Efficacy characteristics of different therapeutic modalities for locally advanced prostate cancer: a Bayesian network meta-analysis of randomized controlled trials

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Background: Though previous studies have investigated the efficacy characteristics of several different therapeutic modalities for locally advanced prostate cancer (LAPCa) patients, the available results remained unestablished. Therefore, the aim of this meta-analysis was conducted to clarify such differences.

Methods: The online PubMed, EMBASE and Web of Science were comprehensively searched for relevant studies published before September 1st, 2017, and eventually eleven relevant studies met the inclusion criteria. The hazard odds ratios (HRs) with 95% credible interval (CI) were utilized to evaluate the efficacy characteristics of several different therapeutic modalities for LAPCa patients by Markov chain Monte Carlo methods.

Results: Five different therapeutic modalities were ultimately enrolled to shed light on the efficacy characteristics for LAPCa patients and seven different clinical outcomes were finally analyzed in this study. The cumulative rank probability of overall survival (OS) or cancer-specific survival (CSS) from best to worst was radiotherapy (RT) + orchiectomy, RT + long-term androgen deprivation therapy (LTADT), RT + short-term androgen deprivation therapy (STADT), LTADT and RT; RT + LTADT, RT + orchiectomy, RT + STADT, LTADT and RT, respectively. Meanwhile, in the terms of progression-free survival (PFS), biochemical failure rate (BFR), disease-free survival (DFS), local progression rate (LPR) and metastasis rate (MR), RT + LTADT as well as RT + STADT had a higher, whereas RT alone or LTADT had a relatively lower treatment effect.

Conclusions: All in all, our results indicated that RT + LTADT or RT + orchiectomy was among the best two therapeutic regimens in the prognostic aspects of the patients with LAPCa. Furthermore, in consideration of reducing invasive treatment of eligible patients, RT + LTADT could yield better survival benefit of LAPCa patients, compared with others. In addition, the results of our analysis might provide a reference in the clinical selection. Larger sample sizes of strictly designed randomised controlled trials (RCTs) were wanted to validate our findings.

Keywords: Locally advanced prostate cancer (LAPCa); androgen deprivation therapy (ADT); salvage radiotherapy (salvage RT); randomized controlled trials (RCTs); network meta-analysis

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Introduction

Prostate cancer (PCa) is one of the most commonly diagnosed malignancy in elderly men worldwide (1). In recent decades, along with the development of the elevated serum prostate-specific antigen (PSA) level measurement, abnormal digital rectal examination (DRE) finding and transrectal ultrasonography (TRUS), the incidence and detection rate of PCa was continuously increasing. Furthermore, it had become the first malignancy of males and the second leading cause of cancer-specific death in the United States (1,2). Therefore, there is an urgent need to find a better therapeutic method of PCa.

Recently, the progress of various treatment modalities has greatly improved the surgical and oncological outcomes of patients with PCa (3). Currently, radical radiotherapy (RT) or radical prostatectomy remained to be the standard treatment for most patients with localised and locally advanced PCa (LAPCa) (4,5). However, one third of PCa patients might suffer biochemical relapse with a rise in serum PSA after radical prostatectomy without salvage treatment (6). Thus, combination therapy with androgen deprivation therapy (ADT) and/or salvage RT had been extensively investigated to improve the symptoms and prognosis in patients with PCa. Although some high-quality phase III clinical trials have performed to compare different combined therapeutic modalities of LAPCa, experts have not yet reached a consensus (7-11).

To explore the best comprehensive management model of patients with LAPCa, several head-to-head meta-analyses had been performed to clarify this point of view in the past years (12-14). However, these studies could merely contain two trial arms and their results remained inconclusive or unclear. Hence, this network meta-analysis was conducted to comprehensively evaluate the relative efficacy of different therapeutic modalities while respecting randomization (15,16). Ultimately, five different therapeutic modalities were enrolled: RT, long-term ADT (LTADT), RT + short-term ADT (RT + STADT), RT + LTADT and RT + orchiectomy; and seven different clinical outcomes were analyzed: overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), cancer-specific survival (CSS), local progression rate (LPR), distant failure/metastasis rate (MR) and biochemical failure rate (BFR). The results of our analysis could provide a hierarchy of five different regimens, and based on which, clinician could choose an optimal therapeutic paradigm.

Methods

Literature search

A systematic literature searched on PubMed, EMBASE and Web of Science was performed to identify all published potentially appropriate studies until September 1st, 2017. The search strategy consisted of seven parts (OS, DFS, PFS, CSS, LPR, distant failure/MR and BFR), using the following keywords for searching in combination with Medical Subject Headings (MeSH) terms: "locally advanced prostate cancer (or LAPCa)", "hormone blockade", "endocrine treatment", "androgen deprivation therapy (or ADT)", "radiotherapy (or RT)", "orchiectomy", "Radical prostatectomy or RP" and randomized controlled trials (RCTs). Besides, additional publications were identified manually, when we searched relevant reviews and the reference list of original articles. Furthermore, because of the data from previously published studies, ethical approval and informed consent were not required.

Study selection criteria

Articles had to meet the following criteria were included in this meta-analysis: (I) RCTs (prospective or retrospective); (II) the language of the article was limited to English; (III) patients were diagnosed as LAPCa; (IV) the included studies should address the survival of therapeutic modalities of LAPCa by assessing OS or CSS or PFS or DFS or LPR or MR or BFR.

In addition, studies would be excluded if they meet the following criteria: (I) the language of the article was non-English; (II) the publication type of study were reviews or letters or case reports or comments or editorials; (III)

Table 1 Characteristics of individual studies included in the meta-analysis

Year	Surname	Study name and/or trial number	Treatment arm [number]	Control arm [number]	Primary end point
2016	Carrie C	GETUG-AFU 16, NCT00423475	RT + STADT [369]	RT [374]	PFS
2011	Jones CU	RTOG-9408, NCT00002597	RT + STADT [987]	RT [992]	OS, CSS, BFS, DFS, LPR, MR
2011	Warde P	ECOG-JPR03, NCT00002633	RT + LTADT [603]	LTADT [602]	OS, CSS, PFS
2010	Bolla M	EORTC-22863, NCT00849082	RT + LTADT [207]	RT [208]	OS, CSS, PFS
2009	Widmark A	SPCG-7/SFUO-3, ISRCTN01534787	RT + LTADT [436]	LTADT [439]	OS, CSS, BFS
2009	Bolla M	EORTC-22961, NCT00003026	RT + LTADT [487]	RT + STADT [483]	OS
2008	Roach M 3rd	RTOG 8610	RT + STADT [224]	RT [232]	OS, CSS, BFS, DFS, LPR, MR
2008	D'Amico AV	NA	RT + STADT [104]	RT [102]	OS
2008	Horwitz EM	RTOG 92-02	RT + LTADT [758]	RT + STADT [763]	OS, DFS, BFS, DFS, LPR, MR
2006	Granfors T	NA	RT + orchiectomy [45]	RT [46]	OS, CSS
2005	Denham JW	TROG 96-01	RT + STADT [267]	RT [270]	CSS, BFS, DFS, MR

