Whether pelvic radiotherapy increased the risk of secondary bladder cancer? A systematic review and meta-analysis

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Abstract

Background The question whether pelvic radiotherapy increases the risk of secondary bladder cancer remains unclear. In this review, we aimed to demonstrate the relationship between exposure to radiation therapy for pelvic malignancies and subsequent second primary bladder cancer risk.

Methods We systematically searched Medline, Embase and Web of Science for all associated studies concerning secondary bladder cancer risk and radiotherapy for primary pelvic cancers up to 15 th December 2019. We extracted related study characteristics and outcomes. Risk of bias was assessed by the Newcastle-Ottawa Scale. Outcomes were synthesized with random effect models and Manhtel-Haenszel weighting. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational studies in Epidemiology (MOOSE) guidelines were used for reporting this systematic review and meta-analysis. We use GRADE system to assess the quality of main outcome.

Results We identified 3958 references after literature searching and eventually 19 studies were selected for meta-analysis. Most studies were cohort studies with moderate risk of bias. Compared with patients treated without radiotherapy, our results showed an increased risk of secondary bladder cancer after radiotherapy for pelvic malignancies (RR 1.75,95% Confidence Interval [CI] 1.50-2.05) with moderate quality of evidence. Similar results were also found in organ-specific analysis of radiation therapy for testicular cancer(RR 2.25,95% CI 1.34-3.78),uterine cancer(RR 2.52,95%CI 1.12-5.67) and prostate cancer(RR 1.64 95%CI 1.39-1.93).Although a varied definitions of latency periods used in different studies, the results showed a consistently increased risk of bladder cancer in all analyzed latency periods, and lag time over 10 years ranked as the highest relative risk(RR 2.98,95%CI 1.88-4.71). When compared with no radiotherapy, EBRT and Any RT significantly increased the risk of second primary bladder cancer (RR 2.08,95%CI 1.67-2.61 and RR 1.77,95%CI 1.49-2.10), but not for BT group (RR 1.58,95%CI 0.98-2.55).

Conclusion In conclusion, pelvic radiotherapy was associated with higher relative risk of secondary bladder cancer compared with those without radiotherapy. These findings may help outpatient counseling and early detection of secondary cancer after diagnosis and treatment of first primary cancer.

Keywords: Secondary Bladder cancer, Pelvic malignancies, Radiotherapy, Meta-analysis

Background

Bladder cancer(BCa) is the tenth most commonly diagnosed cancer worldwide, with an estimated 549,000 new cases and 200,000 deaths(1, 2). The carcinogenesis of bladder cancer is unclear and remains to be fully clarified. The potential pathogenic factors included tobacco smoking, exposure to environmental factors and ionizing radiation, genetic susceptibility and family history. Tobacco smoking is an known important risk factor for bladder cancer(3), accumulating evidence indicated that radiation is associated with increased risk of bladder cancer(4, 5).

With the advancement of radiation technique, radiotherapy has become an essential part of pelvic cancer treatment for radical or palliative or adjuvant intent. Although the concept of precision radiation has been

used to lower the complication rate in clinical practice, patients are at risk suffering early and late radiation-related side effects. Of which, radio-cystitis and proctitis are more often reported and radiation-induced second primary malignancies are considered as the most serious because it shortens the life expectancy. Conventional conformal radiotherapy, External Beam Radiotherapy (EBRT), Brachytherapy(BT)and a combination of EBRT + BT are commonly used RT modality. A systematic review conducted by Rombouts et al(6) suggested that pelvic radiation increased the risk of rectal cancer. Romanenko et al(5) found that chronic exposure to ionizing radiation might contributed to carcinogenesis of bladder cancer after Chernobyl accident. Possible pathogenesis of radiation-induced cancer involved radiation-induced chronic inflammation, oxidative DNA damage, unnormal regulation of cell cycle, inhibition of apoptosis and activation of growth factor receptors and angiogenesis(5). Previous studies showed that radiation-related primary cancer occurred both in the irradiated area and distant area(7–9).

Whether pelvic radiation increase the risk of secondary bladder cancer risk remains unclear. Some studies showed radiotherapy increased risk of second primary bladder cancer(7, 10–14), however, other studies got different results(8, 13, 15, 16). Mazzone et al(17) and Yee et al(18) analyzed the characteristics of secondary bladder cancer, findings indicated that secondary bladder cancer was more often high grade and non-organ confined disease. With the follow-up prolonged, the increasing number of second cancer patients might be an important health concern. The significance of our review was to provide suggestions on screening and early detection of second primary cancer after pelvic RT. Accumulated evidence showed that patients with cancer history increase the risk of second primary cancer(19), we suppose that radiotherapy would exacerbate this situation. We conducted a systematic review and meta-analysis to demonstrate the relationship between the exposure of pelvic radiation and developing secondary bladder cancer.

