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ORIGINAL ARTICLE

Prostate Cancer

Neoadjuvant hormone therapy for patients with high-risk prostate cancer: a systematic review and meta-analysis

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This study aimed to identify the pathological outcomes and survival benefits of neoadjuvant hormone therapy (NHT) combined with radical prostatectomy (RP) and radiotherapy (RT) administered to patients with high-risk prostate cancer (HRPCa). We searched PubMed, Embase, and the Cochrane Library for studies comparing NHT plus RP or RT with RP or RT alone, administered to patients with HRPCa. We used a random-effects model to compute risk estimates with 95% confidence intervals (CIs) and quantified heterogeneity using the I^2 statistic. Subgroup and sensitivity analyses were performed to identify potential sources of heterogeneity. We selected 16 studies. NHT before RP significantly decreased lymph node involvement (risk ratio [RR] = 0.69, 95% CI: 0.56–0.87) and increased the rates of pathological downstaging (RR = 2.62, 95% CI: 1.22–5.61) and organ-confinement (RR = 2.24, 95% CI: 1.54–3.25), but did not improve overall survival and biochemical progression-free survival (bPFS). The administration of NHT before RT to patients with HRPCa was associated with significant benefits for cancer-specific survival (hazard ratio [HR] = 0.51, 95% CI: 0.39–0.68), disease-free survival (HR = 0.51, 95% CI: 0.44–0.60), and bPFS (HR = 0.54, 95% CI: 0.46–0.64). Short-term NHT combined with RT administered to patients with HRPCa conferred significant improvements. Although the advantage of local control was observed when NHT was administered before RP, there was no significant survival benefit associated with HRPCa. Therefore, short-term NHT combined with RT is recommended for implementation in standard clinical practice but not for patients who undergo RP.

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INTRODUCTION

Prostate cancer (PCa) is the second most common malignancy and the fifth leading cause of cancer-related death among males worldwide.[1] PCa is heterogeneous with an inconsistent natural history, varying from indolent to highly aggressive phenotypes. High-risk PCa (HRPCa) represents an increased risk of local and distant progression. Despite ongoing efforts, there is no consensus regarding the optimal treatment for men with HRPCa.[2] Thus, new treatment strategies, including multimodality approaches, are required to treat PCa. Neoadjuvant hormone therapy (NHT) combined with radical prostatectomy (RP) or radiotherapy (RT) may improve the outcomes of PCa.[3]

Administration of neoadjuvant androgen deprivation therapy (ADT) before RP decreases the rates of pT3 (downstaging) and positive surgical margins, and the incidence of lymph node invasion compared with RP alone.[2,4] However, a Cochrane meta-analysis of localized and locally advanced PCa found that this advantage does not confer a survival benefit for PCa, including overall survival (OS) and disease-free survival (DFS).[3] Moreover, Stephenson *et al.*[5] found that according to the D'Amico risk group classification, the 15-year PCa-specific mortality rates were 2%, 10%, and 19% for low-risk, intermediate-risk, and high-risk patients with PCa, respectively. When all risk groups are included, the results of analyzing NHT may vary because of differences between risk groups.[3] The value of NHT before RP administered to patients with HRPCa is the subject of numerous studies,[6–13] although insufficient information is available to assess with certainty its direct clinical and pathological effects.

The survival value of short-term ADT combined with RT for patients with intermediate-risk disease is established, and long-term ADT (2–3 years) is recommended for patients with HRPCa.[2] Unfortunately, prolonged ADT is associated with serious unwanted sequelae such as an increased risk of osteoporosis, depression, and metabolic syndrome.[14] The application of NHT before RT may reduce the cytotoxic synergy of radiation and hormone treatment and the target volume of RT. Previous studies report the association between NHT combined with RT and the survival outcomes of patients with HRPCa,[14–21] although they do not include meta-analyses. The aim of the present meta-analysis was to evaluate the effect of NHT before RP or RT on the pathological and survival outcomes of patients with HRPCa.

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MATERIALS AND METHODS

Search strategy and study selection

We performed this systematic review and meta-analysis based on a prespecified protocol (PROSPERO registration No. CRD42020169710). We searched the PubMed, Embase, and the Cochrane Library databases for relevant studies from inception to February 2020. Language was restricted to English. The search strategy was as follows: ("prostate" OR "prostatic") AND ("neoadjuvant" OR "neo-adjuvant" OR "neo adjuvant").

Randomized controlled trials (RCTs) or cohort studies are included if they simultaneously meet the criteria as follows: (1) compares NHT plus primary therapy (RP or RT) with primary therapy alone, unrestricted duration of NHT; (2) patients diagnosed with HRPCa (clinical stage ≥cT2c, Gleason score 8–10, prostate-specific antigen [PSA] ≥20 ng ml^{-1}, and/or lymph node involvement); (3) includes one of the outcomes of two groups as follows: pathological outcomes (lymph node invasion, pathological downstaging, organ-confined PCa, surgical margin, and seminal vesicle involvement) and survival outcomes (OS, cancer-specific survival [CSS], DFS, and biochemical progression-free survival [bPFS]); and (4) provides the hazard ratio (HR), risk ratio (RR), or both with the corresponding 95% confidence interval (95% CI) data or sufficient data to calculate HR or RR with 95% CI. The exclusion criteria are as follows: (1) study does not meet the inclusion criteria; (2) chemotherapy included in neoadjuvant therapy; (3) investigates long-term versus short-term NHT of patients with HRPCa; and (4) unoriginal research (*e.g.*, meta-analyses, reviews, commentaries, and conference abstracts). When more than one article addresses the same study population, we included the most recent. Two reviewers independently searched for potentially eligible studies. Disagreements were further evaluated and resolved by a third reviewer.

Data extraction and quality assessment

The information extracted from each study was as follows: first author, publication year, study design, median PSA level, the proportion of lymph node involvement, median follow-up duration, numbers of controls and treatments, regimen of NHT, inclusion criteria, types of interventions, and outcomes. The NHT regimen comprised combined hormone therapy with luteinizing hormone-releasing hormone (LHRH) agonists plus antiandrogens, or single-agent hormone deprivation therapies. Definitions of the outcomes are listed in **Supplementary Table 1**. The Cochrane risk-of-bias tool was employed to evaluate the quality of the RCTs,[22] and the quality scores of cohort studies were calculated according to the Newcastle–Ottawa Quality Assessment Scale.[23] Data extraction and quality assessment were conducted by two independent reviewers, and any disagreements were discussed and resolved by a third reviewer.

Statistical analyses

We present the time-to-event outcomes, including OS, CSS, DFS, and bPFS as HRs and 95% CIs. If HR and 95% CI values associated with survival outcomes were unavailable, we used a spreadsheet that provides 11 methods for calculating HRs and 95% CIs depending on the available information.[24] We applied method 9 to studies with a *P* value of a log-rank test, the number of events, and the numbers included in each arm; method 11 was applied when a study only provides Kaplan–Meier curves and numbers at risk.[24] The outcomes of RP and RT were separately calculated. We performed meta-analyses to pool the HRs and 95% CIs of survival outcomes. For each pathological outcome, the event and total number of two groups was extracted to calculate the pooled RRs and 95% CIs. If there were two study designs for one outcome, we conducted one meta-analysis of RCTs and a second meta-analysis of cohort studies to evaluate the consistency of results across varying study designs with different potential biases. A random-effects model was adopted to pool RRs or HRs.[25] The I^2 and Q statistics were calculated to evaluate the degree of heterogeneity. If heterogeneity was high (>50%), sensitivity analyses were performed to identify potential sources of heterogeneity and to assess the stability of the results. Statistical analyses were conducted using R 3.6.2 (Lucent Technologies, Inc., Murray Hill, NJ, USA).

