

Original Article

Concurrent versus sequential chemotherapy with hypofractionated radiotherapy in patients with inoperable locally advanced non-small cell lung cancer

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Abstract: The previous individual studies of chemoradiotherapy in locally advanced non-small cell lung cancer (LA-NSCLC) showed that sequential or concurrent chemotherapy with hypofractionated radiotherapy had obtained favorable survival and acceptable toxicity. However, which treatment scheme has superior therapeutic effects for inoperable LA-NSCLC is inconclusive. The aim of this study was to compare concurrent (concurrent arm) versus sequential chemotherapy (sequential arm) with hypofractionated radiotherapy in the treatment of inoperable LA-NSCLC by pooling data. Relevant studies were identified through searching PubMed, Embase and Web of Science databases till July, 2016. Odds ratio (OR) or risk ratio (RR) with its corresponding 95% confidence interval (CI) was used as pooled statistics for all analyses. The analysis was conducted based on the data from 3 studies with 370 patients. The pooled data showed that 1-year OS was OR=1.64, 95% CI: 1.03-2.61, P=0.037, whereas the combined results for 3-year OS was not improved in concurrent arm compared to sequential arm [OR=0.72, 95% CI: 0.42-1.24, P=0.235]. There was no significant difference of 1-year PFS [OR=1.16, 95% CI: 0.72-1.84, P=0.542] and 3-year PFS [OR=1.09, 95% CI: 0.48-2.50, P=0.833] between these arms. Moreover, no significant difference was found regarding Grade ≥ 3 late adverse events [RR=1.16, 95% CI: 0.78-1.74, P=0.454]. Our study demonstrated that concurrent arm was not significantly better than sequential arm in clinical outcomes. However, concurrent chemotherapy with hypofractionated radiotherapy had a tendency to improve survival and the late adverse events could be tolerated.

Keywords: Non-small cell lung cancer (NSCLC), hypofractionated radiotherapy, concurrent chemotherapy, sequential chemotherapy

Introduction

Lung cancer is the leading cause of cancer-related death and accounts for 1.59 million deaths worldwide [1, 2]. Nearly 80% of the patients have non-small cell lung cancer (NSCLC) and the prognosis is poor, with a 5-year overall survival (OS) rate ranges from 5% to 10% [3, 4]. The standard treatment for locally advanced inoperable NSCLC (LA-NSCLC) is high-dose conventional radiation therapy with concurrent chemotherapy [5, 6]. However, the long treatment time for the conventional fractionation radiotherapy should be considered because NSCLC is a rapidly proliferating cancer cells, and accelerated repopulation of tumor cells occurs during radiotherapy, which is an important factor for NSCLC radiation treatment failure [7]. With improved radiotherapy technol-

ogies, hypofractionated radiotherapy plays a crucial role in the treatment of inoperable NSCLC. Hypofractionated radiotherapy can shorten overall treatment time (OTT), apply a high-dose of radiation in a short period of time, improve the biological effective dose (BED), and might overcome proliferation of tumor cells [8]. Some studies have shown that hypofractionated radiotherapy combined with chemotherapy has obtained the good curative effect [9, 10], but concerning severe of late adverse events, hypofractionated radiotherapy combined with chemotherapy is not widely applied for the treatment of LA-NSCLC.

The data on long term use of hypofractionated radiotherapy with sequential or concurrent chemotherapy in patients with inoperable LA-NSCLC is lacking. Therefore, we conducted a meta-

