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Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

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Abstract

Objectives

Different intrathoracic perfusion therapeutic regimens are available for non-small cell lung cancer (NSCLC) with malignant pleural effusion (MPE). Antiangiogenic agents are often used to control MPE, and the results are satisfactory. Here, we performed a network meta-analysis to reveal optimal combinations of antiangiogenic agents and chemical agents and demonstrate their effectiveness and safety.

Design

Systematic review and network meta-analysis (NMA).

Data sources

PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database (CQVIP) and Chinese National Knowledge Infrastructure (CNKI) were searched from inception to May 2023. Eligible studies were randomized controlled trials that reported on curative effect in MPE.

Data extraction and synthesis

The Cochrane Collaboration tool was used to assess risk of bias. The consistency was evaluated by examining the agreement between direct and indirect effects. NMA was performed and the ranking probabilities of being at each possible rank for each intervention were estimated. Comparison-adjusted funnel plots were obtained to assess publication bias.

Results

A total of 46 studies were included in the analysis. Among them, we included a total of 7 interventions. A total of 3026 patients participated in this analysis. According to the results of the network meta-analysis, some antiangiogenic agents combined with chemotherapy regimens improved ORR, DCR and QOL. The rank probabilities suggested that in terms of ORR, DCR and QOL, Endo + LBP was the first-ranked intervention.

Conclusion

Administration of antiangiogenic agents plus chemical agents significantly improved the clinical response and quality of life. In addition, Endostar plus lobaplatin was the most effective combination.

PROSPERO registration number

CRD42021284786

Keywords NSCLC · MPE · Antiangiogenic agents · Thoracic perfusion · Network meta-analysis

Strengths and limitations of this study

- Antiangiogenic agents plus chemical agents can improve the control rate of MPE via thoracic perfusion. However, the optimal choice remains unclear.
- Comparison of the efficacy and safety of seven different interventions by performing a network meta-analysis.
- To the best of our knowledge, this is the most comprehensive network meta-analysis which includes all the available data of comparative studies.
- No closed loop is formed in network graph.
- More well-designed randomized control trials are needed due to the lack of diversity of drug combinations of included studies.

Introduction

Malignant pleural effusion (MPE) is the accumulation of exudative fluid in the pleural cavity as a result of malignancy; it is usually caused by malignant infiltration of the pleura and often results in dyspnea, chest tightness and shortness of breat(1). According to Global Cancer Statistics released by GLOBOCAN in 2020, lung cancer is the leading cause of cancer deaths worldwide and accounts for the most common cause (approximately 35.6%) of MPE (2),(3). Studies have revealed that lung cancer combined with MPE has a worse prognosis than other malignant tumors, with a median survival of 3.3 months (4). Traditional treatments for MPE include pleurodesis, indwelling pleural catheters and thoracic perfusion of chemotherapeutic agents (4). Currently, with various antiangiogenic agents being approved for cancer treatment, antiangiogenic therapy for MPE has attracted increasing attention.

Vascular endothelial growth factor (VEGF), a proangiogenic factor, has a prominent role in tumor angiogenesis, host vascular endothelial cell activation, malignant proliferation and metastasis (5). High expression levels of VEGF have been confirmed in the serum of patients with cancer and in malignant pleural effusions. Antiangiogenic agents (bevacizumab and Endostar) have been approved for MPE treatment, and the results are satisfactory.

Bevacizumab, a humanized monoclonal antibody with high binding affinity to VEGF, blocks VEGF signaling and decreases the formation of pleural effusion (6). Endostar is a modified and recombinant human endostatin (Rh-endostatin). It is now a common angiogenesis antagonist and has been widely used in clinical practice to treat a wide range of tumors (7).

There have been several studies on the efficacy of intrapleural perfusion with antiangiogenic agents combined with chemotherapy in the treatment of malignant pleural effusion (8),(9), (10), (11), but comparisons between multiple schemes are lacking, and the results are inconsistent. Notably, there are no guidelines for the treatment of MPE; hence, we performed this systematic review and network meta-analysis to identify the optimal combination strategy to aid clinical decision-making. In addition, we used a single-arm meta-analysis to evaluate the therapeutic effect of bevacizumab combined with chemotherapy and Endostar combined with chemotherapy on malignant pleural effusion in NSCLC patients.

Materials and methods

Registration and guidelines

The protocol of this systematic review and network meta-analysis has been registered in PROSPERO (CRD42021284786). The reporting of this network meta-analysis follows the Preferred Reporting Items for Systematic Reviews statement for Network Meta-analyses (PRISMA-NMA) (PRISMA NMA Checklist) (12).

Search strategy and eligibility criteria

We searched electronic databases, including PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database (CQVIP) and Chinese National Knowledge Infrastructure (CNKI), from inception to May 25, 2023, using the following keywords: "Endostar", "recombinant human endostatin", "Rh endostatin", "yh-16"; "Bevacizumab"; "Lung Neoplasms"; "Pleural Effusion, Malignant" and "Drug Therapy". In this search, there were no restrictions on the language or publication date. Publications were considered eligible based on the following criteria: 1) the study design was a randomized controlled trial (RCT); 2) the study participants were adult patients who had a clear histopathological diagnosis of NSCLC with pleural effusion; and 3) study participants in the experimental group or the control group received pleural perfusion of bevacizumab plus chemical agents, Endostar plus chemical agents or chemical agents alone. During treatment, no patients received systematic chemotherapy, chemoradiotherapy, hyperthermia, or other traditional Chinese medicine injections; and 4) the studies included the objective response rate (ORR) and disease control rate (DCR). Furthermore, nonclinical controlled trials, literature reviews, duplicate publications, case reports, animal research papers, conference abstracts, systematic reviews and meta-analyses, and studies with insufficient information for data extraction were excluded.

Types of Outcomes

Outcomes included the ORR, DCR, quality of life (QOL), and adverse reaction rate. The included articles were required to have ORR and DCR outcomes. Referring to previous evaluation criteria (13), we integrated the clinical response criteria as follows: (1) a complete response (CR) occurred when effusion disappeared for more than four weeks; (2) a partial response (PR) occurred when effusion was reduced >50% for more than four weeks; (iii) stable disease (SD) was defined as reduced effusion <50% or increased effusion <25%; and (4) progressive disease (PD) was effusion increased >25% along with other signs of progression or symptomatic reaccumulation of the fluid requiring repeat treatment. The outcome was calculated as follows: ORR= CR + PR; DCR= CR + PR +SD. QOL was measured by the Karnofsky performance score (KPS). Improved (KPS increased by more than 10 points) and stable (KPS changed by less than 10 points) levels were considered to indicate efficacy. The safety outcomes included adverse reactions, such as myelosuppression, hypohepatia and gastrointestinal effects (regardless of the severity (any grade or grade 3 or more)).

Data extraction and quality evaluation

The required data were independently extracted by two reviewers, and the quality assessment of the studies was performed afterward. For eligible studies, the following data were extracted: the first author, study year, proportion of males, mean age, treatment plan, performance status, ORR, DCR, QOL, incidence of treatment-related adverse events (TRAEs) and grade 3 or higher treatment-related adverse events (≥grade 3 TRAEs) related to treatments. The risk of bias for each trial was assessed

using the Cochrane risk of bias method (14), which includes random sequence generation, allocation concealment, blinding to allocated interventions, missing outcome data, selective outcome reporting, and other concerns. Then, an overall judgment was made (low risk, some concerns or high risk). Any conflicts were resolved via consultation with the third researcher.

Statistical analysis

The primary outcome of this study was the ORR. Secondary outcomes were DCR, QOL and TRAEs. Stata 15.0 was used to graphically display the results. The network meta-analysis was performed using the "rjags" and "gemtc" packages in R version 4.2.3. Using the Markov chain Monte Carlo method to conduct 4 MCMC chains simultaneously, the number of simulations was set to 5000, and the number of iterations was set to 20000. The results are shown as odds ratios (ORs) and 95% credible intervals (CrIs). Fixed and random effects models were considered and compared using the deviance information criterion (DIC). If the DIC difference between the random model and the fixed model was less than 5, the fixed model was selected (15)). Heterogeneity was assessed between studies using the I2 statistic. Global and local inconsistencies were unable to be assessed because there were no closed loops in the network. All treatments were ranked according to the surface under the cumulative ranking area curve (SUCRA). Higher SUCRA probabilities indicated better treatment effects (16). Comparison-adjusted funnel plots were employed to assess publication bias. Statistical analyses of the pooled ORRs were performed using R version 4.2.3.

Results

Literature search and study characteristics

We identified 5670 records from 7 electronic databases. After removing duplicates, 4442 titles and abstracts were reviewed, and 130 papers were selected for full-text screening. Finally, 46 studies were included in the network meta-analysis (Fig S1, (17); (18); (19); (20); (21); (22); (23); (24); (25); (26); (27); (28); (29); (30); (31); (32);(33);(34);(35));(36);(37);(38);(39);(40); (41) ;(42) ;(43);(44) (45); (46);(47); (48);(49); (50); (51);(52),(53); (54); (55);(56); (57) (58);(59); (60) (61) (62);Studies were published between 2012 and 2023 and included a total of 3026 patients. The intrapleural administration therapeutic regimens included Endostar + nedaplatin (Endo + NDP), Endostar + DDP (Endo + DDP), Endostar + lobaplatin (Endo + LBP), Bevacizumab + DDP (Bev + DDP), DDP, nedaplatin (NDP) and lobaplatin (LBP). In particular, 32 studies compared Endostar plus chemical agents versus chemical agents alone, 7 studies compared bevacizumab plus chemical agents versus chemical agents alone, and 7 studies compared chemical agents. The general characteristics of the included studies are presented in Table 1. The analyses are presented separately for ORRs, DCRs, QOL, TRAEs and ≥ grade 3 TRAEs. The TRAEs included myelosuppression, hypohepatia and gastrointestinal effects. The networks of studies are presented in Fig 1, the league tables and forest plots are shown in Additional file: Fig S2 and Table S3-11.

Quality Assessment

Fig S3 presents our risk of bias assessments for the studies. Fig S4 presents more details on the risk of bias assessments. There were 41 RCTs among the 46 studies in the lowest categories of risk of bias for random sequence generation. None of the studies reported the processes used for allocation concealment or blinding of outcome assessment; only 1 study mentioned the blinding of participants and personnel. The outcome data of all studies were complete, and no other sources of bias were reported.

NMA

For the ORR, Endo + LBP and Endo + NDP were significantly better than Bev + DDP, with ORs and 95% CrIs of 0.16 (0.05, 0.53) and 0.25 (0.09, 0.68), respectively. For the comparison of Endostar combined with chemotherapy regimens, Endo + LBP and Endo + NDP were superior to Endo + DDP, and the ORs and 95% CrIs were 0.19 (0.06, 0.59) and 0.29 (0.11, 0.75), respectively. Except for Endo + DDP and Endo + DDP, Endostar combined with chemotherapy was superior to some chemotherapy regimens: Endo + LBP was superior to DDP [OR: 0.05 (0.02, 0.15)], NDP [OR: 5.06 (1.39, 19.02)] and LBP [OR: 5.69 (2.37, 14.65)]; Endo + NDP was better than DDP [OR: 0.08 (0.03, 0.2)], NDP [OR: 3.28 (1.65, 6.76)] and LBP [OR: 3.73 (1.17, 12.04)]; and Endo + DDP was better than DDP [OR: 0.27 (0.22, 0.33)]. For bevacizumab combined with chemotherapy regimens, Bev + DDP was significantly better at ORR than DDP [OR: 3.19 (2.11, 4.92)].

The SUCRA rank and probability value results indicated that Endo + LBP (95%) was the most likely to improve the ORR, followed by Endo + NDP (88%), NDP (48%), Endo + DDP (46%), LBP (40%), Bev + DDP (33%), and DDP (0.002%) (Fig 2; Table 2).

For DCR, there were no significant differences in the improvement of the DCR between 3 different Endostar combinations with chemotherapy regimens (Endo + LBP, Endo + NDP and Endo + DDP) or bevacizumab combined with a chemotherapy regimen (Bev+DDP). Endo + LBP was significantly better than Endo + DDP, with an OR and 95% CrI of 0.15 (0.02, 0.93). The DCR was ranked for all treatments by estimating the SUCRA value. The results were as follows: Endo + LBP (95%), Endo + NDP (83%),

Bev + DDP (51%), Endo + DDP (49%), NDP (41%), LBP (30%), and DDP (1%) (Fig 2; Table 2).

Quality of Life

Nineteen studies reported the quality of life, which constituted five pairs of direct comparisons involving six interventions (Endo + DDP, Endo + LBP, Bev + DDP, DDP, NDP and LBP). The network diagram is shown in Fig 1. Compared with DDP alone, Endo + DDP (OR = 0.3, 95% CI [0.22, 0.39]), Endo + LBP (OR = 0.1, 95% CI [0.02, 0.57]), and LBP (OR = 0.31, 95% CI [0.1, 0.93]) were more effective in improving quality of life.

After ranking the six interventions based on the SUCRA values, the results were as follows: Endo + LBP (95%), Endo + DDP (69%), LBP (63%), Bev + DDP (33%), NDP (29%), and DDP (10%), as shown in Fig 2 and Table 2.

Safety and toxicity

Safety and toxicity were determined according to any-grade TRAEs and grade greater than or equal to 3 TRAEs. The adverse reactions mainly included myelosuppression, headache, hypohepatia, renal insufficiency, gastrointestinal effects, electrocardiographic abnormalities and fever. Among all types of adverse reactions, the most frequent occurrences were myelosuppressive, hypohepatia and gastrointestinal effects. The NMA included seven therapeutic regimens for TRAEs of any grade and six therapeutic regimens for TRAEs of grade greater than or equal to 3 (Fig 1). We did not find statistically significant differences in myelosuppression or hypohepatia. A single chemotherapeutic agent caused fewer gastrointestinal reactions.

The probabilities of adverse events were ranked for all treatments by estimating the SUCRA value. A lower SUCRA value indicated a higher probability of AEs and a poorer treatment regimen. The corresponding ranking of incidences is shown in Fig 2 and Table 2.

Publication bias

The comparison-adjusted funnel plots are presented in Fig 3. Overall, no distinct asymmetry was found in the comparison-adjusted funnel plot on the ORR, DCR, QOL, AG-gastrointestinal effects, AG-myelosuppression, G3-myelosuppression and G3-hypohepatia, indicating no evidence of publication bias. However, the comparison-adjusted funnel plot on AG-gastrointestinal effects, G3-gastrointestinal effects and AG-hypohepatia were not symmetric around the zero line, which revealed that there could be small-study effects.

Single-arm meta-analysis

All studies included in the analysis reported the efficacy response of intrapleural perfusion with antiangiogenic agents plus chemical agents for NSCLC patients with MPE (Appendix, Fig S5). The ORRs across the studies varied from 73.8 to 80.4%. The random effects model was used because of significant heterogeneity (I2 = 59%, p <0.01). The analysis showed a pooled ORR of 76.5% (95% CI: 72.5%–80.1%), and the ORR was further analyzed according to different antiangiogenic agent treatment regimens. Subgroup analysis revealed that the pooled ORRs of Endo + LBP and Endo + NDP were similar, which were 80.4% (95% CI: 67.3%–89.1%) and 79.0% (95% CI: 68.8%–86.5%), respectively, followed by Endo + DDP, which was 76.3% (95% CI: 73.4%–78.9%). Bev + DDP was the worst intervention among them, with a pooled ORR of 73.8% (95% CI: 57.4%–85.5%).

Discussion

Currently, to the best of our knowledge, intrapleural perfusion with antiangiogenic agents plus chemical agents in controlling MPE conferred satisfying clinical outcomes for patients with NSCLC. Although Endostar/bevacizumab combined with chemotherapy is widely used to treat malignant pleural effusion, there is a lack of head-to-head direct comparisons to determine the best regimen. Hence, we performed a network meta-analysis. In this analysis, two antiangiogenic agents and three chemical agents formed seven treatment regimens to identify which treatment was optimal in achieving higher clinical responses and QOL and fewer TRAEs. The results suggested the following:

1. Intrapleural administration of Endostar plus lobaplatin was associated with the best ORR and DCR outcomes, followed by Endostar plus nedaplatin.

2. For the ORR, Endo + LBP and Endo + NDP were significantly more favorable than Bev + DDP, while there were no significant differences in the efficacy of Endostar plus chemotherapy or bevacizumab plus chemotherapy with regard to DCR.

Endostar, an endogenous angiogenic inhibitor, can inhibit endothelial cell migration, repress the neovascularization of tumors, block the nutrient supply of tumor cells, and thus prevent tumor proliferation and metastasis. In addition, Endostar reduces the permeability of tumor neovascularization, thereby reducing the production of pleural effusion (63). In 2022, Yimiao Xia et a (8) performed a meta-analysis that included 55 RCTs with a total of 3379 patients with lung cancer to investigate the efficacy, safety and cost-effectiveness of Endostar and platinum in controlling MPE. All the studies in the meta-analysis were published in Chinese. This supported the findings in the current network meta-analysis.

Bevacizumab is another frequently studied antiangiogenic agent and plays an important role in the treatment of several types of tumors (7)). It can prevent VEGF-induced vascular permeability and tumor cell migration, thereby reducing MPE (64). Several studies have demonstrated the efficacy and safety of bevacizumab for the management of MPE. Du et al. compared the efficacy of combined intrapleural therapy with bevacizumab and cisplatin versus cisplatin alone in controlling MPE. The results revealed that bevacizumab plus cisplatin improved the ORR from 50 to 83.3%. However, in our meta-analysis, the pooled ORR of Bev + DDP was 73.8%, and the true efficacy of Bev might have been overestimated. After a literature search, we found no head-to-head comparison between Bev plus other chemical agents and the sole administration of chemical agents other than cisplatin. Therefore, more combination therapeutic regimens still need to be investigated in the future.

MPE is generally considered to be a manifestation of a malignancy in its preterminal stage. Hence, the interventions are palliative in nature. The main goal of treatment is to palliate symptoms and improve quality of life (65). In our study, we found that intrapleural injection of Endostar combined with DDP was the best in terms of improving QOL, while DDP was the worst.

With regard to the safety profile, although there was no significant difference in the incidence of myelosuppression or hypohepatia between therapeutic regimens in our study, regardless of the severity, the incidence of AG-gastrointestinal effects was significantly more frequent with Endo + DDP and Bev + DDP than with LBP and NDP. Furthermore, in the gastrointestinal effect ranking of the six treatment groups, NDP was the safest, and Endostar plus DDP was the least safe (regardless of the severity (any grade or grade 3 or more)). The results of these analyses suggest that safety considerations may be needed when Endostar plus DDP is administered.

This study had some limitations. First, we utilized only Chinese and English databases, which might have led to retrieval bias, and most of the trials did not report concealment or blinding, which might undermine the validity of the overall findings. Second, all the included RCTs were published in China,

and the generalizability of the results is limited. Third, most trials did not report the baseline characteristics, OS or PFS, and eleven trials failed to completely report TRAEs. Fourth, to facilitate the analysis, we did not make a strict distinction in terms of the administration dosage. Finally, the network diagram did not form a typical closed loop, such that the research inconsistencies and credibility of our conclusions cannot be checked. All of these limitations might have resulted in insufficient evaluation of the indicators.

Conclusions

This network meta-analysis comprehensively compared various treatments for thoracic perfusion of MPE in NSCLC patients and described the QOL and toxicity features. To the best of our knowledge, this is the first comprehensive NMA study of its kind. The results showed that antiangiogenic agents combined with chemotherapy regimens could improve clinical effectiveness and quality of life. In our study, Endo+LBP was the most effective. However, high-quality randomized controlled trials with larger sample sizes are needed to further confirm the evidence.

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Abbreviations

NSCLC	Non-small cell lung cancer
MPE	Malignant pleural effusion
VEGF	Vascular endothelial growth factor
Rh-endostatin	Recombinant human endostatin
CQVIP	VIP Database
CNKI	Chinese National Knowledge Infrastructure
RCT	Randomized controlled trial
ORR	Objective response rate
DCR	Disease control rate
QOL	Quality of life
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
KPS	Karnofsky performance score
TRAEs	Treatment-related adverse events
≥grade 3 TRAEs	Grade 3 or higher treatment-related adverse events
CrI	Credible intervals
SUCRA	Surface under the cumulative ranking area curve
CI	Confidence intervals
Endo + NDP	Endostar + nedaplatin
Endo + DDP	Endostar + cisplatin
Endo + LBP	Endostar + lobaplatin
Bev + DDP	Bevacizumab + cisplatin
NDP	Nedaplatin

Contributors

YX conducted overall design, data collection, analysis and draft writing. YYC and LMJ were responsible for data collection, partial analysis and partial draft writing. YNY, WS and XHZ were responsible for data collection, YYC and YX revised the manuscript. YX performed the submission.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethical approval

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data Availability statement

All data are available from the corresponding author upon reasonable request.

Tables

Table 1 Characteristics of the included randomized controlled trials.

Study	Year	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Intervention	outcome
Feng C (17)	2016	Endo_DDP:30 DDP:30	39/21	/	Moderate to large	≥60	Endo 4.5 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,2,3
Jie C (18)	2014	Endo_DDP:30 DDP:30	44/16	54.3±5.6/ 55.6±4.5	Un	Un	Endo 4.5 mg_DDP 40mg: 2/week, 3 cycles DDP 40mg: 2/week, 3 cycles	P1,3
Ruilin C (19)	2016	Endo_DDP:45 DDP:45	53/37	60.6±7.2/ 60.8±7.5	Moderate to large	≥60	Endo 4.5 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Chunxia D (20)	2015	Endo_DDP:19 DDP:19	23/15	61.4	Moderate to large	≥60	Endo 4.5 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Zhongya F (21)	2017	Endo_DDP:27 DDP:27	32/22	59.15±10.26/ 58.71±10.04	Moderate to large	Un	Endo 30 mg_DDP 30mg: 1/week, 3 cycles DDP 30mg: 1/week, 3 cycles	P1
Juan H (22)	2016	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2
Li H (23)	2014	Endo_DDP:25 DDP:25	30/20	41. 5 ± 7. 6	Moderate to large	>60	Endo 30 mg: 2/week _DDP 50mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

Shuwen L (24)	2020	Endo_DDP:20 DDP:20	24/16	62.3±1.7/ 62.5±1.5	Moderate to large	Un	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,3
Yanmin L (25)	2016	Endo_DDP:31 DDP:31	35/27	42.22±6.92/ 42.14±6.89	Un	>60	Endo 30 mg_2/week_DDP 50mg 1/week, 2 cycles DDP 50mg 1/week, 2 cycles	P1,3
Xinxin L (26)	2019	Endo_DDP:30 DDP:30	36/24	52.64±6.55/ 53.31±7.56	Un	≥60	Endo 45 mg/m^2_DDP 30mg: 2/week, 2-3 cycles DDP 30mg 2/week, 2-3 cycles	P1,3
Yafeng L (27)	2018	Endo_DDP:34 DDP:34	38/30	63.19±4.73/ 65.55±5.28	Moderate to large	≥60	Endo 60 mg_DDP 60mg: 2/week DDP 60mg 2/week	P1,2,3
Xiangdong L (28)	2017	Endo_DDP:31 DDP:31	35/27	46.3±10.6/ 45.7±11.3	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Meilin Q (29)	2016	Endo_DDP:21 DDP:21	24/18	59.6	Moderate to large	≥60	Endo 60 mg_DDP 50mg: 1/week, 3 cycles DDP 50mg 1/week, 3 cycles	P1,3
Song Q (30)	2018	Endo_DDP:28 DDP:23	22/27	68.2±4.6/ 68.2±4.6	Un	Un	Endo 30 mg/m^2_DDP 60mg/m^2: 2/week, 3 cycles DDP 60mg/m^2: 2/week, 3 cycles	P1,2,3,4
Qing S (31)	2012	Endo_DDP:40 DDP:40	42/38	37-79	Moderate to large	≥60	Endo 30 mg_2/week_DDP 40mg: 1/week, 3 cycles DDP 40mg 1/week, 3 cycles	P1,2,3

Ning S (32)	2021	Endo_DDP:30 DDP:30	37/23	61.43±6.45/ 62.05±6.29	Un	Un	Endo 60 mg_DDP 40-50mg: 2/week, 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,3
Aihua Q (33)	2018	Endo_DDP:42 DDP:42	43/41	56.84±7.03/ 57.19±8.25	Un	Un	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Ling T (34)	2019	Endo_DDP:48 DDP:48	57/39	59.26±2.43/ 61.54±2.32	Moderate to large	≥60	Endo 30 mg_4/week_DDP 30-40mg/m^2: 2/week, 1 cycle DDP 30-40mg/m^2: 2/week, 1 cycle	P1
Jianren T (35)	2014	Endo_DDP:45 DDP:45	48/42	46.5±11.5/ 47.5±10.5	Moderate to large	≥60	Endo 40 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Haiqin W (36)	2017	Endo_DDP:40 DDP:40	41/39	55.5±2.2/ 55.8±2.9	Large	≥60	Endo 40 mg_DDP 40mg 1/week: 4 cycles DDP 40mg 1/week, 4 cycles	P1,2,3
Rui w (37)	2018	Endo_DDP:30 DDP:30	35/25	61.28±6.32/ 60.54±5.65	Un	≥60	Endo 40 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,3
Yue W (38)	2023	Endo_DDP:47 DDP:47	51/43	53.47±3.25/ 54.09±3.38	Un	≥80	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1
Min X (39)	2020	Endo_DDP:20 DDP:20	27/13	/	Large	≥50	Endo 60 mg_DDP 40-50mg 2/week: 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,2,3,4
Xuezong X (40)	2021	Endo_DDP:75 DDP:75	79/71	63.65±5.11/ 63.87±5.38	Un	Un	Endo 45 mg_DDP 10mg 1/week: 3 cycles	P1,3

