastatic hormonally sensitive PCa, the concurrent use of docetaxel plus ADT was effective and safe (pooled OR of OS: 1.29 [1.01–1.65]: P = 0.04). In all, long-term ADT plus RT and long-term ADT plus docetaxel should be considered as proper treatment option in locally advanced and metastatic hormonally sensitive PCa, respectively. The major limitation for the paper was that only eight RCTs were available.

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INTRODUCTION

Prostate cancer (PCa) is the most common tumor for males in western countries and epidemiological data show that its morbidity is approximately 0.214% in males and 192 000 individuals are diagnosed with PCa annually in the United States.[1] Locally advanced and metastatic PCa accounts for 15% and 5% of the newly diagnosed cases, respectively.[2,3] For locally advanced PCa, one of the most frequently used modalities is androgen-deprivation therapy (ADT), except for radical prostatectomy (RP) and radiation therapy (RT);[4] for metastatic PCa, there is little debate regarding the first-line use of ADT, because many randomized controlled trials (RCTs) have proven its value to prolong survival than placebo.[5,6]

Unfortunately, the optimal treatment regimens on the basis of ADT for locally advanced or metastatic PCa remain controversial.[7] As a heterogeneous tumor comprising hormone-dependent, hormone-sensitive, and hormone-insensitive cells, the latter was not affected by androgen-deprivation. At last, tumor progression was inevitable. Besides, balanced against possible disease control and better survival benefits are data that ADT may lead to serious adverse events and adversely affects the quality-of-life (QoL).[8] To pursue a more effective therapy, in the current study, we therefore performed a systematic review of the published RCTs to compare the long-term survival outcomes, safety, and QoL of ADT alone versus in combination with other approaches (e.g., RT or chemotherapy), in patients with locally advanced and metastatic PCa.

MATERIALS AND METHODS

Inclusion criteria and search strategy

Studies that met all of the following criteria were included: RCTs: (a) in which the study population or subpopulation included locally advanced or metastatic PCa patients, (b) with the comparison between ADT alone and ADT plus other approaches (e.g., RP, RT, or chemotherapy), (c) that reported quantitative data of disease control or survival outcomes, e.g., overall survival (OS), progression-free survival (PFS), cancer-specific mortality (CSM), and so on. Locally advanced PCa was defined as clinical stage T3/4 N0/X M0 disease or clinical T2 tumors with either PSA >40 ng ml^{-1}, or T2 and PSA >20 ng ml^{-1} with a Gleason score >8. Studies were excluded if patients suffered metastatic hormone refractory PCa or had been prior treated for PCa, with the exception of ADT.

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We simultaneously used three databases of OvidSP to search (date: August 4, 2014) relevant studies: Ovid MEDLINE® (1946 to present), EMBASE® (1974 to August 1, 2014), and the Cochrane Central Register of Controlled Trials® (June 2014) at West China Hospital. The search strategy was as follows: ([prostatic Neoplasms or PCa].sh. or [Prostate Neoplasm or carcinoma of prostate].ab.) and ([ADT or endocrine therapy or endocrinotherapy or hormone therapy or goserelin or diphereline or enantone or bicalutamide or flutamide].ab.). The meaning of "sh" and "ab" was MeSH heading and abstract, respectively. The reference lists of other reviews and related articles were also screened. The search strategy was limited to humans, male, and controlled clinical trial.

Data extractions and quality assessment

Two authors (TRS and LY) then reviewed the titles, abstracts, and the full text of each article, independently. Any disagreements were solved by discussion with JHL and LRL. To minimize the clinical and methodological heterogeneity, we only included RCTs. The items extracted from the eligible studies are shown in **Table 1**.

According to the recommendations of the Cochrane collaboration, the quality of the included studies was assessed based on the study design, conduct, and analysis, and each study was evaluated using a three-point scale: yes (low risk of bias), no (high risk of bias) and unclear.[9] The risk of bias for each included study and meta-analysis was performed using Review Manager 5.2. Pooled OR with 95% confidence intervals (CIs) was calculated using Mantel–Haenszel random effects model to estimate the effect when I^2 >75%; otherwise, a fixed effect model was used.

