

Comparison of the effect of postoperative radiotherapy with surgery alone for esophagus squamous cell carcinoma patients

A meta-analysis

Xiao-han Zhao, MD^a, Duo Wang, MD^b, Fang Wang, PhD^b, Shu-chai Zhu, MD^{a,*}

Abstract

Background: This meta-analysis was conducted to evaluate the effect of postoperative radiotherapy for patients having esophagus squamous cell carcinoma after radical surgery.

Methods: A comprehensive research was performed in Pubmed, Embase and Cochrane Library electronic databases from inception until December 10, 2017. We collected all published full articles about comparison of surgery plus postoperative radiotherapy with surgery alone.

Results: Four randomized-controlled trials (RCTs) with 1050 participants and 8 non-randomized-controlled trials with 3248 participants were included and evaluated separately. The risk ratio rate and its 95% confidence interval (CI) were calculated. Both RCTs and non-randomized-controlled trials (NRCTs) groups showed a significant increase in 3-year overall survival (OS) rate ($RR_{RCT}=0.89$, 95% CI: 0.80–0.99; $RR_{NRCT}=0.82$, 95% CI: 0.76–0.88) and decrease locoregional recurrence rate ($RR_{RCT}=0.53$, 95% CI: 0.43–0.66; $RR_{NRCT}=0.47$, 95% CI: 0.32–0.69) after postoperative radiotherapy compared with surgery alone. The 5-year OS rate in the group of NRCTs was markedly enhanced ($RR=0.87$, 95% CI: 0.82–0.92), while that of the RCTs group was not enhanced in a significant way ($RR=0.84$, 95% CI: 0.70–1.02). Subgroup analysis based on pathological lymph node status revealed that postoperative radiotherapy could improve OS regardless of pathological lymph node status (pathological lymph node positive patients: $RR_{5\text{-year OS-RCT}}=0.81$, 95% CI: 0.70–0.93; $RR_{5\text{-year OS-NRCT}}=0.87$, 95% CI: 0.80–0.94; Pathological lymph node negative patients: $RR_{3\text{-year OS-RCT}}=0.76$, 95% CI: 0.59–0.96; $RR_{3\text{-year OS-NRCT}}=0.52$, 95% CI: 0.30–0.89). No effect on distant recurrence rate was detected. Adverse effects induced by postoperative radiotherapy were comparatively modest and tolerable.

Conclusion: Polled results yielded that postoperative radiotherapy was promising in improving OS and reducing the locoregional recurrence rate. More large-scale up-to-date RCTs are needed to further validate the use of postoperative radiotherapy in modern practice.

Abbreviations: DFS = disease free survival, ESCC = esophageal squamous cell carcinoma, NRCT = non-randomized-controlled studies, OS = overall survival, RCTs = randomized-controlled trials, RR = risk ratio.

Keywords: meta-analysis, postoperative radiotherapy, surgery

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1. Introduction

Esophageal cancer is the eighth most common malignancy worldwide and the sixth most common cause of death from cancer.^[1] Esophageal squamous cell carcinoma (ESCC), one of the main subtypes of esophageal cancer and predominantly found in Asia, Africa, and South America, accounts for 90% of cases of esophageal cancer worldwide.^[2]

Esophagectomy with extended lymph node dissection is an essential treatment for ESCC patients with curative intention. However, the prognosis for ESCC patients receiving surgery alone is poor, for example, the 5-year overall survival (OS) rate is less than 30%^[3] while the local-regional recurrence rate is as high as 33%, and the distant recurrence rate is approximately up to 20% depending on the stage.^[4] These data clearly indicate that surgery alone may not be sufficient.

For resectable ESCC, neoadjuvant chemoradiotherapy followed by surgery has been regarded as a standard primary treatment, which was recommended by the National Comprehensive Cancer Network and European Society for Medical

Oncology guidelines.^[5,6] However, there remained a large number of patients receiving upfront surgery, which is especially prevalent in China.^[7] For these patients, adjuvant therapy may be necessary although no study of its impact has been well established.^[8–10]

Since the 1990s, postoperative radiation for esophageal cancer has been attempted, with some critical advanced techniques in radiotherapy treatment emerging in recent years, including 3-dimensional conformal radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, proton radiation, and more, where postoperative radiotherapy has been used more often in esophageal cancer. However, the efficacy of postoperative radiotherapy in treating ESCC is controversial, because some randomized-controlled trials (RCT) conducted earlier failed to confer a survival difference between surgery with and without postoperative radiotherapy.^[11,12] Whereas recently, some RCTs and a series of retrospective studies have reported that postoperative radiotherapy with advanced radiation techniques such as intensity-modulated radiotherapy can dramatically improve OS and locoregional control.^[13–16]

Until now, there has been no systematic review quantitatively assessing the benefit of additional postoperative radiotherapy alone for ESCC patients receiving upfront surgery. To further examine the role of postoperative radiotherapy, this meta-analysis was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Our primary outcomes were OS rates for 3 and 5 years, and data regarding disease-free survival (DFS), recurrence pattern, and adverse effects were also collected if available.

2. Materials and methods

2.1. Study design

This systematic review and meta-analysis were carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.^[17] No ethical approval and patient written informed consent is needed because all processes of the whole study were performed on the basis of previous information.

2.2. Search strategy

A literature search was performed in Pubmed, Embase, and Cochrane Library electronic databases from inception until December 10, 2017, where we used the following search terms: ESCC, radiotherapy, postoperative. MeSH terms and text-words searches were used. Some references were included manually by retrieving original articles to identify other potentially eligible studies.

2.3. Criteria for inclusion and exclusion

The studies met the following criteria were considered to be eligible:

1. All studies that compare postoperative radiotherapy versus surgery alone in ESCC patients, where no exclusion was set based on the type of study design.
2. Surgery was conducted as an esophagectomy with curative intent, and no limitation was set for these procedures.
3. ESCC was diagnosed according to pathological report.
4. No preoperative treatment was conducted and postoperative radiotherapy was used as the major adjuvant treatment.

5. The associated outcomes could be extracted.
6. Only published full papers were considered for inclusion.
7. Publication language was limited to English.
8. For studies reporting the results from duplicate patients, only those with the most comprehensive data were included.

The exclusion criteria are:

1. Duplicate data, reviews, case reports, conferences abstracts, and single-armed studies.
2. Surgery was performed with endoscopic resection or with palliative intent,
3. Presence of confounding factors such as preoperative treatment modalities or utilization of postoperative chemotherapy.

2.4. Assessment of methodological quality

Qualities of the RCTs were evaluated by the Risk of Bias Table in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.^[18] There are 3 levels of bias: high, unclear, or low risk of bias to assess the following items: generation of allocation sequences, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data addressed, presence of biases in reports, and other sources of bias that could influence the study's validity. Non-randomized-controlled trials (NRCTs) were assessed according to the Newcastle–Ottawa Scale, which contains 3 parameters of quality: selection, comparability, and exposure assessment. The Newcastle–Ottawa Scale assigns maximum scores of 4 for selection, 2 for comparability, and 3 for exposure.

2.5. Data extraction and statistical analysis

The following data was extracted from the selected articles by 2 reviewers independently: the name of first author, year of publication, sample size, baselines of patients, recruitment period, country, radiotherapy dose and schedule, site of tumor, OS rates for 3 and 5 years, DFS rates for 1 year and 3 years, locoregional recurrence rate and distant recurrence rate, adverse effects. Any disagreement was discussed with a third reviewer. Statistical analyses were performed with Review Manager 5.3 (Cochrane Collaboration, Oxford, UK), and the primary outcomes were 3-year OS and 5-year OS rates. Subgroup analysis according to pathological lymph node status was also prepared. Other outcomes such as DFS, locoregional recurrence rate, and distant recurrence rate were also evaluated if available. All the outcomes were analyzed using an RR with a 95% confidence interval (CI), which were extracted from article directly if available. Otherwise, Engauge Digitizer version 4.1 (<http://sourceforge.net>) was used to extract the associated data to calculate the RR and its 95% CI. Heterogeneity was evaluated by Cochran's Q statistic and I^2 test, The I^2 yielded results ranging from 0 to 100% ($I^2=0-40%$, low heterogeneity; $I^2=40-60%$, moderate heterogeneity; $I^2=50-90%$, large heterogeneity; and $I^2=75-100%$, extreme heterogeneity). The random-effects model was used if $I^2 \geq 50%$, otherwise, the fix-effects model was utilized. Sensitivity analysis was performed by omitting each study to test the robustness of results and to discover sources of heterogeneity. Publication bias was assessed by funnel plots. P values were considered significant at the .05 level.

