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Endostar (rh-endostatin) improves efficacy of concurrent chemoradiotherapy for locally advanced non-small cell lung cancer: A systematic review and meta-analysis

Meng Yuan[1†] | Yirui Zhai[1†] | Yu Men[1,2] | Jianyang Wang[1] | Lei Deng[1] | Wenqing Wang[1] | Yongxing Bao[1] | Xu Yang[1] | Shuang Sun[1] | Zeliang Ma[1] | Yunsong Liu[1] | Jun Wang[3] | Hui Zhu[4] | Zhouguang Hui[1,2]

[1]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2]Department of VIP Medical Services, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[3]Department of Radiation Oncology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

[4]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Correspondence
Zhouguang Hui, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Panjiayuan Nanli No.17, Chaoyang District, Beijing 100021, China.
Email: drhuizg@163.com

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Abstract

Background: We aimed to clarify the benefits of the addition of rh-endostatin into concurrent chemoradiotherapy (CCRT) versus CCRT alone for locally advanced non-small cell lung cancer (NSCLC) by a meta-analysis.

Methods: PubMed, Embase, Cochrane Central Register of Controlled Trials, Wanfang and Chinese National Knowledge Infrastructure (CNKI) were systematically screened from inception to November 2020 using the prespecified terms. Prospective trials (evaluating or) comparing the efficacy of endostar combined with CCRT and CCRT for locally advanced NSCLC were included. The primary endpoints were risk ratios (RRs) for objective response rate (ORR) and disease control rate (DCR). The secondary endpoints were RRs for overall survival (OS) and adverse events (AEs).

Results: Ten studies with 716 patients were included in this meta-analysis. Endostar combined with CCRT significantly improved ORR and DCR compared with CCRT. The RRs of ORR and DCR for endostar combined with CCRT versus CCRT were 1.263 (95% CI: 1.137–1.403, $p < 0.001$) and 1.274 (95% CI: 1.124–1.444, $p < 0.001$), respectively. Endostar combined with CCRT significantly improved one-year survival rate compared with CCRT with pooled RR = 1.113 (95% CI: 1.006–1.231, $p = 0.038$). Endostar combination treatments had similar incidences of main adverse events compared with CCRT ($p > 0.05$).

Conclusion: Endostar combined with CCRT is associated with significantly higher ORR, DCR and survival rate than CCRT with similar incidences of main adverse events in NSCLC.

KEYWORDS
chemoradiotherapy, endostar, meta-analysis, NSCLC

[†]These authors contributed equally to the work.

INTRODUCTION

With consolidation immunotherapy becoming a new standard of care in unresectable stage III non-small cell lung cancer (NSCLC), the overall survival (OS) has been significantly improved, with 3-year OS rate reaching up to 57%,according to the PACIFIC study.[1] However, this improvement was only observed in patients who responded well to upfront concurrent chemoradiotherapy (CCRT). Unfortunately, response rates of CCRT have reached a plateau over the decades. The clinical efficacy of CCRT is warranted to improve to further lengthen survival in the era of immunotherapy. There is therefore a great need to develop chemoradiosensitizer in combination with CCRT in order to enhance the treatment response.

Inducing angiogenesis is one of the hallmarks of cancer,[2] and therefore, tumor antiangiogenesis has made a promising field of current cancer research. In 1997, Folkman et al. first reported a new protein named endostatin, a 20 kD internal fragment of the carboxy terminus of collagen XVIII, in the conditioned media of hemangioendothelioma cells as an antiangiogenic molecule.[3] Endostar, a recombinant human endostatin (rh-endostatin), was approved by National Medical Products Administration (NMPA) in China for the treatment of NSCLC in 2005. Several clinical trials and meta-analysis have proven that the combination of endostar and platinum-based chemotherapy can improve the treatment response rate.[4–6] Previous trials have also indicated better survival and local control with no severe adverse events resulting from the use of endostar in combination with CCRT in NSCLC.[7,8] However, high-level evidence is lacking for the routine use of endostar concurrently with chemoradiotherapy in patients with locally advanced NSCLC. The aim of this meta-analysis was to investigate the efficacy and safety of endostar combined with CCRT versus standard chemoradiotherapy alone for patients with locally advanced NSCLC.