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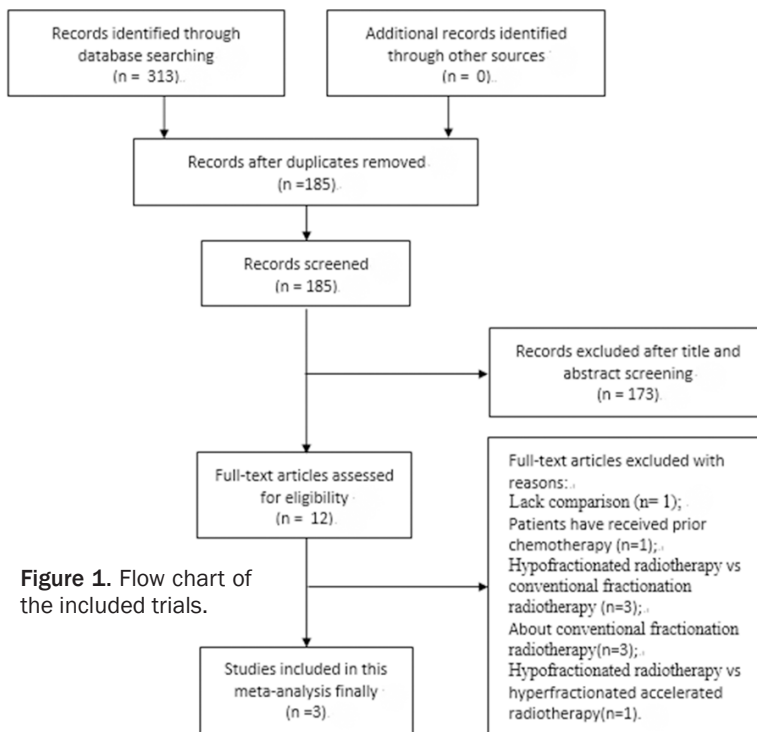


Figure 1. Flow chart of the included trials.

analysis to compare sequential versus concurrent chemotherapy with hypofractionated radiotherapy in the treatment of the inoperable LA-NSCLC, which was looking forward to increasing the precision of the comparisons and the estimate of treatment benefit.

Materials and methods

Search strategy

This meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) [11]. Our literature search was performed via Pubmed, Embase and Web of Science databases. Key terms of search included 'hypofractionated radiotherapy' and 'non-small cell lung cancer' and 'chemotherapy' or 'concurrent' or 'sequential'. At the same time, we also checked abstracts published in major academic conferences. The references of included studies were screened to locate potentially eligible articles.

Eligibility criteria

Studies were included should meet the following eligibility criteria: 1) the study compared sequential versus concurrent chemotherapy and hypofractionated radiotherapy; 2) the subjects had inoperable NSCLC; 3) the study have clear case selection criteria; 4) the outcomes

should include overall survival (OS), progression-free survival (PFS) and adverse events; 5) published as full-text articles; 6) published in English.

Studies were excluded if they were: 1) non-comparative design; 2) patients have received any prior radiotherapy or chemotherapy; 3) enrolled subjects with cancer other than NSCLC; 4) contained previously published data; 5) animal studies; 6) letters, conference abstracts or review articles; 7) not published in English.

Data extraction

Two investigators (W.G. And X.B.G.) independently extracted the following data from the eligible studies using a pre-defined protocol: name of the

first author, date of publication, duration of the study, country, number of patients, matched factors, clinical stage, hypofractionated radiotherapy schedule, concurrent chemotherapy schedule, sequential chemotherapy schedule and study outcomes.

Statistical analysis

We carried out this meta-analysis using the STATA 12.0 software (Stata Corp, College Station, TX, USA). The Cochran's Q test and Higgins I-squared statistic were used to evaluate the heterogeneity of pooled results. If $I^2 > 50\%$ and P for heterogeneity < 0.1 , which show significant heterogeneity, the random-effect model was used; otherwise, the fixed-effects model was conducted. Sensitivity analyses were performed to evaluate the impact of individual studies on the overall estimate. Begg's funnel plot was assessed to find publication bias. P value < 0.05 was considered as statistically significant.

Results

Literature search and summary of studies

Our article selection process is shown in **Figure 1**. The initial search strategy retrieved 313 relative studies published till July, 2016. Duplicates were removed and then there were remaining

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Table 1. Study characteristics.

