



Role of thoracic radiotherapy in extensive stage small cell lung cancer: a systematic review and meta-analysis

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Background: The role of thoracic consolidation radiotherapy in patients with extensive stage small cell lung cancer (ES-SCLC) remains controversial. This study aimed to evaluate the efficacy of thoracic radiotherapy (TRT) in these patients.

Methods: A systematic literature search was performed in PubMed, Embase, and the Cochrane library to identify qualified clinical studies. The hazard ratios (HRs) and 95% confidence intervals (CIs) of overall survival (OS), progression-free survival (PFS) and local recurrence-free survival (LRFS) were extracted, and toxicity of the TRT group versus non-TRT group was analyzed.

Results: A total of 12 studies were included in this meta-analysis, including 936 patients in the TRT group and 1,059 patients in the non-TRT group. The combined results showed that TRT significantly improved OS (HR =0.65; 95% CI: 0.55–0.77, P<0.00001), PFS (HR =0.64; 95% CI: 0.56–0.72, P<0.00001) and LRFS (HR =0.38, 95% CI: 0.26–0.53, P<0.00001). Subgroup analysis showed that OS benefits were observed in patients receiving sequential TRT (HR =0.67; 95% CI: 0.54–0.84, P=0.0006). The addition of TRT significantly improved OS in patients over 65 years of age (HR =0.55; 95% CI: 0.40–0.74, P=0.0001). For patients with only one organ metastasis, there was no significant difference in OS between the two groups (HR =0.61; 95% CI: 0.36–1.01, P=0.06). There was no statistical difference in hematologic toxicity (leukopenia, thrombocytopenia, anemia) and non-hematologic toxicity (nausea or vomiting) between the two groups. The incidence of grade ≥ 3 esophageal toxicity was 4.6% in the TRT group and 0% in the non-TRT group (P=0.0001). Grade ≥ 3 bronchopulmonary toxicity was 2.9% in the TRT group and 0.8% in the non-TRT group (P=0.02).

Conclusions: TRT improves OS, PFS and LRFS in patients with ES-SCLC, with a low increase in esophageal and bronchopulmonary toxicity. More randomized controlled trials (RCTs) are expected to confirm our conclusions.

PROSPERO registration number: CRD42020190575.

Keywords: Small cell lung cancer (SCLC); thoracic radiotherapy (TRT); meta-analysis

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Introduction

Small cell lung cancer (SCLC) accounts for 10–15% of all lung cancers. About 70% of the patients are already in the extensive stage at the initial diagnosis, with a median overall survival (OS) of only 8–10 months (1,2). So far, platinum-based chemotherapy is still the standard treatment for extensive stage small cell lung cancer (ES-SCLC), with a response rate of up to 60–80%. However, most patients (approximately 90%) develop intrathoracic progression within 1 year after completion of chemotherapy. There are few effective treatment options, and the 2-year survival rate is only 5% (3,4).

Since SCLC is sensitive to radiotherapy, many studies have explored the effect of consolidation thoracic radiotherapy (TRT) in ES-SCLC. A randomized controlled trial (RCT) published in 1999 was the first to suggest that the addition of TRT improved OS and first relapse-free survival in ES-SCLC. Patients with complete response (CR) at a distant site and at least partial response (PR) at a local site were selected in the study as they had a better prognosis (5). A subsequent RCT demonstrated TRT improved long-term survival in ES-SCLC, with the 2-year OS rate of 13%. In addition, TRT reduced the incidence of intrathoracic progression ($P < 0.0001$) (6). Recent retrospective analyses and database-based studies have also demonstrated the survival benefits of thoracic consolidation radiotherapy (7–9). However, the latest randomized trial RTOG-0937 found that despite improved progression-free survival (PFS), the median survival in the TRT group (13.8 months) was worse than that in the prophylactic cranial irradiation (PCI) group (15.8 months) (10). In another retrospective study, no PFS or OS benefit of TRT was observed in patients with brain/liver/multi-metastasis (11). Therefore, the role of thoracic consolidation radiotherapy in patients with ES-SCLC remains controversial.

In this meta-analysis, we compared the effects of thoracic consolidation radiotherapy versus chemotherapy alone on survival of patients with ES-SCLC by systematically reviewing RCTs and retrospective studies.

We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-5765>).

Methods

Search strategy

The review was registered in PROSPERO with the

registration number CRD42020190575. PubMed, Embase, and the Cochrane library were systematically searched without any language restriction. All electronic database resources are available from the Nanjing Medical University Library. Our team has mastered the search strategy of electronic databases under the guidance of a medical librarian. Search terms were: (“extensive” or “advanced” or “metastatic” or “stage IV”) and (“radiation” or “radiotherapy”) and (“small cell lung cancer” or “small cell lung carcinoma” or “SCLC”). The last search deadline was July 13, 2020. When necessary, the references quoted in the article were manually retrieved.