METHODS

This meta-analysis was performed following preferred reporting items for systematic reviews and meta-analyses (PRISMA) (supplementary materials). The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42020203424).

Data sources and searches

PubMed, Embase, Cochrane Central Register of Controlled Trials, Wanfang and Chinese National Knowledge Infrastructure (CNKI) were systematically screened from inception to November 2020 using a combination of the main search terms "chemoradiotherapy" and "endostar" and "non-small cell lung cancer" within the restriction of "clinical trial" (detailed search strategy in supplementary materials). Abstracts, letters, editorials and expert opinions, reviews without original data, and case reports were excluded. Manual searches from previous meta-analyses were also performed.

Study selection

We included published studies that met the following criteria: (i) prospective clinical trials; (ii) trials that enrolled NSCLC patients, especially those with unresectble stage III disease; (iii) trials that evaluated the efficacy of endostar combined with CCRT or compared the efficacy of endostar combined with CCRT and CCRT for locally advanced NSCLC; (iv) trials that reported at least one of the following clinical endpoints: objective response rate (ORR), defined as the proportion of patients achieving an objective response; disease control rate (DCR), defined as the proportion of patients achieving an objective response and stable disease; OS, defined as the time from randomization to death; progression free survival (PFS), defined as the time from randomization to first progression (locoregional or distant); adverse events (AEs) defined and graded by the National Cancer Institute's common terminology criteria for adverse events; and (v) articles for which full text in English or Chinese was available were included. If multiple publications of the same trial were retrieved, the most recent and informative publication was included.

Data extraction

Two authors were responsible for screening the titles and abstracts of the retrieved references independently. The full texts of the included studies were assessed based on the aforementioned criteria by two review authors. Any discrepancies were settled by consensus and arbitration by a panel of group discussion. Data on general trial details (study ID, first author, publication year, number of patients, baseline characteristics of the study population) and treatments were extracted. For efficacy outcomes, ORR, DCR, survival rates were extracted. For safety profiles, counts of each specific AE were extracted.

Risk-of-bias assessment

The quality of each eligible randomized controlled trial was evaluated by the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (August 22, 2019 version). The entire scale is constituted by the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. According to the detailed guidance of RoB 2, each domain could be judged as any of the three levels: low risk, high risk or unclear risk of bias.

Data synthesis and statistical analysis

To assess the efficacy and safety of endostar combined with CCRT versus CCRT for locally advanced NSCLC, two different meta-analysis approaches were applied: the fixed effects and the random effects models. Statistical heterogeneity of each study was assessed by I^2 with planned cutoff for significance of $I^2 = 50\%$. If $I^2 \leq 50\%$, which indicates no significant heterogeneity existing between the included studies, a fixed effects model was adopted to combine the results; otherwise, a random effects model was employed. Pooled analysis was reported as risk ratios (RRs) with 95% confidence intervals (CIs). The statistical significance of the pooled RR was determined by the Z-test. Publication bias was assessed using funnel plots, the Egger's and the Begg's tests. The meta-analysis was performed with STATA version 12. All p-values were two-sided, and $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Characteristics of included studies

Our systematic search identified 124 potentially relevant publications. After a full text review, 114 studies were excluded because of duplication, nonclinical or retrospective studies, case reports, review articles or insufficient data to calculate the outcomes of interest. Finally, 10 studies published between June 2009 and March 2020 were eligible and included in the meta-analysis.[7,9–22] The 10 studies consisted of eight randomized controlled trials (RCTs), and two prospective single arm studies with their matched prospective controlled cohorts.[23] Figure 1 outlines the selection process flow. The total number of patients identified in these 10 trials was 716, including 305 patients treated with endostar combined with chemoradiotherapy, and 411 with chemoradiotherapy. The main characteristics of all studies are reported in Table 1.

