

# Meta-analysis of clinical trials comparing the efficacy and safety of liposomal cisplatin versus conventional nonliposomal cisplatin in nonsmall cell lung cancer (NSCLC) and squamous cell carcinoma of the head and neck (SCCHN)

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## Abstract

**Background:** While liposomal cisplatin has shown enhanced drug tolerability and higher targeting property as compared with the conventional cisplatin, the doubt remains whether lipoplatin could improve its anticancer efficacy. What's more, there is still no systematic evaluation of the safety profiles of lipoplatin comparing with original cisplatin. Thus, we performed a systematic literature search for randomized clinical trials directly comparing efficacy and safety of liposomal cisplatin versus its conventional nonliposomal cisplatin.

**Methods:** The electronic search was conducted in PubMed, Embase, The Cochrane Library, and ClinicalTrials.gov from inception to February 10, 2018. The pooled odds ratio (OR) and 95% confidence intervals (CIs) of progressive disease (PD), partial response (PR), stable disease (SD), and adverse events (AEs) were obtained to assess the efficacy and safety. Heterogeneity was estimated using the  $I^2$  test ( $I^2 > 50\%$ , significant heterogeneity).

**Results:** The search yielded 5 clinical trials that meet inclusion criteria, with a total of 523 patients. We found that the liposome encapsulated cisplatin was more clinical efficacious than cisplatin as assessed by PD rate (OR, 0.46; 95% CI, 0.28–0.74;  $P = .002$ ), while subgroup analysis of the only nonsmall cell lung cancer (NSCLC) patients showed higher response rates in PR (OR, 0.46; 95% CI, 0.28–0.74;  $P = .002$ ) and PD (OR, 0.46; 95% CI, 0.28–0.74;  $P = .002$ ) simultaneously. In addition, the toxicity meta-analysis revealed lipoplatin was much less toxic than the original cisplatin, with respect to grade 3 to 4 neurotoxicity (OR, 0.18; 95% CI, 0.04–0.74;  $P = .02$ ), grade 3 to 4 leukopenia (OR, 0.47; 95% CI, 0.26–0.85;  $P = .01$ ), grade 3 to 4 neutropenia (OR, 0.26; 95% CI, 0.09–0.71;  $P = .009$ ), grade 1 and 2 nausea/vomiting (OR, 0.50; 95% CI, 0.32–0.77;  $P = .002$ ), and grade 3 and 4 asthenia (OR, 0.11; 95% CI, 0.03–0.42;  $P = .001$ ).

**Conclusions:** This meta-analysis revealed that with both NSCLC and squamous cell carcinoma of the head and neck (SCCHN) patients, liposomal cisplatin-based chemotherapy offers significant advantages regarding the PD and reduced toxicities relative to conventional cisplatin.

**Abbreviations:** AE = adverse events, CI = confidence interval, NSCLC = nonsmall cell lung cancer, OR = odds ratio, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, RCT = randomized control trial, SCCHN = squamous cell carcinoma of the head and neck, SD = stable disease.

**Keywords:** cisplatin, efficacy, lipoplatin, meta-analysis, safety

## 1. Introduction

Chemotherapy is still one of the most effective approaches to treat cancers in the clinic, but the problems such as cytotoxicity

and low bioavailability limit the future application of chemotherapeutic agents.<sup>[1]</sup> Nanoparticle formulations for packaging existing drugs have been widely used in the treatments of cancers for their tremendous therapeutic potential.<sup>[2,3]</sup> Passive extravasation of nano-carriers contributing to the “enhanced permeability and retention” (EPR) effect can increase tumor-targeted delivery while reducing normal tissue distribution,<sup>[4]</sup> theoretically enhancing the therapeutic efficiency and decreasing systemic toxicity.

Cisplatin, as a classical chemotherapeutic drug, has been recommended for the treatment of various cancers, such as metastatic testicular, ovarian, and transitional cell bladder cancer, nonsmall cell lung cancer (NSCLC), cervical cancer, and also head and neck cancer.<sup>[5]</sup> Unfortunately, its clinical use has been impeded by its severe toxicities, especially nephrotoxicity, neurotoxicity, nausea-vomiting, asthenia, and hematological toxicity.<sup>[6,7]</sup> Lipoplatin (Regulon Inc, Mountain View, CA), a novel FDA-approved liposomal formulation, is designed to enhance tumor targeting and reduce the systemic toxicity of cisplatin.<sup>[8,9]</sup> Many preclinical and clinical trials on lipoplatin have been carried out over the last 2 decades. Data resulting from the trials are promising in terms

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of toxicity profile, higher targeting properties, and longer half-life compared with cisplatin.<sup>[9–12]</sup> Theoretically, this enhanced drug tolerability and tumor drug delivery should result in increased anticancer efficacy. Yet, the pertinent clinical trials have not demonstrated clear evidence of superior efficacy of lipoplatin over conventional cisplatin (Fig. 1). One phase III clinical trial has shown lipoplatin appeared more effective than conventional cisplatin and had a more favorable safety profile, particularly regarding nephrotoxicity, neurotoxicity and asthenia,<sup>[13]</sup> whereas another phase III clinical study has demonstrated liposomal cisplatin reduced nephrotoxicity but had a similar antitumor efficacy compared with conventional formulation.<sup>[14]</sup> There is an urgent need to conduct a meta-analysis addressing pertinent evidence to evaluate whether liposomal cisplatin could enhance antitumor efficacy over conventional nonliposomal cisplatin. Furthermore, there is still no systematic evaluation of the safety profiles comparing lipoplatin with original cisplatin. Therefore, we performed a meta-analysis that incorporates all available clinical trials in this study to evaluate the efficacy and safety of liposomal cisplatin versus conventional nonliposomal cisplatin.