RESULTS

Search results

A total of 508 citations were identified using the search process. Of these, 500 were excluded after reviewing the title, abstract, and

Table 1: Characteristics of included studies (*n*=8)

Study ID	*Study design/ comparison of treatment*	*Sites*	*Population# of PCa*	*ADT/RT/chemotherapy regimen*	*Median follow-up*	*End-points of survival or tumor control*
Studies included locally advanced PCa						
Widmark *et al.*[10]	RCT/ADT versus ADT+EBRT	47 centers in Norway, Sweden, and Denmark	G2–G3, or T3 (78%) (PSA <70 ng ml^{-1}; N0; M0)	ADT: 3 months of total androgen blockade (leuprorelin 3.75 mg 1-month or 11.25 mg every 3 months for 3 months+flutamide 250 mg) followed by continuous flutamide RT: 50 Gy to the prostate and the seminal vesicles, followed by 20 Gy to the prostate	7.6 years	OS, CSM, PSA recurrence
Warde *et al.*[11]	RCT/ADT versus ADT+EBRT	Canada, UK and USA	T3 or T4; T2 with PSA >40 ng ml^{-1} or PSA >20 ng ml^{-1} and Gleason 8–10	Lifelong ADT (bilateral orchiectomy or LHRH agonist) RT: 65–69 Gy to the prostate and seminal vesicles, 45 Gy to the pelvic nodes	6 years	OS, CSS, CSM
Mottet *et al.*[12]	RCT/ADT versus ADT+EBRT	40 centers in France and Tunisia	T3–T4 or pT3N0M0	ADT: Euprorelin 11.25 mg every 3 months for 3 years; flutamide (750 mg d^{-1}) during the first month of Euprorelin intervention. RT: 46 Gy over 5 weeks to the whole pelvis and 22 Gy given over 2–2.5 weeks to the prostate gland and periprostatic area	67 months	OS, PFS, CSS, LR, DM
Fizazi *et al.*[13]	RCT/ADT versus ADT+DE	26 centers in French	T3–T4 (67%), Gleason score 8–10 (42%), PSA>20 ng ml^{-1} (59%)	ADT: Goserelin 10.8 mg every 3 months for 3 years DE: 4 cycles of D 70 mg m^{-2} per 3 weeks+ E 10 mg kg day^{-1} during the first 5 days of every cycle	From 2002 to 2010	PSA response
Studies included metastatic PCa						
Gravis *et al.*[14]	RCT/ADT versus ADT+D	29 centers in France and one in Belgium	Patients with noncastrate metastatic PCa	ADT: Orchiectomy or LHRH-agonists, alone or combined with nonsteroidal anti-androgens Chemotherapy: 9 cycles of D 75 mg m^{-2} on the first day of each 21 days cycle	50 months	OS, PFS
Sweeney *et al.*[15]	RCT/ADT versus ADT+D	US (called ECOG-3805 trial)	Patients with noncastrate metastatic PCa	ADT: Not mentioned Chemotherapy: D dosed 75 mg m^{-2} every 3 weeks for 6 cycles within 4 months of starting ADT	29 months	OS
Noguchi *et al.*[16]	RCT/ADT versus ADT+E	Kurume, Kumamoto and Mie in Japan	Newly diagnosed metastatic PCa	Chemotherapy: E 560 mg day^{-1} ADT: Goserelin 3.60 mg or leuprolide acetate 3.75 mg. Flutamide 125 mg	26 months	OS, CSS, ORR
Hoshi *et al.*[17]	RCT/ADT versus ADT+E	The affiliated hospitals of the Tohoku	Untreated stage D1 or D2 PCa	ADT: Not strictly defined Chemotherapy: E 560 mg day^{-1} treatment was continued until deterioration	ADT versus ADT+E 76.3 versus 92.3 weeks	OS, ORR

#Based on the TNM-classification 1992. PSA recurrence: Defined as an increase of PSA of 2 ng ml^{-1} or more above nadir. PSA response: Defined as serum PSA ≤0.2 ng ml^{-1} after 3 months of treatment. PSA progression: Defined by a rising PSA concentration of >5 ng ml^{-1} or reaching on-study value (minimum 1 ng ml^{-1}). ORR: overall response rates: (Complete response [normalization of the PSA level and in patients with measurable disease, disappearance of all lesions without the occurrence of new ones]+partial remission [a decrease of ≥50% in the sum of the products of the longest diameters of all measurable lesions persisting for ≥4 weeks, improvement in bone scan findings, and reossification of lytic lesions, in addition to no increase in the size of any existing lesions and no appearance of new lesions]). PCa: prostate cancer; RCT: randomized controlled trial; EBRT: external beam radiotherapy; ADT: androgen-deprivation therapy; D: docetaxel; DE: docetaxel-estramustine; E: estramustine; ECOG: Eastern Cooperative Oncology Group; GnRH: gonadotropin-releasing hormone; LHRH: luteinizing hormone-releasing hormone; OS: overall survival; OM: overall mortality; PFS: progression-free survival; CSS: cancer-specific survival; CSM: cancer-specific mortality; LR: locoregional recurrence; DM: distant metastases; PSA: prostate-specific antigen; RT: radiation therapy

