Original Article

The role of postoperative radiotherapy for radically resected esophageal squamous cell carcinoma: a systemic review and meta-analysis

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Background: The role of postoperative radiotherapy (PORT) for radical resected esophageal squamous cell carcinoma (ESCC) remains controversial. This meta-analysis aims to determine whether PORT achieves survival benefit compared with surgery alone (S alone) for radically resected ESCC.

Methods: The PubMed, EMBASE, Web of Science, and Cochrane Library were searched for relevant articles. The primary endpoints were overall survival (OS) and disease-free survival (DFS), reported as hazard ratios (HR) and 95% confidence intervals (CIs).

Results: Six randomized trials and 13 retrospective studies that included a total of 8,198 patients were eligible. PORT provided significant OS benefit compared with S alone in retrospective studies (HR =0.75, 95% CI: 0.65–0.85), but not in randomized controlled trials (RCTs) (HR =0.94, 95% CI: 0.81–1.09). PORT was associated with significantly improved DFS and obvious reduction in the risk of locoregional recurrence compared to S alone in either retrospective studies or RCTs. In the subgroup analysis for retrospective studies, PORT gained superior OS in patients with lymph node-positive (pN+), patients with lymph node-negative (pN0) or pT2–3N0, PORT with three-dimensional radiotherapy (3D-RT), PORT with chemotherapy, and patients with R0 resection, respectively.

Conclusions: The present study shows that PORT can improve DFS and decrease risk of locoregional recurrence in patients with radically resected ESCC, and PORT using 3D-RT or in combination with chemotherapy is likely to be more useful. Further well-designed, prospective studies are needed to confirm the effect of PORT on OS.

Keywords: Esophageal squamous cell carcinoma (ESCC); radical resection; postoperative radiotherapy (PORT); chemotherapy; meta-analysis

Submitted Jan 04, 2018. Accepted for publication Jun 06, 2018.
doi: 10.21037/jtd.2018.06.65
View this article at: http://dx.doi.org/10.21037/jtd.2018.06.65

Introduction

Esophagus cancer (EC) is the eighth most common cancer worldwide and the sixth leading cause of cancer death (1,2). Esophageal adenocarcinoma (EAC) predominates in western countries, while esophageal squamous cell carcinoma (ESCC) is the most common histological type in Asian countries. Surgical management is still considered as the mainstay of treatment for all resectable cases. However, surgery alone (S alone) showed poor long-term outcomes, and the 5-year survival rate was rarely >30% even after curative resection (3,4). Neoadjuvant chemoradiation followed by surgery has been a standard treatment in western countries (5-8). However, many Asian patients still choose surgery as their initial therapy, especially in China.

Postoperative radiotherapy (PORT) is not recommended by the current National Comprehensive Cancer Network (NCCN) guidelines for patients who underwent radical resection (9). However, many patients developed local recurrence or distant metastasis (10). A number of studies have investigated whether PORT leads to improved cure rates compared with S alone, but individual reports have been conflicting (11-29). A meta-analysis of five randomized controlled trials (RCTs) performed by Malthaner *et al.* found no benefit from PORT in patients with ESCC (30). However, all included RCTs were designed more than 20 years ago, employed a conventional two-dimensional radiotherapy (2D-RT) technique, three of them were small with fewer than 50 patients in the treatment group, and two of them included data of palliative resection. Since this meta-analysis, data from one recently published RCT (11) and some retrospective studies including several large retrospective studies (17-25) have demonstrated a potential benefit from PORT in patients with resectable ESCC. Therefore, it is necessary to reevaluate the value of PORT for ESCC. In the present study, we performed a systematic review and meta-analysis of currently available evidences to further determine whether PORT improves survival compared with S alone in radically resected ESCC.

Methods

This meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria (31).

Literature search strategy

PubMed, EMBASE, Web of Science, and the Cochrane Library were searched for the available articles published before September 1, 2017, using the strategy as follows: ((esophageal cancer [Title/Abstract]) OR (esophageal carcinoma [Title/Abstract])) AND ((postoperative [Title/Abstract]) OR (adjuvant [Title/Abstract])) AND ((radiotherapy [Title/Abstract]) OR (radiation therapy [Title/Abstract]) OR (chemoradiotherapy [Title/Abstract])). Only studies in English were considered. All published papers with available full texts were retrieved. Reference lists of retrieved articles were manually scanned for relevant additional studies missed by the electronic search. The study did not involve any experiment on humans or animals, thus ethical approval was not necessary.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (I) types of studies. RCT, or prospective or retrospective cohort study; (II) types of participants. Participants with a histopathological diagnosis of ESCC and resectable disease; (III) types of interventions. Patients with surgery as their initial treatment and compared patients who received radical resection with or without PORT; (IV) outcome: reported survival [overall survival (OS) and/or disease-free survival (DFS)] data. If multiple articles covered the same study population, the study with the most recent and complete survival data was used. Studies were excluded if any of the following criteria were applied: (I) letters, editorials, case reports, and reviews; (II) survival data could not be extracted from the literature.

Data extraction

The data were extracted by two investigators independently, and the consensus was reached in case of any discrepancy for all the data. The following data were extracted from each study: first author, years of publication, duration of the study, country of origin, numbers of patients (with and without PORT), study design, time-to-event data (OS, DFS), locoregional recurrence and distant hematogenous metastases data, and occurrence of grade 3–4 adverse events. In case that studies did not report sufficient data, authors of those studies were contacted for further information by Email if possible.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of retrospective studies (32).