**2. Methods**

We planned and performed this meta-analysis in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Intervention. This study did not require the

ethic approval and informed consent as all analyses were carried out based on the data extracted from previous published trials.

**2.1. Literature search**

A systematic literature search was conducted in PubMed, Embase, The Cochrane Library, and ClinicalTrials.gov from inception to February 10, 2018. The search included the following terms: “liposomal cisplatin,” “cisplatin liposome,” “lipoplatin,” or “SPI-77.” The search was limited to clinical trials without restrictions on publication language. Any potentially relevant meeting abstracts and articles found in their reference lists were reviewed and considered for inclusion.

**2.2. Inclusion and exclusion criteria**

The following criteria were used for inclusion in the meta-analysis: randomized control trials (RCTs), containing both a cohort treated with the liposomal cisplatin and a cohort treated with the conventional formulation; at least 1 objective type of data reported, such as progressive disease (PD), partial response (PR), stable disease (SD), and adverse events (AEs). All cancer types, pretreatment status, and concurrent treatment were allowed. Studies were excluded in the following conditions: case reports; reviews; retrospective or prospective observational cohort studies and single-arm RCTs. Two investigators independently reviewed the articles for eligibility.

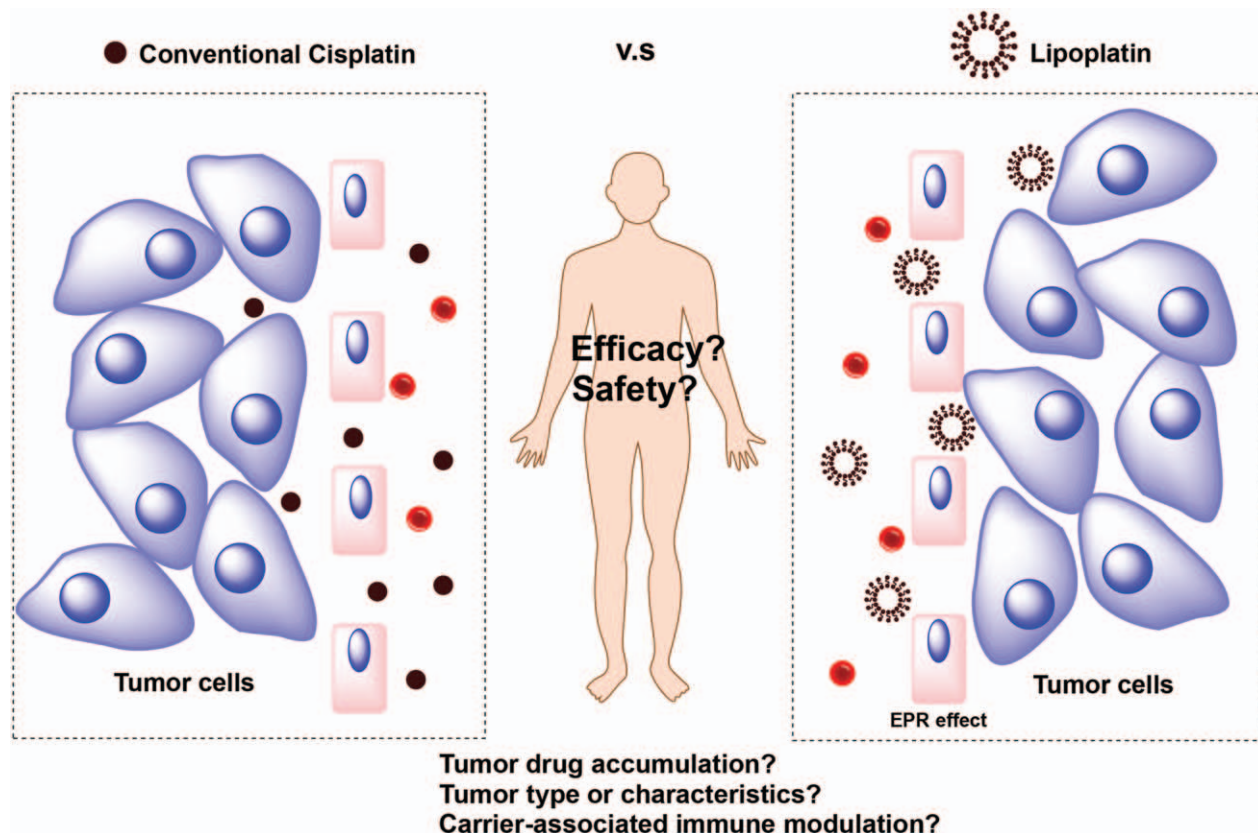


Figure 1. Is lipoplatin superior to conventional cisplatin in efficacy and safety?

