Adjuvant and Salvage Radiotherapy after Prostatectomy: A Systematic Review and Meta-Analysis

Changhao Chen1*, Tianxin Lin1*, Yu Zhou2*, Doudou Li3, Kewei Xu1, Zhihua Li3, Xinxiang Fan1, Guangzheng Zhong1, Wang He1, Xu Chen1, Xianyin He4, Jian Huang1*

1 Department of Urology, Sun Yat-sen Memorial Hospital, Guangzhou, China, 2 Department of Hepatobiliary Surgery, Sun Yat-sen Memorial Hospital, Guangzhou, China, 3 Department of Oncology, Sun Yat-sen Memorial Hospital, Guangzhou, China, 4 Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, China

Abstract

Purpose: In men with adverse prognostic factors (APFs) after radical prostatectomy (RP), the most appropriate timing to administer radiotherapy remains a subject for debate. We conducted a systemic review and meta-analysis to evaluate the therapeutic strategies: adjuvant radiotherapy (ART) and salvage radiotherapy (SRT).

Materials and Methods: We comprehensively searched PubMed, EMBASE, Web of Science and the Cochrane Library and performed the meta-analysis of all randomized controlled trials (RCTs) and retrospective comparative studies assessing the prognostic factors of ART and SRT.

Results: Between May 1998 and July 2012, 2 matched control studies and 16 retrospective studies including a total of 2629 cases were identified (1404 cases for ART and 1185 cases for SRT). 5-year biochemical failure free survival (BFFS) for ART was longer than that for SRT (Hazard Ratio [HR]: 0.37; 95% CI, 0.30–0.46; p < 0.00001, I² = 0%). 3-year BFFS was significantly longer in the ART (HR: 0.38; 95% CI, 0.28–0.52; p < 0.00001, I² = 0%), as did disease free survival (DFS) (RR: 0.53; 95% CI, 0.43–0.66; p < 0.00001, I² = 0%). Exploratory subgroup analysis and sensitivity analysis revealed the similar results with original analysis.

Conclusion: ART therapy offers a safe and efficient alternative to SRT with longer 3-year and 5-year BFFS, better OS and DFS. Our recommendation is to suggest ART for patients with APFs and may reduce the need for SRT. Given the inherent limitations of the included studies, future well-designed RCTs are awaited to confirm and update this analysis.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

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* Email: 914259296@qq.com

† These authors contributed equally to this work.

Introduction

Radical prostatectomy (RP) is a standard and highly effective care treatment for selected patients with prostate cancer assuming with favorable prognostic features [1]. After radical prostatectomy the men with adverse pathological factors (APFs) such as positive surgical margins, seminal vesicle invasion, extra prostatic extension and higher Gleason scores are advised administering radiotherapy [2,3]. In terms of efficacy, prognostic factors and toxicity, the two therapeutic strategies are used: immediate postoperative radiotherapy or adjuvant radiotherapy (ART) and delay postoperative radiotherapy or salvage radiotherapy (SRT) [1,4]. ART is the administration of radiotherapy post-prostatectomy to patients at a higher risk of recurrence due to APFs prior to evidence of disease recurrence, while SRT is the administration of radiotherapy to the prostatic bed and possibly to the surrounding tissues, including lymph nodes, in the patients with prostate specific antigen (PSA) recurrence after surgery but no evidence of distant metastatic disease [5,6]. Delivery of the ART or SRT becomes both therapeutic and diagnostic; PSA response indicates local persistence or recurrence [7,8]. However, when a biochemical recurrence occurred, in the absence of a detectable recurrence, it is hard to distinguish the local recurrence in prostatic bed from distant metastases [9]. A direct comparison evidence of adjuvant and salvage RT is difficult to find due to the numerous confusing factors [2]. Although several studies comparing ART and SRT have been reported, most are small series with unclear results [10,11,12,13,14,15]. The appropriate timing of postoperative RT, either early in the adjuvant setting, or after PSA recurrence in the salvage setting, remains unclear [16,17].
Therefore, we systematically searched and analyzed the available literatures to evaluate the efficiency, safety, and potential advantages of ART and SRT.

**Materials and Methods**

**1. Search strategy**
A literature search was performed in February 2013. The primary sources were the electronic databases of PubMed, EMBASE, MEDLINE, Web of Science and the Cochrane Library. The following MeSH terms and their combinations were searched in [Title/Abstract]: [ART/adjuvant radiotherapy/immediate postoperative radiotherapy/adjuvant RT] and [SRT/salvage radiotherapy/Postoperative radiotherapy/salvage RT] and [prostate cancer/prostatectomy/radical prostatectomy]}. In addition, the reference lists of relevant articles were manually searched to find other potentially eligible studies. References of systematic reviews identified in the background search and references of eligible studies were hand searched. No language restriction was imposed and only the most recent publication was included when duplicates were identified.

**2. Selection criteria**
If either reviewer felt a title and abstract met study eligibility criteria, the full text of the study was retrieved. References of systematic reviews identified in the background search and references of eligible studies were hand searched. The full manuscripts of all articles identified in the search were screened for eligibility criteria by 2 reviewers (Yu Zhou and Tianxin Lin) using a standardized form. Disagreements were resolved through discussion. The eligibility criteria in the ART arm were as follows: 1. Patients must have at least one of the following risk factors: 1) Positive margins; 2) Extra prostatic extension with or without seminal vesicle invasion; 3) lymph node invasion. 2. Patients were irradiated within 6 months of the RP. 3. Patients had an undetectable prostate-specific antigen (PSA) at the start of RT. 4. None received any neoadjuvant therapy. The eligibility criteria of SRT arm defined as: 1. Patients were referred for RT because of a persistent postoperative PSA. 2. Patients manifested a PSA recurrence after a period of undetectable PSA. Articles were excluded based on the following criteria: (1) letters or review articles, (2) laboratory studies, (3) case reports and animal experimental studies, (4) absence of key information such as sample size, hazard ratio (HR) and risk ratio (RR), 95% CI, and P value, (5) the outcomes of interest (as BFFS, OS etc.) were impossible to calculate or the standard deviation and confidence interval of the tested parameters were not reported (Table S1 in File S1). The eligibility criteria in ART arm were as follows: 1. Patients must have at least one of the following risk factors: 1) Positive margins; 2) Extra prostatic extension with or without seminal vesicle invasion; 3) lymph node invasion. 2. Patients were irradiated within 6 months of the RP. 3. Patients had an undetectable prostate-specific antigen (PSA) at the start of RT. 4. None received any neoadjuvant therapy. The eligibility criteria of SRT arm defined as: 1. Patients were referred for RT because of a persistent postoperative PSA. 2. Patients manifested a PSA recurrence after a period of undetectable PSA. Articles were excluded based on the following criteria: (1) letters or review articles, (2) laboratory studies, (3) case reports and animal experimental studies, (4) absence of key information such as sample size, hazard ratio (HR) and risk ratio (RR), 95% CI, and P value, (5) the outcomes of interest (as BFFS, OS etc.) were impossible to calculate or the standard deviation and confidence interval of the tested parameters were not reported (Table S1 in File S1).

