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REVIEW ARTICLE

Comparison of short-term and long-term neoadjuvant hormone therapy prior to radical prostatectomy: a systematic review and meta-analysis

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ABSTRACT

Purpose: This study aimed to evaluate the efficacy of long-term neoadjuvant androgen-deprivation therapy (ADT) before radical prostatectomy (RP).

Methods: We conducted meta-analyses and network meta-analyses, which included randomized controlled trials that assessed patients with prostate cancer (PC) who received either short-term (<6 months) or long-term (≥6 months) neoadjuvant ADT before RP.

Results: Thirteen articles with 2778 patients were eligible for analysis. Short-term neoadjuvant ADT was neither associated with biochemical recurrence (OR 1.19, 95% CI, 0.93–1.51, $p = 0.17$), metastasis (OR 0.73, 95% CI, 0.45–1.19, $p = 0.21$), nor overall mortality (OR 0.72, 95% CI 0.43–1.21, $p = 0.22$); no study investigated survival outcomes in patients on long-term neoadjuvant ADT. In terms of pathologic outcomes, long-term neoadjuvant ADT was significantly associated with a reduced risk of positive surgical margin (SM) and an increased rate of organ-confined disease (OCD) compared to short-term neoadjuvant ADT (OR 0.56, 95% CI 0.39–0.80, $p = 0.001$, and OR 1.48, 95% CI 1.10–1.99, $p = 0.009$, respectively). These findings were confirmed in the network meta-analyses. Meanwhile, only a non-significant trend favoring long-term neoadjuvant ADT was observed for pathologic complete response (OR 1.98, 95% Crl 1.00–3.93).

Conclusion: Long-term neoadjuvant ADT was associated with more favorable pathologic outcomes, but whether these findings translate into favorable survival outcomes still remains unproven due to very limited evidence. Since there are no reliable survival data, long-term neoadjuvant ADT before RP should not be used in clinical practice until more robust evidence arises from ongoing trials.

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Introduction

Androgen deprivation therapy (ADT) effectively reduces both prostate and tumor volumes in most prostate cancer (PC) patients. With its manageable adverse events, ADT is the backbone therapy for advanced and metastatic PC [1]. With the increasing role of radical prostatectomy (RP) in advanced and oligometastatic PC, neoadjuvant ADT has received renewed attention as adjunct treatment [2–4]. This is largely facilitated by the relatively tolerable and safe adverse effect profile of ADT compared to other systemic therapies [1,5,6]. In addition to identifying the right indication, the right treatment schedule is essential for the safety and optimal effectiveness of any therapy. As such, long-term ADT has been shown to provide superior survival compared to short-term ADT in well-designed radiation therapy (RT) trials. In the RP setting, a randomized controlled trial (RCT) with long-term follow-up comparing adjuvant long-term ADT *vs.* deferred ADT revealed survival benefit favoring adjuvant ADT in patients with node-positive PC [7]. We hypothesized that neoadjuvant ADT administered for a sufficient period of time provides advantages in select patients. Furthermore,

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neoadjuvant treatment strategies would be required in case RP is to be deferred for health or system-relevant issues (e.g. pandemics resulting in resource shortage). In this systematic review and meta-analysis, we aimed to summarize and assess the available literature on the significance of short- and long-term neoadjuvant ADT before RP.

Evidence acquisition

This study is registered with the International Prospective Register of Systematic Reviews (CRD: 42021227080).

Search strategy

The present systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement [8]. PubMed, Web of Science, and Scopus were searched in October 2020 to identify relevant articles on the clinical impact and optimal duration of neoadjuvant ADT before RP in patients with PC. Two authors performed the search using the following terms: ('prostate cancer' OR 'prostate carcinoma' OR 'prostatic cancer' OR 'prostatic carcinoma') AND 'neoadjuvant' AND 'prostatectomy' AND ('randomized' OR 'RCT' OR 'phase 2' OR 'phase 3'). The eligible literature was restricted to articles written in English. We also checked the reference lists of relevant publications.