### 2.3. Data extraction

Extraction of study characteristics, efficacy and safety data from text, tables, and figures of included studies was done independently by 2 investigators. For each clinical trial, the following details were extracted and presented: study characteristics (first author, journal, year of publication), trial design characteristics (study design, outcome measurement, type of cancer, therapy regimen for each arm), study population (median age, number of patients evaluated for efficacy and safety endpoints in each arm), efficacy results (PD, PR, and SD) and AEs.

### 2.4. Statistical analysis

All pooled data on the PD, PR and SD, and AEs were analyzed with Review Manager (version 5.3, The Cochrane Collaboration, Oxford, UK). For response rates, the crude OR with the corresponding 95% CI was calculated in the meta-analysis. Heterogeneity was assessed by  $I^2$  index. When  $I^2$  value was < 50%, the fixed-effects model was employed for analysis, and if  $I^2$  value was  $\geq$  50%, random-effects model was used.<sup>[15]</sup> Considered of possible significant heterogeneity or inconsistency, subgroup analysis would be performed to find the possible sources. Results were considered statistically significant for a 2 tailed  $P$  value < .05.

### 2.5. Risk of bias assessment

The risk of bias of RCT studies was evaluated using the criteria described in the Cochrane handbook for systematic reviews of interventions.<sup>[16]</sup> These parameters included details of sequence generation, allocation concealment, treatment blinding, completeness of outcomes data, and presence of selective outcome reporting. The judgment was marked as “high risk,” “unclear risk,” or “low risk.” Trials that met all the criteria were categorized as low risk of bias, whereas those that met none were high risk of bias. The others were classified as unclear risk of bias if the information was insufficient to make a judgment.

## 3. Results

### 3.1. Search results

Based on the search criteria, a total of 361 records were retrieved, among which only 5 RCTs met criteria for inclusion in meta-analysis as summarized in Fig. 2. These studies were published between 2007 and 2010. A total of 523 patients were enrolled in trials and randomly assigned to receive chemotherapy with liposomal or conventional cisplatin (279 and 244 patients respectively). Among the 5 studies, 4 studies had data from NSCLC patients, while only 1 had data from SCCHN patients. In addition, the median age in 3 studies was similar, ranging from 56 to 66 years. The detailed characteristics of these studies, including treatment regimens and patient population, are summarized in Table 1.

### 3.2. Efficacy results analysis

Response results including PD, PR, SD were all evaluated in all 5 trials. The statistical analysis revealed that lipoplatin significantly decreased the PD rate of cancer patients compared with the conventional cisplatin (OR, 0.46; 95% CI, 0.28–0.74;  $P$  = .002) (Fig. 3). Unfortunately, there was no significant difference between liposomal versus conventional formulations in the rates

of PR (OR, 1.37; 95% CI, 0.95–1.98;  $P$  = .09) (Fig. 4) and SD (OR, 1.03; 95% CI, 0.72–1.48;  $P$  = .86) (Fig. 5). No considerable heterogeneities were found in all the terms of PD, PR, and SD. Moreover, among all the 5 trials, 4 studies as mentioned were related to NSCLC, thus subgroup analysis to explore the lipoplatin's efficiency in the treatment of NSCLC patients was carried out. The results revealed that lipid-based cisplatin significantly decreased the PD rate (OR, 0.38; 95% CI, 0.22–0.64;  $P$  = .0003), meanwhile improved the PR rate (OR, 1.53; 95% CI, 1.04–2.25;  $P$  = .03) in NSCLC populations. Nevertheless, lipoplatin regimen did not yield superior SD rate compared with the conventional cisplatin (OR, 0.97; 95% CI, 0.66–1.41;  $P$  = .86).