3. Results

3.1. Study characteristics

A total of 12 studies^[11–16,19–24] (4 RCTs and 8 NRCTs) involving 4298 participants were eligible for this review, which included 1728 patients in the postoperative radiotherapy group and 2570 patients in the surgery alone group. The flowchart of the retrieved studies was presented in Figure 1, and details of the eligible articles were summarized in Table 1. The recruitment period ranged from 1979 to 2015. R0 resections were performed for nearly all patients if reported except in the study from Bo Qiu, which specifically focused on 70 patients with R1 resection. The postoperative TNM stages of participants ranged from stage I to stage IV, and stage II and stage III were the most common. Postoperative chemoradiotherapy cohorts were excluded from the calculation, and only patients receiving postoperative radiotherapy as the main adjuvant treatment were included in this review. Although studies by Wen-cheng Zhang and Gang Chen included a small portion of patients (30 of 190, 79 of 181, respectively) receiving chemotherapy in the postoperative

radiotherapy group, these studies were included in this review after a sensitivity analysis (see Supplemental Digital contents) showed no significant effect on outcome and heterogeneity. Two-dimensional radiotherapy technique was the most frequently introduced technique in studies published in the 20th century, whereas 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy were used extensively since the 21st century. Most radiotherapy targets included tumor bed, anastomosis site, and associated lymph node drainage areas. The total radiation dose ranged from 36 Gy to 60 Gy whereas radiation schedule was similar with an arrangement of 1.8 to 2.0 Gy/fraction per day, 5 times/week. The details for the radiotherapy arrangement were shown in Table 2. Most of these studies were performed in Asia.

3.2. Quality of the included studies

The selected RCTs had a high overall quality, and most of them had a low risk of bias despite allocation concealments being unclear in 3 studies. For NRCTs, the most common

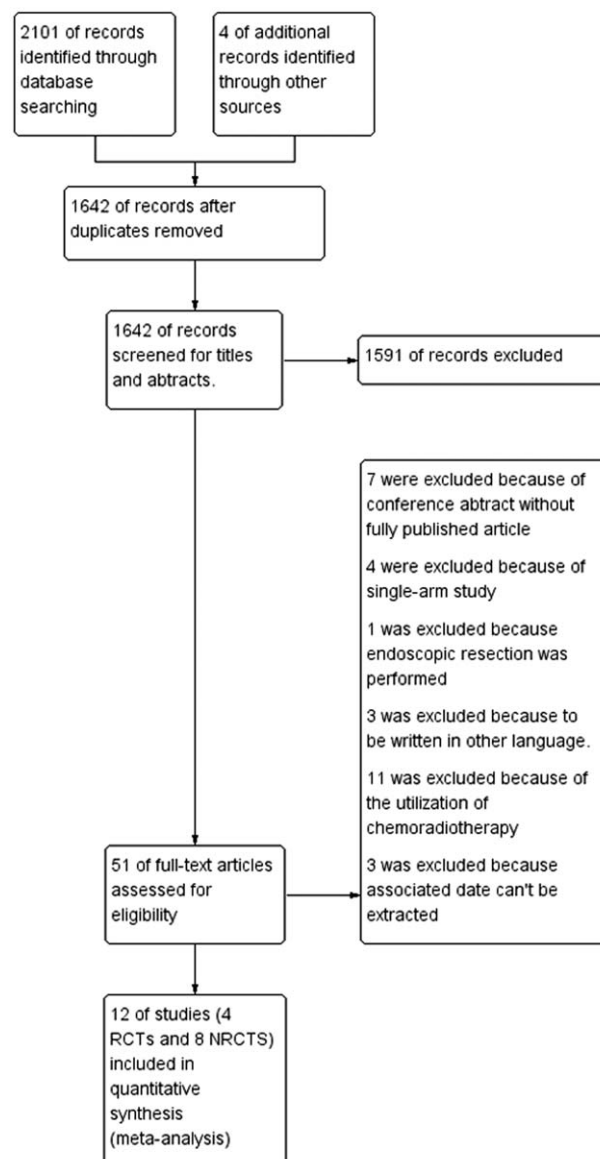


Figure 1. Flow diagram for studies retrieving and inclusion.

Table 1

Basic characteristics for all of the pooled studies in the meta-analysis.

| Study | Year | Study type | Country | Recruitment period | Patients selection | Percentage for RO resection (PRT/SA) | Number of participants (PRT vs SA) |
|----------------------|------|------------|---------|--------------------|---|--------------------------------------|------------------------------------|
| Jinsong Yang, 2017 | 2017 | NRCT | China | 2004–2011 | pT ₃ N ₀ M ₀ | 100%/100% | 83PRT VS 83SA |
| Kyung Hwan Kim, 2017 | 2017 | NRCT | Korea | 1994–2014 | pT _{1–4} N _{0–3} M ₀ | 97.1%/92.7% | 41PRT VS 68SA |
| Bo Qiu, 2017 | 2017 | NRCT | China | 2000–2015 | stage I-III, pT _{1–4} N _{0–3} M ₀ | 0%/0% | 26PRT VS 46SA |
| Shaobin Chen, 2016 | 2016 | NRCT | China | 2004–2009 | stage II-III, pT ₃ N _x M ₀ | 100%/100% | 246PRT VS 446SA |
| Shuai Wang, 2016 | 2016 | RCT | China | 2004–2009 | pT ₂ N ₀ M ₀ (Ku80 overexpression) | NR | 106PRT VS 106SA |
| Wencheng Zhang, 2015 | 2015 | NRCT | China | 2004–2009 | stage II–III | 100%/100% | 190PRT VS 348SA |
| Yaping Xu, 2013 | 2013 | NRCT | China | 2001–2009 | stage I-III, T _{1–4} N _{1–3} M ₀ | 100%/100% | 91PRT VS 372SA |
| Junqiang Chen, 2012 | 2012 | NRCT | China | 1996–2009 | pT _{1–4} N _{1–3} M ₀ | NR | 355PRT VS 590SA |
| Gang Chen, 2009 | 2009 | NRCT | China | 1999–2004 | stage I-III, pT _{1–3} N _{0–3} M ₀ | 100%/100% | 181PRT VS 82SA |
| Zefen Xiao, 2005 | 2005 | RCT | China | 1986–1997 | stage II-III, pT _{2–3} N _x M ₀ | NR | 274PRT VS 275SA |
| Hans U.Zieren, 1995 | 1995 | RCT | Germany | 1988–1991 | stage II-IV, pT _x N _x M _{0–1} | 100%/100% | 35PRT VS 33SA |
| Paul Teniere, 1991 | 1991 | RCT | France | 1979–1985 | pT _x N _x M _{0–1} | NR | 102PRT VS 119SA |

NR=no report, NRCT=Non-randomized controlled trials, PRT=postoperative radiotherapy, RCT=randomized controlled trials, SA=surgery alone.