Clinical efficacy

Comparison of ORR between endostar combined with CCRT and CCRT

Ten studies compared the ORR between endostar in combination with CCRT and CCRT. Figure 2a shows the ORR of the two groups. There was statistically significant benefit on ORR in the endostar combined with the CCRT group. No significant heterogeneity was detected among the included studies, so fixed effects model was adopted for analysis. The

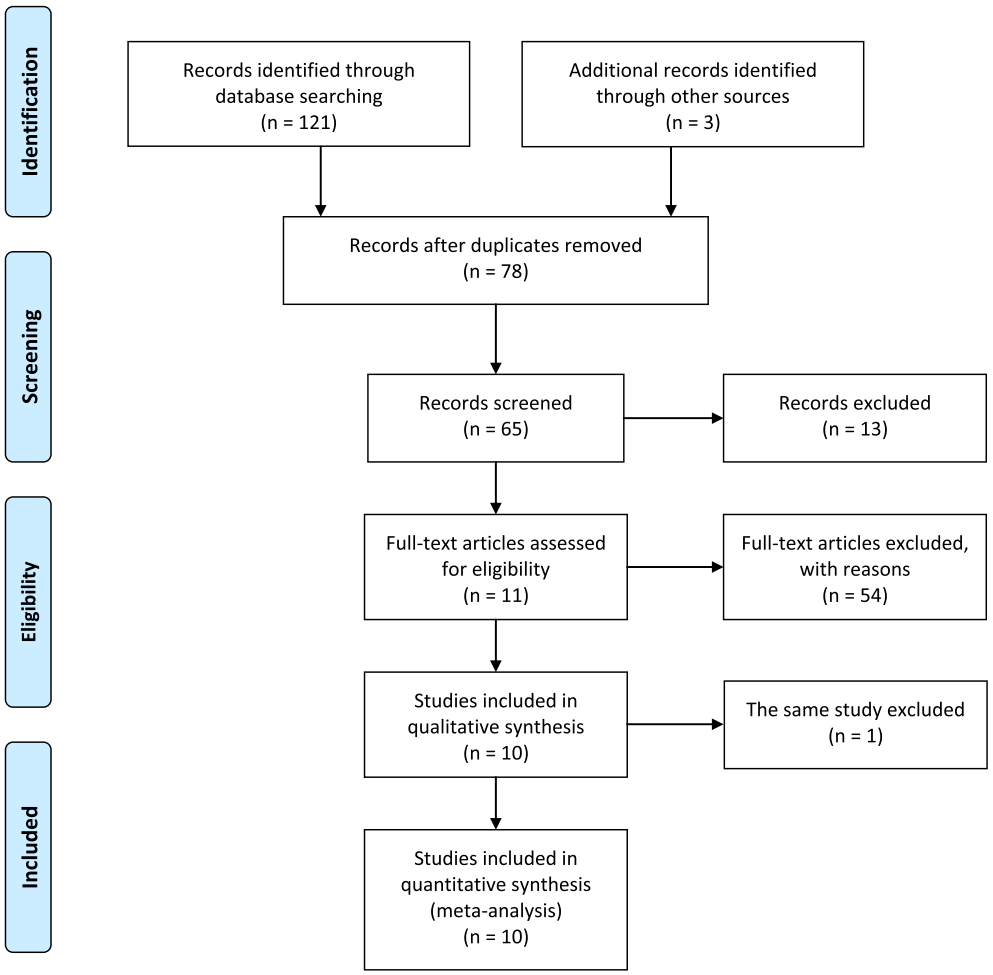

FIGURE 1 Literature search / PRISMA flow chart

TABLE 1 Baseline characteristics of studies included in the meta-analysis

Author	Year	Design	No. of patients	Histology	TNM stage	RT schedule	Endostar dosage
Chen et al.[12]	2013	CCRT+E VS CCRT	42	NSCLC	IIIA, IIB (1997UICC)	60 Gy/2 Gy	7.5 mg/m^2 (15 mg/day)
Jiang et al.[14]	2011	CCRT+E VS CCRT	39	NSCLC	IIIB, IV	60–76 Gy/30–38 f	15 mg/day
Liu et al.[17]	2017	CCRT+E VS CCRT	60	NSCLC	IIIB, IV	Mediastinal foci: 65–70 Gy, thoracic Nonmediastinal foci: 66–90 Gy, Lymph nodes: 65–70 Gy, intracranial Metastases:70–90 Gy, bone Metastases:40–55 Gy, other Metastases:40–60 Gy	15 mg/day
Ma et al.[18]	2009	CCRT+E VS CCRT	46	NSCLC	IIIA, IIIB (1997 UICC)	60–76 Gy/30–38 f	15 mg/day
Xu et al.[20]	2018	CCRT+E VS CCRT	78	AC	III, IV	45–60 Gy/1.8–2.0 Gy/25–30 f	15 mg/day
Yao[21]	2020	CCRT+E VS CCRT	96	AC	Locally advanced	45–60 Gy/1.8–2.0 Gy/25–30 f	15 mg/day