### 3.3. Adverse events analysis

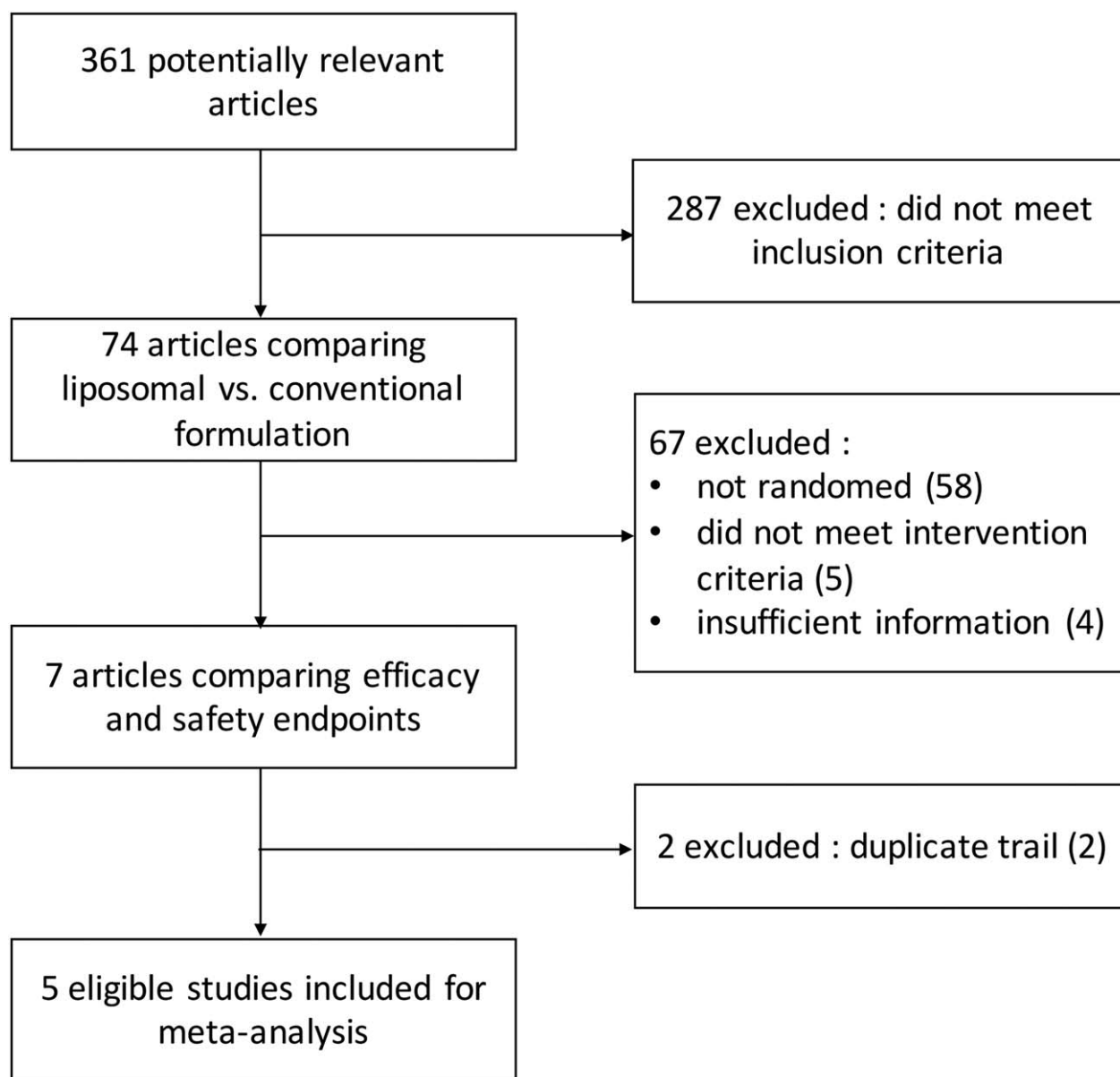
The reporting of the side effects was heterogeneous among the 5 trials. Neurotoxicity, nephrotoxicity, anemia, leukopenia, thrombocytopenia, neutropenia, nausea/vomiting, asthenia, alopecia, diarrhea, and anorexia were evaluated in 2 or 3 trials (see Fig. S1–S21, Supplemental Content, <http://links.lww.com/MD/C630> which presented the forest plots of comparison of toxicities between lipoplatin and conventional nonliposomal cisplatin). Overall, the risk of nephrotoxicity, anemia, thrombocytopenia, alopecia, diarrhea, and anorexia which were both in grade 1 to 2 and grade 3 to 4 between the 2 modalities was comparable, revealing that patients in the liposomal cisplatin group did not experience a greater incidence rate of the above-mentioned side effects. Nevertheless, the meta-analysis results showed significant differences in the incidence of grade 3 to 4 neurotoxicity (OR, 0.18; 95% CI, 0.04–0.74;  $P$  = .02), grade 3 to 4 leukopenia (OR, 0.47; 95% CI, 0.26–0.85;  $P$  = .01), grade 3 to 4 neutropenia (OR, 0.26; 95% CI, 0.09–0.71;  $P$  = .009), grade 1 to 2 nausea/vomiting (OR, 0.50; 95% CI, 0.32–0.77;  $P$  = .002), and grade 3 to 4 asthenia (OR, 0.11; 95% CI, 0.03–0.42;  $P$  = .001), favoring the use of the cisplatin lipid-based formulation when compared with nonliposomal cisplatin. A summary of toxicity meta-analysis is presented in Table 2 (detailed information see Fig. S1–S21, Supplemental Content, <http://links.lww.com/MD/C630>).

### 3.4. Quality assessment

The potential for study design bias is summarized in Fig. 6. All the 5 trials allocated patients to treatment arms randomly, but most of them did not report how the sequences were generated except that Stathopoulos et al<sup>[14]</sup> clarified their randomization was carried out according to the method of random permuted blocks within strata. Otherwise, 2 of the 5 trials were open-label<sup>[7,17]</sup> and 2 did not publish information on blinding,<sup>[13,18]</sup> while only one was conducted with evaluators blinded to treatment assignment.<sup>[14]</sup> Three trials showed evidence of incomplete outcomes' data<sup>[13,17,18]</sup> and 2 trials with reporting biases had no information for key outcome data for interventions.<sup>[13,18]</sup> Together, these trial characteristic suggested a moderate risk of study design bias.