							DDP 1mg, 1/week, 3 cycles	
Yang Y (41)	2013	Endo_DDP:21 DDP:21	27/15	41.5±7.6	Large	Un	Endo 30 mg, DDP 40mg 1/week: 3 cycles DDP 40mg, 1/week, 3 cycles	P1,2,3,4
Lang Y (42)	2016	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg, DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Haixian L (43)	2018	Endo_DDP:26 DDP:26	23/29	41-75/39-75	Moderate to large	Un	Endo 45mg, DDP 30mg 2/week: 2-3 cycles DDP 30mg, 2/week: 2-3 cycles	P1,3
Yun L (44)	2016	Endo_DDP:30 DDP:30	28/32	/	Moderate to large	Un	Endo 30mg, DDP 30mg 3/6 days: 1-2 cycles DDP 30mg, 3/6 days: 1-2 cycles	P1,2
Lei Shi (45)	2016	Endo_LBP:21 LBP:21	25/17	42.3±5.6	Moderate to large	Un	Endo 30mg, 2/week: 3 cycles_LBP: 30mg/m^2: 1/3 week, 1 cycle LBP: 30mg/m^2: 1/3 week, 1 cycle	P1,2,4
Weiying C (46)	2021	Endo_LBP: 30 LBP:30	39/21	50.31±4.27/ 50.16±4.35	Moderate to large	Un	Endo 30mg, LBP: 30mg/m^2: 1/week, 4 cycles LBP: 30mg/m^2: 1/week, 4 cycles	P1,3
Shaoxian C (47)	2019	Endo_NDP: 46 NDP:46	45/47	/	Un	Un	Endo 75mg/m^2 7/week,4 cycles _NDP 30mg/m^2: 1/week, 2-4 cycles NDP 30mg/m^2: 1/week, 2-4 cycles	P1
Jie X (48)	2014	Endo_NDP: 35 NDP:35	43/27	62.5±5.5	Moderate to large	Un	Endo 60mg, NDP 60mg: 1/week, 2 cycles NDP 60mg, 1/week, 2cycles	P1,3

Meiqin Y (49)	2021	Bev_DDP: 29 DDP:29	32/26	69.86±11.36/ 67.92±9.83	Un	≥70	Bev 30mg, d1,q3w_DDP 40mg d1,8,15, q3w: 1 cycle DDP: 40mg, d1, 8, 15, q3w: 1 cycle	P1
Pengtao C (50)	2022	Bev_DDP: 35 DDP:35	45/25	65.16 ±9. 34/ 65.08± 9.26	Un	Un	Bev 30mg, d1,q3w_DDP 50mg d1,8,15, q3w: 1 cycle DDP: 50mg, d1, 8, 15, q3w: 1 cycle	P1,3
Na Z (51)	2019	Bev_DDP: 34 DDP:34	33/35	61.62±2.78/ 61.38±2.94	Un	>60	Bev 300mg, DDP 60mg 1/2weeks: 4 cycles DDP: 60mg, 1/2weeks, 4 cycles	P1,3
Yanhai S (52)	2020	Bev_DDP: 36 DDP:36	45/27	58.58±4.45/ 58.69±4.87	Un	>60	Bev 5mg/kg, DDP 45mg/m^2: 1/week, 3 cycles DDP: 45mg/m^2, 1/week, 3 cycles	P1,3
Danfeng X (53)	2017	Bev_DDP: 41 DDP:41	47/35	58.21±3.25/ 58.96±3.43	Un	Un	Bev 5mg/kg, DDP 60mg: 1/week, 3 cycles DDP: 60mg, 1/week, 3 cycles	P1,3
Bin H (54)	2016	Bev_DDP: 37 DDP:36	53/20	60.28±6.17/ 61.31±6.05	Moderate to large	>70	Bev 5mg/kg, DDP 40mg: 1/week, 3 cycles DDP: 40mg, 1/week, 3 cycles	P1,2,3
Tiejun C (55)	2016	Bev_DDP: 24 DDP:24	31/17	54.6±7.7	Moderate to large	Un	Bev 300mg, DDP 60mg: 1/2 weeks, 1 cycle DDP: 60mg, 1/2 weeks, 1 cycle	P1,3
Maoyu W (56)	2015	NDP: 24 DDP:24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m^2,1/week, 3-4 cycles DDP: 40mg/m^2,1/week, 3-4 cycles	P1,2,3
Shu Z (57)	2022	NDP: 40 DDP:40	48/32	56.78±8.92/ 57.18±9.12	Un	Un	NDP: 40mg/m^2,1/week, 4 cycles DDP: 40mg/m^2,1/week, 4 cycles	P1,3

Jiajia B (58)	2019	NDP: 30 DDP:28	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m^2,1/week, 2-3 cycles DDP: 40mg/m^2,1/week, 2-3 cycles	P1,3
Xiaodong C (59)	2016	NDP: 39 DDP:40	43/36	55.8±8.1/ 58.2±7.3	Large	≥60	NDP: 40mg/m^2,1/week, 2-4 cycles DDP: 40mg/m^2,1/week, 2-4 cycles	P1,3,4
Qiurong H (60)	2017	LBP: 38 DDP:38	41/35	54±7/ 54±7	Un	Un	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Zhihong S (61)	2014	LBP: 30 DDP:30	20/40	38-74	Moderate to large	≥60	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Weiyan G (62)	2019	LBP: 30 DDP:31	37/24	57-69/54-68	Moderate to large	≥60	LBP: 30mg/m^2,1/week, 2-4 cycles DDP: 40mg/m^2,1/week, 2-4 cycles	P1,2,3

M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quality of life (QOL); P3: treatment-related adverse events (TRAEs); P4: survivals.

Table 2 Rank probabilities of each treatment for different outcome measures based on the network meta-analysis

	BEV_DDP	DDP	Endo_DDP	Endo_LBP	Endo_NDP	LBP	NDP
ORR	0.33	0.00002	0.46	0.95	0.88	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83	0.30	0.41
QOL	0.33	0.10	0.69	0.95	/	0.63	0.29
Gastrointestinal effect	0.32	0.28	0.18	0.47	0.56	0.80	0.89
Myelosuppressive	0.63	0.64	0.58	0.40	0.19	0.59	0.47
Hypohepatia	0.55	0.46	0.35	0.57	0.30	0.65	0.62
G3-gastrointestinal effect	0.40	0.35	0.19	/	0.54	0.71	0.81
G3-myelosuppression	0.39	0.48	0.37	/	0.32	0.64	0.81
G3-hypohepatia	0.21	0.30	0.72	/	0.45	0.57	0.74

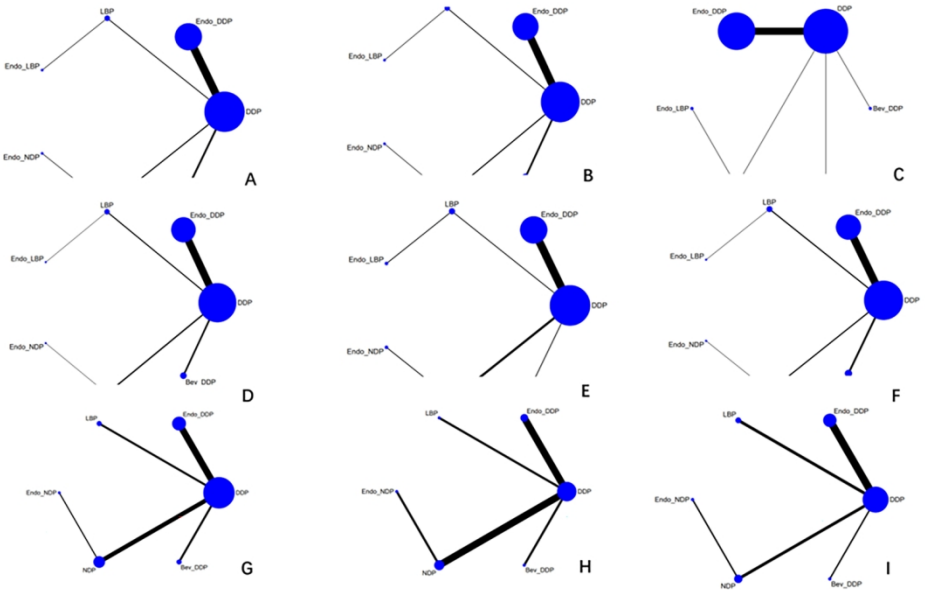
Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate, DCR: Disease control rate, QOL: quality of life, G3: grade 3 or higher.
The data are listed as SUCRA values (rank) and higher SUCRA values indicate better outcomes.

Figure legends

Fig 1 Network graph for different outcomes.

Fig 2 Sequence diagram of the network meta-analysis.

Fig 3 Funnel plots.



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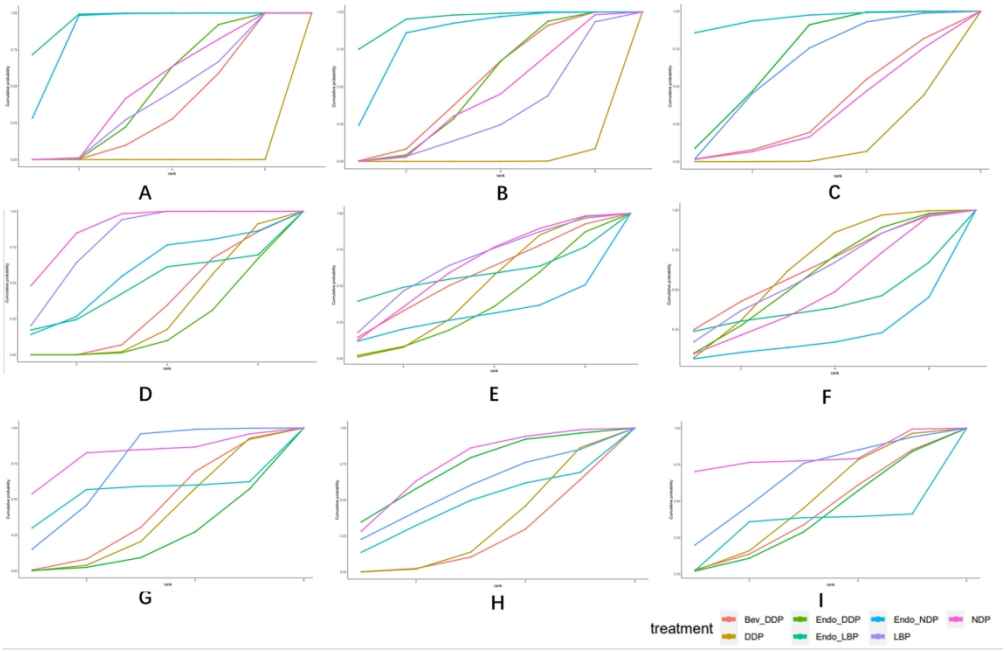

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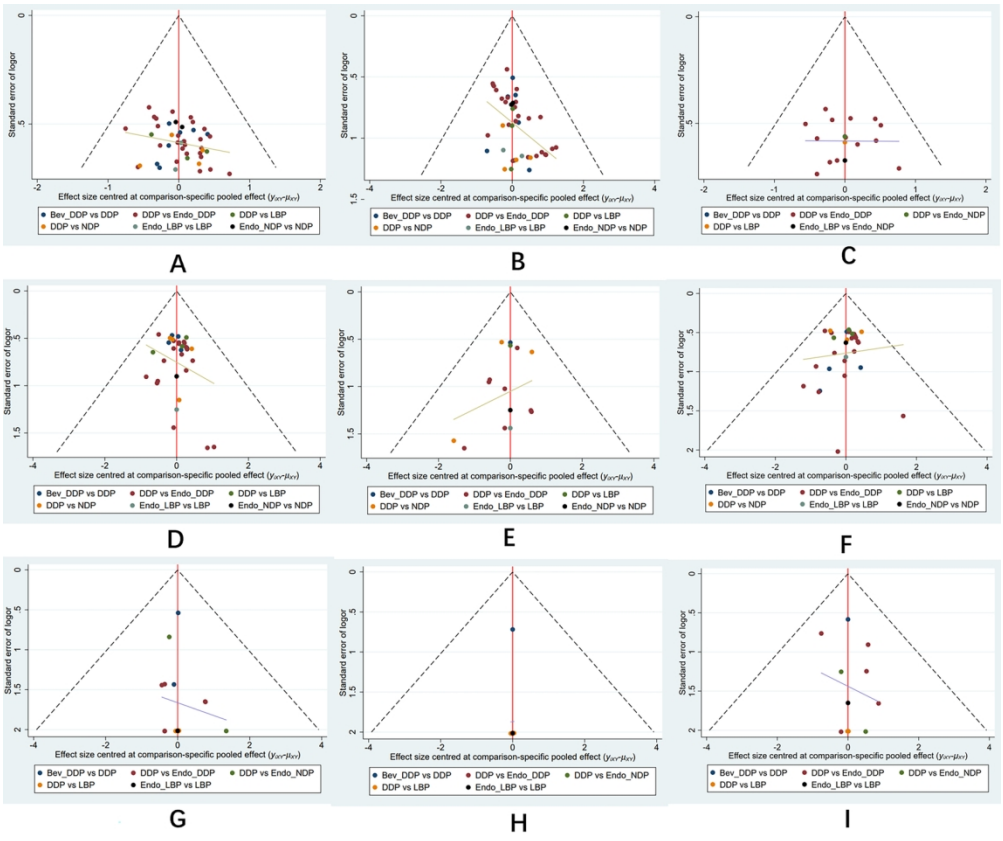


149x124mm (300 x 300 DPI)

Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

Supplementary Materials

Table of Contents

Table S1 PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4,5

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4,5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4,5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4,5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	5

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6-8, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6-8
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Fig. S1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6-8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6-8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6-8

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6-8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	6-8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6-8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6-8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9,10
	23b	Discuss any limitations of the evidence included in the review.	9,10
	23c	Discuss any limitations of the review processes used.	9,10
	23d	Discuss implications of the results for practice, policy, and future research.	9,10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	18
Competing interests	26	Declare any competing interests of review authors.	18

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in this review.	18

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S2 Literature Search Strategy

Database and Search strategy	5670
CNKI	
(主题=肺癌 + 肺恶性肿瘤 + 原发性支气管癌 + 支气管癌) AND (主题=恶性胸腔积液 + 恶性胸腔积液 + 癌性胸水 + 癌性胸腔积液 + 恶性胸膜腔积液 + 恶性胸水 + 恶性胸腹水 + 恶性胸腹水 + 恶性胸腔液) AND (主题=贝伐珠单抗 + 恩度 + 重组人血管内皮抑制素 + 化疗 + 化学疗法 + 化学药物治疗 + 化学治疗)	602
CQVIP	
(((((题名或关键词=肺癌 OR 题名或关键词=肺恶性肿瘤) OR 题名或关键词=原发性支气管癌) OR 题名或关键词=支气管癌) AND ((((((题名或关键词=恶性胸腔积液 OR 题名或关键词=癌性胸水) OR 题名或关键词=癌性胸腔积液) OR 题名或关键词=恶性胸腔积液) OR 题名或关键词=恶性胸水) OR 题名或关键词=恶性胸腹水) OR 题名或关键词=恶性胸腔液)) AND ((((((题名或关键词=贝伐珠单抗 OR 题名或关键词=恩度) OR 题名或关键词=重组人血管内皮抑制素) OR 题名或关键词=化疗) OR 题名或关键词=化学疗法) OR 题名或关键词=化学药物治疗) OR 题名或关键词=化学治疗))	283
Wanfang	
主题:(肺癌 OR 肺恶性肿瘤 OR 原发性支气管癌 OR 支气管癌) and 主题:(恶性胸腔积液 OR 癌性胸水 OR 癌性胸腔积液 OR 恶性胸膜腔积液 OR 恶性胸水 OR 恶性胸腹水 OR 恶性胸腔液) and 主题:(贝伐珠单抗 OR 恩度 OR 重组人血管内皮抑制素 OR 化疗 OR 化学疗法 OR 化学药物治疗 OR 化学治疗)	1538
PubMed	
((((("Drug Therapy"[Mesh]) OR (((((((Drug Therapy[Title/Abstract]) OR (Therapy, Drug[Title/Abstract])) OR (Drug Therapies[Title/Abstract])) OR (Therapies, Drug[Title/Abstract])) OR (Chemotherapy[Title/Abstract])) OR (Chemotherapies[Title/Abstract])) OR (Pharmacotherapy[Title/Abstract])) OR (Pharmacotherapies[Title/Abstract]))) OR (("Bevacizumab"[Mesh]) OR (((((((((Bevacizumab[Title/Abstract]) OR (Mvasi[Title/Abstract])) OR (Bevacizumab-awwb[Title/Abstract])) OR (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) OR (Endostar[Title/Abstract])) OR (recombinant human endostatin[Title/Abstract])) OR (Rh endostatin[Title/Abstract])) OR (yh-16[Title/Abstract])))) AND (("Lung Neoplasms"[Mesh])	495

OR ((((((((((((((((Lung Neoplasms[Title/Abstract]) OR (Pulmonary Neoplasms[Title/Abstract])) OR (Neoplasms, Lung[Title/Abstract])) OR (Lung Neoplasm[Title/Abstract])) OR (Neoplasm, Lung[Title/Abstract])) OR (Neoplasms, Pulmonary[Title/Abstract])) OR (Neoplasm, Pulmonary[Title/Abstract])) OR (Pulmonary Neoplasm[Title/Abstract])) OR (Lung Cancer[Title/Abstract])) OR (Cancer, Lung[Title/Abstract])) OR (Cancers, Lung[Title/Abstract])) OR (Lung Cancers[Title/Abstract])) OR (Pulmonary Cancer[Title/Abstract])) OR (Cancer, Pulmonary[Title/Abstract])) OR (Cancers, Pulmonary[Title/Abstract])) OR (Pulmonary Cancers[Title/Abstract])) OR (Cancer of the Lung[Title/Abstract])) OR (Cancer of Lung[Title/Abstract]))))) AND (("Pleural Effusion, Malignant"[Mesh]) OR ((((((Pleural Effusion, Malignant[Title/Abstract]) OR (Malignant Pleural Effusion[Title/Abstract])) OR (Effusion, Malignant Pleural[Title/Abstract])) OR (Effusions, Malignant Pleural[Title/Abstract])) OR (Malignant Pleural Effusions[Title/Abstract])) OR (Pleural Effusions, Malignant[Title/Abstract]))))	
Embase		
#1	'lung tumor'/exp	727
#2	'lung tumor':ab,ti	
#3	'pulmonary neoplasms':ab,ti	
#4	'neoplasms, lung':ab,ti	
#5	'lung neoplasm':ab,ti	
#6	'neoplasm, lung':ab,ti	
#7	'neoplasms, pulmonary':ab,ti	
#8	'neoplasm, pulmonary':ab,ti	
#9	'pulmonary neoplasm':ab,ti	

#10	'lung cancer':ab,ti	
#11	'cancer, lung':ab,ti	
#12	'cancers, lung':ab,ti	
#13	'lung cancers':ab,ti	
#14	'pulmonary cancer':ab,ti	
#15	'cancer, pulmonary':ab,ti	
#16	'cancers, pulmonary':ab,ti	
#17	'pulmonary cancers':ab,ti	
#18	'cancer of the lung':ab,ti	
#19	'cancer of lung':ab,ti	
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	
#21	'malignant pleura effusion'/exp	
#22	'malignant pleura effusion':ab,ti	
#23	'effusion, malignant pleural':ab,ti	

#24	'effusions, malignant pleural':ab,ti	
#25	'malignant pleural effusions':ab,ti	
#26	'pleural effusions, malignant':ab,ti	
#27	'pleural effusion, malignant':ab,ti	
#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	
#29	'bevacizumab'/exp	
#30	'bevacizumab':ab,ti	
#31	'mvasi':ab,ti	
#32	'bevacizumab-awwb':ab,ti	
#33	'bevacizumab awwb':ab,ti	
#34	'avastin':ab,ti	
#35	'endostar':ab,ti	
#36	'recombinant human endostatin':ab,ti	
#37	'rh endostatin':ab,ti	

#38	'yh-16':ab,ti	
#39	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	
#40	'drug therapy'/exp	
#41	'drug therapy':ab,ti	
#42	'therapy, drug':ab,ti	
#43	'drug therapies':ab,ti	
#44	'therapies, drug':ab,ti	
#45	'chemotherapy':ab,ti	
#46	'chemotherapies':ab,ti	
#47	'pharmacotherapy':ab,ti	
#48	'pharmacotherapies':ab,ti	
#49	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	
#50	#39 OR #49	
#51	#20 AND #28 AND #50	

Cochrane		
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	206
#2	(Lung Neoplasms):ti,ab,kw OR (Pulmonary Neoplasms):ti,ab,kw OR (Neoplasms, Lung):ti,ab,kw OR (Pulmonary Neoplasm):ti,ab,kw OR (Neoplasm, Lung):ti,ab,kw	
#3	(Neoplasms, Pulmonary):ti,ab,kw OR (Neoplasm, Pulmonary):ti,ab,kw OR (Pulmonary Neoplasm):ti,ab,kw OR (Lung Cancer):ti,ab,kw OR (Cancer, Lung):ti,ab,kw	
#4	(Cancers, Lung):ti,ab,kw OR (Lung Cancers):ti,ab,kw OR (Pulmonary Cancer):ti,ab,kw OR (Cancer, Pulmonary):ti,ab,kw OR (Cancers, Pulmonary):ti,ab,kw	
#5	(Pulmonary Cancers):ti,ab,kw OR (Cancer of the Lung):ti,ab,kw OR (Cancer of Lung):ti,ab,kw	
#6	#1 or #2 or #3 or #4 or #5	
#7	MeSH descriptor: [Pleural Effusion, Malignant] explode all trees	
#8	(Pleural Effusion, Malignant):ti,ab,kw OR (Malignant Pleural Effusion):ti,ab,kw OR (Effusion, Malignant Pleural):ti,ab,kw OR (Effusions, Malignant Pleural):ti,ab,kw OR (Malignant Pleural Effusions):ti,ab,kw 725 #9 (Pleural Effusions, Malignant):ti,ab,kw	
#9	(Pleural Effusions, Malignant):ti,ab,kw	
#10	#7 or #8 or #9	
#11	MeSH descriptor: [Bevacizumab] explode all trees	
#12	(Bevacizumab):ti,ab,kw OR (Mvasi):ti,ab,kw OR (Bevacizumab-awwb):ti,ab,kw OR (Bevacizumab awwb):ti,ab,kw OR (Avastin):ti,ab,kw 7448 #13 (Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#13	(Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#14	#11 or #12 or #13	
#15	MeSH descriptor: [Drug Therapy] explode all trees	
#16	(Drug Therapy):ti,ab,kw OR (Therapy, Drug):ti,ab,kw OR (Drug Therapies):ti,ab,kw OR (Therapies, Drug):ti,ab,kw OR (Chemotherapy):ti,ab,kw	

#17	(Chemotherapies):ti,ab,kw OR (Pharmacotherapy):ti,ab,kw OR (Pharmacotherapies):ti,ab,kw	
#18	#15 or #16 or #17	
#19	#14 or #18	
#20	#19 and #6 and #10	
Web of science		
#1	TS=(Lung Neoplasms) OR TS=(Pulmonary Neoplasms) OR TS=(Neoplasms, Lung) OR TS=(Lung Neoplasm) OR TS=(Neoplasm, Lung) OR TS=(Neoplasms, Pulmonary) OR TS=(Neoplasm, Pulmonary) OR TS=(Pulmonary Neoplasm) OR TS=(Lung Cancer) OR TS=(Cancer, Lung) OR TS=(Cancers, Lung) OR TS=(Lung Cancers) OR TS=(Pulmonary Cancer) OR TS=(Cancer, Pulmonary) OR TS=(Cancers, Pulmonary) OR TS=(Pulmonary Cancers) OR TS=(Cancer of the Lung) OR TS=(Cancer of Lung) and 预印本 (排除 – 数据库)	1819
#2	TS=(Pleural Effusion, Malignant) OR TS=(Malignant Pleural Effusion) OR TS=(Effusion, Malignant Pleural) OR TS=(Effusions, Malignant Pleural) OR TS=(Malignant Pleural Effusions) OR TS=(Pleural Effusions, Malignant) and 预印本 (排除 – 数据库)	
#3	TS=(Bevacizumab) OR TS=(Mvasi) OR TS=(Bevacizumab-awwb) OR TS=(Bevacizumab awwb) OR TS=(Avastin) OR TS=(Endostar) OR TS=(recombinant human endostatin) OR TS=(Rh endostatin) OR TS=(yh-16) and 预印本 (排除 – 数据库)	
#4	TS=(Drug Therapy) OR TS=(Therapy, Drug) OR TS=(Drug Therapies) OR TS=(Therapies, Drug) OR TS=(Chemotherapy) OR TS=(Chemotherapies) OR TS=(Pharmacotherapy) OR TS=(Pharmacotherapies) and 预印本 (排除 – 数据库)	
#5	#4 OR #3 and 预印本 (排除 – 数据库)	
#6	#5 AND #2 AND #1 and 预印本 (排除 – 数据库)	

Table S3 The league table of network meta-analysis for ORR according to all interventions.

OR 95%CI						
Bev_DDP						
3.19 (2.11, 4.92)*	DDP					
0.85 (0.53, 1.37)	0.27 (0.22, 0.33)*	Endo_DDP				
0.16 (0.05, 0.53)*	0.05 (0.02, 0.15)*	0.19 (0.06, 0.59)*	Endo_LBP			
0.25 (0.09, 0.68)*	0.08 (0.03, 0.2)*	0.29 (0.11, 0.75)*	1.54 (0.35, 6.84)	Endo_NDP		
0.92 (0.4, 2.03)	0.29 (0.14, 0.56)*	1.08 (0.52, 2.18)	5.69 (2.37, 14.65)*	3.73 (1.17, 12.04)*	LBP	
0.81 (0.38, 1.71)	0.25 (0.13, 0.46)*	0.95 (0.49, 1.81)	5.06 (1.39, 19.02)*	3.28 (1.65, 6.76)*	0.88 (0.35, 2.24)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate.

Table S4 The league table of network meta-analysis for DCR according to all interventions.

OR 95%CI						
Bev_DDP						
3.51 (2.03, 6.28)*	DDP					
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP				
0.15 (0.01, 1.03)	0.04 (0, 0.27)*	0.15 (0.02, 0.93)*	Endo_LBP			
0.36 (0.07, 1.73)	0.1 (0.02, 0.44)*	0.35 (0.07, 1.54)	2.37 (0.21, 33.93)	Endo_NDP		
1.59 (0.46, 5.15)	0.45 (0.15, 1.26)	1.54 (0.48, 4.47)	9.99 (2.38, 76.59)*	4.39 (0.7, 28.93)	LBP	
1.18 (0.32, 3.88)	0.34 (0.1, 0.95)*	1.14 (0.33, 3.36)	7.62 (0.87, 91.12)	3.21 (1.22, 9.55)*	0.74 (0.16, 3.45)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP:

Bevacizumab + cisplatin, DCR: Disease control rate.