Inclusion criteria

The PICOS (Population, Intervention, Comparator, Outcome, and Study design) was applied to our clinical question in this study; patients with PC (P) who received neoadjuvant ADT (short-term or long-term) before RP (I) were compared with those who received no or short-term neoadjuvant ADT before RP (C) in terms of pathologic outcomes and survival outcomes (O) in RCTs (S). The use of ADT was limited to luteinizing hormone-releasing hormone agonists alone or with antiandrogens. To avoid duplicate publications, we retrieved the most recent or most informative publication. The duration of short-term ADT was defined as <6 months, while the duration of long-term ADT was defined as more than six months. We also searched for metastasis-free survival (MFS) because recent studies have highlighted that MFS is a strong surrogate for overall survival (OS) in clinically localized PC [9,10]. The primary endpoints were survival outcomes (biochemical recurrence [BCR]-free survival, MFS, and OS). The secondary endpoints were pathologic outcomes, including surgical margin (SM), organ-confined disease (OCD), and pathologic complete response (pCR).

Data extraction

After initial screening based on the study title and abstract of the extracted studies, two authors performed secondary screening independently based on the full-text review, and excluded studies that were not appropriate for this review. Data were extracted on the first author, publication year, period of recruitment, recruitment region, number of patients, age, inclusion criteria, follow-up period, treatment drug, the primary endpoint of the included studies, SM, OCD, pCR, BCR-free survival, MFS, and OS. All discrepancies in data extraction were resolved by consensus with the co-investigators.

Risk of bias assessment

The 'risk-of-bias' (RoB) tool, which is recommended in Cochrane Reviews, was applied in eligible studies to judge the risk of bias arising from seven domains (Supplementary Figure 1). This procedure was independently performed by two authors. Disagreements were resolved through consultation with co-authors.

Statistical analysis

Forest plots were used to display odds ratios (ORs) and 95% confidence intervals (CIs) for both included studies and meta-analyses. pCR was defined as the absence of any residual tumor cells in a histologic evaluation of a removed specimen. BCR was defined as a PSA level >0.2, 0.4, or 1 ng/mL on two subsequent occasions, depending on each study. MFS was defined from the date of randomization to the date of the first evidence of recorded distant metastasis or death from any cause, but if we could not count the exact number, we adopted either one of them. Relative treatment effects were evaluated using a Bayesian network meta-analysis with random- and fixed-effect models to combine direct and indirect estimates among all interventions [11,12]. We used network plots to visualize the network structure for each outcome. The relative effects were presented as odds ratios (OR) and 95% credible intervals (CrI) using arm-based analyses. We also estimated the relative ranking of each treatment arm for all outcomes using the *P*-score, which was introduced to the surface under the cumulative ranking curve [13]. Heterogeneity was identified using the Cochrane *Q* test and I^2 statistics. When $p > 0.05$, or $I^2 < 50\%$, a fixed-effect model was used; otherwise, a random-effect model was used. All statistical analyses were performed using R Version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria, 2020) and Review Manager 5.4 (The Nordic Cochrane Center, Copenhagen, Denmark), with a statistical significance level of $p < 0.05$.

Evidence synthesis

Systematic search

We identified 735 publications on an initial literature search. After removing 158 duplicate publications, we reviewed the titles and abstracts of 577 relevant studies. Full-text assessment of 103 studies was performed, and ultimately 13 articles with 2778 patients were included in the systematic review (Figure 1). The extracted data from the included studies are shown in Table 1.

Characteristics of included studies

Data on the included studies, except for two, were collected between 1996 and 2003, with seven studies from North