Zhang et al.[22]	2018	CCRT+E VS CCRT	50	NSCLC	Locally advanced	60 Gy/30 f	7.5 mg/m^2 (15 mg/day)
Ding et al.[13]	2011	CCRT+E VS CCRT	28	NSCLC	IIIA, IIIB (UICC sixth)	50–60 Gy/25–30 f, residual disease: SBRT 18–27 Gy/3 Gy	15 mg
Zhai et al.[7]	2019	CCRT+E VS CCRT	67 (+95)	NSCLC	Inoperable stage III (AJCC seventh)	60–66 Gy/2 Gy/30–33 f	7.5 mg/m^2 /24 h
Sun et al.[10]	2016	CCRT+E VS CCRT	19 (+96)	NSCLC	Unresectable stage III	60–66 Gy/30–33 f	7.5 mg/m^2

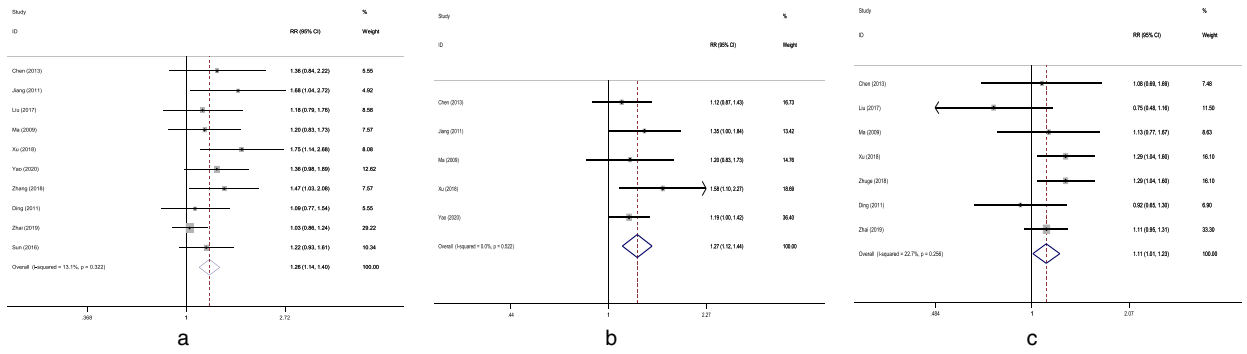

FIGURE 2 (a) Forest plot of objective response rate for endostar combined with CCRT versus CCRT. (b) Forest plot of disease control rate for endostar combined with CCRT versus CCRT. (c) Forest plot of 1-year survival rate for endostar combined with CCRT versus CCRT. RR, risk ratio; CI, confidence interval; CCRT, concurrent chemoradiotherapy

results of the fixed effects model showed that RR for endostar + CCRT compared with CCRT was 1.263 (95% CI: 1.137–1.403, $p < 0.001$). In the sensitivity analysis, exclusion of studies individually did not substantially alter the estimators, with a RR pool oscillating between 1.24 and 1.36. In a second sensitivity analysis, the studies by Jiang et al., Liu et al., and Xu et al. were removed from the meta-analysis due to potential heterogeneous clinical features, as these three studies also included some stage IV patients. Results did not show deviations compared with the original ones,