eventually the full text following the patients, intervention, comparison, and outcome principle recommend by the Cochrane collaboration, leaving seven articles (seven studies) for further analyses. One additional abstract, which was reported at 2014 ASCO Annual Meeting, was achieved from nonelectronic searches. In all, eight RCTs were included in the current study. The study selection flow diagram is shown in **Figure 1**. Of these studies included, three compared ADT versus ADT plus RT (n = 2344)[10–12] and one compared ADT versus ADT plus docetaxel–estramustine (n = 413)[13] in locally advanced PCa; two compared ADT versus ADT plus docetaxel (n = 1175)[14,15] and two compared ADT versus ADT plus estramustine (n = 114) in patients with metastatic PCa.[16,17] All the RCTs included were performed in accordance with the Declaration of Helsinki. As shown in **Figure 2**, regardless of unclear selection bias and no-use of blinding, all the studies were considered to be of a satisfactory quality. Meta-analysis was available for OS in studies that included locally advanced PCa[10–12] and that compared ADT and ADT plus docetaxel.[14,15]

Results of studies included locally advanced prostate cancer (n = 4)

Androgen-deprivation therapy versus androgen-deprivation therapy plus radiation therapy (n = 3)

The trial of Widmark *et al*.[10] also randomized 875 patients to receive lifelong ADT or lifelong ADT plus external-beam radiotherapy (EBRT) like Warde *et al*.[11] After a 7.6-year follow-up, better 10-year survival outcomes were reported in favor of the combined group (overall mortality: P = 0.004; CSM and PSA recurrence [an increase of PSA of 2 ng ml^{-1} or more above nadir]: P < 0.0001). The QoL assessment showed that, at the end of the fourth year, social function (P = 0.010) and diarrhea (P = 0.003) scores were lower in the combined group. At the end of the fifth year, the combined group was more frequent for the stricture (P = 0.035), urge (P = 0.014), incontinence (P = 0.022), and erectile dysfunction (P = 0.027).

An RCT by Warde *et al*.[11] included high-risk patients with a large population size (n = 1205). Six hundred and two and 603 patients were randomly assigned to receive lifelong ADT or lifelong ADT plus EBRT, respectively. After a median follow-up of 6-year, all the 7-year survival outcomes had a significant improvement for the combined group (OS, P = 0.03; cancer-specific survival [CSS], P = 0.0001; CSM, P = 0.0001). As for treatment safety, although grades 1 and 2 gastrointestinal (GI) toxicity increased in the combined group as expected, severe adverse events (grade >3) were low for both GI and genitourinary (GU) toxicity (diarrhea: 0.7% *vs* 1.3%; rectal bleeding: 0.5% *vs* 0.3%; GU: 2.3% *vs* 2%). When focusing on QoL, results of short-term (6 months) but not long-term (36 months) differences between groups were significant for the overall score, physical functioning, and urinary functioning. The curves of QoL scores for both groups were getting closer to each other over time.

An open trial by Mottet *et al*.[12] randomized 264 patients with T3-4 or pT3N0M0 PCa to receive ADT alone (n = 131) or ADT plus EBRT (n = 133). The multivariate analyses revealed that combination group resulted in better outcome regarding 5 years PFS, locoregional recurrence (LR), and distant metastases (DM) than ADT alone (P < 0.0011, 0.0001, and 0.018, respectively). However, there was no significant difference between groups in OS and CSS. Authors also evaluated the safety for both treatment groups. The combined group suffered higher serious adverse events than ADT alone (8% *vs* 2%, respectively), such as diarrhea, pollakiuria, and dysuria. Although four of these patients in the combined group dead, no death was directly related to the treatment.