Table 2

Details for radiotherapy arrangements.

| Study | Radiotherapy schedule | Interval between radiotherapy and surgery | Definition of radiotherapy area |
|----------------------|---|---|--|
| Jinsong Yang, 2017 | 50–60 Gy in total, 1.8–2.0 Gy/fraction | 4–10 weeks post surgery | Upper thoracic tumors: The radiotherapy areas were defined superiorly as the cricothyroid membrane and inferiorly as 2 to 3 cm below the trachea carina, including the lower cervical, supraclavicular region and mediastinal stations 1R/L, 2R/L, 3p, 4R/L, and 7; Middle thoracic tumors: The radiotherapy areas were defined superiorly as the upper margin of the first thoracic vertebral body and inferiorly as 2 to 3 cm below the lower border of the tumor bed, including the lower cervical and supraclavicular region and mediastinal stations 1R/L, 2R/L, 3p, 4R/L, 7, and part of 8. Lower thoracic tumors: the borders were defined superiorly as the upper margin of the first thoracic vertebral body and inferiorly as the left gastric region (including the supraclavicular regions, mediastinal stations 1R/L, 2R/L, 3p, 4R/L, 7, 8 and paracardial and left gastric regions). |
| Kyung Hwan Kim, 2017 | 34.8–59.4 Gy in total, 1.8 Gy/fraction | Within 2 months post surgery | The radiotherapy areas covered the tumor bed, anastomosis site, lymph node drainage areas. Bilateral supraclavicular area was performed on the patients with upper esophageal cancer or involvement of the supraclavicular lymph nodes. |
| Bo Qiu, 2017 | NR | NR | NR |
| Shaobin Chen, 2016 | 50–60 Gy in total, 2.0 Gy/fraction, 5 times/week | 4–8 weeks post surgery | The radiotherapy areas contained the tumor bed, bilateral supraclavicular area, the drainage areas of the lymph nodes in the upper and middle mediastinum. |
| Shuai Wang, 2016 | 50–60 Gy in total, 2.0 Gy/fraction, 5 times/week | NR | The radiotherapy area covered the cervical, bilateral supraclavicular area, and superior mediastinal regions (including the upper thoracic esophageal and tracheal regions). |
| Wencheng Zhang, 2015 | 36–60 Gy in total, 1.8–2.0 Gy/fraction, 5 times/week | 4–6 weeks post surgery | Upper thoracic tumors: the radiotherapy area covered tumor bed, anastomosis site, mediastinal stations 1, 2, 4, 7; Middle and lower thoracic tumors: the radiotherapy area covered the tumor bed, mediastinal stations 2, 4, 7 and left gastric artery. |
| Yaping Xu, 2013 | 40–56 Gy in total | 3–4 weeks post surgery | Upper/middle thoracic tumors: the radiotherapy area covered the tumor bed, bilateral supraclavicular area, mediastinum, and subcarinal area lower thoracic tumors: the radiotherapy area covered the tumor bed, bilateral supraclavicular area mediastinum, subcarinal area and lower thoracic paraesophageal lymph nodes area. |
| Junqiang Chen, 2012 | 36–60 Gy in total, 2.0 Gy/fraction, 5 times/week | 3–4 weeks post surgery | The radiotherapy area covered the tumor bed, bilateral supraclavicular area, mediastinum. |
| Gang Chen, 2009 | 45–60 Gy in total, 4.0 Gy in total, 2.0 Gy/fraction, 5 times/week | NR | The whole mediastinum and bilateral supraclavicular area. |
| Zefen Xiao, 2005 | 30.6 Gy in total, 1.8 Gy/fraction | 3–4 weeks post surgery | The field included the entire mediastinum, site of anastomosis, and left epiploic and paracardiac lymphatics. |
| Hans U.Zieren, 1995 | 30.6 Gy in total, 1.8 Gy/fraction | 3–6 weeks post surgery | The whole mediastinum and bilateral supraclavicular area. |
| Paul Teniere, 1991 | 45 Gy in total, 1.8 Gy/fraction | Within 3 months post surgery | The whole mediastinum and bilateral supraclavicular area. |

NR=no report.

Table 3
A Summary of quality for randomized controlled trials.

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of and outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|--------------------|----------------------------|------------------------|--|------------------------------------|-------------------------|---------------------|------------|
| Shuai Wang 2016 | Unclear | Unclear | Unclear | Unclear | Low risk | Low risk | Low risk |
| Zefen Xiao 2005 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk |
| Hans U.Zieren 1995 | Low risk | Unclear | Low risk | Low risk | Low risk | Low risk | Low risk |
| Paul Teniere 1991 | Low risk | Low risk | Low risk | Low risk | Unclear | Low risk | Low risk |

B Summary of quality for non-randomized controlled trials.

| Study | Year | Is the case definition adequate * | Representativeness of the Cases * | Selection of Controls * | Definition of Controls * | Comparability ** | Ascertainment of Exposure * | Is same method for case and control * | Nonresponse rate * | Scores |
|----------------|------|-----------------------------------|-----------------------------------|-------------------------|--------------------------|------------------|-----------------------------|---------------------------------------|--------------------|--------|
| | | | | | | | | | | |
| Jinsong Yang | 2017 | * | * | * | * | ** | * | * | * | ***** |
| Kyung Hwan Kim | 2017 | * | / | * | * | / | * | * | / | ***** |
| Bo Qiu | 2017 | * | / | * | * | / | * | * | / | ***** |
| Shaobin Chen | 2016 | * | * | * | * | / | * | * | / | ***** |
| Wencheng Zhang | 2015 | * | * | * | * | * | * | * | / | ***** |
| Yaping Xu | 2013 | * | * | * | * | * | * | * | / | ***** |
| Junqiang Chen | 2010 | * | * | * | * | / | * | * | / | ***** |
| Gang Chen | 2009 | * | * | * | * | * | * | * | / | ***** |

selection biases were in the selection of controls from hospital controls, and no study reported a nonresponse rate. As for comparability, most studies enrolled comparable patients whereas in some studies, the postoperative radiotherapy group had a relatively worse baseline level of health than that in the surgery alone group. Details of quality assessment were shown in Table 3. The overall methodological quality of included studies was high.

3.3. 3-year OS rate

Data for 3-year OS was available in 12 studies, among which 4 were RCTs^[11,12,15,16] and 8 were NRCTs.^[13,14,19-24] The results from the RCTs and NRCTs were analyzed separately, and a consistent conclusion showed that the 3-year OS was higher in postoperative radiotherapy group than in the surgery alone group (RR_{rct}=0.89, 95% CI: 0.80-0.99; RR_{nrct}=0.82, 95% CI: 0.76-0.88). There was a modest heterogeneity in the RCTs group ($I^2=47\%$, $P=.13$), and the heterogeneity was very low in NRCTs group ($I^2=6\%$, $P=.38$) (Fig. 2).

3.4. 5-year OS rate

Five-year OS was extracted from 11 studies including 4 RCTs^[11,12,15,16] and 7 NRCTs^[13,14,19-21,23,24]. There was a tendency favoring postoperative radiotherapy in RCTs group although a significant difference was not found (RR=0.84, 95% CI: 0.70-1.02) and a large heterogeneity was detected ($I^2=78\%$, $P=.004$). Postoperative radiotherapy was shown to be beneficial in improving 5-year OS in the NRCTs group (RR=0.87, 95% CI: 0.82-0.92) with low heterogeneity ($I^2=5\%$, $P=.39$) (Fig. 3).

3.5. Subgroup analysis of pathological lymph node status for OS

In order to investigate the relationship between the effectiveness of postoperative radiotherapy and pathological lymph node status for ESCC, subgroup analysis was performed. For pathological lymph node positive (pN+) patients, 1 RCT and 2 NRCTs were available. A tendency towards a better 3-year OS

(RR=0.85, 95%CI: 0.72-1.01) and a significant 5-year OS (RR=0.81, 95% CI: 0.70-0.93) were observed in postoperative radiotherapy group in RCT study. NRCTs showed consistent favor of postoperative radiotherapy in 3-year OS ($I^2=0\%$, $P=.76$; RR=0.79, 95% CI: 0.72-0.88) and 5-year OS ($I^2=0\%$, $P=.67$; RR=0.87, 95% CI: 0.80-0.94). For pathological lymph node negative (pN-) patients, the results from 2 RCTs studies and 1 NRCT study were assessed separately. Survival advantage was obvious in RCTs group for 3-year OS (RR=0.76, 95% CI: 0.59-0.96) with a low heterogeneity ($I^2=0\%$, $P=.35$) while no significant difference was seen for 5-year OS and heterogeneity existed ($I^2=87\%$, $P=.005$; RR=0.80, 95% CI: 0.49-1.32). NRCTs indicated postoperative radiotherapy can improve 3-year and 5-year OS (RR_{3-year}=0.52, 95% CI: 0.30-0.89; RR_{5-year}=0.59, 95% CI: 0.37-0.93) (Fig. 4, Fig. 5).