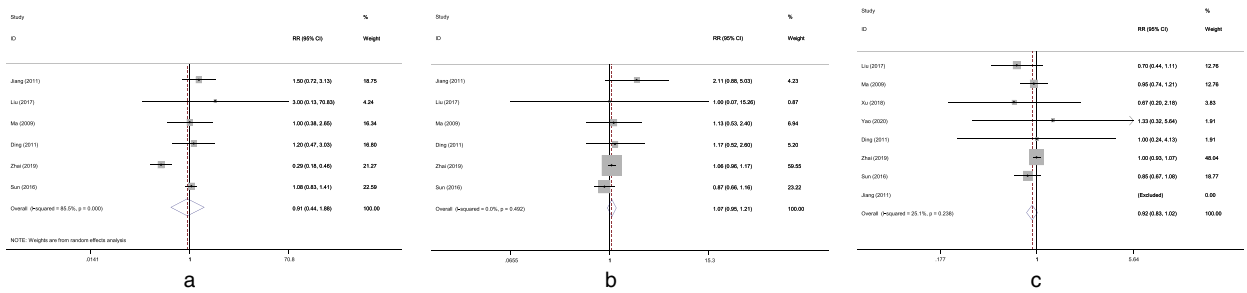

FIGURE 3 (a) Forest plot of radiation-induced pneumonitis for endostar combined with CCRT versus CCRT. (b) Forest plot of radiation esophagitis for endostar combined with CCRT versus CCRT. (c) Forest plot of leukopenia for endostar combined with CCRT versus CCRT. RR, risk ratio; CI, confidence interval; CCRT, concurrent chemoradiotherapy

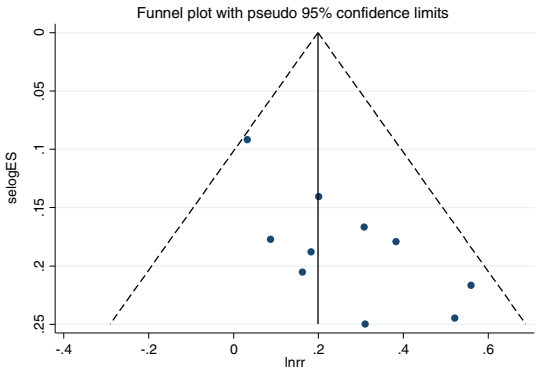

FIGURE 4 Funnel plot of the objective response rate for endostar combined with CCRT versus CCRT. CCRT, concurrent chemoradiotherapy

with RR for endostar + CCRT comparing with CCRT was 1.196 (95% CI: 1.067–1.340, $p = 0.002$).

Comparison of DCR between endostar combined with CCRT and CCRT

Five studies compared the DCR between endostar + CCRT and CCRT. Figure 2b shows the DCR of the two groups. No significant heterogeneity was observed among the included studies. DCR was significantly higher in the endostar + CCRT group with pooled RR = 1.274 (95% CI: 1.124–1.444, $p < 0.001$).

Comparison of survival rates between endostar combined with CCRT and CCRT

There were seven studies reporting the survival rates of endostar + CCRT and CCRT groups. Figure 2c shows the 1-year survival rates of the two groups. No significant heterogeneity was detected among the studies. Pooled analysis with the fixed effects model showed that the 1-year survival rate was significantly improved in the endostar + CCRT group compared with the CCRT group with pooled RR = 1.113 (95% CI: 1.006–1.231, $p = 0.038$).

Adverse events

The most common AEs reported in the included trials were radiation-induced pneumonitis (RIP), radiation-induced esophagitis, leukopenia, nausea and vomiting. Six studies compared the incidence of RIP and radiation-induced esophagitis, respectively. Pooled analysis showed that there was no difference in the incidence of RIP (grades 1–5) and radiation-induced esophagitis (grades 1–5) between two arms with pooled RR = 0.913 (95% CI: 0.445–1.877, $p = 0.805$) and 1.070 (95% CI: 0.946–1.210, $p = 0.282$) (Figure 3a,b). Eight studies reported the incidence rates of leukopenia. The endostar combination arm had a similar incidence rate of leukopenia to the CCRT arm (RR = 0.920, 95% CI: 0.832–1.016, $p = 0.101$). (Figure 3c).

Study quality assessment

Detailed risk-of-bias evaluation is given for each study (supplementary materials). There was no eligible RCT deemed at high risk of bias. Due to the nature of treatments, especially radiotherapy, blinding of participants was not possible in clinical settings, and also information of blinding of participants was hardly given in the articles. However, we believed it was unlikely that deviations would arise due to this in the results, and a "low risk" score was therefore given when appropriate.