Study	Year	Study year	Country	Study design	Matched factor	Clinical stage	No. of patients	CCRT		SCRT		Outcome
								Radiotherapy	Chemotherapy	Radiotherapy	Chemotherapy	
Maguire	2014	2005-2010	UK	RCT	Only patients' performance status statistically different; other matched factors (age, gender, weight, cell type, stage and weight loss) are similar in two arms	III	CCRT: n=70 SCRT: n=60	55 Gy/20 f	Start on the first day of radiotherapy: Cisplatin (20 mg/m ²)+Vinorelbine (15 mg/m ²) 4-6 weeks after concurrent chemoradiation: Cisplatin (80 mg/m ² day 1)+vinorelbine (25 mg/m ² day 1 and 8)	55 Gy/20 f	Cisplatin (80 mg/m ² IV on day 1)+Vinorelbine (25 mg/m ² IV on day 1 and 8)	OS, PFS and adverse events
Belderbos	2007	1999-2003	UK Netherlands Belgium	RCT	Stage distribution was imbalance in two arms; other matched factors (age, sex, WHO performance, lung function and histo logy) are similar in two arms	I-III Unknown	CCRT: n=80 SCRT: n=78	66 Gy/24 f	Cisplatin (6 mg/m ²)	66 Gy/24 f	Gemcitabine (1250 mg/m ² days 1, 8)+ Cisplatin (75 mg/m ² day 2)	OS, PFS and adverse events
Uitterhoeve	2007	1995-2004	Netherlands	Retrospective		I-III Unknown	CCRT: n=56 SCRT: n=26	66 Gy/24 f	Cisplatin (6 mg/m ²)	66 Gy/24 f	Gemcitabin (1250 mg/m ² day 1)+Cisplatin (75 mg/m ² day 2)	OS and adverse events

RCT: randomized controlled trial; OS: overall survival; PFS: progression-free survival; UK: United Kingdom; CCRT: concurrent chemo-radiotherapy; SCRT: sequential chemo-radiotherapy.

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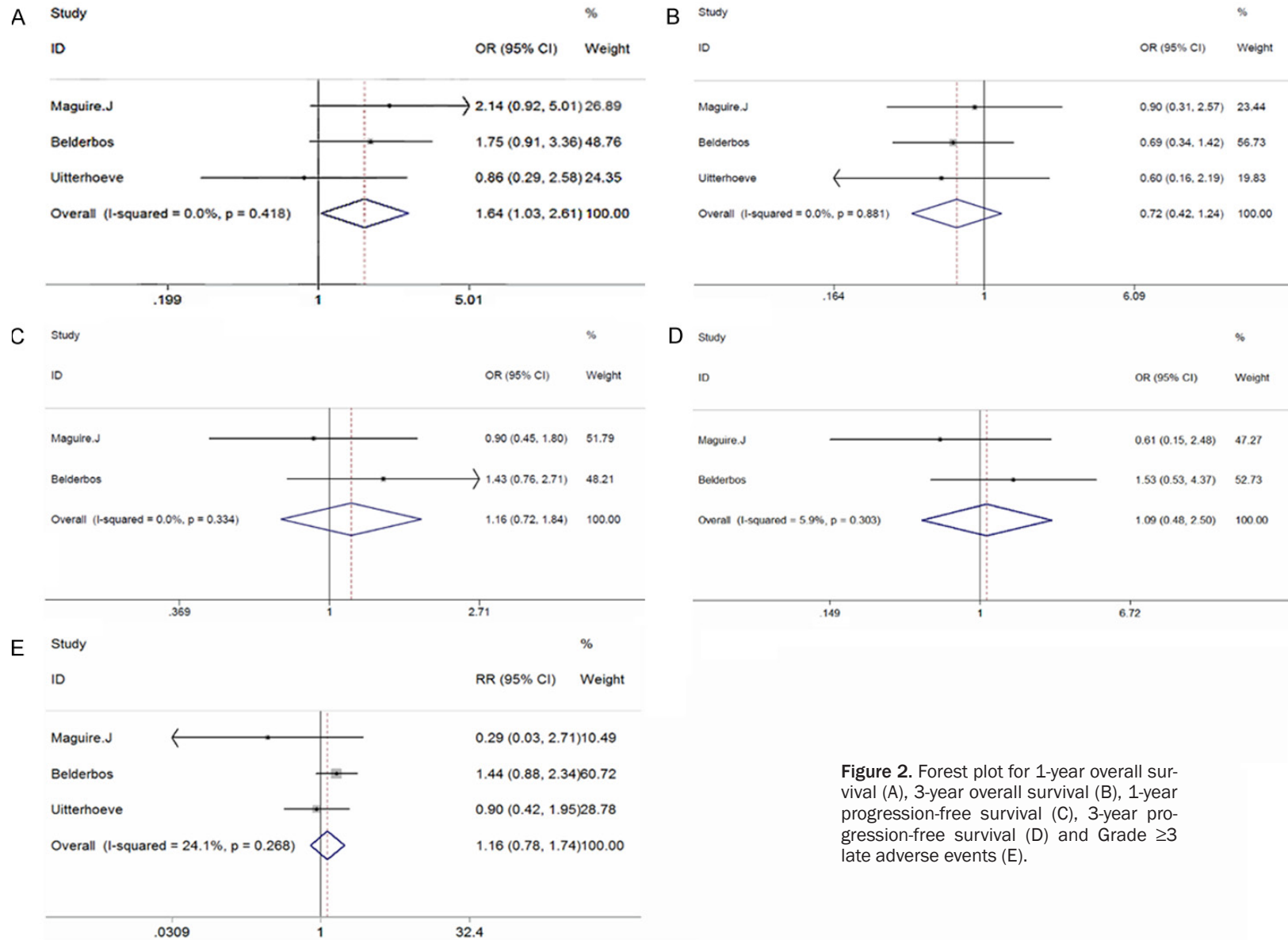


