Adding radiotherapy to androgen deprivation therapy in men with node-positive prostate cancer after radical prostatectomy

A meta-analysis

Lijuan Guo, MDa, Zhaowei Zhu, MDb,*, Xuepei Zhang, MDb,*

Abstract

Background: Several studies have tested the addition of adjuvant radiotherapy (RT) to androgen deprivation therapy (ADT) in node-positive prostate cancer (PCa) after radical prostatectomy (RP). This meta-analysis aims to assess the effects of adding RT to ADT in the treatment of PCa patients with lymph node invasion.

Methods: We systematically searched PubMed and Embase through June 2018 for human studies comparing RT plus ADT versus ADT in men with node-positive PCa after RP. The primary end point was overall survival (OS). Secondary end point was cancer-specific survival (CSS). Hazard ratios (HRs) with 95% confidence intervals (CIs) for the effects of RT plus ADT on OS and CSS were combined across studies using meta-analysis.

Results: Five studies were selected for inclusion. Overall, 15,524 patients were enrolled in the 5 studies. This included 6309 (40.6%) patients receiving ADT, 4389 (28.3%) patients receiving adjuvant RT plus ADT, and 4826 (31.1%) patients receiving observation. In lymph node-positive PCa patients, the addition of adjuvant RT was associated with improved OS (HR: 0.74; 95% CI, 0.59–0.92; P = .008). Moreover, the addition of adjuvant RT was also associated with a dramatic CSS improvement (HR: 0.40; 95% CI, 0.27–0.59; P = .000).

Conclusions: Adding RT to ADT may be a clinically effective treatment option for men with lymph node-positive PCa after RP.

Abbreviations: 3D-CRT = 3-dimensional conformal RT, ADT = androgen deprivation therapy, CIs = confidence intervals, CSS = cancer-specific survival, HRs = hazard ratios, LNI = lymph node invasion, OS = overall survival, PCa = prostate cancer, RP = radical prostatectomy, RT = radiotherapy.

Keywords: androgen deprivation therapy, lymph node invasion, prostate cancer, radical prostatectomy, radiotherapy.

1. Introduction

Prostate cancer (PCa) represents the most common genitourinary malignancy in male patients and the second leading cause of cancer-related death among men in the Europe and United States.[1,2] Radical prostatectomy (RP) is an effective treatment for patients with localized PCa.[3] Large series have demonstrated that RP may be a reasonable first step in a multimodal approach for patients with high-risk and locally advanced PCa.[4–6] Given the decline in PCa screening with the PSA test, there is general concern that PCa patients with lymph node invasion (LNI) may become a larger clinical entity in the future.[7–10] Although the number of positive lymph nodes is a strong predictor of survival in PCa patients following RP,[11–15] the ideal treatment paradigm for these patients is not well defined.

PCa patients with pathological LNI were once considered to harbor a systemic disease. Thus, early androgen deprivation therapy (ADT) was regarded as the treatment of choice and have dramatically improved outcomes in node-positive PCa patients.[16,17] The idea of testing adjuvant radiation therapy (RT) in the presence of LNI came from the evidence that node-positive PCa is not always a systemic and incurable disease.[11–13,18,19] A retrospective study reported a significant protective role for adjuvant RT in patients with PCa and nodal metastases treated with RP and extended pelvic lymph node dissection.[20] Since then, various relevant studies on this association have also been published.[21–24] Current guidelines recommend a variety of options including observation (expectant management), ADT, or a combination of adjuvant RT and ADT.[3] The aim of this systematic review is to conduct a meta-analysis of studies which evaluated the combination of RT with ADT versus ADT alone, in node-positive
PCa after RP, to assess the impact of this therapeutic option in terms of survival outcomes.

2. Methods

2.1. Identification of eligible studies

A literature search was carried out using PubMed and Embase databases in June 2018. The following terms were used: adjuvant radiotherapy, ADT, LNI, node-positive disease, PCa, and radical prostatectomy. No limitations were placed with respect to publication year. Our search was not restricted to the English language. Considering that this was a meta-analysis study, we just retrieved results from previous studies. Thus, the meta-analysis study did not involve patient consent and ethical approval was not necessary.

Two investigators independently performed study selection (GLJ and ZZW). Disagreements were settled by a third author (ZXP). Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion or exclusion criteria. One author (GLJ) performed all data abstraction with independent verification performed by another author (ZZW).