**3. Quality assessments**
Data from the included studies were systematically assessed the quality of all the studies included by two of the authors (Changhao Chen and Doudou Li) that double-checked by both. Any disagreement was resolved by the adjudicating senior authors (Jian Huang). We evaluated the studies for the level of evidence provided according to criteria by the Centre for Evidence-Based Medicine in Oxford, UK [18]. The methodological quality of retrospective studies was rated by the modified Newcastle-Ottawa scale [19,20]. The scale focuses on three factors: patient selection, comparability of the study groups, and assessment of outcome. We allotted the score of 0–9 (allocated as stars) for each study. RCTs and retrospective studies achieving six or more stars were considered to be of high quality (Table S2 in File S1).

**4. Data extraction and outcomes of interest**
Two investigators (Wang He and Yu Zhou) searched the publications independently using standardized data-abstraction forms. When the two investigators discovered different results, an independent expert (Tianxin Lin) in oncology made the final decision of study conclusions. Information collected from these publications included first author, year of publication, targeted treatment, number of patients, patient characteristics, study design (blinded or not), and the outcomes.

The primary outcomes were 5-year BFFS, 3-year BFFS, OS, and DFS. Biochemical recurrence as a detectable or rising PSA value after surgery that is >0.2 ng/ml with a second confirmatory level >0.2 ng/ml. OS of included studies is defined as the time from random assignment to death, irrespective of the cause of death. DFS is defined as the duration of time from random assignment to documented disease relapse or death, whichever occurs first. The secondary outcomes were Metastasis-free survival (MFS).

**5. Statistical analysis**
The Meta-analyses were carried out using Review Manager Version 5.2 software (Review Manager, Version 5.2 for Windows, The Cochrane Collaboration, 2013). The hazard ratio (HR) was used as a summary statistic for long-term outcomes (survival analysis) as described by Parmar et al [21]. An HR of less than 1 represented a survival benefit favoring the simultaneous group. Medians were converted to means using the technique described by Hozo et al [22]. The reported risk ratio (RR) and mean difference (MD) with 95% confidence interval (CI) were used in the analysis. Heterogeneity was assessed with I2 and F statistics. An F2 value of more than 75% was considered to indicate high statistical heterogeneity. Reasons for statistical heterogeneity were explored using sensitivity analyses (exclusion of individual studies). The random-effects model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was used [23]. Simple linear regression was utilized to identify factors associated with 5-year BFFS rate between ART and SRT. Variables tested included median radiation dose, median preoperative PSA and median pre-RT PSA [24]. Prespecified subgroup analyses were performed according to district, patient age, radiation dose and publication year to evaluate ART and SRT. All subgroup analyses followed the same meta-analysis procedure. Sensitivity analyses were performed for high quality studies. Funnel plots were used to screen for potential publication bias.

**Results**

**1. Data retrieval**
Eighteen studies including 2629 cases (1416 cases for ART and 1213 cases for SRT) fulfilled the predefined inclusion criteria and were included in the final analysis (Figure 1). All studies were full-text articles [2,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40, 41,42]. Examination of the references listed for these studies and for the review articles did not yield any further studies for evaluation. Agreement between the three reviewers was 95% for study selection and the quality assessment of trials.

**2. Study characteristics**
The characteristics of included studies are indicated in Table 1. Among the included studies, there was no RCT between ART and SRT. Two retrospective studies were matched in a 1:1 ratio according to preoperative prostate-specific antigen Gleason score, seminal vesicle invasion, surgical margin status, and follow-up from date of surgery [38,39] of level of evidence: 3a; and 9
retrospective studies were retrospective studies compared high-risk series of patients (level of evidence: 3b) [2,27,30,31,32,34,35, 36,41,42]; 7 retrospective studies used no distinction between risk series of patients (level of evidence: 4) [25,26,28,29,33,37,40].

Included trials were published between 1982 and 2010. The selected trials were conducted in United States (9), Italy (2), Belgium (2), Japan (2), Canada (1), Australia (1), and England (1). A total of 2629 randomized participants were included and the sample size ranged from 40 to 431 patients. The follow-up time ranged from the day of discharge to 204 months in Table 2.

Figure 1. Flow diagram of studies identified, included and excluded.
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3. Qualities of included studies

The agreements of the reviewers for selection and validity assessment of the studies were scored by the kappa coefficient (a measure of agreement), which were 0.86 with 93.2% observed agreement and 0.81 with 91.7% observed agreement, respectively. The risks of bias were evaluated by a modification of the Newcastle–Ottawa scale (Table S2 in File S1). Full-length articles were all available for review. Matching criteria between the groups were variable, and little matching information was identified from the conference abstracts. Methods for handling missing data and intention-to-treat analyses were not adequately described in the majority of studies.
Table 1. Study characteristics.