Figure 2. Forest plot for 1-year overall survival (A), 3-year overall survival (B), 1-year progression-free survival (C), 3-year progression-free survival (D) and Grade ≥ 3 late adverse events (E).

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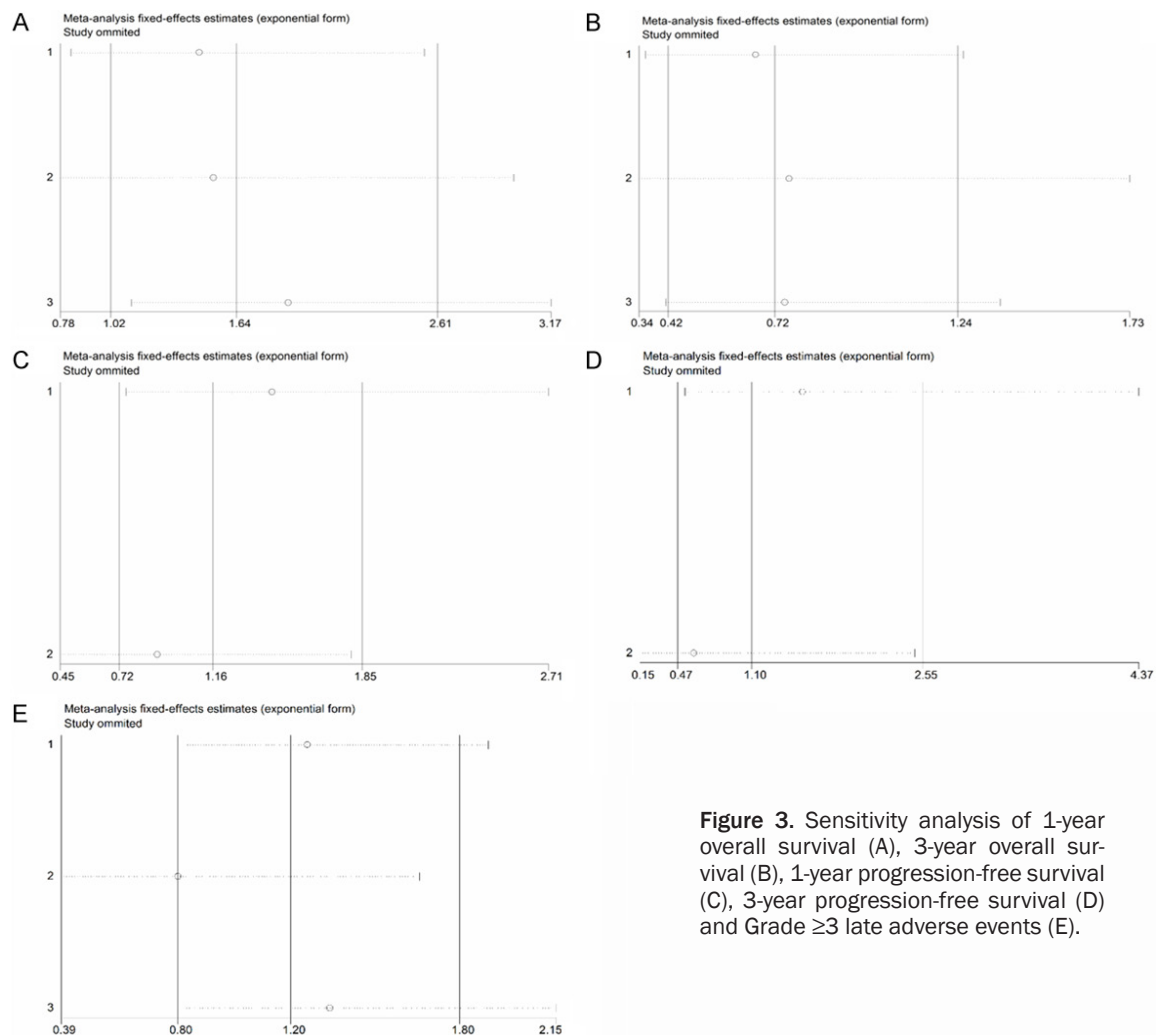


Figure 3. Sensitivity analysis of 1-year overall survival (A), 3-year overall survival (B), 1-year progression-free survival (C), 3-year progression-free survival (D) and Grade ≥ 3 late adverse events (E).

185 articles. Of these, the titles and abstracts of all literatures were reviewed and 173 were excluded; full texts and data integrity were then reviewed and another 9 papers were excluded. Finally, 3 full-text articles met all the eligibility criteria and were finally included in this meta-analysis. The included studies were performed in the UK [12] and Netherlands [13, 14]. All studies were published between 2007 and 2014.

We summarized the characteristics of the included studies in **Table 1**. A total of three studies, including two randomized controlled trials (RCT) [12, 13] and one retrospective study [14], gathered 370 cases of inoperable NSCLC in all. The concurrent arm contained 206 cases and the sequential arm included 164 cases. The median follow-ups for the included studies ranged from 10.5 to 39.0 months. The

majority of patients (89%) are stage III NSCLC. The European Organization for the Research and Treatment of Cancer (EORTC) trial [13] and Uitterhoeve *et al.* [14] used a dose of 66 Gy delivered with a three-dimensional conformal technique, while the total dose of 55 Gy was applied in the SOCCAR trial [12].

Overall survival

Because of homogeneous outcomes of the selected studies ($I^2=0$, $P=0.418$), the fixed-effect model was applied for the OS rate. The pooled results of the studies showed that sequential arm is superior to concurrent arm in 1-year OS [OR=1.64, 95% CI: 1.03-2.61, $P=0.037$] (**Figure 2A**). Three-year OS was similar among two arms [OR=0.72, 95% CI: 0.42-1.24, $P=0.235$] with no heterogeneity ($I^2=0$, $P=0.881$) (**Figure 2B**).