Methods

Literature search and selection criteria

We conducted a systematic literature search by Medline, Embase and Web of Science from database inception through to December 15,2019. References of selected studies were also checked if needed. The detailed search strategy for each database could be referred in Additional file 1. Two researchers (WCD and ZJR) independently reviewed all studies. Title and abstract screening and then full-text review were conducted. Any discrepancies were resolved by consensus□with XH or XL□. Only English language and available full-text articles reported second bladder cancer risk after pelvic radiation for primary pelvic malignancies were included. All the included studies should provide estimated risk and its confidence interval or could be calculated by relevant data. Furthermore, considering possible data overlapping between studies, studies with the largest population or longest follow-up were considered as eligible. Authors were contacted when the data is unavailable. In our review, no RT is defined as patients treated without any kind of radiotherapy, mainly include Radical Prostatectomy (RP) only, Androgen Deprivation Therapy(ADT),chemotherapy, a combination of RP and other therapies, active surveillance.

Data extraction and Quality assessment

Two researchers（WCD and ZJR）independently extracted the general factors (first author, age, follow-up duration, source of patients, sample size) and outcome indicators (relative risk or odds ratio or hazards ratio and 95% confidence intervals) when available. Some studies might provide different latency period to exclude synchronous tumors, we extracted all these data for further analysis. Disagreements were solved by discussion or consensus with a third researcher (XL).Two researchers（WCD and ZJR） independently assessed the risk of bias for included studies by the 'Newcastle-Ottawa Scale（NOS）' with three main criteria: study selection, comparability and ascertainment of exposure or outcome. A star rating scale (0-9 stars) was used to assess the quality of the included nonrandomized studies. Studies score（5 were considered as high risk of bias, score of 5-7 indicated moderate risk of bias, score （7 were suggested low risk of bias.(20)

GRADE for grading the quality of evidence

We use GRADEpro Guideline Developing Tool (McMaster University,2015, developed by Evidence Prime Inc., Hamilton, Canada; https://gradepro.org/) to evaluate the quality of evidence for main outcome. Several aspects were assessed: risk of bias, inconsistence, imprecision, indirectness, publication bias and other considerations. The GRADE system used four-grade classifications (high, moderate, low and very low) for evaluating the quality of evidence.

Statistical analysis

The primary outcome of this analysis was relative risks for secondary bladder cancer incidence after pelvic radiotherapy. Subgroup analysis was performed to analyze the effect of primary pelvic cancer sites, RT modalities, study design and latency periods on the primary outcome. We directly extracted or calculated relative risk and 95% CI of each study. Considered the inherent heterogeneity of our data, a random-effects model with inverse variance weighting of studies was used for our meta-analysis. Heterogeneity was tested by Chi-square test and I^2 metric. It was defined as heterogeneous if a p-value <0.10 and I^2（50%. The significance of the pooled RRs was evaluated by Z-test, and a p-value <0.05 was considered as statistically significant. Sensitivity analyses were performed to assess the robustness of the results by excluding individual study each time. The potential publication bias was analyzed by the symmetry of funnel plot, Egger's linear regression and Begg and Mazumdar's test. Meta-analysis was mainly performed with Review Manager 5.3 (Nordic Cochrane Centre, Cochrane Collaboration,2014) software and partly by Stata software version 14.0(Stata Corporation, College Station, Texas, USA).

Results

Retrieved studies and characteristics

After literature searching, we identified 3589 references before December 15,2019 (Fig. 1). After titles and abstracts screening, we selected 83 manuscripts for full-text review. After that, a total of 844,761 individuals in 19 studies(8, 13, 15, 16, 21-35) were included in our meta-analysis. Fifteen reports were excluded because studies used overlapped populations from the United States Surveillance, Epidemiology, and End Results (SEER) database or was part of SEER data. We also excluded one study (36) for it is part of another study. Overall, we include nineteen non-randomized trials (two case-control studies, seventeen cohort studies). As for primary site,15 studies reported in prostate cancer, 2 in uterine cancer and 2 in testicular cancer. Six of the included studies were from Europe, 5 from North America and 8 from Asia. Patients treated by EBRT, BT, EBRT+BT and not restricted were reported in 6,6,1 and 11 studies. Eleven studies reported latency period, while the remaining studies did not. The publication year ranged from 1991 to 2019. The detailed study characteristics are shown in Table 1. The NOS score of included studies is presented in Table 2. Most studies were of moderate quality (score 5-7), five studies （one case-control and four cohort studies） were of low quality.

Association between previous radiotherapy of primary cancer and risk of secondary bladder cancer

Nineteen studies with totally 844,761 individuals were included to assess the relationship between radiotherapy for primary pelvic malignancies and risk of secondary bladder cancer. The overall meta-analysis result showed that radiotherapy for primary pelvic malignancies increased the risk of secondary bladder cancer (RR 1.75,95%CI 1.50-2.25, I^2=73%), with moderate-quality evidence (Table 3). Of these, 15 studies with a total 724,599 individuals assessed radiation therapy for prostate cancer and risk of secondary bladder cancer. Previous radiotherapy for prostate cancer was significantly associated with second primary bladder cancer risk (RR 1.64,95%CI 1.39-1.93, I^2=73%) (Fig. 2), with moderate-quality evidence (Table 3).

Radiotherapy of primary uterine cancer and risk of secondary bladder cancer was reported in 2 studies with totally 94,237 participants were analyzed. Radiotherapy for uterine cancer significantly increased the relative risk of primary bladder cancer after radiation therapy (RR 2.52,95%CI 1.12 to 5.67, I2=14%) (Fig. 2), with moderate-quality evidence (Table 3). Two studies with a total of 25925 primary testicular cancer participants were analyzed. Radiotherapy for testicular cancer significantly increased the secondary bladder cancer risk (RR,2.25,95%CI 1.34-3.78, I^2=60%) (Fig. 2), with moderate-quality evidence (Table 3).