RESULTS

Study selection and characteristics

We identified 7506 candidate studies. After reviewing the titles, abstracts, and full text, 16 articles were judged eligible, among which eight analyzed NHT followed by RP and eight analyzed NHT followed by RT. Full details of the identification process are presented in **Figure 1**. The studies included five RCTs and 11 cohort studies, comprising 67 616 patients with PCa recruited from 2000 to 2019. The median follow-up durations differed from 22.8 months to 13.2 years, although the median follow-up of 13 studies was ≥41 months. The regimen of NHT included LHRH agonists, anti-androgens, or both (11 studies), and was available in five studies (median: 4.3 months, standard deviation [s.d.]: 1.07). **Supplementary Table 2** summarizes the detailed characteristics of the 16 eligible studies, and the outcomes of risk and quality assessment are shown in **Supplementary Figure 1** and **Supplementary Table 3.**

NHT plus RP versus RP alone

Two RCTs and six cohort studies investigated the role of neoadjuvant hormones administered before RP (**Supplementary Table 2**). Four studies only included patients with localized HRPCa. The remaining four and two studies involved lymph node dissection and extended pelvic lymph node dissection, respectively.

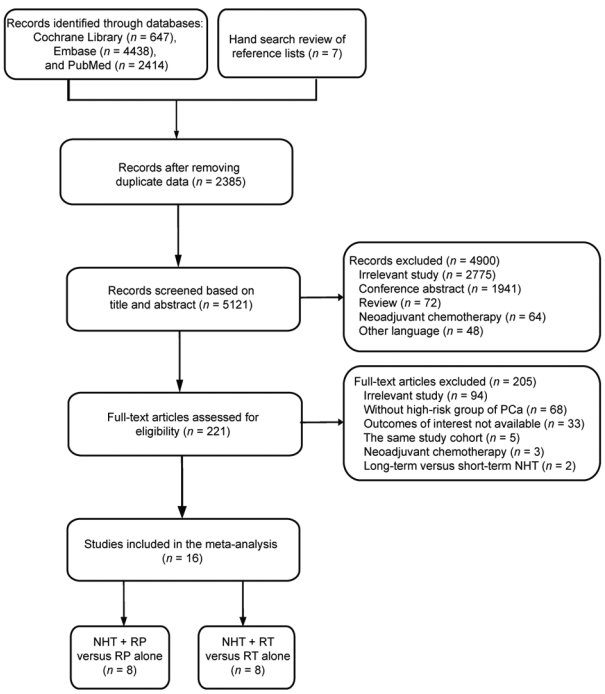

Figure 1: Selection of relevant articles. NHT: neoadjuvant hormone therapy; RP: radical prostatectomy; RT: radiotherapy.

Time-to-event outcomes were shown as follows. Three cohort studies evaluated the effects of NHT on OS of patients with PCa undergoing prostatectomy. McClintock *et al.*[9] analyzed the National Cancer Database and found that NHT before RP was significantly associated with a 1.39-fold increased risk of death of 62 252 patients with HRPCa (HR = 1.39, 95% CI: 1.01–1.91). Kim *et al.*[7] and Tosco *et al.*[13] found that NHT did not confer a benefit upon overall survival (P = 0.91 and 0.31, respectively) after >49 months of follow-up. Here, we show that the administration of NHT before RP did not prolong the OS of patients with HRPCa (HR = 1.13, 95% CI: 0.74–1.74) with low heterogeneity (I^2 = 44.6%, P = 0.16), as shown in **Figure 2a**. Three cohort studies analyzed bPFS, defined as elevated postoperative serum PSA (>0.2 ng ml^{-1}). All studies demonstrate that NHT before RP does not confer a significant bPFS advantage versus RP alone (pooled HR = 1.00, 95% CI: 0.78–1.54, I^2 = 0%; **Figure 2b**).

The following were the pooled results of pathological outcomes. Shelley *et al.*[3] found that that NHT before RP significantly improves local pathological variables of patients with localized and locally advanced PCa. Here, we show that NHT before RP significantly decreased the rate of lymph node involvement (RR = 0.69, 95% CI: 0.56–0.87, I^2 = 0%) and increased the pathological downstaging rate (RR = 2.62, 95% CI: 1.22–5.61, I^2 = 80.4%) as well as the rate of organ confinement (RR = 2.24, 95% CI: 1.54–3.25, I^2 = 66.1%), as shown in **Figure 3a–3c**. However, NHT did not reduce the rates of positive surgical margins (RR = 0.81, 95% CI: 0.60–1.09, I^2 = 74.5%) and seminal vesicle invasion (RR = 1.08, 95% CI: 0.79–1.48, I^2 = 0%), as shown in **Figure 3d–3e**.

Considering the high heterogeneity and different study designs, we conducted subgroup meta-analyses according to study design to evaluate the consistency of the results. The pathological downstaging rate was significantly higher for patients receiving NHT in RCTs (RR = 2.61, 95% CI: 1.24–5.51, I^2 = 34.9%), but not in cohort studies with high heterogeneity (RR = 2.85, 95% CI: 0.49–16.59, I^2 = 89.7%), as shown in **Figure 4**. Consistent with the pooled results, NHT before RP was associated with a higher rate of organ confinement in cohort studies (RR = 1.97, 95% CI: 1.35–2.88, I^2 = 67.7%) and RCTs (RR = 3.30, 95% CI: 1.70–6.39, I^2 = 0%), as shown in **Figure 4**. Unlike the pooled results,