Inclusion and exclusion criteria

The studies which compared the clinical efficacy of TRT combined with chemotherapy and chemotherapy alone for ES-SCLC were eligible for inclusion. Studies that met the following criteria were excluded: (I) insufficient survival data; (II) not ES-SCLC; (III) review, comments, survey, conference abstract, meta-analysis; (IV) not platinum-based chemotherapy as a control group; (V) not TRT.

Data extraction

Two authors (AML and YYX) independently screened eligible studies and extracted the data. Disagreements were resolved by consulting the third author (HZ). The following information was extracted: author, year of publication, country, study period, number of participants, study type, treatment regimen (including chemotherapy, TRT and PCI), and survival data. We evaluated OS, PFS, local recurrence-free survival (LRFS) and toxicity in the meta-analysis. If both univariate and multivariate analyses of survival data were provided in the study, multivariate analysis results were applied because they reduced confounding bias. Similarly, if survival data both before and after propensity score matching (PSM) were presented in the article, the results after PSM were used.

Quality assessment and statistical analysis

The quality of retrospective studies was evaluated using the Newcastle-Ottawa Scale (NOS). The possible NOS score of each article ranged from 0 to 9, and studies with a score greater than 6 were considered to be of high quality (12). The quality of RCTs was assessed using the Cochrane risk of bias tool (13). Two authors (AML and HZ) independently

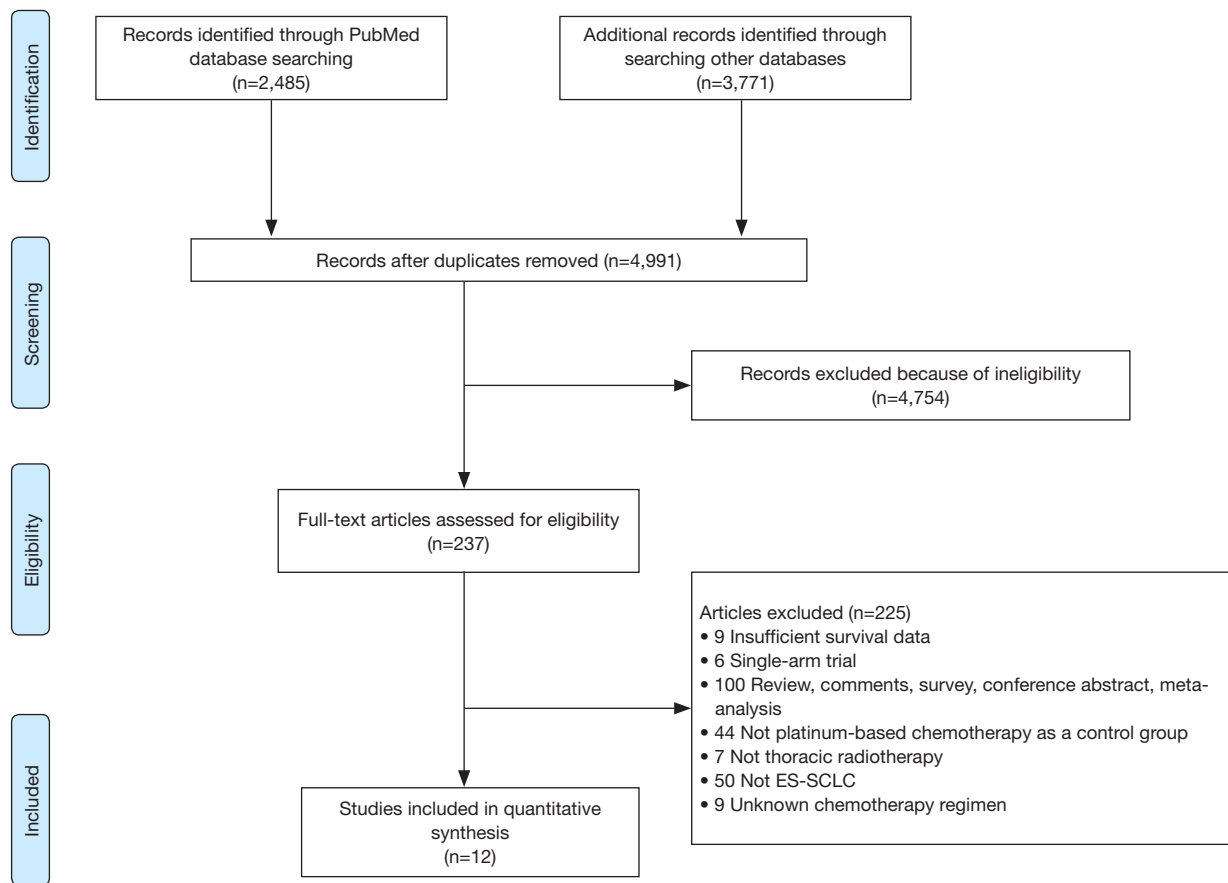


Figure 1 Flow diagram of study selection procedure.

evaluated the included studies. Any inconsistency was resolved by consensus.

Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) was used for statistical analysis. A $P < 0.05$ was considered statistically significant. The effects of thoracic consolidation radiation on OS, PFS and LRFS in patients with ES-SCLC were evaluated by hazard ratios (HRs) and the corresponding 95% confidence interval (CIs). If the HRs and 95% CIs were not directly reported in the included article, we used Engauge Digitizer version 11.1 (<http://sourceforge.net/projects/digitizer/>) to estimate them from the Kaplan-Meier curve (14,15). Risk ratio (RR) was used to analyze toxicity. Heterogeneity was tested by Cochrane's Q test and I-square (I^2). The random-effects model was used when significant heterogeneity was observed ($P < 0.1$ or $I^2 > 50%$); otherwise, the fixed-effects model was applied. Potential publication bias was assessed by funnel plots. Sensitivity analysis was performed when necessary to explore possible sources of

heterogeneity.

Results

Study selection and characteristics

We initially retrieved 6,256 studies from the electronic databases, of which 1,265 were duplicates. A total of 4,754 studies were excluded by screening titles and abstracts. After reading the full text of the remaining 237 studies, 12 studies were eventually included in the meta-analysis: 3 RCTs and 9 retrospective studies (5-6,8-11,16-21). The selection process of the study is shown in *Figure 1*.

A total of 1,995 patients with ES-SCLC were included in this meta-analysis, of whom 936 received thoracic consolidation radiotherapy (TRT group) and 1,059 received chemotherapy alone (non-TRT group). The basic characteristics of the included studies are shown in *Table 1*. Four retrospective studies performed PSM (8,16-18). Two retrospective studies evaluated the role of TRT in

Table 1 Baseline characteristics of included studies

Source	Country	Study period	No. of patients	Study type	ChT regimen	TRT approach	TRT regimen	TRT Y/N	PCI approach	PCI regimen PCI Y/N	Outcome
Zhu, 2011	China	January 2003–December 2006	119	Retrospective cohort	EP/EC	Sequential (after ChT)	40–60 Gy at 1.8–2.0 Gy/Fr	60/59	NA	30 Gy	2/117 OS, PFS and Toxicity
Gore, 2017	US, Canada, Israel	March 2010–February 2015	86	Randomized controlled (phase-II)	Platinum based chemotherapy	Sequential (after ChT)	45 Gy/15 Fr	44/42	Concurrent with TRT	25 Gy/10 Fr	86/0 OS, Time to progression and Toxicity
Jeremic, 1999	Yugoslavia	January 1988–June 1993	109	Randomized controlled (phase-III)	EP/EC	ChT followed by concurrent TRT-ChT	54 Gy/36 Fr	55/54	Sequential (after TRT)	25 Gy/10 Fr	109/0 OS, LRFS, DMFS and PFS
Slotman, 2015	Netherlands, UK, Norway, Belgium	February 2009–December 2012	495	Randomized controlled (phase-III)	Standard chemotherapy (platinum etoposide)	Sequential (after ChT)	30 Gy/10 Fr	247/248	Concurrent with TRT	20 Gy/5 Fr, 25 Gy/10 Fr, 30 Gy/10 Fr, 30 Gy/12 Fr, 30 Gy/15 Fr	495/0 OS, PFS and Toxicity
Qi, 2019	China	January 2010–January 2018	80, aged ≥65 years	Match-controlled	EP/EC	Sequential (after ChT)/ Concurrent with ChT	30–60 Gy at 1.8–3 Gy/Fr	40/40	NA	NA	NA OS, PFS, LRFS
An, 2017	China	January 2006–December 2013	118, aged ≥65 years	Retrospective cohort	EP/EC	NA	48–60 Gy at 1.8–2.0 Gy/Fr	59/59	Sequential (after TRT)	25 Gy /10 Fr	43/49 OS, PFS and Toxicity
Deng, 2019	China	January 2007–December 2012	144	Match-controlled	EP/EC	Sequential (after ChT)	32–67 Gy/25–33 Fr	72/72	NA	NA	0/144 OS, PFS
Luan, 2015	China	January 2005–December 2008	165	Retrospective cohort	EP/EC	Sequential (after ChT)	40–62 Gy at 1.5–2 Gy/Fr	82/83	NA	30 Gy	5/160 OS, PFS and Toxicity
Luo, 2017	China	January 2011–December 2015	90	Match-controlled	EP/EC	Sequential (after ChT)	45–60 Gy/15–30 Fr	45/45	Sequential (after TRT)	25 Gy/10 Fr	3/87 OS, PFS, LRFS

Table 1 (continued)

Table 1 (continued)