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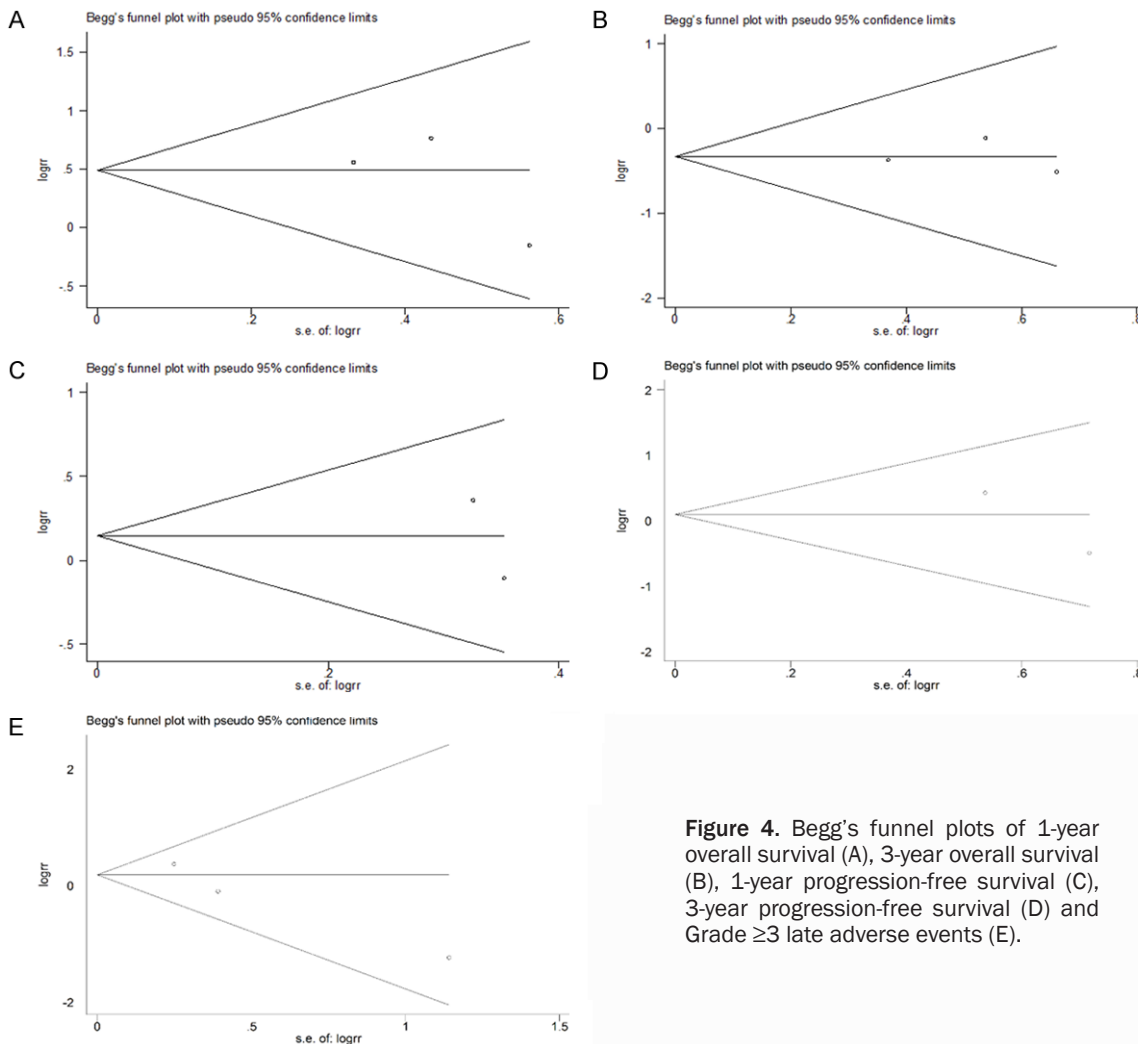


Figure 4. Begg's funnel plots of 1-year overall survival (A), 3-year overall survival (B), 1-year progression-free survival (C), 3-year progression-free survival (D) and Grade ≥ 3 late adverse events (E).