Following the literature search, all duplicates were excluded. Commentaries, editorials, review articles, and those not subject to peer review were also excluded. References of relevant review articles were checked to identify additional eligible studies. In the event of multiple publications from the same study population, the most recent information was considered in the meta-analysis.

To perform treatment comparisons, all studies had to include a control arm comprising treatment with ADT alone. In addition, they had to include an experimental arm which comprised adjuvant RT and ADT. Finally, only 5 retrospective cohort studies were included in this systematic review and meta-analysis.

2.2. Data collection and study quality

We used preferred reporting items for systematic reviews and meta-analyses for reporting of this systematic review and meta-analysis. For each eligible study, the following information were collected, if available:

- Main inclusion criteria: age, stage, previous treatment, Gleason score, preoperative PSA, number of lymph nodes removed and examined, number of positive lymph nodes
- Details of study treatment: type of ADT allowed, RT technique, timing of treatment
- Study design: primary end point, secondary end point, study hypothesis
- Patients enrollment and follow-up: date of start and date of end of accrual; number of patients assigned to control arm (ADT alone), number of patients assigned to experimental arm (adjuvant RT and ADT), median follow-up
- Overall survival (OS): number of deaths in each arm, median OS, hazard ratio (HR) with 95% confidence interval (CI)
- Cancer-specific survival (CSS): number of events in each arm, median CSS, HR with 95% CI

2.3. Statistical methods

Primary end point of the study was OS. Secondary end point was CSS. For both OS and CSS, the summary measure was HR (with 95% CI). Touijer et al demonstrated that adjuvant RT + ADT was associated with better CSS than observation or ADT alone. We used the method of Song et al[25] to perform the indirect treatment comparison between adjuvant RT + ADT and ADT alone. CIs are widely used in reporting statistical analyses of research data, and are usually considered to be more informative than P-values from significance tests. However, 2 published articles reported estimated
Table 1
Characteristics of the 5 trials included in the meta-analysis.

|                           | Da PLF 2009 | Briganti A 2011 | Touijer KA 2018 | Abdullah F 2018 | Gupta M 2018 |
|---------------------------|-------------|-----------------|-----------------|-----------------|--------------|
| **Main inclusion criteria**|             |                 |                 |                 |              |
| Stage                     | PCa patients with LNI | pT2–4 pN+ M0 PCa patients | PCa patients with LNM | pN1 M0 PCa patients | PCa patients with LNMM |
| Previous treatment        | RP and ePLND | RP and PLND     | RP and PLND     | RP and PLND     | RP and PLND |
| Treatment                 | LHRH analogue | Orchiectomy, LHRH agonist or antiandrogen | Bilateral orchiectomy or LHRH agonist | NA | Medical or surgical hormonal suppression |
| RT (experimental arm)     | Prostatic bed 26% pelvis plus prostatic bed 74% | Whole-pelvis and prostatic bed | Whole-pelvis | The pelvis was included for 78% of these patients | Prostatic bed and pelvic lymph nodes |
| Timing of treatment       | NA          | RT: within 3 mo after surgery; ADT: immediately after RP | Within 6 mo of surgery | With 1 yr from surgery | NA |
| **Study design**          |             |                 |                 |                 |              |
| Primary endpoint          | BCR-free survival | CSS | CSS | OS | OS |
| Secondary endpoint        | CSS         | OS              | CSS             | NA             | NA |
| Hypothesis                | An early combination of RT and HT might improve long-term outcomes | Combination of RT plus HT might improve the CSS and OS of patients with LNI | NA | NA | NA |
| **Patient enrollment and follow-up** | January 1988 | September 1988 | 1988 | 2004 | 2004 |
| Accrual start             |             |                 |                 |                 |              |
| Accrual stop              | December 2007 | January 2003 | 2010 | 2015 | 2013 |
| No. of patients           | 250         | 364             | 1338            | 5498            | 8074 |
| ADT alone                 | 121         | 247             | 676             | 3200            | 2065 |
| ADT plus RT               | 129         | 117             | 325             | 2298            | 1520 |
| Median follow-up          | 91.2 mo     | 95.1 mo         | 69 mo           | 49 mo           | 48 mo |