Table S5 The league table of network meta-analysis for QOL according to all interventions.

OR 95%CI						
Bev_DDP						
1.56 (0.52, 4.94)	DDP					
0.47 (0.15, 1.52)	0.3 (0.22, 0.39)*	Endo_DDP				
0.16 (0.02, 1.26)	0.1 (0.02, 0.57)*	0.34 (0.05, 1.95)	Endo_LBP			
0.49 (0.1, 2.39)	0.31 (0.1, 0.93)*	1.05 (0.31, 3.25)	3.06 (0.82, 12.66)	LBP		
1.09 (0.21, 5.56)	0.7 (0.21, 2.22)	2.35 (0.69, 7.75)	6.93 (0.85, 60.14)	2.25 (0.45, 11.58)	NDP	

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, QOL: quality of life.

Table S6 League tables of all grades myelosuppressive event comparison of all interventions.

OR 95%CI						
Bev_DDP						
0.99 (0.55, 1.76)	DDP					
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP				
0.68 (0.1, 4.32)	0.69 (0.11, 4.01)	0.71 (0.11, 4.25)	Endo_LBP			
0.46 (0.1, 2.05)	0.47 (0.11, 1.84)	0.49 (0.11, 1.98)	0.68 (0.07, 6.89)	Endo_NDP		
0.96 (0.42, 2.18)	0.98 (0.54, 1.74)	1.01 (0.53, 1.94)	1.42 (0.27, 8.33)	2.08 (0.47, 9.88)	LBP	
0.85 (0.37, 1.93)	0.86 (0.48, 1.54)	0.89 (0.46, 1.71)	1.25 (0.2, 8.81)	1.83 (0.53, 6.94)	0.88 (0.39, 2.02)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S7 League tables of all grades gastrointestinal effect event comparison of all interventions.

OR 95%CI						
Bev_DDP						
0.93 (0.58, 1.49)	DDP					
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP				
1.58 (0.04, 24.01)	1.7 (0.05, 24.68)	1.86 (0.05, 27.49)	Endo_LBP			
2.15 (0.22, 15.02)	2.31 (0.25, 15.24)	2.52 (0.27, 17.04)	1.37 (0.04, 70.76)	Endo_NDP		
4 (1.82, 8.94)*	4.29 (2.3, 8.26)*	4.69 (2.36, 9.59)*	2.52 (0.19, 83.76)	1.87 (0.25, 18.75)	LBP	
5.01 (2.37, 10.84)*	5.39 (3.02, 9.89)*	5.89 (3.07, 11.51)*	3.19 (0.2, 113.19)	2.32 (0.39, 20.25)	1.26 (0.53, 2.99)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S8 League tables of all grades hypohepatia e event comparison of all interventions.

OR 95%CI						
Bev_DDP						
0.86 (0.29, 2.5)	DDP					
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP				
1.2 (0.02, 64.26)	1.39 (0.03, 65.71)	1.63 (0.03, 80.3)	Endo_LBP			
0.43 (0.01, 8)	0.5 (0.01, 7.53)	0.58 (0.02, 9.69)	0.34 (0, 38.81)	Endo_NDP		
1.2 (0.25, 5.83)	1.39 (0.45, 4.41)	1.62 (0.44, 6.12)	1 (0.03, 40.32)	2.82 (0.14, 112.79)	LBP	
1.09 (0.29, 4.08)	1.26 (0.58, 2.74)	1.47 (0.54, 4.05)	0.91 (0.02, 45.55)	2.5 (0.18, 81.39)	0.91 (0.22, 3.56)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S9 League tables of G3-myelosuppressive event comparison of all interventions.

OR 95%CI					
Bev_DDP					
1.19 (0.37, 3.93)	DDP				
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP			
0.02 (0, 1158726093196.45)	0.02 (0, 946584795528.83)	0.02 (0, 1200464612598)	Endo_NDP		
3.03 (0.17, 114.1)	2.48 (0.19, 79.56)	3.18 (0.2, 112.91)	179.3 (0, 1315890418292750)	LBP	
2806.8 (0, 7080696058054300)	2358.54 (0, 5857536555380624)	3012.84 (0, 7540937082788929)	86977.28 (0.72, 28713088892365632)	877.08 (0, 2259231168436329)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S10 League tables of G3-gastrointestinal effect event comparison of all interventions.

OR 95%CI			
Bev_DDP			
0.87 (0.32, 2.38)	DDP		
0.43 (0.05, 3.16)	0.5 (0.06, 2.74)	Endo_DDP	
146.72 (0, 2.25957982568521e+21)	170.13 (0, 2.60852595759042e+21)	346.11 (0, 5.58712188787727e+21)	Endo_NDP

4.96 (0.76, 48.98)	5.6 (1.18, 45.11)*	11.87 (1.1, 198.58)*	0.04 (0, 138950642090604784)	LBP	
97135.18 (0, 1.05993280385622e+20)	110659.48 (0, 1.25474480157232e+20)	230346.59 (0, 2.61196338258981e+20)	1349.63 (0, 1822912067429389107200)	18857.28 (0, 21936173709446430720)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S11 League tables of G3-hypohepatia event comparison of all interventions.

		OR 95%CI			
Bev_DDP					
1.36 (0.33, 5.91)	DDP				
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP			
3.64 (0, 4662.71)	2.67 (0, 2952.95)	0.17 (0, 561.64)	Endo_NDP		
7.15 (0.05, 3005.42)	5.2 (0.05, 1901.09)	0.37 (0, 382.55)	2.15 (0, 16410.56)	LBP	
18.95 (0.38, 4882.5)	13.51 (0.37, 3023.28)	1.03 (0, 666.32)	5.38 (0.05, 2025.4)	2.79 (0, 3102.18)	NDP

*p<0.05

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Figure S1 The flow diagram of the study selection process for the network meta-analysis.

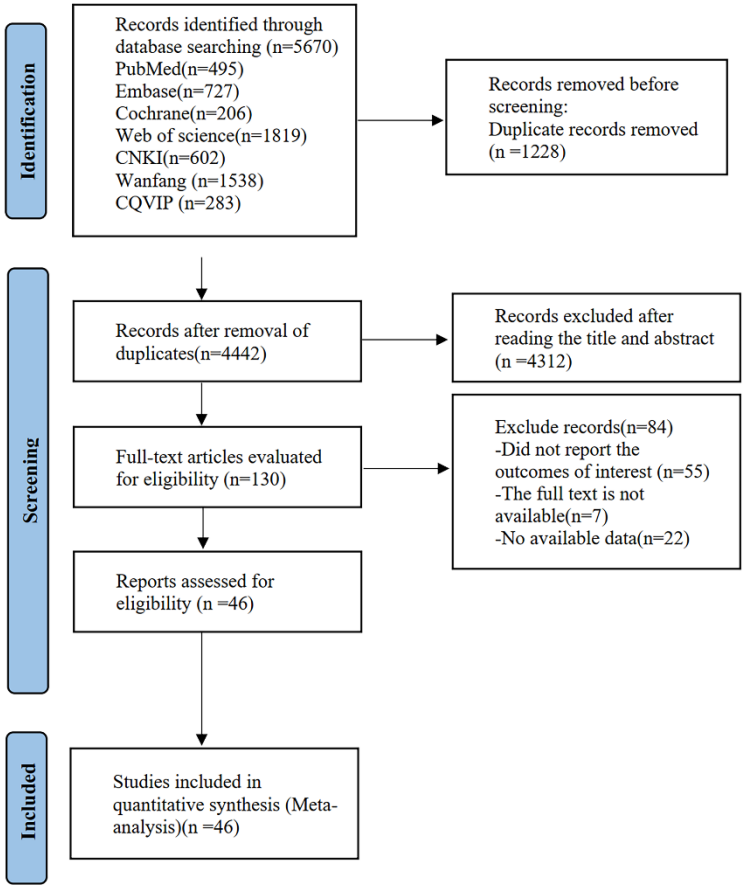
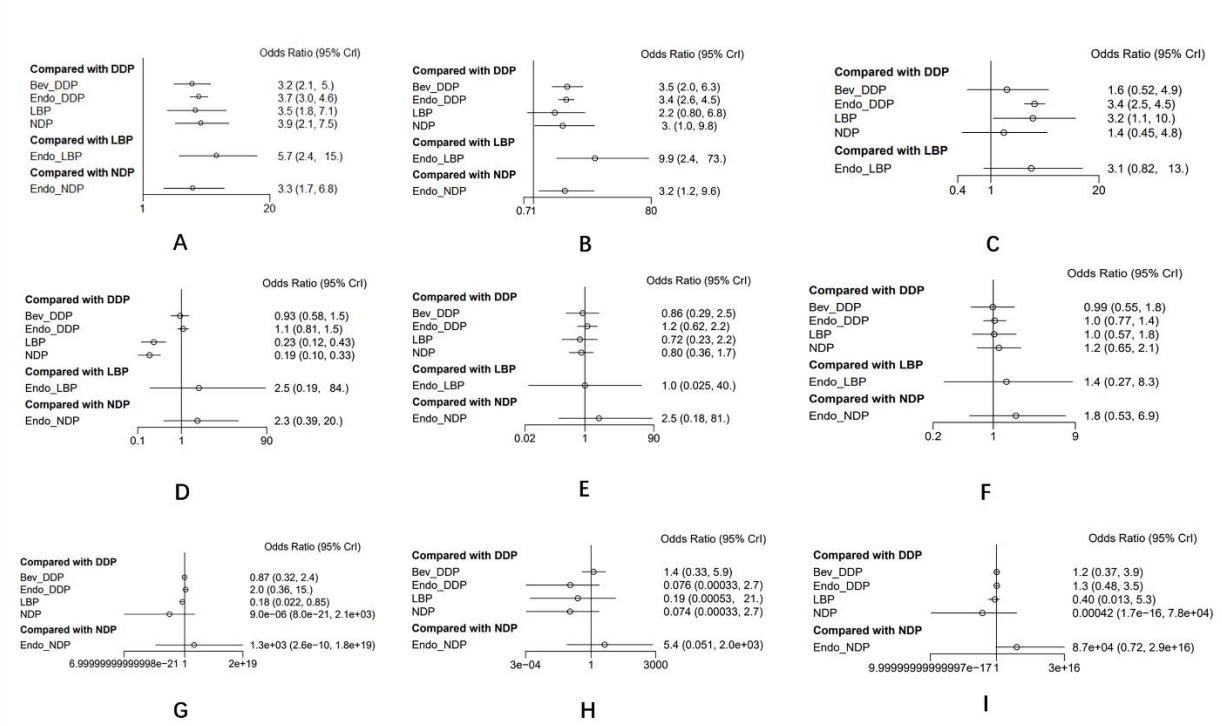


Figure S2 Forest plots of efficacy outcomes by Bayesian framework.



(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive.

ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG,any-grade; G3,grade 3 or higher, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Figure S3 Assessment of risk of bias

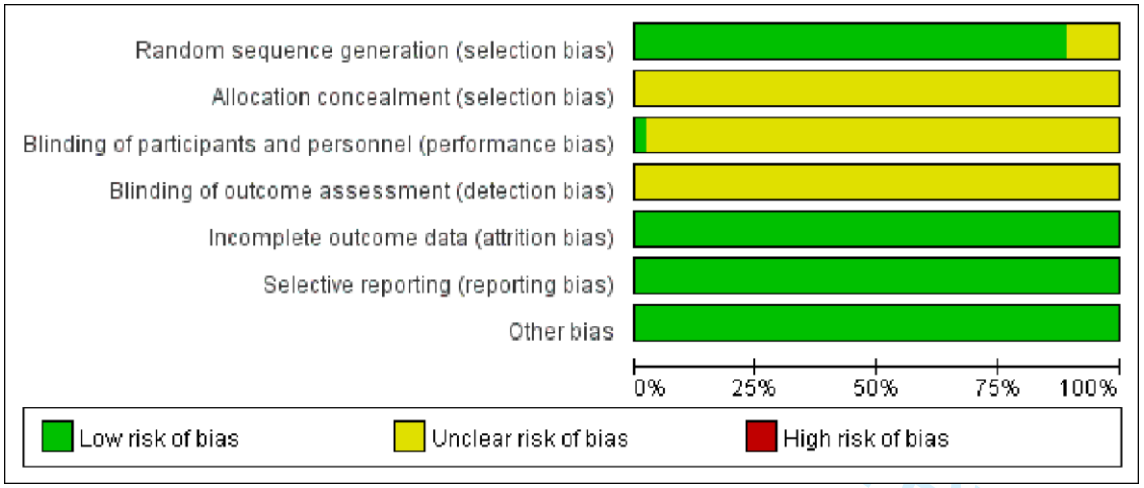


Figure S4 Bias risk summary of the included studies.

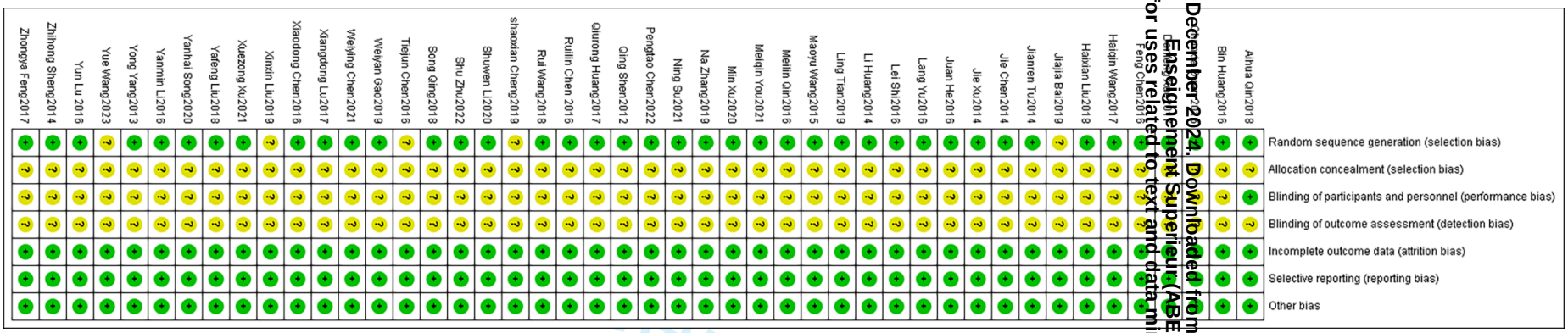
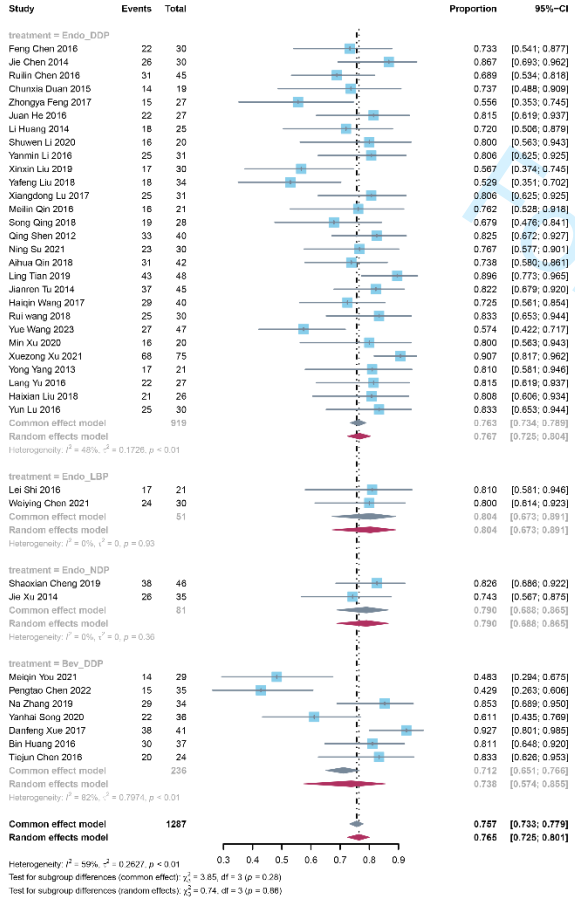


Figure S5 Single-arm meta-analysis of the ORR of patients intrapleural perfusion with antiangiogenic agents plus chemical agents.



ORR, objective response rate; Endo_DDP: Endostar + cisplatin; Endo_LBP: Endostar + lobaplatin; Endo_NDP: Endostar + nedaplatin; Bev_DDP: Bevacizumab + cisplatin.

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Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

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Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

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Abstract

Objectives: Different intrathoracic perfusion therapeutic regimens are available for non-small cell lung cancer (NSCLC) with malignant pleural effusion (MPE). Antiangiogenic agents are often used to control MPE, and the results are satisfactory. Here, we performed a network meta-analysis to reveal optimal combinations of antiangiogenic agents and chemical agents and assess their effectiveness and safety.

Design: Systematic review and network meta-analysis (NMA).

Data sources: PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database and Chinese National Knowledge Infrastructure were searched from inception to May 2023. Eligible studies were randomized controlled trials that reported on curative effect in MPE.

Data extraction and synthesis: The Cochrane Collaboration tool was used to assess risk of bias. The consistency was evaluated by examining the agreement between direct and indirect effects. NMA was performed and the ranking probabilities of being at each possible rank for each intervention were estimated. Comparison-adjusted funnel plots were obtained to assess publication bias.

Results: A total of 46 studies were included in the analysis. Among them, we included a total of 7 interventions. A total of 3026 patients participated in this analysis. According to the results of the network meta-analysis, some antiangiogenic agents combined with chemotherapy regimens improved objective response rate (ORR) and disease control rate (DCR) and quality of life (QOL). The rank probabilities suggested that in terms of ORR, DCR and QOL, Endostar plus lobaplatin was the first-ranked intervention.

Conclusion: Administration of antiangiogenic agents plus chemical agents significantly improved the clinical response and quality of life. In addition, Endostar plus lobaplatin was the most effective combination.

PROSPERO registration number:

CRD42021284786

Keywords: NSCLC · MPE · Antiangiogenic agents · Thoracic perfusion · Network meta-analysis

Strengths and limitations of this study

1.This study is the first network meta-analysis to determine the optimal combinations of antiangiogenic and chemical agents and assess their effectiveness and safety.

2.One advantage is our exclusive inclusion of randomized controlled trials, which significantly reduces potential confounding bias.

3. Another advantage is that the large number of studies and the considerable sample size, which enhance the statistical power of our analysis.

4. A limitation of our study is the absence of closed loops within the network, which prevents a formal assessment of inconsistency.

Introduction

Malignant pleural effusion (MPE) is the accumulation of exudative fluid in the pleural cavity as a result of malignancy; it is usually caused by malignant infiltration of the pleura and often results in dyspnea, chest tightness and shortness of breat[1]. According to Global Cancer Statistics released by GLOBOCAN in 2020, lung cancer is the leading cause of cancer deaths worldwide and accounts for the most common cause (approximately 35.6%) of MPE [2 3]. Studies have revealed that lung cancer combined with MPE has a worse prognosis than other malignant tumors, with a median survival of 3.3 months [4]. Traditional treatments for MPE include pleurodesis, indwelling pleural catheters and thoracic perfusion of chemotherapeutic agents [4]. Currently, with various antiangiogenic agents being approved for cancer treatment, antiangiogenic therapy for MPE has attracted increasing attention.

Vascular endothelial growth factor (VEGF), a proangiogenic factor, has a prominent role in tumor angiogenesis, host vascular endothelial cell activation, malignant proliferation and metastasis [5]. High expression levels of VEGF have been confirmed in the serum of patients with cancer and in malignant pleural effusions. Antiangiogenic agents (bevacizumab and Endostar) have been approved for MPE treatment, and the results are satisfactory.

Bevacizumab, a humanized monoclonal antibody with high binding affinity to VEGF, blocks VEGF signaling and decreases the formation of pleural effusion [6]. Endostar is a modified and recombinant human endostatin (Rh-endostatin). It is now a common angiogenesis antagonist and has been widely used in clinical practice to treat a wide range of tumors [7].

There have been several studies on the efficacy of intrapleural perfusion with antiangiogenic agents combined with chemotherapy in the treatment of malignant pleural effusion [8-11], but comparisons between multiple schemes are lacking, and the results are inconsistent. Network meta-analysis (NMA) allows for the comparison of multiple treatment regimens simultaneously, which is particularly valuable given the lack of direct head-to-head comparisons in the existing literature. Although some

meta-analyses exist on individual treatments, our NMA provides a comprehensive comparative effectiveness analysis across multiple regimens, offering a broader perspective on the optimal treatment strategy for MPE in NSCLC. Notably, there are no guidelines for the treatment of MPE; hence, we performed this systematic review and network meta-analysis to identify the optimal combination strategy to aid clinical decision-making.

Materials and methods

Registration and guidelines

The protocol of this systematic review and network meta-analysis has been registered in PROSPERO (CRD42021284786). The reporting of this network meta-analysis follows the Preferred Reporting Items for Systematic Reviews statement for Network Meta-analyses (PRISMA-NMA) (PRISMA NMA Checklist) [12] (Table S1).

Search strategy and eligibility criteria

We searched electronic databases, including PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database (CQVIP) and Chinese National Knowledge Infrastructure (CNKI), from inception to May 25, 2023, using the following keywords: "Endostar", "recombinant human endostatin", "Rh endostatin", "yh-16"; "Bevacizumab"; "Lung Neoplasms"; "Pleural Effusion, Malignant" and "Drug Therapy" (Table S2). In this search, there were no restrictions on the language or publication date. Publications were considered eligible based on the following criteria: 1) the study design was a randomized controlled trial (RCT); 2) the study participants were adult patients who had a clear histopathological diagnosis of NSCLC with pleural effusion; and 3) the included studies must compare at least two of the following treatments, including pleural perfusion of bevacizumab plus chemical agents, Endostar plus chemical agents or chemical agents alone. During treatment, no patients received systematic chemotherapy, chemoradiotherapy, hyperthermia, or

other traditional Chinese medicine injections; and 4) the studies included the objective response rate (ORR) and disease control rate (DCR). Furthermore, nonclinical controlled trials, literature reviews, duplicate publications, case reports, animal research papers, conference abstracts, systematic reviews and meta-analyses, and studies with insufficient information for data extraction were excluded. Title and abstract screening and full-text screening were conducted independently and in duplicate by two reviewers. Discrepancies were resolved through discussion with a third reviewer.

Types of Outcomes

Outcomes included the ORR, DCR, quality of life (QOL), and adverse reaction rate. The included articles were required to have ORR and DCR outcomes. Referring to previous evaluation criteria [13], we integrated the clinical response criteria as follows: (1) a complete response (CR) occurred when effusion disappeared for more than four weeks; (2) a partial response (PR) occurred when effusion was reduced >50% for more than four weeks; (iii) stable disease (SD) was defined as reduced effusion <50% or increased effusion <25%; and (4) progressive disease (PD) was effusion increased >25% along with other signs of progression or symptomatic reaccumulation of the fluid requiring repeat treatment. The ORR was defined as the ratio of the total number of patients experiencing CR and PR to the total number of patients. DCR was defined as the ratio of the total number of patients experiencing CR, PR, and SD to the total number of patients. QOL was measured by the Karnofsky performance score (KPS). Improved (KPS increased by more than 10 points) and stable (KPS changed by less than 10 points) levels were considered to indicate efficacy. The safety outcomes included adverse reactions, such as myelosuppression, hypohepatia and gastrointestinal effects (regardless of the severity (any grade or grade 3 or more)). The variations in dosing and scheduling across studies were minimal and consistent enough that we considered them unlikely to significantly influence the therapeutic effects. Thus, the same interventions with the different doses and

schedules were grouped together.

Data extraction and quality evaluation

The required data were independently extracted by two reviewers, and the quality assessment of the studies was performed afterward. For eligible studies, the following data were extracted: the first author, study year, proportion of males, mean age, treatment plan, volume of MPE, performance status, ORR, DCR, QOL, incidence of treatment-related adverse events (TRAEs) and grade 3 or higher treatment-related adverse events (≥grade 3 TRAEs) related to treatments. The risk of bias for each trial was assessed using the Cochrane risk of bias method [14], which includes random sequence generation, allocation concealment, blinding to allocated interventions, missing outcome data, selective outcome reporting, and other concerns. A study is classified as low risk only if all evaluated items are deemed low risk. Conversely, if any item is judged high risk, the study is classified as high risk. Studies with any item rated as unclear are classified accordingly. Each study was independently evaluated by two reviewers, and any discrepancies were resolved through discussion with a third reviewer.

Statistical analysis

The primary outcome of this study was the ORR. Secondary outcomes were DCR, QOL and TRAEs (including any grade (AG)-gastrointestinal effect, AG-hypohepatia, AG-myelosuppressive effects, grade 3 or higher (G3)-gastrointestinal effect, G3-hypohepatia, and G3-myelosuppressive effects). Stata 15.0 was used to graphically display the results. The network meta-analysis was performed using the "rjags" and "gemtc" packages in R version 4.2.3. We used non-informative uniform and normal prior distribution. A multiple treatments comparison was conducted by a Bayesian network framework with a Monte Carlo Markov Chain (MCMC) model. We employed the MCMC method to run 4 MCMC chains simultaneously, setting the number of simulations to 5000 and the number of iterations to 20000. The

convergence of the model was assessed by the Brooks-Gelman-Rubin diagnostic and visual inspection of trace plots. The results are shown as odds ratios (ORs) and 95% credible intervals (CrIs). Fixed and random effects models were considered and compared using the deviance information criterion (DIC). For each model, goodness-of-fit to data was evaluated using residual deviance [15].Heterogeneity was assessed using the 'getmc' package. Between-study variance (τ^2) Cochran's Q and I^2 statistic were calculated to quantify heterogeneity. Global and local inconsistencies were unable to be assessed because there were no closed loops in the network. All treatments were ranked according to the surface under the cumulative ranking area curve (SUCRA). Higher SUCRA probabilities indicated better treatment effects [16]. To determine if potential effect modifiers influence the outcomes, we conducted a meta-regression analysis. This analysis considered variables such as sample size (categorized into <50, ≥50 and <100, ≥100), mean age (<60 years, ≥60 years), and sex ratio (male/female <1, male/female ≥1) as potential covariates. Comparison-adjusted funnel plots were employed to assess publication bias. Statistical analyses of the pooled ORRs were performed using R version 4.2.3.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Literature search and study characteristics

We identified 5670 records from 7 electronic databases. After removing duplicates, 4442 titles and abstracts were reviewed, and 130 papers were selected for full-text screening. Finally, 46 studies were included in the network meta-analysis (Fig1, Table S3[17-62]). Studies were published between 2012 and 2023 and included a total of 3026 patients. The intrapleural administration therapeutic regimens included Endostar + nedaplatin (Endo + NDP), Endostar + DDP (Endo + DDP), Endostar + lobaplatin (Endo + LBP), Bevacizumab + DDP (Bev + DDP), DDP, nedaplatin (NDP) and lobaplatin (LBP). In particular, 32 studies compared Endostar plus chemical agents versus chemical agents alone, 7 studies compared bevacizumab plus chemical agents versus chemical agents alone, and 7 studies compared the effects of different chemical agents. The general characteristics of the included studies are presented in Table S3. The primary outcome of this study was the ORR. Secondary outcomes were DCR, QOL and TRAEs (including any grade (AG)-gastrointestinal effect, AG-hypohepatia, AG-myelosuppressive effects, grade 3 or higher (G3)-gastrointestinal effect, G3-hypohepatia, and G3-myelosuppressive effects). The analyses are presented separately for ORRs, DCRs, QOL, TRAEs and ≥ grade 3.