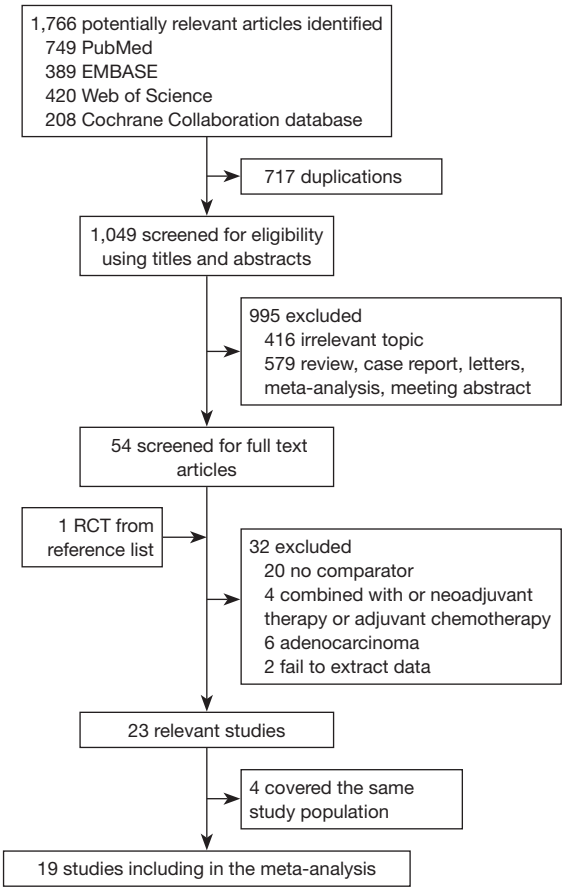

Figure 1 Literature search and selection. RCT, randomized controlled trial.

The NOS comprises of three items: patient selection, comparability of the study groups, and assessment of outcomes. The quality of each cohort study was scored on a scale ranging from 0 to 9 by two independent researchers. Six stars or greater was considered to be sufficiently high-quality studies.

The methodological quality of RCTs was assessed by Cochrane risk of bias tool (33), which consists of the following five domains: sequence generation, allocation concealment, blinding, incomplete data, and selective reporting. An RCT was finally rated as "low risk of bias" (all key domains indicated as low risk), "high risk of bias" (one or more key domains indicated as high risk), and "unclear risk of bias".

Statistical analysis

Statistical analysis was performed using the software Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA MP14.0 (Stata Corporation, College station, TX, USA). Because the median survival or survival rates at a specific point in time were not expected to be reliable surrogate measures for the pooled survival analysis, hazard ratios (HRs) and their 95% CIs were used as summary statistics for OS in the present meta-analysis. Crude HRs with 95% CIs were either extracted directly from the original reports or calculated by the Kaplan-Meier curves based on the methods of Parmar *et al.* (34) and Tierney *et al.* (35). A statistical test for heterogeneity was performed by the Chi-square (χ^2) and I-square (I^2) test with significance set at $P<0.10$ and/or $I^2>50\%$. If significant heterogeneity existed, a random-effects analysis model was used; otherwise, a fixed-effects model was used. In addition, we conducted subgroup and meta-regression analysis to search for the source of heterogeneity. The stability of the pooled results was evaluated by a sensitivity analysis in which the data of an individual study was removed each time. The funnel plot, Begg's test (36), and the Egger's linear regression test (37) were performed to investigate any potential publication bias. If evidence of publication bias was observed, the trim and fill method (38) was applied to correct the bias. A P value <0.05 was considered to be statistically significant.

Results

Literature search results and characteristics of included studies

The literature search and study selection procedures are shown in *Figure 1*. The initial search from the electronic database retrieved 1,766 articles. After removing the duplicates, 1,049 citations were identified. Of these, 995 were excluded through an abstract review. The remaining 54 articles were screened through a full-text review for further eligibility. Because two Taiwan Cancer Registry-based articles, two articles of Xiao *et al.*, and three articles of Chen *et al.* covered the same study population, four of them were excluded, and three articles (12,14,25) with the most recent and complete survival data were retained. Finally, 6 RCTs and 13 retrospective studies assessing 8,198 patients (2,779 patients receiving PORT and 5,419 patients receiving S alone) were included in the meta-analysis. For six included RCTs, five of them (12-16) were the same with that enrolled in the previous meta-analysis performed by Malthaner *et al.* (30), and the remaining one was new

Table 1 Baseline characteristics of included studies

First author, year	Areas	Time range	Patients (N) (PORT/S alone)	Study design	Quality*
Lv, 2010 (11)	China	1997–2004	61/64	RCT	Low
Xiao, 2003 (12)	China	1986–1997	220/275	RCT	Low
Zieren, 1995 (13)	Germany	1988–1991	33/35	RCT	Low
Ténière, 1991 (14)	French	1979–1985	102/119	RCT	Low
Fok, 1993 (15)	Hong Kong	1986–1989	30/30	RCT	Low
Fok, 1994 (16)	Hong Kong	1968–1981	39/42	RCT	Low
Yang, 2017 (17)	China	2004–2011	95/583	RS	7
Worni, 2012 (18)	United States	1998–2008	160/476	RS	8
Hwang, 2016 (19)	Taiwan	2008–2011	416/679	RS	7
Xu, 2013 (20)	China	2001–2009	258/467	RS	7
Zhang, 2015 (21)	China	2004–2009	190/348	RS	6
Zou, 2016 (22)	China	2006–2011	105/160	RS	7
Hsu, 2014 (23)	Taiwan	2001–2011	104/186	RS	7
Qiu, 2017 (24)	China	2000–2015	50/46	RS	6
Chen, 2010 (25)	China	1993–2007	438/1,277	RS	7
Chen, 2016 (26)	China	2004–2009	246/446	RS	7
Lyu, 2014 (27)	China	2008–2010	154/143	RS	8
Chen, 2009 (28)	China	1999–2002	64/29	RS	7
Shimizu, 2005 (29)	Japan	1994–1999	14/14	RS	7

*, Cochrane risk of bias tool was used to assess the quality of RCTs, and the Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of retrospective studies. PORT, postoperative radiotherapy; S alone, surgery alone; RCT, randomized controlled trial; RS, retrospective study.

eligible (11). Two RCTs (11,15) included data of palliative resection and radical resection, but only data of radical resection were extracted. Characteristics of the eligible studies were summarized in *Table 1*.