ADT = androgen deprivation therapy, BCR = biochemical recurrence, CSS = cancer-specific survival, ePLND = extended pelvic lymph node dissection, HT = hormonal therapy, LHRH = luteinizing hormone-releasing hormone, LNI = lymph node invasion, LNMM = lymph node metastasis, NA = not available, OS = overall survival, PCa = prostate cancer, RP = radical prostatectomy, RT = radiotherapy.
### Table 2
Main characteristics of enrolled patients.

| Da PLF 2009 | Briganti A 2011 | Touijer KA 2018 | Abdullah F 2018 | Gupta M 2018 |
|-------------|-----------------|-----------------|-----------------|-----------|
| Age (yr)    | ADT alone:      | ADT alone:      | ADT alone:      | ADT alone: |
| Median 67.6 yr (Range: 51–80) | Median 66.7 yr (Range: 47–80) | Median 66 yr (IQR: 60–70) | Median 63.0 yr (IQR: 57.0–68.0) | Median 62.01 yr (IQR: 57–67) |
| ADT and RT: | ADT alone:      | ADT and RT:     | ADT and RT:     | ADT and RT: |
| Median 65 yr (Range: 47–72) | Median 65 yr (IQR: 59–69) | Median 61.0 yr (IQR: 56.0–66.0) | Median 60.08 yr (IQR: 55–65) |
| Gleason score | ADT alone:    | ADT alone:      | ADT alone:      | ADT alone: |
| ADT alone: | ADT alone:      | ADT alone:      | ADT alone:      | ADT alone: |
| ADT and RT: | ADT alone:      | ADT and RT:     | ADT and RT:     | ADT and RT: |
| Preoperative PSA | ADT alone:     | ADT alone:      | ADT alone:      | ADT alone: |
| Median 15 (range: 4.9–103) | Median 18.5 (range: 1.6–616) | Median 14 (IQR: 8–27) | Median 11.2 (IQR: 6.6–24.0) | Median 11.2 (IQR: 6.6–24.0) |
| ADT and RT: | ADT and RT:     | ADT and RT:     | ADT and RT:     | ADT and RT: |
| Median 16 (range: 2.8–148) | Median 19.5 (range: 2.8–321) | Median 15 (IQR: 8–31) | Median 10.2 (IQR: 6.0–20.4) | Median 10.2 (IQR: 6.0–20.4) |
| Stage | ADT alone:      | ADT alone:      | ADT alone:      | ADT alone: |
| pT2 a/b/c 13.2% | pT2 a/b/c 1.6% | pT2/pT3a 37% | pT2/pT3a 36% | pT2 12.7% |
| pT3a 19.8% | pT3a 8.5% | pT3b 59% | pT3b 59% | pT3 81.9% |
| pT3b 57.0% | pT3b 84.6% | pT4 4.0% | pT4 5.3% | pT4 5.4% |
| ADT and RT: | ADT and RT:     | ADT and RT:     | ADT and RT:     | ADT and RT: |
| pT2 a/b/c 3.9% | pT2 a/b/c 2.6% | pT2/pT3a 22% | pT2/pT3a 32% | pT2 8.9% |
| pT3a 10.9% | pT3a 8.5% | pT3b 63% | pT3b 63% | pT3 84.9% |
| pT3b 64.3% | pT3b 79.5% | pT4 14% | pT4 4.8% | pT4 6.3% |
| pT4 20.9% | pT4 9.4% | | | |
| Number of lymph nodes removed and examined | ADT alone:      | ADT alone:      | ADT alone:      | ADT alone: |
| Median 15 (range: 3–44) | Median 13 (range: 2–33) | Median 12 (IQR: 9–17) | Median 10.0 (IQR: 6.0–16.0) | Median 10.0 (IQR: 6.0–16.0) |
| ADT and RT: | ADT and RT:     | ADT and RT:     | ADT and RT:     | ADT and RT: |
| Median 16 (range: 5–52) | Median 14 (range: 2–22) | Median 9.0 (IQR: 5.0–15.0) | NA | NA |
| Number of positive lymph nodes | ADT alone:      | ADT alone:      | ADT alone:      | ADT alone: |
| Median 1 (range: 1–31) | Median 2 (range: 1–10) | Median 2 (IQR: 1.0–3.0) | Median 1.0 (IQR: 1.0–3.0) | Median 1.0 (IQR: 1.0–3.0) |
| ADT and RT: | ADT and RT:     | ADT and RT:     | ADT and RT:     | ADT and RT: |
| Median 2 (range: 1–14) | Median 2 (range: 1–10) | Median 1.0 (IQR: 1.0–2.0) | Median 1.0 (IQR: 1.0–2.0) | Median 1.0 (IQR: 1.0–2.0) |

ADT = androgen deprivation therapy, IQR = interquartile range, NA = no available, PSA = prostate specific antigen, RT = radiotherapy.
effects and P-values, but do not give CIs\(^{20,21}\). Thus, we used the method of Altman et al\(^{26}\) to obtain the CIs.