Quality Assessment

Fig 2 presents our risk of bias assessments for the studies. There were 41 RCTs among the 46 studies in the unclear risk of bias for random sequence generation. None of the studies reported the processes used for allocation concealment or blinding of outcome assessment; only 1 study mentioned the blinding of participants and personnel. The outcome data of all studies were complete, and no other sources of bias were reported.

NMA

All included studies with a total of 3026 patients reported the data of ORR. The

network of studies is presented in Fig S1. Bev+ DDP exhibited a significantly higher ORR than DDP alone, yet it was lower compared to the combinations of Endo+ LBP and Endo+ NDP. DDP alone showed a significantly lower ORR than all evaluated treatment regimens, including Endo+ DDP, Endo+ LBP, Endo+ NDP, LBP, and NDP. Furthermore, Endo+ DDP had a lower ORR compared to both Endo+ LBP and Endo+ NDP, whereas Endo+ LBP and Endo+ NDP each displayed significantly higher ORRs than either LBP or NDP alone (Fig S2; Table 1).

The SUCRA rank and probability value results indicated that Endo + LBP (95%) was the most likely to improve the ORR, followed by Endo + NDP (88%), NDP (48%), Endo + DDP (46%), LBP (40%), Bev + DDP (33%), and DDP (0.002%) (Fig S3; Table 2).

All included studies with a total of 3026 patients reported the data of DCR. The network of studies is presented in Fig S1. Bev+ DDP demonstrated a significantly higher DCR compared to DDP alone. DDP, in turn, exhibited a lower DCR relative to Endo+ DDP, Endo+ LBP, Endo+ NDP, and NDP alone. Among these, Endo+ DDP showed a significantly lower DCR than Endo+ LBP, which itself recorded a higher DCR than Endo+ NDP. Moreover, Endo+ NDP achieved a significantly higher DCR compared to NDP alone (Fig S2; Table S4). The DCR was ranked for all treatments by estimating the SUCRA value. The results were as follows: Endo + LBP (95%), Endo + NDP (83%), Bev + DDP (51%), Endo + DDP (49%), NDP (41%), LBP (30%), and DDP (1%) (Fig S3; Table 2).

Quality of Life

Nineteen studies reported the quality of life, which constituted five pairs of direct comparisons involving six interventions (Endo + DDP, Endo + LBP, Bev + DDP, DDP, NDP and LBP). The network diagram is shown in Fig S1. DDP was associated with a lower quality of life compared to Endo + DDP (OR = 0.3, 95% CI [0.22, 0.39]), Endo + LBP (OR = 0.1, 95% CI [0.02, 0.57]), and LBP (OR = 0.31, 95% CI [0.1, 0.93]) (Fig S2; Table S5).

After ranking the six interventions based on the SUCRA values, the results were as follows: Endo + LBP (95%), Endo + DDP (69%), LBP (63%), Bev + DDP (33%), NDP (29%), and DDP (10%), as shown in Fig S3 and Table 2.

Safety and toxicity

Thirty-two studies with a total of 2018 patients reported the data of safety profiles. Safety and toxicity were determined according to any-grade TRAEs and grade greater than or equal to 3 TRAEs. The adverse reactions mainly included myelosuppression, headache, hypohepatia, renal insufficiency, gastrointestinal effects, electrocardiographic abnormalities and fever. Among all types of adverse reactions, the most frequent occurrences were myelosuppressive, hypohepatia and gastrointestinal effects. The NMA included seven therapeutic regimens for TRAEs of any grade and six therapeutic regimens for TRAEs of grade greater than or equal to 3 (Fig S1). We did not find statistically significant differences in myelosuppression or hypohepatia. A single chemotherapeutic agent caused fewer gastrointestinal reactions (Table S6-S11).

The probabilities of adverse events were ranked for all treatments by estimating the SUCRA value. A lower SUCRA value indicated a higher probability of AEs and a poorer treatment regimen. The corresponding ranking of incidences is shown in Fig S3 and Table 2.

Meta-regression analysis

Table 3 showed the results of the meta-regression analysis for demographic and clinical variables (sample size, mean age and sex). Results indicated that one of these variables have significant impact on the ORR and DCR.

Publication bias

The comparison-adjusted funnel plots are presented in Fig S4. Overall, no distinct asymmetry was found in the comparison-adjusted funnel plot on the ORR, DCR,

QOL, AG-gastrointestinal effects, AG-myelosuppression, G3-myelosuppression and G3-hypohepatia, indicating no evidence of publication bias. However, the comparison-adjusted funnel plot on AG-gastrointestinal effects, G3-gastrointestinal effects and AG-hypohepatia were not symmetric around the zero line, which revealed that there could be small-study effects.

Discussion

Currently, to the best of our knowledge, intrapleural perfusion with antiangiogenic agents plus chemical agents in controlling MPE conferred satisfying clinical outcomes for patients with NSCLC. Although Endostar/bevacizumab combined with chemotherapy is widely used to treat malignant pleural effusion, there is a lack of head-to-head direct comparisons to determine the best regimen. Hence, we performed a network meta-analysis. In this analysis, two antiangiogenic agents and three chemical agents formed seven treatment regimens to identify which treatment was optimal in achieving higher clinical responses and QOL and fewer TRAEs. The results suggested the following:

1. Intrapleural administration of Endostar plus lobaplatin was associated with the best ORR and DCR outcomes, followed by Endostar plus nedaplatin.

2. For the ORR, Endo + LBP and Endo + NDP were significantly more favorable than Bev + DDP, while there were no significant differences in the efficacy of Endostar plus chemotherapy or bevacizumab plus chemotherapy with regard to DCR.

Endostar, an endogenous angiogenic inhibitor, can inhibit endothelial cell migration, repress the neovascularization of tumors, block the nutrient supply of tumor cells, and thus prevent tumor proliferation and metastasis. In addition, Endostar reduces the permeability of tumor neovascularization, thereby reducing the production of pleural effusion [63]. In 2022, Yimiao Xia et al. [8] performed a meta-analysis that included 55 RCTs with a total of 3379 patients with lung cancer to investigate the efficacy, safety and cost-effectiveness of Endostar and platinum in controlling MPE. All the studies in the meta-analysis were published in Chinese. This supported the findings in the current network meta-analysis.

Bevacizumab is another frequently studied antiangiogenic agent and plays an important role in the treatment of several types of tumors [7]. It can prevent VEGF-induced vascular permeability and tumor cell migration, thereby reducing MPE [64]. Several studies have demonstrated the efficacy and safety of bevacizumab for the management of MPE. Du et al. compared the efficacy of combined intrapleural

therapy with bevacizumab and cisplatin versus cisplatin alone in controlling MPE. The results revealed that bevacizumab plus cisplatin improved the ORR from 50 to 83.3%. However, in our meta-analysis, the pooled ORR of Bev + DDP was 73.8%, and the true efficacy of Bev might have been overestimated. After a literature search, we found no head-to-head comparison between Bev plus other chemical agents and the sole administration of chemical agents other than cisplatin. Therefore, more combination therapeutic regimens still need to be investigated in the future.

MPE is generally considered to be a manifestation of a malignancy in its preterminal stage. Hence, the interventions are palliative in nature. The main goal of treatment is to palliate symptoms and improve quality of life [65]. In our study, we found that intrapleural injection of Endostar combined with DDP was the best in terms of improving QOL, while DDP was the worst.

With regard to the safety profile, although there was no significant difference in the incidence of myelosuppression or hypohepatia between therapeutic regimens in our study, regardless of the severity, the incidence of AG-gastrointestinal effects was significantly more frequent with Endo + DDP and Bev + DDP than with LBP and NDP. Furthermore, in the gastrointestinal effect ranking of the six treatment groups, NDP was the safest, and Endostar plus DDP was the least safe (regardless of the severity (any grade or grade 3 or more)). The results of these analyses suggest that safety considerations may be needed when Endostar plus DDP is administered.

This study had some limitations. First, we utilized only Chinese and English databases, which might have led to retrieval bias, and most of the trials did not report concealment or blinding, which might undermine the validity of the overall findings. Second, all the included RCTs were published in China, and the generalizability of the results is limited. Third, all of the included studies are at unclear risk of bias, and many comparisons rely solely on indirect evidence, as there are no closed loops within the network. This can lead to potentially misleading SUCRA rankings. Therefore, SUCRA rankings should be interpreted with caution. Fourth, although we did not impose restrictions based on the indexing status of journals during the

literature search inclusion criteria, some of these journals are of low quality. The potential influence of journal quality on our results warrants cautious interpretation. Fifth, the absence of closed loops in the network precludes the formal assessment of inconsistency, which is a crucial aspect of NMA. Future studies should aim to include more diverse treatment comparisons to allow for a comprehensive inconsistency evaluation.

Conclusions

This network meta-analysis comprehensively compared various treatments for thoracic perfusion of MPE in NSCLC patients and described the QOL and toxicity features. To the best of our knowledge, this is the first comprehensive NMA study of its kind. The results showed that antiangiogenic agents combined with chemotherapy regimens could improve clinical effectiveness and quality of life. In our study, Endo+LBP was the most effective. However, high-quality randomized controlled trials with larger sample sizes are needed to further confirm the evidence.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

YX conducted overall design, data collection, analysis and draft writing. YYC and LMJ were responsible for data collection, partial analysis and partial draft writing. YNY, WS and XHZ were responsible for data collection, YYC and YX revised the manuscript. YX was responsible for the conduct of the study as a guarantor.

Data Availability statement:

Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Conflicts of interest: The authors declare no conflict of interest.

Ethical approval: Not applicable.

Consent for publication: Not applicable

Abbreviations

NSCLC	Non-small cell lung cancer
MPE	Malignant pleural effusion
VEGF	Vascular endothelial growth factor
Rh-endostatin	Recombinant human endostatin
CQVIP	VIP Database
CNKI	Chinese National Knowledge Infrastructure
RCT	Randomized controlled trial
ORR	Objective response rate
DCR	Disease control rate
QOL	Quality of life
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
KPS	Karnofsky performance score
TRAEs	Treatment-related adverse events
≥grade 3 TRAEs	Grade 3 or higher treatment-related adverse events
CrI	Credible intervals
SUCRA	Surface under the cumulative ranking area curve

CI	Confidence intervals
Endo + NDP	Endostar + nedaplatin
Endo + DDP	Endostar + cisplatin
Endo + LBP	Endostar + lobaplatin
Bev + DDP	Bevacizumab + cisplatin
NDP	Nedaplatin

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Table 1 The league table of network meta-analysis for ORR according to all interventions.

OR 95% CrIs						
Bev_DDP						
3.19 (2.11, 4.92)*	DDP					
0.85 (0.53, 1.37)	0.27 (0.22, 0.33)*	Endo_DDP				
0.16 (0.05, 0.53)*	**0.05 (0.02, 0.15)***	**0.19 (0.06, 0.59)***	Endo_LBP			
0.25 (0.09, 0.68)*	**0.08 (0.03, 0.2)***	**0.29 (0.11, 0.75)***	**1.54 (0.35, 6.84)**	Endo_NDP		
0.92 (0.4, 2.03)	0.29 (0.14, 0.56)*	**1.08 (0.52, 2.18)**	5.69 (2.37, 14.65)*	**3.73 (1.17, 12.04)***	LBP	
0.81 (0.38, 1.71)	0.25 (0.13, 0.46)*	**0.95 (0.49, 1.81)**	**5.06 (1.39, 19.02)***	3.28 (1.65, 6.76)*	**0.88 (0.35, 2.24)**	NDP

Abbreviation: *p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate.

Table 2 Rank probabilities of each treatment for different outcome measures based on the network meta-analysis

	BEV_DDP	**DDP**	**Endo_DDP**	**Endo_LBP**	**Endo_NDP**	**LBP**	**NDP**
ORR	0.33	0.00002	0.46	0.95	0.88	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83	0.30	0.41
QOL	0.33	0.10	0.69	0.95	/	0.63	0.29
Gastrointestinal effect	0.32	0.28	0.18	0.47	0.56	0.80	0.89
Myelosuppressive	0.63	0.64	0.58	0.40	0.19	0.59	0.47
Hypohepatia	0.55	0.46	0.35	0.57	0.30	0.65	0.62
G3-gastrointestinal effect	0.40	0.35	0.19	/	0.54	0.71	0.81
G3-myelosuppression	0.39	0.48	0.37	/	0.32	0.64	0.81
G3-hypohepatia	0.21	0.30	0.72	/	0.45	0.57	0.74

Abbreviation: Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate, DCR: Disease control rate, QOL: quality of life, G3: grade 3 or higher.
The data are listed as SUCRA values (rank) and higher SUCRA values indicate better outcomes.

Table 3 Meta-regression analysis for the impact of potential factors on the outcomes

	Overall response rate		Disease control rate	
	β coefficient (95%CI)	P value	β coefficient (95%CI)	P value
Sample size	-0.65 (-1.91, 0.62)	0.316	-0.73 (-2.47, 1.00)	0.408
Mean age	0.36 (-0.59, 1.31)	0.459	0.18 (-1.28, 1.64)	0.810
Sex	0.12 (-0.84, 1.08)	0.811	-1.26 (-2.72, 0.20)	0.091

Abbreviation: 95%CI: 95% confidence interval.

Figure legends

Fig 1 The flow diagram of the study selection process for the network meta-analysis

Fig 2 Assessment of risk of bias.

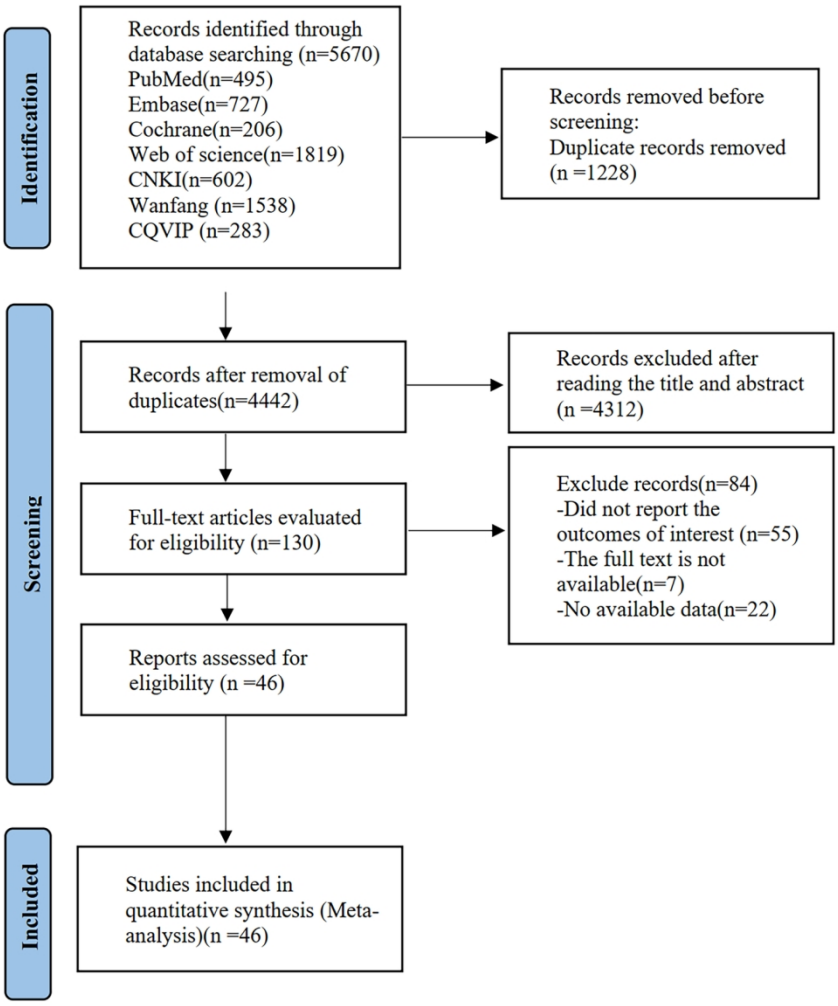

Fig 1

149x171mm (300 x 300 DPI)

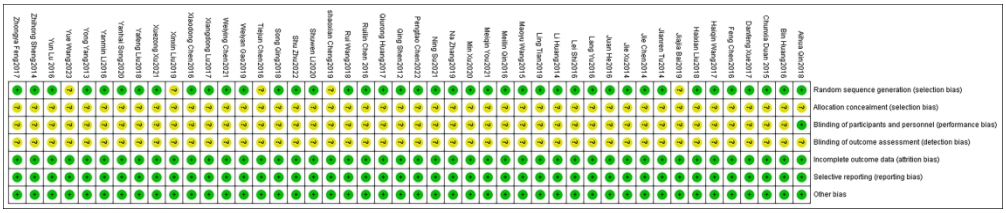

Fig 2

455x93mm (300 x 300 DPI)

Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

Supplementary Materials

Table of Contents

Table S1 PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3, 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5, 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7, 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7, 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8-9, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8-9
Study characteristics	17	Cite each included study and present its characteristics.	9, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9, Fig.2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-12

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	12-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	14

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S2 Literature Search Strategy

Database and Search strategy	5670
CNKI	
(主题=肺癌 + 肺恶性肿瘤 + 原发性支气管癌 + 支气管癌) AND (主题=恶性胸腔积液 + 恶性胸腔积液 + 癌性胸水 + 癌性胸腔积液 + 恶性胸膜腔积液 + 恶性胸水 + 恶性胸腹水 + 恶性胸腹水 + 恶性胸腔液) AND (主题=贝伐珠单抗 + 恩度 + 重组人血管内皮抑制素 + 化疗 + 化学疗法 + 化学药物治疗 + 化学治疗)	602
CQVIP	
(((((题名或关键词=肺癌 OR 题名或关键词=肺恶性肿瘤) OR 题名或关键词=原发性支气管癌) OR 题名或关键词=支气管癌) AND ((((((题名或关键词=恶性胸腔积液 OR 题名或关键词=癌性胸水) OR 题名或关键词=癌性胸腔积液) OR 题名或关键词=恶性胸腔积液) OR 题名或关键词=恶性胸水) OR 题名或关键词=恶性胸腹水) OR 题名或关键词=恶性胸腔液)) AND ((((((题名或关键词=贝伐珠单抗 OR 题名或关键词=恩度) OR 题名或关键词=重组人血管内皮抑制素) OR 题名或关键词=化疗) OR 题名或关键词=化学疗法) OR 题名或关键词=化学药物治疗) OR 题名或关键词=化学治疗))	283
Wanfang	
主题:(肺癌 OR 肺恶性肿瘤 OR 原发性支气管癌 OR 支气管癌) and 主题:(恶性胸腔积液 OR 癌性胸水 OR 癌性胸腔积液 OR 恶性胸膜腔积液 OR 恶性胸水 OR 恶性胸腹水 OR 恶性胸腔液) and 主题:(贝伐珠单抗 OR 恩度 OR 重组人血管内皮抑制素 OR 化疗 OR 化学疗法 OR 化学药物治疗 OR 化学治疗)	1538
PubMed	
((((("Drug Therapy"[Mesh]) OR (((((((Drug Therapy[Title/Abstract]) OR (Therapy, Drug[Title/Abstract])) OR (Drug Therapies[Title/Abstract])) OR (Therapies, Drug[Title/Abstract])) OR (Chemotherapy[Title/Abstract])) OR (Chemotherapies[Title/Abstract])) OR (Pharmacotherapy[Title/Abstract])) OR (Pharmacotherapies[Title/Abstract]))) OR (("Bevacizumab"[Mesh]) OR (((((((((Bevacizumab[Title/Abstract]) OR (Mvasi[Title/Abstract])) OR (Bevacizumab-awwb[Title/Abstract])) OR (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) OR (Endostar[Title/Abstract])) OR (recombinant human endostatin[Title/Abstract])) OR (Rh endostatin[Title/Abstract])) OR (yh-16[Title/Abstract])))) AND (("Lung Neoplasms"[Mesh])	495

OR ((((((((((((((((Lung Neoplasms[Title/Abstract]) OR (Pulmonary Neoplasms[Title/Abstract])) OR (Neoplasms, Lung[Title/Abstract])) OR (Lung Neoplasm[Title/Abstract])) OR (Neoplasm, Lung[Title/Abstract])) OR (Neoplasms, Pulmonary[Title/Abstract])) OR (Neoplasm, Pulmonary[Title/Abstract])) OR (Pulmonary Neoplasm[Title/Abstract])) OR (Lung Cancer[Title/Abstract])) OR (Cancer, Lung[Title/Abstract])) OR (Cancers, Lung[Title/Abstract])) OR (Lung Cancers[Title/Abstract])) OR (Pulmonary Cancer[Title/Abstract])) OR (Cancer, Pulmonary[Title/Abstract])) OR (Cancers, Pulmonary[Title/Abstract])) OR (Pulmonary Cancers[Title/Abstract])) OR (Cancer of Lung[Title/Abstract])) OR (Cancers of Lung[Title/Abstract])) OR (Cancer of Lung[Title/Abstract]))))) AND (("Pleural Effusion, Malignant"[Mesh]) OR ((((((Pleural Effusion, Malignant[Title/Abstract]) OR (Malignant Pleural Effusion[Title/Abstract])) OR (Effusion, Malignant Pleural[Title/Abstract])) OR (Effusions, Malignant Pleural[Title/Abstract])) OR (Malignant Pleural Effusions[Title/Abstract])) OR (Pleural Effusions, Malignant[Title/Abstract]))))		
Embase		
#1	'lung tumor'/exp	727
#2	'lung tumor':ab,ti	
#3	'pulmonary neoplasms':ab,ti	
#4	'neoplasms, lung':ab,ti	
#5	'lung neoplasm':ab,ti	
#6	'neoplasm, lung':ab,ti	
#7	'neoplasms, pulmonary':ab,ti	
#8	'neoplasm, pulmonary':ab,ti	
#9	'pulmonary neoplasm':ab,ti	

#10	'lung cancer':ab,ti	
#11	'cancer, lung':ab,ti	
#12	'cancers, lung':ab,ti	
#13	'lung cancers':ab,ti	
#14	'pulmonary cancer':ab,ti	
#15	'cancer, pulmonary':ab,ti	
#16	'cancers, pulmonary':ab,ti	
#17	'pulmonary cancers':ab,ti	
#18	'cancer of the lung':ab,ti	
#19	'cancer of lung':ab,ti	
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	
#21	'malignant pleura effusion'/exp	
#22	'malignant pleura effusion':ab,ti	
#23	'effusion, malignant pleural':ab,ti	

#24	'effusions, malignant pleural':ab,ti	
#25	'malignant pleural effusions':ab,ti	
#26	'pleural effusions, malignant':ab,ti	
#27	'pleural effusion, malignant':ab,ti	
#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	
#29	'bevacizumab'/exp	
#30	'bevacizumab':ab,ti	
#31	'mvasi':ab,ti	
#32	'bevacizumab-awwb':ab,ti	
#33	'bevacizumab awwb':ab,ti	
#34	'avastin':ab,ti	
#35	'endostar':ab,ti	
#36	'recombinant human endostatin':ab,ti	
#37	'rh endostatin':ab,ti	

#38	'yh-16':ab,ti	
#39	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	
#40	'drug therapy'/exp	
#41	'drug therapy':ab,ti	
#42	'therapy, drug':ab,ti	
#43	'drug therapies':ab,ti	
#44	'therapies, drug':ab,ti	
#45	'chemotherapy':ab,ti	
#46	'chemotherapies':ab,ti	
#47	'pharmacotherapy':ab,ti	
#48	'pharmacotherapies':ab,ti	
#49	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	
#50	#39 OR #49	
#51	#20 AND #28 AND #50	

Cochrane		
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	206
#2	(Lung Neoplasms):ti,ab,kw OR (Pulmonary Neoplasms):ti,ab,kw OR (Neoplasms, Lung):ti,ab,kw OR (Lung Neoplasm):ti,ab,kw OR (Neoplasm, Lung):ti,ab,kw	
#3	(Neoplasms, Pulmonary):ti,ab,kw OR (Neoplasm, Pulmonary):ti,ab,kw OR (Pulmonary Neoplasm):ti,ab,kw OR (Lung Cancer):ti,ab,kw OR (Cancer, Lung):ti,ab,kw	
#4	(Cancers, Lung):ti,ab,kw OR (Lung Cancers):ti,ab,kw OR (Pulmonary Cancer):ti,ab,kw OR (Cancer, Pulmonary):ti,ab,kw OR (Cancers, Pulmonary):ti,ab,kw	
#5	(Pulmonary Cancers):ti,ab,kw OR (Cancer of the Lung):ti,ab,kw OR (Cancer of Lung):ti,ab,kw	
#6	#1 or #2 or #3 or #4 or #5	
#7	MeSH descriptor: [Pleural Effusion, Malignant] explode all trees	
#8	(Pleural Effusion, Malignant):ti,ab,kw OR (Malignant Pleural Effusion):ti,ab,kw OR (Effusion, Malignant Pleural):ti,ab,kw OR (Effusions, Malignant Pleural):ti,ab,kw OR (Malignant Pleural Effusions):ti,ab,kw 725 #9 (Pleural Effusions, Malignant):ti,ab,kw	
#9	(Pleural Effusions, Malignant):ti,ab,kw	
#10	#7 or #8 or #9	
#11	MeSH descriptor: [Bevacizumab] explode all trees	
#12	(Bevacizumab):ti,ab,kw OR (Mvasi):ti,ab,kw OR (Bevacizumab-awwb):ti,ab,kw OR (Bevacizumab awwb):ti,ab,kw OR (Avastin):ti,ab,kw 7448 #13 (Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#13	(Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#14	#11 or #12 or #13	
#15	MeSH descriptor: [Drug Therapy] explode all trees	
#16	(Drug Therapy):ti,ab,kw OR (Therapy, Drug):ti,ab,kw OR (Drug Therapies):ti,ab,kw OR (Therapies, Drug):ti,ab,kw OR (Chemotherapy):ti,ab,kw	

#17	(Chemotherapies):ti,ab,kw OR (Pharmacotherapy):ti,ab,kw OR (Pharmacotherapies):ti,ab,kw	
#18	#15 or #16 or #17	
#19	#14 or #18	
#20	#19 and #6 and #10	
Web of science		
#1	TS=(Lung Neoplasms) OR TS=(Pulmonary Neoplasms) OR TS=(Neoplasms, Lung) OR TS=(Lung Neoplasm) OR TS=(Neoplasm, Lung) OR TS=(Neoplasms, Pulmonary) OR TS=(Neoplasm, Pulmonary) OR TS=(Pulmonary Neoplasm) OR TS=(Lung Cancer) OR TS=(Cancer, Lung) OR TS=(Cancers, Lung) OR TS=(Lung Cancers) OR TS=(Pulmonary Cancer) OR TS=(Cancer, Pulmonary) OR TS=(Cancers, Pulmonary) OR TS=(Pulmonary Cancers) OR TS=(Cancer of the Lung) OR TS=(Cancer of Lung) and 预印本 (排除 – 数据库)	1819
#2	TS=(Pleural Effusion, Malignant) OR TS=(Malignant Pleural Effusion) OR TS=(Effusion, Malignant Pleural) OR TS=(Effusions, Malignant Pleural) OR TS=(Malignant Pleural Effusions) OR TS=(Pleural Effusions, Malignant) and 预印本 (排除 – 数据库)	
#3	TS=(Bevacizumab) OR TS=(Mvasi) OR TS=(Bevacizumab-awwb) OR TS=(Bevacizumab awwb) OR TS=(Avastin) OR TS=(Endostar) OR TS=(recombinant human endostatin) OR TS=(Rh endostatin) OR TS=(yh-16) and 预印本 (排除 – 数据库)	
#4	TS=(Drug Therapy) OR TS=(Therapy, Drug) OR TS=(Drug Therapies) OR TS=(Therapies, Drug) OR TS=(Chemotherapy) OR TS=(Chemotherapies) OR TS=(Pharmacotherapy) OR TS=(Pharmacotherapies) and 预印本 (排除 – 数据库)	
#5	#4 OR #3 and 预印本 (排除 – 数据库)	
#6	#5 AND #2 AND #1 and 预印本 (排除 – 数据库)	

Table S3 Characteristics of the included randomized controlled trials.