Source	Country	Study period	No. of patients	Study type	ChT regimen	TRT approach	TRT regimen	TRT Y/N	PCI approach	PCI regimen PCI Y/N	Outcome
Qin, 2016	China	January 2000–March 2010	94	Retrospective cohort	EC/EP or sequential paclitaxel with cisplatin	Sequential (after ChT)/ Concurrent with ChT	40–60 Gy at 1.8–2.0 Gy/Fr	32/62	NA	NA	5/89 OS, PFS and Toxicity
Zhang, 2019	China	January 2005–January 2016	305	Retrospective cohort	EC/EP or platinum-based chemotherapy	Sequential (after ChT)	40–60 Gy/20–30 Fr or 30–45 Gy/10–15 Fr	105/200	NA	25 Gy	34/271 OS, PFS and Toxicity
Xu, 2017	China	May 2010–May 2015	190	Match-controlled	EC/EP	Sequential (after ChT)	30–60 Gy at 1.8–3 Gy/Fr	95/95	NA	NA	11/179 OS, PFS, LC

ChT, chemotherapy; TRT, thoracic radiotherapy; PCI, prophylactic cranial irradiation; Y, yes; N, no; EP, etoposide and cisplatin; EC, etoposide and carboplatin; OS, overall survival; PFS, progression free survival; NA, not available; Gy, gray; Fr, fractions; LC, local control; DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival.

patients aged ≥ 65 years (16,19). One retrospective study analyzed the prognosis of patients with oligometastases and polymetastases separately (18).

Quality assessment

All the retrospective studies scored ≥ 7 , and were considered to have high quality. As shown in Table 2, all three RCTs claimed randomization, but no methods for random assignment sequence generation and allocation concealment were reported. The age distribution of patients in the experimental group and the control group in trial RTOG-0937 was unbalanced (10).

OS

All twelve studies reported OS results. Combined analysis showed that TRT significantly improved OS (HR =0.65; 95% CI: 0.55–0.77, $P < 0.00001$) (Figure 2A). As significant heterogeneity was observed ($I^2 = 62\%$), the random-effects model was applied.

PFS

All twelve studies reported PFS results. The pooled HR with a random effects model was 0.64 (95% CI: 0.56–0.72, $P < 0.00001$) (Figure 2B), which indicated that the TRT group had significantly better PFS than non-TRT group.

LRFS

Four studies compared LRFS between TRT and non-TRT groups. The combined analysis with a random effects model showed that TRT significantly improved LRFS (HR =0.38; 95% CI: 0.26–0.53, $P < 0.00001$) (Figure 2C).

Subgroup analysis

We performed subgroup analysis based on study type to assess the effect of TRT on OS and PFS. The combined HRs for OS of three RCTs and nine retrospective studies were 0.88 (95% CI: 0.65–1.18, $P = 0.39$) and 0.59 (95% CI: 0.49–0.71, $P < 0.00001$), respectively (Figure 3A). The random-effects model was applied as significant heterogeneity was observed ($I^2 = 54\%$ for RCTs). The pooled HR for PFS of three RCTs was 0.71 (95% CI: 0.61–0.82, $P < 0.00001$), and it was 0.61 (95% CI: 0.52–0.73, $P < 0.00001$) for retrospective studies (Figure 3B). The random-effects

Table 2 Quality assessment of included studies

Source	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other bias
Gore, 2017	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High risk
Jeremic, 1999	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Slotman, 2015	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Selection		Comparability		Outcome	Score
Qi, 2019	***		**		**	7
An, 2017	***		**		***	8
Deng, 2019	****		**		***	9
Luan, 2015	****		*		**	7
Luo, 2017	****		**		**	8
Qin, 2016	***		*		***	7
Zhang, 2019	****		*		**	7
Xu, 2017	****		**		*	7
Zhu, 2011	****		*		***	8

*, one point. Randomized trials were assessed by the Cochrane risk of bias tool. Retrospective studies were assessed by NOS method. A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability, according to the instruction of NOS.

model was applied as I^2 of the pooled retrospective studies was 57%.

Comparison of OS between the TRT and non-TRT groups according to clinicopathologic features

Nine studies reported OS in patients receiving sequential TRT in combination with platinum-based chemotherapy. The pooled analysis using a random effects model showed that the sequential TRT group had better OS than the non-TRT group (HR =0.67; 95% CI: 0.54–0.84, $P=0.0006$) (Figure 4A). For patients aged ≥ 65 years, the TRT group had better OS than the non-TRT group (HR =0.55; 95% CI: 0.40–0.74, $P=0.0001$). The fixed effects model was used as $I^2=0\%$ (Figure 4B). Three studies reported OS in patients with oligometastatic disease (defined as only one organ metastasis). The pooled HR with a random effects model was 0.61 (95% CI: 0.36–1.01, $P=0.06$) (Figure 4C).