3.6. DFS rate

5 studies were used to calculate DFS for 1 year and 3 years including 2 RCTs and 3 NRCTs. Neither RCTs nor NRCTs showed any difference in 1-year or 3-year DFS. The RR rates for 1-year DFS were 0.79 (95% CI: 0.54-1.18) in RCTs group and 0.65 (95% CI: 0.38-1.09) in NRCTs group respectively. The RR rates for 3-year DFS were 0.83 (95%CI: 0.63-1.09) in RCTs group and 0.82 (95% CI: 0.58-1.17) in NRCTs group respectively. The heterogeneity for 1-year DFS was small in the RCTs group ($I^2=0\%$, $P=.38$), and higher in NRCTs group ($I^2=73\%$, $P=.02$). There was a heterogeneity in both RCTs and NRCTs group for 3-year DFS ($I^2=57\%$, $P=.13$; $I^2=81\%$, $P=.006$, respectively) (Fig. 6, Fig. 7).

3.7. Locoregional recurrence rate and distant recurrence rate

Locoregional recurrence rate and distant recurrence rate were evaluated separately by 2 RCTs and 5 NRCTs. Both RCTs and NRCTs groups suggested that postoperative radiotherapy can reduce the likelihood of locoregional recurrence rate (RR_{RCT}=0.53, 95% CI: 0.43-0.66; RR_{NRCT}=0.47, 95% CI: 0.32-0.69). Modest heterogeneity was found in the RCTs group ($I^2=49\%$,

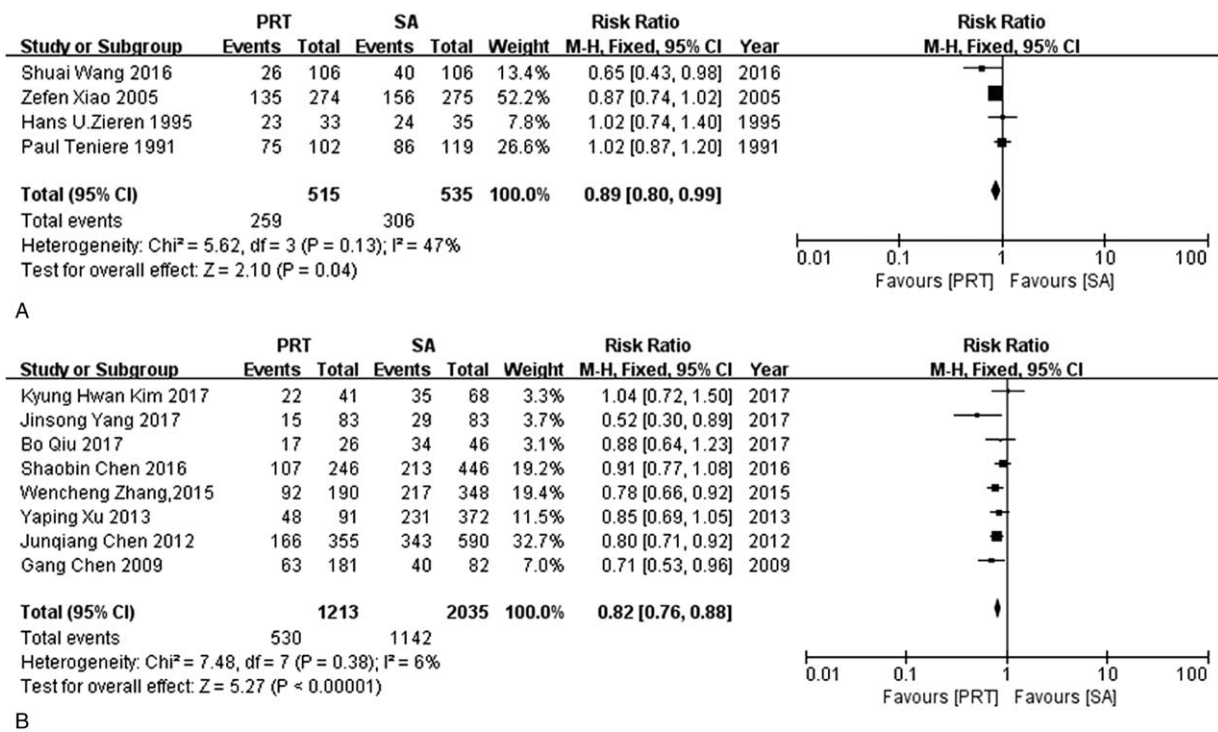


Figure 2. Forest plot of risk ratio for 3-year overall survival. (A) The pooled results from randomized-controlled trials; (B) the pooled results from non-randomized-controlled trials. PRT=postoperative radiotherapy, SA=surgery alone.

$P = .16$) and significant heterogeneity was seen in NRCTs group ($I^2 = 84\%$, $P < .0001$). For distant recurrence rate, Neither the RCTs group nor NRCTs group found a significant difference between postoperative radiotherapy and surgery alone ($RR_{RCT} =$

1.29 , 95% CI: $0.94-1.77$, $RR_{NRCT} = 0.91$, 95% CI: $0.72-1.15$). Heterogeneity was considered to be low in RCTs group whereas modest in NRCTs group ($I^2_{RCT} = 0\%$, $P = .84$, $I^2_{NRCT} = 63\%$, $P = .03$) (Fig. 8, Fig. 9).

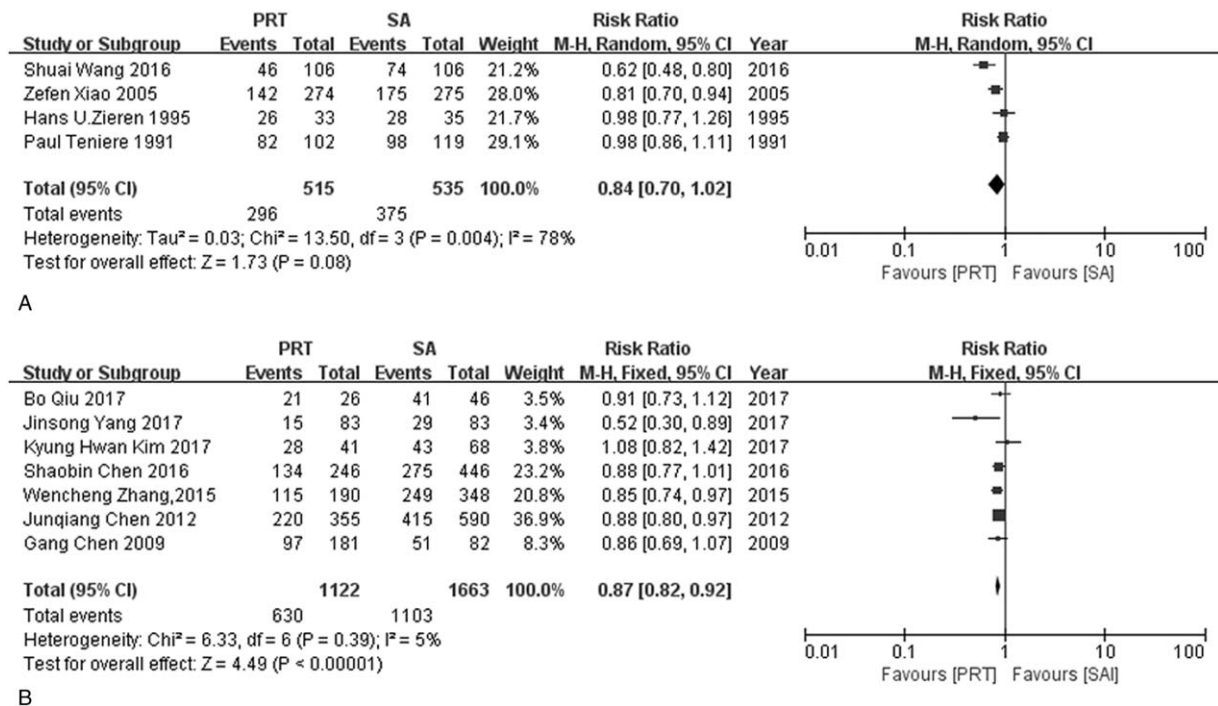


Figure 3. Forest plot of risk ratio for 5-year overall survival. (A) The pooled results from randomized-controlled trials; (B) the pooled results from non-randomized-controlled trials. PRT=postoperative radiotherapy, SA=surgery alone.