| Reference          | Year | Sample Size | Inclusion Period | Country/District | Follow-up (month) | Study type | Level of evidence | Quality score |
|--------------------|------|-------------|------------------|------------------|-------------------|------------|-------------------|---------------|
| Hudson et al.[29]  | 2008 | 40          | 2002-2007        | England          | 34(25–47)         | RET        | 3b                |               |
| Wadasaki et al.[30]| 2006 | 57          | 1997-2004        | Japan            | 33(12–98)         | RET        | 3b                |               |
| TAYLOR et al.[2]   | 2003 | 146         | 1987–1998        | United States    | 53 (ART: 68; SRT: 35) | RET        | 3b                |               |
| HAGAN et al.[34]   | 2004 | 157         | 1989–1997        | United States    | ART: 53.3(12–104); SRT: 66.4(7–331) | RET        | 3b                |               |
| Detti et al.[39]   | 2012 | 307         | 1995–2010        | Italy            | ART: 39.6(15.6–159.6); SRT: 54(19.2–135.6) | RET        | 3b                |               |
| OST et al.[36]     | 2010 | 178         | 1999–2009        | Belgium          | 36(3–120)         | Matched control | 3a            |               |
| Budiharto et al.[38]| 2010 | 219         | 1991–2004        | Belgium.         | ART: 103.5(55–190); SRT: 121(60–194) | RET        | 4                 |               |
| Trabulsi et al.[37]| 2008 | 192         | 1987–2002        | United States    | ART: 94(26–190); SRT: 97(30–207) | Matched control | 3a            |               |
| BARBARA et al.[40] | 2008 | 431         | 1996–2006        | Italy            | ART: 32(0–129); SRT: 97(0–108) | RET        | 3b                |               |
| PACHOLKE et al.[35]| 2004 | 163         | 1982–2000        | United States    | ART: 70(4–153); SRT: 69(2–167) | RET        | 4                 |               |
| Saxaki et al.[33]  | 2006 | 105         | 1996–2004        | Japan            | 23(3–68)          | RET        | 4                 |               |
| Tsien et al.[32]   | 2003 | 95          | 1986–1997        | United States    | ART: 121.2(57.6–174); SRT: 103.6(24–204) | RET        | 3b                |               |
| Do et al.[25]      | 2002 | 115         | 1987–1996        | United States    | ART: 90.8(26–157); SRT: 86.6(20–149) | RET        | 3b                |               |
| Catton et al.[24]  | 2001 | 11          | 1987–1994        | Canada           | 44.4(2.4–108)     | RET        | 4                 |               |
| Valicenti et al.[23]| 1998 | 79          | 1992–1997        | United States    | 39                 | RET        | 4                 |               |
| Vicini et al.[27]  | 1999 | 61          | 1987–1993        | United States    | ART: 49(21–100); SRT: 468(7–78) | RET        | 4                 |               |
| Nudell et al.[28]  | 1999 | 105         | 1993–1998        | United States    | ART: 38.3 SRT: 67.3 | RET        | 3b                |               |
| Mayer et al.[26]   | 2002 | 66          | 1987–1999        | Austria          | ART: 58.5(67–141.5); SRT: 56.4(8.4–115.2) | RET        | 4                 |               |

ART = adjuvant radiotherapy; SRT = salvage radiotherapy; RET = retrospective.

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## Table 2. Characteristics of included studies.

