

# Twice-daily vs higher-dose once-daily thoracic radiotherapy for limited-disease small-cell lung cancer

## A PRISMA-compliant meta-analysis

Lin Yang, MD<sup>a</sup>, Libo Liu, MM<sup>b</sup>, Yanjie Yang, MM<sup>c</sup>, Yao Lei, BM<sup>d</sup>, Tianyi Wang, MD<sup>e</sup>, Xiaocui Wu, BM<sup>a</sup>, Xiaoling Guo, MD<sup>f,\*</sup>

### Abstract

**Introduction:** The optimal dose and fractionation of thoracic radiotherapy (RT) for limited-disease small-cell lung cancer (LD-SCLC) remain controversial. This meta-analysis was performed to compare the efficacy and RT toxicity between twice-daily thoracic RT (45Gy with 1.5Gy twice daily) and higher-dose once-daily RT (60–72Gy with 1.8Gy/2Gy once daily) administered with chemotherapy in LD-SCLC patients.

**Methods:** PubMed, EMBASE, Web of Science, and the Cochrane Library were searched up to March 19, 2020 for studies that compared twice-daily thoracic RT (45Gy with 1.5Gy twice daily over 3 weeks) with higher-dose once-daily RT (60–72Gy with 1.8Gy/2Gy once daily over 6–8 weeks) in LD-SCLC patients.

**Results:** Five studies involving 13,726 patients were included in this analysis. Compared with the once-daily thoracic RT group, the 1-year overall survival (OS) rate ( $P < .001$ ), the 2-year OS rate ( $P < .001$ ), the 5-year OS rate ( $P < .001$ ), the mOS ( $P < .001$ ), and the 1-year LRFS rate ( $P = .048$ ) were significantly improved in the twice-daily RT group. The toxic effects of RT (esophagitis:  $P = .293$ ; pneumonitis:  $P = .103$ ) were similar in both groups.

**Conclusion:** Compared with the higher-dose once-daily regimen, the twice-daily thoracic radiotherapy regimen improved efficacy but did not increase RT toxicity in LD-SCLC patients.

**Abbreviations:** CI = confidence intervals, ITT = intention-to-treat, LD = limited disease, LRFS = locoregional recurrence-free survival, mLRFS = median LRFS, mOS = median OS, mOSR = median OS ratio, mPFS = median PFS, mPFSR = median PFS ratio, MSR = median survival ratio, NCCN = National Comprehensive Cancer Network, NOS = Newcastle–Ottawa Scale, NSCLC = non-small-cell lung cancer, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RCTs = randomized controlled trials, RT = radiotherapy, SCLC = small-cell lung cancer.

**Keywords:** limited-disease small-cell lung cancer, meta-analysis, once-daily, thoracic radiotherapy, twice-daily

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All the data are based on published studies; no additional data are available.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

<sup>a</sup> Department of Radiation Oncology, <sup>b</sup> Department of Gastrointestinal Oncology, <sup>c</sup> Department of Pneumology, Cancer Centre, 981 Hospital, PLA, Pu-Ning Road, Shuangqiao District, Chengde, China, <sup>d</sup> Department of Pulmonary Oncology, 307 Hospital, PLA, Fengtai District, Beijing, <sup>e</sup> Department of Orthopedics, <sup>f</sup> Department of Neuro-Oncology, Cancer Centre, 981 Hospital, PLA, Shuangqiao District, Chengde, China.

\* Correspondence: Xiaoling Guo, Department of Neuro-Oncology, Cancer Centre, 981 Hospital, PLA, Shuangqiao District, Chengde 067000, China (e-mail: 13165521862@163.com).

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## 1. Introduction

Small-cell lung cancer (SCLC), which is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases,<sup>[1]</sup> accounts for 10% to 15% of all lung cancers.<sup>[2]</sup> At the time of diagnosis, 30% to 40% of SCLC patients present with limited disease (LD) confined to the chest.<sup>[3]</sup> Two meta-analyses<sup>[4,5]</sup> showed that the addition of thoracic radiotherapy (RT) to platinum-based chemotherapy for LD-SCLC improves survival and local control, thus establishing a combined modality therapy for LD-SCLC. Early concurrent chemoradiotherapy is recommended for patients with LD-SCLC, which is based on both randomized trials<sup>[6,7]</sup> and meta-analyses<sup>[8–12]</sup> showing that early concurrent RT results in improved overall survival (OS) compared with late concurrent or sequential RT.

The optimal dose and fractionation of thoracic RT for LD-SCLC remain controversial. The National Comprehensive Cancer Network (NCCN) guidelines for SCLC (version 1.2019) recommend either 2 Gy once daily to a total dose of 60 to 70 Gy over 6 to 7 weeks or 1.5 Gy twice daily to a total dose of 45 Gy over 3 weeks as acceptable options depending on individual patient characteristics. However, while both of these NCCN guideline-recommended RT regimens are technical and logistical alternatives in clinical practice, questions remain as to which regimen should be chosen. It is essential to determine which of these 2 NCCN guideline-recommended RT regimens may lead to better efficacy and/or lower toxicity. CONVERT<sup>[13]</sup> is the only completed randomized phase 3 trial to compare 2 NCCN guideline-recommended RT regimens. However, its primary end point failed to reach the expectation, and the results showed that a 66 Gy once-daily treatment showed neither superiority nor equivalence to 45 Gy twice-daily treatment in patients with LD-SCLC. Other randomized phase 3 trials comparing twice-daily thoracic RT (45 Gy with 1.5 Gy twice daily over 3 weeks) with higher-dose once-daily RT (60–70 Gy with 2 Gy once daily over 6–7 weeks) administered with chemotherapy for the treatment of LD-SCLC (CALGB 30610/GTOG 0538, etc.) are currently underway. However, the results will not be available for several years. Several retrospective studies with the same purpose described above have been published,<sup>[14–16]</sup> but the outcomes were inconsistent. A meta-analysis may provide us with an evidence-based recommendation for therapeutic decision-making, and to date, no meta-analysis of twice-daily vs higher-dose once-daily thoracic RT in LD-SCLC has been published. In this study, we performed a meta-analysis to compare the efficacy and RT toxicity between twice-daily thoracic RT (45 Gy with 1.5 Gy twice daily over 3 weeks) and higher-dose once-daily RT (60–72 Gy with 1.8 Gy/2 Gy once daily over 6–8 weeks, approximately 60–70 Gy with 2 Gy once daily over 6–7 weeks, which is the NCCN guideline-recommended RT regimen for once-daily treatment), administered with chemotherapy in LD-SCLC patients.