For the three trials above, the pooled OR of OS >5 years (5–10 years) was 1.43 (95%CI 1.20–1.71) with a low heterogeneity (I^2 = 10%) when compared ADT plus RT with ADT (P < 0.0001) (**Figure 3**).

Androgen-deprivation therapy versus androgen-deprivation therapy plus docetaxel–estramustine (n = 1)

In the RCT by Fizazi *et al*.[13] 413 patients with locally advanced PCa were randomly received ADT alone or ADT plus docetaxel–estramustine (DE). A PSA response (PSA ≤0.2 ng ml^{-1} after 3 months of treatment) was obtained in 15% in the ADT group and 34% in the ADT plus DE group (P < 0.0001). Chemotherapy was well-tolerated for only five patients (2.4%) developed a neutropenic fever, and no toxicity-related death occurred. Toxicity of moderate to severe hot flashes occurred less often in the combined group (2% *vs* 22%; P < 0.001). Although chemotherapy had a negative impact on QoL (global health status, P = 0.01; fatigue, P = 0.003; role functioning, P = 0.003; social functioning, P = 0.006) at 3 months, but this effect disappeared at 1-year.

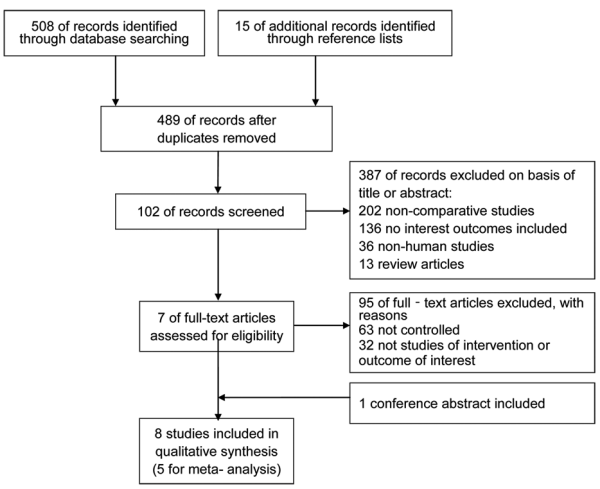

Figure 1: Flow diagram for included and excluded articles.

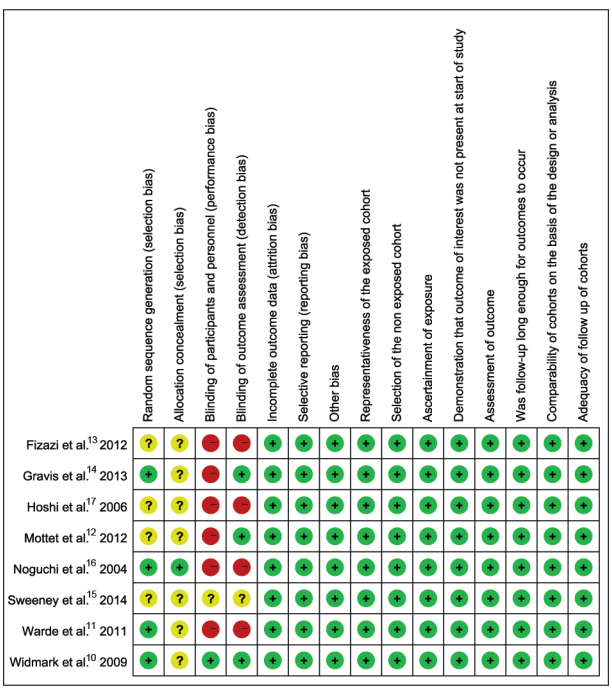

Figure 2: Quality evaluation for each included studies.

Studies included metastatic prostate cancer (n = 4)

Androgen-deprivation therapy versus androgen-deprivation therapy plus docetaxel (n = 2)

The RCT by Gravis *et al*.[14] enrolled 385 patients with metastatic noncastrate PCa. They were randomized to receive ADT alone (n = 193) or ADT plus docetaxel (n = 192). Median OS had no differences (P = 0.955), but median PFS was longer for combined group (P = 0.015). All the 72 serious adverse events reported were in the combined group, of which the most frequent were neutropenia (40 [21%]), febrile neutropenia (6 [3%]), and abnormal liver function tests (three [2%]). All the four treatment-related deaths occurred in the combined group. Another RCT by Sweeney *et al*.[15] included the same population but with a large scale, 393 in ADT arm and 397 in the combined group. The median OS was longer for combined group (P = 0.0006). Particularly for the "high volume" subgroup (visceral metastases and/or 4 or more bone metastases), a prolonged median OS of 17 months was achieved when docetaxel was added (P = 0.0012). All the toxic reaction occurred in the combined group: 2% for Grade (G) 3/4 Neutropenic fever, 2% for G3 neuropathy, and only one case for treat-related death.

