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Review

Influence of Concomitant Androgen Deprivation Therapy and Its Duration for Salvage Radiation After Radical Prostatectomy: A Systematic Review and Network Meta-analysis According to Published Data

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Abstract

Background and objective: Recently published data comparing the impact and duration of androgen deprivation therapy (ADT) on metastasis-free survival (MFS), progression-free survival (PFS), and overall survival (OS) in patients undergoing salvage radiation therapy (sRT) after radical prostatectomy have not been compared directly; this study aims to address this knowledge gap.

Methods: We performed a systematic review and network meta-analysis (NMA) on MFS, PFS, and OS using data from the RADICALS-HD, NRG/RTOG 9601, RTOG 0534, and GETUG-AFU 16 trials, as well as three trials from the ARTISTIC meta-analysis (GETUG-AFU 17, RADICALS-RT, and RAVES) on adjuvant versus salvage radiotherapy. The primary outcome was MFS; the secondary outcomes were PFS and OS. Stratification was made according to ADT duration (ADT for 24 mo vs ADT for 6 mo vs no ADT). Subgroup analyses addressed high-risk cohorts with Gleason score ≥8 and positive surgical margins (PSMs).

Key findings and limitations: Data from 3710 prostate cancer patients were analyzed. Addition of ADT to sRT improved MFS and PFS significantly, regardless of the duration, but had no significant effect on OS. Hazard ratios (HRs) for ADT for 24 mo versus no ADT were 0.70 (confidence interval [CI] 0.53–0.92) for MFS, 0.51 (CI 0.43–0.61) for PFS, and 0.80 (CI 0.63–1.01) for OS; for ADT for 6 mo versus no ADT, the respective HRs were 0.79 (CI 0.65–0.97), 0.57 (CI 0.48–0.67), and 0.93 (CI 0.72–1.20). In subgroup

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analyses, ADT for 24 mo was ranked highest for MFS in patients with PSMs and Gleason score ≥8.

Conclusions and clinical implications: The NMA supports the addition of ADT to sRT, particularly a 24-mo duration, which provides the best MFS and PFS outcomes. While OS did not improve significantly, patients with Gleason score ≥8 or PSMs also benefit from prolonged ADT.

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ADVANCING PRACTICE

What does this study add?

Our network meta-analysis offers a more comprehensive understanding of the currently available data, including all seven randomized controlled trials on concomitant androgen deprivation therapy (ADT) in patients undergoing salvage radiotherapy (sRT). We provide robust evidence supporting the addition of ADT to sRT to improve metastasis-free and progression-free survival, especially in patients with high-risk features such as Gleason score >8 and positive surgical margins.

Clinical Relevance

Biochemical recurrence after radical prostatectomy is mainly treated by radiotherapy. One debatable question remains the use of concomitant androgen deprivation therapy and its optimal duration, to optimize cancer outcomes wihtout compromise health-related quality-of-life. The imbalance between benefits and risk of ADT may be challenging to evaluate in daily practice. Several randomized trials have been published using different ADT durations and regimens. The authors performed a systematic review and network meta-analysis (NMA) on MFS, PFS, and OS using data from the RADICALS-HD, NRG/RTOG 9601, RTOG47 0534, and GETUG-AFU16 trials, as well as three trials from the ARTISTIC meta-analysis (GETUG-AFU17, RADICALS-RT, RAVES) on adjuvant vs. salvage radiotherapy. The results presented here provide interesting data to guide salvage treatment decision-making. Associate Editor: Guillaume Ploussard.

Patient Summary

Addition of androgen deprivation therapy to salvage radiotherapy in patients with disease recurrence offers a survival benefit compared with salvage radiotherapy alone. Particularly, patients with high-risk features such as a high Gleason score of >8 and positive surgical margins benefit from prolonged ADT.

1. Introduction

Salvage radiotherapy (sRT) serves as a potential curative treatment for patients undergoing radical prostatectomy (RP) experiencing biochemical recurrence [1–3]. Moreover, in cases where adjuvant radiotherapy (aRT) is required after RP due to high-risk features, such as positive surgical margins (PSMs), extracapsular extension (ECE), or seminal vesicle invasion, sRT may be considered an alternative for patients who refuse aRT [4,5]. The impact of concomitant androgen deprivation therapy (ADT) and its duration in patients undergoing RP and subsequent sRT was initially examined within four different randomized controlled phase 3 trials (RCT), suggesting a significant survival benefit of concomitant ADT (both for 6 and for 24 mo among different studies) with sRT regarding metastasis-free survival (MFS), progression-free survival (PFS), and overall survival (OS) compared with sRT alone [6–9]. Moreover, in 2022, combined results were presented in the DADSPORT meta-analysis (MA), suggesting improved MFS for 6 mo of ADT [ADT6], although both primary and sensitivity analyses excluding patients with prostate-specific antigen (PSA) >1.5 ng/ml showed no clear improvement in OS between no ADT, ADT6, and 24 mo of ADT (ADT24) [10]. Since then, several important updates from the RADICALS-HD trial have been published, particularly the results from the three-way randomization (0 vs ADT6 vs ADT24), providing new insights into the optimal duration of ADT and its differential benefits across patient subgroups [7,11,12]. Notably, no previous network meta-analysis (NMA) has assessed the efficacy of ADT6 or ADT24 in this context, combining the information of all available studies and leading to the highest level of evidence. Therefore, we conducted an NMA including the three-way randomization of the RADICALS-HD study, as well as further studies mentioned above to perform indirect comparisons (no ADT vs ADT6 vs ADT24).

This study seeks to address the current knowledge gap by applying the NMA methodology, with MFS as the primary study outcome and PFS and OS as the secondary outcomes. Additionally, further subgroup analyses addressed

patients with high-risk features at RP, such as Gleason score ≥8 or PSMs. We hypothesized that different cancer-control outcomes may exist with respect to administration and length of ADT. Specifically, we also hypothesized that with further comparisons between no ADT versus ADT6 and no ADT versus ADT24, and longer follow-up data, the resulting MFS, PFS, and OS findings will provide more robust and generalizable evidence to improve clinical decision-making regarding optimal ADT duration.