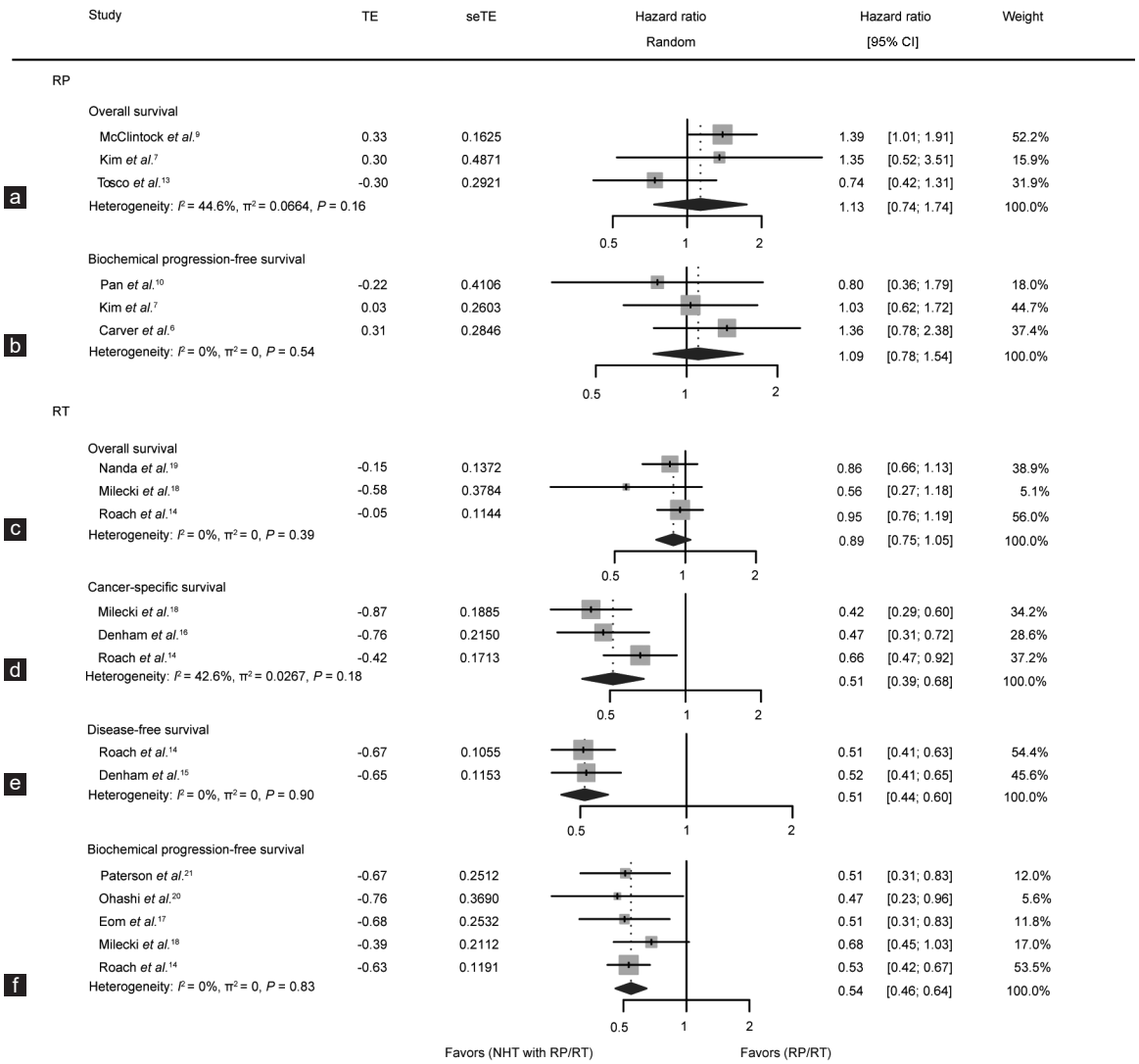

Figure 2: Meta-analyses of the survival outcomes of patients with HRPCa administered NHT plus RP or RT versus RP or RT alone (hazard ratios). (**a**) Overall survival and (**b**) biochemical progression-free survival associated with RP. (**c**) Overall survival, (**d**) cancer-specific survival, (**e**) disease-free survival, and (**f**) biochemical progression-free survival associated with RT. HRPCa: high-risk prostate cancer; NHT: neoadjuvant hormone therapy; RP: radical prostatectomy; RT: radiotherapy; TE: estimate of treatment effect; seTE: standard error of TE; CI: confidence interval.

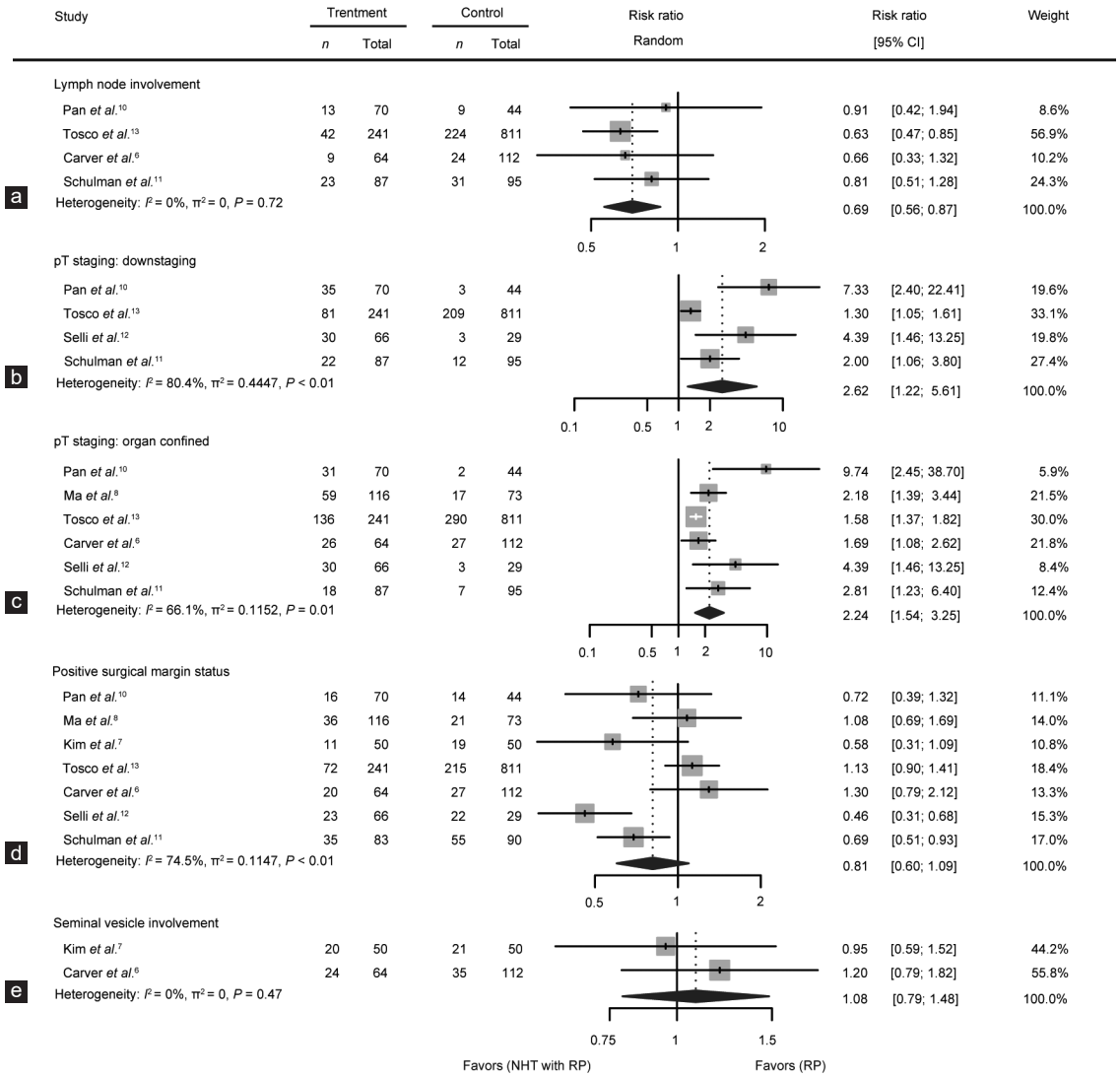

Figure 3: Meta-analyses of the pathological outcomes of patients with HRPCa administered NHT plus RP versus RP alone (risk ratios). (**a**) Lymph node involvement. (**b**) pT staging: downstaging. (**c**) pT staging: organ confined. (**d**) Positive surgical margins. (**e**) Seminal vesicle involvement. HRPCa: high-risk prostate cancer; NHT: neoadjuvant hormone therapy; RP: radical prostatectomy; RT: radiotherapy; CI: confidence interval; pT: pathological tumor.