NA, not available; RT, radiotherapy; LTADT, long-term androgen deprivation therapy; STADT, short-term androgen deprivation therapy; OS, overall survival; CSS, cancer-specific survival; PFS, progression-free survival; BFR, biochemical failure rate; DFS, disease-free survival; LPR, local progression rate; MR, metastasis rate.

non-sufficient and unavailable data could extracted for our analyses in these articles; (IV) duplication of previous publications.

Data extraction

Two blind reviewers (ZQ Qin and Y Wang) individually extracted all available data involved in eligible references according to the study selection criteria mentioned above. Any disagreement was resolved by consensus and discussion. If consensus could not be reached, a third investigator (YX Zheng) acted as an arbitrator until a consensus was reached. The following information was recorded for each selected study: name of first author, year and journal of publication, study name and/or trial number, management model in each clinical trial arms and number of patients and primary endpoints of each study. All of the aforementioned data were comprehensively presented in *Tables 1*,*2*.

Risk of bias assessment

Two investigators independently evaluated the quality of each reference according to the Cochrane Handbook (17). In addition, the quality of eligible studies was evaluated the potential source of bias as follows: (I) random sequence generation; (II) allocation concealment; (III) blinding of participants and personnel; (IV) blinding of outcome assessment; (V) incomplete outcome data; (VI) selective reporting; (VII) other bias. The judgments were graded as a low, high or unclear risk of bias (http://www.cochrane-handbook.org). Ultimately, the results presented as a risk of bias summary and a risk of bias graph (*Figures 1*,*2*).

Statistical analysis

A pair-wise meta-analysis was performed to make direct comparison between two PE oral drugs, and the results were evaluated by the hazard ratio (HR) with corresponding 95% credible interval (CI). I-square test was adopted to assess the heterogeneity and I^2>50% was considered as existence of significant heterogeneity. Z test was performed to determine the statistical significance and a P value of <0.05 was considered statistically significant. All results were reported with 95% CIs. The HR and 95% CI: were extracted from the Kaplan-Meier curve in the study with Engauge Digitizer 4.1 and Tierney JF's methods where no HR was provided in published data (18). In addition, all above statistical analyses in traditional meta-analysis were conducted by Stata software (version 12.0; StataCorp LP, College Station, TX, USA).

We used Der Simonian-Laird random-effects model in conventional pairwise meta-analysis (19). To incorporate

Table 2 Prognostic data of individual studies included in the meta-analysis

Author	Treatment arm	Control arm	HR	95% CI
Overall survival (OS)				
Jones CU	RT + STADT	RT	1.17	1.01–1.35
D'Amico AV	RT + STADT	RT	1.8	1.1–2.9
Roach M 3rd	RT + STADT	RT	1.18	0.96–1.46
Bolla M	RT + LTADT	RT	1.67	1.25–2.22
Granfors T	RT + orchiectomy	RT	1.69	0.85–3.33
Warde P	RT + LTADT	LTADT	1.29	1.02–1.64
Widmark A	RT + LTADT	LTADT	1.47	1.12–1.92
Horwitz EM	RT + LTADT	RT + STADT	1.08	0.95–1.24
Bolla M	RT + LTADT	RT + STADT	1.42	1.09–1.85
Time to progress (TTP)/progression-free survival (PFS)				
Carrie C	RT + STADT	RT	PFS: 2.0	PFS: 1.52–2.63
Bolla M	RT + LTADT	RT	PFS: 2.38	PFS: 1.81–3.03
Warde P	RT + LTADT	LTADT	TTP: 3.33	TTP: 2.56–4.35
Cancer-specific survival (CSS)				
Jones CU	RT + STADT	RT	1.86	1.27–2.74
Denham JW	RT + STADT	RT	1.79	1.02–3.13
Roach M 3rd	RT + STADT	RT	1.52	1.11–2.08
Bolla M	RT + LTADT	RT	2.63	1.67–4.17
Granfors T	RT + orchiectomy	RT	1.92	0.96–3.85
Warde P	RT + LTADT	LTADT	1.85	1.28–3.70
Widmark A	RT + LTADT	LTADT	2.27	1.52–3.33
Disease-free survival (DFS)				
Jones CU	RT + STADT	RT	1.38	1.22–1.56
Denham JW	RT + STADT	RT	1.79	1.45–2.22
Roach M 3rd	RT + STADT	RT	1.91	1.58–2.322
Horwitz EM	RT + LTADT	RT + STADT	1.54	1.38–1.72
Local progression rate (LPR)				
Jones CU	RT + STADT	RT	1.5	1.17–1.93
Roach M 3rd	RT + STADT	RT	1.21	0.92–1.59
Horwitz EM	RT + LTADT	RT + STADT	1.52	1.17–1.98
Distant failure/metastasis rate (MR)				
Jones CU	RT + STADT	RT	1.45	1.03–2.06
Denham JW	RT + STADT	RT	1.49	1.01–2.22
Roach M 3rd	RT + STADT	RT	1.48	1.12–1.95
Horwitz EM	RT + LTADT	RT + STADT	1.73	1.36–2.19
Biochemical failure rate (BFR)				
Jones CU	RT + STADT	RT	1.74	1.48–2.04
Denham JW	RT + STADT	RT	2.38	1.61–3.57
Roach M 3rd	RT + STADT	RT	1.85	1.49–2.30
Widmark A	RT + LTADT	LTADT	6.25	5–8.33
Horwitz EM	RT + LTADT	RT + STADT	1.84	1.61–2.10

HR, hazard ratio; CI, credible interval; RT, radiotherapy; LTADT, long-term androgen deprivation therapy; STADT, short-term androgen deprivation therapy.