2. Methods

2.1. Methodology

We conducted a systematic review of MAs and RCTs involving patients with local or locally advanced nonmetastatic prostate cancer (PCa) undergoing RP and subsequently receiving sRT or aRT (Table 1). Studies were included based on varying durations of ADT exposure (0, 6, or 24 mo) and outcomes of MFS, PFS, and OS. Additionally, antihormonal therapy with bicalutamide was grouped under the ADT category due to its shared therapeutic objective of reducing androgen-driven tumor progression. Based on these criteria, we included seven RCTs in our systematic review, of which four qualified for inclusion for the subsequent NMA (Fig. 1). Owing to patients' intervention arm crossover, only the three-way randomization of the RADICALS-HD trial was included in this NMA to provide most unbiased outcomes. Furthermore, in the RTOG 0534 study, a third arm, namely, sRT + ADT + pelvic lymph node radiation, was present. However, to facilitate the most accurate comparison of concomitant ADT with sRT, we excluded this arm from the current analysis. The most recent updated results were derived from several publications [6–9,11,12]. Our study search and inclusion criteria adhered to the guidelines for Preferred Reporting of Items for Systematic Reviews and Meta-analysis (PRISMA) [13–15].

2.2. Search strategy, study selection, and data collection

The search strategy was based on prior studies on ADT administration comparisons and its duration, as well as previous NMAs, as reported recently [16,17]. PubMed was systematically searched between September 28 and September 30, 2024 to identify all relevant reports addressing ADT following sRT and varying durations of ADT from 1998 until 2025. Additionally, references from editorials, commentaries, and review articles were reviewed manually and cross-referenced to ensure comprehensive coverage of the literature. Our search terms included the following: (prostate cancer OR prostate carcinoma OR prostatic carcinoma OR prostatic cancer) AND (androgen deprivation therapy OR androgen suppression) AND (salvage radiotherapy OR postoperative radiotherapy) AND (randomized).

2.3. Study review methodology

Two independent reviewers (Q.C.L. and M.W.) conducted initial screening of the literature on ADT following sRT, adhering to the PRISMA guidelines and in alignment with the established methodology [18–22]. The suitability of each publication was determined based on data extraction and critical assessment. Any disagreements were resolved through consensus with a senior author (P.M.). A risk of bias assessment was performed according to the Cochrane Collaboration's tool for assessing the risk of bias (Supplementary Fig. 1) [23].

2.4. Outcome measures

The primary endpoint of the current NMA was MFS, defined as the time from randomization to the documented occurrence of metastasis or all cause death in all four studies. The secondary outcomes were PFS, defined as the time from randomization to documented biochemical, radiographic, or clinical progression, and OS, defined as the time from randomization to death from any cause or censoring at the date of the last follow-up. Subgroup analyses were performed for patients with Gleason score ≥8 and PSMs, when at least two studies provided hazard ratios (HRs).

Additionally, we compared the cohorts of the four studies included in the NMA (NRG/RTOG 9601, GETUG-AFU 16, RADICALS-HD, and RTOG 0534) versus the cohorts of the three sRT arms of the studies (RAVES, GETUG-AFU 17, and RADICALS-RT) that were analyzed in the prospectively planned MA by Vale et al [17].

2.5. Statistical analysis

For MFS, PFS, and OS, a naïve NMA was conducted to compare ADT durations (0 vs 6, 0 vs 24, and 6 vs 24 mo) through both direct and indirect treatment comparisons [24,25]. Contrast-based analyses estimated differences in HRs and standard errors from published HRs and confidence intervals (CIs) [26]. Relative treatment effects were reported as HRs with 95% CIs, and the relative ranking of treatments was assessed using P scores according to a previous methodology [27,28]. All analyses were performed in R software (version 4.4, R Foundation for Statistical Computing, Vienna, Austria) [29].

3. Results

3.1. Systematic review: descriptive characteristics of the included studies

Based on the search criteria and search methodology, seven RCTs were included in this systematic review, of which four were used for the NMA (Table 1). The combined population of all four trials consisted of 3710 patients. The sample sizes ranged from 166 to 564 for the treatment arms and from 162 to 578 for the control arms. The inclusion criteria consisted of local and locally advanced PCa (pT2–4) without nodal involvement (pN0) or metastatic disease (cM0) with high-risk features such PSMs or ECE. NRG/RTOG 9601 and GETUG-AFU 16 included only patients without any previous radiotherapy (RT) and chemotherapy. Previous preoperative short-term ADT was allowed, except for GETUG-AFU 16. The primary outcome of the GETUG-AFU 16 and RTOG 0534 studies were PFS, while OS was the primary outcome in the NRG/RTOG 9601 study and MFS in the RADICALS-HD study. The median follow-up ranged from 8.2 yr (RTOG

Table 1 – Summary of prospectively randomized controlled studies using androgen deprivation therapy (ADT) with salvage radiotherapy (sRT) or adjuvant radiotherapy (aRT) in patients who underwent prostatectomy with locally advanced prostate cancer