Toxicity

Grade III or higher toxicity was analyzed in 6 studies,

including 570 cases in the TRT group and 694 cases in the non-TRT group. The pooled results with a fixed effects model indicated the TRT group had a higher risk of grade III or higher toxicity than the non-TRT group (RR =1.34; 95% CI: 1.17–1.53, $P<0.0001$) (Figure 5). Table 3 shows the comparison of common grade III or higher toxicity between the TRT group and the non-TRT group. The pooled RRs were 1.26 (95% CI: 0.82–1.95, $P=0.29$) for grade ≥ 3 leucopenia, 0.67 (95% CI: 0.44–1.03, $P=0.07$) for grade ≥ 3 thrombocytopenia, 0.92 (95% CI: 0.53–1.59, $P=0.76$) for grade ≥ 3 anemia, 0.61 (95% CI: 0.35–1.08, $P=0.09$) for grade ≥ 3 nausea or vomiting, 13.89 (95% CI: 3.63–53.19, $P=0.0001$) for grade ≥ 3 esophageal toxicity and 2.63 (95% CI: 1.21–5.72, $P=0.02$) for grade ≥ 3 bronchopulmonary toxicity.

Sensitivity analysis and publication bias

The funnel plot was applied to test publication bias. No substantial publication bias was observed with respect to OS (Figure 6). We also performed sensitivity analysis by deleting one study at a time. The results showed that the effect of TRT on OS, PFS and LRFS was reliable.

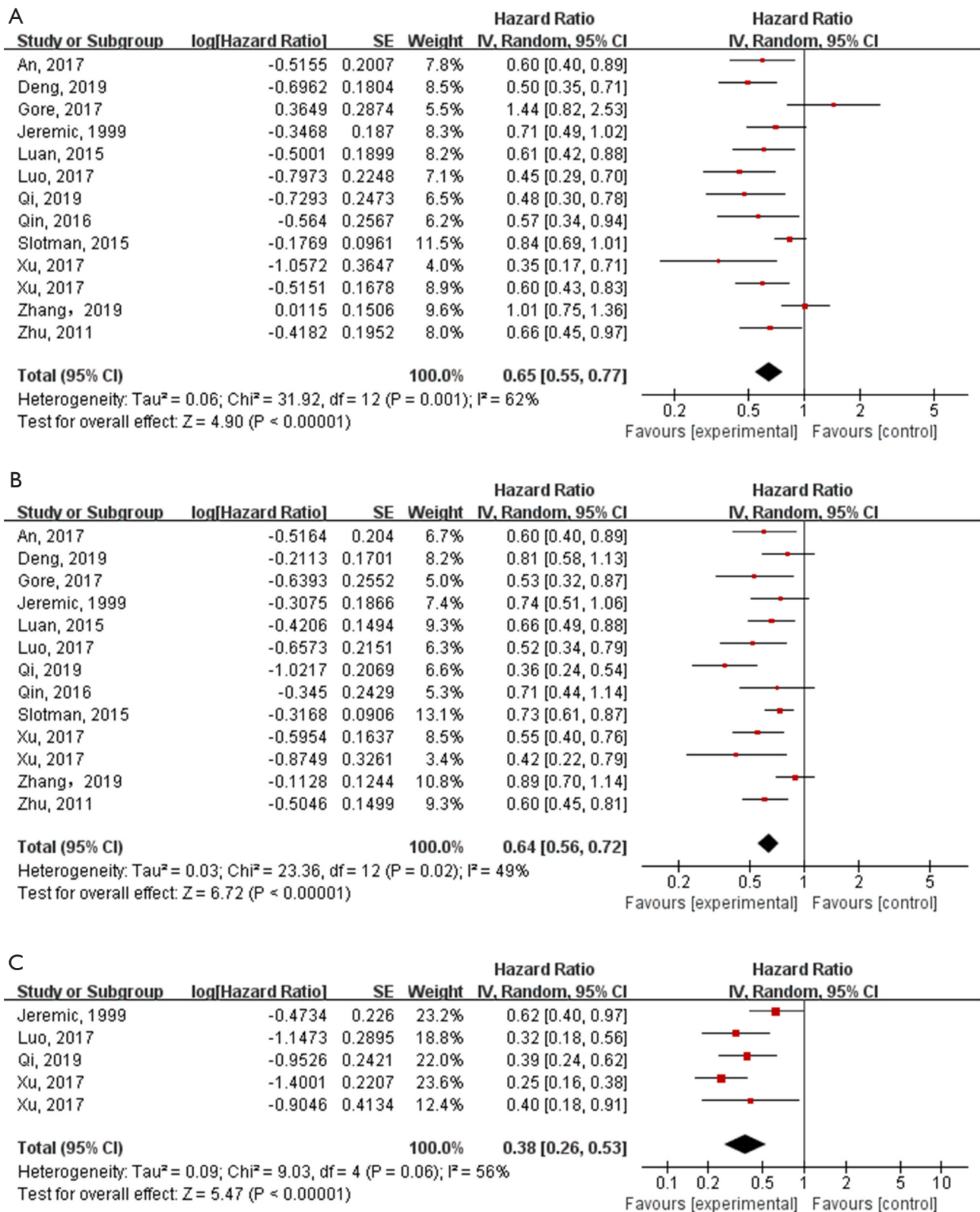


Figure 2 Forest plots of HRs for OS, PFS and LRFS in patients with ES-SCLC. (A) OS; (B) PFS; (C) LRFS. OS, overall survival; PFS, progression-free survival; LRFS, local recurrence-free survival; ES-SCLC, extensive stage small cell lung cancer.