The pooled OR of OS for the two trials was 1.29 (95%CI 1.01–1.65) with a moderate heterogeneity (I^2 = 63%) when compared ADT plus RT with ADT (P = 0.04) (**Figure 4**).

Androgen-deprivation therapy versus androgen-deprivation therapy plus estramustine (n = 2)

Noguchi *et al*.[16] randomly divided 57 patients with newly diagnosed metastatic PCa into two groups, receiving ADT alone and ADT plus estramustine. They found that ADT plus estramustine showed longer clinical CSS than ADT alone (P = 0.03), although there was no difference in the OS and response rate of tumor (P = 0.796 and P > 0.05). Serious side effects only occurred two in the combination group and one in ADT alone group for cardiovascular disorders and one in the ADT alone group for diarrhea. A similar study by Hoshi *et al*.[17] found that OS was significantly prolonged in the combination group (P = 0.0394). However, the response rate of tumor had no differences between groups (P = 0.6723). Both treatment groups tolerated treatment well. Side effects were 7/26 (26.9%) in the ADT group and 14/31 (45.2%) in the combination group, with no significant difference (P = 0.2517) observed between the groups. Serious side effects (grade 3 or higher) were rather low, only one in each group for cardiovascular disorders and two in the combination group for GI toxicity. The detailed results of long-term survival for all studies were summarized at **Table 2**.

DISCUSSION

To our knowledge, this is the first systematic review addressing the long-term survival outcomes, safety, and QoL of ADT alone versus combined with RT or chemotherapy in patients with locally advanced and metastatic PCa. We reported published evidence from eight high-quality RCTs.

Our pooled results showed that in patients with locally advanced PCa, ADT plus RT can substantially improve the OS approximately 1.5 times than ADT alone; combined regimens also strongly favored better outcomes for other end-points, e.g., PFS, LR, or DM, though some of the difference are not significant. The risk of adverse effects and decrease of short-term QoL (6 months) from added RT are fully acceptable, and the differences between groups shrink over time. Added DE regimen to ADT can improve PSA response rate in locally advanced PCa without reducing safety or long-term QoL (after 1-year), but the long-term outcomes on relapse and survival have not been proved. In metastatic hormonally sensitive PCa, ADT plus docetaxel could prolong OS safely, especially for those with visceral metastases and/or 4 or more bone metastases; improved OS or CSS was achieved for estramustine plus ADT than ADT alone, but it should be interpreted with caution due to the small sample size with low statistical power. In brief, ADT plus RT should be the standard rather than ADT alone in locally advanced PCa; it is not safe to say that ADT plus docetaxel or estramustine is better than ADT alone for metastatic PCa.

As primary management, long-term ADT alone is standard care for metastatic or locally advanced PCa and the use of ADT rapidly increased in the past 20 years.[18] Currently, the standardized ADT regimen was widely used for localized and metastatic PCa, which was usually composed of a kind of luteinizing hormone-releasing hormone agonist (LHRHa), with or without an anti-androgen agent. However, the optimal option based on ADT had not reached a consensus, and the desire was urgent to achieve a longer survival and better QoL, particularly for metastatic cases generally suffered poor prognosis.

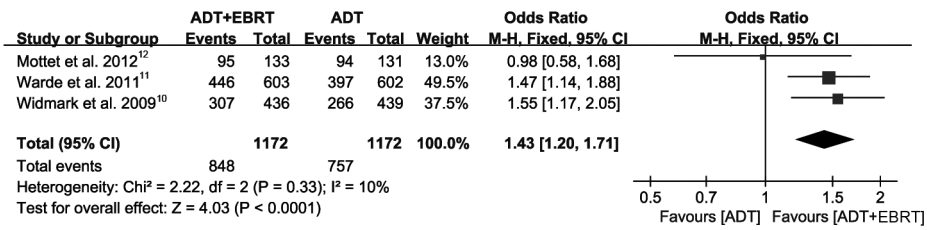

Figure 3: Forest plot of pooled odds ratio when compared androgen-deprivation therapy alone versus combined with radiation therapy for locally advanced prostate cancer.