	Study						
	NRG/RTOG 9601	GETUG-AFU 16	RADICALS-HD [a]	RTOG 0534	GETUG-AFU 17 sRT arm	RAVES sRT arm	RADICALS-RT sRT arm
Author	Shipley et al [6]	Carrie et al [8]	Parker et al [7,11,12]	Pollack et al [9]	Sargos et al	Kneebone et al	Parker et al [7,11,12]
Enrollment years	1998–2003	2006–2010	2008–2015	2008–2015	2008–2016	2009–2015	2007–2016
Study design	ADT vs no ADT in sRT	ADT vs no ADT in sRT	ADT 6 mo vs ADT 24 mo vs no ADT in sRT	ADT vs no ADT in sRT	sRT vs aRT	sRT vs aRT	sRT vs aRT
Duration of ADT (mo)	0 vs 24	0 vs 6	0 vs 6 vs 24	0 vs 6	6	0	0 vs 6 vs 24
Inclusion criteria	pT2-T3, positive surgical margins, extracapsular extension, N0, no previous CTx or RT, no previous ADT other than preoperative short-term ADT, PSA 0.2–4 ng/ml, CT and bone scans showed cM0, life expectancy >10 yr	pT2-pT4, pN0, no previous RT or ADT, PSA 0.2–2 ng/ml, life expectancy >10 yr	T2-T3, cM0, no previous RT, previous ADT <8 mo, ADT within 6 mo before surgery allowed, PSA <5 ng/ml	pT2-T3, Gleason <9, pN0, cM0, no previous CTx, no previous ADT >6 mo prior or 3 mo after RP, PSA 0.1–2 ng/ml	pT3a-pT4a, pN0, positive margins, and extracapsular extension	pT2-T3b, positive margins or extracapsular extension or seminal vesical invasion, postoperative PSA <0.1 ng/ml. No previous ADT, pelvic RT, nodal or distant metastases	PSA <0.2 ng/ml, M0, and at least one of the following: pT3–4, Gleason 7–10, positive margins, preoperative PSA 10 ng/ml
Performance status	Karnofsky >80	ECOG 0–1	NA	ECOG 0–1	ECOG 0–1	ECOG 0–1	NA
Primary endpoint	OS	PFS	MFS	PFS	EFS	BCRFS	FFDM
Definition of PSA progression	PSA ≥0.3 ng/ml over PSA nadir	PSA ≥0.5 ng/ml over PSA nadir	Not specified	PSA ≥2 ng/ml over PSA nadir	PSA ≥0.4 ng/ml at.6 mo after RT or ≥1 ng/ml at any time from randomization	PSA ≥0.4 ng/ml over PSA nadir	Not specified
Total number	760	742	492	1716	424	333	1396
Enrolled patients (control/treatment)	376/384	373/369	166/164/162	564/578	212	167	699
Median follow-up (yr)	13	9.3	9	8.2	6.25	6.1	4.9
Median age (Control/Treatment)	65 vs 65	66.8 (61.5–71.9) vs 69.5 (62.9–72.1)	65 (61–69) vs 66 (61–69) vs 67 (62–69)	64 (42–84) vs 64 (39–80)	64.0 (58.8–68.3)	64 (59–68)	65 (60–68)
Median PSA (control vs treatment)	0.6 vs 0.6 ng/ml	0.3 vs 0.3 ng/ml	0.23. (0.15–0.40) vs 0.20 (0.10–0.40) vs 0.21 (0.10–0.40)	0.32 (0.1–1.96) vs 0.40 (0.1–1.93)	0.24 (0.22–0.29)	NA	0.2 (0.1–0.3)
Gleason score 8–10 (control vs treatment)	17% vs 17%	11% vs 11%	16% vs 15% vs 13%	16% vs 17%	11%	15%	17%
Positive surgical margins (control vs treatment)	75% vs 75%	53% vs 47%	66% vs 66% vs 65%	51% vs 50%	NA	68%	63%
Duration of ADT (mo)	0 vs 24	0 vs 6	0 vs 6 vs 24	0 vs 6	6	0	0 vs 6 vs 24
Administered ADT	Bicalutamide	Goserelin	Bicalutamide or degarelix	Flutamide/bicalutamide + LHRH	Triptorelin	–	LHRH or bicalutamide
MFS (control vs treatment)	HR 0.63 (CI 0.46–0.87)	HR 0.73 (CI 0.54–0.98)	HR 1.01 (CI 0.57–1.76) [b] HR 0.95 (CI 0.54–1.68) [c]	HR 0.80 (CI 0.58–1.1)	NA	NA	Not mature
PFS (control vs treatment)	HR 0.51 (CI 0.42–0.61)	HR 0.54 (CI 0.43–0.68)	NA [b] NA [c]	HR 0.60 (CI 0.47–0.77)	Median EFS 120 mo, EFS defined as PFS	NA	NA
OS (control vs treatment)	HR 0.77 (CI 0.59–0.99)	HR 0.93 (CI 0.63–1.39)	HR 1.12 (CI 0.59–2.16) [b] HR 1.07 (CI 0.54–2.12) [c]	HR 0.87 (CI 0.59–1.29)	Median OS not reached	NA	Not mature

(*continued on next page*)

Table 1 (continued)

	Study						
	NRG/RTOG 9601	GETUG-AFU 16	RADICALS-HD [a]	RTOG 0534	GETUG-AFU 17 sRT arm	RAVES sRT arm	RADICALS-RT sRT arm
MFS in Gleason 8–10 sRT patients	HR 0.35 (CI 0.18–0.67)	HR 0.53 (CI 0.23–1.24)	HR 0.69 (CI 0.23–2.02) [b] HR 0.43 (CI 0.12–1.65) [c]	NA	NA	NA	NA
MFS in positive surgical margin patients	HR 0.57 (CI 0.38–0.81)	HR 0.69 (CI 0.44–1.08)	HR 0.67 (CI 0.36–1.25) [b] HR 0.76 (CI 0.41–1.40) [c]	NA	NA	NA	NA

BCRFS = biochemical recurrence–free survival; CI = confidence interval; CT = computed tomography; CTx = chemotherapy; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; FFDM = freedom from distant metastases; HR = hazard ratio; LHRH = luteinizing hormone-releasing hormone; MFS = metastasis-free survival; NA = not available; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy.

[a] Three-way randomization of the RADICALS-HD trial was included in this network meta-analysis.

[b] HR of 0 versus 6 mo of ADT.

[c] HR of 0 versus 24 mo of ADT.