| Reference | Group | N     | Age               | Gleason score ≤6/7/≤8 | Radiation dose (Gy) 3D-CRT | Intervention (months) | Preoperative PSA (ng/ml) | Pre-RT PSA (ng/ml) | 5-year BFFS (%) | SVI N (%) | ECE N (%) | PSM N (%) | Preoperative hormones N(%) | Postoperative Hormones N(%) |
|-----------|-------|-------|-------------------|------------------------|-----------------------------|-----------------------|-------------------------|---------------------|-----------------|-------------|-----------|----------|--------------------------|-----------------------------|
| Hudson et al.[29] | ART | 12    | 64(59-67)         | 2/10 (including7)     | 3/9/0                       | NR                    | <10: 3(25):≤10: 9(75) | <0.5: 10(83)>; 0.5: 2(17) | NR              | 4(33)       | NR        | 12(100)   | 10(83)                  | NR                          |
| SRT       | 28    | 64(59-67) | 12/16             | 13/15/0                | 60-64                      | 8/40                  | NR                      | <10: 13(46)>; 0.5: 9(32)>; 0.5: 19(68) | NR              | 4(14)       | NR        | 19(68)    | 21(75)                  | NR                          |
| Wadasaki et al.[30] | ART | 15    | 66(56–76)         | 7/5/3                  | NR                         | NR                    | <0.1                   | 0.6                 | NR              | NR          | NR        | NR        | NR                      | NR                          |
| SRT       | 42    | 69(57–76) | 20/13/9           | NR                     | 60-66                      | 57/57                 | 1(1–3)                 | NR                 | NR              | NR          | NR        | NR        | NR                      | NR                          |
| TAYLOR et al.[2] | ART | 75    | 66(59–67)         | 9/35/30                | 27/48/0                    | 60(5–70)              | NR                      | 0.5                 | NR              | NR          | NR        | NR        | NR                      | NR                          |
| SRT       | 71    | 61    | 18/27/24          | 12/59/0                | 70(50–78)                 | NR                    | NR                     | NR                 | NR              | NR          | NR        | NR        | NR                      | NR                          |
| HAGAN et al.[34] | ART | 69    | 70.3              | 33/36/0                | NR                         | NR                    | 2.9±1.9                | 10.9±5.6            | 0.8±0.83        | 79          | 36(52)    | 41(59)    | 46(67)                  | 0                           |
| SRT       | 88    | 68.3  | NR                | 60/28/0                | 64±1.2                    | NR                    | 40.3±11.2              | 12.0±4.6            | 4.5±1.62         | 45          | 13(15)    | 60(73)    | 42(48)                  | 0                           |
| Detti et al.[39] | ART | 203   | 65±7.3            | 44/77/82               | 22/181/0                  | 200(99)               | NR                     | 19.2±37.5           | 0.47±1.73       | 64          | 0         | 101(50)   | 28(14)                  | 30(15)                     |
| SRT       | 104   | 67.0±6.0 | 25/26/53          | 23/81/0                | 66.8±4.1                  | 9(94)                 | NR                     | 22.7±17.3           | 1.73±3.19        | 33          | 0         | 24(23)    | 18(17)                  | 27(26)                     |
| OST et al.[36] | ART | 89    | 63(51–77)         | 64/25 (including7)    | 21/63/5                   | 74                    | NR                     | 3(1–13)             | 0.03±0.47       | 85          | 23(26)    | 56(63)    | 68(76)                  | NR                          |
| SRT       | 89    | 64(42–75) | 21/63/5           | NR                     | 76                        | NR                    | 15(3–132)              | 10.05(3.5–148)    | 0.8             | 65          | 22(25)    | 64(72)    | 59(66)                  | NR                          |
| Budiharto et al.[38] | ART | 130   | 64(07-67)         | 76/44/10               | 34/96/0                   | 60(60–66)             | 130(100)               | NR                 | 10.00±30.8      | <0.2        | 90        | 93(72)    | 46(35)                  | NR                          |
| SRT       | 89    | 64(048–78) | 29/45/13          | 31/58/0                | 68                        | 89(100)               | NR                     | 9.0(37–159.4)      | 0.3(0–4–1 96) | 65          | 31(56)    | 52(58)    | NR                     | NR                          |
| Trabulsi et al.[37] | ART | 96    | 63(07–75)         | 22/57/17               | 0/96/0                    | 64(859–70)            | NR                     | NR                 | 9.0(17–39)      | PSA<0.2 ng/mL | 73          | 23        | NR        | 80(83)                  | NR                          |
| SRT       | 96    | 62(042–76) | 22/57/17          | 0/96/0                 | 60(50–70)                 | NR                    | NR                     | 8.3(1.1–65.9)      | 0.7(0.2–2)      | 50          | 23        | NR        | 80(83)                  | NR                          |
| BARBARA. et al.[40] | ART | 258   | 65(47–78)         | 39/206/13              | 258(100)                  | 4(1–9)                | 9.2(20.9–0.0)          | NR                 | 79.7           | NR          | NR        | 156(60.5)  | 49(19)                  | NR                          |
| SRT       | 173   | 68(47–81) | 74/85/4           | 70(48–78)              | 17/100                   | 29(1–46)              | 9.8(1.7–75)            | NR                 | 60.5           | NR          | NR        | 58(33.5)  | 30(18)                  | NR                          |
| PACHOLKE et al.[35] | ART | 107   | 65                | 28/31/48               | 4/90/13                   | 57(50–65)             | NR                     | NR                 | 9.5            | 0          | 80        | 87(81)     | 70(65)                  | 38(38)                     |
| SRT       | 56    | 66    | 13/16/25          | 9/44/2                 | 60(50–65)                 | NR                    | NR                     | NR                 | 15.2           | 1.2        | 39        | 35(64)     | 30(55)                  | 16(29)                    |
| Sarak et al.[33] | ART | 73    | 66(36–77)         | NR                     | NR                        | NR                    | 13(0.53–26.8)          | NR                 | 93             | 4          | NR        | 15        | NR                     | 4                          |
| SRT       | 32    | 68(58–89) | NR               | NR                     | 60(40–70)                 | NR                    | NR                     | NR                 | 60             | 10         | NR        | 29        | NR                     | 24                          |
| Tsien et al.[32] | ART | 38    | 63(43.8–75.7)     | 11/16/8                | 2/36                      | 64(59.4–69.0)         | 38                    | 2.8(0.9–6.3)        | 11.6(1.1–99.6)  | NR          | 50        | 15(39)    | 35(93)                  | 34(89)                    |
| SRT       | 57    | 64.2(42.1–78.6) | 17/27/8           | 19/38                  | 65(0.60–75.0)             | 57                    | 27(3.3–116.2)         | 13.3(0.2–120.0)    | 1.2(0.2–18.4)   | 35          | 9(16)     | 39(68)     | 27(47)                  | NR                          |
| Reference          | Group | N  | Age         | Gleason score ≤6/7/≥8 | Postoperative stage T2/pT3/pT4 | Radiation dose (Gy) | 3D-CRT | Interval (months) | Preoperative PSA (ng/ml) | Pre-RT PSA (ng/ml) | 5-year BFFS (%) | SVI (N%) | ECE (N%) | PSM (N%) | Preoperative hormones (N%) | Postoperative Hormones (N%) |
|--------------------|-------|----|-------------|------------------------|--------------------------------|---------------------|--------|------------------|--------------------------|----------------------|----------------|-----------|----------|----------|----------------|-----------------------------|
| Do et al.[25]      | ART   | 42 | NR          | 33/9                   | NR                             | NR                  | NR     | NR               | 27.6                     | NR                   | 40             | 21 (50)   | 21 (50) | 23 (55) | NR                 | 0                           |
|                    | SRT   | 73 | NR          | 61/12                  | NR                             | 64.8                | NR     | NR               | 24.9                     | 2.8                  | 26             | 27 (37)   | 41 (56) | 36 (49) | NR                 | 0                           |
| Catton et al.[24]  | ART   | 54 | NR          | 51/3                   | NR                             | NR                  | NR     | NR               | NR                       | NR                   | NR             | 81         | 19 (35)  | 22 (41) | 52 (96) | NR                 | 0                           |
|                    | SRT   | 59 | NR          | 50/9                   | NR                             | NR                  | NR     | NR               | NR                       | 2.8                  | 30             | 17 (29)   | 23 (39) | 42 (72) | NR                 | 0                           |
| Valicenti et al.[23]| ART  | 52 | NR          | 46/7                   | NR                             | 64.8                | NR     | NR               | 10.0                     | NR                   | 81             | 15 (29)   | 37 (71) | 44 (85) | NR                 | 0                           |
|                    | SRT   | 27 | NR          | 14/13                  | NR                             | 64.8                | NR     | NR               | 12.0                     | NR                   | 25             | 14 (52)   | 13 (48) | 15 (56) | NR                 | 0                           |
| Vicini et al.[27]  | ART   | 38 | 66 (51–75)  | NR                     | NR                             | 59.4                | 50.4–61.2 | NR               | 8.2–5.6                  | NR                   | 67             | NR         | NR      | 24 (62) | NR                 | 0                           |
|                    | SRT   | 23 | 65 (52–79)  | NR                     | NR                             | 61.2 (59.4–68)      | NR     | NR               | 10 (4–60)                | NR                   | 16             | NR         | 23 (100) | NR      | 0                  |
| Nudell et al.[28]  | ART   | 36 | 60.3        | 13/18/5                | 9/27/0                        | 66.33 (55–73)       | NR     | 3.7              | 9.3                      | NR                   | 57             | NR         | 11 (30) | 26 (71) | 35 (97) | NR                 | 0                           |
|                    | SRT   | 69 | NR          | 54/15                  | NR                             | 67.3                | NR     | NR               | 14.2                     | 1.0                  | 54             | 20 (29)   | 48 (69) | 55 (80) | NR                 | 0                           |
| Mayer et al.[26]   | ART   | 29 | 64          | NR                     | 70 (60–70.4)                  | NR                  | 2.1 (1.4–3.9) | NR               | 11.9 (4.1–166.0)         | 0.3 (0.0–0.4)        | 85.2           | NR         | NR      | 7 (24)  | NR                 | 6 (21)                      |
|                    | SRT   | 37 | 66          | NR                     | 70 (NR)                      | NR                  | NR     | NR               | NR                       | NR                   | NR             | 34         | NR      | NR      | 4 (11)  | NR                 | 11 (30)                     |

Values are given as mean±s.d./median (range) ART = adjuvant radiotherapy; SRT = salvage radiotherapy; NR = not reported; BFFS: Biochemical Failure-Free Survival; PSM: Positive surgical margins; ECE: extracapsular extension; SVI: seminal vesicle invasion.
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3. Primary outcomes

3.1 5-year BFFS. Among the 18 clinical trials included in the meta-analysis, 14 reported HR for 5-year BFFS and the corresponding 95% CIs. These studies assessed 5-year BFFS in 2413 patients showed clearly significant difference between the ART and SRT (HR: 0.37; 95% CI: 0.30–0.46; \( p \leq 0.00001 \)). Sensitivity analysis by removing individual studies did not indicate heterogeneity of being caused by a single study (Fig. S2 in File S1).