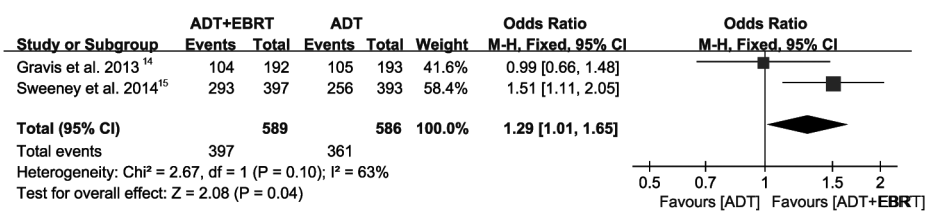

Figure 4: Forest plot of pooled odds ratio when compared androgen-deprivation therapy alone versus combined with docetaxel for metastatic prostate cancer.

Table 2: Results of long-term survival of included studies (*n*=8)

Study ID	*Comparison of therapy/ simple size*	*Death counts (ADT alone vs combination)*	*End-points (95% CI) (ADT alone vs combination)*					
			OS	*PFS*	*CSS*	*LR/DM/PSA recurrence or progression or response*	*Other end-points*	*Report[§] of toxicity or QoL*
Studies included locally advanced PCa								
Widmark *et al.*[10]	ADT versus ADT+EBRT 439 versus 436	79 *vs.* 37	10 years OS: 60.6% *vs.* 70.4%, *P*=0.004	NA	NA	10 years PSA recurrence: 74.7% *vs.* 25.9%, *P*<0.0001	10 years CSM: 23.9% *vs.* 11.9%, *P*<0.0001	QoL
Warde *et al.*[11]	ADT versus ADT+EBRT 602 versus 603	175 *vs.* 145	7 years OS: 66% (60–70) *vs.* 74% (70–78); HR: 0.77 (0.61–0.98), *P*=0.03	NA	7 years: 79% (64–83) *vs.* 90% (86–93), *P*=0.0001	NA	7 years CSM: 19% *vs.* 9%; HR: 0.54 (0.27–0.78), *P*=0.0001	Toxicity and QoL
Mottet *et al.*[12]	ADT versus ADT+EBRT 131 versus 133	8 *vs.* 21	5 years OS: 71.5% *vs.* 71.4%, *P*>0.05	5 years: 15.4% *vs.* 64.7%[&], *P*<0.0011	5 years: 86.2% *vs.* 93.2%, *P*=0.0586	ADT combination *vs.* alone (5 years) LR: 9.8% *vs.* 29.2%; HR: 3.6 (1.9–6.8), *P*<0.0001 DM: 3.0% *vs.* 10.8%, *P*<0.018	NA	Toxicity
Fizazi *et al.*[13]	ADT versus ADT+DE 206 versus 207	NA	NA	NA	NA	PSA response: 15% *vs.* 34%, *P*<0.0001	NA	Toxicity and QoL
Studies included metastatic PCa								
Gravis *et al.*[14]	ADT versus ADT+D 193 versus 192	88 *vs.* 88	Median OS: 54.2 *vs.* 58.9 months, *P*=0.955	15.4 *vs.* 23.5 months, *P*=0.015	NA	NA	NA	Toxicity
Sweeney *et al.*[15]	ADT versus ADT+D 393 versus 397	137 *vs.* 104	Median OS: 42.3 *vs.* 52.7, *P*=0.0006	NA	NA	NA	NA	Toxicity
Noguchi *et al.*[16]	ADT versus ADT+E 28 versus 29	11 *vs.* 14	OS: 11/28 *vs.* 14/29, 27.8 versus 35.9 months, *P*=0.796	12/28 *vs.* 17/29; 14.6 *vs.* 25.4 months, *P*=0.03	NA	NA	ORR: 55 (12/28) *vs.* 76% (22/29), *P*>0.05	Toxicity
Hoshi *et al.*[17]	ADT versus ADT+E 31 versus 26	NA	5 years OS: 45.8% *vs.* 64.1%, *P*=0.039	NA	NA	NA	ORR: 65.2% (15/23) *vs.* 69.2% (18/26) *P*=0.6723	Toxicity