## 2. Methods

### 2.1. Eligibility criteria

Studies that met the following criteria were included:

1. The subjects were LD-SCLC patients.
2. Patients in 1 arm received twice-daily thoracic RT (45 Gy with 1.5 Gy twice daily over 3 weeks) with chemotherapy, and

patients in the other arm received higher-dose once-daily RT (60–72 Gy with 1.8 Gy/2 Gy once daily over 6–8 weeks) with chemotherapy. Studies with a median RT dose of 45 Gy in the twice-daily group or 60 to 72 Gy in the once-daily group were permitted.

3. The once-daily and twice-daily arms were compared in terms of survival and/or adverse effects of RT.

### 2.2. Literature search strategy

PubMed, EMBASE, Web of Science, and the Cochrane Library were comprehensively searched for studies that compared twice-daily thoracic RT (45 Gy with 1.5 Gy twice daily over 3 weeks) with higher-dose once-daily RT (60–72 Gy with 1.8 Gy/2 Gy once daily over 6–8 weeks) in patients with LD-SCLC (data cutoff date: March 19, 2020). The following search terms were used: “cancer”, “tumor”, “carcinoma”, “neoplasm”, “small cell”, “small-cell”, “lung”, “scl”, “limited”, “radiotherapy”, “radiation therapy”, “irradiation”, “standard\*”, “convention\*”, “once-daily”, “once daily”, “1 fraction per day”, “qd”, “hyperfraction\*”, “twice-daily”, “twice daily”, “2 fraction per day”, and “bid”. The search strategies used to search the electronic databases are presented in Table 1. The search was limited to English publications in human subjects.

### 2.3. Study selection, data extraction, and quality assessment

Two reviewers began by independently performing the initial search, after which they deleted duplicate records, reviewed the titles and abstracts for relevance, and identified whether each study should be excluded or assessed further. If deemed necessary, the full text of the article was retrieved and reviewed in detail to identify eligibility according to the predefined inclusion criteria. Then, 2 reviewers independently abstracted data, including the name of the first author, publication year, study design, number of chemotherapy cycles at the start of radiation, chemotherapy regimen, number of chemotherapy cycles delivered, radiation schedule (Gy/fraction), radiation techniques, delivery of elective nodal irradiation, and delivery of prophylactic cranial irradiation, as well as sample size, 1-year overall survival rate, 2-year OS rate, 5-year OS rate, median OS (mOS), 1-year locoregional recurrence-free survival (LRFS) rate, 2-year LRFS rate, 5-year LRFS rate, median LRFS (mLRFS), 1-year progression-free survival (PFS) rate, 2-year PFS rate, 5-year PFS rate, median PFS (mPFS), esophagitis rate and pneumonitis rate (the definitions and grading scales of esophagitis and pneumonitis are detailed in the Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0) in each arm. Finally, 2 reviewers independently evaluated the methodological quality of the included studies according to the Newcastle–Ottawa Scale (NOS).<sup>[17]</sup> The reviewers resolved disagreements by discussion.

### 2.4. Statistical analysis

Time-point survival rates (1-year PFS rate, 1-year OS rate, 1-year LRFS rate, etc.), median survival (mOS, mLRFS, and mPFS), and radiation toxicity (esophagitis and pneumonitis) rates were abstracted from the published data. If data on the time-point survival rates were not reported directly, they were estimated by 2 reviewers from Kaplan–Meier curves using the Engauge Digitizer v4.1 (<http://digitizer.sourceforge.net/>) screenshot tool.<sup>[18,19]</sup> If

**Table 1**

**Search strategies of electronic databases.**

Database	Data cutoff date	Results	Search strategy
PubMed	March 19, 2020	136	(((radiotherapy) OR (radiation therapy) OR (irradiation)) AND (((small cell) OR (small-cell) OR ((cancer) OR (tumor) OR (neoplasm) OR (carcinoma))) AND ((lung) OR (scic))) AND (((standard*) OR (convention*)) OR (once-daily)) OR (once daily) OR (one fraction per day) OR (qd)) AND (((hyperfraction*) OR (twice-daily)) OR (twice daily)) OR (2 fraction per day)) OR (bid)
Web of Science	March 19, 2020	158	# 12 AND #10 AND #9 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = (hyperfraction* OR twice-daily OR two fraction per day OR bid)) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = (standard* OR convention* OR once-daily OR once daily OR one fraction per day OR qd)) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years #8 AND #7 AND #6 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = limited) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = (radiotherapy OR radiation therapy OR irradiation)) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years #5 OR #4 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = scic) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years #3 AND #2 AND #1 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = lung) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = (small cell OR small-cell)) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years (ALL = (cancer OR tumor OR neoplasm OR carcinoma)) AND LANGUAGE: (English) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCL-S, CPCL-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years
EMBASE	March 19, 2020	272	('radiotherapy'/exp OR radiotherapy OR 'radiation therapy' OR 'radiation therapy' OR (('radiation'/exp OR radiation) AND ('therapy'/exp OR therapy)) OR 'irradiation'/exp OR irradiation) AND ((small AND ('cell'/exp OR cell) OR 'small cell') AND ('cancer'/exp OR cancer OR 'tumor'/exp OR tumor OR 'neoplasm'/exp OR neoplasm OR 'carcinoma'/exp OR carcinoma) AND ('lung'/exp OR lung) OR scic) AND limited AND (standard* OR convention* OR 'once daily' OR (once AND daily) OR '1 fraction per day' OR (1 AND fraction AND per AND ('day'/exp OR day)) OR qd) AND (hyperfraction* OR 'twice daily' OR (twice AND daily) OR '2 fraction per day' OR (2 AND fraction AND per AND ('day'/exp OR day)) OR bid)
Cochrane Library	March 19, 2020	91	(((radiotherapy) OR (radiation therapy) OR (irradiation)) AND (((small cell) OR (small-cell) OR ((cancer) OR (tumor) OR (neoplasm) OR (carcinoma))) AND ((lung) OR (scic))) AND (limited) AND (((standard*) OR (convention*)) OR (once-daily)) OR (once daily) OR (1 fraction per day) OR (1 AND fraction AND per AND ('day'/exp OR day)) OR (2 fraction per day)) OR (twice-daily)) OR (twice daily)) OR (2 fraction per day) OR (bid)):it,ab,kw

data on median survival were not reported directly, they were estimated from Kaplan–Meier curves by 2 reviewers using the Engauge Digitizer v4.1 screenshot tool as the time at which 50% of patients had progressed or died. Differences were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) for binary outcomes. The time-point survival rates were analyzed as binary outcomes, and differences were expressed as ORs with 95% CIs.<sup>[20,21]</sup> For each study, the median survival ratio (MSR) was computed as  $m_{\text{twice-daily}}/m_{\text{once-daily}}$  ( $m_{\text{twice-daily}}$  = median survival of twice-daily arm;  $m_{\text{once-daily}}$  = median survival of once-daily arm), and the  $\ln(\text{MSR})$  and  $\text{se}[\ln(\text{MSR})]$  were estimated as  $\ln(m_{\text{twice-daily}}/m_{\text{once-daily}})$  and  $\sqrt{1/n}$  ( $n$  = total sample size analyzed in the study), respectively. The median survival was analyzed using  $\ln(\text{MSR})$  and  $\text{se}[\ln(\text{MSR})]$ , and the differences were expressed as the MSR with 95% CIs. Heterogeneity across the included studies was evaluated by the Q-test  $I^2$  statistic.  $P > .1$  and  $I^2 < 50\%$  indicated a lack of interstudy heterogeneity, and pooled estimates were calculated using a fixed-effects model;  $P < .1$  or  $I^2 > 50\%$  indicated that the studies were heterogeneous, and a random-effects model was applied.<sup>[22]</sup> Publication and selection bias were investigated through funnel plots. Data were analyzed using Stata 15.1 (StataCorp LLC, Texas, USA). A two-sided  $P$  value  $< .05$  was considered statistically significant.