0534) to 13 yr (NRG/RTOG 9601). The median age ranged from 64 yr (RTOG 0534) to 69.5 yr (GETUG-AFU 16). Moreover, the median PSA ranged from 0.21 ng/ml (RADICALS-HD) to 0.60 ng/ml (NRG/RTOG 9601). The proportion of patients with Gleason score ≥8 was highest in NRG/RTOG 9601 (17%) and lowest in GETUG-AFU 16 (11%). Similarly, highest proportions of patients with PSMs were reported in NRG/RTOG 9601 (75%) and lowest in GETUG-AFU 16 (47%).

3.2. *Comparison with sRT arms of the ARTISTIC MA*

ADT was given only in GETUG-AFU 17 (ADT6) and RADICALS-RT (no ADT vs ADT6 vs ADT24), whereas no ADT was given in RAVES. The exact proportions of the different ADT durations of the sRT arm (n = 699) of the RADICALS-RT trial were not provided. The sample sizes of the three included sRT arms varied from n = 167 (RAVES) to n = 699 (RADICALS-RT). The median follow-up for the three sRT arms ranged from 4.9 yr (RADICALS-RT) to 6.25 yr (GETUG-AFU 17), which were shorter than those of the four NMA studies, where the median follow-up ranged from 8.2 to 13 yr. The median PSA levels ranged from 0.2 ng/ml (RADICALS-RT) to 0.24 ng/ml (GETUG-AFU 17) at sRT, which were similar to the median PSA values of 0.21 ng/ml in RADICALS-HD, but not in NRG/RTOG 9601, which was 0.60 ng/ml at sRT. The proportion of patients with a Gleason score of ≥8 varied between 11% (GETUG-AFU 17) and 17% (RADICALS-RT), aligning with the proportions reported in the four NMA studies. Regarding PSMs, the proportions of patients ranged between 63% (RAVES) and 68% (RADICALS-RT), which were consistent with those observed in the four NMA studies.

Median MFS data were either unavailable or too immature for an analysis in all three studies. However, in the RADICALS-RT trial, the 9-yr MFS rate was 91% (CI 83–95%) for the sRT arm. MFS data were not reported in the GETUG-AFU 17 trial and not defined as an outcome in the RAVES trial. Regarding PFS (defined as event-free survival in GETUG-AFU 17 and as biochemical progression-free survival in RAVES), the median PFS in GETUG-AFU 17 was 120 mo, with a 5-y PFS rate of 90% (CI 85–94%) for the sRT arm versus 92% (CI 86–95%) for the aRT arm. In RAVES, the 5-yr PFS rate was 87% (CI 82–93%) for the sRT arm versus 86% (CI 81–92%) for the aRT arm. In RADICALS-RT, the PFS rate was 88% for the sRT arm versus 85% for the aRT arm, though no CI was provided.

Median OS was either not reached or too immature for assessment across all three studies. In GETUG-AFU 17, the 5-yr OS rate was 99% (CI 96–100%) for the sRT arm versus 96% (CI 92–98%) for the aRT arm. In RAVES, the 5-yr OS rate was 98% (CI 89–98%) for the sRT arm versus 99% (CI 97–100%) for the aRT arm. In RADICALS-RT, OS data were too immature to report. For all the above-mentioned survival rates, p values were not statistically significant if provided.

3.3. *Network meta-analysis: MFS*

In MFS analyses, both ADT6 and ADT24 were associated with significantly favorable MFS compared with no ADT at sRT (Fig. 2A). The highest MFS efficacy was recorded for

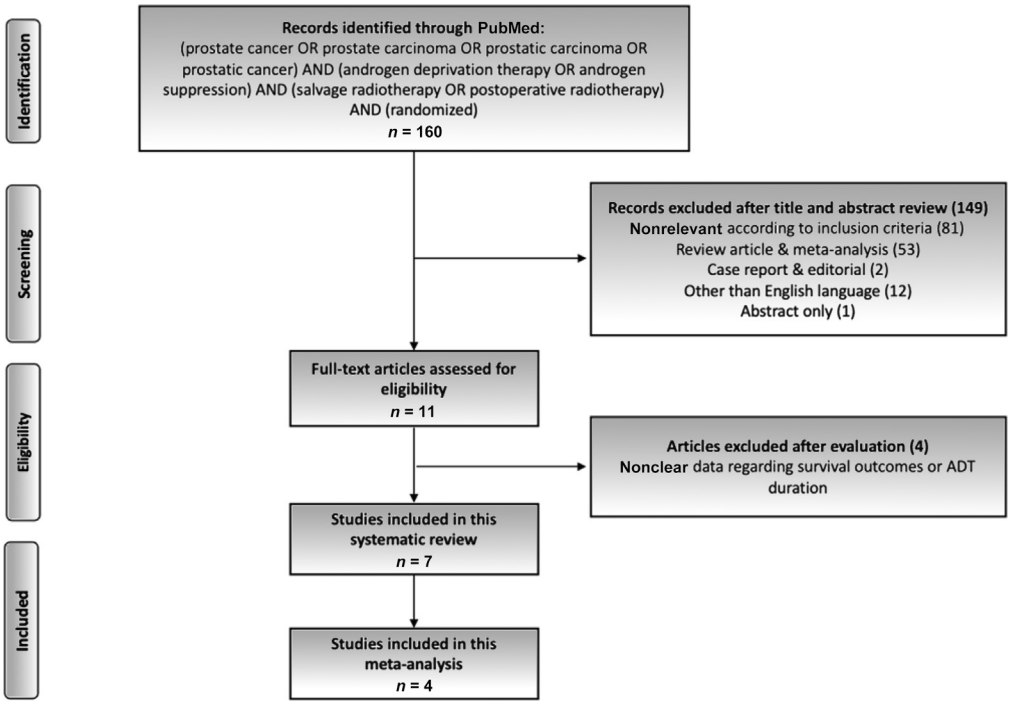


Fig. 1 – PRISMA flowchart depicting studies that were included for the network meta-analysis addressing metastasis-free, progression-free, and overall survival. ADT = androgen deprivation therapy; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

ADT24 (HR = 0.70, CI 0.53–0.92) versus no ADT. For ADT6, HR was 0.79 (CI 0.65–0.97), relative to no ADT. Similarly, NMA-derived ranking indicated a higher likelihood of providing maximal MFS benefit for ADT24 (P score = 0.88) compared with ADT6 (P score = 0.61) and no ADT (P score = 0.01).