Assessment of included studies

The two researchers showed good consistency in assessing the study quality of nineteen included studies (*Table 1*). All of the retrospective studies demonstrated a score of ≥6 (*Table S1*). The qualities of the included RCTs were generally low. One RCT were considered to be in "high risk", and the remaining RCTs were classified as "unclear" with respect to the risk of bias (*Figure S1*).

Primary outcomes: OS and DFS

Multivariable adjusted HRs for OS were used to calculate pooled HR for 4 of 19 studies (22,24-25,28), and univariable adjusted HRs were used for others. Multivariable adjusted HRs for DFS were used to calculate pooled HR for 2 of 5 studies (22,23), and univariable adjusted HRs were used for others. Significantly statistical difference was observed between PORT and S alone groups in a pooled analysis of OS for 5,657 patients from all included retrospective studies (HR =0.75, 95% CI: 0.65–0.85, $P_{heterogeneity}<0.0001$), but not for 1,050 patients from all included RCTs (HR =0.94, 95% CI: 0.81–1.09, $P_{heterogeneity}=0.13$) (*Figure 2*). PORT was associated with significantly improved DFS compared to S alone both for retrospective studies

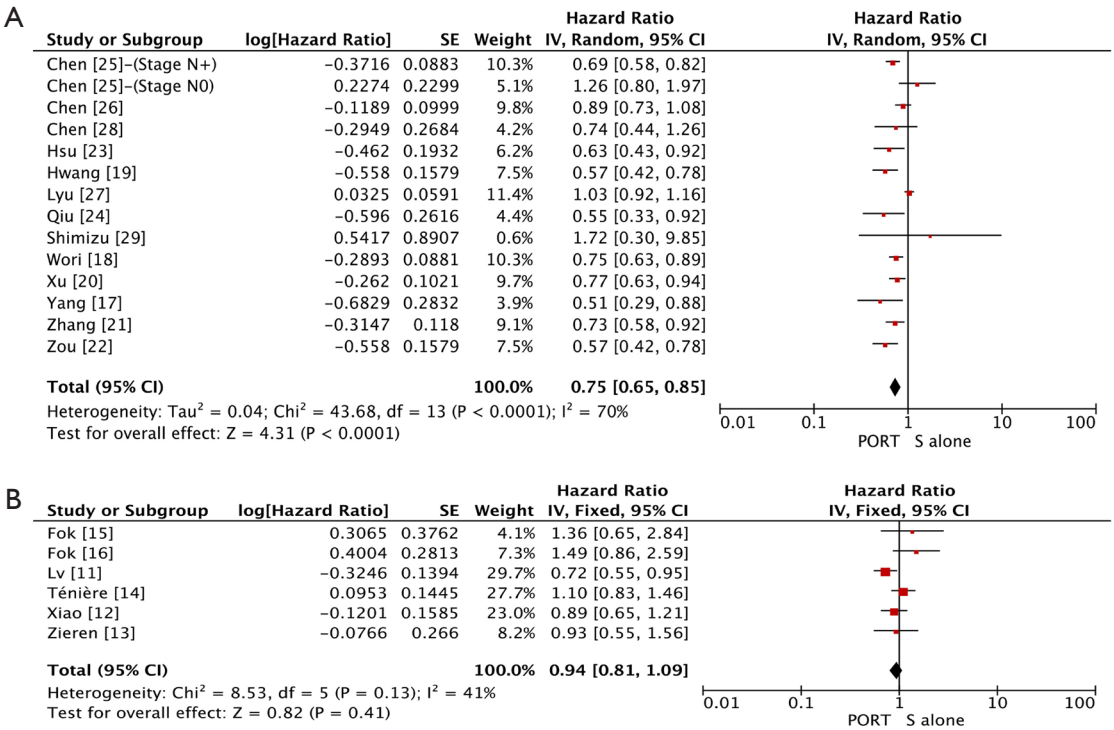

Figure 2 Forest plots of HRs for OS. (A) In retrospective studies; (B) in RCTs. PORT, postoperative radiotherapy; S alone, surgery alone; RCTs, randomized controlled trials; OS, overall survival; CI, confidence interval; SE, standard error; IV, inverse variance method; HR, hazard ratio.

(5 studies with 1,378 patients; HR =0.72, 95% CI: 0.62–0.83, $P_{heterogeneity}$=0.12) and RCTs (3 studies with 414 patients; HR =0.69, 95% CI: 0.54–0.88, $P_{heterogeneity}$=0.69) (*Figure 3*).