### 2.5. Ethical approval

Ethics approval is not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

## 3. Results

### 3.1. Study identification and selection

Using our search strategy, 657 records were retrieved from the initial database search. After duplicate articles were excluded, 352 records remained. After a simple reading of the titles and abstracts of the articles, 254 records were removed. The remaining 98 full-text articles were reviewed in detail, and 93 of them were also removed. Finally, 5 studies were included in this meta-analysis.<sup>[13–16,23]</sup> The selection process is shown in Figure 1.

### 3.2. Study characteristics

Five studies involving 13,726 patients were included in this analysis, including 2 studies reported by Corinne Favrre-Finn,<sup>[13,23]</sup> which were verified not to be redundant in that the last patient was randomized in March 2008 in 1 study<sup>[23]</sup> and the first patient was recruited on April 7, 2008, in the other.<sup>[13]</sup> The key characteristics of the included studies are summarized in Table 2.<sup>[13–16,23]</sup> Three studies were retrospective,<sup>[14–16]</sup> and 2 were prospective.<sup>[13,23]</sup> In all, 3221 of the 13,726 patients were included in the twice-daily group receiving 45 Gy RT with 1.5 Gy twice daily over 3 weeks, and 10,505 were included in the higher-dose once-daily group receiving 60 to 72 Gy RT with 1.8 Gy/2 Gy once daily over 6 to 8 weeks. Only 1 of the 5 included studies reported the objective response rate (ORR).<sup>[15]</sup> Three out of 5 studies reported LRFS-related data (1 or more of the 1-year LRFS rate, 2-year LRFS rate, 5-year LRFS rate, mLRFS, and LRFS Kaplan–Meier curves),<sup>[13,15,16]</sup> 3 reported PFS-related data (1 or more of the 1-year PFS rate, 2-year PFS rate, 5-year PFS rate, mPFS, and PFS Kaplan–Meier curves),<sup>[13,15,16]</sup> 4 reported

radiation toxicity (both esophagitis and pneumonitis),<sup>[13,15,16,23]</sup> and all 5 included studies reported OS-related data (1 or more of the 1-year OS rate, 2-year OS rate, 5-year OS rate, mOS, and OS Kaplan–Meier curves).<sup>[13–16,23]</sup> Since pooled data of 60 to 72 Gy RT with 1.8 Gy/2 Gy once daily vs 45 Gy RT with 1.5 Gy twice daily were not reported, data from Davids study<sup>[14]</sup> were included in this analysis in 2 independent parts (60–61.2 Gy/1.8–2 Gy once-daily vs 45 Gy/1.5 Gy twice-daily, and 62–72 Gy/1.8–2 Gy once-daily vs 45 Gy/1.5 Gy twice daily) and were analyzed independently as if they were from 2 different studies.

### 3.3. Quality assessment

The NOS results are summarized in Table 3.<sup>[13–16,23]</sup> Among the 3 retrospective studies, 1 received 8 stars, and 2 received 7 stars. Both prospective studies received 9 stars.