Subgroup analysis by study design, latency period and pattern of RT

When stratified by study design, the results indicated that pooled cohort studies (RR,1.77,95%CI 1.50 to 2.08, I2=75%) showed significantly increased risk ratio of secondary bladder cancer, but not for pooled case-control studies (RR,2.12,95%CI,0.57-7.81, I^2=51%)（Table 4）. Subgroup analysis based on latency periods demonstrated that an increased risk of secondary bladder cancer is associated with different latency period over 6 months(RR 1.67, 95% CI 1.58-1.75,I^2=0), over 1 year (RR 2.27, 95% CI 1.76-2.91,I^2=14%), over 5 years(RR 2.27, 95% CI 1.70-3.02,I^2=83%) and over 10 years(RR 2.98, 95% CI 1.88-4.71,I^2=94%)（Table 4）,with low to moderate-quality evidence(Table 3).When analyzed by RT modality,

EBRT and Any RT significantly increased the risk of second primary bladder cancer (RR 2.08 95%CI 1.67-2.61 and RR 1.77 95%CI 1.49-2.10), but not for BT group (RR 1.58 95%CI 0.98-2.55), Table 4, with low to moderate-quality evidence(Table 3).Subgroup analysis based on source of patients showed radiotherapy for pelvic malignancies was significantly associated with second primary bladder cancer risk in Asia, North American and Europe) Table 4, with low to moderate quality evidenceTable 3.

Sensitivity analysis and publication bias

A sensitivity analysis was conducted for risk of secondary bladder cancer and radiotherapy for pelvic malignancies by excluding individual studies each time, and the results showed overall RRs were not influenced by individual study (Fig. 6), indicating the results of this meta-analysis are relatively stable. No publication bias for pelvic radiotherapy and risk of second primary bladder risk was not observed in the results based either on Egger's tests (P = 0.093) or funnel plots (Table 5, Fig. 6). No publication bias was found based on the symmetry of funnel plots or Begg's and Egger's test (P = 0.101) for the relation between any RT and secondary bladder cancer risk (Fig. 6, Table 5).

Discussion

In this review, we mainly focus on the relation between radiotherapy for pelvic malignancies and second primary bladder cancer risk. The findings of this analysis demonstrated that the risk ratio of secondary bladder cancer was increased in participants treated with radiation therapy for primary pelvic malignancies with moderate quality-evidence. Importantly, these findings were consistent in different source of patients and all analyzed latency periods. The significance of our review lied in early detection of second primary cancer and provided suggestions on individual follow-up after diagnosis and treatment of first primary malignancy.

Convincing evidence indicated that radiation exposure is associated with cancer risk. Preston et al (4) reported that radiation increased risk of solid cancers among atomic bomb survivors in Hiroshima and Nagasaki. Similarly, Romanenko et al (5) identified possible mechanism for bladder cancer induced by persistently low-dose exposure to ionizing radiation after Chernobyl accident. Whether pelvic radiation increased the risk of second cancersA meta-analysis conducted by Rombouts et al(6) found radiation was related to increased risk of second primary rectal cancer. Similar results were also confirmed by a previous systematic review by Wallis et al(37), which concluded that RT for prostate cancer increased risk of second cancer of bladder, colon and rectum. Our findings showed pelvic radiation therapy was associated with secondary bladder cancer risk. The excess risk of second primary bladder cancer induced by RT for prostate cancer, uterine cancer and testicular cancer were 64%, 152% and 125% respectively. In pooled analysis, the absolutely excess relative risk of secondary cancers induced by pelvic radiation is 75% compared with no RT. Not all included studies in RT for prostate cancer and uterine cancer group showed consistently increased risk of bladder cancer. Different definitions of latency period, age at exposure, diverse follow-up time and various sources of patients might explain the inconsistency of the results. Importantly, confounding factors such as Human Papillomavirus (HPV) infection and tobacco

smoking influenced both cervical cancer and bladder cancer. Since the lack of related data, further well-designed studies are needed to explore the potential association between these factors and radiation-induced second cancer. Furthermore, all studies analyzed in RT for testicular cancer showed consistently increased risk of bladder cancer. Besides, the risk of radiation-induced secondary bladder cancer was also determined by dose of RT, age at exposure, susceptibility of organs and tissues,durations of RT and other possible confounding factors.

When analyzed by subgroups, our review found that second primary bladder cancer risk statistically increased in all analyzed latency periods. Since a lack of evidence or agreement, the latency periods of second cancer in our review varied by different primary cancer cites, various doses of RT and duration of RT. Without this evidence, we would not decide whether a secondary cancer was due to radiation. Arai et al(22) proposed a definition for radiation-related cancer, which defined as a different histologic type from primary cancer after radiotherapy for at least 2 years and developed in the irradiated area. The reasonability of this definition needed to be clarified by future studies. From the standpoint of etiology, the process of radiation-induced DNA damage and deficiency of DNA injury repair mechanism might be a chronic process and the risk of secondary tumors increased with longer follow-up. Studies(38) suggested that the median time from pelvic radiotherapy to develop urothelial cancer was 8 years. To determine a reasonable latency period would be of great importance for the exploration on pathogenesis of secondary bladder cancer.