Study	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Intervention	outcome
F. Chen et al. 2016 [17]	Endo_DDP:30 DDP:30	39/21	/	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,2,3
Chen et al. 2014[18]	Endo_DDP:30 DDP:30	44/16	54.3±5.6/ 55.6±4.5	NR	NR	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg: 2/week, 3 cycles	P1,3
R. Chen et al. 2016[19]	Endo_DDP:45 DDP:45	53/37	60.6±7.2/ 60.8±7.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Duan et al. 2015[20]	Endo_DDP:19 DDP:19	23/15	61.4	Moderate to large	≥60	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Feng 2017[21]	Endo_DDP:27 DDP:27	32/22	59.15±10.26/ 58.71±10.04	Moderate to large	NR	Endo 30 mg_DDP 30mg: 1/week, 3 cycles DDP 30mg: 1/week, 3 cycles	P1
He et al. 2016[22]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2
Huang 2014[23]	Endo_DDP:25 DDP:25	30/20	41. 5 ± 7. 6	Moderate to large	>60	Endo 30 mg 2/week _DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

Li 2020[24]	Endo_DDP:20 DDP:20	24/16	62.3±1.7/ 62.5±1.5	Moderate to large	NR	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,3
Li 2016[25]	Endo_DDP:31 DDP:31	35/27	42.22±6.92/ 42.14±6.89	NR	>60	Endo 30 mg 2/week_DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3
Liu et al. 2019[26]	Endo_DDP:30 DDP:30	36/24	52.64±6.55/ 53.31±7.56	NR	≥60	Endo 45 mg/m^2_DDP 30mg: 2/week, 2-3 cycles DDP 30mg: 2/week, 2-3 cycles	P1,3
Liu et al. 2018[27]	Endo_DDP:34 DDP:34	38/30	63.19±4.73/ 65.55±5.28	Moderate to large	≥60	Endo 60 mg _DDP 60mg: 2/week DDP 60mg: 2/week	P1,2,3
Lu and Zhang 2017[28]	Endo_DDP:31 DDP:31	35/27	46.3±10.6/ 45.7±11.3	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Qin 2016[29]	Endo_DDP:21 DDP:21	24/18	59.6	Moderate to large	≥60	Endo 60 mg_DDP 50mg: 1/week, 3 cycles DDP 50mg: 1/week, 3 cycles	P1,3
Qing et al. 2018[30]	Endo_DDP:28 DDP:23	22/27	68.2±4.6/ 68.2±4.6	NR	NR	Endo 35 mg/m^2_DDP 60mg/m^2: 2/week, 3 cycles DDP 60mg/m^2: 2/week, 3 cycles	P1,2,3,4
Shen et al. 2012[31]	Endo_DDP:40 DDP:40	42/38	37-79	Moderate to large	≥60	Endo 30 mg 2/week_DDP 40mg: 1/week, 3 cycles DDP 40mg: 1/week, 3 cycles	P1,2,3
Su et al. 2021[32]	Endo_DDP:30 DDP:30	37/23	61.43±6.45/ 62.05±6.29	NR	NR	Endo 60 mg_DDP 40-50mg: 2/week, 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,3

Qin 2018[33]	Endo_DDP:42 DDP:42	43/41	56.84±7.03/ 57.19±8.25	NR	NR	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Tian et al. 2019[34]	Endo_DDP:48 DDP:48	57/39	59.26±2.43/ 61.54±2.32	Moderate to large	≥60	Endo 30 mg 4/week_DDP 30-40mg/m^2: 2/week, 1 cycle DDP 30-40mg/m^2: 2/week, 1 cycle	P1
Tu et al. 2014[35]	Endo_DDP:45 DDP:45	48/42	46.5±11.5/ 47.5±10.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Wang et al. 2017[36]	Endo_DDP:40 DDP:40	41/39	55.5±2.2/ 55.8±2.9	Large	≥60	Endo 40 mg_DDP 40mg/week: 4 cycles DDP 40mg: 1/week, 4 cycles	P1,2,3
Wang 2018[37]	Endo_DDP:30 DDP:30	35/25	61.28±6.32/ 60.54±5.65	NR	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,3
Wang 2023[38]	Endo_DDP:47 DDP:47	51/43	53.47±3.25/ 54.09±3.38	NR	≥80	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1
Xu et al. 202[39]	Endo_DDP:20 DDP:20	27/13	/	Large	≥50	Endo 60 mg_DDP 40-50mg: 2/week: 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,2,3,4
Xu et al. 2021[40]	Endo_DDP:75 DDP:75	79/71	63.65±5.11/ 63.87±5.38	NR	NR	Endo 45 mg_DDP 10mg: 1/week: 3 cycles DDP 10mg: 1/week, 3 cycles	P1,3
(Yang et al. 2013[41]	Endo_DDP:21 DDP:21	27/15	41.5±7.6	Large	NR	Endo 30 mg_DDP 40mg 1/week: 3 cycles	P1,2,3,4

						DDP 40mg: 1/week, 3 cycles	
Yu 2016[42]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Liu and Tan 2018[43]	Endo_DDP:26 DDP:26	23/29	41-75/39-75	Moderate to large	NR	Endo 45mg_DDP 30mg: 2/week: 2-3 cycles DDP 30mg: 2/week: 2-3 cycles	P1,3
Lu et al. 2016[44]	Endo_DDP:30 DDP:30	28/32	/	Moderate to large	NR	Endo 30mg_DDP 30mg: 3 days: 1-2 cycles DDP 30mg: 3/6 days: 1-2 cycles	P1,2
Shi et al. 2016[45]	Endo_LBP:21 LBP:21	25/17	42.3±5.6	Moderate to large	NR	Endo 30mg 2/week: 3 cycles_LBP: 30mg/m^2: 1/3 week, 1 cycle LBP: 30mg/m^2: 1/3 week, 1 cycle	P1,2,4
Chen 2021[46]	Endo_LBP: 30 LBP:30	39/21	50.31±4.27/ 50.16±4.35	Moderate to large	NR	Endo 30mg_LBP: 30mg/m^2: 1/week, 4 cycles LBP: 30mg/m^2: 1/week, 4 cycles	P1,3
Cheng et al. 2019[47]	Endo_NDP: 46 NDP:46	45/47	/	NR	NR	Endo 7.5mg/m^2 7/week, 4 cycles _NDP 30mg/m^2: 1/week, 2-4 cycles NDP 30mg/m^2: 1/week, 2-4 cycles	P1
Xu et al. 2014[48]	Endo_NDP: 35 NDP:35	43/27	62.5±5.5	Moderate to large	NR	Endo 60mg_NDP 60mg: 1/week, 2 cycles NDP 60mg: 1/week, 2cycles	P1,3
You et al. 2021[49]	Bev_DDP: 29 DDP:29	32/26	69.86±11.36/ 67.92±9.83	NR	≥70	Bev 300mg, d1,q3w_DDP 40mg d1,8,15, q3w: 1 cycle DDP: 40mg d1, 8, 15, q3w: 1 cycle	P1

Chen and Ai 2022[50]	Bev_DDP: 35 DDP:35	45/25	65.16 ±9. 34/ 65.08± 9.26	NR	NR	Bev 300mg, d1,q3w_DDP 50mg d1,8,15, q3w: 1 cycle DDP: 50mg d1, 8, 15, q3w: 1 cycle	P1,3
Zhang et al. 2019[51]	Bev_DDP: 34 DDP:34	33/35	61.62±2.78/ 61.38±2.94	NR	>60	Bev 300mg_DDP 60mg: 2weeks: 4 cycles DDP: 60mg 1/2weeks, 4cycles	P1,3
Song 2020[52]	Bev_DDP: 36 DDP:36	45/27	58.58±4.45/ 58.69±4.87	NR	>60	Bev 5mg/kg_DDP 45mg/m^2, 1/week, 3 cycles DDP: 45mg/m^2, 1/week, 3cycles	P1,3
Xue and Zhao 2017[53]	Bev_DDP: 41 DDP:41	47/35	58.21±3.25/ 58.96±3.43	NR	NR	Bev 5mg/kg_DDP 60mg: 1/week, 3 cycles DDP: 60mg, 1/week, 3cycles	P1,3
Huang 2016[54]	Bev_DDP: 37 DDP:36	53/20	60.28±6.17/ 61.31±6.05	Moderate to large	>70	Bev 5mg/kg_DDP 40mg: 1/week, 3 cycles DDP: 40mg, 1/week, 3cycles	P1,2,3
T. Chen et al. 2016[55]	Bev_DDP: 24 DDP:24	31/17	54.6±7.7	Moderate to large	NR	Bev 300mg_DDP 60mg: 1/2weeks, 1 cycle DDP: 60mg, 1/2 weeks, 1 cycle	P1,3
Wang et al. 2015[56]	NDP: 24 DDP:24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m^2,1/week,3-4 cycles DDP: 40mg/m^2,1/week,3-4cycles	P1,2,3
Zhu et al. 2022[57]	NDP: 40 DDP:40	48/32	56.78±8.92/ 57.18±9.12	NR	NR	NDP: 40mg/m^2,1/week,4 cycles DDP: 40mg/m^2,1/week,4 cycles	P1,3
Bai 2019[58]	NDP: 30 DDP:28	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3
X. Chen et al. 2016[59]	NDP: 39 DDP:40	43/36	55.8±8.1/ 58.2±7.3	Large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3,4

Huang et al. 2017[60]	LBP: 38 DDP:38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Sheng 2014[61]	LBP: 30 DDP:30	20/40	38-74	Moderate to large	≥60	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Gao et al. 2019[62]	LBP: 30 DDP:31	37/24	57-69/54-68	Moderate to large	≥60	LBP: 30mg/m^2,1/week, 2-4 cycles DDP: 40mg/m^2,1/week, 2-4 cycles	P1,2,3

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, NR, not reported.
Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quality of life (QOL); P3: treatment-related adverse events (TRAEs); P4: survivals.

Table S4 The league table of network meta-analysis for DCR according to all interventions.

OR 95% CrIs						
Bev_DDP						
3.51 (2.03, 6.28)*	DDP					
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP				
0.15 (0.01, 1.03)	**0.04 (0, 0.27)***	**0.15 (0.02, 0.93)***	Endo_LBP			
0.36 (0.07, 1.73)	**0.1 (0.02, 0.44)***	**0.35 (0.07, 1.54)**	**2.37 (0.21, 33.93)**	Endo_NDP		
1.59 (0.46, 5.15)	0.45 (0.15, 1.26)	**1.54 (0.48, 4.47)**	9.99 (2.38, 76.59)*	**4.39 (0.7, 28.93)**	LBP	
1.18 (0.32, 3.88)	0.34 (0.1, 0.95)*	**1.14 (0.33, 3.36)**	**7.62 (0.87, 91.12)**	3.21 (1.22, 9.5)	**0.74 (0.16, 3.45)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

Table S5 The league table of network meta-analysis for QOL according to all interventions.

OR 95% CrIs						
Bev_DDP						
1.56 (0.52, 4.94)	DDP					
0.47 (0.15, 1.52)	0.3 (0.22, 0.39)*	Endo_DDP				
0.16 (0.02, 1.26)	**0.1 (0.02, 0.57)***	**0.34 (0.05, 1.95)**	Endo_LBP			
0.49 (0.1, 2.39)	0.31 (0.1, 0.93)*	**1.05 (0.31, 3.25)**	3.06 (0.82, 12.66)	LBP		
1.09 (0.21, 5.56)	0.7 (0.21, 2.22)	**2.35 (0.69, 7.75)**	**6.93 (0.85, 60.14)**	**2.25 (0.45, 11.58)**	NDP	

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, QOL: quality of life.

Table S6 League tables of all grades myelosuppressive event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.99 (0.55, 1.76)	DDP					
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP				
0.68 (0.1, 4.32)	**0.69 (0.11, 4.01)**	**0.71 (0.11, 4.25)**	Endo_LBP			
0.46 (0.1, 2.05)	**0.47 (0.11, 1.84)**	**0.49 (0.11, 1.98)**	**0.68 (0.07, 6.89)**	Endo_NDP		
0.96 (0.42, 2.18)	0.98 (0.54, 1.74)	**1.01 (0.53, 1.94)**	1.42 (0.27, 8.33)	**2.08 (0.47, 9.88)**	LBP	
0.85 (0.37, 1.93)	0.86 (0.48, 1.54)	**0.89 (0.46, 1.71)**	**1.25 (0.2, 8.81)**	1.83 (0.53, 6.94)	**0.88 (0.39, 2.02)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S7 League tables of all grades gastrointestinal effect event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.93 (0.58, 1.49)	DDP					
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP				
1.58 (0.04, 24.01)	**1.7 (0.05, 24.68)**	**1.86 (0.05, 27.49)**	Endo_LBP			
2.15 (0.22, 15.02)	**2.31 (0.25, 15.24)**	**2.52 (0.27, 17.04)**	**1.37 (0.04, 70.76)**	Endo_NDP		
4 (1.82, 8.94)*	4.29 (2.3, 8.26)*	**4.69 (2.36, 9.59)***	2.52 (0.19, 83.76)	**1.87 (0.25, 18.78)**	LBP	
5.01 (2.37, 10.84)*	5.39 (3.02, 9.89)*	**5.89 (3.07, 11.51)***	**3.19 (0.2, 113.19)**	2.32 (0.39, 20.25)	**1.26 (0.53, 2.99)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP:

Bevacizumab + cisplatin.

Table S8 League tables of all grades hypohepatia e event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.86 (0.29, 2.5)	DDP					
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP				
1.2 (0.02, 64.26)	**1.39 (0.03, 65.71)**	**1.63 (0.03, 80.3)**	Endo_LBP			
0.43 (0.01, 8)	**0.5 (0.01, 7.53)**	**0.58 (0.02, 9.69)**	**0.34 (0, 38.81)**	Endo_NDP		
1.2 (0.25, 5.83)	1.39 (0.45, 4.41)	**1.62 (0.44, 6.12)**	1 (0.03, 40.32)	**2.82 (0.14, 112.78)**	LBP	
1.09 (0.29, 4.08)	1.26 (0.58, 2.74)	**1.47 (0.54, 4.05)**	**0.91 (0.02, 45.55)**	2.5 (0.18, 81.39)	**0.91 (0.22, 3.56)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S9 League tables of G3-myelosuppressive event comparison of all interventions.

OR 95% CrIs					
Bev_DDP					
1.19 (0.37, 3.93)	DDP				
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP			
0.02 (0, 1158726093196.45)	**0.02 (0, 946584795528.83)**	**0.02 (0, 1200464612598)**	Endo_NDP		
3.03 (0.17, 114.1)	2.48 (0.19, 79.56)	**3.18 (0.2, 112.91)**	**179.3 (0, 13158904182927350)**	LBP	
2806.8 (0, 7080696058054300)	2358.54 (0, 5857536555380624)	**3012.84 (0, 7540937082788929)**	86977.28 (0.72, 28713088892365632)	**877.08 (0, 2259231168436329)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.
Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S10 League tables of G3-gastrointestinal effect event comparison of all interventions.

OR 95% CrIs					
Bev_DDP					
0.87 (0.32, 2.38)	DDP				
0.43 (0.05, 3.16)	0.5 (0.06, 2.74)	Endo_DDP			
146.72 (0, 2.25957982568521e+21)	**170.13 (0, 2.60852595759042e+21)**	**346.11 (0, 5.58712188787727e+21)**	Endo_NDP		
4.96 (0.76, 48.98)	5.6 (1.18, 45.11)*	**11.87 (1.1, 198.58)***	**0.04 (0, 1389506420906047 84)**	LBP	
97135.18 (0, 1.05993280385622e+20)	110659.48 (0, 1.25474480157232e+20)	**230346.59 (0, 2.61196338258981e+20)**	1349.63 (0, 1822912067429389107)	**18857.28 (0, 21936173709446430720)**	ND P

*p<0.05. Data bolded in black indicate they are from an indirect comparison.
ORs between the included interventions according to the results of network meta-analysis.
Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S11 League tables of G3-hypohepatia event comparison of all interventions.

OR 95% CrIs			
Bev_DDP			
1.36 (0.33, 5.91)	DDP		
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP	
3.64 (0, 4662.71)	**2.67 (0, 2952.95)**	**0.17 (0, 561.64)**	Endo_NDP

7.15 (0.05, 3005.42)	5.2 (0.05, 1901.09)	**0.37 (0, 382.55)**	**2.15 (0, 16410.56)**	LBP	
18.95 (0.38, 4882.5)	13.51 (0.37, 3023.28)	**1.03 (0, 666.32)**	5.38 (0.05, 2025.4)	**2.79 (0, 3102.18)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

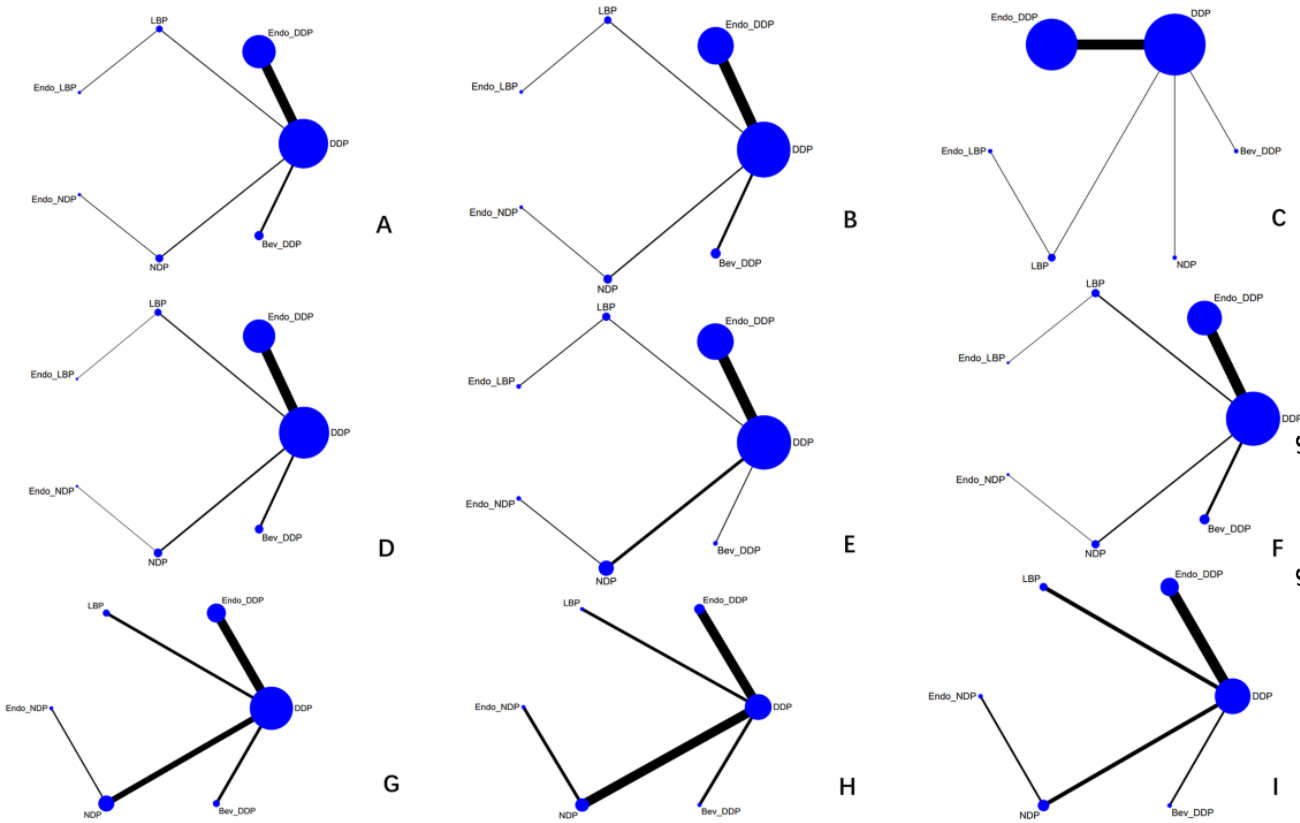

Fig S1 Network graph for different outcomes.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

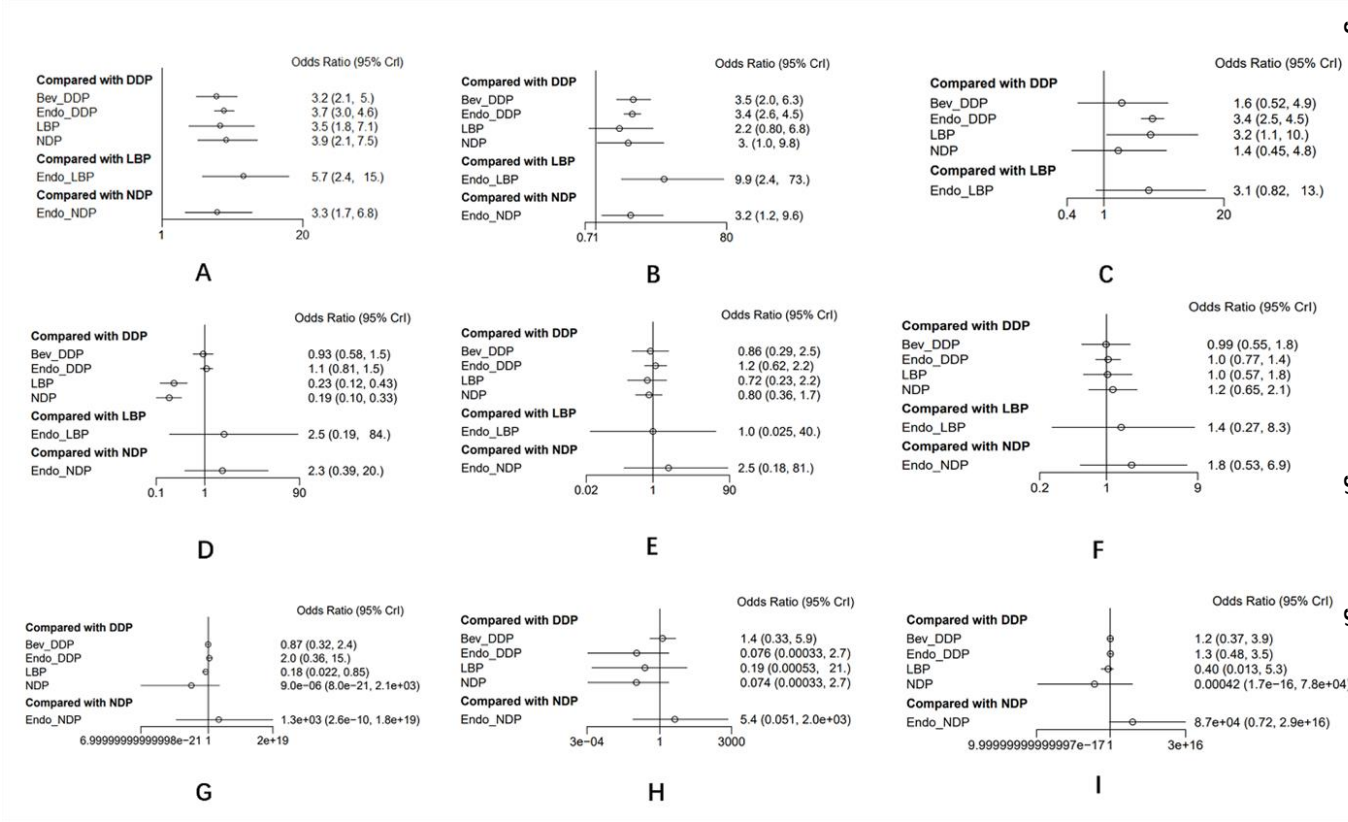

Fig S2 Forest plots of efficacy outcomes by Bayesian framework.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