In assessing heterogeneity among studies, we used the Cochran Q test and \(I^2\) statistics. For the Q statistic, a P-value of less than .10 was used as an indication of the presence of heterogeneity; for \(I^2\), a value > 50% was considered a measure of severe heterogeneity. All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX). A 2-tailed P-value of less than .05 was considered to be statistically significant.

3. Results

We conducted the meta-analysis following the PRISMA statement guidelines\(^{27}\). The selection process of studies eligible for the meta-analysis is reported in Figure 1. Our literature search identified 579 unique references. After a full text review of 12 manuscripts, we identified 5 relevant studies.

3.1. Characteristics and quality of the studies

Table 1 lists the main characteristics of the 5 studies included in the meta-analysis. ADT in both arms consisted of orchiectomy, luteinizing hormone releasing hormone agonist, and/or androgen blockade. RT consisted of local radiation to the prostatic bed, pelvic lymph nodes area or whole-pelvis. Adjuvant ADT and RT were usually started immediately after RP or within 3 to 12 month after surgery. The protocols and methods of all included studies were reviewed and generally deemed to be low risk of bias with adequate randomization.

3.2. Patient characteristics

Overall, there were 15,524 patients included in the 5 studies. This included 6309 (40.6%) patients receiving ADT, 4389 (28.3%) patients receiving ADT plus RT, and 4826 (31.1%) patients receiving observation. Patients were enrolled in these studies between 1988 and 2015 (Table 1). The main characteristics of these patients receiving ADT or ADT plus RT are described in Table 2. The median age ranged from 60.08 to 67.6 years, and men in the adjuvant ADT group were older. There were several differences between the 5 studies. Touijer et al reported that men receiving ADT + RT had higher rates of Gleason score (8–10) and higher pathologic state than men receiving ADT only\(^{22}\). However, Briganti et al observed no significant differences in terms of pre- and postoperative characteristics between patients receiving ADT or ADT plus RT\(^{21}\). The 2 groups of patients were comparable with regard to number of lymph nodes removed and number of positive lymph nodes.

Table 3 summarizes the number of patients and survival data reported in each study. Overall, 10,698 patients were included for the main comparison (ADT vs ADT plus RT). However, only 1 study provided number of deaths in each group\(^{24}\) and most patients who received ADT or ADT plus RT have not reached median survival.

3.3. Overall survival

As shown in Figure 2A, the addition of RT to ADT in node-positive PCa patients was associated with a statistically significant OS benefit (HR: 0.74; 95% CI, 0.59–0.92; \(P = .008\)). There was significant heterogeneity among the 3 studies (\(P = .009, I^2 = 67.4\%\)) (Fig. 2A).

3.4. Cancer specific survival

As shown in Figure 2B, the addition of RT to ADT in node-positive PCa patients was associated with a statistically significant benefit in CSS (HR: 0.40; 95% CI, 0.27–0.59;
Although the diagnosis of PCa has shifted to early clinical stages in the PSA era, lymph node metastases are indeed still diagnosed in a wide range of patients. Controversy exists regarding the optimal treatment for patients with node-positive PCa after RP, and most patients are typically treated according to their physician’s preferences or institutional practice patterns.

This meta-analysis shows that the addition of adjuvant RT to ADT in patients with lymph node-positive PCa contributes to a dramatic improvement in OS and CSS. A quantitative synthesis of the available evidence on this treatment strategy can be really helpful for clinical decisions. To the best of our knowledge, this meta-analysis represents the first synthesis of all the evidence produced to date.