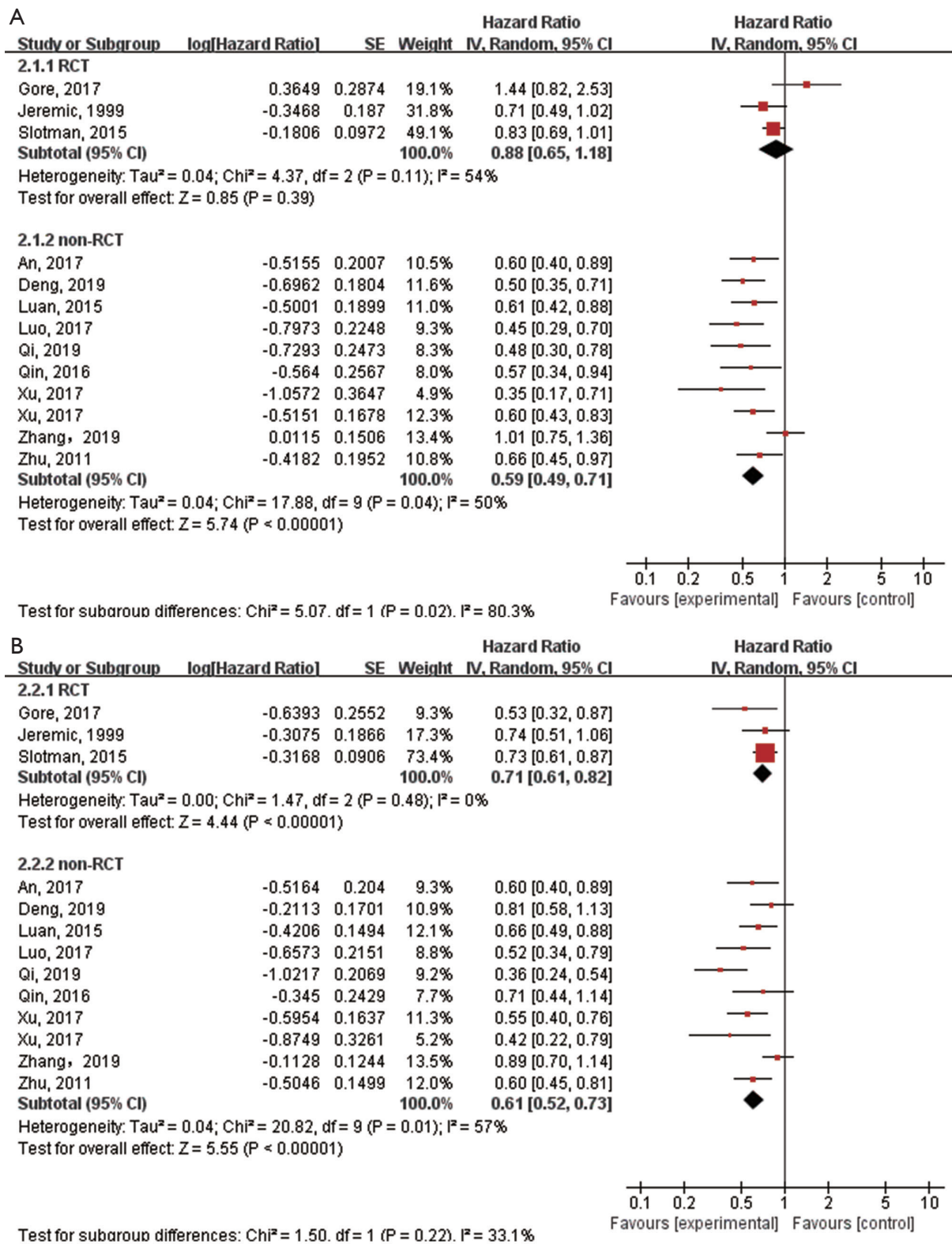


Figure 3 Forest plots for subgroup analysis of HRs for OS and PFS by study type. (A) OS; (B) PFS. OS, overall survival; PFS, progression-free survival.