the rate of positive surgical margins in RCTs decreased in the NHT plus RP group compared with that of RP alone, with high heterogeneity (RR = 0.57, 95% CI: 0.38–0.86, I^2 = 62.4%), but remained unchanged in cohort studies (RR = 1.00, 95% CI: 0.79–1.27, I^2 = 33.5%), as shown in **Figure 4**. After omitting one study, sensitivity analyses revealed that the difference in the outcome of the pathological downstaging rates was not significant (**Supplementary Figure 2**). The heterogeneity may be caused by pooling different study designs (**Figure 4**).

NHT plus RT versus RT alone

Three RCTs and five cohort studies investigated the role of neoadjuvant hormones before RT (**Supplementary Table 2**). Only one study included patients with pelvic lymph node involvement and randomly assigned them to receive combined ADT, and the other studies included patients with localized HRPCa. Six studies used external beam radiotherapy alone, and two studies applied brachytherapy plus external beam radiotherapy. Radiotherapy was utilized in combination with neoadjuvant, concomitant ADT, or both, except for one study in which all patients were treated with adjuvant ADT from the last day of irradiation.

Time-to-event outcomes were shown as follows. Four studies were eligible for the analysis of OS and CSS. Three studies assessed OS and reported that NHT before RT did not improve OS compared with RP alone (pooled HR = 0.89, 95% CI: 0.75–1.05, I^2 = 0%; **Figure 2c**). With a median follow-up of 4.6 years, Nanda *et al.*[19] validated that NHT did not increase the risk of all-cause mortality of patients with HRPCa (HR = 0.86, 95% CI: 0.66–1.13). Another cohort study found that NHT before RT improved the outcome of CSS (HR = 0.42, 95% CI 0.29–0.60), but not of OS (HR = 0.56, 95% CI: 0.27–1.18). The randomized Radiation Therapy Oncology Group (RTOG) 86.10 trial conducted by Roach *et al.*[14] (13.2-year follow-up) demonstrated that 4 months of NHT before RT had a significant impact on CSS of men with locally advanced PCa (HR = 0.66, 95% CI: 0.47–0.92), with no statistically significant impact on OS (HR = 0.95, 95% CI: 0.76–1.19). Similarly, long-

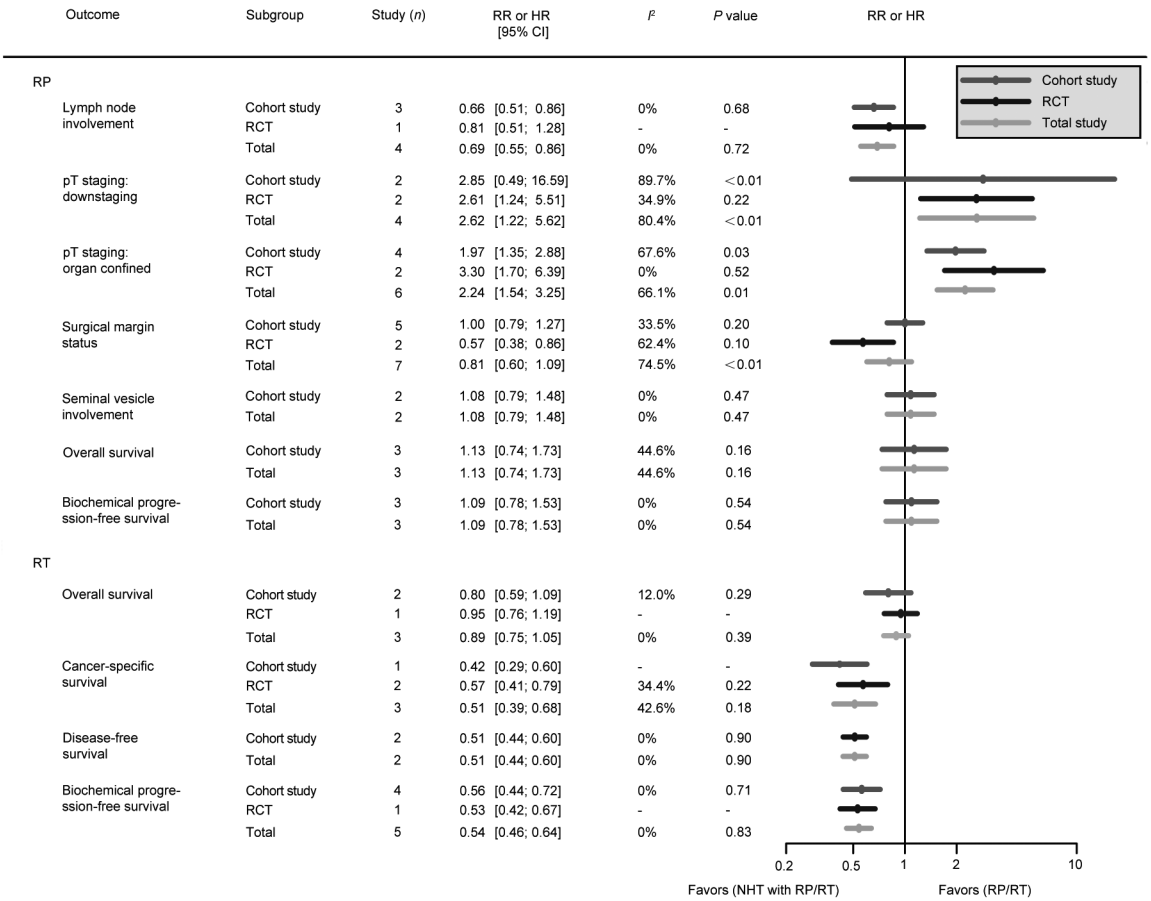

Figure 4: Subgroup analyses of pathological and survival outcomes according to study design. HRPCa: high-risk prostate cancer; NHT: neoadjuvant hormone therapy; RT: radiotherapy; RP: radical prostatectomy; RCT: randomized controlled trial; HR: hazard ratio; RR: risk ratio; pT: pathological tumor; CI: confidence interval; - : minus.

term outcomes (median: 10.6 years) reported by the randomized RTOG 96.01 trial shows that 6-month NHT combined with RT significantly decreased the risk of cancer-specific mortality for patients with HRPCa (HR = 0.47, 95% CI: 0.31–0.72). Here, we found that short-term NHT before RT significantly prolonged CSS of patients with HRPCa (HR = 0.51, 95% CI: 0.39–0.68) with low heterogeneity (I^2 = 42.6%, P = 0.18), as shown in **Figure 2d**.