3.4. *Network meta-analysis: PFS*

In PFS analyses, both ADT6 and ADT24 were associated with significantly better PFS relative to no ADT at sRT (Fig. 2B). Specifically, the highest PFS efficacy was recorded for ADT24 (HR = 0.51, CI 0.43–0.61), followed by ADT6 (HR = 0.57, CI 0.48–0.67), relative to no ADT. Similarly, NMA-derived ranking indicated a higher likelihood of providing maximal PFS benefit for ADT24 (P score = 0.90) versus ADT6 (P score = 0.60) versus no ADT (P score = 0.00).

3.5. *Network meta-analysis: OS*

In OS analyses, ADT6 and ADT24 were associated with more favorable OS compared with no ADT at sRT, but did not reach significance (Fig. 2C), with an HR of 0.80 recorded for ADT24 (CI 0.63–1.01) and 0.93 recorded for ADT6 (CI 0.72–1.20), relative to no ADT. Nonetheless, NMA-derived ranking indicated a higher likelihood of providing maximal OS benefit for ADT24 (P score = 0.88) compared with ADT6 (P score = 0.45) and no ADT (P score = 0.16).

3.6. *MFS in Gleason ≥8 and PSM sRT patients*

Subgroup analyses were performed for patients with Gleason score ≥8 and PSMs, addressing, respectively, 11–17% and 47–75% of patients of the four included studies. In both subgroups, highest MFS efficacy was recorded for ADT24 (HR = 0.36 and HR = 0.61, respectively), followed by ADT6 (HR = 0.48 and HR = 0.68, respectively), relative to no ADT (Fig. 3A). Similarly, NMA-derived ranking indicated a higher likelihood of providing maximal MFS benefit for ADT24 (P score = 0.91 and P score = 0.84, respectively) compared with ADT6 (P score = 0.59 and P score = 0.65, respectively) and no ADT (P score = 0.01 and P score = 0.00, respectively; Fig. 3B).

4. Discussion

We conducted a systematic review and NMA addressing the influence of concomitant ADT and its duration at sRT after RP with more mature data from several updates of the RADICALS-HD trial [7,11,12]. To date, no previous NMA has incorporated these updated results yet. Four RCTs were included in this NMA with different ADT durations (0 vs 6 vs 24 mo) to provide a rank order of their effectiveness in cancer-control outcomes. We initially hypothesized that different cancer-control outcomes may exist with respect to the administration and length of ADT, specifically in patients with high-risk features at RP. We tested these hypotheses and made several noteworthy observations.

First, baseline inclusion criteria varied slightly between the four NMA studies and the three additional sRT arms of the ARTISTIC MA. For example, all four NMA studies accepted previous preoperative short-term ADT, except GETUG-AFU 16. Regarding tumor staging, all studies included patients with pT2-pT3 PCa, while GETUG-AFU 16 also accepted pT4 PCa. High-risk features, including Gleason score ≥8, PSMs, and ECE, were only published explicitly in the NRG/RTOG 9601 trial. In contrast, the ARTISTIC MA included all three high-risk features mentioned, likely explaining the higher proportion of patients with these

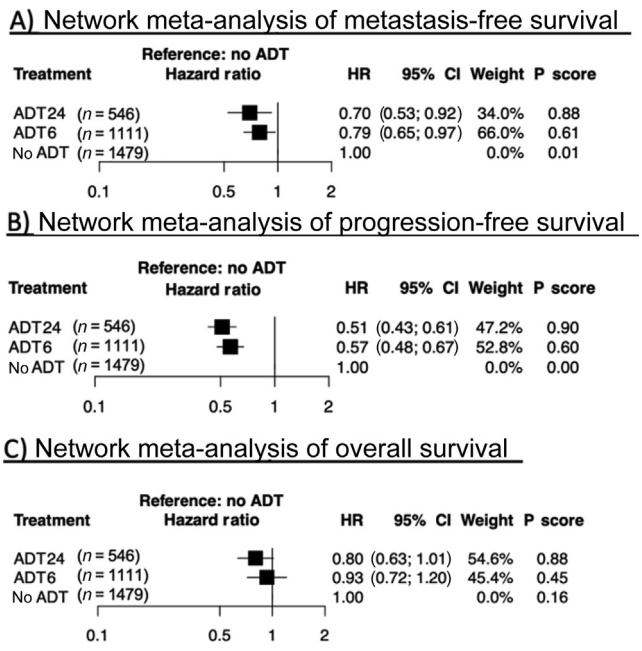


Fig. 2 – Forest plots of network meta-analyses comparing no ADT, ADT for 6 mo (ADT6) and ADT for 24 mo (ADT24) regarding (A) metastasis-free survival, (B) progression-free survival, and (C) overall survival. ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio.

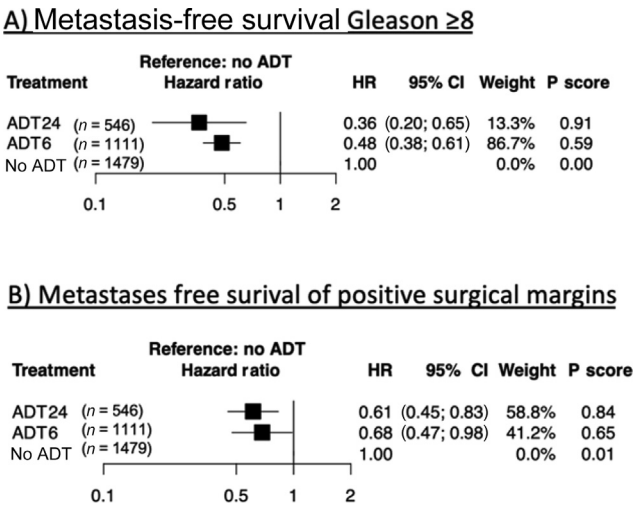


Fig. 3 – Forest plots of network meta-analyses comparing no ADT, ADT for 6 mo (ADT6), and ADT for 24 mo (ADT24) regarding metastasis-free survival of (A) Gleason >8 and (B) positive surgical margin subgroups. ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio.

high-risk features in these studies. Notably, NRG/RTOG 9601 had the highest proportion of patients with Gleason score ≥8 (17%) and PSMs (75%), but reported better MFS, PFS, and OS than the other studies, where worse outcomes may have been expected. This may suggest improved survival outcomes with concomitant ADT in D'Amico high-risk patients. However, NRG/RTOG 9601 had the longest median follow-up among all four NMA studies. Extended follow-up may have influenced the resulted HRs. Apart from these, other baseline characteristics were largely consistent across the studies.