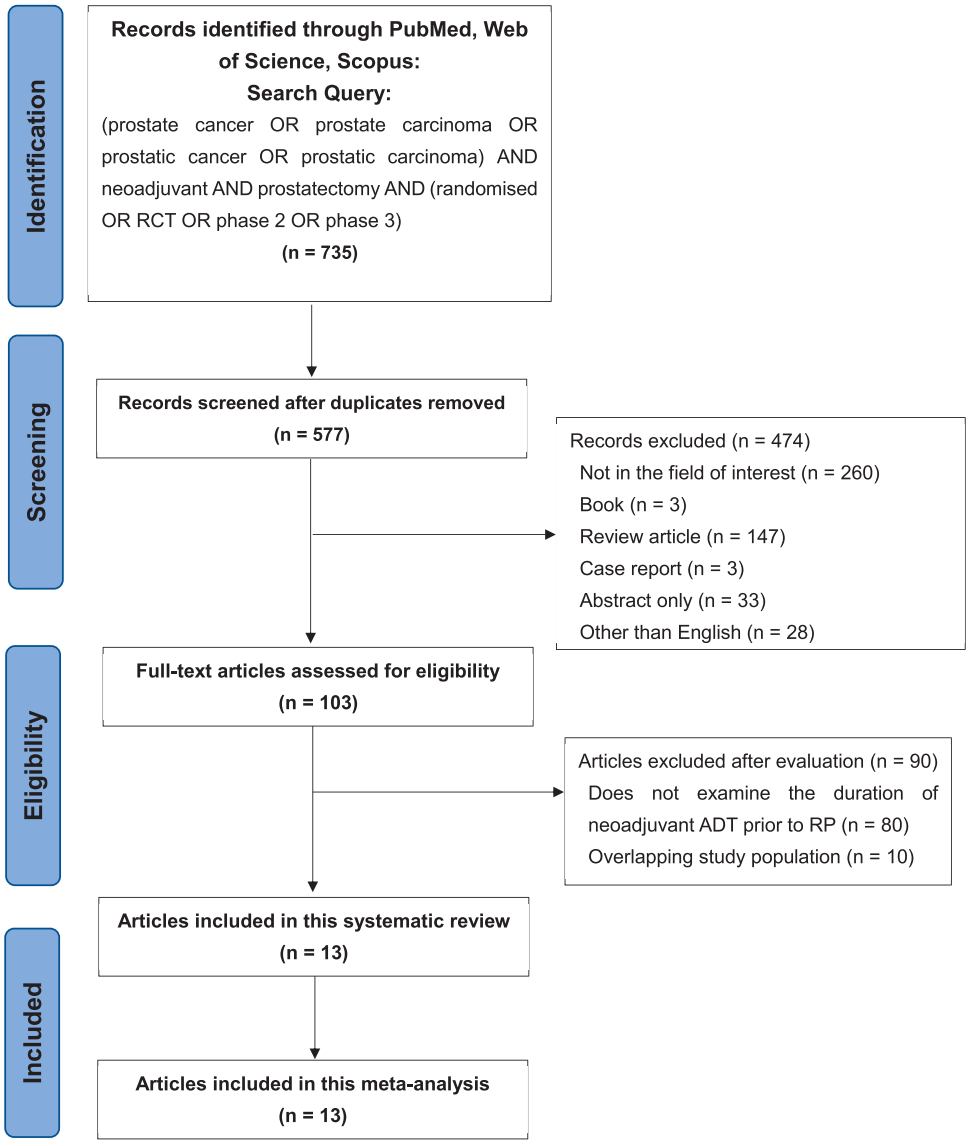

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart for article selection process to analyze the effect of neoadjuvant ADT before radical prostatectomy.

America and six studies from Europe. The duration of median follow-up was 65.5 months. The median duration of administration is 3 (interquartile range [IQR]: 3–3) months in the short-term neoadjuvant group, and 8 (IQR: 6–8) months in the long-term group. Based on the National Comprehensive Cancer Network risk classification, ten studies included patients at low risk. Of these, eight studies were set up with pathologic outcomes as primary endpoints, five studies were with BCR (despite variable definitions in each study), and no study was set up with other survival outcomes apart from BCR, including MFS or OS.

Meta-analyses for RP alone vs. short-term neoadjuvant ADT

Survival outcomes

Six studies including 1299 patients [14–19] provided data on BCR-free survival. The forest plot (Figure 2(A)) showed that short-term neoadjuvant ADT did not significantly impact on BCR-free survival (OR 1.19, 95% CI 0.93–1.51, $p = 0.17$), with no significant heterogeneity ($p = 0.51$, I^2 0%). Both MFS and OS were investigated in four studies [14,17–19], with a total of 850 patients included. Compared to RP alone, patients receiving short-term neoadjuvant ADT showed no significant improvement in either MFS or OS (OR 0.73, 95% CI 0.45–1.19, $p = 0.21$, and OR 0.72, 95% CI 0.43–1.21, $p = 0.22$, respectively) (Figure 2(B,C)). The Cochrane Q test ($p = 0.84$ and $p = 0.91$) and I^2 test (both 0%) detected no significant heterogeneity in terms of MFS and OS, respectively.

Pathologic outcomes

Ten studies including 1924 patients [14–23] and six studies including 1217 patients [14,17,21–24] were investigated for SM and OCD, respectively. The forest plots (Supplementary Figures 2(A,B)) revealed that compared to RP alone, short-term neoadjuvant ADT was significantly associated with a reduced rate of SM and an increased rate of OCD (OR 0.33, 95% CI 0.27–0.40, $p < 0.00001$, and OR 2.20, 95% CI

Table 1. Characteristics of eligible studies.