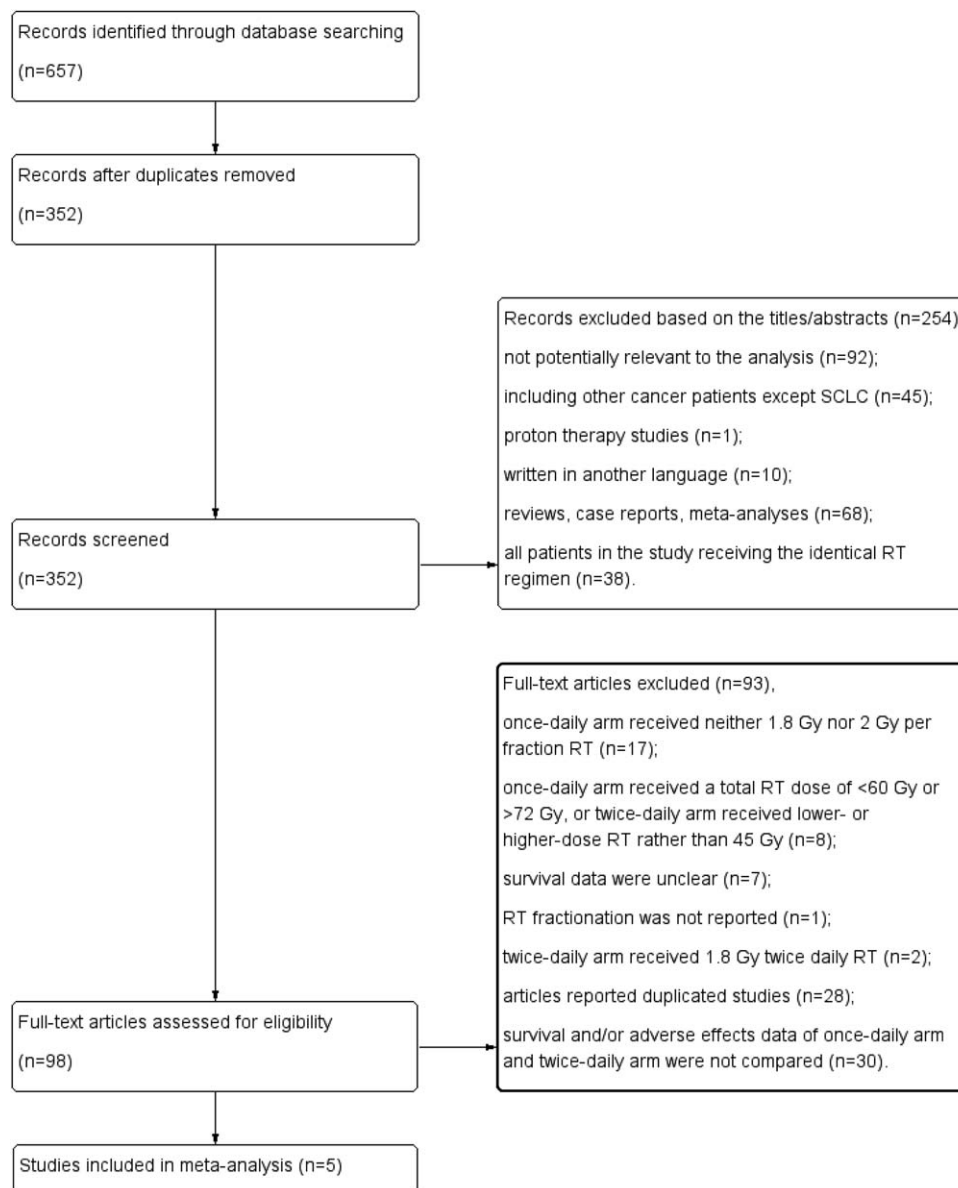
### 3.4. Efficacy analysis

Among the 3 studies that reported the PFS-related data,<sup>[13,15,16]</sup> 2 reported the 1-year PFS rate,<sup>[15,16]</sup> 2 reported the 2-year PFS rate,<sup>[15,16]</sup> 2 reported the 5-year PFS rate,<sup>[15,16]</sup> and 3 reported the mPFS.<sup>[13,15,16]</sup> No heterogeneity was found between the 2 studies<sup>[13,15,16]</sup> that reported the 1-year PFS rate ( $P = .681$ ,  $I^2 = 0\%$ ); therefore, a fixed-effects model was applied. No significant increase in the 1-year PFS rate was found in the twice-daily thoracic RT arm compared with the higher-dose once-daily RT arm (OR 0.77, 95% CI: 0.44–1.38,  $P = .384$ , Fig. 2A). Similar results were observed in the 2-year PFS rate (heterogeneity:  $P = .817$ ,  $I^2 = 0\%$ ; OR 0.94, 95% CI: 0.52–1.70,  $P = .837$ , Fig. 2B) and the 5-year PFS rate (heterogeneity:  $P = .396$ ,  $I^2 = 0\%$ ; OR 0.79, 95% CI: 0.27–2.29,  $P = .663$ , Fig. 2C). Significant heterogeneity was found across the 3 studies<sup>[13,15,16]</sup> that reported the mPFS ( $P = .019$ ,  $I^2 = 74.8\%$ ); therefore, a random-effects model was applied. The pooled median PFS ratio (mPFSR) was 1.02, with a 95% CI from 0.85 to 1.21 ( $P = .866$ ). This result indicates no significant improvement in mPFS between the twice-daily thoracic RT group and the higher-dose once-daily RT group (Fig. 2D).

Among the 5 studies that reported OS-related data,<sup>[13–16,23]</sup> 5 reported the 1-year OS rate,<sup>[13–16,23]</sup> 4 reported the 2-year OS rate,<sup>[13–16]</sup> 4 reported the 5-year OS rate,<sup>[13–16]</sup> and 5 reported the mOS.<sup>[13–16,23]</sup> No significant heterogeneity was found among the 5 studies<sup>[13–16,23]</sup> that reported the 1-year OS rate ( $P = .843$ ,  $I^2 = 0\%$ ); therefore, a fixed-effects model was applied. A significant increase in the 1-year OS rate was seen in the twice-daily thoracic RT group compared with the higher-dose once-daily RT group (OR 1.24, 95% CI: 1.15–1.33,  $P < .001$ , Fig. 3A). Similar results were observed in the 2-year OS rate (heterogeneity:  $P = .995$ ,  $I^2 = 0\%$ ; OR 1.27, 95% CI: 1.19–1.35,  $P < .001$ , Fig. 3B), the 5-year OS rate (heterogeneity:  $P = .819$ ,  $I^2 = 0\%$ ; OR 1.42, 95% CI: 1.31–1.53,  $P < .001$ , Fig. 3C) and the mOS [heterogeneity:  $P = .264$ ,  $I^2 = 22.6\%$ ; median OS ratio (mOSR) 1.14, 95% CI: 1.12–1.16,  $P < .001$ , Fig. 3D], though only 4 studies reported the 2-year OS ratio and the 5-year OS ratio.<sup>[13–16]</sup>

Among the 3 studies that reported LRFS-related data,<sup>[13,15,16]</sup> 2 reported the 1-year LRFS rate,<sup>[13,16]</sup> 3 reported the 2-year LRFS rate,<sup>[13,15,16]</sup> 2 reported the 5-year LRFS rate,<sup>[13,16]</sup> and 1 reported the mLRFS.<sup>[13]</sup> No heterogeneity was observed between the 2 studies<sup>[13,16]</sup> that reported the 1-year LRFS rate ( $P = .635$ ,  $I^2 = 0\%$ ); therefore, a fixed-effects model was applied. A significant improvement was observed in the 1-year





**Figure 1.** Selection process for the studies included in the meta-analysis.

LRFS rate in the twice-daily thoracic RT arm compared with the higher-dose once-daily RT arm (OR 1.45, 95% CI: 1.00–2.10,  $P=.048$ , Fig. 4A). No significant heterogeneity was observed among the 3 studies<sup>[13,15,16]</sup> that reported the 2-year LRFS rate ( $P=.212$ ,  $I^2=35.5\%$ ); therefore, a fixed-effects model was applied. Although no statistically significant difference ( $P=.057$ ) was found in the 2-year LRFS rate between the twice-daily and once-daily groups, there was a trend toward improved local control for the twice-daily group, with an estimated OR of 1.33 and a 95% CI from 0.99 to 1.78 (Fig. 4B). Significant heterogeneity was observed between the 2 studies<sup>[13,16]</sup> that reported the 5-year LRFS rate ( $P=.126$ ,  $I^2=57.2\%$ ); therefore, a random-effects model was applied. The pooled OR was 1.67, with a 95% CI from 0.72 to 3.90 ( $P=.235$ , Fig. 4C). This result indicates no significant improvement in the 5-year LRFS rate between the twice-daily group and the once-daily group. Only

1 mLRFS dataset was obtained; therefore, the analysis of mLRFS was not pursued.