Subgroup and meta-regression analyses of OS in retrospective studies are detailed in *Table 2*. Except subgroup of PORT with 2D-RT (HR =0.86, 95% CI: 0.6–1.22, $P_{heterogeneity}$=0.08), and PORT without chemotherapy (HR =0.86, 95% CI: 0.7–1.05, $P_{heterogeneity}$=0.002), PORT was associated with significantly improved OS in sample size ≥100 (HR =0.75, 95% CI: 0.65–0.87, $P_{heterogeneity}$<0.001), sample size <100 (HR =0.67, 95% CI: 0.46–0.95, $P_{heterogeneity}$=0.4), patients with lymph node-positive (pN+) (HR =0.73, 95% CI: 0.6–0.89, $P_{heterogeneity}$<0.001), patients with lymph node-negative (pN0) (HR =0.8, 95% CI: 0.67–0.95, $P_{heterogeneity}$=0.14), PORT with 3D-RT (HR =0.65, 95% CI: 0.56–0.76, $P_{heterogeneity}$=0.48), and PORT with chemotherapy (HR =0.6, 95% CI: 0.5–0.72, $P_{heterogeneity}$=0.87), respectively. Significant difference of OS was also observed between PORT and S alone for patients with pT2–3N0M0 (4 studies with 653 patients; HR =0.74, 95% CI: 0.6–0.91, $P_{heterogeneity}$=0.11) and patients with R0 resection (9 studies with 3,867 patients; HR =0.73, 95% CI: 0.66–0.8, $P_{heterogeneity}$=0.18). Results of meta-regression analysis demonstrated that PORT with/without chemotherapy was the evident contributor of heterogeneity (P=0.037) (*Table 2*). Subgroup analysis of OS in RCTs was not performed due to lack of number of studies.

Sensitivity analyses were carried out to assess whether individual studies influenced the results in retrospective studies and RCTs, respectively. When individual studies were removed one at a time from the analyses for OS, the corresponding pooled HRs were not markedly altered by any single study (HR lies between 0.72 and 0.76 in retrospective studies and between 0.92 and 1.1 in RCTs), confirming the stability of the presented results (*Figure S2*).

Secondary outcomes: locoregional recurrence and distant hematogenous metastasis

The pooled results showed that PORT significantly decreased the risk of locoregional recurrence compared to

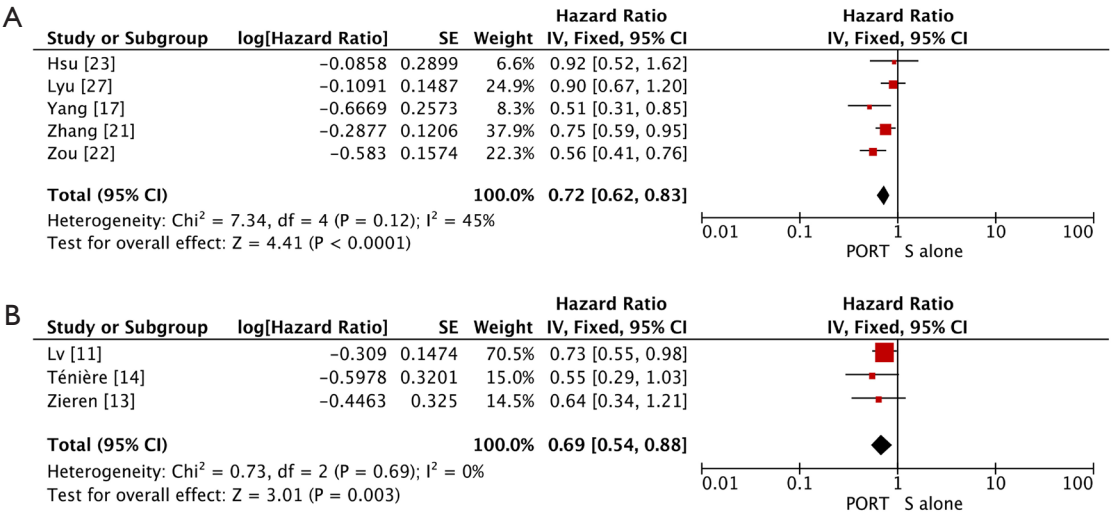

Figure 3 Forest plots of HRs for DFS. (A) In retrospective studies; (B) in RCTs. PORT, postoperative radiotherapy; S alone, surgery alone; RCTs, randomized controlled trials; DFS, disease-free survival; CI, confidence interval; SE, standard error; IV, inverse variance method; HR, hazard ratio.

Table 2 Subgroup and meta-regression analysis of effect on OS from PORT in retrospective studies

Group	No. of studies	Ref. of studies	No. of patients (PORT/S alone)	HR	95% CI	P	Heterogeneity		Meta-regression (P value)
							I^2	P	
Sample size									0.644
≥100	11	(17-23,25-27)	1,837/3,603	0.75	0.65–0.87	<0.001	75	<0.001	
<100	3	(24,28,29)	128/89	0.67	0.46–0.95	0.03	0	0.4	
pN stage									0.794
pN+	10	(19-23,25-27)	1,299/1,938	0.73	0.6–0.89	0.007	79	<0.001	
pN0	8	(17-19,22,23,25,26,28)	484/1,533	0.8	0.67–0.95	0.01	37	0.14	
Adjuvant chemotherapy									0.037
Yes	6	(19,22-24,28,29)	364/452	0.6	0.5–0.72	<0.001	0	0.87	
No	7	(17,24-28)	993/2,024	0.86	0.7–1.05	0.15	72	0.002	
RT technology									0.184
2D-RT	4	(25,28,29)	516/1,320	0.86	0.6–1.22	0.4	56	0.08	
3D-RT	4	(17,21-23)	434/647	0.65	0.56–0.76	<0.001	0	0.48	

PORT, postoperative radiotherapy; S alone, surgery alone; RT, radiotherapy; 2D-RT, two-dimensional radiotherapy; 3D-RT, three-dimensional radiotherapy.

S alone in either retrospective studies (5 studies with 1,468 patients; OR =0.40, 95% CI: 0.24–0.68, $P_{heterogeneity}$=0.007) or RCTs (4 studies with 622 patients; OR =0.32, 95% CI: 0.22–0.45, $P_{heterogeneity}$=0.61) (*Figure 4*). There was no significant difference of distant hematogenous metastases between PORT and S alone both for retrospective studies (5 studies with 1,468 patients; OR =1.18, 95% CI: 0.63–2.21, $P_{heterogeneity}$=0.003) and RCTs (4 studies with 622 patients; OR =1.27, 95% CI: 0.88–1.84, $P_{heterogeneity}$=0.28) (*Figure S3*).