Our meta-analysis shows an OS and CSS improvement that are not only statistically significant but also clinically relevant. The addition of adjuvant RT to ADT is associated with a 26% reduction in the risk of death from all causes (HR: 0.74), and the reduction in the risk of death from PCa is 60% (HR: 0.40). The efficacy demonstrated by adjuvant RT plus ADT in patients with lymph node-positive PCa is not surprising. Previous randomized studies have observed a positive impact of adjuvant RT in patients with locally advanced PCa.[31-33] Thompson et al reported that RT resulted in significantly reduced risk of PSA relapse and disease recurrence in men who had undergone RP for pathologically advanced PCa.[32] Bolla and colleagues found that immediate external irradiation after RP improves biochemical progression-free survival and local control in patients with positive surgical margins or pT3 PCa who are at high risk of progression.[31] Therefore, adjuvant RT would contribute to optimizing local control and preventing distant metastases and death.[31-34]

Noteworthy, details of the RT treatment were different among the 5 studies.[20-24] Da Pozzo LF stated that 34 patients received irradiation of the prostatic bed only (median dose: 66.6 Gy), while the other 95 patients also received pelvis irradiation.

Figure 2. Forest plot for meta-analysis of combination of radiotherapy (RT) with androgen deprivation therapy (ADT) versus ADT alone in men with node-positive prostate cancer after radical prostatectomy: (A) Overall survival; (B) Cancer-specific survival.
involvement. Noteworthy, patients with high-volume nodal metastases reported that patients with a single nodal metastasis appeared to be at a uniform risk of cancer recurrence and death. Cheng et al. addressed the approach in PCa patients with LNI.

Techniques, combination of adjuvant RT and ADT significantly improved OS and CSS, reinforcing the need for a multimodal approach in PCa patients with LNI.

It has been widely accepted that not all PCa patients with LNI are at a uniform risk of cancer recurrence and death. Cheng et al. reported that patients with a single nodal metastasis appeared to have long-term outcomes as favorable as those without nodal involvement. Noteworthy, patients with high-volume nodal metastases have significantly inferior survival rates compared to patients with lower volume of LNI, regardless of adjuvant treatment administration. However, whether adjuvant RT + ADT was effective in preventing progression and recurrence according to the extent of nodal invasion was not available in the present meta-analysis.

Using a previously developed algorithm, Touijer et al. divided PCa patients into 5 groups and found that around 25% of the patients treated with RT + ADT would not benefit from adjuvant RT. These consisted of patients who had locally limited disease (<T3a disease with negative margins and less than or equal to 2 positive nodes) and thus have a good disease control with surgery alone or those with extensive LNI disease (more than 4 positive nodes) who probably harbor a systemic disease beyond the reach of local control at the time of surgery. In another recent study, Gupta M also observed that the use of adjuvant RT + ADT did not confer significant OS benefit in up to 30% of patients without high-risk features, who may be managed with observation and forego the morbidity associated with immediate ADT or radiation. The identification of important risk factors for disease progression may help risk-stratify and individualize treatments for this heterogeneous group of node-positive PCa patients and warrants further investigation in prospective randomized controlled studies.

There are some limitations in our meta-analysis and some important caveats have to be stressed for data interpretation. First, the included studies were retrospective in nature, and there might be partial overlapping of the study populations. Synthesizing data from predominantly retrospective studies may overestimate the pooled estimates. However, prospective randomized data which investigates the impact of adjuvant RT in node-negative PCa patients are not available. Second, the use of published aggregate data compared with individual patient data meta-analysis limits the ability to perform meaningful analysis of subgroup effects or of effect modification. Third, no standardized template and doses of adjuvant RT were used for all patients. Fourth, the type of adjuvant ADT was not standardized, and its duration was extremely heterogeneous among different studies. Finally, inherent in any meta-analysis of published data is the possibility of publication bias, that is small studies with null results tend not to be published.

5. Conclusions

Our meta-analysis clearly shows a significant impact on OS and CSS with the concomitant administration of adjuvant RT and ADT in patients with lymph node-positive PCa. These findings may provide guidance to patients and clinicians when making treatment decisions and may help inform the design of future comparative studies. Future work should focus on risk stratification and identifying which patients are most likely to benefit from combination treatment.