### 3.5. Toxicity analysis

Four of the 5 studies included in the analysis reported RT toxicity.<sup>[13,15,16,23]</sup> Significant heterogeneity was found across the 4 studies<sup>[13,15,16,23]</sup> that reported the incidence of esophagitis ( $\geq$ Grade 3;  $P=.107$ ,  $I^2=50.8\%$ ); therefore, a random-effects model was applied. No significant increase in esophagitis incidence was found in the twice-daily thoracic RT arm compared with the higher-dose once-daily RT arm (OR 1.50, 95% CI: 0.71–3.17,  $P=.293$ , Fig. 5A). No heterogeneity was found across the 4 studies<sup>[13,15,16,23]</sup> that reported the incidence of pneumonitis ( $\geq$ Grade 3;  $P=.798$ ,  $I^2=0\%$ ); therefore, a fixed-effects model was applied, and no significant increase in the pneumonitis rate was found in the twice-daily thoracic RT arm

**Table 2**  
The characteristics of the included studies.

Author	Year	Study design	Sample size		Number of chemotherapy cycles at start of radiation	CT regimen	RT (total dose)/fraction			Delivery of elective nodal irradiation	Radiation techniques	Delivery of PCI
			Once-daily arm	Twice-daily arm			Once-daily arm	Twice-daily arm				
Dan Han	2015	Retrospective	80	63	Once daily: 1-2* (46/80) <sup>†</sup> 3-6 (24/80) Sequential (10/80) Twice daily: 1-2 (42/63) 3-6 (15/63) Sequential (6/63)	Etoposide, cisplatin or etoposide, carboplatin or irinotecan, cisplatin or irinotecan, carboplatin	4-6	60 Gy/2 Gy	45 Gy/1.5 Gy	No	Intensity-modulated radiation therapy	Once daily (40/80) <sup>‡‡</sup> Twice daily (3/63)
Corinne Faivre-Finn	2017	Prospective	273	274	Once daily: 2 (240/273) Sequential (6/273) No radiotherapy (26/273) Twice daily: 2 (249/274) Sequential (5/274)	Etoposide, cisplatin or etoposide, carboplatin	1-6 <sup>‡</sup> Once daily: 4 <sup>‡</sup> (156/273) <sup>  </sup> 6 (63/273) Twice daily: 4 (161/274) 6 (66/274)	66 Gy/2 Gy	45 Gy/1.5 Gy	No	3D conformal radiotherapy	Once daily (220/273) Twice daily (229/274)
John M. Watkins	2010	Retrospective	17	54	No radiotherapy (20/274) 1-2	Etoposide, cisplatin or etoposide, carboplatin or cisplatin → carboplatin/etoposide or topotecan/paclitaxel → carboplatin/etoposide	Once daily: 4 <sup>†</sup> (2-6) <sup>**</sup> 14/17 <sup>**</sup> Twice daily: 4 (1-6) 48/54	60 Gy <sup>††</sup> /1.8-2 Gy	45 Gy <sup>††</sup> /1.5 Gy	No	3D conformal radiotherapy	Once daily (9/17)  Twice daily (34/54)
David Schreiber (60 to 61.2 Gy in once-daily arm)	2015	Retrospective	5095	2821	NS	89.2% patients received multiagent chemotherapy 7.7% received either single agent chemotherapy or the number of agents was not documented	NS	60-61.2 Gy/1.8-2 Gy	45 Gy/1.5 Gy	NS	NS	NS
David Schreiber (62 to 72 Gy in once-daily arm)	2015	Retrospective	5017	2821				62-72 Gy/1.8-2 Gy	45 Gy/1.5 Gy			
C. Faivre-Finn	2011	Prospective	23	9	2	Cisplatin/etoposide	4	66 Gy/2 Gy	45 Gy/1.5 Gy	No	3D conformal radiotherapy	NS

NS=not specified, PCI=prophylactic cranial irradiation.

\* Number of chemotherapy cycles at the start of radiation in the once-daily arm.

† (Number of patients receiving 1-2 cycles of chemotherapy at start of radiation in once-daily arm) / (Total number of patients in once-daily arm).

‡ Number of chemotherapy cycles delivered in all patients in the study.

§ Number of chemotherapy cycles delivered in once-daily arm.

|| (Number of patients receiving 4 cycles of chemotherapy in once-daily arm) / (Total number of patients in once-daily arm).

¶ Median number of chemotherapy cycles delivered in once-daily arm.

# Range of chemotherapy cycles delivered in once-daily arm.

\*\* (Number of patients receiving median 4 cycles of chemotherapy in once-daily arm)/(Total number of patients in once-daily arm).

†† Median total dose.

‡‡ (Number of patients receiving PCI in once-daily arm) / (Total number of patients in once-daily arm).

**Table 3**  
**Results of quality assessment for studies using NOS.**

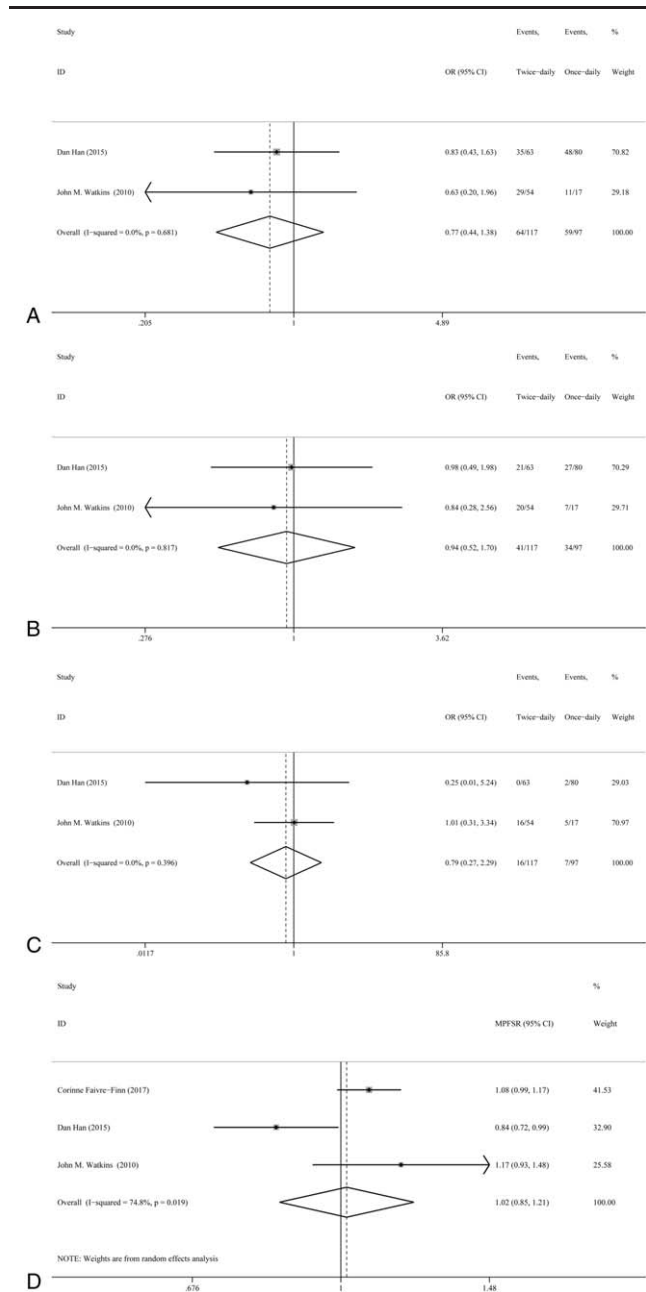
Study	Study design	Selection	Comparability	Exposure	Outcome
Dan Han (2015)	Case-control	***†	**	***	
John M. Watkins (2010)	Case-control	***, †	**	***	
David Schreiber (2015)	Case-control	***, †	‡	***	
Corinne Faivre-Finn (2017)	Cohort	****	**		***
C. Faivre-Finn (2011)	Cohort	****	**		***