The randomized TROG 86.10 and 96.01 trials investigated DFS and demonstrated that the DFS rate of achieved using NHT before RT was significantly higher compared with those administered RT alone (pooled HR = 0.51, 95% CI: 0.44–0.60, I^2 = 0%; **Figure 2e**).

Five studies analyzed bPFS, which was determined using the Phoenix definition (PSA level >2 ng ml^{-1}, higher than the PSA nadir value after RT). Four cohort studies indicated that bPFS was significantly decreased in the NHT group compared with that of RT alone (pooled HR = 0.56, 95% CI: 0.44–0.72, I^2 = 0%; **Figure 4**). The randomized TROG 86.10 randomized trials validated the value of NHT of HRPCa (HR = 0.53, 95% CI: 0.42–0.67; **Figure 4**). Here, we show that short-term NHT before RT significantly improved the bPFS of patients with HRPCa (HR = 0.54, 95% CI: 0.46–0.64) with low heterogeneity (I^2 = 0%, P = 0.83), as shown in **Figure 2f**.

When we conducted subgroup meta-analyses stratified according to study design, we found that the results of meta-analyses of subgroups were consistent with that of the pooled results (**Figure 4**). NHT before RT was significantly associated with lower risk of cancer-specific death, disease progression, and biochemical recurrence, but not with all-cause death.

DISCUSSION

There is no consensus regarding the optimal treatment of HRPCa,[2] and multimodal approach is necessary because of the poor prognosis of this disease. Numerous studies investigated the effect of NHT administered to patients with HRPCa before RP or RT to assure improved cancer control.[6–21] We believe that the present meta-analysis proves that the use of NHT before RP did not generate meaningful survival benefits, including OS and bPFS, for patients with HRPCa. Although NHT before RT did not significantly prolong OS, significant improvements in CSS, DFS, and bPFS were recognized when NHT before RT was compared with RT alone. Further, the administration of NHT before RP significantly decreased the rate of lymph node involvement and increased the rates of pathological downstaging and organ confinement, although it did not reduce the rates of positive surgical margins and seminal vesicle involvement.

The meta-analysis conducted by Shelley *et al.*[3] of randomized trials of patients with localized and locally advanced PCa revealed

that NHT before RP confers a significant benefit upon local control, which is associated with lower rates of positive surgical margins, pT3 (downstaging), and lymph node involvement. However, this advantage did not prolong OS and DFS, thus NHT combined with RP is not considered the standard clinical practice.[2] Most studies included patients of all risk groups, which is a limitation of the present review for performing sub-group analysis.[3] The results acquired from analyzing all risk groups combined may be imprecise. Therefore, we only selected studies that included information of patients with HRPCa who were administered NHT.

We found that NHT improved the pathological outcomes of HRPCa, such as reducing lymph node involvement and increasing the rates of pathological downstaging and organ confinement. In contrast, OS or bPFS was not improved when NHT was combined with RP. Several reasons may explain the discrepancy between the survival outcomes and pathological benefits when using NHT. First, the median follow-up (average: 42.9 months) was insufficient to identify significant differences between the treatment of NHT plus RP and RP alone. Second, the potential selection bias of retrospective cohort studies might lead to the outcomes deviating from the actual situation. Six of the eight studies were retrospective, which may underestimate the value of NHT for HRPCa. Third, the pathological benefits of patients receiving NHT were greater with increased treatment duration (up to 8 months).[27] The duration of NHT was 3–6 months or not available in the included studies, which may be insufficient to achieve a significantly increased OS. Unfortunately, our literature search did not find studies that evaluated the differences of survival outcomes between long-term and short-term NHT before RP, of patients with PCa. Compared with radiotherapy, surgical resection might be more attractive for HRPCa in that surgery allows more precise pathologic and nodal staging, and reduces the use of ADT.[4] However, considering the lack of RCTs focused on HRPCa, the influence of NHT on patients with HRPCa cannot be definitively evaluated when combined with RP. More prospective trials are needed to evaluate the survival benefit of the addition of NHT to surgery for high-risk patients.

Short-term ADT (around 6 months) plays an important role in improving the survival of intermediate-risk PCa patients administered RT.[2] Some clinical trials showed that long-term ADT (2–3 years) plus RT significantly improved the survival outcomes over short-term ADT plus RT.[28–30] However, the effect of short-term ADT on patients with HRPCa is undefined. Shelley *et al.*[3] found that the DFS and bPFS of patients with localized and locally advanced PCa who were treated with NHT before RT significantly improved, although OS and CSS did not. The present meta-analysis selected studies that contained data for NHT administered to patients with HRPCa because of the prognostic differences among risk groups. We show here that there were significant improvements in CSS, DFS, and bPFS. However, the three selected studies did not establish the benefit of NHT for OS.[14,18,19]

In the randomized TROG 96.01 trial, 818 patients with T2b-T4N0M0 PCa were assigned to the arms of RT alone, 3-month NHT plus RT, and 6-month NHT plus RT.[16] Compared with RT alone, 3-month NHT had no effect on CSS and OS. In contrast, 6-month NHT decreased prostate cancer-specific mortality and all-cause mortality. To determine whether prolonging the duration of NHT confers greater improvement of survival outcomes, two RCTs compared survival between short-term and prolonged NHT before RT.[31,32] Further, the OS, CSS, and bPFS of patients with localized PCa did not significantly improve after longer administration of NHT (8 months *vs* 4 months, or 8 months *vs* 3 months).[31,32] However, Crook *et al.*[32] found that high-risk patients in the 8-month arm had a significant improvement of 5-year DFS rate compared with that in the 3-month arm. Unfortunately, these two RCTs did not compare the survival outcomes between the NHT arms and non-NHT arm, thus the impact of short-term NHT on patients with HRPCa was unknown. In conclusion, NHT before RT plays a significant role in the survival outcomes of patients with HRPCa. The optimal duration of NHT cannot be determined, usually from 3 months to 6 months in the included studies.[14–21]

Although combined long-term ADT with RT is recommended for patients with HRPCa,[28–30] prolonged ADT can multiply the occurrence of adverse effects such as increased risks of cardiovascular disease, osteoporosis, depression, and metabolic syndrome.[14,33,34] Further, long-term ADT adversely affects the quality of life.[35] Therefore, the administration of short-term neoadjuvant ADT before RT significantly improves the survival outcomes of high-risk patients and may reduce the cytotoxic synergy of radiation and hormone manipulation, thus avoiding these adverse effects.[14]

Chemotherapy (docetaxel or estramustine)[10,36–41] and novel antiandrogens such as abiraterone[42] serve as neoadjuvants combined with neoadjuvant ADT to manage HRPCa. These agents achieve significant local control and prolong the OS and bPFS of patients with HRPCa who undergo prostatectomy. However, the potential for perioperative complications should be carefully considered.[40] Moreover, the heterogeneity of HRPCa requires more precisely targeted multimodal therapies combined with NHT.