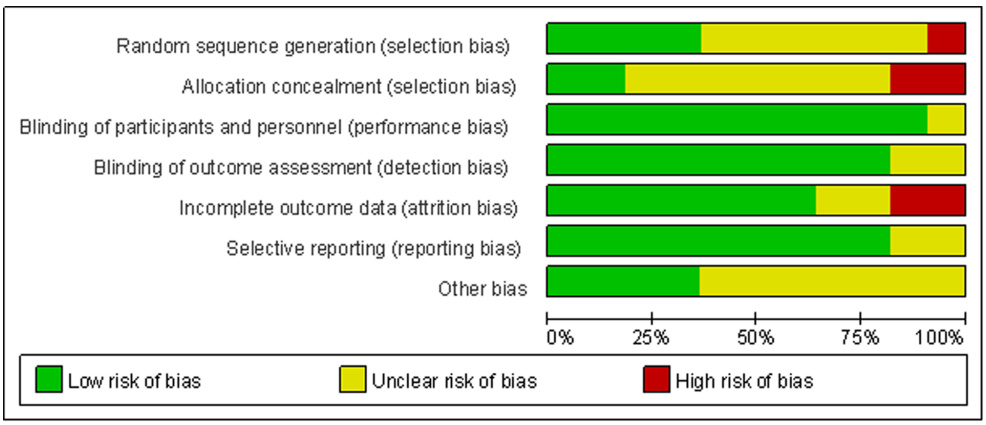

Figure 1 Risk of bias graph. Review author's judgement for each risk of bias item presented as percentages of all included studies.

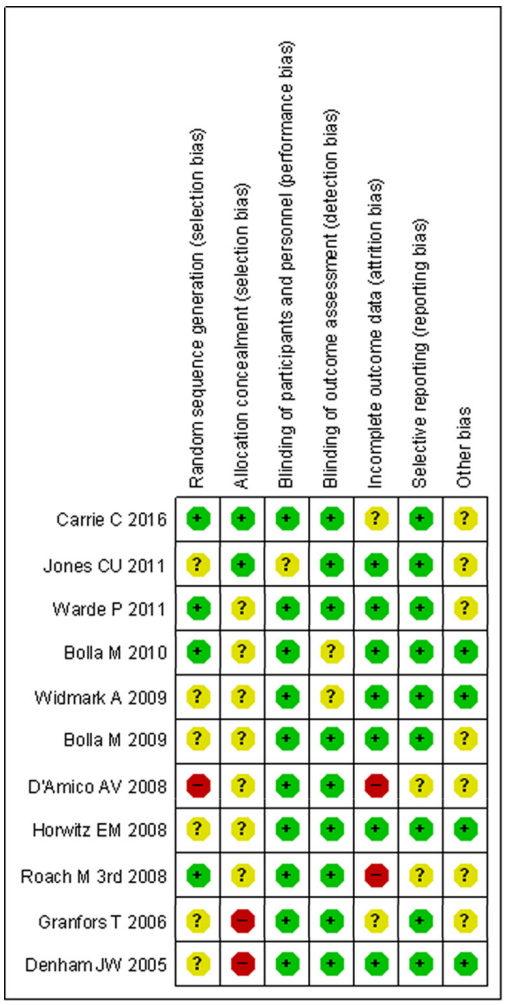

Figure 2 Risk of bias summary. Review author's judgement for each risk of bias item for individual studies.

direct and indirect evidence into a single comparison, we performed a random-effects network meta-analysis was conducted based on a Bayesian framework and used Markov chain Monte Carlo methods to obtain pooled estimates by using package "gemtc" version 0.8.2 of R-3.4.0 software (16,20). Next, network plots were generated to demonstrate the comparison scheme for each LAPCa therapeutic modalities. The HR with 95% CI was calculated by Markov chain Monte Carlo methods. The function mtc.run would be used to generate samples by means of the Markov chain Monte Carlo sampler. We set 10,000 simulations for each chain as the "burn-in" period, yielding 50,000 iterations to obtain the HR of model parameters, when three Markov chains run simultaneously. The model convergence was accessed by Brooks-Gelman-Rubin plots method, trace plot and density plot (*Figures S1,S2*) (21). Meanwhile, rank probabilities would be calculated, which indicated the hierarchy of each treatment. Based on the results of rank probabilities, clinical surgeons could make the choice which treatment would be best, second and so on (22). The matrix as well as the plot of the treatment rank probabilities would be provided by the "gemtc" package simultaneously.

Besides, the pooled HRs from network meta-analysis and traditional meta-analysis were used to estimate the consistency between direct and indirect comparisons. To access the inconsistency, the node-splitting method was applied by reporting its Bayesian P value, by means of separating the evidence concerning certain comparison into direct and indirect evidence, when a loop connecting three arms existed (23). Last but not least, the mtc.anohe command of the "gemtc" package would be utilized

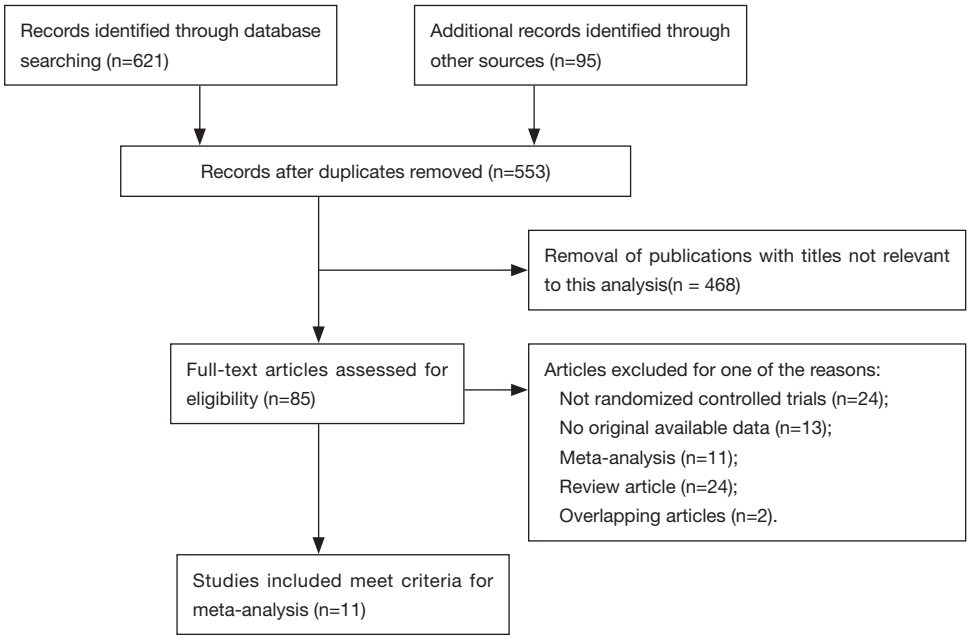

Figure 3 The flow diagram of the literature selection process.

to evaluate the global heterogeneity on the bias of the magnitude of heterogeneity variance parameter I^2.