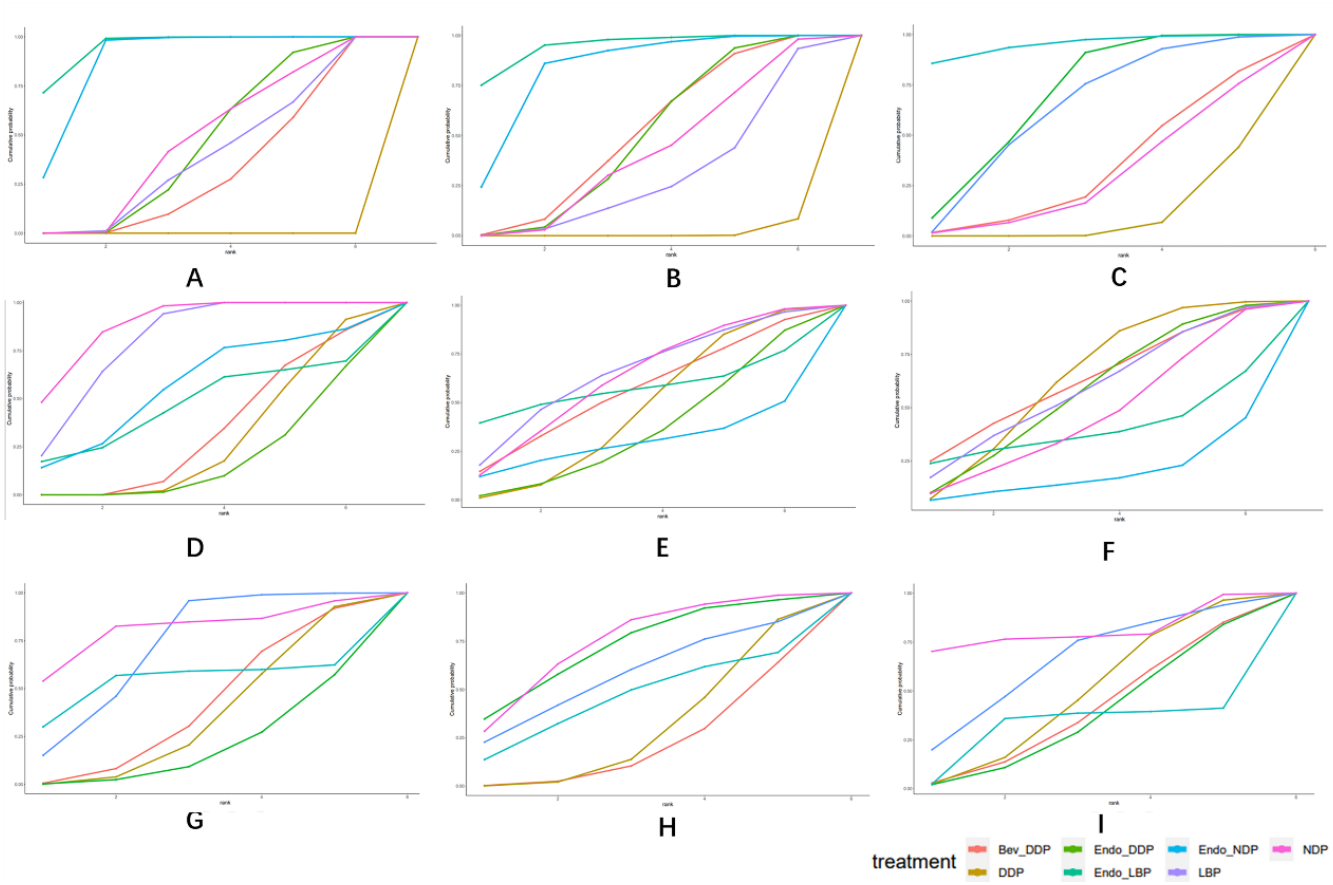

Fig S3 Sequence diagram of the network meta-analysis.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

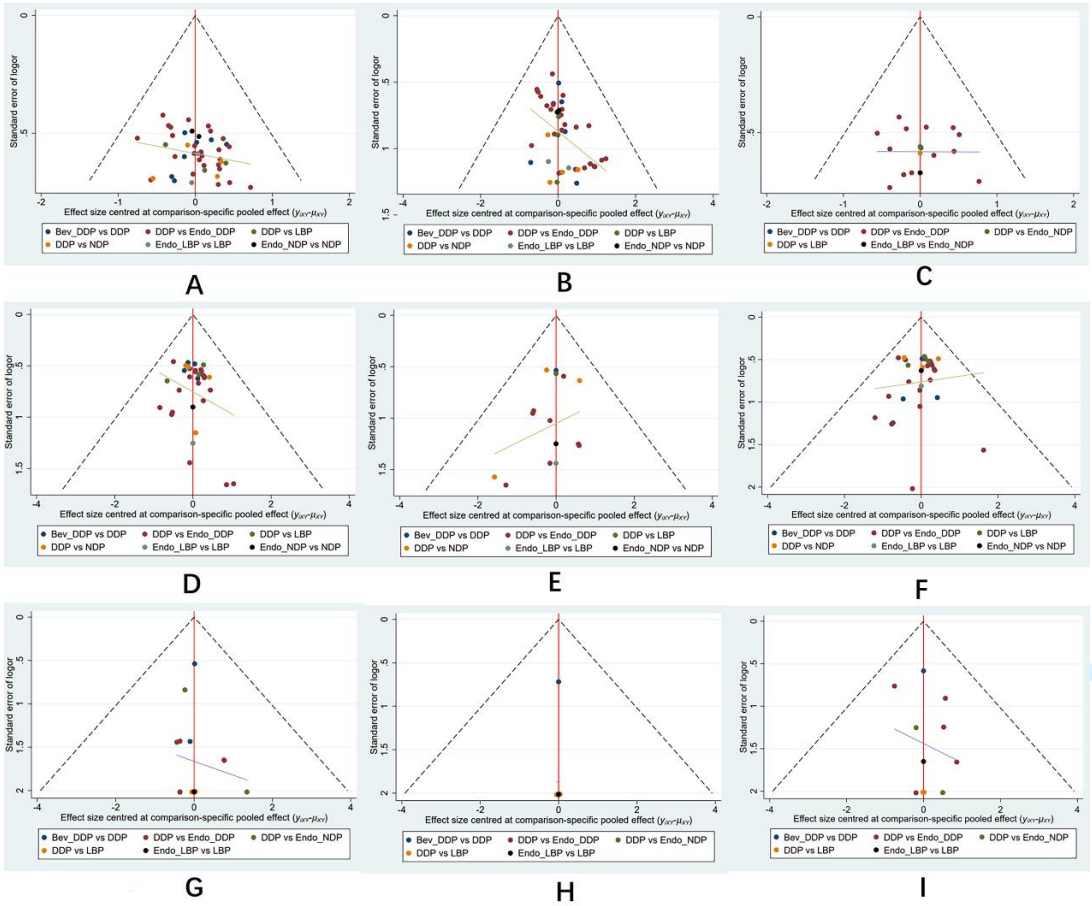

Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive.

ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

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Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

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Abstract

Objectives: Different intrathoracic perfusion therapeutic regimens are available for non-small cell lung cancer with malignant pleural effusion (MPE). Antiangiogenic agents are often used to control MPE, and the results are satisfactory. Here, we performed a network meta-analysis to reveal optimal combinations of antiangiogenic agents and chemical agents and assess their effectiveness and safety.

Design: Systematic review and network meta-analysis.

Data sources: PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database and Chinese National Knowledge Infrastructure were searched from inception to May 2023. Eligible studies were randomized controlled trials that reported on curative effect in MPE.

Data extraction and synthesis: The Cochrane Collaboration tool was used to assess risk of bias. The consistency was evaluated by examining the agreement between direct and indirect effects. Network meta-analysis was performed and the ranking probabilities of being at each possible rank for each intervention were estimated. Comparison-adjusted funnel plots were obtained to assess publication bias.

Results: A total of 46 studies were included in the analysis. Among them, we included a total of 7 interventions. A total of 3026 patients participated in this analysis. According to the results of the network meta-analysis, some antiangiogenic agents combined with chemotherapy regimens improved objective response rate (ORR) and disease control rate (DCR) and quality of life (QOL). The rank probabilities suggested that in terms of ORR, DCR and QOL, Endostar plus lobaplatin was the first-ranked intervention.

Conclusion: Administration of antiangiogenic agents plus chemical agents significantly improved the clinical response and quality of life. In addition, Endostar plus lobaplatin was the most effective combination.

PROSPERO registration number:

CRD42021284786

Keywords: Non-small cell lung cancer · MPE · Antiangiogenic agents · Thoracic perfusion · Network meta-analysis

Strengths and limitations of this study

1. The large number of studies and the considerable sample size enhanced the statistical power of our analysis.
2. The risk of bias tool recommended by Cochrane was used to assess the risk of bias of included RCTs.
3. Meta-regression analysis was performed to determine if potential effect modifiers influence the outcomes.
4. The absence of closed loops within the network prevented a formal assessment of inconsistency.

Introduction

Malignant pleural effusion (MPE) is the accumulation of exudative fluid in the pleural cavity as a result of malignancy; it is usually caused by malignant infiltration of the pleura and often results in dyspnea, chest tightness and shortness of breat[1]. According to Global Cancer Statistics released by GLOBOCAN in 2020, lung cancer is the leading cause of cancer deaths worldwide and accounts for the most common cause (approximately 35.6%) of MPE [2 3]. Studies have revealed that lung cancer combined with MPE has a worse prognosis than other malignant tumors, with a median survival of 3.3 months [4]. Traditional treatments for MPE include pleurodesis, indwelling pleural catheters and thoracic perfusion of chemotherapeutic agents [4]. Currently, with various antiangiogenic agents being approved for cancer treatment, antiangiogenic therapy for MPE has attracted increasing attention.

Vascular endothelial growth factor (VEGF), a proangiogenic factor, has a prominent role in tumor angiogenesis, host vascular endothelial cell activation, malignant proliferation and metastasis [5]. High expression levels of VEGF have been confirmed in the serum of patients with cancer and in malignant pleural effusions. Antiangiogenic agents (bevacizumab and Endostar) have been approved for MPE treatment, and the results are satisfactory.

Bevacizumab, a humanized monoclonal antibody with high binding affinity to VEGF, blocks VEGF signaling and decreases the formation of pleural effusion [6]. Endostar is a modified and recombinant human endostatin (Rh-endostatin). It is now a common angiogenesis antagonist and has been widely used in clinical practice to treat a wide range of tumors [7].

There have been several studies on the efficacy of intrapleural perfusion with antiangiogenic agents combined with chemotherapy in the treatment of malignant pleural effusion [8-11], but comparisons between multiple schemes are lacking, and the results are inconsistent. Network meta-analysis (NMA) allows for the comparison of multiple treatment regimens simultaneously, which is particularly valuable given the lack of direct head-to-head comparisons in the existing literature. Although some

meta-analyses exist on individual treatments, our NMA provides a comprehensive comparative effectiveness analysis across multiple regimens, offering a broader perspective on the optimal treatment strategy for MPE in non-small cell lung cancer (NSCLC). Notably, there are no guidelines for the treatment of MPE; hence, we performed this systematic review and network meta-analysis to identify the optimal combination strategy to aid clinical decision-making.

Materials and methods

Registration and guidelines

The protocol of this systematic review and network meta-analysis has been registered in PROSPERO (CRD42021284786). The reporting of this network meta-analysis follows the Preferred Reporting Items for Systematic Reviews statement for Network Meta-analyses (PRISMA-NMA) (PRISMA NMA Checklist) [12] (Table S1).

Differences Between Protocol and Review

The initial protocol registered in PROSPERO (CRD42021284786) listed a broader range of outcomes, including dyspnea, pain, functional status. However, post data extraction, it was observed that there was insufficient data for these planned outcomes across the included studies, preventing a robust meta-analysis. As a result, we focused on those outcomes for which sufficient data were available: ORR, DCR, QOL, and TRAEs. This adjustment was necessary to maintain the integrity and validity of the analysis.

Search strategy and eligibility criteria

We searched electronic databases, including PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database (CQVIP) and Chinese National Knowledge Infrastructure (CNKI), from inception to May 25, 2023, using the following keywords: "Endostar", "recombinant human endostatin", "Rh endostatin", "yh-16";

"Bevacizumab"; "Lung Neoplasms"; "Pleural Effusion, Malignant" and "Drug Therapy" (Table S2). In this search, there were no restrictions on the language or publication date. In addition to searching electronic databases, we also reviewed relevant systematic reviews to identify primary studies that met our inclusion criteria. Publications were considered eligible based on the following criteria: 1) the study design was a randomized controlled trial (RCT); 2) the study participants were adult patients who had a clear histopathological diagnosis of NSCLC with pleural effusion; and 3) the included studies must compare at least two of the following nine treatments, including pleural perfusion of bevacizumab plus chemical agents, Endostar plus chemical agents or chemical agents alone. During treatment, no patients received systematic chemotherapy, chemoradiotherapy, hyperthermia, or other traditional Chinese medicine injections; and 4) the studies included the objective response rate (ORR) and disease control rate (DCR). Furthermore, nonclinical controlled trials, literature reviews, duplicate publications, case reports, animal research papers, conference abstracts, systematic reviews and meta-analyses, and studies with insufficient information for data extraction were excluded. Title and abstract screening and full-text screening were conducted independently and in duplicate by two reviewers. Discrepancies were resolved through discussion with a third reviewer.

Types of Outcomes

Outcomes included the ORR, DCR, quality of life (QOL), and adverse reaction rate. The included articles were required to have ORR and DCR outcomes. Referring to previous evaluation criteria [13], we defined the clinical response criteria as follows: (1) a complete response (CR) occurred when effusion disappeared for more than four weeks; (2) a partial response (PR) occurred when effusion was reduced >50% for more than four weeks; (iii) stable disease (SD) was defined as reduced effusion <50% or increased effusion <25%; and (4) progressive disease (PD) was effusion increased >25% along with other signs of progression or symptomatic reaccumulation

of the fluid requiring repeat treatment. The ORR was defined as the ratio of the total number of patients experiencing CR and PR to the total number of patients. DCR was defined as the ratio of the total number of patients experiencing CR, PR, and SD to the total number of patients. QOL was measured by the Karnofsky performance score (KPS). Improved (KPS increased by more than 10 points) and stable (KPS changed by less than 10 points) levels were considered to indicate efficacy. The safety outcomes included adverse reactions, such as myelosuppression, hypohepatia and gastrointestinal effects (regardless of the severity (any grade or grade 3 or more)).

Data extraction and quality evaluation

The required data were independently extracted by two reviewers, and the quality assessment of the studies was performed afterward. For eligible studies, the following data were extracted: the first author, study year, proportion of males, mean age, treatment plan, volume of MPE, performance status, ORR, DCR, QOL, incidence of treatment-related adverse events (TRAEs) and grade 3 or higher treatment-related adverse events (≥grade 3 TRAEs) related to treatments. The risk of bias for each trial was assessed using the Cochrane risk of bias method [14], which includes random sequence generation, allocation concealment, blinding to allocated interventions, missing outcome data, selective outcome reporting, and other concerns. A study is classified as low risk only if all evaluated items are deemed low risk. Conversely, if any item is judged high risk, the study is classified as high risk. Studies with any item rated as unclear are classified accordingly. Each study was independently evaluated by two reviewers, and any discrepancies were resolved through discussion with a third reviewer.

Statistical analysis

The primary outcome of this study was the ORR. Secondary outcomes were DCR, QOL and TRAEs (including any grade (AG)-gastrointestinal effect, AG-hypohepatia, AG-myelosuppressive effects, grade 3 or higher (G3)-gastrointestinal effect,

G3-hypohepatia, and G3-myelosuppressive effects). The variations in dosing and scheduling across studies were minimal and consistent enough that we considered them unlikely to significantly influence the therapeutic effects. Thus, the same interventions with the different doses and schedules were grouped together.

Stata 15.0 was used to graphically display the results. The network meta-analysis was performed using the "rjags" and "gemtc" packages in R version 4.2.3. We used non-informative uniform and normal prior distribution. Non-informative uniform priors were used for the heterogeneity parameter (τ), representing the standard deviation of the random effects across studies. This choice was made to allow for a wide range of possible values and to minimize prior influence on the estimation process. Specifically, a uniform prior with a range of U(0, 5) was used for τ.Normal priors were applied to the treatment effects (log-odds ratios) for each intervention comparison. The treatment effects were modeled using $N(0, 10^2)$priors, indicating that we expected the treatment effects to be centered around zero with a wide range of possible values to capture any uncertainty in the effects.

The network meta-analysis model was estimated using the Monte Carlo Markov Chain (MCMC) method. We employed the MCMC method to run 4 MCMC chains simultaneously, setting the number of simulations to 5000 and the number of iterations to 20000. The convergence of the model was assessed by the Brooks-Gelman-Rubin diagnostic and visual inspection of trace plots. The results are shown as odds ratios (ORs) and 95% credible intervals (CrIs). Fixed and random effects models were considered and compared using the deviance information criterion (DIC). For each model, goodness-of-fit to data was evaluated using residual deviance [15].Heterogeneity was assessed using the 'getmc' package. Between-study variance (τ^2) Cochran's Q and I^2 statistic were calculated to quantify heterogeneity. Global and local inconsistencies were unable to be assessed because there were no closed loops in the network. All treatments were ranked according to the surface under the cumulative ranking area curve (SUCRA). Higher SUCRA probabilities indicated better treatment effects [16]. To determine if potential effect modifiers

influence the outcomes (ORR and DCR), we conducted a meta-regression analysis. This analysis considered variables such as sample size (categorized into <50, ≥50 and <100, ≥100), mean age (<60 years, ≥60 years), and sex ratio (male/female <1, male/female ≥1) as potential covariates. Comparison-adjusted funnel plots were employed to assess publication bias. Statistical analyses of the pooled ORRs were performed using R version 4.2.3.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Literature search and study characteristics

We identified 5670 records from 7 electronic databases. After removing duplicates, 4442 titles and abstracts were reviewed, and 130 papers were selected for full-text screening. Finally, 46 studies were included in the network meta-analysis (Fig1, Table S3[17-62]). Studies were published between 2012 and 2023 and included a total of 3026 patients. The intrapleural administration therapeutic regimens included Endostar + nedaplatin (Endo + NDP), Endostar + DDP (Endo + DDP), Endostar + lobaplatin (Endo + LBP), Bevacizumab + DDP (Bev + DDP), DDP, nedaplatin (NDP) and lobaplatin (LBP). In particular, 32 studies compared Endostar plus chemical agents versus chemical agents alone, 7 studies compared bevacizumab plus chemical agents versus chemical agents alone, and 7 studies compared the effects of different chemical agents. The general characteristics of the included studies are presented in Table S3.

Quality Assessment

Fig 2 presents our risk of bias assessments for the studies. There were 41 RCTs among the 46 studies in the unclear risk of bias for random sequence generation.

None of the studies reported the processes used for allocation concealment or blinding of outcome assessment; only 1 study mentioned the blinding of participants and personnel. The outcome data of all studies were complete, and no other sources of bias were reported.

NMA

Objective response rate

All included studies with a total of 3026 patients reported the data of ORR, with 1945 patients demonstrating an overall response. The network of studies is presented in Fig S1. Bev+ DDP exhibited a significantly higher ORR than DDP alone, yet it was lower compared to the combinations of Endo+ LBP and Endo+ NDP. DDP alone showed a significantly lower ORR than all evaluated treatment regimens, including Endo+ DDP, Endo+ LBP, Endo+ NDP, LBP, and NDP. Furthermore, Endo+ DDP had a lower ORR compared to both Endo+ LBP and Endo+ NDP, whereas Endo+ LBP and Endo+ NDP each displayed significantly higher ORRs than either LBP or NDP alone (Fig S2; Table 1).

The SUCRA rank and probability value results indicated that Endo + LBP (95%) was the most likely to improve the ORR, followed by Endo + NDP (88%), NDP (48%), Endo + DDP (46%), LBP (40%), Bev + DDP (33%), and DDP (0.002%) (Fig S3; Table 2).

Disease control rate

All included studies with a total of 3026 patients reported the data of DCR, with 2586 patients achieving disease control. The network of studies is presented in Fig S1. Bev+ DDP demonstrated a significantly higher DCR compared to DDP alone. DDP, in turn, exhibited a lower DCR relative to Endo+ DDP, Endo+ LBP, Endo+ NDP, and NDP alone. Among these, Endo+ DDP showed a significantly lower DCR than Endo+ LBP, which itself recorded a higher DCR than Endo+ NDP. Moreover, Endo+ NDP achieved a significantly higher DCR compared to NDP alone (Fig S2; Table

S4). The DCR was ranked for all treatments by estimating the SUCRA value. The results were as follows: Endo + LBP (95%), Endo + NDP (83%), Bev + DDP (51%), Endo + DDP (49%), NDP (41%), LBP (30%), and DDP (1%) (Fig S3; Table 2).

Quality of Life

Nineteen studies, involving a total of 1173 patients reported the quality of life, with 654 patients achieving high quality of life. These studies constituted five pairs of direct comparisons involving six interventions (Endo + DDP, Endo + LBP, Bev + DDP, DDP, NDP and LBP). The network diagram is shown in Fig S1. DDP was associated with a lower quality of life compared to Endo + DDP (OR = 0.3, 95% CrI [0.22, 0.39]), Endo + LBP (OR = 0.1, 95% CrI [0.02, 0.57]), and LBP (OR = 0.31, 95% CrI [0.1, 0.93]) (Fig S2; Table S5).

After ranking the six interventions based on the SUCRA values, the results were as follows: Endo + LBP (95%), Endo + DDP (69%), LBP (63%), Bev + DDP (33%), NDP (29%), and DDP (10%), as shown in Fig S3 and Table 2.

Safety and toxicity

Thirty-five studies reported the data of safety profiles. Including a total of 582 patients for any-grade gastrointestinal effect, and 37 patients for grade 3 or higher gastrointestinal effect. A total of 527 patients reported any grade myelosuppressive effect, with 37 patients achieving grade greater than or equal to 3. A total of 122 patients reported any grade hypohepatia, with 9 patients achieving grade greater than or equal to 3. The adverse reactions mainly included myelosuppression, headache, hypohepatia, renal insufficiency, gastrointestinal effects, electrocardiographic abnormalities and fever. Among all types of adverse reactions, the most frequent occurrences were myelosuppressive, hypohepatia and gastrointestinal effects. The NMA included seven therapeutic regimens for TRAEs of any grade and six therapeutic regimens for TRAEs of grade greater than or equal to 3 (Fig S1). We did

not find statistically significant differences in myelosuppression or hypohepatia. A single chemotherapeutic agent caused fewer gastrointestinal reactions (Table S6-S11).

The probabilities of adverse events were ranked for all treatments by estimating the SUCRA value. A lower SUCRA value indicated a higher probability of AEs and a poorer treatment regimen. The corresponding ranking of incidences is shown in Fig S3 and Table 2.

Meta-regression analysis

Table 3 showed the results of the meta-regression analysis for demographic and clinical variables (sample size, mean age and sex). Results indicated that none of these variables have significant impact on the ORR and DCR.

Publication bias

The comparison-adjusted funnel plots are presented in Fig S4. Overall, no distinct asymmetry was found in the comparison-adjusted funnel plot on the ORR, DCR, QOL, AG-gastrointestinal effects, AG-myelosuppression, G3-myelosuppression and G3-hypohepatia, indicating no evidence of publication bias. However, the comparison-adjusted funnel plot on AG-gastrointestinal effects, G3-gastrointestinal effects and AG-hypohepatia were not symmetric around the zero line, which revealed that there could be small-study effects.

Discussion

Currently, to the best of our knowledge, intrapleural perfusion with antiangiogenic agents plus chemical agents in controlling MPE conferred satisfying clinical outcomes for patients with NSCLC. Although Endostar/bevacizumab combined with chemotherapy is widely used to treat malignant pleural effusion, there is a lack of head-to-head direct comparisons to determine the best regimen. Hence, we performed a network meta-analysis. In this analysis, two antiangiogenic agents and three chemical agents formed seven treatment regimens to identify which treatment was

optimal in achieving higher clinical responses and QOL and fewer TRAEs. The results suggested the following:

1. Intrapleural administration of Endostar plus lobaplatin was associated with the best ORR and DCR outcomes, followed by Endostar plus nedaplatin.

2. For the ORR, Endo + LBP and Endo + NDP were significantly more favorable than Bev + DDP, while there were no significant differences in the efficacy of Endostar plus chemotherapy or bevacizumab plus chemotherapy with regard to DCR.

Endostar, an endogenous angiogenic inhibitor, can inhibit endothelial cell migration, repress the neovascularization of tumors, block the nutrient supply of tumor cells, and thus prevent tumor proliferation and metastasis. In addition, Endostar reduces the permeability of tumor neovascularization, thereby reducing the production of pleural effusion [63]. In 2022, Yimiao Xia et al. [8] performed a meta-analysis that included 55 RCTs with a total of 3379 patients with lung cancer to investigate the efficacy, safety and cost-effectiveness of Endostar and platinum in controlling MPE. All the studies in the meta-analysis were published in Chinese. This supported the findings in the current network meta-analysis.

Bevacizumab is another frequently studied antiangiogenic agent and plays an important role in the treatment of several types of tumors [7]. It can prevent VEGF-induced vascular permeability and tumor cell migration, thereby reducing MPE [64]. Several studies have demonstrated the efficacy and safety of bevacizumab for the management of MPE. Du et al. [65] compared the efficacy of combined intrapleural therapy with bevacizumab and cisplatin versus cisplatin alone in controlling MPE. The results revealed that bevacizumab plus cisplatin improved the ORR from 50 to 83.3%. However, in our meta-analysis, the pooled ORR of Bev + DDP was 73.8%, and the true efficacy of Bev might have been overestimated. After a literature search, we found no head-to-head comparison between Bev plus other chemical agents and the sole administration of chemical agents other than cisplatin. Therefore, more combination therapeutic regimens still need to be investigated in the future.