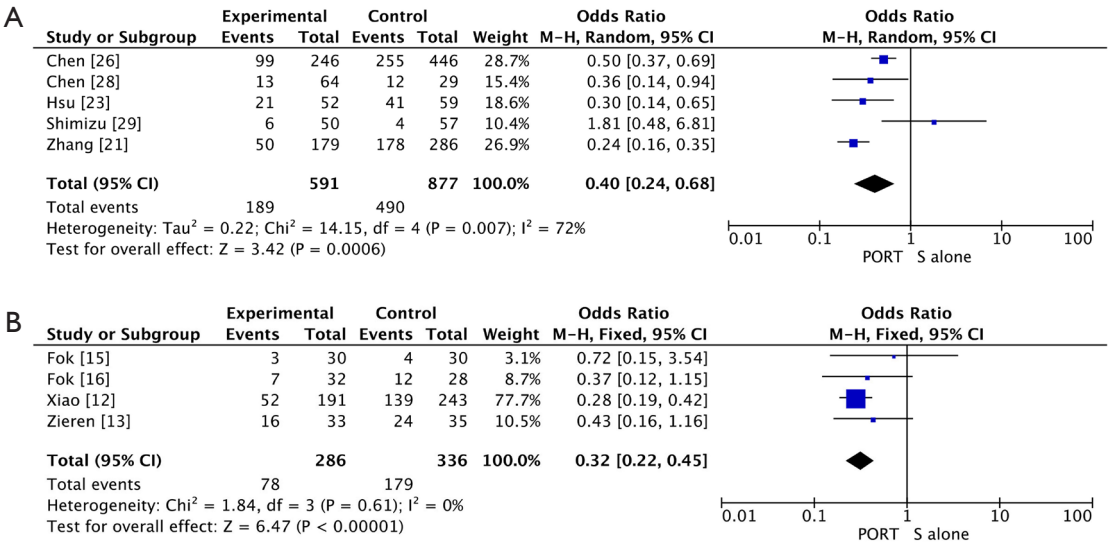

Figure 4 Forest plots of ORs for locoregional recurrence. (A) In retrospective studies; (B) in RCTs. PORT, postoperative radiotherapy; S alone, surgery alone; RCTs, randomized controlled trials; CI, confidence interval; SE, standard error; M-H, Mantel-Haenszel; OR, odds ratio.

Toxicity

Toxicities were largely underreported in the included publications. Grade 3 or 4 hematological toxicities were reported in five studies (2–18.1%) (20-22,24,29). Grade 3 or 4 radiation pneumonitis and esophagitis were observed in five studies (1.9–6.6%) (17,20-22,24) and in three studies (2.9–9.5%) (17,21,22), respectively. Grade 3 or 4 late toxicities were reported in four studies (12,16,17,21). One studies (12) reported non-cancerous pericardial effusion or pleural effusion (3.2%) and radiation lung fibrosis (2.3%) in PORT group. Anastomotic stenosis (reported in two studies) was similar between PORT and S alone group (OR =1.94, 95% CI: 0.8–4.69) (12,21). One studies (12) reported gastrointestinal bleeding in PORT group (2%), and another (21) reported that either in PORT (2%) or S alone group (2%). Only one studies (16) reported anastomotic leakage in PORT group (2%).

Assessment of publication bias

Publication bias in terms of OS was assessed in retrospective studies, but not done in RCTs due to the lack of number of studies. The funnel plot is shown in *Figure S4*. Although the Begg's test results indicated no publication bias (P=0.511), Egger's test suggested a borderline significant probability of publications bias (P=0.084). However, the trim and fill method demonstrated that no missing studies were detected, indicating that our results were reliable.

Discussion

Neoadjuvant chemoradiotherapy (CRT) remains to be the standard treatment modality for locally advanced EC based on the results of the CROSS trial (7). The CROSS study demonstrated a 14% increase in 5-year OS for patients with EC (both squamous cell carcinoma and adenocarcinoma) treated with neoadjuvant CRT compared with surgery alone (7). In the latest network meta-analysis conducted by Montagnani *et al.*, 25 trials were included, neoadjuvant CRT was associated with the most robust survival advantage across different multimodality treatment options, but adjuvant CRT was associated with a non-significant benefit (39). However, we have to be confronted with is that the initial treatment for majority of patients' trends to be surgery in China for various reasons. Although postoperative multidisciplinary treatment including RT and CRT has been vigorously implemented, there are no current practical guidelines suggesting postoperative treatments, possibly due to the absence of a large randomized trial or a high-quality meta-analysis demonstrating its survival benefits.

To our knowledge, this is the first meta-analysis to evaluate the role of PORT in radical resected ESCC. The

meta-analysis enrolled a total of 19 studies (including 6 RCTs and 13 retrospective studies) with 8,198 patients. The primary findings were that PORT provided significant OS benefit compared with S alone in retrospective studies, but not in RCTs; PORT was associated with significantly improved DFS, obvious reduction in the risk of locoregional recurrence and a similar incidence of distant hematogenous metastasis when compared to S alone in either retrospective studies or RCTs. There was significant heterogeneity for OS in retrospective studies. Based on subgroup and meta-regression analysis of OS in retrospective studies, PORT with/without chemotherapy was identified as an evident contributor of heterogeneity. The sensitivity analysis for OS revealed that the corresponding pooled HRs were robust when individual studies were removed one at a time from the analyses.