Reasons for lost stars:

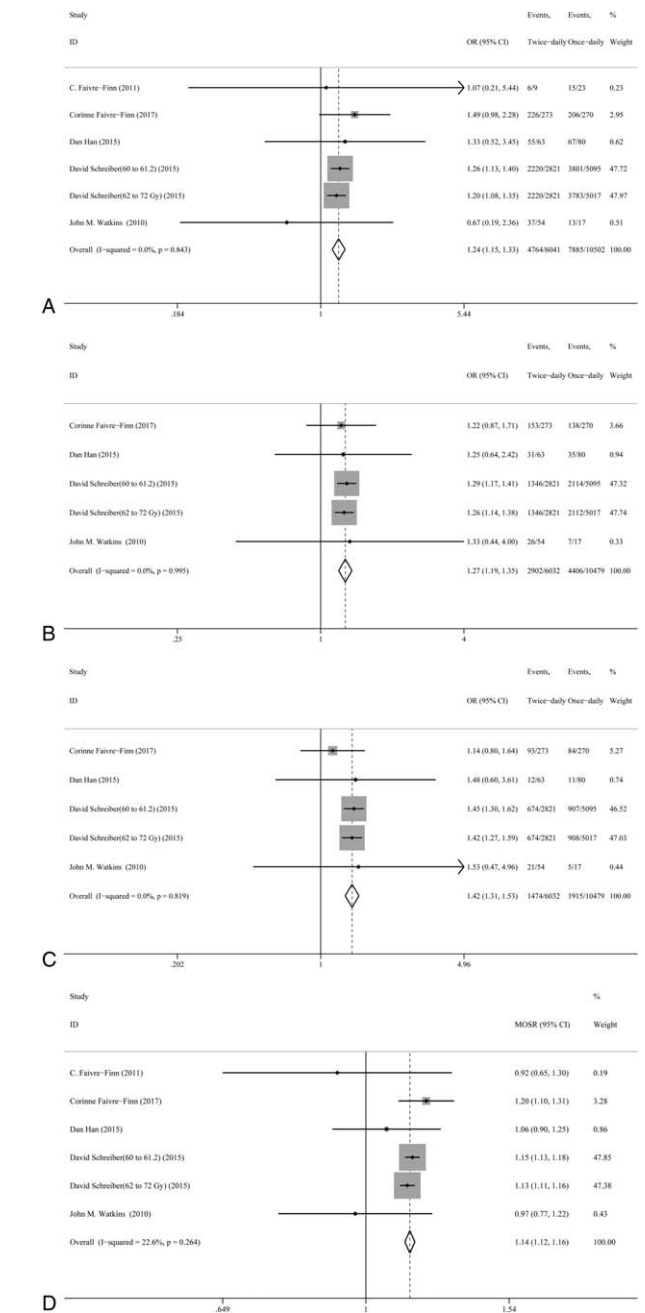
\* the case was defined by record linkage.

† hospital controls were selected.

‡ there was no description of whether the study controlled for any additional factor, such as gender or age.



**Figure 2.** PFS in the twice-daily group vs the higher-dose once-daily group. (A) 1-year PFS rate. (B) 2-year PFS rate. (C) 5-year PFS rate. (D) mPFS.



**Figure 3.** OS in the twice-daily group vs the higher-dose once-daily group. (A) 1-year OS rate. (B) 2-year OS rate. (C) 5-year OS rate. (D) mOS.

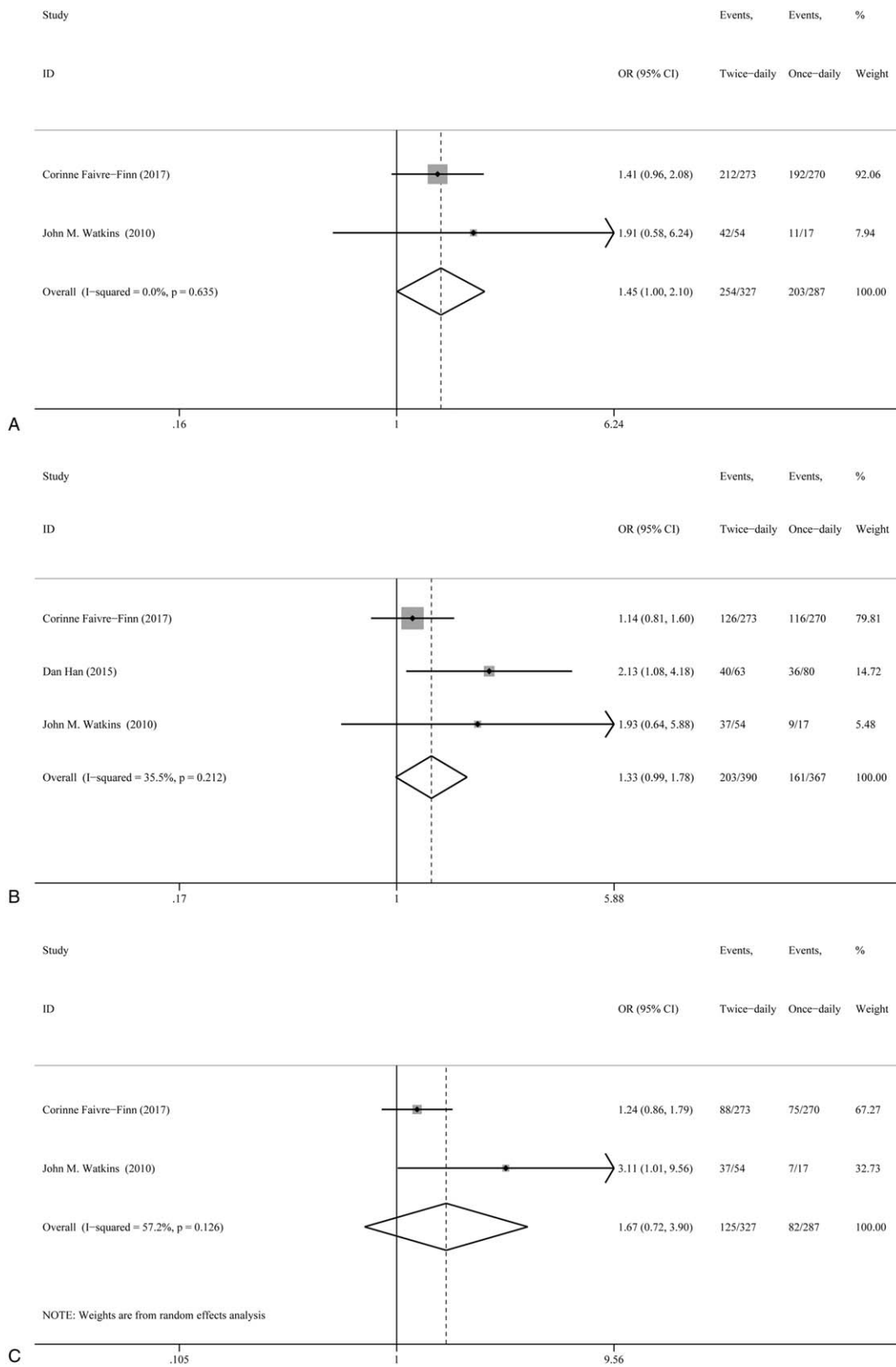


Figure 4. LRFs in the twice-daily group vs the higher-dose once-daily group. (A) 1-year LRFs rate. (B) 2-year LRFs rate. (C) 5-year LRFs rate.