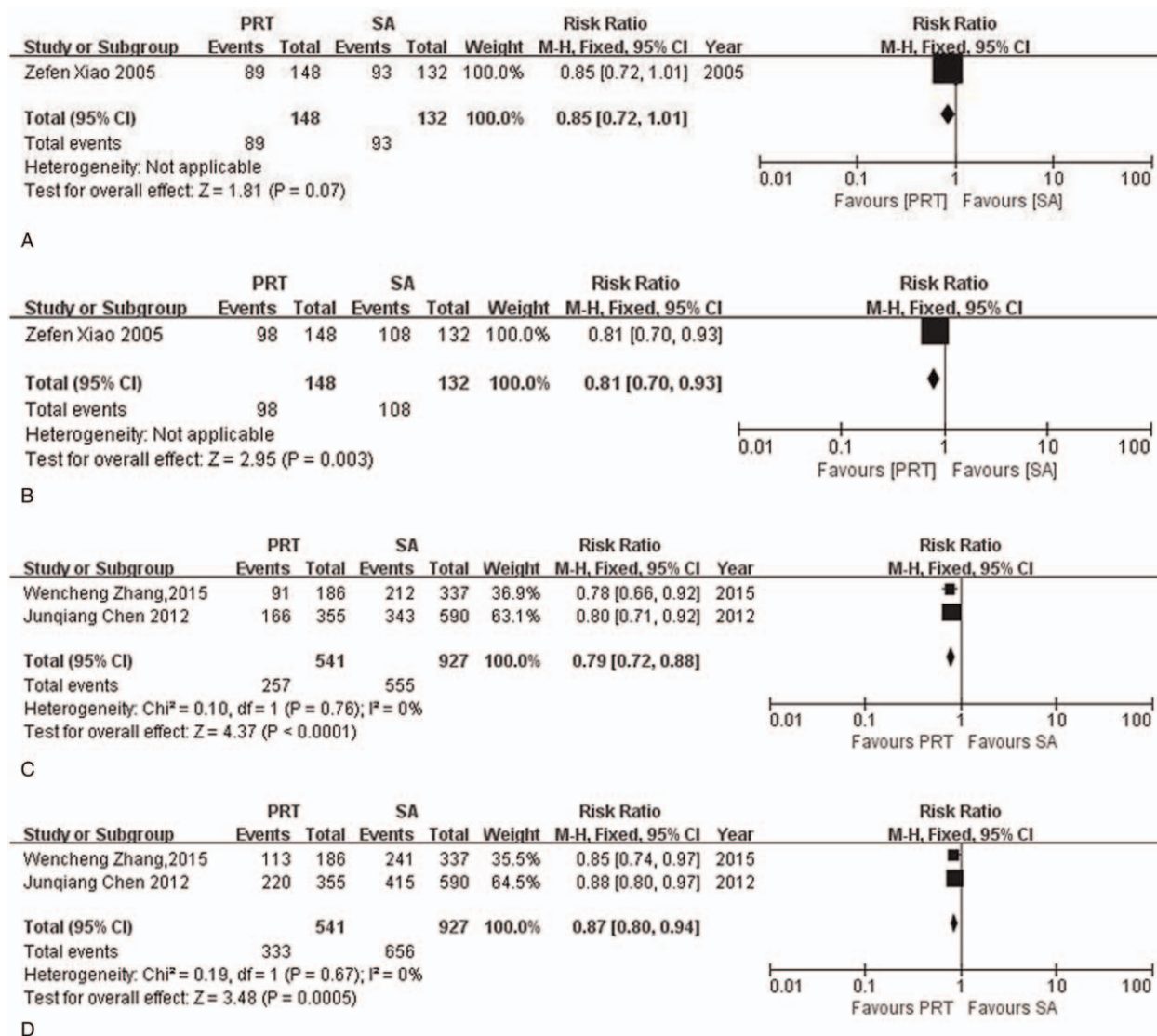


Figure 4. Forest plot of risk ratio for overall survival rate in pathological lymph node positive (pN+) patients. (A) The polled results for 3-year overall survival rate from randomized-controlled trial; (B) the polled results for 5-year overall survival rate from randomized-controlled trial; (C) the polled results for 3-year overall survival rate from non-randomized-controlled trials; (D) the polled results for 5-year overall survival rate from non-randomized-controlled trials. NOTE: PRT=postoperative radiotherapy, SA=surgery alone.

3.8. Adverse effects

There were a total of 7 studies reporting adverse effects associated with postoperative radiotherapy. Common Terminology Criteria for Adverse Events was commonly used to evaluate adverse effects. The most common side effects were radiation esophagitis, radiation pneumonitis, leucopenia, vomiting, and nausea. The incidence of grade 4 or 5 adverse effects was rare, and the probability for grade 3 adverse effects ranged from 1.9% to 9.5%. The likelihood for anastomotic stenosis was similar between postoperative radiotherapy and surgery alone. The details were shown in Table 4. The radiation after surgery was tolerated by most patients.

3.9. Sensitivity analysis and publication bias

The sensitivity analysis showed robust conclusions for NRCTs group and less sound results for RCTs group. The overall result for sensitivity analysis was relatively credible. More details for

sensitivity analysis were shown in supplementary digital contents (Tables 1A-P, <http://links.lww.com/MD/C645>). Funnel plots were presented in Figure 10, which showed no significant publication bias among the included studies.

4. Discussion

As one of the major subsets of esophageal cancer, ESCC has many unique features. According to genomic analyses, ESCC shares some common pathogenic mechanisms with head and neck squamous cell carcinoma,^[25] where postoperative radiotherapy always takes a vital part of the treatment regimen. The location of ESCC is always in the upper third of the thoracic esophageal,^[26] making it difficult to perform a surgery with comprehensive lymph node resection and likely to leave behind residual lesions. In addition, locoregional recurrence rate is likely to be a cause of treatment failure in ESCC^[4,27] and postoperative radiotherapy is regarded as a method for locoregional control.