MPE is generally considered to be a manifestation of a malignancy in its

preterminal stage. Hence, the interventions are palliative in nature. The main goal of treatment is to palliate symptoms and improve quality of life [66]. In our study, we found that intrapleural injection of Endostar combined with DDP was the best in terms of improving QOL, while DDP was the worst.

With regard to the safety profile, although there was no significant difference in the incidence of myelosuppression or hypohepatia between therapeutic regimens in our study, regardless of the severity, the incidence of AG-gastrointestinal effects was significantly more frequent with Endo + DDP and Bev + DDP than with LBP and NDP. Furthermore, in the gastrointestinal effect ranking of the six treatment groups, NDP was the safest, and Endostar plus DDP was the least safe (regardless of the severity (any grade or grade 3 or more)). The results of these analyses suggest that safety considerations may be needed when Endostar plus DDP is administered.

The transitivity assumption, which underlies the validity of network meta-analysis, was assessed by comparing the distribution of key covariates across the included studies. These covariates—mean age, sex ratio, and sample size—were relatively balanced across the different treatment comparisons, suggesting that the assumption of transitivity is plausible. However, it is important to note that unmeasured or inadequately reported effect modifiers could still potentially influence the results. Future studies should aim to collect more homogeneous data and consider additional covariates that may impact treatment effects.

This study had some limitations. First, we utilized only Chinese and English databases, which might have led to retrieval bias, and most of the trials did not report concealment or blinding, which might undermine the validity of the overall findings. Second, all the included RCTs were published in China, and the generalizability of the results is limited. Third, all of the included studies are at unclear risk of bias, and many comparisons rely solely on indirect evidence, as there are no closed loops within the network. This can lead to potentially misleading SUCRA rankings. Therefore, SUCRA rankings should be interpreted with caution. Fourth, although we did not impose restrictions based on the indexing status of journals during the

literature search inclusion criteria, some of these journals are of low quality. The potential influence of journal quality on our results warrants cautious interpretation. Fifth, the absence of closed loops in the network precludes the formal assessment of inconsistency, which is a crucial aspect of NMA. Future studies should aim to include more diverse treatment comparisons to allow for a comprehensive inconsistency evaluation.

Conclusions

This network meta-analysis comprehensively compared various treatments for thoracic perfusion of MPE in NSCLC patients and described the QOL and toxicity features. To the best of our knowledge, this is the first comprehensive NMA study of its kind. The results showed that antiangiogenic agents combined with chemotherapy regimens could improve clinical effectiveness and quality of life. In our study, Endo+LBP was the most effective. However, high-quality randomized controlled trials with larger sample sizes are needed to further confirm the evidence.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

YX conducted overall design, data collection, analysis and draft writing. YYC and LMJ were responsible for data collection, partial analysis and partial draft writing. YNY, WS and XHZ were responsible for data collection, YYC and YX revised the manuscript. YX was responsible for the conduct of the study as a guarantor.

Data Availability statement:

Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Conflicts of interest: The authors declare no conflict of interest.

Ethical approval: Not applicable.

Consent for publication: Not applicable

Abbreviations

NSCLC	Non-small cell lung cancer
MPE	Malignant pleural effusion
VEGF	Vascular endothelial growth factor
Rh-endostatin	Recombinant human endostatin
CQVIP	VIP Database
CNKI	Chinese National Knowledge Infrastructure
RCT	Randomized controlled trial
ORR	Objective response rate
DCR	Disease control rate
QOL	Quality of life
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
KPS	Karnofsky performance score
TRAEs	Treatment-related adverse events
≥grade 3 TRAEs	Grade 3 or higher treatment-related adverse events
CrI	Credible intervals
SUCRA	Surface under the cumulative ranking area curve

1	CI	Confidence intervals
2	Endo + NDP	Endostar + nedaplatin
3	Endo + DDP	Endostar + cisplatin
4	Endo + LBP	Endostar + lobaplatin
5	Bev + DDP	Bevacizumab + cisplatin
6	NDP	Nedaplatin

7

8

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Table 1 The league table of network meta-analysis for ORR according to all interventions.

OR 95% CrIs						
Bev_DDP						
3.19 (2.11, 4.92)*	DDP					
0.85 (0.53, 1.37)	0.27 (0.22, 0.33)*	Endo_DDP				
0.16 (0.05, 0.53)*	**0.05 (0.02, 0.15)***	**0.19 (0.06, 0.59)***	Endo_LBP			
0.25 (0.09, 0.68)*	**0.08 (0.03, 0.2)***	**0.29 (0.11, 0.75)***	**1.54 (0.35, 6.84)**	Endo_NDP		
0.92 (0.4, 2.03)	0.29 (0.14, 0.56)*	**1.08 (0.52, 2.18)**	5.69 (2.37, 14.65)*	**3.73 (1.17, 12.04)***	LBP	
0.81 (0.38, 1.71)	0.25 (0.13, 0.46)*	**0.95 (0.49, 1.81)**	**5.06 (1.39, 19.02)***	3.28 (1.65, 6.76)*	**0.88 (0.35, 2.24)**	NDP

Abbreviation: *p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate.

Table 2 Rank probabilities of each treatment for different outcome measures based on the network meta-analysis

	BEV_DDP	**DDP**	**Endo_DDP**	**Endo_LBP**	**Endo_NDP**	**LBP**	**NDP**
ORR	0.33	0.00002	0.46	0.95	0.88	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83	0.30	0.41
QOL	0.33	0.10	0.69	0.95	/	0.63	0.29
Gastrointestinal effect	0.32	0.28	0.18	0.47	0.56	0.80	0.89
Myelosuppressive	0.63	0.64	0.58	0.40	0.19	0.59	0.47
Hypohepatia	0.55	0.46	0.35	0.57	0.30	0.65	0.62
G3-gastrointestinal effect	0.40	0.35	0.19	/	0.54	0.71	0.81
G3-myelosuppression	0.39	0.48	0.37	/	0.32	0.64	0.81
G3-hypohepatia	0.21	0.30	0.72	/	0.45	0.57	0.74

Abbreviation: Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate, DCR: Disease control rate, QOL: quality of life, G3: grade 3 or higher.
The data are listed as SUCRA values (rank) and higher SUCRA values indicate better outcomes.

Table 3 Meta-regression analysis for the impact of potential factors on the outcomes

	Overall response rate		**Disease control rate**	
	β coefficient (95%CI)	P value	β coefficient (95%CI)	P value
Sample size	-0.65 (-1.91, 0.62)	0.316	-0.73 (-2.47, 1.00)	0.408
Mean age	0.36 (-0.59, 1.31)	0.459	0.18 (-1.28, 1.64)	0.810
Sex	0.12 (-0.84, 1.08)	0.811	-1.26 (-2.72, 0.20)	0.091

Abbreviation: 95%CI: 95% confidence interval.

Figure legends

Fig 1 The flow diagram of the study selection process for the network meta-analysis

Fig 2 Assessment of risk of bias.

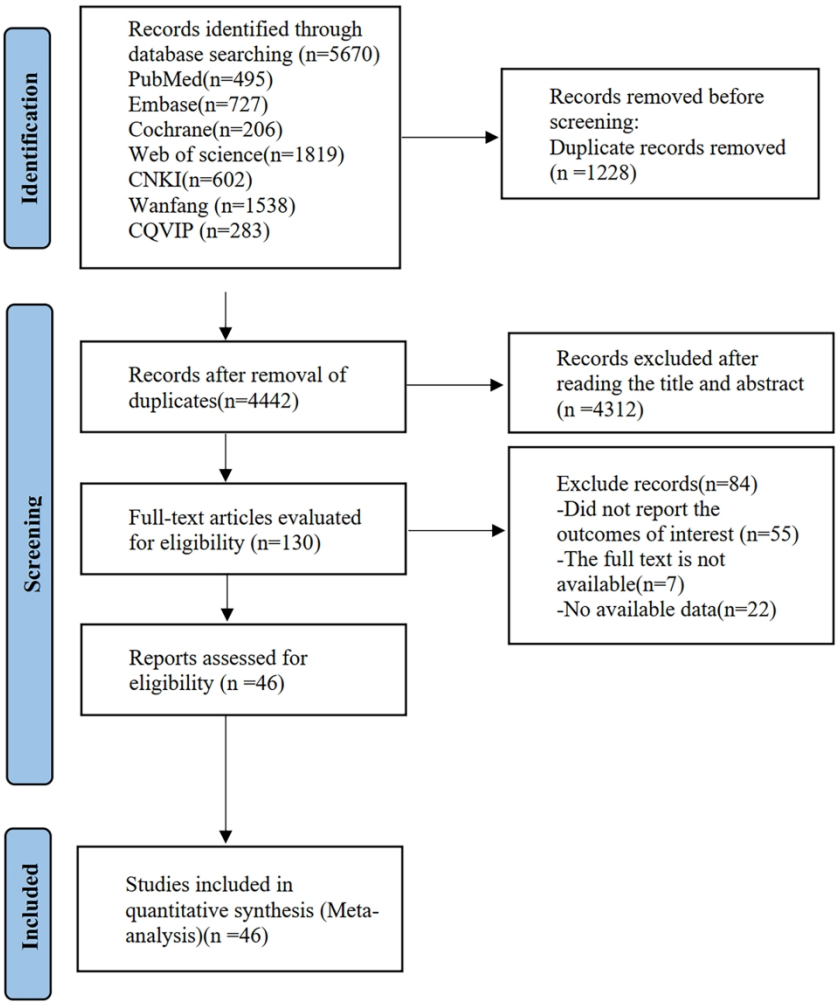

Fig 1

149x171mm (600 x 600 DPI)

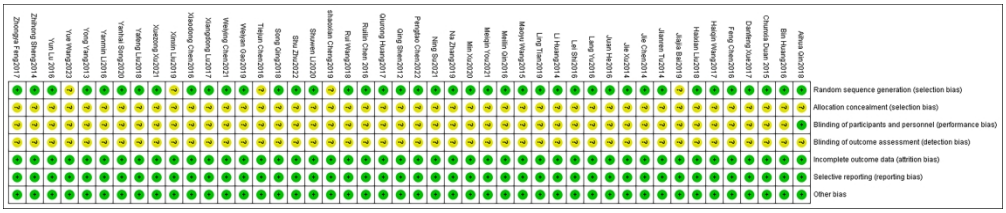

Fig 2

455x93mm (300 x 300 DPI)

Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

Supplementary Materials

Table of Contents

Table S1 PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3, 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5, 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7, 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7, 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8-9, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8-9
Study characteristics	17	Cite each included study and present its characteristics.	9, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9, Fig.2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-12

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	12-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	14

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S2 Literature Search Strategy

Database and Search strategy	5670
CNKI	
(主题=肺癌 + 肺恶性肿瘤 + 原发性支气管癌 + 支气管癌) AND (主题=恶性胸腔积液 + 恶性胸腔积液 + 癌性胸水 + 癌性胸腔积液 + 恶性胸膜腔积液 + 恶性胸水 + 恶性胸腹水 + 恶性胸腹水 + 恶性胸腔液) AND (主题=贝伐珠单抗 + 恩度 + 重组人血管内皮抑制素 + 化疗 + 化学疗法 + 化学药物治疗 + 化学治疗)	602
CQVIP	
(((((题名或关键词=肺癌 OR 题名或关键词=肺恶性肿瘤) OR 题名或关键词=原发性支气管癌) OR 题名或关键词=支气管癌) AND ((((((题名或关键词=恶性胸腔积液 OR 题名或关键词=癌性胸水) OR 题名或关键词=癌性胸腔积液) OR 题名或关键词=恶性胸腔积液) OR 题名或关键词=恶性胸水) OR 题名或关键词=恶性胸腹水) OR 题名或关键词=恶性胸腔液)) AND ((((((题名或关键词=贝伐珠单抗 OR 题名或关键词=恩度) OR 题名或关键词=重组人血管内皮抑制素) OR 题名或关键词=化疗) OR 题名或关键词=化学疗法) OR 题名或关键词=化学药物治疗) OR 题名或关键词=化学治疗))	283
Wanfang	
主题:(肺癌 OR 肺恶性肿瘤 OR 原发性支气管癌 OR 支气管癌) and 主题:(恶性胸腔积液 OR 癌性胸水 OR 癌性胸腔积液 OR 恶性胸膜腔积液 OR 恶性胸水 OR 恶性胸腹水 OR 恶性胸腔液) and 主题:(贝伐珠单抗 OR 恩度 OR 重组人血管内皮抑制素 OR 化疗 OR 化学疗法 OR 化学药物治疗 OR 化学治疗)	1538
PubMed	
((((("Drug Therapy"[Mesh]) OR (((((((Drug Therapy[Title/Abstract]) OR (Therapy, Drug[Title/Abstract])) OR (Drug Therapies[Title/Abstract])) OR (Therapies, Drug[Title/Abstract])) OR (Chemotherapy[Title/Abstract])) OR (Chemotherapies[Title/Abstract])) OR (Pharmacotherapy[Title/Abstract])) OR (Pharmacotherapies[Title/Abstract]))) OR (("Bevacizumab"[Mesh]) OR (((((((((Bevacizumab[Title/Abstract]) OR (Mvasi[Title/Abstract])) OR (Bevacizumab-awwb[Title/Abstract])) OR (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) OR (Endostar[Title/Abstract])) OR (recombinant human endostatin[Title/Abstract])) OR (Rh endostatin[Title/Abstract])) OR (yh-16[Title/Abstract])))) AND (("Lung Neoplasms"[Mesh])	495

OR ((((((((((((((((Lung Neoplasms[Title/Abstract]) OR (Pulmonary Neoplasms[Title/Abstract])) OR (Neoplasms, Lung[Title/Abstract])) OR (Lung Neoplasm[Title/Abstract])) OR (Neoplasm, Lung[Title/Abstract])) OR (Neoplasms, Pulmonary[Title/Abstract])) OR (Neoplasm, Pulmonary[Title/Abstract])) OR (Pulmonary Neoplasm[Title/Abstract])) OR (Lung Cancer[Title/Abstract])) OR (Cancer, Lung[Title/Abstract])) OR (Cancers, Lung[Title/Abstract])) OR (Lung Cancers[Title/Abstract])) OR (Pulmonary Cancer[Title/Abstract])) OR (Cancer, Pulmonary[Title/Abstract])) OR (Cancers, Pulmonary[Title/Abstract])) OR (Pulmonary Cancers[Title/Abstract])) OR (Cancer of Lung[Title/Abstract])) OR (Cancer of the Lung[Title/Abstract])) OR (Cancer of Lung[Title/Abstract]))))) AND (("Pleural Effusion, Malignant"[Mesh]) OR ((((((Pleural Effusion, Malignant[Title/Abstract]) OR (Malignant Pleural Effusion[Title/Abstract])) OR (Effusion, Malignant Pleural[Title/Abstract])) OR (Effusions, Malignant Pleural[Title/Abstract])) OR (Malignant Pleural Effusions[Title/Abstract])) OR (Pleural Effusions, Malignant[Title/Abstract]))))	
Embase		
#1	'lung tumor'/exp	727
#2	'lung tumor':ab,ti	
#3	'pulmonary neoplasms':ab,ti	
#4	'neoplasms, lung':ab,ti	
#5	'lung neoplasm':ab,ti	
#6	'neoplasm, lung':ab,ti	
#7	'neoplasms, pulmonary':ab,ti	
#8	'neoplasm, pulmonary':ab,ti	
#9	'pulmonary neoplasm':ab,ti	

#10	'lung cancer':ab,ti	
#11	'cancer, lung':ab,ti	
#12	'cancers, lung':ab,ti	
#13	'lung cancers':ab,ti	
#14	'pulmonary cancer':ab,ti	
#15	'cancer, pulmonary':ab,ti	
#16	'cancers, pulmonary':ab,ti	
#17	'pulmonary cancers':ab,ti	
#18	'cancer of the lung':ab,ti	
#19	'cancer of lung':ab,ti	
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	
#21	'malignant pleura effusion'/exp	
#22	'malignant pleura effusion':ab,ti	
#23	'effusion, malignant pleural':ab,ti	

#24	'effusions, malignant pleural':ab,ti	
#25	'malignant pleural effusions':ab,ti	
#26	'pleural effusions, malignant':ab,ti	
#27	'pleural effusion, malignant':ab,ti	
#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	
#29	'bevacizumab'/exp	
#30	'bevacizumab':ab,ti	
#31	'mvasi':ab,ti	
#32	'bevacizumab-awwb':ab,ti	
#33	'bevacizumab awwb':ab,ti	
#34	'avastin':ab,ti	
#35	'endostar':ab,ti	
#36	'recombinant human endostatin':ab,ti	
#37	'rh endostatin':ab,ti	

#38	'yh-16':ab,ti	
#39	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	
#40	'drug therapy'/exp	
#41	'drug therapy':ab,ti	
#42	'therapy, drug':ab,ti	
#43	'drug therapies':ab,ti	
#44	'therapies, drug':ab,ti	
#45	'chemotherapy':ab,ti	
#46	'chemotherapies':ab,ti	
#47	'pharmacotherapy':ab,ti	
#48	'pharmacotherapies':ab,ti	
#49	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	
#50	#39 OR #49	
#51	#20 AND #28 AND #50	

Cochrane		
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	206
#2	(Lung Neoplasms):ti,ab,kw OR (Pulmonary Neoplasms):ti,ab,kw OR (Neoplasms, Lung):ti,ab,kw OR (Pulmonary Neoplasm):ti,ab,kw OR (Neoplasm, Lung):ti,ab,kw	
#3	(Neoplasms, Pulmonary):ti,ab,kw OR (Neoplasm, Pulmonary):ti,ab,kw OR (Pulmonary Neoplasm):ti,ab,kw OR (Lung Cancer):ti,ab,kw OR (Cancer, Lung):ti,ab,kw	
#4	(Cancers, Lung):ti,ab,kw OR (Lung Cancers):ti,ab,kw OR (Pulmonary Cancer):ti,ab,kw OR (Cancer, Pulmonary):ti,ab,kw OR (Cancers, Pulmonary):ti,ab,kw	
#5	(Pulmonary Cancers):ti,ab,kw OR (Cancer of the Lung):ti,ab,kw OR (Cancer of Lung):ti,ab,kw	
#6	#1 or #2 or #3 or #4 or #5	
#7	MeSH descriptor: [Pleural Effusion, Malignant] explode all trees	
#8	(Pleural Effusion, Malignant):ti,ab,kw OR (Malignant Pleural Effusion):ti,ab,kw OR (Effusion, Malignant Pleural):ti,ab,kw OR (Effusions, Malignant Pleural):ti,ab,kw OR (Malignant Pleural Effusions):ti,ab,kw 725 #9 (Pleural Effusions, Malignant):ti,ab,kw	
#9	(Pleural Effusions, Malignant):ti,ab,kw	
#10	#7 or #8 or #9	
#11	MeSH descriptor: [Bevacizumab] explode all trees	
#12	(Bevacizumab):ti,ab,kw OR (Mvasi):ti,ab,kw OR (Bevacizumab-awwb):ti,ab,kw OR (Bevacizumab awwb):ti,ab,kw OR (Avastin):ti,ab,kw 7448 #13 (Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#13	(Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#14	#11 or #12 or #13	
#15	MeSH descriptor: [Drug Therapy] explode all trees	
#16	(Drug Therapy):ti,ab,kw OR (Therapy, Drug):ti,ab,kw OR (Drug Therapies):ti,ab,kw OR (Therapies, Drug):ti,ab,kw OR (Chemotherapy):ti,ab,kw	

#17	(Chemotherapies):ti,ab,kw OR (Pharmacotherapy):ti,ab,kw OR (Pharmacotherapies):ti,ab,kw	
#18	#15 or #16 or #17	
#19	#14 or #18	
#20	#19 and #6 and #10	
Web of science		
#1	TS=(Lung Neoplasms) OR TS=(Pulmonary Neoplasms) OR TS=(Neoplasms, Lung) OR TS=(Lung Neoplasm) OR TS=(Neoplasm, Lung) OR TS=(Neoplasms, Pulmonary) OR TS=(Neoplasm, Pulmonary) OR TS=(Pulmonary Neoplasm) OR TS=(Lung Cancer) OR TS=(Cancer, Lung) OR TS=(Cancers, Lung) OR TS=(Lung Cancers) OR TS=(Pulmonary Cancer) OR TS=(Cancer, Pulmonary) OR TS=(Cancers, Pulmonary) OR TS=(Pulmonary Cancers) OR TS=(Cancer of the Lung) OR TS=(Cancer of Lung) and 预印本 (排除 – 数据库)	1819
#2	TS=(Pleural Effusion, Malignant) OR TS=(Malignant Pleural Effusion) OR TS=(Effusion, Malignant Pleural) OR TS=(Effusions, Malignant Pleural) OR TS=(Malignant Pleural Effusions) OR TS=(Pleural Effusions, Malignant) and 预印本 (排除 – 数据库)	
#3	TS=(Bevacizumab) OR TS=(Mvasi) OR TS=(Bevacizumab-awwb) OR TS=(Bevacizumab awwb) OR TS=(Avastin) OR TS=(Endostar) OR TS=(recombinant human endostatin) OR TS=(Rh endostatin) OR TS=(yh-16) and 预印本 (排除 – 数据库)	
#4	TS=(Drug Therapy) OR TS=(Therapy, Drug) OR TS=(Drug Therapies) OR TS=(Therapies, Drug) OR TS=(Chemotherapy) OR TS=(Chemotherapies) OR TS=(Pharmacotherapy) OR TS=(Pharmacotherapies) and 预印本 (排除 – 数据库)	
#5	#4 OR #3 and 预印本 (排除 – 数据库)	
#6	#5 AND #2 AND #1 and 预印本 (排除 – 数据库)	

Table S3 Characteristics of the included randomized controlled trials.

Study	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Intervention	outcome
F. Chen et al. 2016 [17]	Endo_DDP:30 DDP:30	39/21	/	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,2,3
Chen et al. 2014[18]	Endo_DDP:30 DDP:30	44/16	54.3±5.6/ 55.6±4.5	NR	NR	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg: 2/week, 3 cycles	P1,3
R. Chen et al. 2016[19]	Endo_DDP:45 DDP:45	53/37	60.6±7.2/ 60.8±7.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Duan et al. 2015[20]	Endo_DDP:19 DDP:19	23/15	61.4	Moderate to large	≥60	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Feng 2017[21]	Endo_DDP:27 DDP:27	32/22	59.15±10.26/ 58.71±10.04	Moderate to large	NR	Endo 30 mg_DDP 30mg: 1/week, 3 cycles DDP 30mg: 1/week, 3 cycles	P1
He et al. 2016[22]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2
Huang 2014[23]	Endo_DDP:25 DDP:25	30/20	41. 5 ± 7. 6	Moderate to large	>60	Endo 30 mg 2/week _DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

Li 2020[24]	Endo_DDP:20 DDP:20	24/16	62.3±1.7/ 62.5±1.5	Moderate to large	NR	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,3
Li 2016[25]	Endo_DDP:31 DDP:31	35/27	42.22±6.92/ 42.14±6.89	NR	>60	Endo 30 mg 2/week_DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3
Liu et al. 2019[26]	Endo_DDP:30 DDP:30	36/24	52.64±6.55/ 53.31±7.56	NR	≥60	Endo 45 mg/m^2_DDP 30mg: 2/week, 2-3 cycles DDP 30mg: 2/week, 2-3 cycles	P1,3
Liu et al. 2018[27]	Endo_DDP:34 DDP:34	38/30	63.19±4.73/ 65.55±5.28	Moderate to large	≥60	Endo 60 mg _DDP 60mg: 2/week DDP 60mg: 2/week	P1,2,3
Lu and Zhang 2017[28]	Endo_DDP:31 DDP:31	35/27	46.3±10.6/ 45.7±11.3	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Qin 2016[29]	Endo_DDP:21 DDP:21	24/18	59.6	Moderate to large	≥60	Endo 60 mg_DDP 50mg: 1/week, 3 cycles DDP 50mg: 1/week, 3 cycles	P1,3
Qing et al. 2018[30]	Endo_DDP:28 DDP:23	22/27	68.2±4.6/ 68.2±4.6	NR	NR	Endo 35 mg/m^2_DDP 60mg/m^2: 2/week, 3 cycles DDP 60mg/m^2: 2/week, 3 cycles	P1,2,3,4
Shen et al. 2012[31]	Endo_DDP:40 DDP:40	42/38	37-79	Moderate to large	≥60	Endo 30 mg 2/week_DDP 40mg: 1/week, 3 cycles DDP 40mg: 1/week, 3 cycles	P1,2,3
Su et al. 2021[32]	Endo_DDP:30 DDP:30	37/23	61.43±6.45/ 62.05±6.29	NR	NR	Endo 60 mg_DDP 40-50mg: 2/week, 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,3

Qin 2018[33]	Endo_DDP:42 DDP:42	43/41	56.84±7.03/ 57.19±8.25	NR	NR	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Tian et al. 2019[34]	Endo_DDP:48 DDP:48	57/39	59.26±2.43/ 61.54±2.32	Moderate to large	≥60	Endo 30 mg 4/week_DDP 30-40mg/m^2: 2/week, 1 cycle DDP 30-40mg/m^2: 2/week, 1 cycle	P1
Tu et al. 2014[35]	Endo_DDP:45 DDP:45	48/42	46.5±11.5/ 47.5±10.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Wang et al. 2017[36]	Endo_DDP:40 DDP:40	41/39	55.5±2.2/ 55.8±2.9	Large	≥60	Endo 40 mg_DDP 40mg/week: 4 cycles DDP 40mg: 1/week, 4 cycles	P1,2,3
Wang 2018[37]	Endo_DDP:30 DDP:30	35/25	61.28±6.32/ 60.54±5.65	NR	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,3
Wang 2023[38]	Endo_DDP:47 DDP:47	51/43	53.47±3.25/ 54.09±3.38	NR	≥80	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1
Xu et al. 202[39]	Endo_DDP:20 DDP:20	27/13	/	Large	≥50	Endo 60 mg_DDP 40-50mg: 2/week: 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,2,3,4
Xu et al. 2021[40]	Endo_DDP:75 DDP:75	79/71	63.65±5.11/ 63.87±5.38	NR	NR	Endo 45 mg_DDP 10mg: 1/week: 3 cycles DDP 10mg: 1/week, 3 cycles	P1,3
(Yang et al. 2013[41]	Endo_DDP:21 DDP:21	27/15	41.5±7.6	Large	NR	Endo 30 mg_DDP 40mg 1/week: 3 cycles	P1,2,3,4