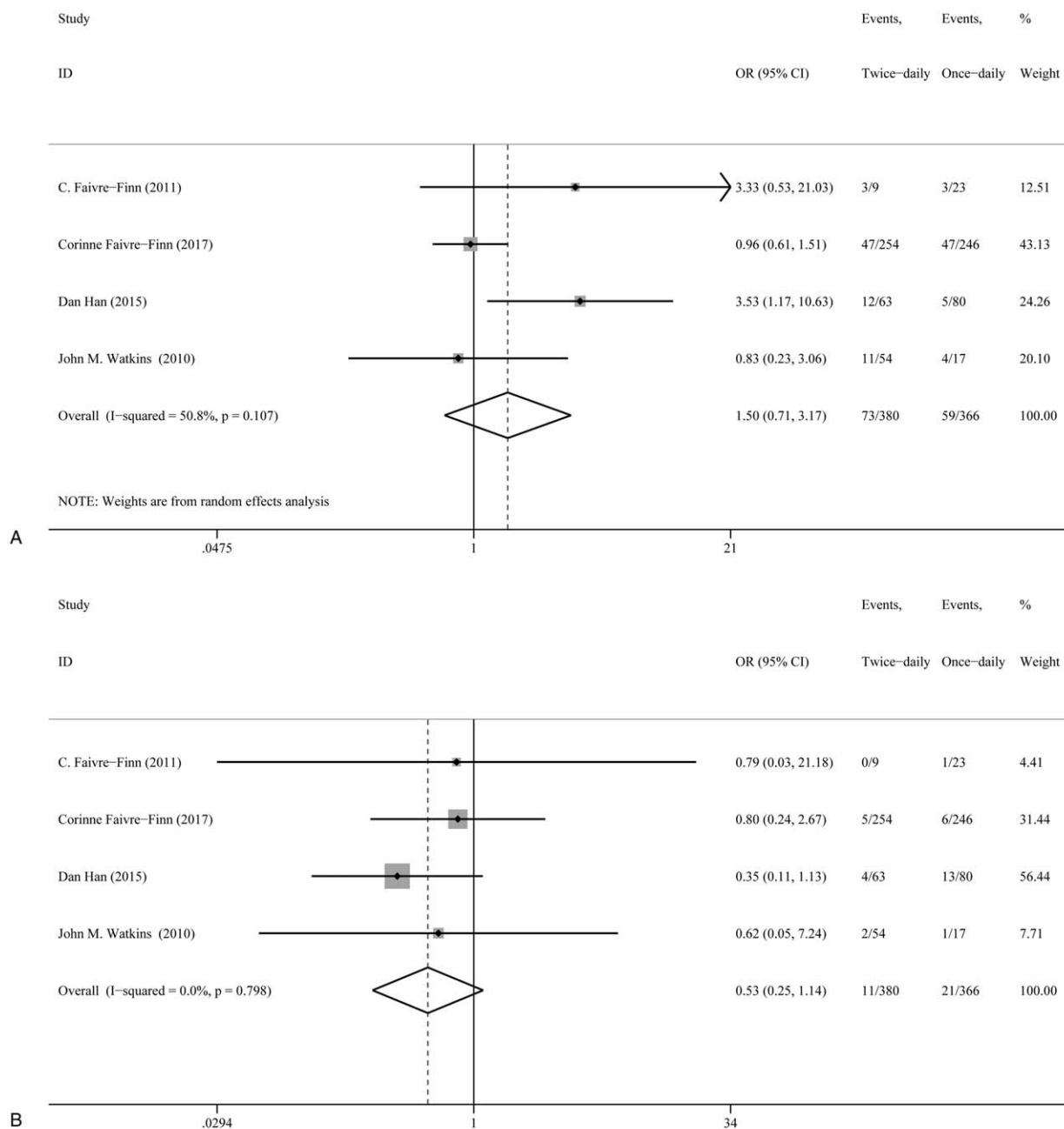


Figure 5. RT toxicity in the twice-daily group vs the higher-dose once-daily group. (A) Esophagitis. (B) Pneumonitis.

compared with the higher-dose once-daily RT arm (OR 0.53, 95% CI: 0.25–1.14,  $P = .103$ , Fig. 5B).

**3.6. Publication bias**

A funnel plot to evaluate publication bias requires that at least 10 studies be included in the meta-analysis; otherwise, the test power will be too low to assess the symmetry of the funnel plot.<sup>[24,25]</sup> The meta-analysis described here included only 5 studies. Therefore, we did not generate a funnel plot.

**4. Discussion**

This is the first meta-analysis to evaluate the survival and radiation toxicity in LD-SCLC patients treated with twice-daily

thoracic RT (45 Gy with 1.5 Gy twice daily over 3 weeks) vs higher-dose once-daily RT (60–72 Gy with 1.8 Gy/2 Gy once daily over 6–8 weeks) with chemotherapy. We found that OS-related survival data, including 1-year OS rate, 2-year OS rate, 5-year OS rate, and mOS, were significantly improved in the twice-daily thoracic RT group compared with the once-daily RT group. According to the LRFS-related survival data, significant improvement was observed in the 1-year LRFS rate in the twice-daily group vs the once-daily group; a trend toward improved 2-year LRFS rate and 5-year LRFS rate was also observed in the twice-daily group compared with the once-daily group, although the difference between the 2 groups was not statistically significant. However, no significant difference was observed between the twice-daily group and the once-daily group

in all PFS-related survival data, including the 1-year PFS rate, 2-year PFS rate, 5-year PFS rate, and mPFS. Even a trend toward an increased 1-year PFS rate, 2-year PFS rate and 5-year PFS rate was seen in the once-daily thoracic group compared with the twice-daily group. The RT toxicities were similar in both groups.