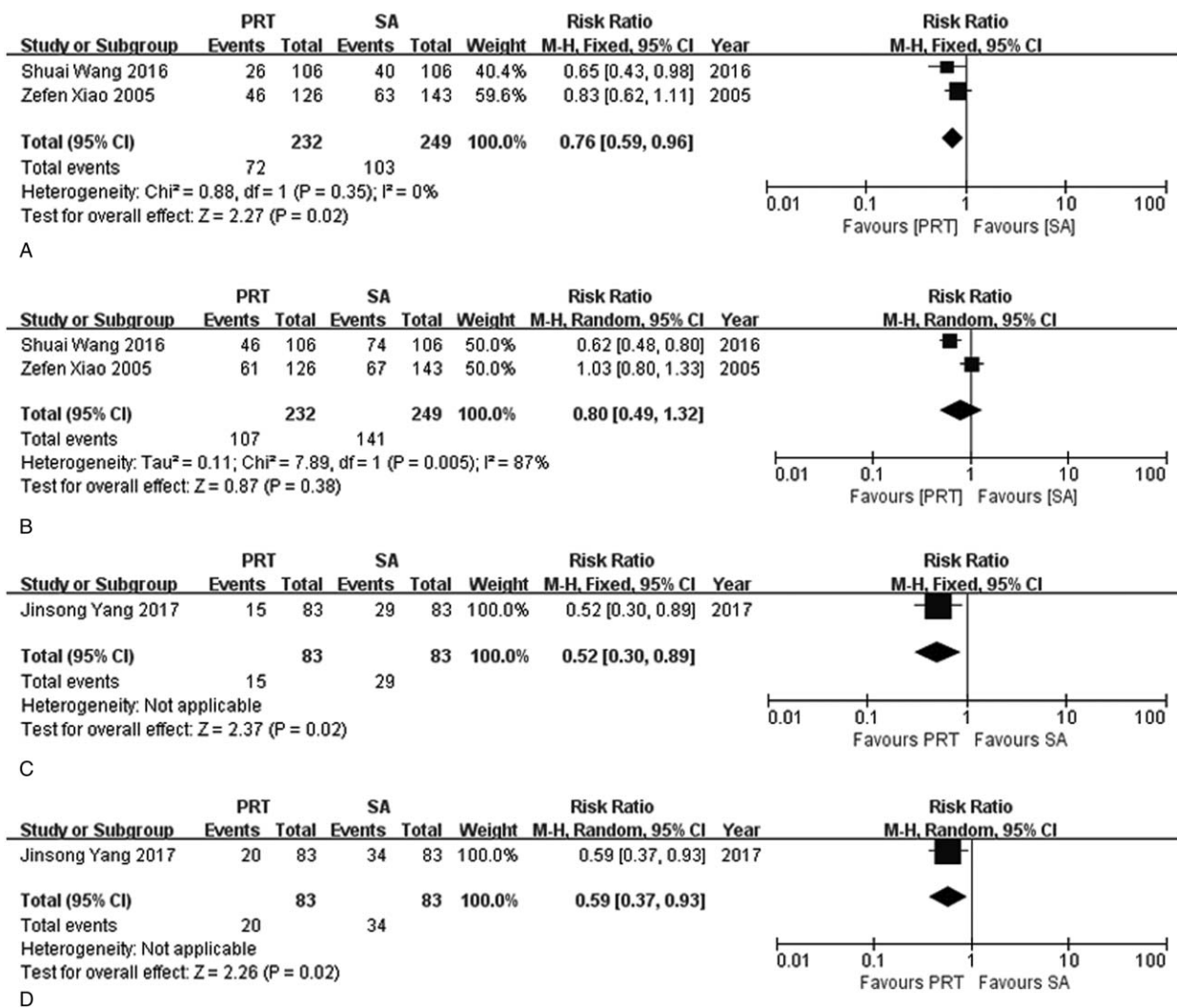


Figure 5. Forest plot of risk ratio for overall survival rate in pathological lymph node negative (pN-) patients. (A) The polled results for 3-year overall survival rate from randomized-controlled trials; (B) the polled results for 5-year overall survival rate from randomized-controlled trials; (C) the polled results for 3-year overall survival rate from non-randomized-controlled trial; (D) the polled results for 5-year overall survival rate from non-randomized-controlled trial. NOTE: PRT = postoperative radiotherapy, SA = surgery alone.

Based on these characteristics, postoperative radiotherapy may bring with some benefits theoretically. Although some clinical trials have already verified the advantage of postoperative radiotherapy, there existed other studies demonstrating that postoperative radiotherapy did not improve survival outcomes and suggesting surgery alone for ESCC patients without prior neoadjuvant treatment.^[10] Until now, no consistent conclusion has been reached about this issue. Our study, based on 4 RCTs and 8 NRCTs, including 4298 participants, is the first large-scale meta-analysis to compile clinical data and quantitatively assess the value of postoperative radiotherapy as the major adjuvant treatment for ESCC patients.

OS was considered as the primary outcome and calculated according to RCTs and NRCTs separately. In NRCTs group, postoperative radiotherapy was demonstrated to show a clear advantage in improving both 3-year OS and 5-year OS as compared with surgery alone. Results from the RCTs group indicated a significant improvement in 3-year OS rate and a tendency towards better 5-year OS rate in postoperative radiotherapy cohorts. These results illustrated that postoperative

radiotherapy is promising method to improve surgery outcome, though heterogeneity was present in the data, suggesting that more RCTs are needed for further validation.

The recommendation for postoperative radiotherapy in RCTs group was not as well established as in the NRCTs group, which may be a result of an insufficient number of participants in RCTs group, besides, the majority of RCTs studies were published 10 to 20 years earlier than NRCTs studies, traditional 2-dimensional radiotherapy method was utilized as the major treatment modality in these RCTs studies, which was observed to be inferior to modern radiation methods in conformal degree of the target area and organ protection, an OS disadvantage was also shown.^[28–32] Thus the effect of radiotherapy might be underestimated in RCTs group.

Earlier published RCTs using traditional 2-dimensional radiotherapy radiation techniques as postoperative treatment initially showed a detrimental effect in many malignancies such as non-small cell lung cancer and breast cancer, until recent RCTs were conducted and a clear OS advantage was show with modern radiation techniques.^[33–36] This improvement may also be

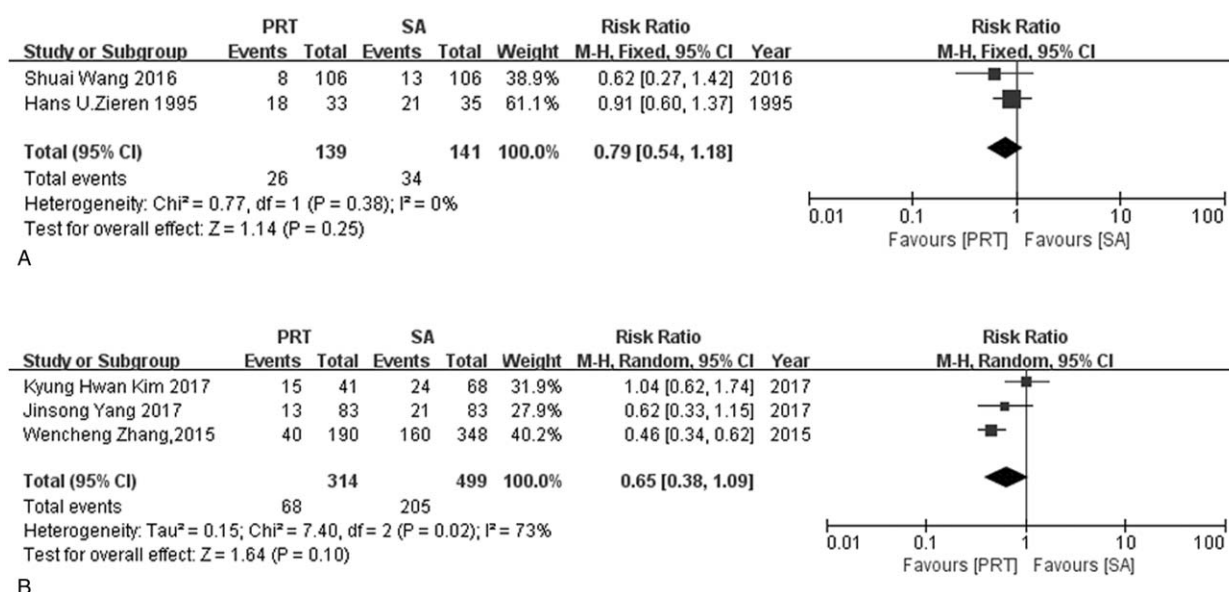


Figure 6. Forest plot of risk ratio for 1-year disease free survival rate. (A) The pooled results from randomized-controlled trials; (B) the pooled results from non-randomized-controlled trials. PRT=postoperative radiotherapy, SA=surgery alone.

present in the treatment of ESCC. Notably, with increasing of publication year, the tendency in favor of postoperative radiotherapy became more and more evident in RCTs group, and we thereby hypothesize that the 5-year OS rate of postoperative radiotherapy will be clearly demonstrated and the heterogeneity in 3-year OS rate will be less if more modern RCTs are conducted in the future.