	Recruitment year	No. patients		Age		ADT duration (months)	Treatment drug	Inclusion criteria (clinical stage or PSA threshold)	Endpoint	Definition of PSA progression	Follow-up duration (months)
		Treatment	Control	Treatment	Control						
Dalkin, 1996 [22]	NR	28	28	Mean 66	Mean 65	3 *vs.* 0	Goserelin	cT1,T2a or T2b. PSA > 4	Pathologic outcome		NR
Labrie, 1997 [23]	1988–	90	71	NR	NR	3 *vs.* 0	Flutamide + Leuprolide	Clinical stage B0-C2	Pathologic outcome		NR
van der Kwast, 1999 [25]	NR	22	18	Mean 63	Mean 61	6 *vs.* 3	Flutamide + Leuprolide	Clinically localized PC	Pathologic outcome		NR
Schulman, 2000 [14]	1991–1995	191	209	NR	NR	3 *vs.* 0	Flutamide + Goserelin	cT2-T3, PSA < 100	Biochemical recurrence	>1 ng/ml on two subsequent occasions or development of distant metastases or local recurrence	48
Gleave, 2001 [26]	1995–1998	247	253	Mean 63	Mean 63	8 *vs.* 3	Flutamide + Leuprolide	cT1b, T1c, T2	Biochemical recurrence	>0.4 ng/ml on two subsequent occasions	NR
Aus, 2002 [18]	1991–1994	63	63	Mean 67	Mean 66	3 *vs.* 0	Triptorelin	cT1b-3aNxM0	Pathologic outcome		82 (8–104)
Selli, 2002 [21]	1996–2000	122 (six months) 143 (three months)	128	Mean Short-term: 65 Long-term: 66	Mean 65.7	6 *vs.* 3 *vs.* 0	Bicalutamide + Goserelin	cT2-T3N0M0	Biochemical recurrence	>1 ng/ml on two subsequent occasions	NR
Soloway, 2002 [16]	1992–1994	137	138	Mean 64.9	Mean 65.4	3 *vs.* 0	Flutamide + Leuprolide	cT2b, PSA < 50	Biochemical recurrence	>0.4 ng/ml	60
Bullock, 2002 [24]	1993–1994	101	91	Mean 62.5	Mean 62.2	3 *vs.* 0	Cyproterone acetate	cT1-T2	Pathologic outcomes		NR
Klotz, 2003 [19]	1993–1994	112	101	Median 64	Median 63	3 *vs.* 0	Cyproterone acetate	cT1-T2, PSA < 50	Biochemical recurrence	>0.2 ng/ml on two subsequent occasions	71 (7–117)
Prezioso, 2004 [15]	NR	81	86	Mean 64.9	Mean 64.5	3 *vs.* 0	Cyproterone + Leuprolide	cT1a-T2b	Pathologic outcome		6
Gravina, 2007 [20]	2002–2003	61	58	Median 69	MEDIAN 67	4 *vs.* 0	Bicalutamide	cT2-T3a	Pathologic outcome		NR
Yee, 2010 [17]	1992–1996	72	64	Median 61	Median 61	3 *vs.* 0	Goserelin + Flutamide	clinically localized PC	Pathologic outcome		96

ADT: androgen deprivation therapy; PSA: prostate specific antigen; NR: not recorded.

1.57–3.07, $p < 0.00001$, respectively). The Cochrane Q test ($p = 0.33$ and $p = 0.14$) and I^2 test (13 and 39%) detected no significant heterogeneity in terms of both SM and OCD, respectively.

Meta-analyses for short-term vs. long-term neoadjuvant ADT

Pathologic outcomes

Three RCTs including 805 patients [21,25,26] reported data on SM and OCD. Long-term neoadjuvant ADT was significantly associated with a reduced risk of positive SM (OR 0.56, 95% CI 0.39–0.80, $p = 0.001$) and an increased rate of OCD (OR 1.48, 95% CI 1.10–1.99, $p = 0.0004$) compared to short-term ADT. There was no significant heterogeneity among trials in terms of SM ($p = 0.31$, I^2 16%), or OCD ($p = 0.95$, I^2 0%) (Figure 3).

Network meta-analyses for RP alone vs. short-term vs. long-term neoadjuvant ADT

The network of eligible RCTs are visually represented in plots regarding positive SM, OCD, and pCR (Supplementary Figure 3).