Publication bias

In terms of publication bias for the ORR of endostar + CCRT versus CCRT, the funnel plot did not indicate any evident risk of publication bias due to the symmetrical distribution (Figure 4a,b). The results of the Begg's test were z = 1.43 ($p = 0.152$) and z = 1.53 ($p = 0.125$), and that of

the Egger's test were t = 3.51 (p = 0.008) and t = 2.89 (p = 0.014).

DISCUSSION

This is the first systematic review and meta-analysis to compare the efficacy and safety of endostar (rh-endostatin) combined with CCRT versus CCRT for NSCLC with modern RT techniques (IMRT/3DCRT: 100%). In this meta-analysis of 716 patients, endostar combined with CCRT was demonstrated to significantly improve the clinical efficacy compared with CCRT, and with similar incidences of main AEs in NSCLC.

During tumor progression, an "angiogenic switch" is almost always activated and remains on, causing normally quiescent vasculature to continually sprout new vessels that help sustain expanding neoplastic growths.[24] The blood vessels produced within tumors by chronically activated angiogenesis and an unbalanced mix of proangiogenic signals are typically aberrant: tumor neovasculature is marked by precocious capillary sprouting, convoluted and excessive vessel branching, distorted and enlarged vessels, erratic blood flow, microhemorrhaging, leakiness, and abnormal levels of endothelial cell proliferation and apoptosis.[25,26] Studies in the 1990s revealed that type XVIII collagen (endostatin) could act as endogenous inhibitors of angiogenesis.[27] When the circulating levels of an endogenous inhibitor are genetically increased, tumor growth is impaired,[28,29] suggesting that such endogenous angiogenesis inhibitors might act as intrinsic barriers to induction and/or persistence of angiogenesis by incipient neoplasias. Endostar, a recombinant human endostatin, can specifically inhibit the activity of vascular endothelial growth factor to block angiogenesis as well as induce cancer cell apoptosis.[30] A preclinical study has demonstrated that endostar could improve antitumor efficacy of chemotherapy via modulation of the balance between vascular endothelial growth factor (VEGF)-A and thrombospondin-1 in Lewis lung carcinoma.[31] Endostar has also been shown to be efficient and safe in the treatment of NSCLC in clinical trials and has been approved by NMPA in China for the treatment of NSCLC.[32] Some previous meta-analyses have also demonstrated that endostar combined with chemotherapy could improve the response rate and prognosis of patients with advanced NSCLC without increasing the risk of toxicity.[5,6]

Zhang and colleagues previously reported that endostar was found to downregulate hypoxia-inducible factor-1α (HIF-1α) and VEGF expression, and enhance the radioresponse to human lung adenocarcinoma cancer cells.[33] The study by Zheng et al.[34] suggested that endostar is involved in the regulation of metabolism and tumor microenvironment hypoxia, which may be responsible for the enhanced antitumor effect of endostar in combination with radiotherapy. The study by Meng et al.[35] indicated decreased hypoxia in animals and patients upon endostar treatment, which also enhanced the radioresponse within the vasculature-remodeling period. Upon these and other preclinical findings, several clinical trials have been carried out to demonstrate the efficacy of endostar in combination with radiotherapy and chemoradiotherapy in NSCLC. The preliminary clinical study of Jiang et al. reported that the total effective rates (CR + PR) in the endostar + radiotherapy group were 80%, which was significantly improved compared with the radiotherapy alone group (44%, $\chi 2$ = 6.87, p = 0.009). Results from the phase II HELPER study, which sought to evaluate the efficacy and toxicity of the addition of endostar to concurrent etoposide, cisplatin (EP) and radiotherapy for treatment of patients with NSCLC, indicated a prolonged median survival time of 34.7 months compared with results from historical studies which treated patients with concurrent EP and radiotherapy alone.[7,36–38] The 2- and 3-year OS rates (59.9% and 47.7%) in the HELPER study were also superior to previous studies. RR and CR rates in the HELPER study (76.1% and 19.1%) were better than those reported in RTOG 9410, SWOG 9504, NPC95-01 and PROCLAIM.[36,38–40] However, the number of patients in every single trial is too limited to achieve a definite conclusion. Accordingly, high-level evidence is still lacking for routine use of endostar concurrent with chemoradiotherapy in NSCLC. Hence, we conducted this meta-analysis to confirm the efficacy and safety of endostar in combination with CCRT in locally advanced NSCLC.