Second, the current NMA offers a more comprehensive assessment of cancer-control outcomes compared with the results from the DADSPORT MA. Regarding MFS, ADT24 versus no ADT resulted in better survival outcomes than ADT6 versus no ADT (HR = 0.70 vs HR = 0.79). Moreover, ADT24 achieved highest ranking in the NMA-derived P score (0.88 > 0.61 > 0.01). These findings are consistent with the MFS outcomes observed in NRG/RTOG9601 and GETUG-AFU 16, where concomitant ADT was associated with improved MFS [6,8].

In terms of PFS, ADT24 versus no ADT also demonstrated better survival outcomes than ADT6 versus no ADT (HR = 0.50 vs HR = 0.57). ADT24 also achieved highest ranking in the NMA-derived P score (0.90 > 0.60 > 0.00). These results align with the PFS outcomes recorded in NRG/RTOG 9601, GETUG-AFU 16, and RTOG 0534, where concomitant ADT also contributed to improved PFS [6,8,9].

Regarding OS, ADT24 versus no ADT and ADT6 versus no ADT did not improve survival significantly, with ADT24 closely missing statistical significance with HRs of 0.80 (CI 0.63–1.01) and 0.93 (CI 0.72–1.20). However, ADT24 ranked highest in the NMA-derived P score (0.88 > 0.45 > 0.16). These findings are in agreement with those of the DADSPORT MA, where ADT did not improve OS, irrespective of its duration. The lack of significance may stem from the absence of differentiation between cancer-specific and other-cause mortality, as well as missing adjustments for therapeutic regimens in metastatic hormone-sensitive and castration-resistant PCa. Additionally, potential confounders such as comorbidities could not be fully accounted for, which may have impacted OS results.

Third, we performed subgroup analyses to evaluate the impact of different ADT durations in high-risk patient populations. In subgroups with Gleason score ≥8, both ADT24 versus no ADT and ADT6 versus no ADT were associated with notably improved and significantly better MFS (HR = 0.36 and HR = 0.48, respectively). Regarding NMA-derived ranking, ADT24 ranked highest (P score 0.91 > 0.59 > 0.00). Similarly, in subgroups with PSMs, both ADT24 versus no ADT and ADT6 versus no ADT were associated with significantly better MFS (HR = 0.61 and HR = 0.68, respectively). Again, ADT24 ranked highest (P score 0.84 > 0.65 > 0.01) in the NMA-derived ranking. These findings underscore the potential benefit of longer ADT durations in these high-risk populations. These findings are particularly of interest, since these patients are at the highest risk of biochemical recurrence, when refusing aRT in clinical practice.

Fourth, we compared the study cohorts of the current NMA (Table 1) with those of the three sRT arms of the ARTISTIC MA (Table 1) to provide further insights into survival outcomes, as the patient populations in both MA sets received concomitant ADT with sRT or sRT alone. In RADICALS-RT, MFS was improved with concomitant ADT, similar to GETUG-AFU 16 and NRG/RTOG 9601. The 5-yr PFS rates were comparable with those of RAVES and RADICALS-RT, as well as of GETUG-AFU 16 and RTOG 0534. GETUG-AFU 17 and RAVES reported 5-yr OS rates of 99% and 98% in the sRT arms. Similarly, GETUG-AFU 16 and NRG/RTOG9601 also reported minimally improved 10- and 12-yr OS in sRT with ADT6 ver-

sus sRT. However, the magnitude of OS data should be interpreted with caution and not be directly compared due to differences in follow-up time.

The above-mentioned similarities of MFS and PFS between the four NMA studies and the three studies from the ARTISTIC MA strongly indicate the potential survival benefit of concomitant ADT with sRT. Specifically, the consistent improvements in MFS and PFS across these studies suggest that the addition of ADT, whether for 6 or 24 mo, may play a critical role in delaying disease progression and reducing the incidence of distant metastasis in patients undergoing sRT. However, it is important to note that differences in OS outcomes were not significant in the current NMA. Notably, when comparing GETUG-AFU 17 and RAVES, both studies showed similar 5-yr OS rates despite differing treatment regimens. In GETUG-AFU 17, patients received ADT6 along with sRT, while patients in RAVES did not receive ADT with sRT. Despite this, there was no substantial difference in 5-yr OS between the two cohorts, suggesting that the addition of ADT may not significantly affect OS within the short-term follow-up period examined in these trials.

Despite the demonstrated survival benefits of ADT24, its adverse effects should be considered carefully [30,31]. Notably, ADT has been linked to an increased risk of diabetes, cardiovascular disease, kidney injury, and bone loss, as well as sexual dysfunction and changes in body composition, including weight gain, muscle mass reduction and gynecomastia, particularly with prolonged ADT durations and significantly impacted patients' quality of life [31–33]. Furthermore, prolonged ADT not only extends the duration of these symptoms, but may also lead to delayed or incomplete recovery of testosterone levels following cessation of ADT [34,35]. As such, ADT24 may not be appropriate for all patients requiring sRT after RP, but should rather be reserved for high-risk subgroups. In the current NMA, patients with a Gleason score of $\geq$8 derived the greatest benefit from ADT24, followed by those with PSMs and the overall cohort in terms of MFS (HR = 0.36, 0.61, and 0.70, respectively). Accordingly, ADT6 may be more suitable for patients without high-risk factors at sRT, whereas ADT24 should be considered for high-risk populations. Nevertheless, thorough patient counseling regarding the potential adverse effects, particularly prolonged and incomplete testosterone recovery, is essential.