Positive surgical margins

Twelve studies, including 2560 patients, were eligible for this network meta-analysis [14–17,20–27]. When short-term neoadjuvant ADT was used as the reference, network estimates showed that long-term neoadjuvant ADT was significantly associated with a reduced risk of positive SM (OR 0.56, 95% CrI 0.37–0.86) (Figure 4(A)). Ranking analysis showed that long-term ADT was the most effective (ranking *P* score = 0.9981), followed by short-term ADT and RP only (Supplementary Table 1).

Organ-confined disease

Seven studies, including 1839 patients, were eligible for this network meta-analysis [14,17,21–24,26]. When short-term neoadjuvant ADT was used as the reference, network estimates showed that long-term neoadjuvant ADT was significantly associated with an increased rate of OCD (OR 2.08, 95% CrI 1.02–4.24) (Figure 4(B)). Ranking analysis showed that long-term ADT was the most effective (ranking *P* score = 0.9987), followed by short-term ADT and RP only (Supplementary Table 1).

Pathologic CR

Four studies, including 1101 patients, were eligible for this network meta-analysis [14,25,26]. When short-term neoadjuvant ADT was used as the reference, network estimates showed an increased rate of pCR in favor of long-term neoadjuvant ADT, but 95% CrI included the null value (OR 1.98, 95% CrI 1.00–3.93) (Figure 4(C)). Ranking analysis showed that long-term ADT was the most effective (ranking *P* score = 0.9858), followed by short-term ADT and RP only (Supplementary Table 1).