When we analyzed the 10 prospective clinical trials of endostar combined with CCRT, a significant benefit of endostar combined with CCRT versus CCRT in ORR was found (RR = 1.263, 95% CI: 1.137–1.403, $p < 0.001$). DCR was also significantly increased by combining endostar and CCRT (RR = 1.274, 95% CI: 1.124–1.444, $p < 0.001$). As for the survival, seven studies reported 1-year survival rates, and only one reported 3-year survival rates. Our meta-analysis showed that the 1-year survival rate was significantly improved in the endostar + CCRT group compared with the CCRT group (RR = 1.113, 95% CI: 1.006–1.231, p = 0.038). The data of 3-year survival were relatively limited and insufficient to reach a decisive conclusion. Therefore, more high-quality prospective clinical trials are warranted to evaluate the long-term efficacy of this combination treatment.

The AEs found in our systematic review were mainly RIP, radiation-induced esophagitis, leukopenia, nausea and vomiting, most of which were grade 1 or 2 and well tolerated. This meta-analysis showed that there was no difference in the incidence of main AEs between endostar + CCRT and CCRT. In this review, we found that the risk of grade ≥ 2 RIP (22.4%) in the study by Zhai et al.[7] of endostar combination treatment was lower than that (76.8%) of the study by Liang et al,[23] a group of which adopted the same CCRT regimen. In the preclinical mice model of Zhang et al., endostar administration was demonstrated to effectively attenuate the magnitude of the increase in inflammatory cells as well as the elevation of TGF-β1 expression in lung tissues after radiation-induced lung injury (RILI), suggesting that endostar may be a novel protective agent against RILI.[41] Whether an endostar combination can

relieve the AEs associated with treatment should be further evaluated and followed up in future studies.

There are other antiangiogenic agents in addition to endostar. Bevacizumab has also been evaluated in phase I/II trials in combination with chemoradiotherapy, but has been found to induce high rates of pneumonitis and pulmonary hemorrhage, especially in patients with squamous cell carcinoma.[42–44] However, in our meta-analysis, the addition of endostar did not increase the rate of pneumonitis and pulmonary hemorrhage. Preclinical studies have reported that endostar could induce apoptosis in cardiomyocytes, resulting in cardiotoxicity.[45] However, few cases of endostar-associated cardiotoxicity have been reported in the clinical trials, which may indicate that endostar is actually safe in clinical practice. However, it may also be due to the fact that it takes longer for patients to develop cardiovascular toxicity, and during the relatively limited follow-up, no associated toxicity was observed. In addition, in NSCLC, the antiangiogenic action in combination with esophageal or tracheal injury might cause tracheoesophageal or tracheomediastinal fistula, which have previously been reported in bevacizumab combination therapy.[46,47] However, such severe adverse events have not been reported in patients treated with endostar.

Several considerations should be mentioned when interpreting the results of our meta-analysis. First, most of the trials included in this meta-analysis involved Chinese patients which may have led to patient selection bias. Second, only a few studies reported long-term survival, and therefore, the long-term efficacy of endostar combined with CCRT requires further evaluation by high-quality randomized controlled trials. Third, in three studies, some stage IV NSCLC patients were also included, which to some extent might decline the homogeneity. Therefore, we excluded these three studies in the sensitivity analysis and it showed similar results to the primary analysis, which indicated that the results were robust and consistent. Additionally, we cannot conclude about the optimal time window of endostar, and the preferable CT regimen or RT scheme in combination. However, a platinum-based CT and a total RT dose of 60–66 Gy for locally advanced NSCLC as administered in most trials may be reasonable options.

In conclusion, for locally advanced NSCLC, endostar combined with CCRT is associated with significantly higher ORR and DCR without increased risk of main adverse events compared with CCRT. More randomized controlled trials are needed to confirm the long-term survival benefits of endostar combination treatments, especially in this era of immunotherapy.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

ORCID

Meng Yuan https://orcid.org/0000-0001-7704-8633
Lei Deng https://orcid.org/0000-0001-5919-5074
Shuang Sun https://orcid.org/0000-0002-1274-0087
Jun Wang https://orcid.org/0000-0002-9733-1433
Zhouguang Hui https://orcid.org/0000-0002-7189-4692

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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