This meta-analysis contains certain limitations. First, the combination of RCTs and cohort studies may introduce methodological heterogeneity. We therefore chose to perform subgroup meta-analyses according to study design to evaluate the consistency of results acquired from the two types of studies. Second, because of the lack of studies focusing on the effect of NHT on HRPCa, we only selected 16 studies, of which 11 are retrospective. This may affect the validity of our conclusions. Nevertheless, the present meta-analysis is the first and most comprehensive of its kind to specifically identify the association between NHT before RP or RT and the pathological and survival outcomes of patients with HRPCa. The major strengths of our meta-analysis are as follows: first, we selected only studies including the information of NHT for patients with HRPCa so that the potential bias introduced by patients with low-risk or intermediate-risk PCa was eliminated. Second, when analyzing survival outcomes, we extracted HRs and 95% CIs, which encompass temporal information and therefore more accurately reflect prognosis. Third, unlike the study of Hu *et al.*[43] combining RP and RT as standard therapy, we analyzed RP and RT, respectively.

CONCLUSIONS

In summary, the pooled results of our meta-analysis provide compelling evidence that the administration of NHT before RP significantly improved the pathological outcomes of patients with HRPCa. However, the advantages of local control did not confer a survival benefit, indicated by OS and bPFS. Although NHT before RT does not significantly improve OS, our analyses revealed significant improvements of CSS, DFS, and bPFS when NHT before RT was compared with RT. The optimal duration of NHT was not determined (typically from 3 months to 6 months). When considering NHT, physicians should make decisions based on the benefits, adverse effects, and costs.

AUTHOR CONTRIBUTIONS

GMZ, WL, and YY designed the study, collected, analyzed and interpreted the clinical data, and wrote the manuscript. XL and YL

analyzed part of the data. GMZ supervised the project and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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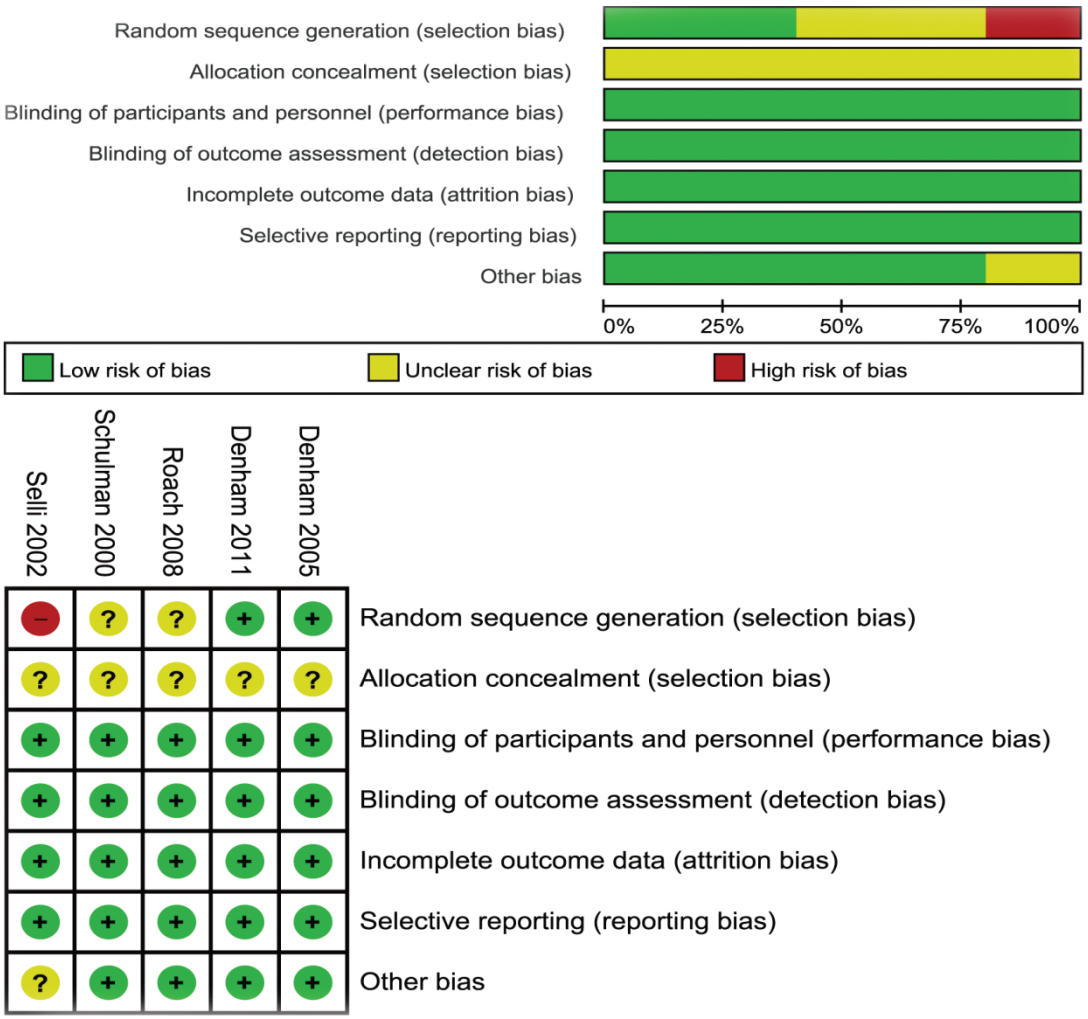
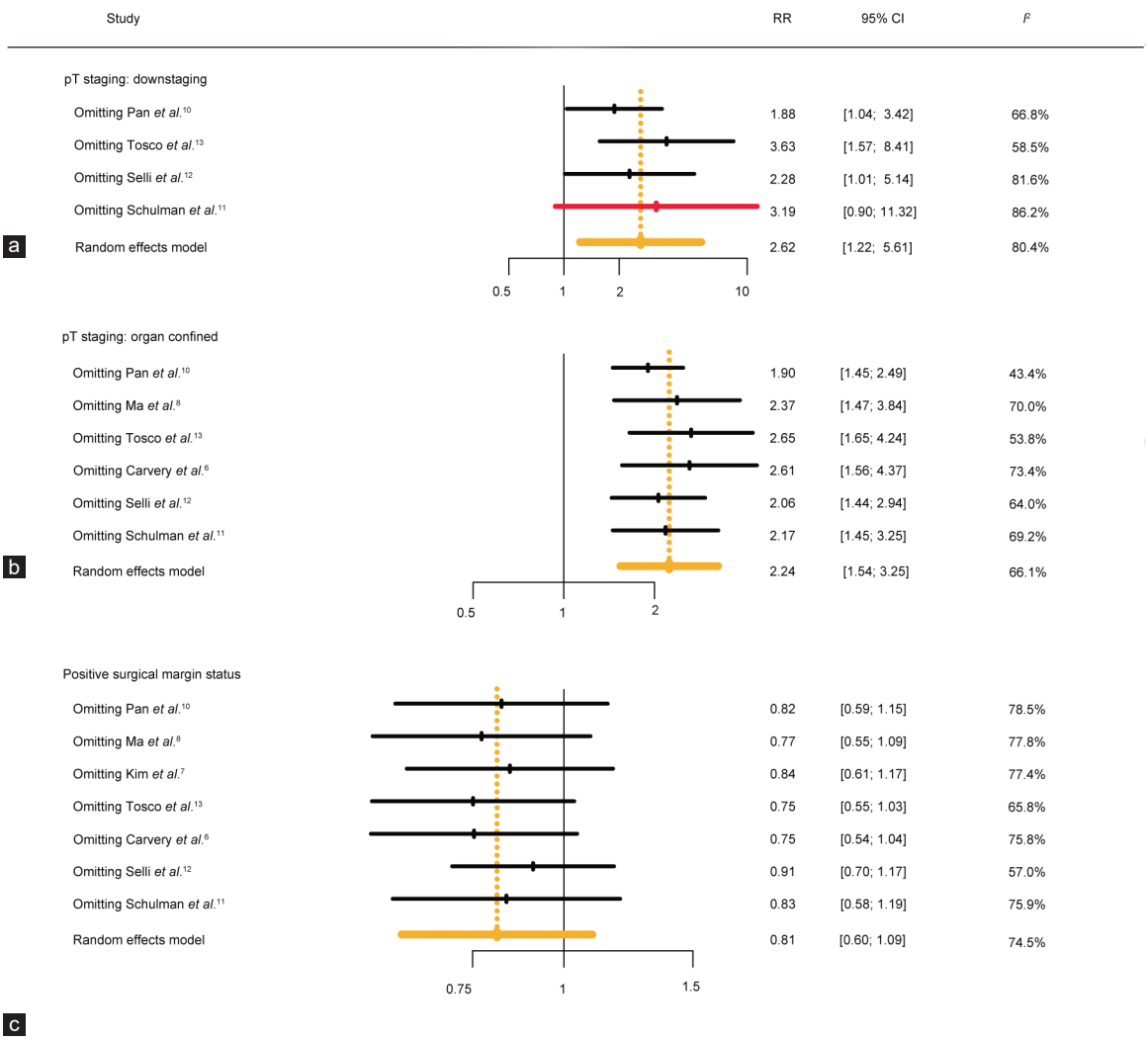