Our study has several limitations that should be considered. The included studies varied in the inclusion criteria, treatment protocols, and follow-up durations, introducing certain heterogeneity, for which NMAs can unfortunately not statistically adjust and which may affect long-term survival data and overall result interpretation. Missing reported RCT data on clinical variables such as PSA levels, T stage, and N stage limited further subgroup analyses, which can only be aggregated through novel study data. Additionally, the definition of PSA progression varies slightly across the included studies (Table 1). While these differences are minor, it is important to acknowledge this as a limitation of the current NMA. Additionally, we included the three-way randomization of the RADICALS-HD trial (n = 492) in our NMA, despite its smaller sample size compared with the two-way randomization (n = 1480 and n = 1523) due to potential for crossovers (Fig. 4). However, the smaller cohort size may have influenced the robustness of the results. Moreover, in NRG/RTOG 9601

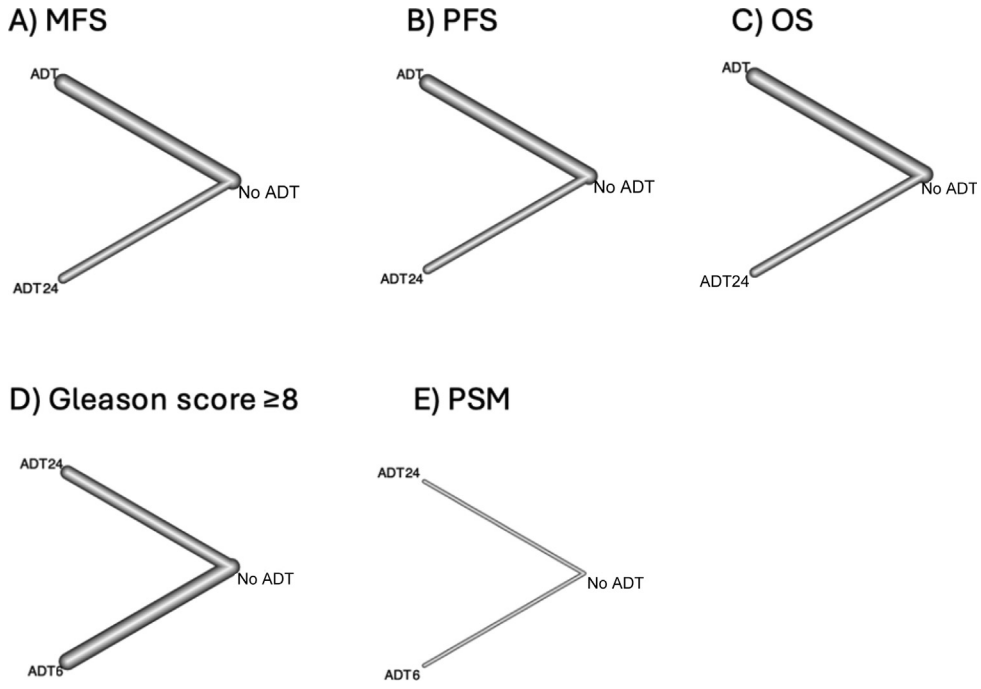


Fig. 4 – Network meta-analysis graphs for each of the overall cohort regarding (A) metastasis-free survival (MFS), (B) Progression-free survival (PFS), and (C) overall survival (OS), as well as MFS analyses in subgroups with (D) Gleason score ≥8 and (E) PSM. ADT = androgen deprivation therapy; ADT6 = ADT for 6 mo; ADT24 = ADT for 24 mo; PSM = positive surgical margin.

(study period: 1998–2003), bicalutamide was administered as an antihormonal therapeutic agent and the standard of care. Despite differences between ADT and bicalutamide, the latter was often grouped within the broader ADT spectrum in previous studies [36,37]. Although it is important to acknowledge the differences between ADT and bicalutamide, we deem it suitable in the context of this NMA to group both the agents due to their shared effect of reducing androgen-driven tumor progression. Unfortunately, no statistical method is able to adjust for these differences in baseline outcomes or concomitant treatments, and it is crucial to interpret the findings in these lights. However, when we performed additional sensitivity analyses excluding NRG/ROG9601 patients, a similar trend was observed for our overall study outcomes.

Taken together, the current NMA provides the most comprehensive evaluation of the available and recently published data, offering additional information to the currently underexplored comparison between ADT6 and ADT24. The NMA revealed that ADT24 versus no ADT outperformed ADT6 versus no ADT regarding MFS and PFS, and consistently ranked higher in terms of NMA-derived ranking. However, the results were insignificant for OS due to possible restrictions such as missing differences between cancer-specific and other-cause mortality. Subgroup analyses further demonstrated a greater MFS benefit of ADT24 in high-risk populations with Gleason scores $\geq$8 or PSMs; ADT24 provided greater MFS benefits than ADT6, highlighting advantages of longer ADT durations in optimizing cancer control in these groups.

5. Conclusions

The current NMA provides robust evidence supporting the addition of ADT to sRT. Specifically, a 24-mo duration of ADT is associated with significantly improved MFS and PFS, relative to no ADT. Although OS was improved with ADT24 compared with ADT6 versus no ADT in the P score ranking, respective HRs for OS did not reach statistical significance. Notably, patients with Gleason scores $\geq$8 and PSMs benefit from prolonged ADT, suggesting a more favorable treatment outcome in these high-risk subgroups.

Author contributions: Quynh Chi Le had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wenzel, Mandel, Le.

Acquisition of data: Le, Wenzel, Siech, Hoeh.

Analysis and interpretation of data: Wenzel, Mandel, Graefen, Maurer, Saad, Le.