Results

A total of 716 studies identified by previous search strategy were enrolled in the present network meta-analysis. Then, full text screen was carried out and 468 studies were excluded since they were reviews, duplicate reports and conference articles. Seventy-four articles were disregarded after titles and abstracts filtering. Finally, 11 articles including a total 8,998 patients were included in our study for further evaluation, which had been accrued between March 2002 and February 2017 (7-10,24-30). This included studies covered five different therapeutic modalities: RT, LTADT, RT + STADT, RT + LTADT, RT + orchiectomy; and seven different clinical outcomes: OS, DFS, PFS, CSS, LPR, MR and BFR. All of these enrolled studies were RCTs and the quality of evidence was evaluated by the Cochrane Handbook (*Figures 1,2*).The flowchart of literature search and selection procedure was shown in *Figure 3*. In addition, the network structure diagrams were displayed in *Figure 4*. Meanwhile, the thicknesses of the lines were proportional to the number of comparisons, and the diameters of the circles were proportional to the number of treatments included in the network meta-analysis.

OS

The results of OS were calculated by 9 studies including 5 therapeutic modalities (RT, LTADT, RT + STADT, RT + LTADT and RT + orchiectomy) and the network structure diagrams were displayed in *Figure 4A*. The efficacy of different therapeutic paradigms for HRs and corresponding 95% CIs was detailed in *Figure 5*. As indicated in the result, RT + LTADT showed better survival benefit, compared with RT or LTADT (HR =0.66, 95% CI: 0.47–0.84; HR =0.73, 95% CI: 0.54–0.99, separately); RT + STADT displayed a longer OS, compared with RT (HR =0.79, 95% CI: 0.61–0.97). The cumulative rank probability of five therapeutic regimens from best to worst was RT + orchiectomy > RT + LTADT > RT + STADT > LTADT > RT (*Figure 6*). In the above-mentioned study, we found that all Bayesian P values of node-splitting method were greater than 0.05 in terms of OS, which indicated that the direct and indirect evidence was consistent (*Figure 7*).

CSS

A total of seven studies including 5 therapeutic modalities (RT, LTADT, RT + STADT, RT + LTADT and RT + orchiectomy) contributed to the analysis of CSS. The network structure diagrams were presented in *Figure 4B*

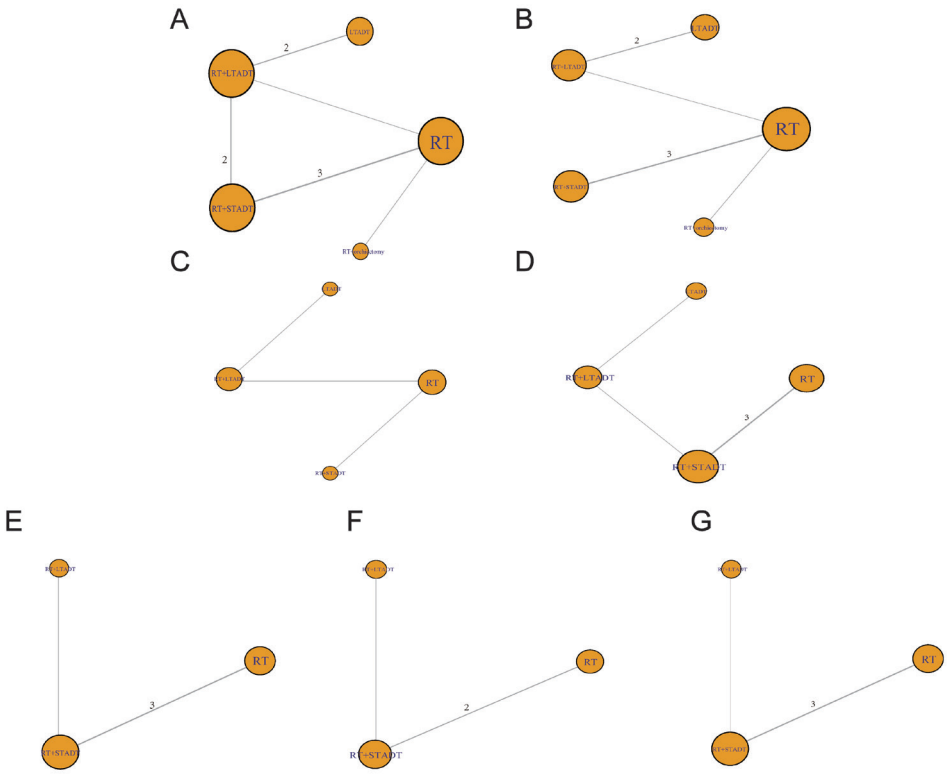

Figure 4 Network structure diagrams. (A) OS; (B) CSS; (C) DFS; (D) BFR; (E) PFS; (F) LPR; (G) MR. The thicknesses of the lines were proportional to the number of comparisons; the diameters of the circles were proportional to the number of treatments. OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; BFR, biochemical failure rate; PFS, progression-free survival; LPR, local progression rate; MR, metastasis rate.

and the efficacy of five therapeutic paradigms was shown in *Figure 5B*. Meanwhile, RT + LTADT showed better survival benefit, compared with RT or LTADT (HR =0.38, 95% CI: 0.19–0.78; HR =0.48, 95% CI: 0.29–0.80, respectively); RT + STADT displayed a longer CSS, compared with RT (HR =0.59, 95% CI: 0.39–0.88). The cumulative rank probability from first to last was RT + LTADT > RT + orchiectomy > RT + STADT > LTADT > RT (*Figure 6B*). Due to the absence of a loop connecting three arms, the node-splitting method was not calculated.