## 4. Discussion

Liposomes have been used to improve the therapeutic index of cytotoxic agents by modifying drug absorption, reducing metabolism, prolonging biological half-life, or reducing toxicity. Over the last 2 decades, a few anticancer nanoparticles based on



**Figure 2.** Flow diagram of systematic literature search for clinical trials comparing anticancer efficacy and safety of liposomal cisplatin versus conventional nonliposomal cisplatin.

liposomal platforms have been met efficacy criteria for regulatory approval, such as Caelyx and Myocet.<sup>[19]</sup> Although the liposomes have presented numerous advantages compared with their conventional chemotherapy, especially in the preclinical trials, there are concerns about their potential for their antitumor efficacy and toxicity to patients in clinic. For instance, Petersen et al<sup>[20]</sup> in a meta-analysis had previously found that liposomal doxorubicin did not show superior antitumor efficacy compared with the conventional doxorubicin in clinical trial settings, which indicated that the purported advantages of liposomal doxorubicin formulation in preclinical studies did not translate to the clinical trials successfully.

Lipoplatin is a liposomal formulation of cisplatin that is widely used in chemotherapy regimes.<sup>[21]</sup> Yet, the fundamental question also remains whether lipid-based cisplatin could significantly improve the therapeutic index of nonliposomal cisplatin in clinic.

Our study is the first to systematically and objectively quantify the efficacy of liposomal cisplatin in comparison with conventional nonliposomal cisplatin. The liposome encapsulated cisplatin proved to be more clinical efficacious than cisplatin in the response rate of PD in cancer patients in our current study. Interestingly, further subgroup analysis of only the NSCLC patients showed higher response rates of PR and PD simultaneously. The improvement of PR might be related to the cancer type, whose specific parameters such as vascularity and immunogenicity can influence the pharmacokinetics and pharmacodynamics of liposomal drugs.<sup>[20]</sup> Analysis of overall survival (OS) and progression-free survival (PFS) were not performed in our study for the reason only 1 trial reported these endpoints, showing an average of 51 weeks versus 43 weeks (lipoplatin vs cisplatin) on OS, meanwhile an average of 30 weeks versus 26 weeks (lipoplatin vs cisplatin) concerning PFS.

**Table 1**  
**Characteristics of selected clinical trials.**

Study (y)	Treatment arms	Number of patients	Median age (y)	Concurrent treatments	Type of trail	Cancer type	TNM stage
Boulikas <sup>[18]</sup>	Cisplatin liposome 120mg/m <sup>2</sup> every 21 d	33	NS	Gemcitabine	Phase III	NSCLC	NS
	cisplatin 100mg/m <sup>2</sup> every 21 d	26	NS				
Jehn <sup>[17]</sup>	Cisplatin liposome 100mg/m <sup>2</sup> every 21 d	25	56	5-FU	Phase III	SCCHN	IVa/IVb/IVc
	cisplatin 100mg/m <sup>2</sup> every 21 d	21	58				
Kosmas <sup>[13]</sup>	Cisplatin liposome 120mg/m <sup>2</sup> every 21 d	60	NS	Gemcitabine	Phase III	NSCLC	NS
	cisplatin 100mg/m <sup>2</sup> every 21 d	41	NS				
Mylonakis <sup>[7]</sup>	Cisplatin liposome 120mg/m <sup>2</sup> every 21 d	47	64	Gemcitabine	Phase II	NSCLC	IIIb/IV
	cisplatin 100mg/m <sup>2</sup> every 21 d	41	66				
Stathopoulos <sup>[14]</sup>	Cisplatin liposome 200mg/m <sup>2</sup> every 14 d	114	65	Paclitaxel	Phase III	NSCLC	IIIa/IIIb/IV
	cisplatin 75mg/m <sup>2</sup> every 14 d	115	66				

NS=not specified, NSCLC=non-small-cell lung cancer, SCCHN=squamous cell carcinoma of the head and neck.

Although Stathopoulos et al<sup>[14]</sup> in a phase III trial had also observed the OS endpoint, the detailed results of the survival time were not reported and no significant difference was found between the 2 arms. Therefore, whether lipid-based cisplatin could contribute to enhanced OS and PFS remains to be determined and more clinical data are needed. Otherwise, almost no clinical trials explored the effect of empty liposomes on the clinical efficacy since recent preclinical studies<sup>[22,23]</sup> had observed that nondrug loaded nanoparticles including liposomes enhanced tumor growth in comparison with vehicle control in tumor-bearing mice unfortunately. This might be contributed to the polarization of tumor-associated macrophages, as well as the enhanced tumor angiogenesis by the empty nanocarriers.<sup>[22]</sup> Patients treated with nano-formulations might have the same immune responses, and whether the antitumor efficacy of nanodrug is offset by the tumor immunogenicity is still doubtful. Additional prospective clinical trials and preclinical mechanistic studies are needed to elucidate the role of drug vehicles in the antitumor efficacy.