There may be several possible explanations why RCTs failed to show OS benefit with the use of PORT. Firstly, 2D-RT technique was used in all included RCTs. Compared with 2D-RT technique, 3D-RT delivered a high dose to the tumor target volume while potentially minimizing the radiation dose to the organ at risk. Most of individual studies of PORT using 3D-RT showed consistent OS benefit compared to S alone (17,21-23), while the results of studies using 2D-RT were various. In current meta-analysis, PORT significantly improved OS for PORT using 3D-RT, but not for that using 2D-RT when compared to S alone. Secondly, adjuvant chemotherapy was not used in combination with PORT in most of included RCTs (12-16). Only one included RCT (11) used PORT with chemotherapy and showed significant improved OS. OS benefit from PORT with adjuvant chemotherapy was also reported in several retrospective studies (19,22,23). A meta-analysis comparing surgery followed by adjuvant CRT to surgery without adjuvant CRT (non-CRT) for resectable esophageal carcinoma concluded that CRT could gain a survival benefit (40). In the present analysis, PORT showed significant improvement of OS compared with S alone in subgroup of PORT with chemotherapy, but not in subgroup of PORT alone which accounted for the most of heterogeneity of the treatment effect on OS. Thirdly, data from included RCTs were of low quality, and the sample size of them were small (three of them were with fewer than 50 patients in PORT group). Thus, it might be underpowered to detect the difference in OS.

The survival effect of PORT for different lymph node status remains undetermined. Most of the retrospective studies showed the survival benefit of PORT in patients with pN+ compared with S alone (19-23,25,26). Results from one RCT performed by Xiao *et al.* (12) showed that the 1-, 3-, and 5-year survival rates for patients with pN+ were 69.7%, 24.7%, and 14.7% in S alone group and 72.3%, 38.2%, and 29.2% in PORT group, respectively. These differences nearly reached statistical significance (P=0.0698). In line with these individual studies, PORT could gain significant OS and DFS compared with S alone for patients with pN+ in the present analysis. However, there was still lack of consensus on the value of PORT for patients with pN0 or pT2–3N0. Two RCTs (12,14) using 2D-RT technique showed no survival improvement of PORT for patients with pN0 or pT2–3N0. However, results from one more recent large retrospective studies using 3D-RT showed that PORT was strongly associated with an improved OS and DFS in pT3N0M0 ESCC patients (17). In current meta-analysis, significant OS and DFS benefit from PORT were observed for patients with pN0 or pT2–3N0. Whether PORT using 3D-RT technique is critical in improving survival for patients with pN0 or pT2–3N0 needs further investigation.

There are several limitations in our meta-analysis. Firstly, all of included RCTs were of low quality which might be underpowered to detect the difference in OS. Secondly, significant heterogeneity was seen in pooled-analysis of OS (I^2=70%) in retrospective studies. By using subgroup and meta-regression analysis, PORT with/without chemotherapy was identified as evident contributor of heterogeneity. Thirdly, a few HRs were not directly reported in the texts, and hence calculated from the Kaplan-Meier curve. This may result in bias and error. Fourthly, several individual studies did not report resection status, and a part of patients with R1 resection should be contained which might be a confounding factor. However, subgroup analysis of R0 resection showed a survival benefit from PORT (HR =0.73, 95% CI: 0.66–0.8). Finally, majority of included studies were performed in China, thus, extending the conclusions to other regions should be discreet. Other confounding factors may also affect the survival, such as radiation doses, tumor location, pathological grade, and operation type. However, we could not conduct a subgroup analysis of that due to lack of detailed data or number of studies.

Conclusions

The present study shows that PORT can improve DFS and decrease risk of locoregional recurrence in patients with

radically resected ESCC, and PORT using 3D-RT or in combination with chemotherapy is likely to be more useful. Further well-designed, prospective studies are needed to confirm the effect of PORT on OS.

Acknowledgements

None.

Footnote

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

Ethical Statement: The study did not involve any experiment on humans or animals, thus ethical approval was not necessary.

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Cite this article as: Liu T, Liu W, Zhang H, Ren C, Chen J, Dang J. The role of postoperative radiotherapy for radically resected esophageal squamous cell carcinoma: a systemic review and meta-analysis. J Thorac Dis 2018;10(7):4403-4412. doi: 10.21037/jtd.2018.06.65

Supplementary

Table S1 Quality assessment of thirteen retrospective studies using the Newcastle-Ottawa scale

First author, year	Selection				Comparability		Outcome			Score
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	
Yang, 2017 (17)	–	*	*	*	*	*	*	*	–	7
Worni, 2012 (18)	*	*	*	*	*	*	*	*	–	8
Hwang, 2016 (19)	*	*	*	*	*	*	*	–	–	7
Xu, 2013 (20)	–	*	*	*	*	–	*	*	*	7
Zhang, 2015 (21)	–	*	*	*	*	–	*	*	–	6
Zou, 2016 (22)	–	*	*	*	*	*	*	*	–	7
Hsu, 2014 (23)	–	*	*	*	*	*	*	*	–	7
Qiu, 2017 (24)	–	*	*	*	*	–	*	*	–	6
Chen, 2010 (25)	–	*	*	*	*	–	*	*	*	7
Chen, 2016 (26)	–	*	*	*	*	–	*	*	*	7
Lyu, 2014 (27)	–	*	*	*	*	*	*	*	*	8
Chen, 2009 (28)	–	*	*	*	*	–	*	*	*	7
Shimizu, 2005 (29)	–	*	*	*	*	*	*	*	–	7

–, zero point; *, one point. Item 1, representativeness of the exposed cohort; item 2, selection of the non-exposed cohort; item 3, ascertainment of exposure; item 4, demonstration that outcome of interest was not present at start of study; item 5, comparability of cohorts on the basis of the design (study controls for the most important factor); item 6, comparability of cohorts on the basis of the design (study controls for other additional factor); item 7, assessment of outcome; item 8, follow-up long enough for outcomes to occur; item 9, adequacy of follow-up of cohorts.