[&]Data were calculated according to the phoenix definition-the event of biochemical progression was established when an increase of 2 ng ml^{-1} above the PSA nadir occurred; [§]Dates in details were shown in result section of manuscript. NA: not applicable; CI: confidence interval; QoL: quality-of-life; ADT: androgen-deprivation therapy; OS: overall survival; PFS: progression-free survival; CSS: cancer-specific survival; LR: locoregional recurrence; DM: distant metastases; PSA: prostate specific antigen; D: docetaxel; DE: docetaxel-estramustine; E: estramustine; EBRT: external beam radiotherapy; HR: hazard ratio; PCa: prostate cancer; CSM: cancer-specific mortality; ORR: overall response rates

For patients with clinically locally advanced PCa, the common first-line treatment options are RP, RT, brachytherapy, and ADT, alone or combined, but the optimal option remains controversial.[7] Previous systematic review and/or meta-analysis[19,20] summarized the survival and tumor control evidences based on RP or RT, e.g., RP/RT versus RP/RT plus adjuvant or neoadjuvant ADT. Since a favorable survival was achieved with the addition of ADT in these studies, here, we compared ADT-based regimens not only concerning the survival and tumor control, but also the safety and QoL between groups. Although the mechanism of androgen suppression plus radiotherapy had not been disclosed (likely including both sensitization of the cancer cell to radiation and modification of the metastatic process[21]), here, we substantially unfolded their synergy effect. Further studies are also needed to unfold the long-term outcomes on survival and tumor control of ADT plus DE schemes, and to establish standardized ADT plus RT schemes (e.g., proper dose and duration) to make its benefits to the fullest.

For patients with metastatic PCa, treatment is primarily palliative, relying mainly on the suppression of systemic androgen hormone levels. A number of previous RCTs included in metastatic PCa were focused on the comparison of combined ADT (ADT plus anti-androgen agent) versus monotherapy. A meta-analysis of 27 RCTs[22] composed of 12% M0 and 88% M+ PCa patients, and found that the comparison of combined ADT (orchiectomy or LHRHa plus nilutamide, flutamide, or cyproterone acetate) versus ADT alone resulted in no OS difference. However, ADT plus flutamide or nilutamide resulted in better OS (27.6% *vs* 24.7%, *P* = 0.005), while ADT plus cyproterone acetate resulted in worse OS (15.4% *vs* 18.1%, *P* = 0.04). Here, the attempt of ADT plus docetaxel, alone or combined with anti-androgens, could prolong OS in metastatic noncastrate PCa. Furthermore, the rate of treat-related death (5/589) was very low. We believed that ADT plus docetaxel would become a standard-of-care for men with newly

diagnosed metastatic hormonally sensitive PCa. On the other hand, although ADT plus estramustine prolonged OS or CSS than ADT alone, the small sample size with low statistical power hold back the conclusion that the combined regimens are better.

LIMITATIONS

First, only eight RCTs were included in the study, and the statistical significance of this analysis might be quite low. Therefore, a substantial number of relevant trials with regard to the subject are necessary and urgent. Second, for the three studies comparing ADT with ADT plus RT, the dose of RT used is low (<70 Gy) by modern standards for three studies.[10–12] The development of new RT techniques has allowed for a 25% increase in RT dose since the improvement in survival has been proved for high-dose than conventional-dose with modern RT dose fractionation schemes.[23] Another limitation was that all studies did not report data for skeletal adverse events (e.g., loss of bone mass and fractures), which might seriously affect the QoL of patients. If the addition of RT or chemotherapy can affect the skeletal-related events has not been verified.

SUMMARIES

In summary, for locally advanced PCa, the addition of RT to long-term ADT can improve the outcomes of survival and tumor control with fully acceptable adverse effects and QoL than ADT alone; however, added DE to ADT lacks data related to the long-term outcomes on relapse and survival. For newly diagnosed metastatic hormonally sensitive PCa, particularly for cases with visceral metastases and/or 4 or more bone metastases, the concurrent use of docetaxel plus ADT was necessary. It is too soon to say that ADT plus estramustine is better than ADT alone for metastatic PCa.

AUTHOR CONTRIBUTIONS

JHL and LRL wrote the paper. TRS and LY collected the data. YM analyzed the data. QW and PH commented in detail on the drafts. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing financial interests.

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