3.2 3-year BFFS. All 14 trials provided data on this endpoint, and the definitions of biochemical failure used by the trials were similar. All 14 trials detected longer biochemical progression-free survival with ART compared with SRT that was statistically significant. Pooling the results of the trials in a meta-analysis (Figure 4) produced an HR of 0.38 (95% CI: 0.28–0.52; \( p < 0.00001 \)), which represents a 62% decrease in 3-year BFFS with ART compared to SRT.

3.3 Overall Survival Rate. All the studies evaluating OS presented a significant difference between the ART and SRT (HR: 0.53; 95% CI: 0.41–0.68; \( p < 0.00001 \)) (Fig. 5). Studies evaluating OS presented no evidence of significant heterogeneity between the ART arm and SRT arm \( (I^2 = 0\% \, , \, p = 0.47) \). Sensitivity analysis removing individual studies showed clinical heterogeneity of being caused by 2 studies [30,33] and the result of the other 4 trials demonstrated the advantage of ART (OR: 0.49; 95% CI: 0.38–0.64; \( p < 0.001 \, , \, I^2 = 0\% \) ) (Table 2).

3.4 Disease-Free Survival Rate. Pooling the data of 7 studies consisting of 1302 patients that demonstrated DFS indicated ART was significant better than SRT (RR: 0.53; 95% CI: 0.43–0.66; \( p < 0.00001 \, , \, I^2 = 0\% \) ). We performed a sensitivity analysis including only 6 high-quality studies [29,30,31,37,39,42]. The results were similar to the original analysis (RR: 0.52; 95% CI: 0.43–0.65; \( p < 0.00001 \, , \, I^2 = 0\% \) ) (Figure 5).

4. Secondary outcomes

4.1 Metastasis-Free Survival Rate. Although not an outcome of interest to this review, we collected data from 5 studies including a total of 472 patients that reported MFS rate showed no significance difference between ART and SRT (RR: 0.81; 95% CI: 0.48–1.36; \( p = 0.43 \), \( I^2 = 0\% \)). Sensitivity analysis by removal of individual studies did not indicate heterogeneity of being caused by a single study (Fig. S2 in File S1).

5. Subgroup analysis

5.1 ART versus SRT for 3-year BFFS, 5-year BFFS in age ≥65 years old and age <65 years old. The results showed that biochemical failure free survivals in ART arm had improved 5-year BFFS in patient both younger and older than 65 year old (HR: 0.38; 95% CI: 0.28–0.53; \( p < 0.001 \, , \, I^2 = 0\% \) ) and 3-year BFFS (HR: 0.37; 95% CI: 0.27–0.51, \( I^2 = 0\% \) ) (Fig. S3, S4, S5 in File S1).

5.2 ART versus SRT for OS, 3-year BFFS and 5-year BFFS in Asia, Europe, and Northern America. In subgroup meta-analyses performed separately, there were no significant differences in this subgroup analysis compared with the original analysis. 11 studies reported 3-year BFFS and 7 studies reported OS both showed no significant difference between groups (HR: 0.37; 95% CI: 0.26–0.54; \( p = 0.51 \, , \, I^2 = 0\% \) ) (Table 3).

5.3 ART versus SRT for OS, DFS, 3-year BFFS and 5-year BFFS in radiation dose <70 Gy and radiation dose ≥70 Gy. The results indicated that there were no significant differences in this subgroup analysis compared with the original analysis in OS (RR: 0.53; 95% CI: 0.41–0.68; \( p = 0.47 \, , \, I^2 = 0\% \) ) and 3-year BFFS (HR: 0.38; 95% CI: 0.28–0.52; \( p = 0.59 \, , \, I^2 = 0\% \) ) (Fig. S9-S12 in File S1).
5.3 ART versus SRT for 3-year BFFS and 5-year BFFS in publication year from 1998 to 2005 and from 2006 to 2010. The pooling data demonstrated that there were similar results that ART group was significant better than SRT in this subgroup analysis compared with the original analysis in biochemical failure free survival. However, 3-year and 5-year BFFS presented no significant difference between groups (HR: 0.37; 95% CI, 0.30–0.46; \( p = 0.98, I^2 = 0\% \); HR: 0.37; 95% CI, 0.30–0.46; \( p = 0.98, I^2 = 0\% \)) (Fig. S13–S14 in File S1).

6. Sensitivity analysis and Publication bias

2 matched control studies and 16 retrospective studies that scored five or more stars on the modified Newcastle-Ottawa scale were included in sensitivity analysis (Table 4). There was no change in the significance of any of the outcomes except for 3-year and 5-year BFFS, which was shown that the heterogeneity obviously decreased. We applied funnel plots to evaluate publication bias of the included studies. All of the funnel plots were symmetrical. All studies lie inside the 95% CIs, with an even distribution around the vertical, indicating no obvious publication bias (Figure 6).
In 2014, an estimated 233,000 men were diagnosed with prostate cancer and prostate cancer surpassed lung cancer as the most common cancer in men [43]. In approximately two-thirds of men, radical prostatectomy constitutes a cure but within 10 years up to one-third of patients manifest recurrent disease [44,45].

**Discussion**

In 2014, an estimated 233,000 men were diagnosed with prostate cancer and prostate cancer surpassed lung cancer as the most common cancer in men [43]. In approximately two-thirds of men, radical prostatectomy constitutes a cure but within 10 years up to one-third of patients manifest recurrent disease [44,45]. When the patients with localized prostate cancer who undergo a radical prostatectomy (RP) will remain disease free, patients with APFs were known to be at an increased risk for developing a biochemical recurrence and distant metastatic disease. APFs that have been significantly associated with an increased chance for a biochemical recurrence include higher preoperative prostate-specific antigen (PSA), extracapsular extension (ECE), seminal vesicle invasion (SVI), and positive surgical margins (PSM).