Subgroup analysis on pattern of RT used, findings indicated increased risk of bladder cancer in EBRT group, but not for BT group. Similar results were supported by a systematic review conducted by Rombouts et al(6) and colleagues. Significant differences between the two RT modes are doses of radiation, duration of radiation and volume of irradiated tissue might be the possible interpretation Not all studies showed that EBRT increased secondary bladder cancer risk, this was in light of different definitions about latency periods and source of patients. There were also inconsistent results in all included studies in the BT group. A possible explanation was that Aksnessaether et al(39) used high dose rate BT for prostate cancer treatment, which increased the aforementioned risk. High dose radiotherapy caused a higher risk of secondary bladder cancer than low dose radiotherapy(40). In the first decade of this century, intensity-modulated radiotherapy (IMRT) became popular because it reduced the radiation-related toxicity and meanwhile improve survival(41). New radiation techniques like proton radiation and stereotactic body radiotherapy (SBRT) could lower the treatment toxicity and second primary malignancy(42). Contemporary radiologic technique such as Stereotactic ablative radiotherapy (SABR) and Flattening Filter Free (FFF) induced a lower second cancer risk in distant organs.

To our knowledge, this is the first systematic review assessing relationships between pelvic radiotherapy for primary pelvic malignancies and risk of secondary bladder cancer. The large sample size was an important strength of this study. According to this meta-analysis, all three malignant tumors showed consistently increased risk of second primary bladder cancer. The publication bias and heterogeneity in our analysis is relatively small. Besides, we also use GRADE system to evaluate the evidence of the main outcome. We acknowledged that this review had several inherent limitations. Firstly, although we

excluded studies that used overlapped data, we could not thoroughly include all available data in SEER database. As mentioned in Methods, we included studies with largest sample size or longest follow-up duration to overcome overlapping data. Secondly, we only included limited cancer types in our analysis. We failed to include any study on colorectal cancer for insufficient data. Thirdly, we failed to conduct any subgroup analysis on age, dose of radiation and duration of RT because the lack of related data. Fourthly, our study lacked information of important confounding factors like smoking status and status of HPV infection of included patients, which we thought were an important risk factor that might induced confusion. Finally, included studies had moderate risk of bias, and more prospective studies are needed to explore this question.

Conclusions

In general, findings of this meta-analysis showed radiotherapy for pelvic malignancies (prostate cancer, uterine cancer and testicular cancer) increased the secondary bladder cancer risk. When compared with no RT treatment, EBRT increased the risk of second primary bladder cancer. When stratified by latency periods, radiotherapy also increased risk ratio of bladder cancer in lag time over 6 moths, 1 year, 5 years and 10 years. These findings indicated that cancer patients treated with radiotherapy should be monitored closely and was of significance in outpatient counseling. Further studies are needed to explore the possible mechanism of radiotherapy-induced bladder cancer.

Abbreviations

ADT: Androgen deprivation therapy; BCa: Bladder cancer; CI: Confidence Interval; FFF: Flattening Filter Free ; HPV: Human Papillomavirus; IMRT: Intensity-modulated radiotherapy; MOOSE: Meta-analysis of Observational Studies in Epidemiology; NOS: Newcastle-Ottawa scale; OR: Odds ratio; PCa: Prostate cancer; PRISMA: Preferred Reporting Items for Systematic Review and Meta-analysis; RR: Relative risk; SABR: Stereotactic ablative radiotherapy; SBRT: Stereotactic body radiotherapy; SEER: Surveillance, Epidemiology, and End Results; TCa: Testicular cancer; UCa: Uterine cancer.