All the 5 clinical studies had compared the adverse effects of lipoplatin with nonliposomal cisplatin, and our analysis is the

first meta-analysis to our knowledge that combined the results of existing clinical trials and offered more practical results. Our analysis revealed cisplatin liposomal formulation was much less toxic than the original cisplatin. This minimized toxicity might be attributed to the tumor targeting profile of the lipid-based cisplatin, which reduced the drug accumulation in normal tissues.<sup>[10]</sup> In contrast, it should be clearly noticed that both liposomal and nonliposomal cisplatin formulations in the 5 clinical trials were in combination with one another cytotoxic agent, such as gemcitabine, 5-FU, or paclitaxel. So the toxicities in the patients were induced by lipoplatin/cisplatin and one of those chemotherapeutic agents together, not reflecting the real side effects of the cisplatin formulations themselves. What's more, the safety of the empty nano-vehicles also remains unclear. Therefore, more clinical trials should be encouraged to carry on to explore the real side effects of the lipoplatin itself, as well as the empty nanocarriers.

The current meta-analysis is limited by insufficient quantity of randomized clinical trials. Several trials in our initial search results were excluded because they compared liposomal formulation to standard of care regimens that did

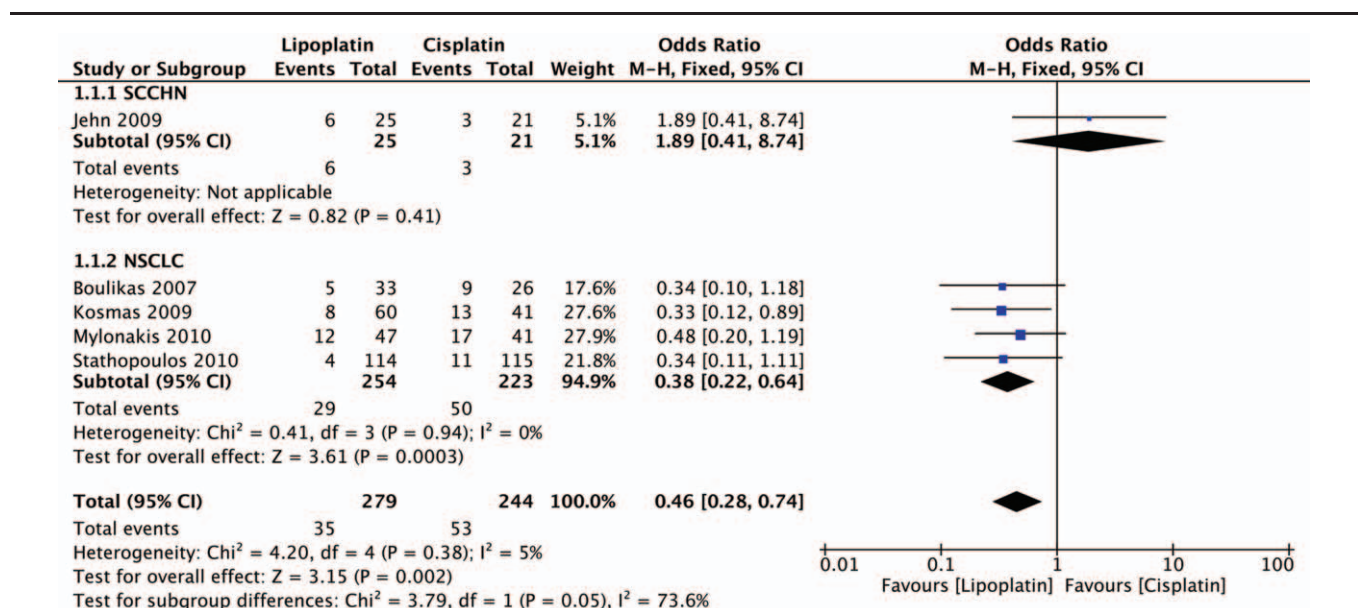


Figure 3. Forest plot of progressive disease (PD) rate.