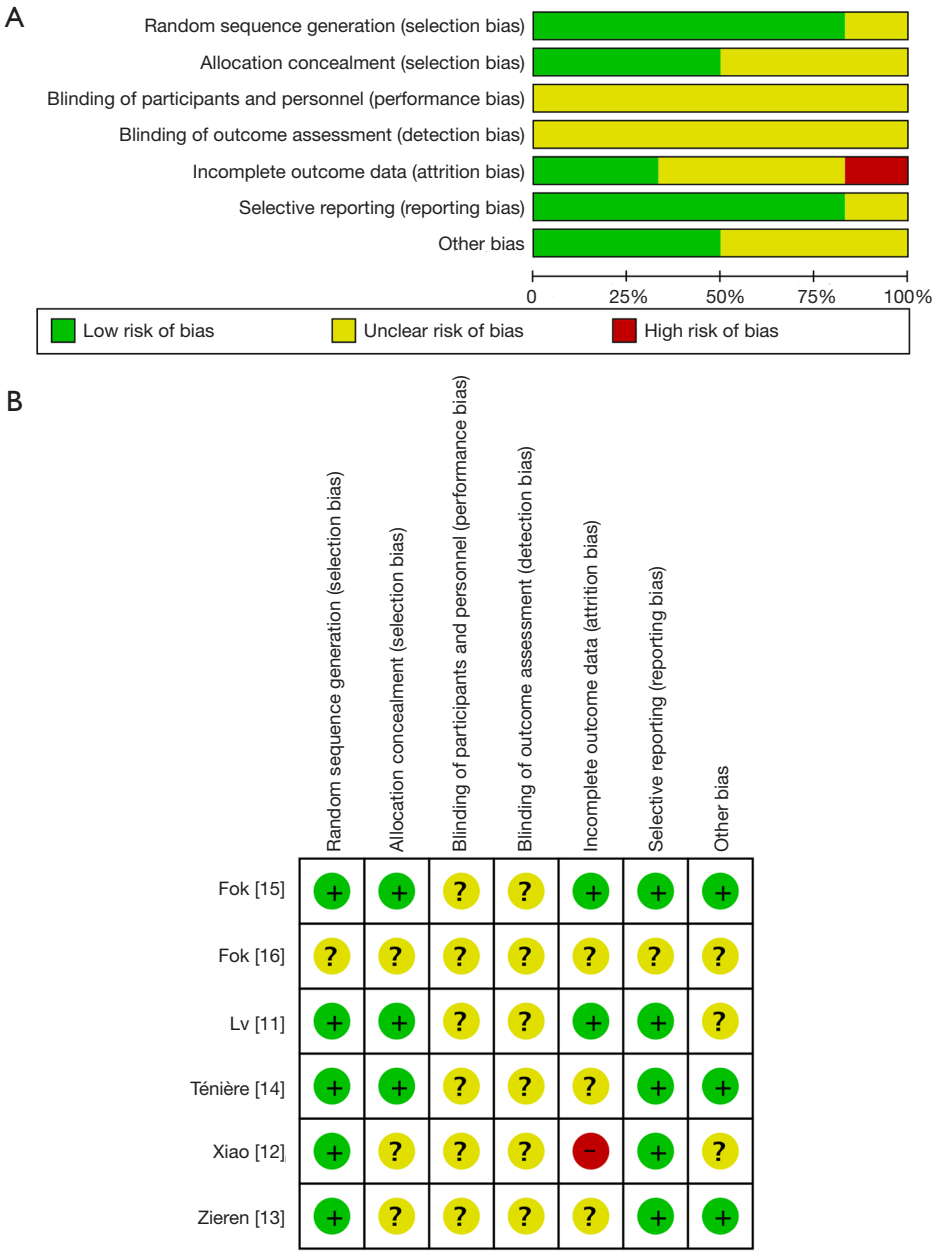

Figure S1 Assessment of risk of bias in RCTs. (A) Methodological quality graph: authors' judgment about each methodological quality item presented as percentages across all included studies; (B) methodological quality summary: authors' judgment about each methodological quality item for each included study, "+" low risk of bias; "?" unclear risk of bias; "–" high risk of bias.