Declarations

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

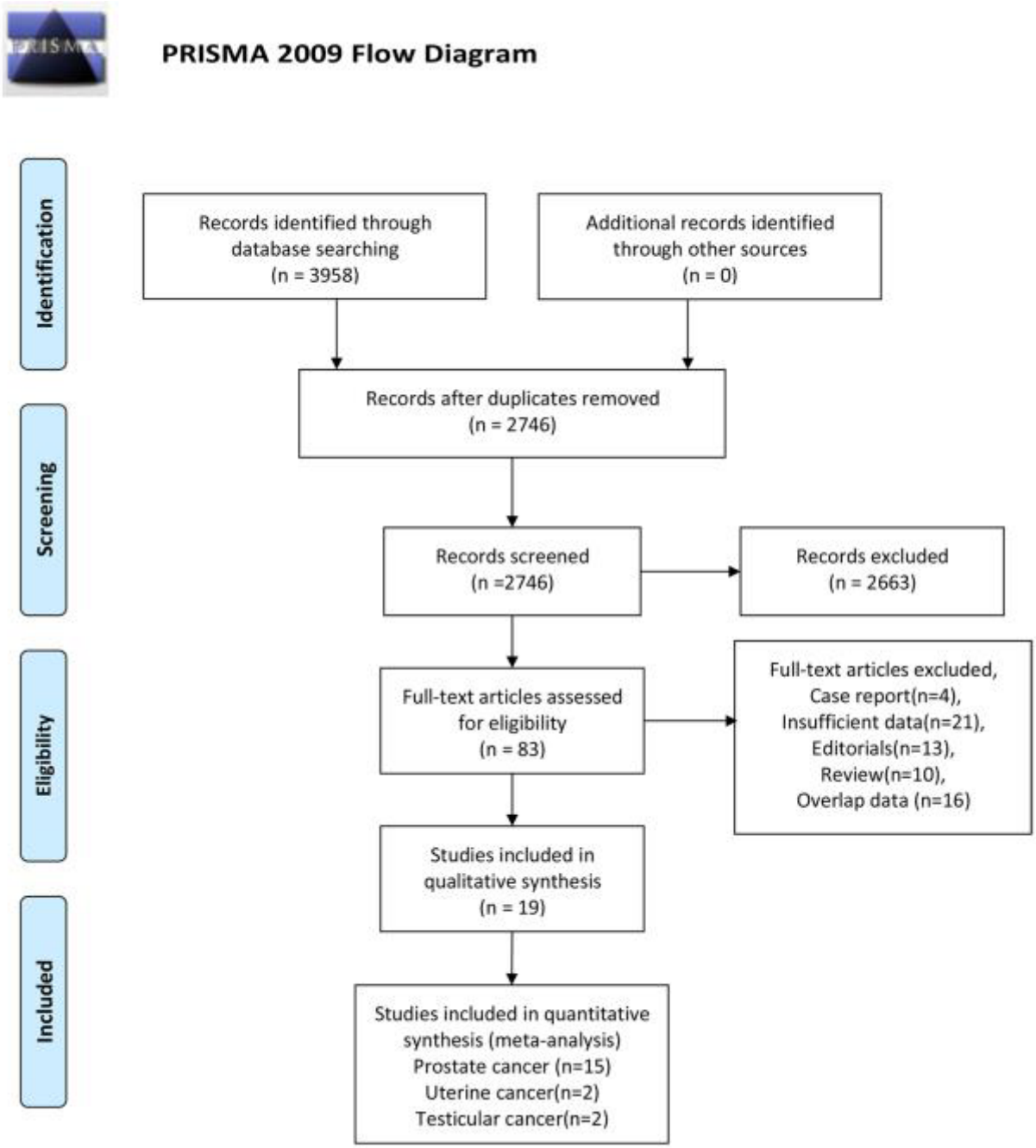

Figure 1

Flow chart of study selection

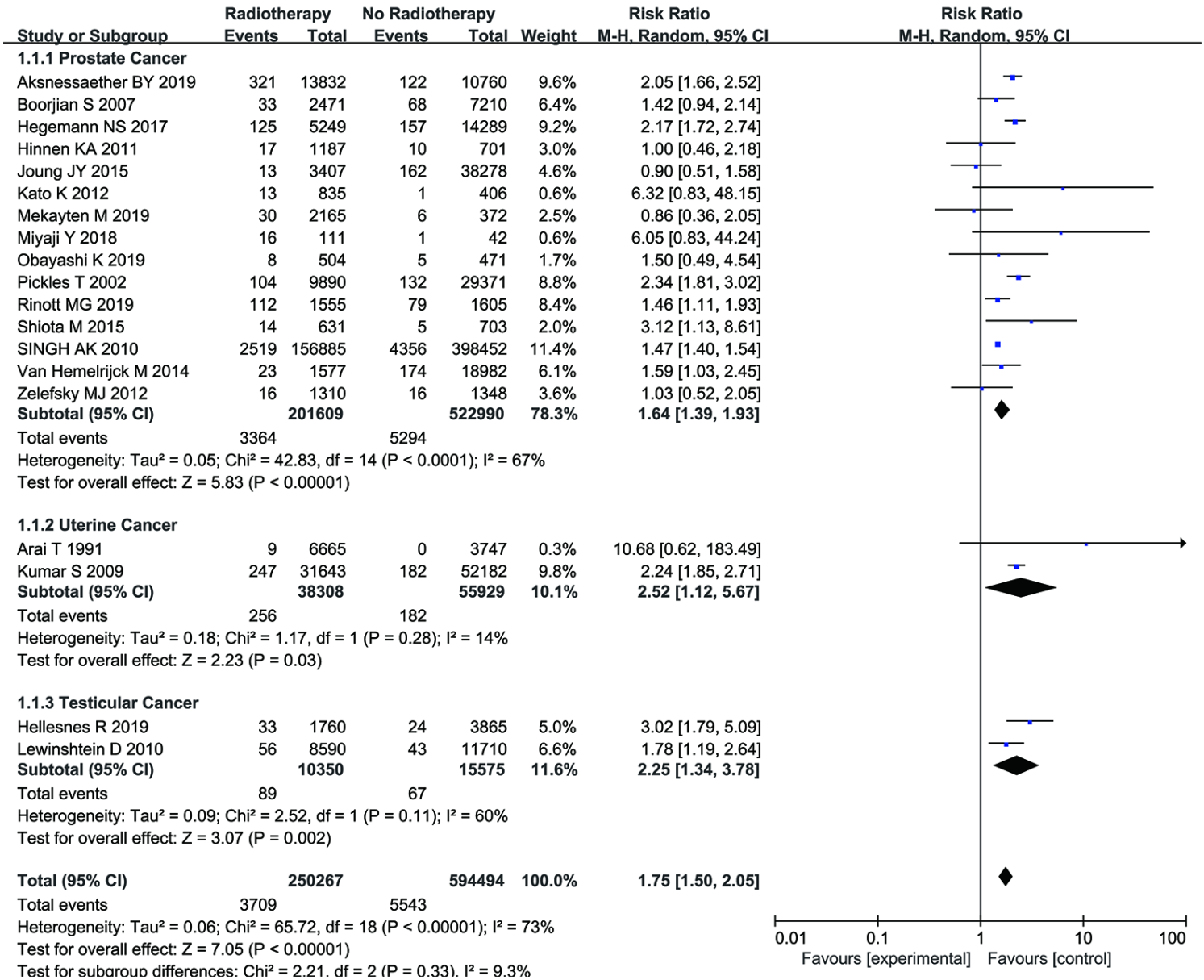

Figure 2

Previous radiotherapy for prostate cancer was significantly associated with second primary bladder cancer risk (RR 1.64,95%CI 1.39-1.93, I2=73%)