CONVERT<sup>[13]</sup> is the largest, phase 3, randomized study to compare twice-daily thoracic RT with a higher dose of RT delivered once daily, given concurrently with chemotherapy in LD-SCLC. The results of CONVERT reveal a trend toward improved OS and local PFS in the twice-daily group compared with the once-daily group, although the difference was not statistically significant. Our results of OS and LRFS in the meta-analysis were consistent with those of CONVERT, although the PFS results were contradictory to the OS and LRFS results in our meta-analysis. However, among the 3 groups of efficacy-related survival data in this meta-analysis, the OS-related survival data were most convincing because all 5 studies included in this meta-analysis reported OS. Furthermore, OS is considered the gold standard for clinical outcome.<sup>[22]</sup> LRFS-related survival data were less convincing than OS-related survival data because only 2 of 5 studies included in this meta-analysis reported LRFS-related survival data. PFS-related survival data were the least convincing, not just because only 2 studies reported LRFS-related survival data but also because the interpretation of PFS, which is affected by local PFS and metastatic PFS, would have been too complex after chemoradiotherapy.<sup>[13]</sup>

Several factors may explain the survival benefit observed in the twice-daily thoracic RT group. First, the accelerated repopulation of SCLC is a potential cause of treatment failure after both chemotherapy and radiation therapy,<sup>[14,26]</sup> and thus, the use of a short overall RT treatment time was supported to avoid early cancer cell repopulation.<sup>[8–13]</sup> The twice-daily regimen has a much shorter duration of RT than the once-daily regimen because of the lower number of fractions (30 vs 30–40) and the shorter RT treatment time (21 days vs 42–56 days) and may help to diminish the detrimental effect of accelerated repopulation. Second, specific to the fractionation regimen, twice-daily fractionation is thought to offer a potential radiobiological advantage in rapidly proliferating SCLCs.<sup>[16,27–29]</sup> Third, in prospective studies included in this meta-analysis, more intention-to-treat (ITT) patients in the twice-daily group received full-dose RT because of the lower overall dose of RT in this group, which meant it was possible to achieve the protocol dose and volume constraints for organs at risk, such as the lungs and spinal cord, in a greater proportion of patients than in the once-daily group.<sup>[13]</sup> Finally, in retrospective studies included in this meta-analysis, patients receiving twice-daily RT had better performance status and started RT earlier than those receiving once-daily RT due to better tolerability.<sup>[14]</sup> Both good performance status<sup>[14]</sup> and early radiation therapy<sup>[8–12]</sup> may improve survival.

The Intergroup 0096 study established twice-daily thoracic RT with concurrent chemotherapy as the preferred regimen for the treatment of LD-SCLC.<sup>[14,27]</sup> However, twice-daily radiation has been underutilized in actual practice.<sup>[13,14,30,31]</sup> Several potential reasons may explain why twice-daily thoracic radiation has yet to be widely adopted. The main reason is that a twice-daily thoracic radiation regimen may increase the risk of severe acute toxicity, particularly esophagitis. The Intergroup 0096 study<sup>[27]</sup> reported a 20% increase in the rate of severe (grade 3–4) esophagitis (32% with twice-daily vs 16% with once-daily treatment). However, modern radiation techniques (three-dimensional conformal RT, intensity-modulated radiation therapy, etc.) and the omission of

elective nodal irradiation may lead to reduced toxicity. A recent CONVERT<sup>[13]</sup> study found that when patients were treated with three-dimensional conformal RT without elective nodal irradiation, the rate of severe esophagitis ( $\geq$ grade 3) was 18.5% in the twice-daily group, which was an approximate 13% decrease compared with 32% in the Intergroup 0096 study.<sup>[27]</sup> In our meta-analysis, the overall rate of severe esophagitis ( $\geq$ grade 3) in the twice-daily group was 19.2% (73/380), with the highest incidence of 33.3% (3/9) and lowest incidence of 18.5% (47/254), which are similar to the values in the CONVERT study.<sup>[13]</sup> Furthermore, recent studies,<sup>[13,16]</sup> as well as our meta-analysis, demonstrated no significant difference in thoracic RT toxicity between the 45 Gy twice-daily and 60 to 72 Gy once-daily groups, including the occurrence of esophagitis and pneumonitis. Therefore, a twice-daily regimen should not be rejected due to current concerns about the increased risk of thoracic radiation toxicity.

The primary aim of our meta-analysis was to compare 45 Gy thoracic RT with 1.5 Gy twice daily over 3 weeks with a higher dose of 60 to 70 Gy RT with 2 Gy once daily over 6 to 7 weeks concurrent with chemotherapy for the treatment of LD-SCLC. However, the number of studies that met the criteria was too small to perform a meta-analysis. Given that 72 Gy approximates 70 Gy and that 1.8 Gy per fraction once-daily RT is also commonly used in actual practice, studies with a total dose up to 72 Gy in the once-daily arm, 1.8 Gy per fraction in the once-daily arm, and median RT doses of 45 Gy in the twice-daily group or 60 to 72 Gy in the once-daily group, were included to increase the number of studies included in our meta-analysis.

Our study has several limitations. First, the number of studies enrolled in this meta-analysis was small. Only 5 studies met the eligibility criteria and were included in the analysis. Second, the study reported by Schreiber<sup>[14]</sup> did not compare the chemotherapy characteristics between the twice-daily and once-daily groups, although in the other 4 studies included in our meta-analysis, thoracic RT was delivered concurrently with chemotherapy, and no statistically significant difference was found in chemotherapy cycle number at the time of thoracic RT between the twice-daily and once-daily groups. Finally, not all the included studies were randomized controlled trials (RCTs), which are the gold standard for clinical research and have less bias than other study designs.

## 5. Conclusion

This meta-analysis revealed that compared with the higher-dose once-daily regimen, the twice-daily thoracic radiation regimen improved efficacy but did not increase RT toxicity in LD-SCLC patients. Our results indicate that compared with the higher-dose once-daily regimen, a twice-daily thoracic radiation regimen should be recommended for LD-SCLC patients. It is important to validate these findings in RCTs with larger cohorts.

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## Author contributions

**Conceptualization:** Lin Yang, Xiaocui Wu, Xiaoling Guo.

**Data curation:** Lin Yang, Libo Liu, Yanjie Yang, Yao Lei, Xiaocui Wu.

**Formal analysis:** Lin Yang, Libo Liu, Yanjie Yang, Yao Lei.

**Funding acquisition:** Tianyi Wang.

**Methodology:** Lin Yang, Libo Liu, Yao Lei, Tianyi Wang.

**Software:** Libo Liu, Yao Lei, Tianyi Wang.

**Supervision:** Xiaoling Guo.

**Validation:** Xiaoling Guo.

**Writing – original draft:** Lin Yang, Libo Liu, Yanjie Yang, Yao Lei, Tianyi Wang, Xiaocui Wu, Xiaoling Guo.

**Writing – review & editing:** Lin Yang, Libo Liu, Xiaoling Guo.

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