### Figure 4. Forest plot for Biochemical Failure-Free Survival (BFFS): 3-years BFFS.

![Figure 4](https://example.com/figure4.png)

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### Figure 5. Forest plot for Survival Rate: Disease-free Survival (DFS); overall survival (OS).

![Figure 5](https://example.com/figure5.png)

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Table 3. Subgroup Analysis for Survival Rate.

| Group                          | Pooled analysis (17 studies) |
|-------------------------------|-------------------------------|
|                               | Studies                      |
|                               | Mean difference (95% CI) Z P I² (%) |
| Age                           |                               |
| 3-year BFFS (Age ≤65 y; ≥65 y) | 10 Articles (n=1704)          |
|                               | 0.37(0.21–0.57) 5.91 0.95 0   |
| 5-year BFFS (Age ≤65 y; ≥65 y) | 10 Articles (n=1704)          |
|                               | 0.36(0.29–0.46) 8.43 0.63 0   |
| DFS (Age ≤65 y; ≥65 y)         | 5 Articles (n=1043)           |
|                               | 0.54(0.43–0.67) 5.62 0.16 49.3|
| District                      |                               |
| 3-year BFFS (District of Asia; Europe; North America) | 11 Articles (n=1621) |
|                               | 0.37(0.26–0.54) 5.25 0.51 0   |
| 5-year BFFS (District of Asia; Europe; North America) | 14 Articles (n=2413) |
|                               | 0.37(0.30–0.46) 8.85 0.65 0   |
| OS (District of Asia; Europe; North America) | 7 Articles (n=1194) |
|                               | 0.53(0.41–0.68) 4.96 0.47 0   |
| Radiation dose                |                               |
| 3-year BFFS (Radiation dose <70 Gy; ≥70 Gy) | 14 Articles (n=2413) |
|                               | 0.38(0.28–0.52) 6.09 0.59 0   |
| 5-year BFFS (Radiation dose <70 Gy; ≥70 Gy) | 14 Articles (n=2413) |
|                               | 0.37(0.30–0.46) 8.85 0.65 0   |
| OS (Radiation dose <70 Gy; ≥70 Gy) | 7 Articles (n=1194) |
|                               | 0.53(0.41–0.68) 4.96 0.47 0   |
| DFS (Radiation dose <70 Gy; ≥70 Gy) | 7 Articles (n=1302) |
|                               | 0.53(0.43–0.66) 5.98 0.63 0   |
| Publication year               |                               |
| 3-year BFFS (Publication year 1998–2005; 2006–2010) | 11 Articles (n=1432) |
|                               | 0.38(0.26–0.55) 5.04 0.83 0   |
| 5-year BFFS (Publication year 1998–2005; 2006–2010) | 11 Articles (n=1854) |
|                               | 0.36(0.29–0.45) 8.73 0.54 0   |

BFFS: Biochemical Failure-Free Survival; DFS: disease-free survival; OS: overall survival.

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Adjuvant Radiotherapy vs Salvage Radiotherapy: Meta-Analysis

Overall survival is certainly the outcome of greatest importance for any cancer therapy as it incorporates them effect of mortality secondary to cancer, the interventions used, and all other causes. Given the relatively natural history of prostate cancer, it is anticipated that lengthy follow-up is necessary to assess differences in OS. With regard to the RCTs of ART, SWOG 8794 and EORTC 22911, OS was less clear, with benefits reported in SWOG 8794 with long-term data [31]. Our study included 7 clinical trials that demonstrated the OS benefit with ART and ART following RP in patients with APFs prolong the OS compared to SRT. The other primary outcome of the study was BFFS. Biochemical recurrence as a detectable PSA (typically <0.2 ng/ml). With a median follow-up of 3 and 5 years, a significant improvement in BFFS was noted for the ART arm. In summary, all the included studies of ART versus SRT demonstrated improved in outcomes in patients after RP with APFs who received ART.

To better determine possible relationships between ART and SRT, the subgroup analyses were conducted according to age, district, and radiation dose and publication year. Our exploratory subgroup analyses revealed some interesting, hypothesis-generating findings. The 3-year, 5-year BFFS and DFS for ≥65 years age group were similar with <65 years age group. In the district arm, there were no significance differences in 3-year BFFS, 5-year BFFS and DFS. Furthermore, we observed the radiation dose with <70 Gy comparing ≥70 Gy between ART and SRT, suggesting that the ≥70 Gy group was equivalent to <70 Gy group in 3-year and 5-year BFFS, OS, DFS. Based on our analysis, we don’t recommend delivering a higher equivalent dose for patients after RP through a shorter course and larger fraction RT schedules. Finally, we hypothesized that the efficiency of ART and SRT reported in men after RP may have increased over the past decade because of the improvement of imaging and RT techniques. Therefore, we explored the impact of publication year on 2
Table 4. Results of meta-analysis comparison of ART and SRT.

| Outcomes of interest | Overall analysis | Sensitivity analysis |
|----------------------|------------------|---------------------|
|                      | ART studies, patients, no. | SRT studies, patients, no. | HR/RR (95% CI) | Study heterogeneity |
| Primary outcomes     |                  |                  |                | Study重新 | \( \chi^2 \) | df | I 2, % | \( p \) value |
| 3-year BFFS          | 1090             | 1026             | 0.38(0.28–0.52) | <0.001         | 4.75 | 13 0 | 0.38  | 0.71 |
| 5-year BFFS          | 1090             | 1026             | 0.37(0.30–0.46) | <0.001         | 10.56 | 13 0 | 0.47  | 0.49 |
| OS                   | 948              | 871              | 0.53(0.41–0.68) | <0.001         | 5.62  | 6 0  | 0.63  | 0.63 |
| DFS                  | 540              | 475              | 0.53(0.43–0.66) | <0.001         | 4.32  | 6 0  | 0.63  | 0.76 |

**Secondary outcomes**

| DFS                  | 393              | 363              | 0.76(0.60–0.96) | 0.48          | 2.51  | 4 0  | 0.64  | 0.52 |
| MFS                  | 209              | 226              | 0.76(0.65–0.90) | 0.001         | 4.18  | 6 0  | 0.63  | 0.65 |

*: Included studies applied HR; : Included studies applied RR.