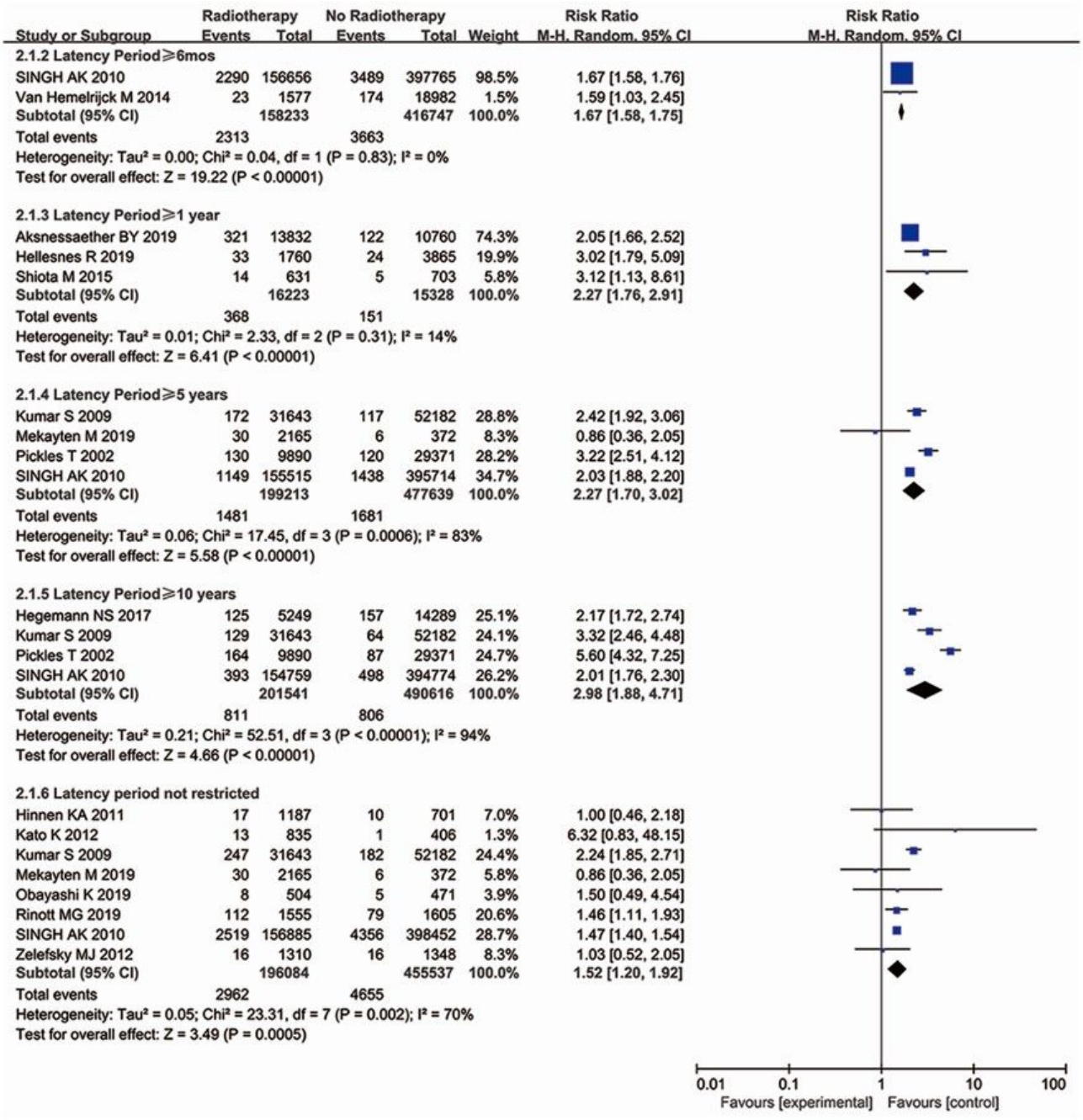

Figure 3

Legend not available in this version

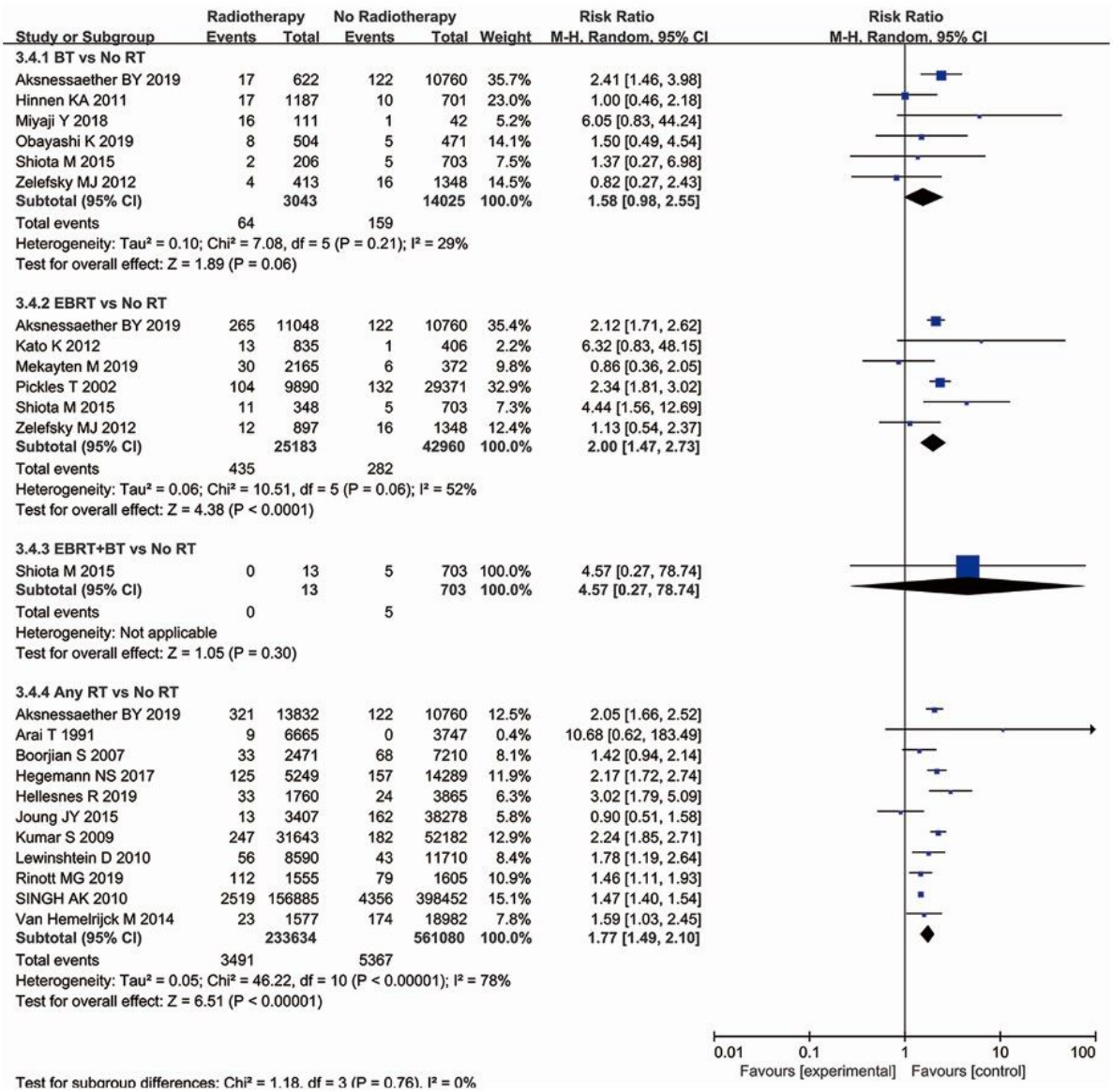

Figure 4

Legend not available in this version

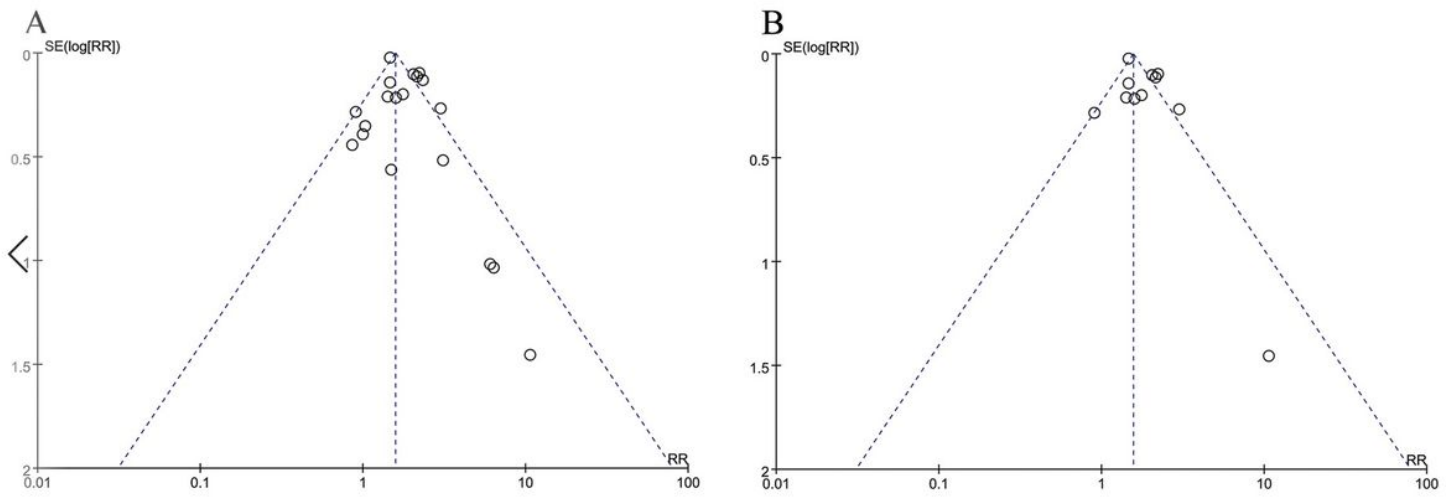

Figure 5