Drafting of the manuscript: Le, Wenzel, Mandel.

Critical revision of the manuscript for important intellectual content: Saad, Preisser, Tilki, Graefen, Maurer, Kriegmair, Karakiewicz, Chun, Siech, Hoeh.

Statistical analysis: Le, Wenzel, Mandel.

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Appendix A. Supplementary material

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References

[1] Fukuda I, Aoki M, Kimura T, Ikeda K. Radiotherapy after radical prostatectomy for prostate cancer: clinical outcomes and factors influencing biochemical recurrence. Ir J Med Sci 2023;192:2663–71.
[2] Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S. Management of biochemical recurrence after primary curative treatment for prostate cancer: a review. Urol Int 2018;100:251–62.
[3] Morgan TM, Boorjian SA, Buyyounouski MK, et al. Salvage therapy for prostate cancer: AUA/ASTRO/SUO guideline part II: treatment delivery for non-metastatic biochemical recurrence after primary radical prostatectomy. J Urol 2024;211:518–25.
[4] Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96–02/AUO AP 09/95 trial. Eur Urol 2014;66:243–50.
[5] Sigg S, Arnold W, Grossmann NC, et al. Why do men reject adjuvant radiotherapy following radical prostatectomy? A systematic survey. Urol Int 2024;108:211–8.
[6] Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376:417–28.
[7] Parker CC, Clarke NW, Cook AD, et al. Adding 6 months of androgen deprivation therapy to postoperative radiotherapy for prostate cancer: a comparison of short-course versus no androgen deprivation therapy in the RADICALS-HD randomised controlled trial. Lancet 2024;403:2405–15.
[8] Carrie C, Magné N, Burban-Provost P, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. Lancet Oncol 2019;20:1740–9.

[9] Pollack A, Karrison TG, Balogh AG, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet 2022;399:1886–901.
[10] UroToday. ESMO 2022: Duration of Androgen Suppression with Post-Operative Radiotherapy (DADSPORT): a collaborative meta-analysis of aggregate data. https://www.urotoday.com/conference-highlights/esmo-2022/esmo-2022-prostate-cancer/139430-esmo-2022-duration-of-androgen-suppression-with-post-operative-radiotherapy-dadsport-a-collaborative-meta-analysis-of-aggregate-data.html.
[11] Parker CC, Clarke NW, Cook AD, et al. Randomised trial of no, short-term, or long-term androgen deprivation therapy with postoperative radiotherapy after radical prostatectomy: results from the three-way comparison of RADICALS-HD (NCT00541047). Eur Urol 2024;86:422–30.
[12] Parker CC, Kynaston H, Cook AD, et al. Duration of androgen deprivation therapy with postoperative radiotherapy for prostate cancer: a comparison of long-course versus short-course androgen deprivation therapy in the RADICALS-HD randomised trial. Lancet 2024;403:2416–25.
[13] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol 2021;134:178–89.
[14] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
[15] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84.
[16] Burdett S, Fisher D, Parker CC, et al. LBA64 Duration of androgen suppression with post-operative radiotherapy (DADSPORT): A collaborative meta-analysis of aggregate data. Ann Oncol 2022;33:S1428–9.
[17] Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet (Lond Engl) 2020;396:1422.
[18] Hoeh B, Garcia CC, Wenzel M, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer: updated network meta-analysis stratified by disease volume. Eur Urol Focus 2023;9:838–42.
[19] Hoeh B, Wenzel M, Tian Z, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer patients: an updated network meta-analysis including ARANOTE data. Eur Urol Focus. In press. https://doi.org/10.1016/j.euf.2024.11.004.
[20] Mandel P, Hoeh B, Wenzel M, et al. Triplet or doublet therapy in metastatic hormone-sensitive prostate cancer patients: a systematic review and network meta-analysis. Eur Urol Focus 2023;9:96–105.
[21] Wenzel M, Nocera L, Collà Ruvolo C, et al. Overall survival and adverse events after treatment with darolutamide vs. apalutamide vs. enzalutamide for high-risk non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis. Prostate Cancer Prostatic Dis 2022;25:139–48.
[22] Wenzel M, Würnschimmel C, Nocera L, et al. Overall survival after systemic treatment in high-volume versus low-volume metastatic hormone-sensitive prostate cancer: systematic review and network meta-analysis. Eur Urol Focus 2022;8:399–408.
[23] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[24] Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Mak 2013;33:607–17.
[25] van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth. Methods 2012;3:285–99.
[26] Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol 2010;10:54.
[27] Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15:58.
[28] Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.
[29] R: The R project for statistical computing. https://www.r-project.org/.
[30] Shimabukuro T, Ohmi C, Nagamitsu R, Shiraishi K, Matsuyama H. Adverse effects of androgen deprivation therapy on patients with prostate cancer and its effect on overall survival. Jpn J Urol 2021;112:81–8 (In Japanese).
[31] Nguyen PL, Alibhai SMH, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol 2015;67:825–36.
[32] Sun M, Choueiri TK, Hamnvik OPR, et al. Comparison of gonadotropin-releasing hormone agonists and orchiectomy: effects of androgen-deprivation therapy. JAMA Oncol 2016;2:500–7.
[33] Wirth MP, See WA, McLeod DG, et al. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. J Urol 2004;172(5 Pt 1):1865–70.
[34] Nascimento B, Miranda EP, Jenkins LC, Benfante N, Schofield EA, Mulhall JP. Testosterone recovery profiles after cessation of androgen deprivation therapy for prostate cancer. J Sex Med 2019;16:872–9.
[35] Ho AY, Li EV, Bennett R, et al. Testosterone recovery after androgen deprivation therapy. Urol Oncol 2025;43:65.e1–e8.
[36] Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314–25.
[37] Hussain M, Tangen CM, Thompson IM, et al. Phase III intergroup trial of adjuvant androgen deprivation with or without mitoxantrone plus prednisone in patients with high-risk prostate cancer after radical prostatectomy: SWOG S9921. J Clin Oncol 2018;36:1498–504.