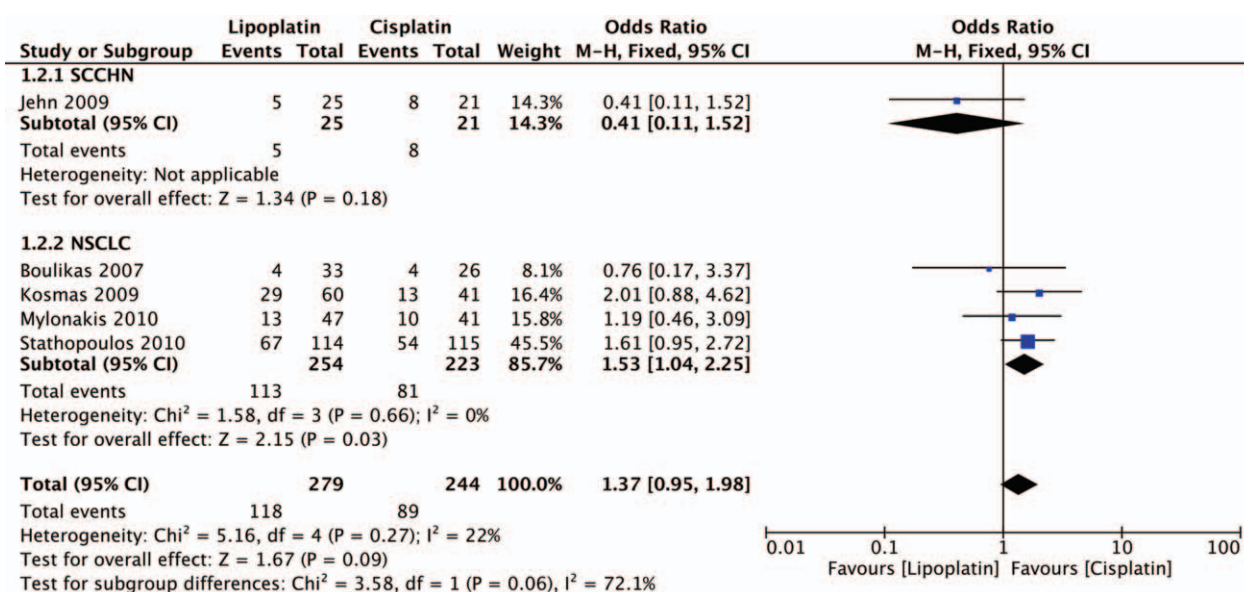


Figure 4. Forest plot of partial response (PR) rate.

not contain the equivalent conventional formulation. Clearly, more clinical trials directly comparing carrier-mediated and conventional chemotherapy formulations are needed. Additionally, despite having covered several data based in our electronic search, with no limits used for publication date and language, some relevant clinical trials might not have been identified. Besides, our analysis centered on extracted data but not original data. Since an original data-based meta-analysis may produce more reliable estimation for association,<sup>[24]</sup> investigators should carefully study our results, especially for positive association in subgroup analysis. Moreover, the 2 regimens in each group were not the same, which may influence our results. Additionally, we included 2 studies<sup>[13,18]</sup> which were only

published as abstracts, leading to insufficient details of patient characteristics for NSCLC patients. Overall, the intensity of its argumentation shall be improved through further development of additional large samples rigorously designed and high-quality RCTs.

### 5. Conclusion

In conclusion, liposomal cisplatin-based chemotherapy offers significant advantages regarding the PD and reduced toxicities of neurotoxicity, leukopenia, neutropenia, nausea/vomiting, and asthenia relative to conventional cisplatin in NSCLC and SCCHN patients. But there was no significant difference between

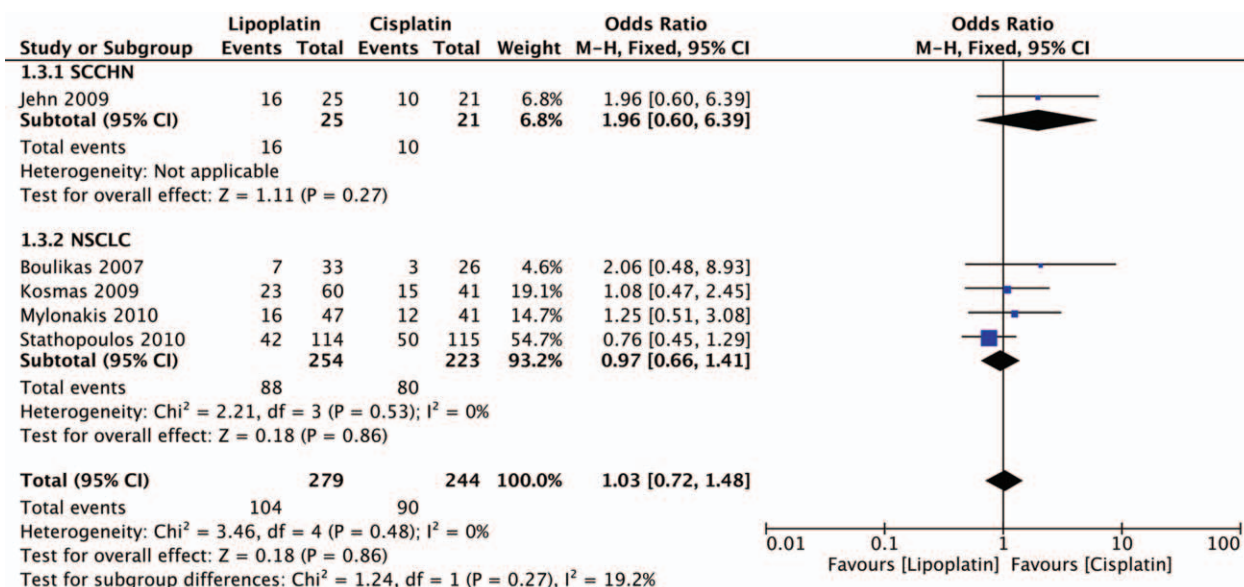


Figure 5. Forest plot of stable disease (SD) rate.