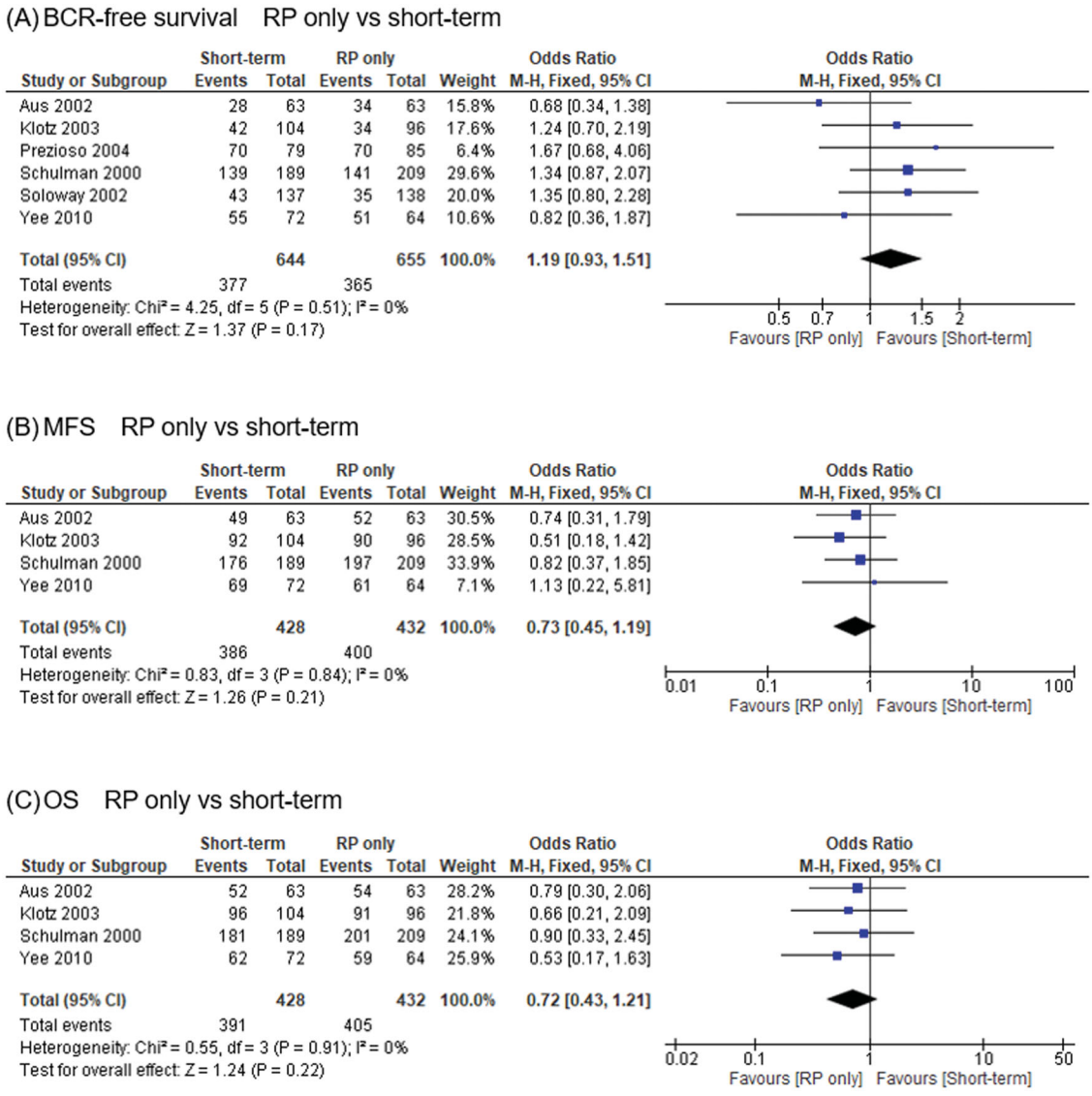

Figure 2. Forest plots showing the association of short-term neoadjuvant ADT followed by radical prostatectomy in biochemical recurrence-free survival (A), metastasis-free survival (B), and overall survival (C).

Discussion

In this systematic review and meta-analysis, we assessed the clinical impact of neoadjuvant ADT before RP on survival and pathologic outcomes, especially focusing on the duration of neoadjuvant ADT. In our meta-analyses, we found that the use of long-term neoadjuvant ADT was significantly associated with higher rates of favorable pathologic outcomes compared to short-term neoadjuvant ADT which in turn was superior to RP alone; in addition, our network meta-analyses confirmed these findings consistently. While short-term neoadjuvant ADT did not result in a clear survival improvement, the lack of RCTs to investigate meaningful survival outcomes (i.e. MFS or OS) weakened the validity of this endpoint assessment. The survival data for long-term neoadjuvant ADT was too limited for any conclusions, except for BCR-free survival, where the evidence shows no benefit. In agreement with our analyses, as pathologic response does not always translate into a survival advantage, current guidelines limit the use of neoadjuvant ADT followed by RP to clinical trials [28]. However, with the increased use of RP in locoregionally advanced and oligometastatic PC, multimodal therapy with a systemic component is becoming more and more needed. In this regard, we believe that as part of the multimodal approaches for the treatment of PC with unfavorable biology, neoadjuvant systemic therapy, which is likely to affect occult and small volume micrometastases, will play a more important role, specifically with the advent of novel androgen pathway targeting therapies.

There are several potential explanations for the failure of short-term neoadjuvant ADT to improve survival compared to RP alone. First, the primary endpoints in all previous RCTs were either pathologic outcomes or BCR-free survival, which were too weak surrogate endpoints compared to MFS or OS [29–31]. Since no previous RCT comparing neoadjuvant ADT plus RP with RP alone was designed to investigate MFS and/or OS as primary endpoints, the statistical power for these outcomes was limited [32]. Second, the median follow-up of the included RCTs was relatively short (median follow-up: ~5.5 years) to allow a mature analysis of survival outcomes.