Supplementary Figure 1: Risk of bias and bias summary of randomized controlled trials.



Supplementary Figure 2: Sensitivity analyses. (**a**) pT staging: downstaging. (**b**) pT staging: organ-confined. (**c**) Positive surgical margins. pT staging: pathological Tumor staging; RR: risk ratio; CI: confidence interval.

Supplementary Table 1: Definition of outcomes used in this review

Outcomes	*Definition*
Overall survival	Percentage of subjects in a study who have survived for a defined period of time. Any causes of deaths are counted
Cancer-specific survival	The percentage of subjects in a study who have survived a particular disease for a defined period of time. In calculating the percentage, only deaths from prostate cancer are counted
Disease-free survival	Cancer that has returned after a period of time during which the cancer could not be detected. Failure is defined as death as a result of any cause, local progression, regional metastasis, biochemical failure, or distant metastasis
Biochemical progression-free survival	PSA level rises to a specific level after radical prostatectomy or radiotherapy for a defined period of time
Positive lymph nodes	Prostate cancer has spread to the lymph nodes (generally the pelvic lymph nodes)
pT staging: downstaging	Pathologically confirmed downstaging compared to clinical tumor stage
pT staging: organ confined	The pathological tumor stage is <pT3a
Positive surgical margins status	Cancer cells that are in contact with the inked outer surface (margin) are described as positive
Seminal vesicle involvement	Pathologically confirmed that tumor extends through the prostatic capsule and invades the seminal vesicle(s).

pT: pathological; PSA: prostate-specific antigen

Supplementary Table 2: Characteristics and interventions of studies included in the meta-analysis

Author	*Study design*	*Risk level*	*Median PSA level (ng ml^{-1})*		*Lymph node involvement (%)*		*Inclusion criteria*	*Dose (NHT)*	*Interventions*	*Number of treatment*	*Number of control*	*Median follow-up*
			NHT	*No-NHT*	*NHT*	*No-NHT*						
Pan *et al.* 2019[10]	Cohort study	Very high risk	71.2	60.3	24.7	13.63	Patients had clinical stage more than cT3a, or primary Gleason pattern 5, or ≥5 cores with Gleason sum 8–10, or serum PSA ≥50 ng ml^{-1}, or with pelvic metastatic lymph node involvement Patient with resectable tumor could be treated with RP and ePLND Patients had a good general performance status with ECOG score 0–1	Goserelin acetate: 3.6 mg every 28 days and flutamide: 250 mg tid (duration: 4 cycles to 6 cycles of total androgen blockade)	NHT followed by RP and ePLND versus RP and ePLND alone	70	44	22.8 months
McClintock *et al.* 2019[9]	Cohort study	High risk	NA	NA	-	-	Patients with adenocarcinoma and no metastasis to the lymph nodes or other organs at the time of PCa diagnosis (cT1–T4N0M0) NCCN risk groups (high: T3a, Gleason score 8–10 or PSA >20 ng ml^{-1})	NA	NHT followed by RP versus RP alone	3293	58,959	65.28 months
Ma *et al.* 2019[8]	Cohort study	High risk	19.96	17.6	-	-	Localized high-risk PCa (clinical stage of T1 or T2 with a PSA level >20 ng ml^{-1} or Gleason score >7) and limited progressive PCa (clinical stage ≥T3)	GnRH agonist alone (3.75/11.25 mg of leuprolide or 3.6/10.8 mg of goserelin acetate), an androgen receptor antagonist alone, or a combination of the two. (duration: <3 months, 3–6 months, or >6 months)	NHT followed by RP versus RP alone	116	73	26 months
Kim *et al.* 2018[7]	Cohort study	High risk	NA	NA	27.9	7.2	Patients with one or more risk factors: stage ≥T3 and/or PSA >20 ng ml^{-1} and/or Gleason score sum 8–10; any stage T with pelvic nodal involvement; and clinical stage T3b or T4 disease without evidence of nodal involvement or metastasis	NHT: goserelin acetate and flutamide (the median duration: 4 months)	NHT followed by RP versus RP alone	50	50	49.1 months
Tosco *et al.* 2017[13]	Cohort study	High risk	11.0	14.0	29.5	36.2	Patients meeting one or more of the following criteria: clinical stage T3–T4, PSA >20 ng ml^{-1} or biopsy Gleason score 8–10	NA (The indication, duration and type of NHT depended on institutional protocols)	NHT followed by RP versus RP alone	241	811	56 months
Carver *et al.* 2006[6]	Cohort study	Clinical T3	21.8	10.0	14	21	Patients with cT3 PCa	NA	NHT followed by RP versus RP alone	64	112	6.4 years
Schulman *et al.* 2000[11]	RCT	Clinical T3	NA	NA	26.4	32.6	T3N × M0 prostatic carcinoma and a PSA level of <100 ng ml^{-1}	Goserelin acetate: 3.6 mg every month and flutamide: 250 mg tid (duration: 3 months)	NHT followed by RP versus RP alone	87	95	4 years
Selli *et al.* 2002[12]	RCT	Clinical T3	10	10.2	-	-	C1 (cancer with extracapsular extension; pT3a); C2 (seminal vesicle invasion; pT3b; TNM, 1997 revision)	Zoladex depot: 3.5 mg every 28 days and Casodex: 50 mg per day (duration: for 12 weeks or 24 weeks)	NHT followed by RP versus RP alone	66	29	NA
Ohashi *et al.* 2014[20]	Cohort study	High risk	11.95	11.95	-	-	High risk localized PCa: PSA level higher than 20 ng ml^{-1}, and/or Gleason score ≥8, and/or Stage T3 Prostate volumes >40 cc usually underwent ADT	GnRH agonist alone or in combination with an anti-androgen (median duration: 4 months)	NHT followed by RT (I-125 brachytherapy plus EBRT) versus RT alone	101	105	60 months
Nanda *et al.* 2014[19]	Cohort study	High risk	14.9	20.0	-	-	High risk localized PCa: PSA level higher than 20 ng ml^{-1}, and/or Gleason score≥8, and/or Stage T3 Men in the study had no or at least a single risk factor and no documented history of coronary artery disease at the time of enrollment	NA (median duration: 4 months)	NHT followed by RT (brachytherapy with or without EBRT) versus RT alone	1007	353	4.6 years