DFS or BFR

The efficacy of four different therapeutic modalities (RT, LTADT, RT + LDADT and RT + STADT) was also compared in the terms of PFS and BFR, and network structure diagrams were presented in *Figure 4C,D*, separately. The efficacy of four therapeutic paradigms for HRs and corresponding 95% CIs was presented in *Figure 5C,D*. We could easily found that, in the case of BFR, RT + LTADT showed longer survival, compared with RT or LTADT (HR =0.29, 95% CI: 0.084–0.91; HR =0.16, 95% CI: 0.057–0.44, respectively); RT + STADT displayed better survival, compared with RT (HR =0.53, 95% CI: 0.28–0.93). The results of cumulative probability sorting were RT + LTADT > RT + STADT >RT > LTADT and RT + LTADT > RT + STADT > RT > LTADT in PFS and BFR, respectively (*Figure 6C,D*). The node-splitting method was omitted, because of the absence of a loop connecting three arms.

PFS, LPR or MR

Since the limited data, we compared only three different therapeutic modalities (RT, RT + LDADT and RT + STADT) in the terms of DFS, LPR or MR, and the networks of comparisons were shown in *Figure 4E,F,G*,

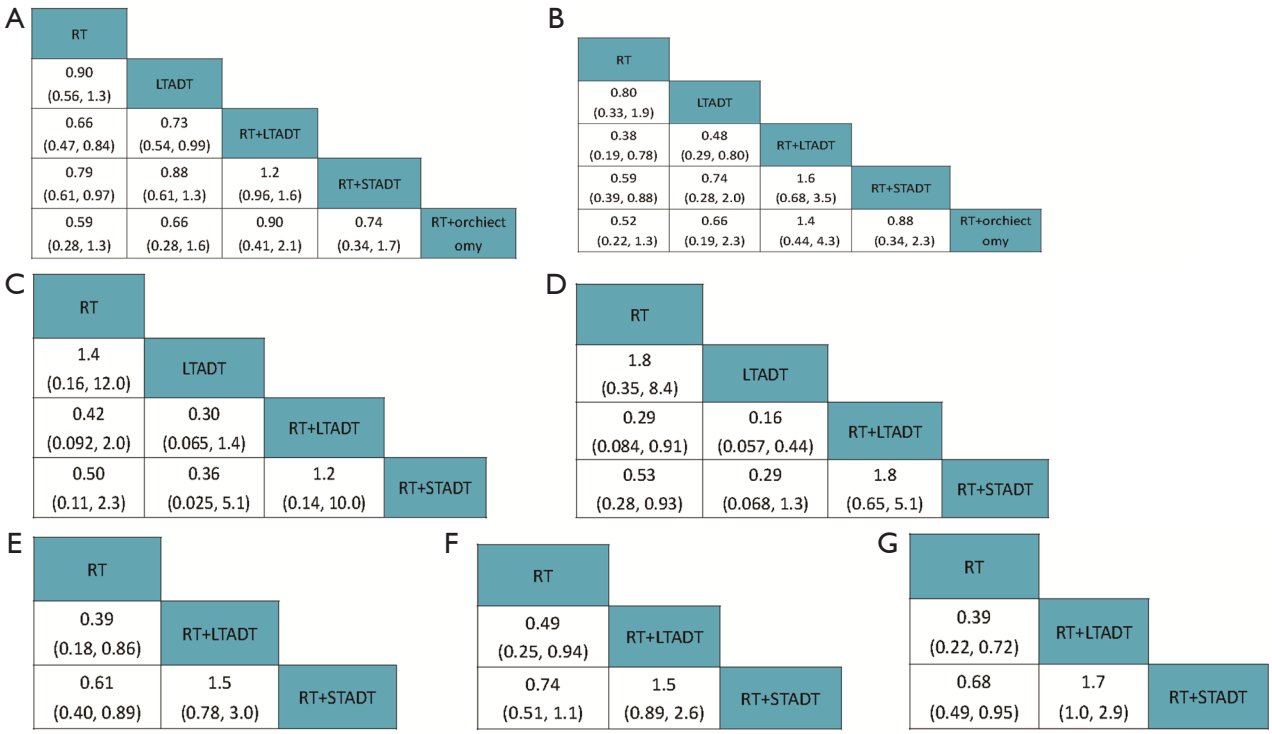

Figure 5 The efficacy characteristics of several different therapeutic modalities for LAPCa patients. (A) OS; (B) CSS; (C) DFS; (D) BFR; (E) PFS; (F) LPR; (G) MR. LAPCa, locally advanced prostate cancer; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; BFR, biochemical failure rate; PFS, progression-free survival; LPR, local progression rate; MR, metastasis rate.

separately. Moreover, the efficacy of different therapeutic paradigms for HRs and corresponding 95% CIs was presented in *Figure 5E,F,G*, respectively. Obviously, we found that the cumulative rank probability from best to worst was RT + LTADT > RT + STADT > RT, RT + LTADT > RT + STADT > RT and RT + LTADT > RT + STADT > RT in DFS, LPR and MR, respectively (*Figure 6E,F,G*). Owing to the absence of a loop connecting three arms, the node-splitting method could not be applied.

Node-splitting method

When a loop connecting three arms existed, the node-splitting method was implemented by reporting its Bayesian P value, by means of separating the evidence concerning certain comparison into direct and indirect evidence, to access the inconsistency. In the above-mentioned study, we found that all Bayesian P values of node-splitting method were greater than 0.05 in terms of OS, which indicated that the direct and indirect evidence was consistent (*Figure 7*).

Discussion

Technological and medicinal advancement has widened treatment options for LAPCa. Apart from radical prostatectomy, RT and ADT was crucial portion of comprehensive treatment strategy of the diseases. Although these therapeutic methods had supported by several randomized phase III clinical trials, the lack of comprehensive comparison of efficacy limited the clinical application of the treatments (7,24,31,32). Therefore, in our network meta-analysis, 11 relevant articles were enrolled and five different therapeutic modalities (RT, LTADT, RT + STADT, RT + LTADT or RT + orchiectomy) and seven different clinical outcomes were ultimately analyzed. Due to the absence of relevant studies on radical prostatectomy in the RCTs, radical prostatectomy was not involved in this article. Among the involved five different therapeutic modalities, our results demonstrated that RT + LTADT or RT + orchiectomy was among the best two therapeutic regimens in the prognostic aspects of the patients with LAPCa. In other words, RT + LTADT could have a comparable survival benefit as RT + orchiectomy.