**Table 2**  
**Comparison of toxicities between liposomal cisplatin and conventional nonliposomal cisplatin.**

Analyses	Heterogeneity		Model	OR	95% CI	P
	P	I <sup>2</sup>				
Neurotoxicity						
G1-2	.02	75%	Random	0.77	(0.19, 3.09)	.71
G3-4	1	0%	Fixed	0.18	(0.04, 0.74)	.02
Nephrotoxicity						
G1-2	.004	88%	Random	0.26	(0.04, 1.54)	.14
G3-4	.93	0%	Fixed	0.18	(0.03, 1.08)	.06
Anemia						
G1-2	.53	0%	Fixed	0.83	(0.52, 1.33)	.44
G3-4	.43	0%	Fixed	0.42	(0.14, 1.24)	.12
Leukopenia						
G1-2	.64	0%	Fixed	1.27	(0.79, 2.02)	.32
G3-4	.95	0%	Fixed	0.47	(0.26, 0.85)	.01
Thrombocytopenia						
G1-2	.12	53%	Random	1.27	(0.45, 3.61)	.66
G3-4	.21	38%	Random	0.61	(0.09, 4.23)	.61
Neutropenia						
G1-2	.99	0%	Fixed	1.89	(0.96, 3.72)	.07
G3-4	.69	0%	Fixed	0.26	(0.09, 0.71)	.009
Nausea/vomiting						
G1-2	.45	0%	Fixed	0.50	(0.32, 0.77)	.002
G3-4	.70	0%	Fixed	0.20	(0.03, 1.18)	.08
Asthenia						
G1-2	.74	0%	Fixed	0.92	(0.61, 1.40)	.71
G3-4	.28	15%	Fixed	0.11	(0.03, 0.42)	.001
Alopecia						
G1-2	.18	45%	Random	0.92	(0.40, 2.08)	.83
G3-4	.82	0%	Random	1.19	(0.67, 2.11)	.55
Diarrhea						
G1-2	.08	67%	Random	0.81	(0.03, 22.13)	.9
G3-4	.15	52%	Random	0.58	(0.05, 6.36)	.66
Anorexia						
G1-2	.64	0%	Fixed	1.01	(0.51, 1.98)	.98

liposomal versus conventional formulations in the rates of PR and SD. Additionally, after subgroup analysis of NSCLC populations, our study revealed that lipoplatin regimen yielded both superior PD and PR rates compared with the conventional

cisplatin. But for OS and PFS, further studies are still needed to confirm the benefit. More importantly, the contribution of the EPR effect and the microenvironment to clinical efficacy is currently unclear and remains to be fully elucidated.

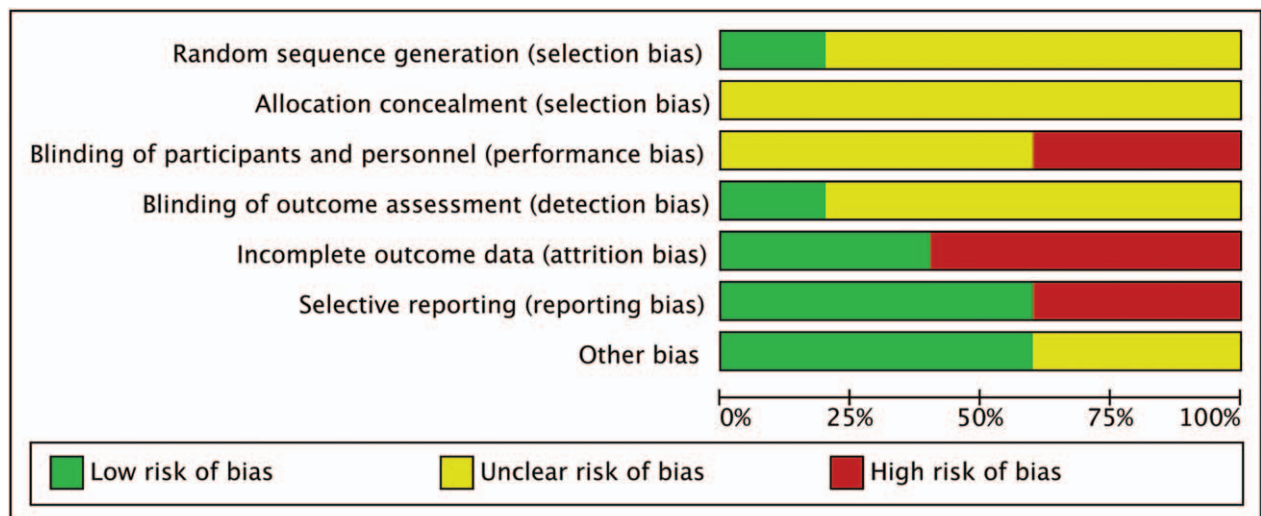


Figure 6. Risk of bias graph of the included clinical trials.

## Author contributions

**Data curation:** Bei Xu, Min Zeng.

**Funding acquisition:** Lin Yu.

**Methodology:** Jiafu Feng.

**Software:** Jiawei Zeng.

**Visualization:** Jiafu Feng.

**Writing – original draft:** Bei Xu.

**Writing – review & editing:** Lin Yu.

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