The present meta-analysis has the following limitations that must be taken into account. The main limitation is that all the included studies were retrospective samples. Inadequate random sequence generation and blinding tended to increase the risk of bias. Secondly, the other main limitation is lack of toxicity comparison between ART and SRT. After administering post-RT, possible short-term and long-term urinary, bowel and sexual side effects might occur. However, due to long time span and lack of necessary information on the SRT toxicity within the multi-institutional database did not allow us to compare differences in such an endpoint between the two treatment approaches. Moreover, few study focused on the use of androgen deprivation therapy (ADT) in patients who underwent prostatectomy and then ART or SRT. It is difficult to accumulate data regarding the use of ADT in conjunction with RT. As it is the key point, randomized controlled trials are needed to provide definitive evidence. Finally, the included literature doesn’t reflect implementation of these matched control studies and 16 retrospective studies. However, the 5-year BFFS arm and 3-year BFFS arm demonstrated that the publication year didn’t reach statistical significance.

Assuming that the residual tumor burden after prostatectomy would be many logarithms smaller than in the case of radical irradiation, the dose of radiotherapy used in the postoperative setting was generally 20–25% lower (around 60 vs. 76–80 Gy) than that commonly used in the case of radical irradiation [50], but both the appropriate dose for ART and SRT, and whether patients benefited from increasing the dose remain unclear so far. Of the included studies, the dosage of radiotherapy also varied widely. Therefore, we introduced simple linear regression to analyze the relationship between RT dose and prognosis of the patients, revealing that the 3-year BFFS was improved by increasing RT dose in patients receiving SRT. However, in patients receiving ART, the 5-year BFFS was not statistical change with the RT dose. Our results were in consist with the previous studies which had described the higher SRT dose might improve the 5-year BFFS in single-institution [51,52] and multi-institutional [53,54]. Besides the relationship between RT dose and survival benefits, we also analyzed the predictive values of pre-operative and pre-RT PSA on 5-year BFFS. Our results demonstrated that patients with high PSA burden, no matter preoperative or pre-RT all indicated poor prognosis. This finding was in accordance with the results of most previous studies [55,56]. It was worth noting that increased PSA value of patients receiving SRT revealed a more obvious correlation with decreased 5-year BFFS compared that of patients receiving ART. Previous analyses by King et al had separately described the importance of SRT dose and pre-SRT PSA [24,57]. It was possible that high PSA is an indicator of aggressive disease that was less likely to be cured by SRT.

Currently two cooperative groups with Phase III trials will hopefully help to determine the appropriate timing for RT in the postoperative setting. The RADICALS trial administered by the Medical Research Council in England, is randomizing patients with APFs to ART or SRT (initiated following two consecutive PSA rises ≥0.1 ng/ml or three consecutive PSA rises. The second study, a Phase III trial conducted by Trans-Tasman Radiation Oncology Group randomize patients to ART, initiated within 4 months following a RP or early SRT initiated once the PSA levels are ≥0.2 ng/ml. The primary end point of this study will be PSA failure. However, data from these trials are not expected to become available for another decade. In the meantime, there is no consensus on whether patients should be treated with ART or SRT. The study of this system review and meta-analysis focus on this issue, hopefully providing the important advice to answer this question.
newer methods, with only one-quarter of the studies (6/18) reporting use of 3D-CRT techniques and even less reporting use of IMRT techniques.

Nevertheless, this meta-analysis was conducted at an appropriate time, because enough data have accumulated for inspection by meta-analytical methods and we reach the conclusions that
reported 3-year and 5-year BFFS, OS and DFS indicated that ART might reduce the need for SRT. We applied multiple strategies to identify studies, strict criteria to include and evaluate the methodological quality of the studies, and subgroup and sensitivity analysis to minimize the heterogeneity. Thus, we provided the most update information in this area.

Conclusions

This meta-analysis indicates that ART therapy offers a safe and efficient alternative to SRT with longer 3-year and 5-year BFFS, better OS and DFS. Our recommendation is to suggest ART for all patients with APFs and may reduce the need for SRT. Given the inherent limitations of the included studies, future well-designed RCTs are awaited to confirm and update the findings of this analysis.

Supporting Information

Checklist S1 PRISMA Checklist.

(DOC)

File S1 Supplementary data: Table S1. Study Eligibility Criteria for Inclusion in the Review. Table S2. Risk of bias in retrospective studies using modified (Newcastle-Ottawa scale).

Figure S1 Scatter plots of 5-year biochemical failure-free survival (BFFS) against median salvage radiotherapy (ART) dose, median PSA before ART group (ng/ml) and median preoperative PSA of ART group (ng/ml). (Dotted lines represent results of simple linear regression). Figure S2 Forest plot for Metastasis-free survival (MFS). Figure S3 Forest plot for 3-year BFFS in subgroup analysis A) age of included patients was <65 years old B) age ≥65 years old. Figure S4 Forest plot for 5-year BFFS in subgroup analysis A) age of included patients was <65 years old B) age ≥65 years old. Figure S5 Forest plot for Disease Free Survival in subgroup analysis A) age of included patients was younger than 65 years old B) age wasn’t younger than 65 years old. Figure S6 Forest plot for 3-year BFFS in subgroup analysis A) district of included patients was Northern American; B) district of patient was Asian; C) district of patient was European.

Figure S7 Forest plot for 5-year BFFS in subgroup analysis A) district of included patients was European; B) district of patient was Asian; C) district of patient was Northern American. Figure S8 Forest plot for Overall Survival in subgroup analysis A) district of included patients was Asian; B) district of patient was European; C) district of patient was Northern American. Figure S9 Forest plot for 3-year BFFS in subgroup analysis A) radiation dose of included patients was <70 Gy; B) radiation dose of included patients was ≥ 70 Gy. Figure S10 Forest plot for 3-year BFFS in subgroup analysis A) radiation dose of included patients was <70 Gy; B) radiation dose of included patients was ≥ 70 Gy. Figure S11 Forest plot for Disease Free Survival in subgroup analysis A) radiation dose of included patients was <70 Gy; B) radiation dose of included patients was ≥ 70 Gy. Figure S12 Forest plot for Overall Survival in subgroup analysis A) radiation dose of included patients was <70 Gy; B) radiation dose of included patients was ≥ 70 Gy. Figure S13 Forest plot for 3-year BFFS in subgroup analysis A) publication year (1990–2005); B) publication year (1990–2005). Figure S14 Forest plot for 3-year BFFS in subgroup analysis A) publication year (1990–2005); B) publication year (1990–2005).