Progression-free survival

We used the fixed-effect model to analyze PFS because there was no statistical heterogeneity across studies, all the data revealed that there was no significant difference in 1-year PFS [OR=1.16, 95% CI: 0.72-1.84, $P=0.542$] and 3-year PFS [OR=1.09, 95% CI: 0.48-2.50, $P=0.833$] between two arms. (Figure 2C, 2D).

Analyses by trial characteristics

There was also no evidence of statistical difference according to whether concurrent polychemotherapy (doublet or triplet) or concurrent single-agent chemotherapy (Cisplatin only) was used in the concurrent arm ($P=0.233$). A trend was seen for a better OS if the total dose of radiotherapy was delivered over 60 Gy in the concurrent arm, although the effect of higher radiotherapy dose on OS was not statistically significant in our study ($P=0.233$).

Late adverse events

Hypofractionated radiotherapy with concurrent chemotherapy is the main concern of late adverse events. The most common late adverse events are oesophagitis, pneumonitis and haematological toxicity. Our results showed that there was no significant difference between concurrent and sequential arm for Grade 3 to 4 late adverse events [RR=1.16, 95% CI: 0.78-1.74, $P=0.454$] (Figure 2E). There was no evidence of important statistical heterogeneity with an I^2 value of 24.1%.

Sensitivity analysis and publication bias

Sensitivity analysis was performed to demonstrate whether the meta-analysis result is robust (Figure 3A-E). The results of sensitivity analysis revealed that no individual studies affected the pooled OR and RR significantly, showing a statistically stability result.

Publication bias was estimated for five study outcomes including 1-year OS (A), 3-year OS (B), 1-year PFS (C), 3-year PFS (D) and late adverse events (E). As shown in **Figure 4**, no significant publication bias was revealed ($P>0.05$).

Discussion

With the development of radiation technology, hypofractionated radiotherapy combined with chemotherapy for LA-NSCLC patients gradually becomes an imperative therapeutic tool [15-18]. Currently, previous trials showed that sequential or concurrent chemotherapy with hypofractionated radiotherapy had obtained favorable survival and acceptable toxicity [15, 16]. In 2011, a total of 34 cases with inoperable stage III NSCLC in Zhu *et al.* trial received hypofractionated radiotherapy (initially 50 Gy/20 fractions, then a fraction dose of 3 Gy) combined with sequential chemotherapy (two cycles of chemotherapy were given before radiotherapy) [15]. Radiation adverse events were minimal and no patient experiencing a grade 3 or above non-hematological adverse events. The 3-year OS, LR-PFS were 32.1% and 60.9%, respectively. Recently, a prospective study [16] showed that hypofractionated radiotherapy combined with concurrent vinorelbine and carboplatin was an alternative to treat inoperable LA-NSCLC patients. The underlying mechanisms may be that sequential chemoradiotherapy would improve survival because of a decreased distant metastases rate, while concurrent combinations with chemotherapy given at radiosensitizing doses would improve survival because of an increased local control rate [19]. However, which treatment scheme has superior therapeutic effects for inoperable LA-NSCLC is inconclusive.

Our meta-analysis was designed to compare clinical outcomes and adverse events between concurrent arm and sequential arm for the treatment of inoperable LA-NSCLC. The present study is the first meta-analysis focusing on the comparison of hypofractionated radiotherapy with concurrent or sequential chemotherapy in patients with inoperable LA-NSCLC. It has been confirmed conventional fractionated radiotherapy with concurrent chemotherapy of LA-NSCLC is superior to sequential administration in clinical trials [20, 21] and meta-analysis [22]. Vitro studies [23] have demonstrated that