Current National Comprehensive Cancer Network guideline indicates that the status of pathological lymph nodes is an important factor in determining the necessity of adjuvant treatment for adenocarcinoma of esophagus cancer, and thus a subgroup analysis of OS according to lymph node status was

performed to explore the prognostic value of lymph node status. There were robust conclusions in NRCTs group that postoperative radiotherapy was beneficial to improve 3-year and 5-year OS rate for both pN+ and pN- patients. RCTs group demonstrated a clearly superior 3-year OS rate for pN+ patients and 5-year OS rate for pN- patients. The other outcomes showed a tendency in favor of postoperative radiotherapy, although had no significant difference. We speculated that the reason for this may result from the small number of participants. The baseline difference might be the source of heterogeneity. In conclusion, regardless of pathological lymph node status, postoperative radiotherapy is worthy of trying to increase survival rate for ESCC patients. On

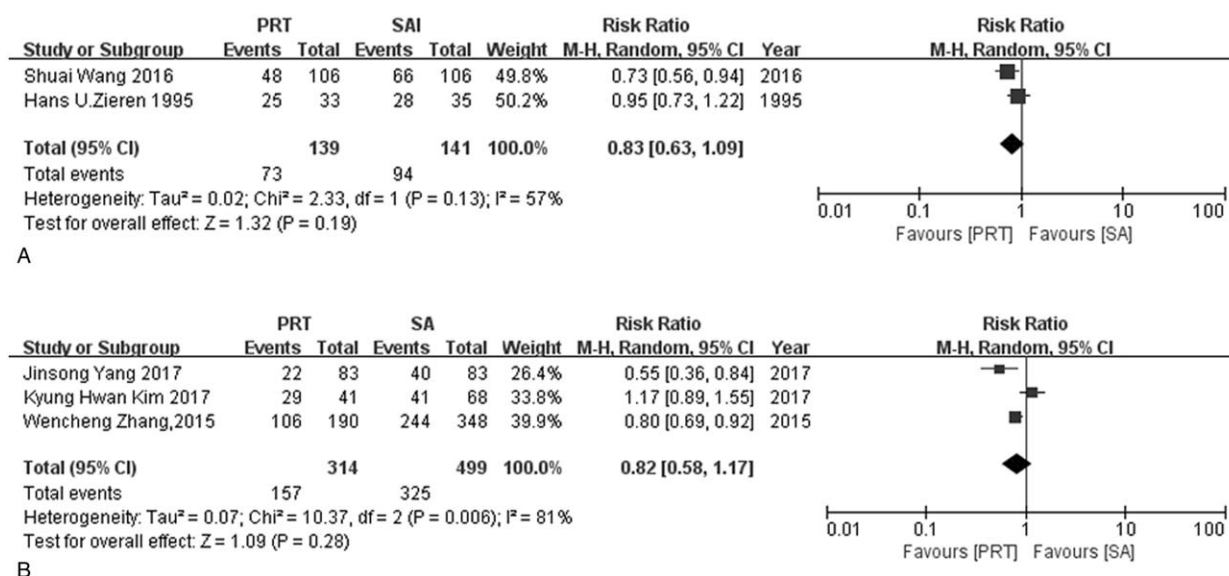


Figure 7. Forest plot of risk ratio for 3-year disease free survival rate. (A) The pooled results from randomized-controlled trials; (B) the pooled results from non-randomized-controlled trials. PRT=postoperative radiotherapy, SA=surgery alone.

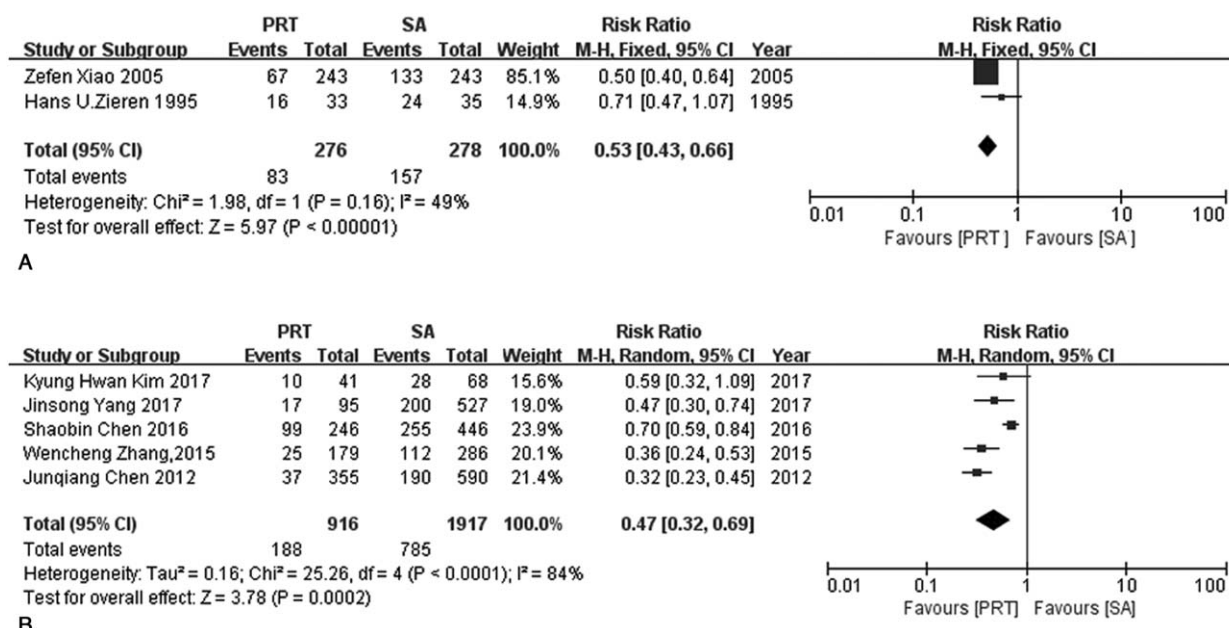


Figure 8. Forest plot of risk ratio for locoregional recurrence rate. (A) The polled results from randomized-controlled trials; (B) the polled results from non-randomized-controlled trials. PRT = postoperative radiotherapy, SA = surgery alone.

the other hand, more underlying factors affecting the prognosis of postoperative radiotherapy are needed to be explored. Notably, among lymph node negative patients, most participants in postoperative radiotherapy group had a comparatively late T stage (stage T3) or negative prognosis factors (Ku80 positive), and pT1–2N0M0 ESCC patients were only a small part of the sample. Thus more clinical trials are needed to verify the value of

postoperative radiotherapy for early stage (pT1–2N0M0) ESCC with a comparatively good prognosis.

There was a tendency favoring postoperative radiotherapy in 1 and 3-year DFS, whereas neither RCTs nor NRCTs found any difference, the relatively small sample size (2RCTs and 3NRCTs) may decrease the ability to detect a significant difference and eliminate heterogeneity. The result from Kyung Hwan Kim was

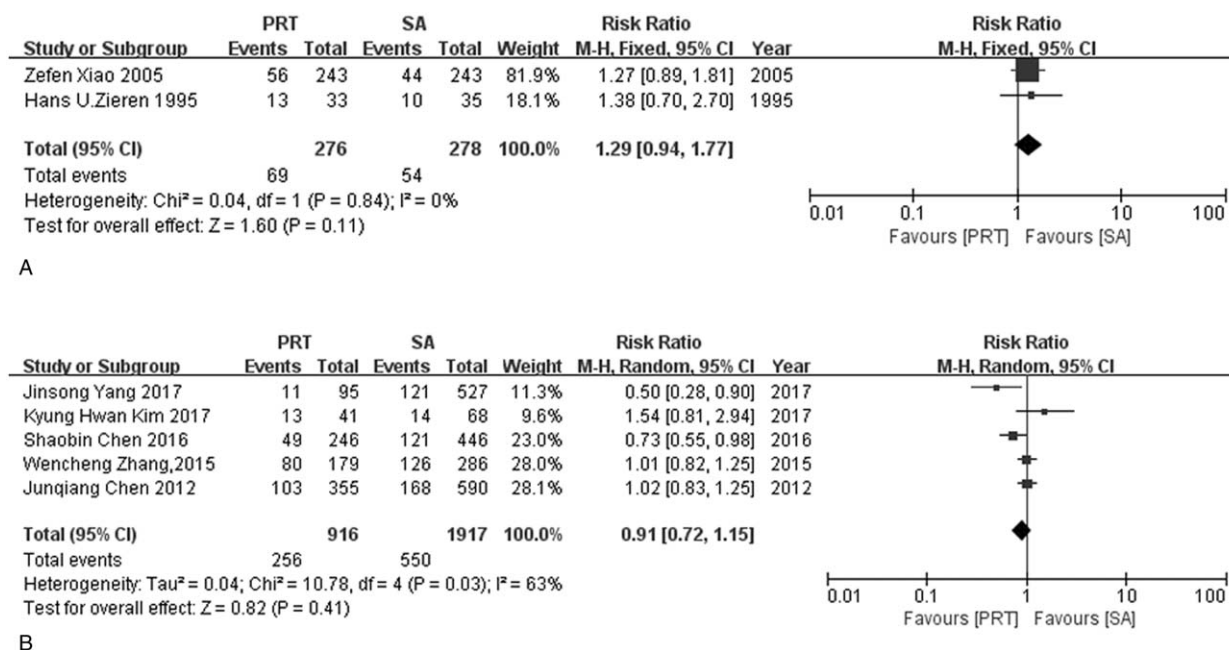


Figure 9. Forest plot of risk ratio for distant recurrence rate. (A) The polled results from randomized-controlled trials; (B) the polled results from non-randomized-controlled trials. PRT = postoperative radiotherapy, SA = surgery alone.