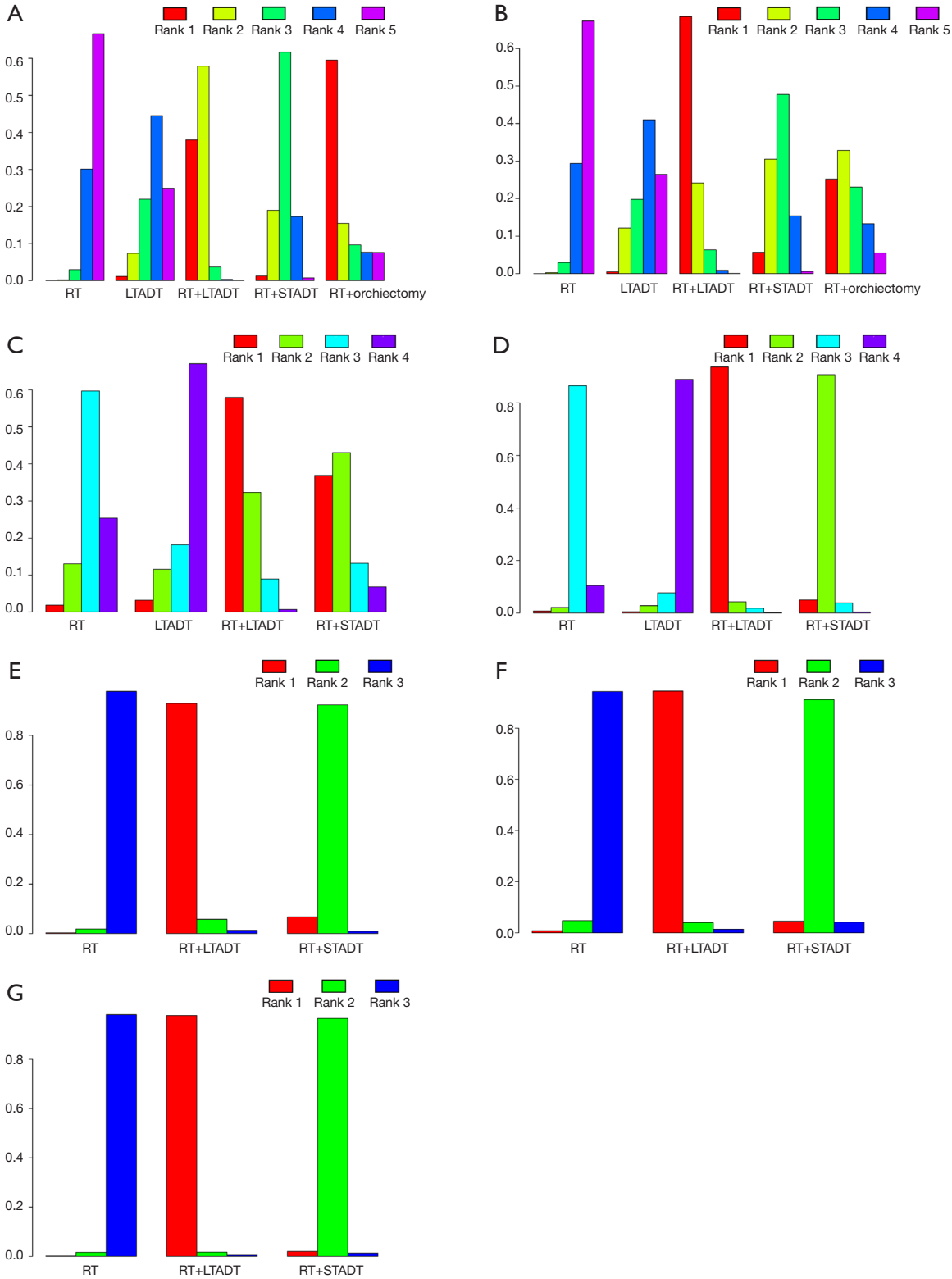

Figure 6 Rank of probability for effective outcomes. (A) OS; (B) CSS; (C) DFS; (D) BFR; (E) PFS; (F) LPR; (G) MR. OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; BFR, biochemical failure rate; PFS, progression-free survival; LPR, local progression rate; MR, metastasis rate.

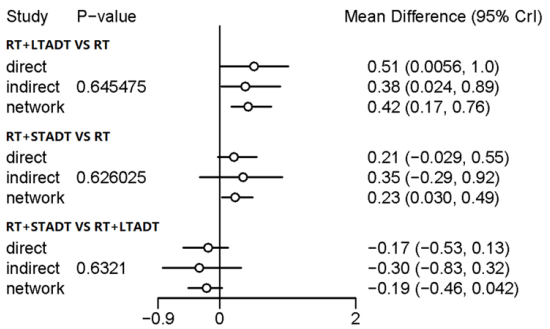

Figure 7 Node-splitting method in comparison between direct and indirect evidence in terms of OS. OS, overall survival.

To date, radical prostatectomy remains one of the standard treatments for LAPCa in men younger than 70 years. However, 30–70% of men have biochemical relapse at 5 years, depending on their initial prognosis (4). Although no standard salvage treatment has been defined, retrospective studies have suggested a potential benefit from salvage RT or ADT with a biochemical complete response seen in half of relapsing patients (10,11,24,26,29). The RTOG 85-31 study by Pilepich *et al.* have demonstrated for the first time that RT combined ATD could obtain a survival benefit (33). The results of this clinical trial containing 977 patients showed that androgen suppression applied as an adjuvant after definitive RT was associated with a reduction in disease progression, and a statistically significant improvement in absolute survival was observed preferentially in PCa patients with a Gleason score of 7–10 in 10 year follow-up. The study performed by Bria *et al.* (34) compared applied RT alone and combination of RT and ADT in the treatment of LAPCa. Their results showed that the BFR, clinical progression, local relapse, and distant metastases were all decreased in combined treatment, to a certain degree. Meanwhile, we also found that combined treatment did not increase the risk of toxicity. In addition, other studies have reported that addition of ADT to conventional-dose RT could improve OS and CSS of the patients with LAPCa (35-37).

Recently, increasing relevant published studies revealed conflicting results about the combination of RT and ADT. It was reported that ADT had no significant clinical effect on the incidence of pelvic recurrences or OS of patient with LAPCa (38-40). However, the treatment method, ADT after RT, has the benefit from the patient with LAPCa, which was reported in a trial performed by Zagars *et al.* (41). In this network meta-analysis, significant benefits of PFS and freedom form metastases were discovered in RT-combined-ADT treatment arm compared with RT treatment arm. But, the data about OS of LAPCa patients were similar between these two arms.