a combination of radiotherapy and chemotherapy can significantly improve biological effects of hypofractionated radiotherapy. Thus, in theory, hypofractionated radiotherapy with concurrent chemotherapy should also be better than sequential chemotherapy with hypofractionated radiotherapy. However, we found hypofractionated radiotherapy with concurrent chemotherapy did not improve OS or PFS relative to sequential administration with hypofractionated radiotherapy. This may be because the low-dose single-agent chemotherapy was employed in concurrent arm, whereas intensity of chemotherapy is the key to concurrent chemoradiotherapy (CRT) [24]. The intensity of concurrent CRT in most trials of conventional fractionated radiotherapy were similar to sequential CRT. However, out of the consideration of the severity of late adverse events, the dose of concurrent chemotherapy with hypofractionation in our study was significantly lower than that of the sequential arm. The low-dose of Cisplatin chemotherapy only had the radiosensitizing effect in the concurrent arm. Under the premise of the adverse events which could be tolerated, future research should focus on improving the dose of concurrent chemotherapy with hypofractionation. There is no convincing evidence that concurrent poly-chemotherapy is superior to low-dose chemotherapy (Cisplatin only) alone, especially when it is combined with a high radiation dose. Our results also demonstrated this view, and the combination of concurrent low-dose Cisplatin with radiation appears to be a good option.

Can high-dose radiotherapy (total radiotherapy dose >60 Gy) improve results? The short OTT and high BED might have been a favorable factor in treatment outcomes. We observed the trend for a better OS if the total dose of radiotherapy was delivered over 60 Gy, although the effect of higher radiotherapy dose on OS was not statistically significant in our study. In the CHART-study [25], the reduction of the OTT from 6 weeks to 12 days resulted in improved outcome with radiotherapy alone, revealing an influence of cancer cell repopulation. Several other research reported the improved results while shortening the OTT for radiotherapy alone or for CRT [26-29]. The dose-relationship for local control and survival of lung cancer has been proved [30]. A Cochrane study [31] showed the dominant effect of CRT is indepen-

dent of the irradiation dose applied. Socinsky *et al.* [32] also recommended that increasing the radiation dose during concomitant treatment schedules might have a positive effect on local control. The studies of Schild, Keene and Jeremic showed encouraging 5-year survival rates ranging from 23% to 36%, which high radiation doses were delivered in short OTT combined with low-dose Cisplatin or low-dose Carboplatin and Paclitaxel [33-35].

Hypofractionated radiation schedules applied fewer fractions and larger single dose, which could theoretically increase late adverse events relative to the conventional fractionated radiotherapy. However, in this analysis the incidence of the Grade ≥ 3 late adverse events were not significantly different for sequential or concurrent chemotherapy with hypofractionation. This is in agreement with the results of the meta-analysis of Rowell [31]. All the data suggested that the adverse events could be tolerated and that hypofractionation with concurrent chemotherapy did not seem to significantly increase the late adverse events.

In addition to the inherent defects that were related to meta-analysis, our study also had a number of other limitations. First, our meta-analysis only contained a few studies and the number of patients in both arms were limited, some bias may exist in our study when the data were pooled. Second, we failed to analyze acute adverse events because the data is insufficient. Third, the patients included in our meta-analysis were all Caucasian ethnicity, therefore, the conclusions of this study should be treated with caution when applied to other ethnic populations.

Still, our study had some shining points. First, the heterogeneity of our results was small, which indicated the robustness of the statistic results. Second, there was no significant publication bias, which showed that our results were stable.

In conclusion, this study demonstrated that concurrent chemotherapy with hypofractionation was not significantly better than sequential administration with hypofractionated radiotherapy in clinical outcomes, while concurrent arm had a tendency to improve survival. Late adverse events were not significantly improved relative to sequential chemotherapy with hypo-

fractionated radiotherapy. However, these findings should be utilized cautiously when directed in clinical treatment due to the limitations listed above. A large number of well-designed clinical trials and high quality prospective studies should be conducted to further confirm the results.

Disclosure of conflict of interest

None.

Authors' contributions

Wei Guo, Xiaobin Gu, Xianshu Gao designed the study, collected, analyzed, and interpreted the data, and wrote the article. Mingwei Ma, Ming Cui, Mu Xie, Yun Bai and Chuan Peng participated in the study, collected, analyzed, and interpreted data, and critically revised the article. All authors read and approved the final manuscript.

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