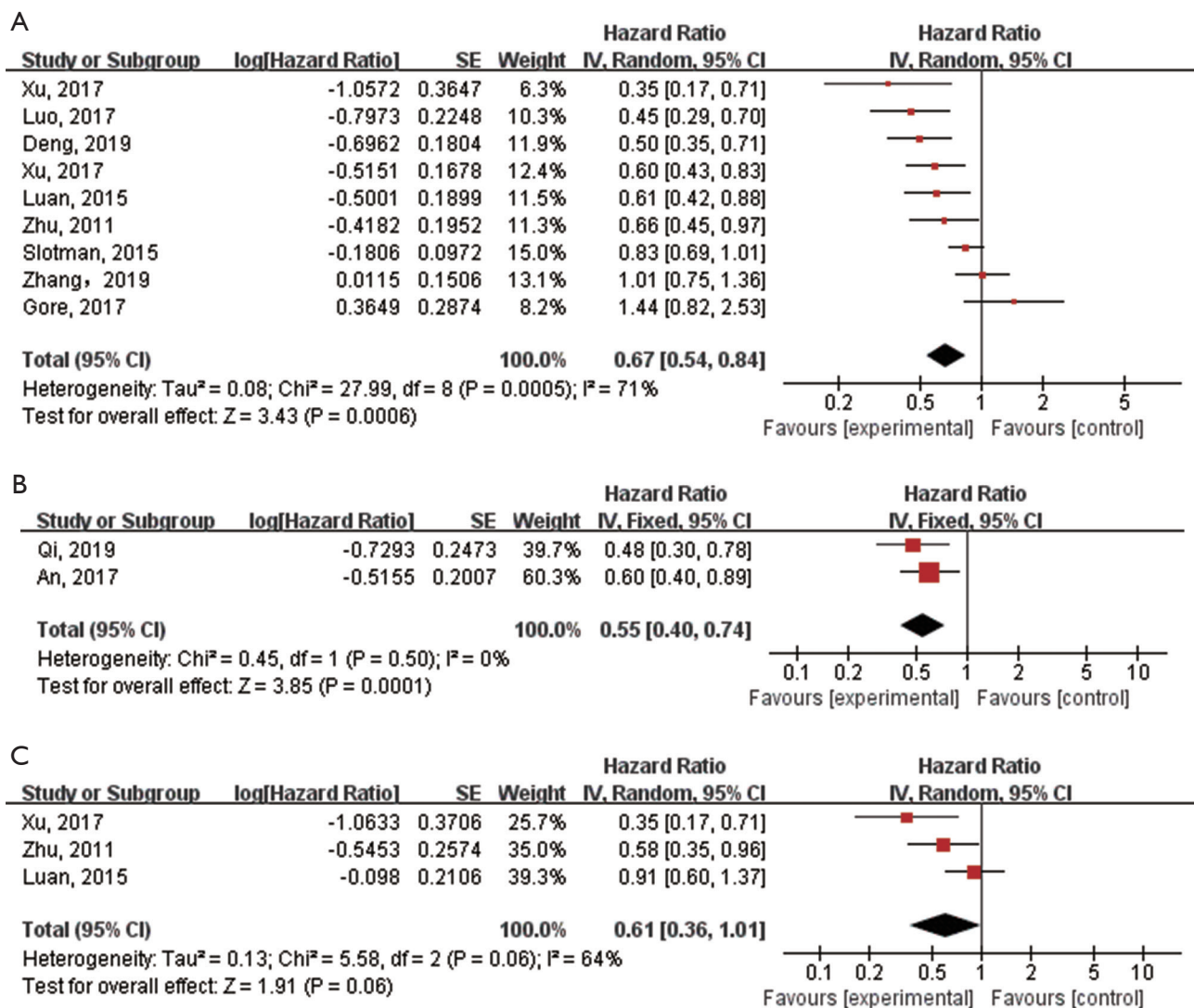


Figure 4 Forest plots of HRs for OS in patients with different clinicopathological features. (A) Patients receiving sequential TRT; (B) patients over 65 years old; (C) patients with oligometastatic disease. OS, overall survival.

Discussion

This meta-analysis compared the clinical efficacy of TRT combined with chemotherapy with chemotherapy alone in ES-SCLC based on 12 studies. The combined results showed that TRT significantly improved both OS and PFS. In addition, TRT reduced the risk of intrathoracic progression and improved LRFS.

Subgroup analysis according to the study type was conducted due to significant heterogeneity of the combined results. The benefits of TRT on OS and PFS were observed in the subgroup of retrospective studies. In the subgroup of RCTs, TRT still improved PFS in patients with ES-SCLC.