According to the National Comprehensive Cancer Network (NCCN) guidelines, the patients with intermediate-risk PCa should be treated with a combined treatment modality including 4–6 months of ADT, whereas the patients with high-risk features benefit at maximum from long-term hormonal therapy (2–3 years) (7,24,28,42). The European Association of Urology suggested a role for radical prostatectomy and pelvic lymph-node dissection or RT plus androgen deprivation as primary treatments for high-risk or locally advanced PCa (43). Although ADT combined with RT has been increasingly accepted for clinical decision-making, the biochemical mechanism was still not fully elucidated. To date, several mechanisms include pro-apoptosis, anti-angiogenesis, and increasing the sensitivity of cells to oxidative stress were proposed (44). It was reported that ADT not only had cytoreductive properties and the potential to control micrometastatic disease, but also could enhance RT sensitivity of the lesion (44-46). This might explain the combined treatment group had better survival rate.

Of note, urologists and oncologists should balance outcomes and adverse events based on a correct assessment of cancer stage and risk to make a decision of LTADT or STADT management strategy. In the clinical trial RTOG 86-10, the patients were randomly grouped with bulky T2–T4 tumors to radiation with or without goserelin and flutamide (47). Significant benefits of OS, disease-specific mortality, distant metastasis and BFS were seen in combined treatment (8). In addition, the patients with a Gleason score of 6 or less benefited most from STADT. However, the result was conflicted with RTOG 85-31, where LTADT was delivered (48). In RTOG 94-08, RT alone or RT combined STADT were performed in 1979 patients with stage T1b to T2b PCa and PSA less or equal than 20 ng/mL (29). In this network meta-analysis, the 10-year OS was better in combined treatment (62% *vs.* 57%, P=0.03) and the benefit was mostly seen with intermediate-risk LAPCa patients rather than low-risk LAPCa patients. In addition, the combination of LTADT and RT was shown to significantly improve OS, compared with STADT in patients with high-risk PCa (7,27). In terms of dose-escalated RT, the study from Liauw *et al.* enrolled a total of 238 patients with intermediate-risk (PSA: 10–20 ng/mL, Gleason =7, or stage T2b–c) adenocarcinoma of the prostate by treating with

external beam RT between 1989 and 2006, and 112 LAPCa patients (47%) received neoadjuvant and concurrent ADT (3). Moreover, the results demonstrated that intermediate-risk PCa patients with percentage of positive cores > or =50% had the highest risk for biochemical failure after dose-escalated RT, and might be most likely to derive a benefit from ADT (49).

Although the usage of ADT combined with RT was undoubtedly associated with significant clinical benefits, the occurrence of adverse events required the attention of urologist and oncologist. Complications such as vasomotor symptoms, erectile dysfunction, and impairment of cognitive function could significantly reduce the quality of life of LTADT patients (50,51). In addition, the use of LTADT was associated to an increased age-related loss of bone mineral density, which could lead to pathological fracture (52). Besides, LTADT combined RT could also increase the risk of genitourinary and gastrointestinal morbidity (53). Ultimately, the aggravated financial burden of LAPCa patients limited the performance of LTADT. It should be noted that orchiectomy had a good androgen blocking effect, whereas some patients had poor psychological receptivity. Hence, surgeons should carefully discuss with LAPCa patients to clarify the physical and psychological consequences before operation.

To a certain extent, several limitations should be paid attention to, before fully understanding this article. Firstly, the mechanism of combination therapy of RT and ADT applied in LAPCa patients had not yet fully elucidated. Secondly, the number of studies included in this study was limited. Hence, more high-quality researches need to further focus on the influence of different therapeutic methods in the future. Thirdly, among those enrolled studies, the definition of STADT and the drugs to block androgen were not consistent. Meanwhile, inclusion criteria for data of each patient in previous articles were different a lot. Fourthly, limitations were found in the included references, such as limited sample sizes, some biases and short follow-up time. Thus, further exploration in these efficacy characteristics of different therapeutic modalities for LAPCa might be conducted in subsequent years. Last but not least, Due to the absence of relevant studies on radical prostatectomy in the RCTs, radical prostatectomy was not involved in this article, though it had gained more and more attention in recent years. Accordingly, it was required that further studies could be performed to elucidate the differences in the effectiveness of different therapeutic modalities for LAPCa if individual data were available.

Conclusions

In summary, the results of the current network meta-analysis indicated that RT + LTADT or RT + orchiectomy was among the best two therapeutic regimens in the prognostic aspects of the patients with LAPCa. Furthermore, in consideration of reducing invasive treatment of eligible patients, RT + LTADT could yield better survival benefit of LAPCa patients, compared with others. Additional high-quality and multicentre large-scale RCTs are needed to further to confirm these new options in subsequent articles.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