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Author Contributions

Conceived and designed the experiments: JH CHC. Performed the experiments: JH YZ TXL. Analyzed the data: XXF CHC DDL ZHL. Contributed reagents/materials/analysis tools: DDL KWX GZZ XYH. Conceived and designed the experiments: JH CHC. Performed the experiments: JH YZ TXL. Analyzed the data: XXF CHC DDL ZHL. Contributed reagents/materials/analysis tools: DDL KWX GZZ XYH. Provided the most update information in this area.

References

1. Parin AW, Poudr CR, Clemens JQ, Epstein JI, Walsh PC (1993) Serial PSA after anatomic radical prostatectomy: The Johns Hopkins experience after 10 years. Urol Clin North Am 20: 713–725.
2. Taylor N, Kelly JP, Kahani DA, Babaian RJ, Pisters LL, et al. (2003) Adjuvant and salvage radiotherapy after radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 56: 753–763.
3. Wiegel T, Bottle D, Steiner U, Siegmann A, Golz R, et al. (2009) 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 27: 2924–2930.
4. Jereczek-Fossa BA, Orecchia R (2007) Evidence-based radiation oncology: definitive, adjuvant and salvage radiotherapy for non-metastatic prostate cancer. Radiother Oncol 84: 197–215.
5. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, et al. (2015) Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 190: 441–449.
6. Lehnneras B, Edgren M, Haggman M, Nurlen Bj, Nilsson S (2003) Postoperative radiotherapy after prostatectomy—a review. Scand J Urol Nephrol 37: 10–15.
7. Schild SE (2001) Radiation therapy (RT) after prostatectomy: The case for salvage therapy as opposed to adjuvant therapy. Int J Cancer 96: 94–98.
8. Erickson BK, Martin JV, Shah MS, Straughn JI, Leath CR (2014) Reasons for failure to deliver National Comprehensive Cancer Network (NCCN)-adherent care in the treatment of epithelial ovarian cancer at an NCCN cancer center. Gynecol Oncol.
9. Ancher MS (2004) Salvage radiotherapy for recurrent prostate cancer: the earlier the better. JAMA 291: 1380–1382.
10. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ, Dotan ZA, et al. (2006) Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 98: 713–717.
11. Swindle P, Eastham JA, Olott M, Kattan MW, Wheeler T, et al. (2005) Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 174: 903–907.
12. Kopelan PA, Katcher J, Levin HS, Klein EA (1997) Stage T1–2 prostate cancer: a multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiat Oncol Biol Phys 37: 1043–1052.
13. Lee HM, Solaz MJ, Lupinacci P, Gomella LG, Valicenti RK (2004) Long-term outcome of patients with prostate cancer and pathologic seminal vesicle invasion (pT3b): effect of adjuvant radiotherapy. Urology 64: 84–89.
14. Ohori M, Wheeler TM, Kattan MW, Goto Y, Scardino PT (1995) Prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 154: 1818–1824.
15. Lowe BA, Liebermann S (1997) Disease recurrence and progression in untreated pathologic stage T3 prostate cancer: selecting the patient for adjuvant therapy. J Urol 158: 1452–1456.
16. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, et al. (2005) Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 366: 572–578.
17. Schild SE (1998) Radiation therapy after prostatectomy: now or later? Semin Radiat Oncol 8: 132–139.
18. Akakura N (2001) [Significance of constitutive expression of hypoxia-inducible factor-I alpha (HIF-1 alpha) protein in pancreatic cancer]. Hokkaido Igaku Zasshi 76: 375–384.
19. Won MS, Im N, Park S, Boovannabh SK, Jin Y, et al. (2009) A novel benzimidazole analogue inhibits the hypoxia-inducible factor (HIF)-1 pathway. Biochem Biophys Res Commun 385: 16–21.
20. Ayrapetov MK, Xu C, Sun Y, Zhu K, Parmar K, et al. (2011) Activation of HIFα/β by the prolylhydroxylase inhibitor dimethylglycine decreases radiosensitivity. PLoS One 6: e26064.

21. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17: 2815–2834.

22. Hozzo SP, Djallogbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5: 13.

23. Ospina JD, Coimbra F, Riss K, Drezan J, Corrêa JC, et al. (2013) A tensor-based population value decomposition to explain rectal toxicity after prostate cancer radiotherapy. Med Image Comput Comput Assist Interv 16: 387–394.

24. Ohri N, Dicker AP, Trabulsi EJ, Shosolter TN (2012) Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. Eur J Cancer 48: 837–844.

25. Valicenti RK, Gomella LG, Ismail M, Mulholland SG, Petersen RO, et al. (1999) Effect of higher radiation dose on biochemical control after radical prostatectomy for pT3N0 prostate cancer. Int J Radiat Oncol Biol Phys 42: 501–506.

26. Catton C, Gospodarowicz M, Warde P, Panzarella T, Catton P, et al. (2001) Adjuvant and salvage radiation therapy for radical prostatectomy for adenocarcinoma of the prostate. Radiother Oncol 59: 51–60.

27. Do LV, Do TM, Smith R, Parker RG (2002) Postoperative radiotherapy for carcinoma of the prostate: impact on both local control and distant disease-free survival. Am J Clin Oncol 25: 1–8.

28. Mayer R, Pummer K, Quehenberger F, Mayer E, Fink L, et al. (2002) Postprostatectomy radiotherapy for high-risk prostate cancer. Urology 59: 732–739.

29. Vicini FA, Ziaja EL, Kestin LL, Brabbins DS, Stromberg JS, et al. (1999) Treatment outcome with adjuvant and salvage irradiation after radical prostatectomy for prostate cancer. Urology 54: 111–117.

30. Nudel DM, Grossfeld GD, Weinberg VK, Roach MR, Carroll PR (1999) Radiotherapy after radical prostatectomy: treatment outcomes and failure patterns. Urology 54: 1049–1057.

31. Hudson E, Kynaston H, Varma M, Carter A, Staffurth J, et al. (2008) Postoperative adjuvant and salvage radiotherapy for patients with prostate cancer in Japan; Changing trends in national practice between 1996–98 and 1999–2001: Patterns of care matched control analysis of adjuvant and salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys 80: 1316–1322.