However, the pooled analysis of RCTs showed that there was no significant difference in OS between the two groups, which was consistent with the previous meta-analysis (including the same three RCTs) (22). Moderate degree of heterogeneity was observed in the RCT subgroup, which was mainly affected by the negative results of the RTOG-0937 (10). Baseline characteristics of the TRT group and the non-TRT group in RTOG-0937 were unbalanced, and there were more elderly patients (65 years or older) in the TRT group, which may increase the risk of bias. In addition, the TRT group included more patients with poor performance status, 2–4 metastatic lesions, and PR to initial

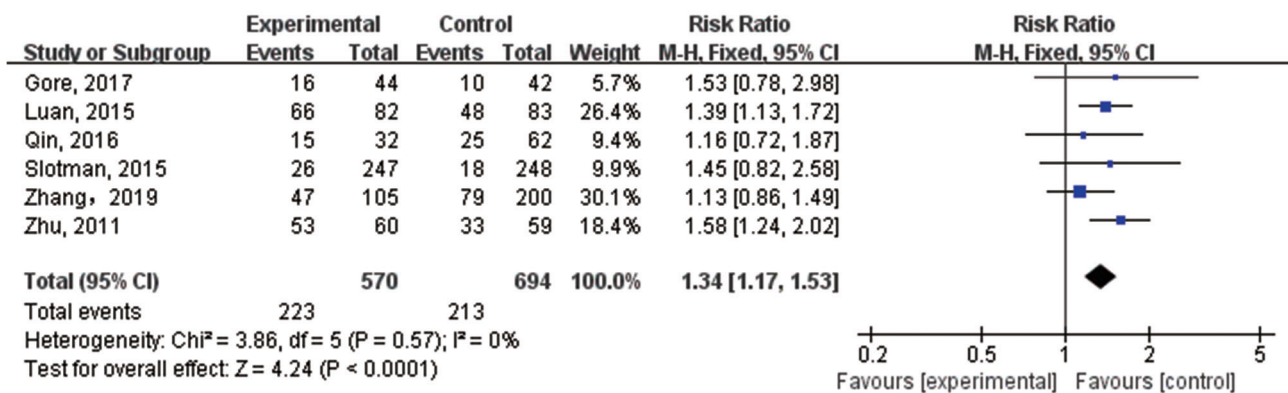


Figure 5 Forest plot of RR for grade III or higher toxicity in patients with ES-SCLC. ES-SCLC, extensive stage small cell lung cancer.

Table 3 Comparison of common grade III or higher toxicity between the TRT group and the non-TRT group

Toxicity (grade ≥ 3)	No. of studies	TRT group			Non-TRT group			RR (95% CI)	Heterogeneity (I ²)	P value
		Events (n)	Total (n)	%	Events (n)	Total (n)	%			
Leucopenia	5	116	273	42.5	98	300	32.7	1.26 (0.82–1.95)	70%	0.29
Thrombocytopenia	5	27	273	9.9	42	300	14	0.67 (0.44–1.03)	0%	0.07
Anemia	5	22	273	8.1	25	300	8.3	0.92 (0.53–1.59)	0%	0.76
Nausea/vomiting	5	16	476	3.4	28	506	5.5	0.61 (0.35–1.08)	46%	0.09
Esophageal toxicity	6	27	581	4.6	0	716	0	13.89 (3.63–53.19)	0%	0.0001
Bronchopulmonary toxicity	7	18	625	2.9	6	748	0.8	2.63 (1.21–5.72)	3%	0.02

Grade ≥ 3 esophageal toxicity includes: esophagitis, dysphagia; Grade ≥ 3 bronchopulmonary toxicity includes: dyspnea, cough, pneumonitis. TRT, thoracic radiotherapy; RR, risk ratio.

chemotherapy, which may further weaken the survival advantage of consolidation radiotherapy.

Considering that the survival benefit of platinum-based chemotherapy and concurrent TRT was superior to sequential TRT in patients with limited-stage SCLC, we explored the role of sequential radiotherapy in ES-SCLC (23). Our analysis suggested that sequential TRT had better OS than the control group. The effect of concurrent TRT in ES-SCLC was not evaluated due to insufficient data. Of the twelve included studies, only one randomized study compared survival in patients receiving concurrent TRT with those receiving chemotherapy alone. The results showed that concurrent TRT provided a significant survival benefit (5).

In the meta-analysis, we further explored the role of TRT in patients with ES-SCLC with different clinicopathologic features. The pooled results showed that the addition of TRT still improved the prognosis of patients over 65 years

of age. In addition, previous studies have demonstrated that ES-SCLC patients with a single metastatic site were more suitable for radiotherapy as they had lower disease burden (16,24,25). However, our study did not observe the benefit of TRT for OS in patients with only one organ metastasis. Since only three studies have reported OS in patients with oligometastatic disease and they were all retrospective studies, this conclusion should be considered with caution. The study of Zhang *et al.* was not included in this subgroup analysis because they excluded patients with brain or liver metastases from the oligometastatic population. In their study, TRT significantly increased PFS and OS in patients with oligometastatic ES-SCLC without brain or liver metastasis (11). It is worth noting that a secondary analysis of the CREST trial found that both OS and PFS benefits were observed in patients with two or fewer metastases (no brain metastasis). No difference in survival was observed between patients with 0–1 metastatic sites and 2 metastatic

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-5765>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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