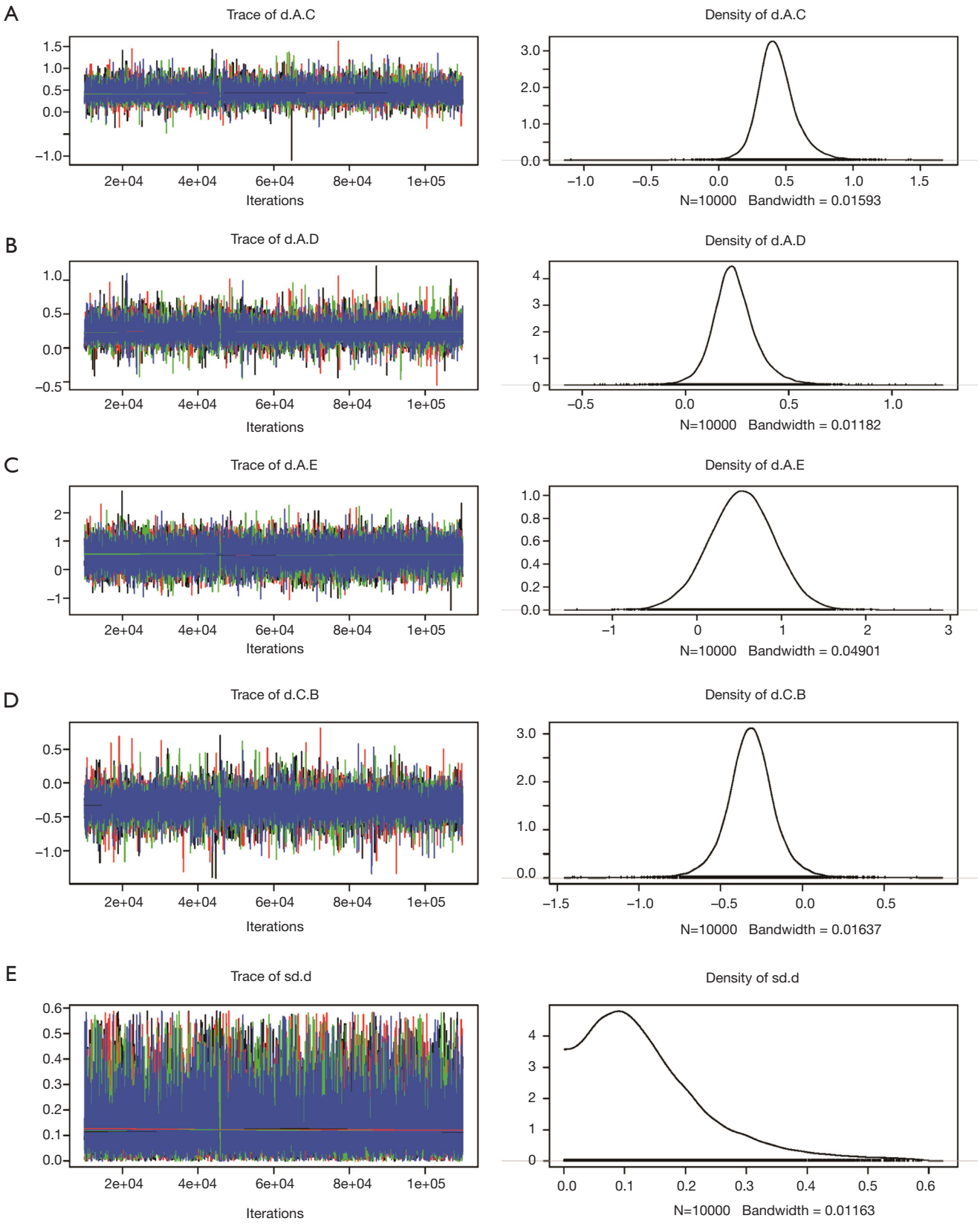

Figure S1 Brooks-Gelman-Rubin plots method. (A) RT; (B) LTADT; (C) RT + LTADT; (D) RT + STADT; (E) RT + orchiectomy. RT, radiotherapy; LTADT, long-term androgen deprivation therapy; STADT, short-term androgen deprivation therapy.

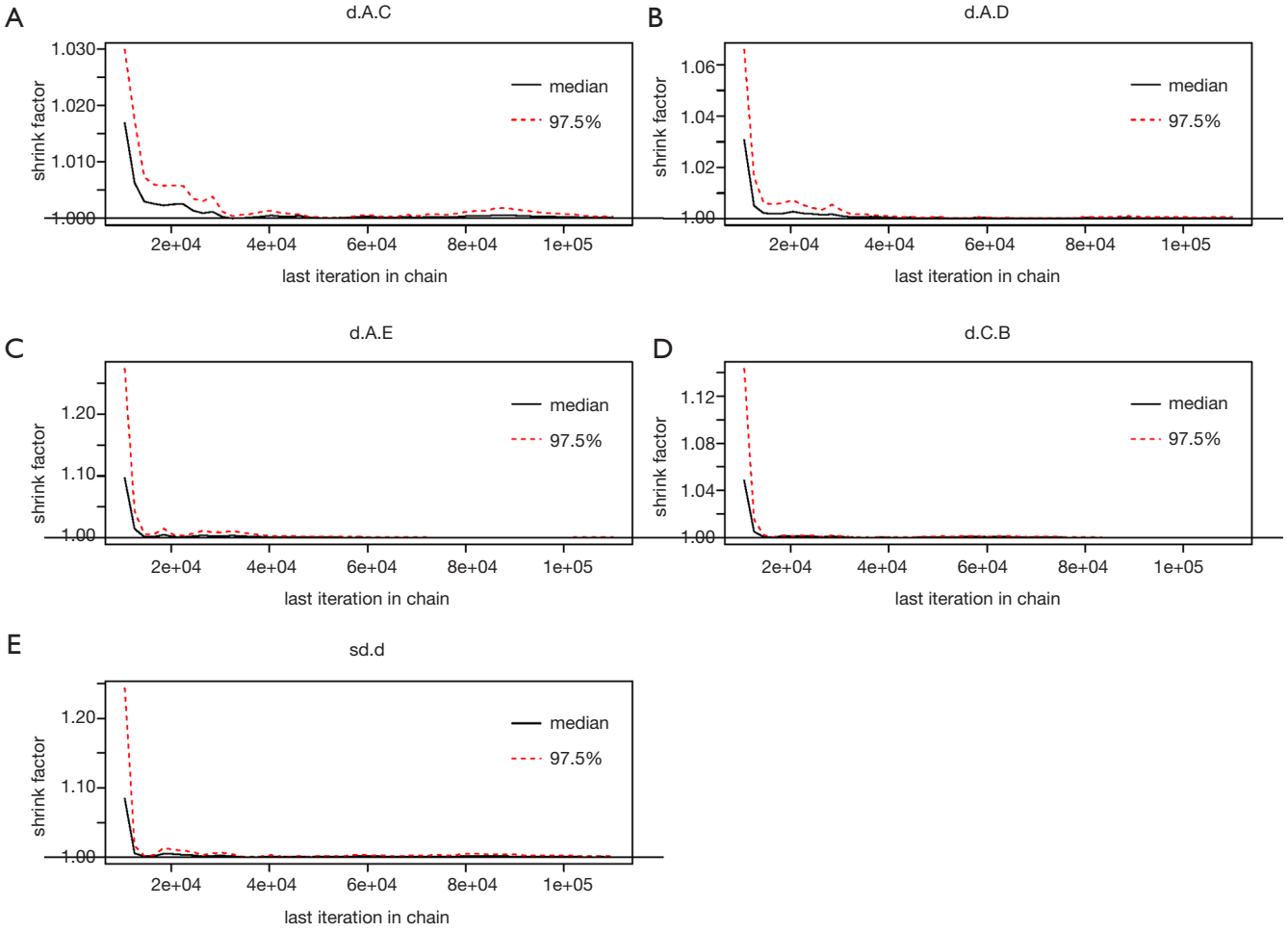

Figure S2 Trace plot and density plot. (A) RT; (B) LTADT; (C) RT + LTADT; (D) RT + STADT; (E) RT + orchiectomy. RT, radiotherapy; LTADT, long-term androgen deprivation therapy; STADT, short-term androgen deprivation therapy.