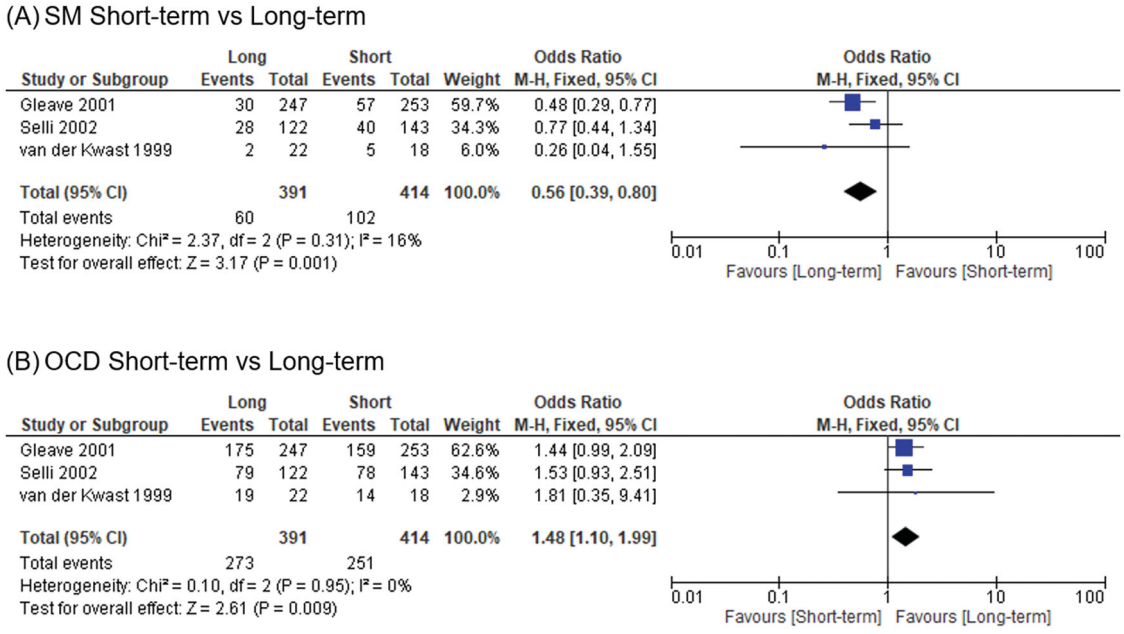

Figure 3. Forest plots showing the comparison of short-term *vs.* long-term neoadjuvant ADT followed by radical prostatectomy in positive soft tissue surgical margin (A) and organ-confined disease (B).

MFS, which occurs at a median time of 7 years after RP [33], is, on the other hand, a good surrogate for patients with both localized castration-naive or resistant PC [9,10]. Third, patients recruited to the studies had heterogeneous diseases, as reflected by the varied distribution patterns of clinical stage or Gleason score. Most of the studies (71.4%) included patients with low-risk diseases since the recruitment year peaked in the early 1990s when the appropriate risk classification system had not yet been developed [30,31,34]. In addition to these arguments, the optimal duration of neoadjuvant ADT on which we focused in this study remains debatable [35]. According to our meta-analysis and network meta-analysis, despite no available literature mentioned survival, long-term neoadjuvant ADT conferred significantly improved pathologic outcomes compared to RP alone and short-term neoadjuvant ADT plus RP.

In breast cancer, neoadjuvant therapies, including endocrine and chemotherapies, are well-established approaches, partly because pCR following neoadjuvant treatment proved an important surrogate for survival [36,37]. Similar to breast cancer, pCR in PC may correlate with a long-term survival benefit [38], which is most likely to occur with long-term neoadjuvant ADT. The use of long-term neoadjuvant ADT, despite not reaching a statistically significant difference, showed a trend toward better pCR compared to short-term neoadjuvant ADT, potentially presenting a more solid surrogate endpoint for neoadjuvant treatment strategies.

Recently, increasing evidence suggests that a more intense neoadjuvant ADT therapy using androgen receptor axis-targeted (ARAT) agents show encouraging results [39]. A randomized phase II trial assessing pathologic outcomes in PC patients treated with neoadjuvant enzalutamide plus leuprolide alone or in combination with abiraterone plus prednisone demonstrated favorable pCR outcomes (10% with abiraterone and 8% without abiraterone, respectively) [40]. Interestingly, the use of enzalutamide or docetaxel alone did not achieve pCR, suggesting an important role for neoadjuvant ADT using agonists or antagonists in the treatment of PC [41,42]. The PROTEUS trial (NCT03767244) which assesses ADT plus six cycles of apalutamide administered in a neoadjuvant and adjuvant setting, will provide a further understanding of the role of neoadjuvant hormonal therapy for aggressive PC. A potential risk-based strategy may be necessary to allocate the therapy to the patients most likely to benefit: ADT with an antagonist or agonist alone for patients with intermediate-risk (especially for unfavorable intermediate-risk) disease and ADT combined with ARTA for patients with high-risk non-metastatic PC, followed by local therapy with curative intent. Indeed, this assumption might be supported by the finding of Gleave et al. who found that patients with intermediate-risk PC (PSA between 10 and 20 μg/L) benefited greatly, and those at high-risk (Gleason score 4 or 5) benefited little from long-term ADT regarding the risk of positive SM [26].

We acknowledge several limitations to our analyses. First and foremost, most of the eligible studies were published in the early 2000s. Prostatectomies were performed by many surgeons with variable surgical experience/performance. Neoadjuvant therapies might also trigger desmoplastic reactions, resulting in increased operative difficulties and complications, or vice-versa. The endpoints of the reported studies fell short of clinical significance (i.e. SM and BCR) and important effects, such as adverse events remain unreported. Although we applied pCR as a promising pathologic surrogate, only half of the studies incorporated a central review by an expert pathologist. Finally, OS, the only definite endpoint has not been reported. Despite these limitations, our study has important implications. We clarified that to date, there is no RCT to investigate the meaningful oncological outcomes (MFS or OS) as primary endpoints.