Author contributions

The research project was designed by Zhaowei Zhu and Xuepei Zhang, organized and executed by Lijuan Guo and Zhaowei Zhu. The first draft of the manuscript was written by Lijuan Guo, and the manuscript was reviewed and critiqued by Zhaowei Zhu and Xuepei Zhang. All authors read and approved the final manuscript.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
[2] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[3] Mottern N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618–29.
[4] Yousepowitch O, Eggener SE, Serio AM, et al. Secondary therapy, metastatic progression, and cancer-specific mortality in men with clinically high-risk prostate cancer treated with radical prostatectomy. Eur Urol 2008;53:930–9.
[5] Gontero P, Marchiorio G, Pisani R, et al. Is radical prostatectomy feasible in all cases of locally advanced non-bone metastatic prostate cancer? Results of a single-institution study. Eur Urol 2007;51:922–9.
[6] Huo CY, Joniau S, Oyen R, et al. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007;51:121–8.
[7] Sammon JD, Abdollah F, Choueiri TK, et al. Prostate-specific antigen screening after 2012 US preventive services task force recommendations. JAMA 2015;314:2077–9.
[8] Jemal A, Fedewa SA, Ma J, et al. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. JAMA 2015;314:2054–61.
[9] Barocas DA, Mallin K, Gravers AJ, et al. Effect of the USPSTF grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the United States. J Urol 2015;194:1587–93.
[10] Tran PT, Rivalucau TJ, Dicker AP. Adjuvant radiation for node-positive disease after prostatectomy: more good news, but who will listen. J Clin Oncol 2014;32:3917–9.
[11] Mandel P, Kriegmair MC, Bogdan K, et al. Association between lymph node counts and oncological outcomes in lymph node positive prostate cancer. Eur Urol Focus 2017;3:248–55.
[12] Briganti A, Karnes JR, Da PLF, et al. Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. Eur Urol 2009;55:261–70.
[13] Schumacher MC, Burkhard FC, Thalmann GN, et al. Good outcome for patients with few lymph node metastases after radical retroperitoneal prostatectomy. Eur Urol 2008;54:344–52.
[14] Bourjany SA, Thompson RH, Siddiqui S, et al. Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. J Urol 2007;178:864–70.
[15] Daneshmand S, Quack ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. J Urol 2004;172:2252–5.
[16] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472–9.
[17] Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy.
lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999;341:1781–8.
[18] Bader P, Burkhard FC, Markwalder R, et al. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure. J Urol 2003;169:849–54.
[19] Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol 2009;55:1251–65.
[20] Da PLF, Cozzarini C, Briganti A, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. Eur Urol 2009;55:1003–11.
[21] Briganti A, Karnes RJ, Da PLF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. Eur Urol 2011;59:832–40.
[22] Touijer KA, Karnes RJ, Passoni N, et al. Survival outcomes of men with lymph node-positive prostate cancer after radical prostatectomy: a comparative analysis of different postoperative management strategies. Eur Urol 2018;73:890–6.
[23] Abdollah F, Dalela D, Sood A, et al. Impact of adjuvant radiotherapy in node-positive prostate cancer patients: the importance of patient selection. Eur Urol 2018;74:253–6.
[24] Gupta M, Patel HD, Schwen ZR, et al. Adjuvant radiation with androgen-deprivation therapy for men with lymph node metastases after radical prostatectomy: identifying men who benefit. BJU Int 2018;123:252–60.
[25] Song F, Altman DG, Gleave AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003;326:472.
[26] Altman DG, Bland JM. How to obtain the confidence interval from a P value. BMJ 2011;343:d2090.
[27] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[28] Heidenreich A, Ohlmann CH, Polyakov S. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. Eur Urol 2007;52:29–37.
[29] Briganti A, Chun FK, Salonia A, et al. Validation of a nomogram predicting the probability of lymph node invasion among patients undergoing radical prostatectomy and an extended pelvic lymphadenectomy. Eur Urol 2006;49:1019–26.
[30] Heidenreich A, Varga Z, Von Knobel R. Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. J Urol 2002;167:1681–6.
[31] Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005;366:572–8.
[32] Thompson IM, Tangen CM, Paradela J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006;296:2329–35.
[33] Thompson IM, Tangen CM, Paradela J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956–62.
[34] Wielg T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;27:2924–30.
[35] Cheng L, Zincke H, Blute ML, et al. Risk of prostate carcinoma death in patients with lymph node metastasis. Cancer 2001;91:66–73.
[36] Palapattu GS, Allaf ME, Trock BJ, et al. Prostate specific antigen progression in men with lymph node metastases following radical prostatectomy: results of long-term followup. J Urol 2004;172:1860–4.
[37] Abdollah F, Karnes RJ, Saadai N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol 2014;32:3939–47.