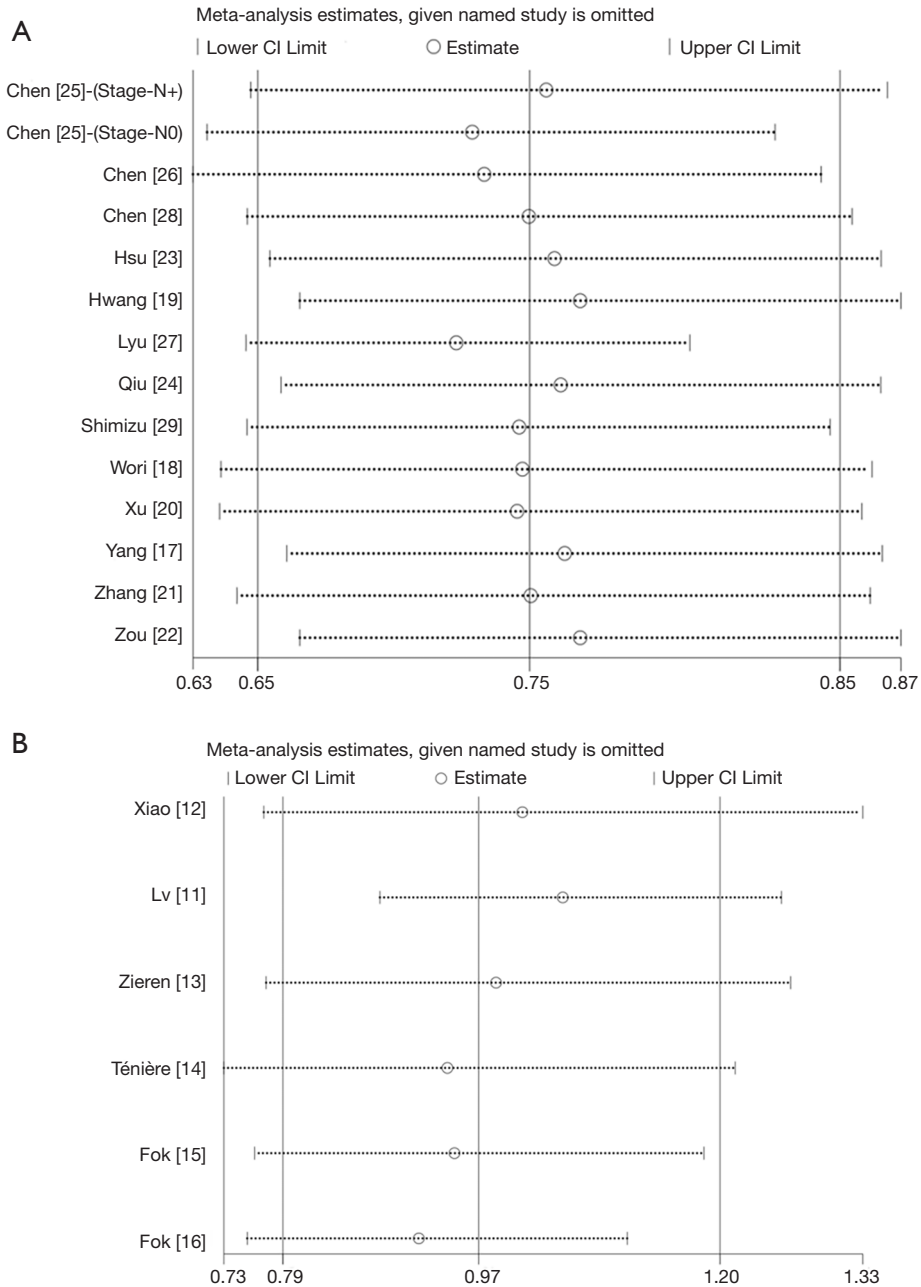

Figure S2 Sensitivity analysis for the comparison of OS between PORT and S alone. (A) In retrospective studies; (B) in RCTs. OS, overall survival; PORT, postoperative radiotherapy.

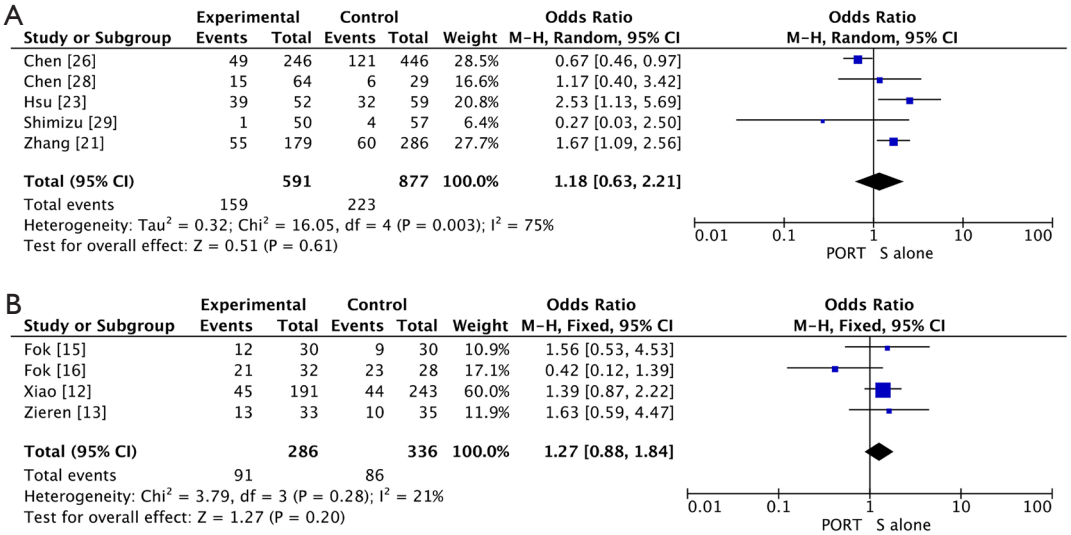

Figure S3 Forest plots of ORs for distant hematogenous metastases. (A) In retrospective studies; (B) in RCTs. PORT, postoperative radiotherapy; S alone, surgery alone; RCTs, randomized controlled trials; CI, confidence interval; SE, standard error; M-H, Mantel-Haenszel; OR, odds ratio.

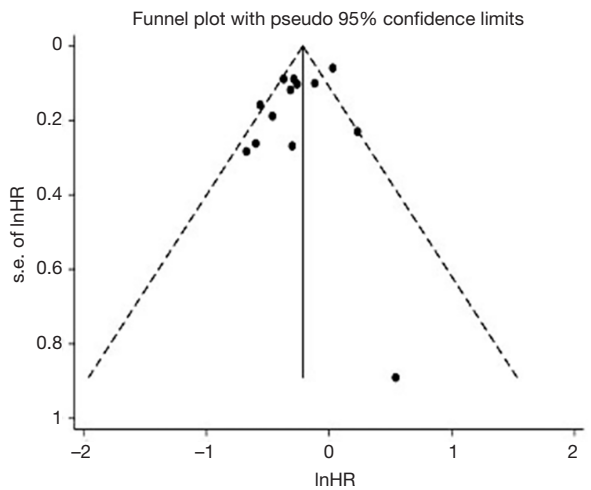

Figure S4 Funnel plot of retrospective studies with pseudo 95% CI.