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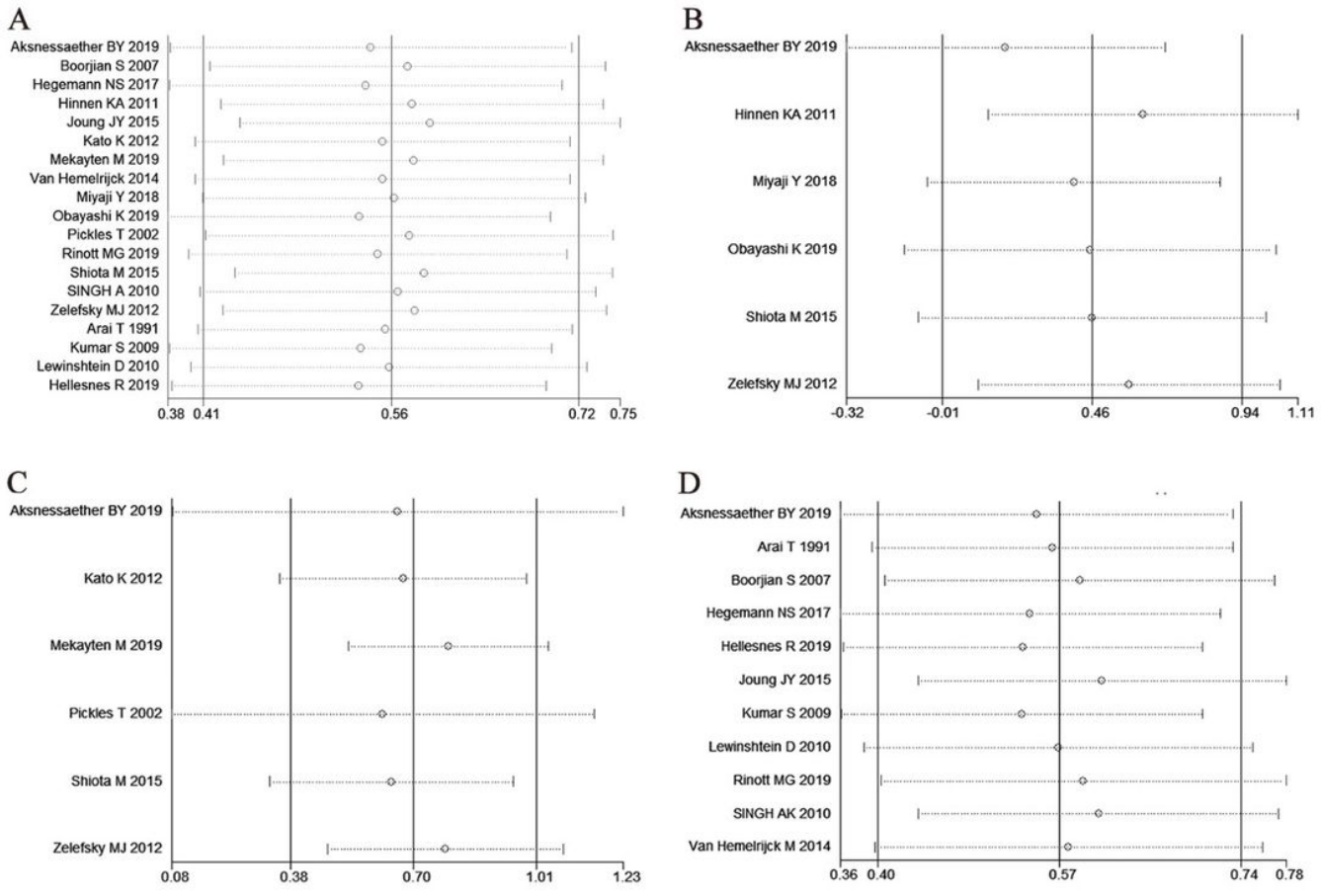

Figure 6

A sensitivity analysis was conducted for risk of secondary bladder cancer and radiotherapy for pelvic malignancies by excluding individual studies each time, and the results showed overall RRs were not influenced by individual study

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table3.docx
- Table5.docx
- Table4.docx
- Table.2.docx
- Additionalfile1SearchStrategy.docx
- PRISMA2009checklist.doc