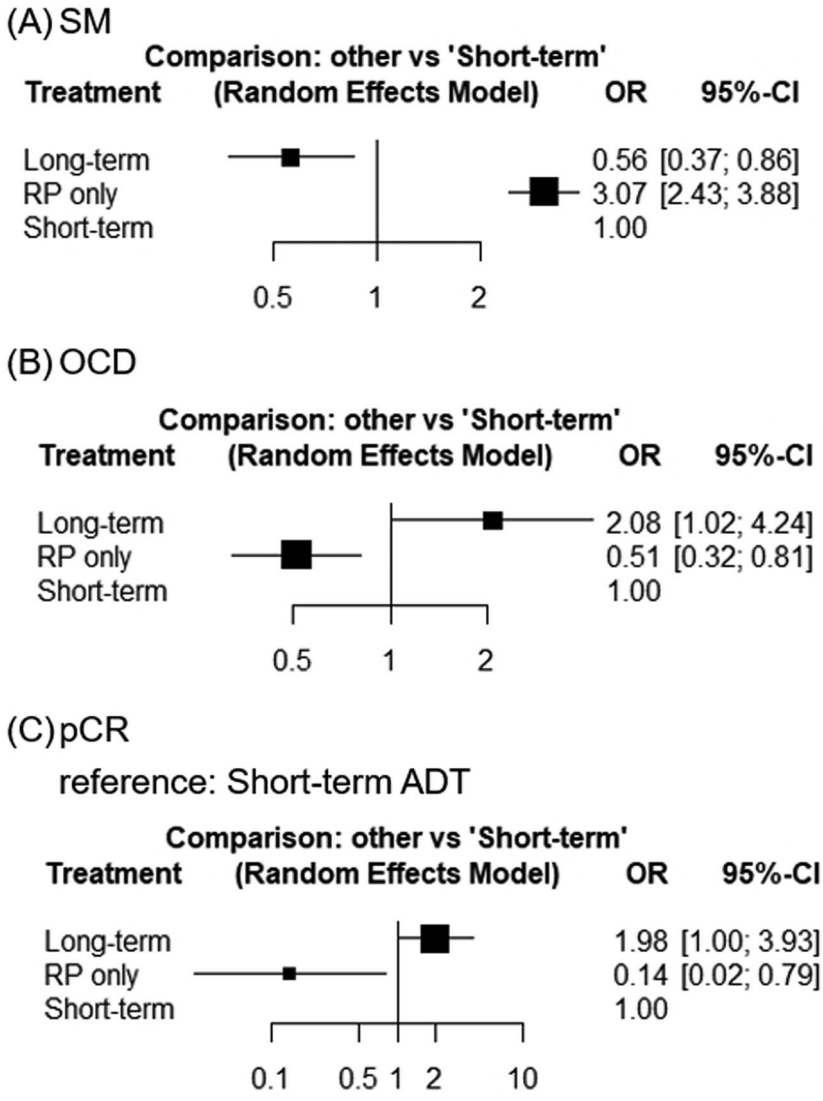

Figure 4. Forest plots according to the Bayesian network meta-analysis showing the comparison of short-term *vs.* long-term neoadjuvant ADT followed by radical prostatectomy in positive soft tissue surgical margin (A), organ-confined disease (B), pathologic complete response (C).

Conclusions

We found that the use of long-term neoadjuvant ADT provides a significant benefit in pathologic outcomes compared to short-term ADT. Given the favorable trend in an increased rate of pCR, long-term neoadjuvant ADT before RP has the potential to improve patient outcomes. However, due to the lack of available RCTs to properly investigate survival benefits in patients with PC receiving long-term neoadjuvant ADT, neoadjuvant ADT should not be used outside the clinical trial due to the considerable risk of adverse events. Considering the importance of preoperative treatment strategy as part of combined modality management of PC patients with unfavorable biology, robust evidence from well-designed ongoing trials is warranted.

Author contributions

S. Katayama: project development, data collection, and manuscript writing. K. Mori: data management. B. Pradere: manuscript editing. H. Mostafaei and V. M. Schuettfort: data management. F. Quhal, R. Sari Motlagh E. Laukhtina, N. C. Grossmann, P. Rajwa, A. Aydh, and F. König: data collection. R. Mathieu, P. Nyirady, P. I. Karakiewicz, and Y. Nasu: manuscript editing. S. F. Shariat: project development and manuscript editing.

Disclosure statement

All authors state that they have no conflict of interest that might bias this work.

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