Table 4
Adverse effects from postoperative radiotherapy cohorts.

| Study | Adverse effects |
|----------------------|---|
| Jinrong Yang, 2017 | Grade 3 toxicity: esophagitis 9 (9.5%), pneumonitis 2 (2.1%), pain 5 (5.3%), gastritis 4 (4.2%), anastomotic stenosis 5 (5.3%) |
| Kyung Hwan Kim, 2017 | No significant difference was found in adverse effect between PRT and SA group. |
| Bo Qiu, 2017 | ≥grade 3 toxicity was not observed |
| Shaobin Chen, 2016 | NR |
| Shuai Wang, 2016 | NR |
| Wencheng Zhang, 2015 | Grade 3 toxicity: esophagitis 6 (3.2%), radiation pneumonitis 11 (5.8%), leucopenia 7 (3.7%). No difference is found between PRT and SA group for anastomotic and death from gastrointestinal bleeding. |
| Yaping Xu, 2013 | ≥ grade 3 toxics: Pneumonitis 17 (6.6%), neutropenia 12 (4.7%), thrombocytopenia 5 (1.9%), anemia 12 (4.7%), nausea/vomiting 11 (4.2%), anorexia 15 (5.8%), dysphagia 30 (11.6%), |
| Junqiang Chen, 2012 | NR |
| Gang Chen, 2009 | NR |
| Zefen Xiao, 2005 | NR |
| Hans U.Zieren, 1995 | 18 (55%) reported skin reactions, 29 (88%) general weakness, 24 (73%) dysphagia, 7 (21%) nausea |
| Paul Teniere, 1991 | 1 (0.98%) died of unknown reason after first section of radiotherapy, 4 (3.33%) had an interruption of radiotherapy because of complications. |

NR=no report.

the biggest source of heterogeneity, and in this study, the T classification in postoperative radiotherapy group was worse than in the surgery alone group (percentage for T3-T4:75.6% vs 39.7%). Thus the potential benefit from radiation may be hidden. After sensitivity analysis supporting deletion of the result from Kyung Hwan Kim, a DFS advantage was shown in NRCTs group although the heterogeneity persisted (RR=0.70, 95% CI: 0.49–0.99, $I^2=63\%$).

As for recurrence rate, both RCTs and NRCTs group demonstrated a consistent conclusion that postoperative radiotherapy was effective in reducing locoregional recurrence rate. Heterogeneity was modest in RCTs group and may be attributed to the relatively small number of studies included. In NRCTs group, the results from Shaobin Chen was the main source of heterogeneity, and after a sensitivity analysis indicated deletion of the report from Shaobin Chen, the heterogeneity was low ($I^2=25\%$, $P=0.26$) and postoperative radiotherapy was still shown to be effective for locoregional control (RR=0.39, 95% CI: 0.31–0.50), indicating the robustness of the conclusion. Baseline differences in participants from Shaobin Chen’s study maybe the source for the heterogeneity. On the other hand, no difference in distant metastases was detected between postoperative radiotherapy and surgery alone, indicating that postoperative radiotherapy may eradicate residual lesions left behind after

surgery. In cases where it does not fully prevent systematic spread of tumor cells, supplementary chemotherapy for patients with high risk of distant metastases may be considered.

There were some limitations within this study. First, recently published randomized-controlled studies were limited until the last literature retrieval, and retrospective studies constituted the majority. Therefore some biases were inevitable because of the retrospective nature of the included studies. Second, there were variations in surgical procedures, radiotherapy target delineation, and treatment schedules. Third, most included studies did not perform sufficient subgroup analysis. Only subgroup analysis for lymph node status was feasible, and the sample size was small. Finally, the majority of the included studies come from Asia, so further evidence is needed to conclude if the results will be consistent for ESCC patients worldwide.

Despite the drawbacks mentioned above, this meta-analysis is still informative. In this article, postoperative radiation was first thoroughly evaluated using several outcomes such as 3-year and 5-year OS rate, 1-year and 3-year DFS rate, locoregional recurrence rate, distant recurrence rate and adverse effects, subgroup analysis according to lymph node status was also performed. Results from RCTs and NRCTs were calculated separately to remain objective in this study, and basically conclusive results were reached in 2 groups. Though NRCTs

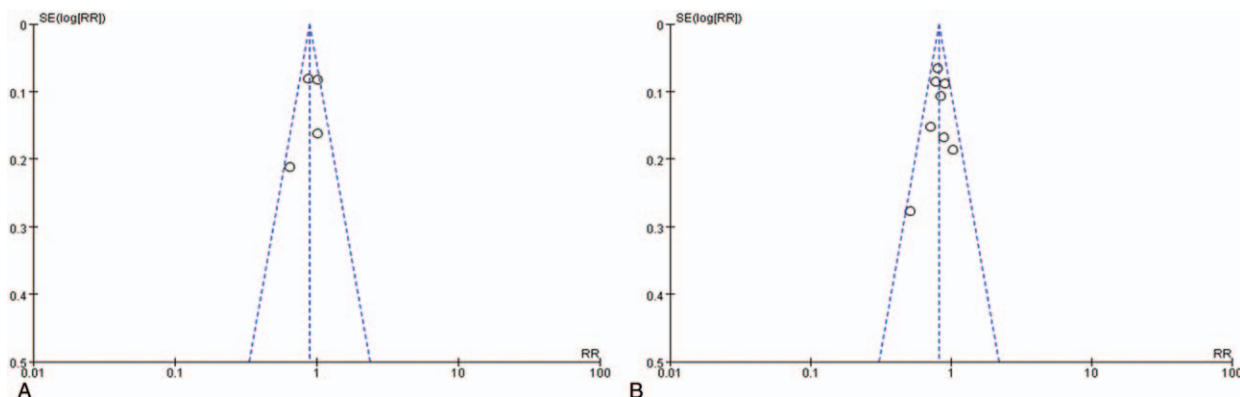


Figure 10. Funnel plots. (A) Funnel plot from randomized-controlled trials; (B) Funnel plot from non-randomized-controlled trials.

constituted the most considerable portion, the overall quality of included studies was high and most researches were conducted recently and well-designed, reflecting contemporary radiation techniques. All studies were published with full articles and details for our detailed evaluation. The comparatively large sample size decreased potential bias from confounding factors. Finally, the baselines of the postoperative radiotherapy group in NRCTs were comparable or even worse than surgery alone group, which strengthens the results favoring postoperative radiotherapy.

Taken together, postoperative radiotherapy can improve the OS rate and reduce locoregional recurrence rate for ESCC patients. With advanced radiation techniques and the improvements of associated treatments, surgery alone might not be the optimal treatment. Postoperative radiotherapy is a promising choice for ESCC patients with upfront surgery. More large-scale up-to-date RCTs are needed to validate the use of postoperative radiotherapy in modern practice further.

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Author contributions

The literature search was conducted by Xiao-han Zhao and Duo Wang independently. Discrepancies were resolved through discussion with Shu-chai Zhu until a final consensus was reached. Two reviewers (Xiao-han Zhao, Duo Wang) independently performed the methodological quality assessment, and discrepancies were discussed with a third reviewer (Fang Wang) until a consensus was reached.

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