Contd...

Supplementary Table 2: Contd...

Author	*Study design*	*Risk level*	*Median PSA level (ng ml^{-1})*		*Lymph node involvement (%)*		*Inclusion criteria*	*Dose (NHT)*	*Interventions*	*Number of treatment*	*Number of control*	*Median follow-up*
			NHT	*No-NHT*	*NHT*	*No-NHT*						
Denham *et al*. 2011[16]	RCT	High risk	14.6	16.4	-	-	Patients with one or more of the following are regarded as high risk: stage T2c, T3, or T4 disease; a Gleason score of >7; or initial PSA concentration of more than 20g l^{-1}; without evidence of lymph-node involvement and metastases No upper limit on PSA level was set	Goserelin acetate: 3.6 mg every month and flutamide: 250 mg tid (duration: 6 months)	NHT followed by RT and continued during RT versus RT alone. Prostate/seminal vesicles 66 Gy, 33 fractions/6.5–7.0 weeks	224	222	10.6 years
Denham *et al*. 2005[15]	RCT	High risk	14.6	16.4	-	-	Patients with one or more of the following are regarded as high risk: stage T2c, T3, or T4 disease; a Gleason score of >7; or initial PSA concentration of more than 20 g l^{-1}; without evidence of lymph-node involvement and metastases No upper limit on PSA level was set	Goserelin acetate: 3.6 mg every month and flutamide: 250 mg tid (duration: 6 months)	NHT followed by RT and continued during RT versus RT alone. Prostate/seminal vesicles 66 Gy, 33 fractions/6.5–7.0 weeks	224	222	5.9 years
Milecki *et al*. 2009[18]	Cohort study	High risk	37.3	38.1	73	59	Patients with one or more of the following are regarded as high risk: Gleason score >7 or initial PSA level >20 ng ml^{-1} or T3 All patients represented good general performance status defined as 0 or 1 according to ECOG classification All patients had a histological diagnosis of adenocarcinoma	Goserelin acetate: 10.8 mg every 3 months and flutamide: 250 mg tid for 4 weeks (the median duration: 4.4 months)	NHT followed by WPRT and continued during WPRT versus RT alone. Prostate/seminal vesicles 70.2 Gy/1 weeks	70	92	55 months
Paterson *et al*. 2016[21]	Cohort study	High risk	12.8	13.0	NA	NA	Patients >70 years of age who were diagnosed with histologically confirmed, localized, or locally advanced adenocarcinoma of the prostate Patients suitable and those opting for primary RT, neoadjuvant/adjuvant hormonal therapy for 24 months, and radiotherapy Patients with one or more of high-risk factors: Gleason score 8–10 or initial PSA level ≥20 ng ml^{-1} or stage ≥T2c	NA	NHT followed by RT versus RT alone	167	117	40.9 months
Eom *et al*. 2014[17]	Cohort study	High risk	NA	NA	-	-	High-risk group: Gleason score ≥8 or PSA >20 ng ml^{-1} or stage ≥T3a Localized patients (cT1–T4, N0, and M0) with >3 years of follow-up	GnRH agonist combined with anti-androgen agent (n=84). Anti-androgen agent alone (18). Bilateral orchiectomy (*n*=1; median duration: 3.3 months)	NHT followed by RT and continued during RT versus RT alone. (1.8 Gy per fraction in 7–10 weeks)	69	27	91.2 months
Roach *et al*. 2008[14]	RCT	B2+C	22.6	33.8	NA	NA	Patients with bulky (defined as 5 cm × 5 cm) tumors (T2–T4) according to the 1988 American Joint Committee on Cancer TNM staging system Patients were eligible with or without pelvic lymph node involvement and were randomly assigned to receive combined ADT	Goserelin acetate: 3.6 mg every month and flutamide: 250 mg tid for 2 months before RT (duration: 112 days)	NHT followed by RT and continued during RT versus RT alone (regional lymphatics 44 Gy–46 Gy/ prostate 65 Gy–70 Gy, 1.8 Gy–2 Gy 1 day given 4 times–5 times a week)	224	232	13.2 years

NA: not available; PCa: prostate cancer; PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radiotherapy; ePLND: extended pelvic lymph node dissection; ECOG: Eastern Cooperative Oncology Group; NHT: neoadjuvant hormone therapy; ADT: adjuvant deprivation therapy; EBRT: external beam radiation therapy; WPRT: whole pelvic radiation therapy; NCCN: National Comprehensive Cancer Network; GnRH: gonadotropin-releasing hormone; RCT: randomized controlled trial; TNM: tumor, regional lymph node, metastasis; - : no relevant data

Supplementary Table 3: Quality evaluation of the included cohort studies

Study	*Selection*	*Comparability*	*Outcomes*	*Sum*
Pan *et al.*, 2019[10]	★★★★	★	★	6
McClintock *et al.*, 2019[9]	★★★★	★★	★★★	9
Ma *et al.*, 2019[8]	★★★★	★★	★	7
Kim *et al.*, 2018[7]	★★★★	★★	★★	8
Tosco *et al.*, 2017[13]	★★★★	★★	★★★	9
Carver *et al.*, 2006[6]	★★★★	★★	★★★	9
Ohashi *et al.*, 2014[20]	★★★★	—	★★★	7
Nanda *et al.*, 2014[19]	★★★★	★	★★★	8
Milecki *et al.*, 2009[18]	★★★★	★★	★★	8
Paterson *et al.*, 2016[21]	★★★★	★	★★★	8
Eom *et al.*, 2014[17]	★★★★	★★	★★★	9

★ indicates that the study meets the following criterions. Selection: representativeness of the exposed cohort (★), selection of the nonexposed cohort (★),ascertainment of exposure (★), demonstration that outcome of interest was not present at start of study (★); comparability: comparability of cohorts on the basis of the design or analysis (★★); outcomes: assessment of outcome (★), follow-up long enough for outcomes to occur (★), adequacy of follow-up of cohorts (★).