						DDP 40mg: 1/week, 3 cycles	
Yu 2016[42]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Liu and Tan 2018[43]	Endo_DDP:26 DDP:26	23/29	41-75/39-75	Moderate to large	NR	Endo 45mg_DDP 30mg: 2/week: 2-3 cycles DDP 30mg: 2/week: 2-3 cycles	P1,3
Lu et al. 2016[44]	Endo_DDP:30 DDP:30	28/32	/	Moderate to large	NR	Endo 30mg_DDP 30mg: 3 days: 1-2 cycles DDP 30mg: 3/6 days: 1-2 cycles	P1,2
Shi et al. 2016[45]	Endo_LBP:21 LBP:21	25/17	42.3±5.6	Moderate to large	NR	Endo 30mg 2/week: 3 cycles_LBP: 30mg/m^2: 1/3 week, 1 cycle LBP: 30mg/m^2: 1/3 week, 1 cycle	P1,2,4
Chen 2021[46]	Endo_LBP: 30 LBP:30	39/21	50.31±4.27/ 50.16±4.35	Moderate to large	NR	Endo 30mg_LBP: 30mg/m^2: 1/week, 4 cycles LBP: 30mg/m^2: 1/week, 4 cycles	P1,3
Cheng et al. 2019[47]	Endo_NDP: 46 NDP:46	45/47	/	NR	NR	Endo 7.5mg/m^2 7/week, 4 cycles _NDP 30mg/m^2: 1/week, 2-4 cycles NDP 30mg/m^2: 1/week, 2-4 cycles	P1
Xu et al. 2014[48]	Endo_NDP: 35 NDP:35	43/27	62.5±5.5	Moderate to large	NR	Endo 60mg_NDP 60mg: 1/week, 2 cycles NDP 60mg: 1/week, 2cycles	P1,3
You et al. 2021[49]	Bev_DDP: 29 DDP:29	32/26	69.86±11.36/ 67.92±9.83	NR	≥70	Bev 300mg, d1,q3w_DDP 40mg d1,8,15, q3w: 1 cycle DDP: 40mg d1, 8, 15, q3w: 1 cycle	P1

Chen and Ai 2022[50]	Bev_DDP: 35 DDP:35	45/25	65.16 ±9. 34/ 65.08± 9.26	NR	NR	Bev 300mg, d1,q3w_DDP 50mg d1,8,15, q3w: 1 cycle DDP: 50mg d1, 8, 15, q3w: 1 cycle	P1,3
Zhang et al. 2019[51]	Bev_DDP: 34 DDP:34	33/35	61.62±2.78/ 61.38±2.94	NR	>60	Bev 300mg_DDP 60mg, 2weeks: 4 cycles DDP: 60mg 1/2weeks, 4cycles	P1,3
Song 2020[52]	Bev_DDP: 36 DDP:36	45/27	58.58±4.45/ 58.69±4.87	NR	>60	Bev 5mg/kg_DDP 45mg/m^2, 1/week, 3 cycles DDP: 45mg/m^2, 1/week, 3cycles	P1,3
Xue and Zhao 2017[53]	Bev_DDP: 41 DDP:41	47/35	58.21±3.25/ 58.96±3.43	NR	NR	Bev 5mg/kg_DDP 60mg, 1/week, 3 cycles DDP: 60mg, 1/week, 3cycles	P1,3
Huang 2016[54]	Bev_DDP: 37 DDP:36	53/20	60.28±6.17/ 61.31±6.05	Moderate to large	>70	Bev 5mg/kg_DDP 40mg: 1/week, 3 cycles DDP: 40mg, 1/week, 3cycles	P1,2,3
T. Chen et al. 2016[55]	Bev_DDP: 24 DDP:24	31/17	54.6±7.7	Moderate to large	NR	Bev 300mg_DDP 60mg: 1/3weeks, 1 cycle DDP: 60mg, 1/2 weeks, 1 cycle	P1,3
Wang et al. 2015[56]	NDP: 24 DDP:24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m^2,1/week,3-4 cycles DDP: 40mg/m^2,1/week,3-4cycles	P1,2,3
Zhu et al. 2022[57]	NDP: 40 DDP:40	48/32	56.78±8.92/ 57.18±9.12	NR	NR	NDP: 40mg/m^2,1/week,4 cycles DDP: 40mg/m^2,1/week,4 cycles	P1,3
Bai 2019[58]	NDP: 30 DDP:28	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3
X. Chen et al. 2016[59]	NDP: 39 DDP:40	43/36	55.8±8.1/ 58.2±7.3	Large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3,4

Huang et al. 2017[60]	LBP: 38 DDP:38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Sheng 2014[61]	LBP: 30 DDP:30	20/40	38-74	Moderate to large	≥60	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Gao et al. 2019[62]	LBP: 30 DDP:31	37/24	57-69/54-68	Moderate to large	≥60	LBP: 30mg/m^2,1/week, 2-4 cycles DDP: 40mg/m^2,1/week, 2-4 cycles	P1,2,3

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, NR, not reported.
Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quality of life (QOL); P3: treatment-related adverse events (TRAEs); P4: survivals.

Table S4 The league table of network meta-analysis for DCR according to all interventions.

OR 95% CrIs						
Bev_DDP						
3.51 (2.03, 6.28)*	DDP					
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP				
0.15 (0.01, 1.03)	**0.04 (0, 0.27)***	**0.15 (0.02, 0.93)***	Endo_LBP			
0.36 (0.07, 1.73)	**0.1 (0.02, 0.44)***	**0.35 (0.07, 1.54)**	**2.37 (0.21, 33.93)**	Endo_NDP		
1.59 (0.46, 5.15)	0.45 (0.15, 1.26)	**1.54 (0.48, 4.47)**	9.99 (2.38, 76.59)*	**4.39 (0.7, 28.93)**	LBP	
1.18 (0.32, 3.88)	0.34 (0.1, 0.95)*	**1.14 (0.33, 3.36)**	**7.62 (0.87, 91.12)**	3.21 (1.22, 9.52)*	**0.74 (0.16, 3.45)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

Table S5 The league table of network meta-analysis for QOL according to all interventions.

OR 95% CrIs						
Bev_DDP						
1.56 (0.52, 4.94)	DDP					
0.47 (0.15, 1.52)	0.3 (0.22, 0.39)*	Endo_DDP				
0.16 (0.02, 1.26)	**0.1 (0.02, 0.57)***	**0.34 (0.05, 1.95)**	Endo_LBP			
0.49 (0.1, 2.39)	0.31 (0.1, 0.93)*	**1.05 (0.31, 3.25)**	3.06 (0.82, 12.66)	LBP		
1.09 (0.21, 5.56)	0.7 (0.21, 2.22)	**2.35 (0.69, 7.75)**	**6.93 (0.85, 60.14)**	**2.25 (0.45, 11.58)**	NDP	

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, QOL: quality of life.

Table S6 League tables of all grades myelosuppressive event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.99 (0.55, 1.76)	DDP					
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP				
0.68 (0.1, 4.32)	**0.69 (0.11, 4.01)**	**0.71 (0.11, 4.25)**	Endo_LBP			
0.46 (0.1, 2.05)	**0.47 (0.11, 1.84)**	**0.49 (0.11, 1.98)**	**0.68 (0.07, 6.89)**	Endo_NDP		
0.96 (0.42, 2.18)	0.98 (0.54, 1.74)	**1.01 (0.53, 1.94)**	1.42 (0.27, 8.33)	**2.08 (0.47, 9.88)**	LBP	
0.85 (0.37, 1.93)	0.86 (0.48, 1.54)	**0.89 (0.46, 1.71)**	**1.25 (0.2, 8.81)**	1.83 (0.53, 6.94)	**0.88 (0.39, 2.02)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S7 League tables of all grades gastrointestinal effect event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.93 (0.58, 1.49)	DDP					
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP				
1.58 (0.04, 24.01)	**1.7 (0.05, 24.68)**	**1.86 (0.05, 27.49)**	Endo_LBP			
2.15 (0.22, 15.02)	**2.31 (0.25, 15.24)**	**2.52 (0.27, 17.04)**	**1.37 (0.04, 70.76)**	Endo_NDP		
4 (1.82, 8.94)*	4.29 (2.3, 8.26)*	**4.69 (2.36, 9.59)***	2.52 (0.19, 83.76)	**1.87 (0.25, 18.78)**	LBP	
5.01 (2.37, 10.84)*	5.39 (3.02, 9.89)*	**5.89 (3.07, 11.51)***	**3.19 (0.2, 113.19)**	2.32 (0.39, 20.25)	**1.26 (0.53, 2.99)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP:

Bevacizumab + cisplatin.

Table S8 League tables of all grades hypohepatia e event comparison of all interventions.

		OR 95% CrIs				
Bev_DDP						
0.86 (0.29, 2.5)	DDP					
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP				
1.2 (0.02, 64.26)	**1.39 (0.03, 65.71)**	**1.63 (0.03, 80.3)**	Endo_LBP			
0.43 (0.01, 8)	**0.5 (0.01, 7.53)**	**0.58 (0.02, 9.69)**	**0.34 (0, 38.81)**	Endo_NDP		
1.2 (0.25, 5.83)	1.39 (0.45, 4.41)	**1.62 (0.44, 6.12)**	1 (0.03, 40.32)	**2.82 (0.14, 112.78)**	LBP	
1.09 (0.29, 4.08)	1.26 (0.58, 2.74)	**1.47 (0.54, 4.05)**	**0.91 (0.02, 45.55)**	2.5 (0.18, 81.39)	**0.91 (0.22, 3.56)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S9 League tables of G3-myelosuppressive event comparison of all interventions.

		OR 95% CrIs			
Bev_DDP					
1.19 (0.37, 3.93)	DDP				
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP			
0.02 (0, 1158726093196.45)	**0.02 (0, 946584795528.83)**	**0.02 (0, 1200464612598)**	Endo_NDP		
3.03 (0.17, 114.1)	2.48 (0.19, 79.56)	**3.18 (0.2, 112.91)**	**179.3 (0, 13158904182927350)**	LBP	
2806.8 (0, 7080696058054300)	2358.54 (0, 5857536555380624)	**3012.84 (0, 7540937082788929)**	86977.28 (0.72, 28713088892365632)	**877.08 (0, 2259231168436329)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.
Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S10 League tables of G3-gastrointestinal effect event comparison of all interventions.

OR 95% CrIs					
Bev_DDP					
0.87 (0.32, 2.38)	DDP				
0.43 (0.05, 3.16)	0.5 (0.06, 2.74)	Endo_DDP			
146.72 (0, 2.25957982568521e+21)	**170.13 (0, 2.60852595759042e+21)**	**346.11 (0, 5.58712188787727e+21)**	Endo_NDP		
4.96 (0.76, 48.98)	5.6 (1.18, 45.11)*	**11.87 (1.1, 198.58)***	**0.04 (0, 1389506420906047 84)**	LBP	
97135.18 (0, 1.05993280385622e+20)	110659.48 (0, 1.25474480157232e+20)	**230346.59 (0, 2.61196338258981e+20)**	1349.63 (0, 1822912067429389107)	**18857.28 (0, 21936173709446430720)**	ND P

*p<0.05. Data bolded in black indicate they are from an indirect comparison.
ORs between the included interventions according to the results of network meta-analysis.
Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S11 League tables of G3-hypohepatia event comparison of all interventions.

OR 95% CrIs			
Bev_DDP			
1.36 (0.33, 5.91)	DDP		
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP	
3.64 (0, 4662.71)	**2.67 (0, 2952.95)**	**0.17 (0, 561.64)**	Endo_NDP

7.15 (0.05, 3005.42)	5.2 (0.05, 1901.09)	**0.37 (0, 382.55)**	**2.15 (0, 16410.56)**	LBP	
18.95 (0.38, 4882.5)	13.51 (0.37, 3023.28)	**1.03 (0, 666.32)**	5.38 (0.05, 2025.4)	**2.79 (0, 3102.18)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

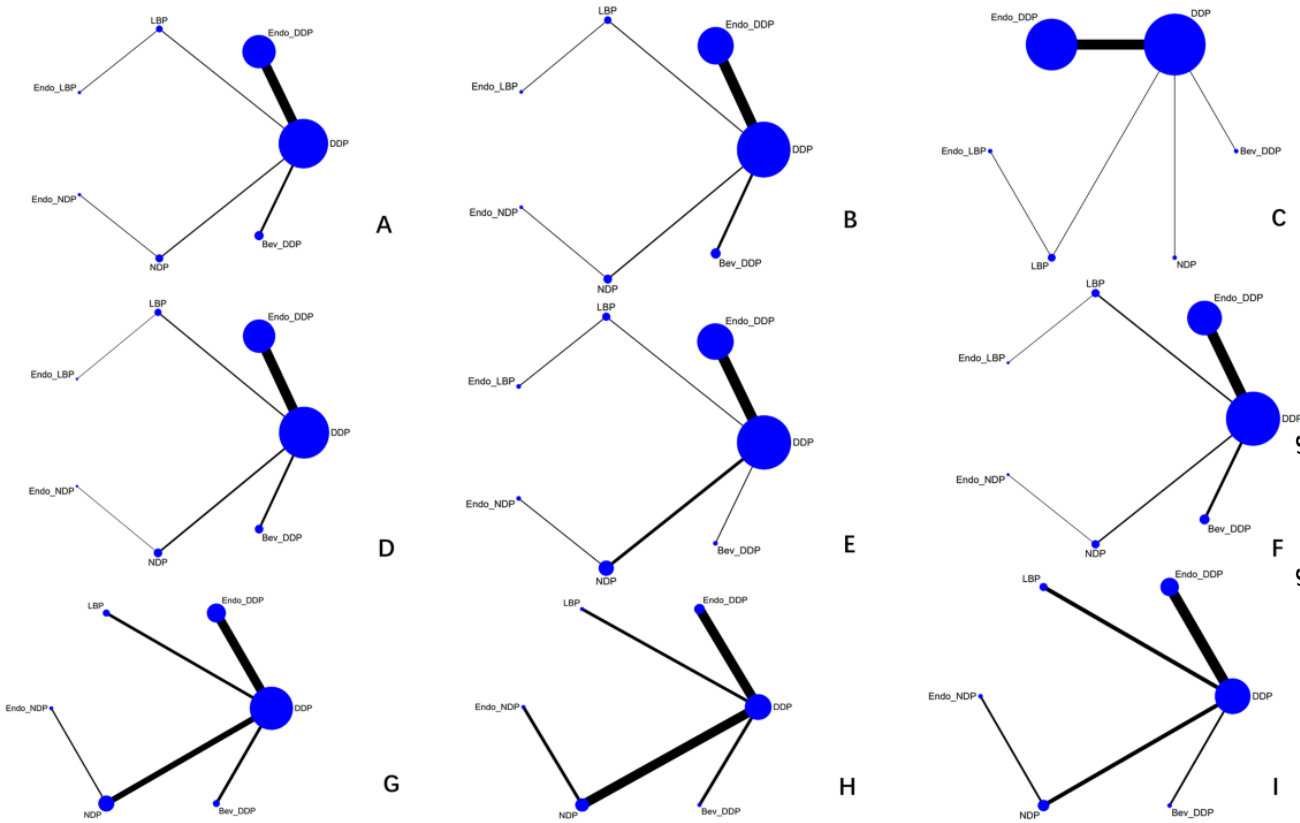

Fig S1 Network graph for different outcomes.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

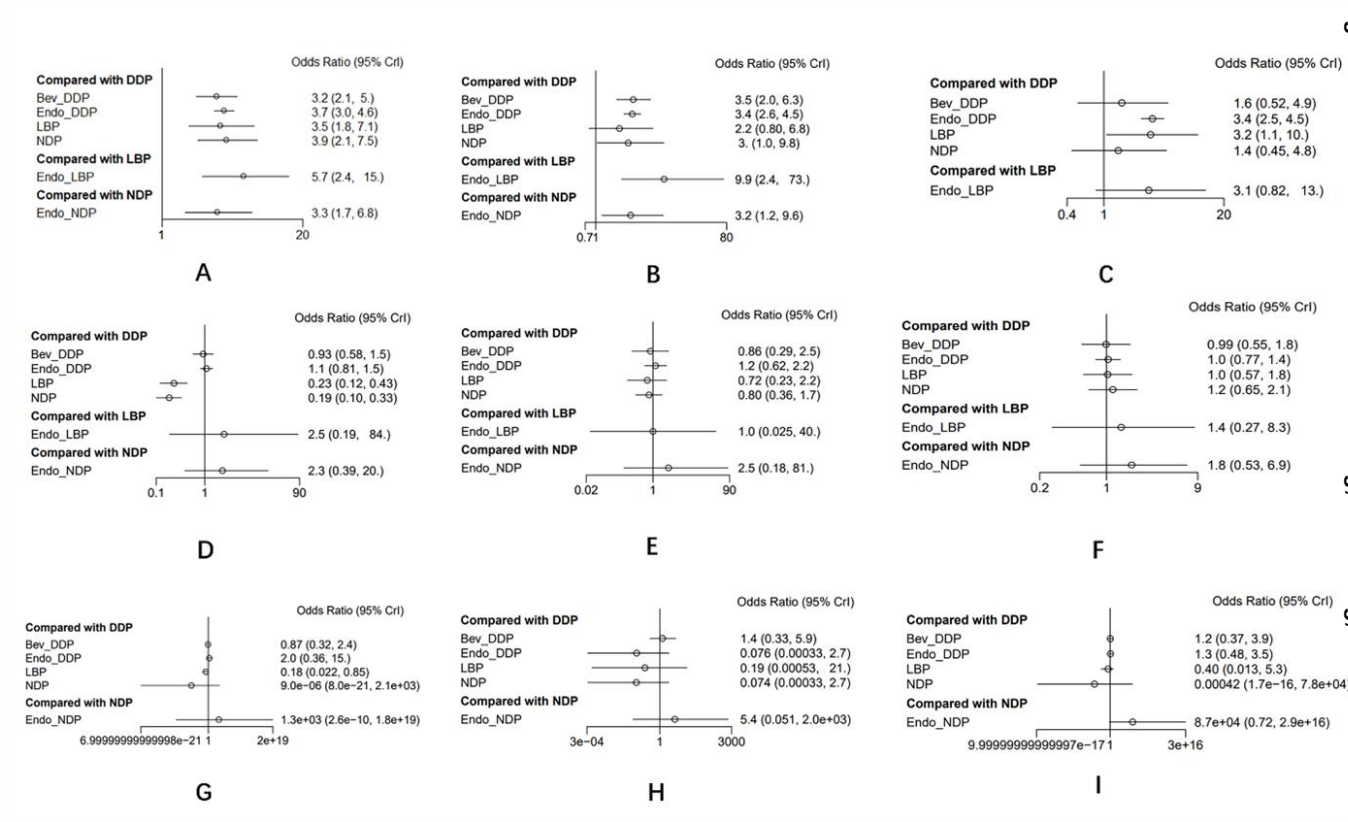

Fig S2 Forest plots of efficacy outcomes by Bayesian framework.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

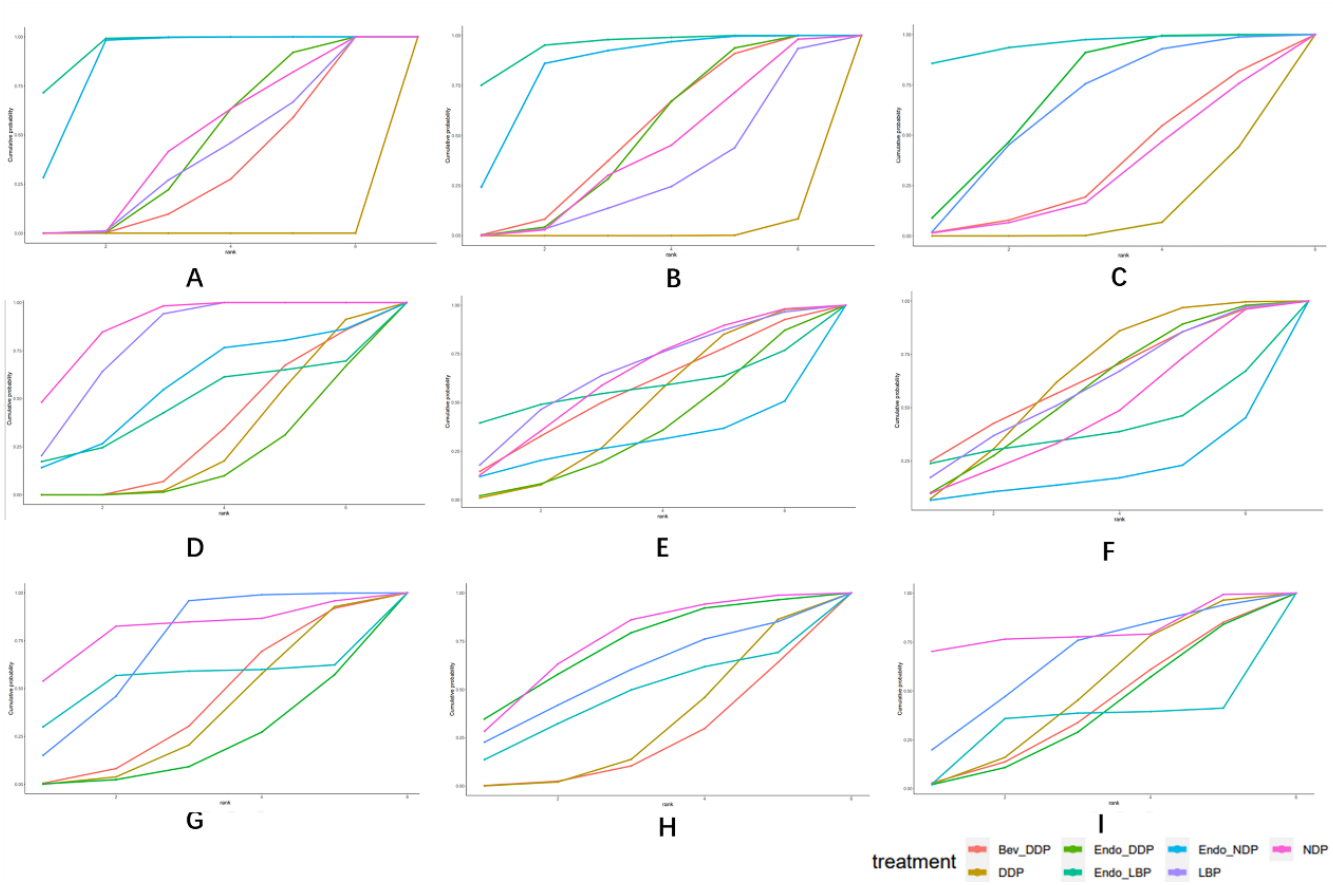

Fig S3 Sequence diagram of the network meta-analysis.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

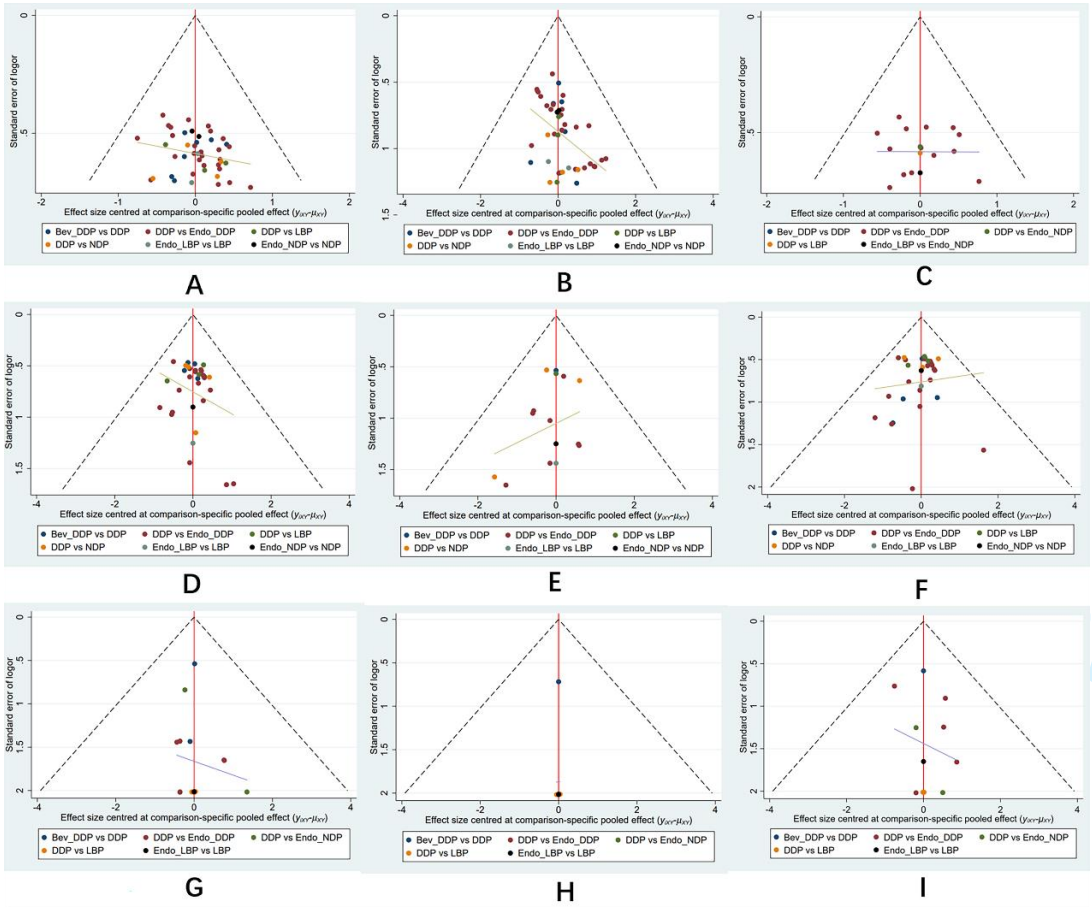

Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive.

ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

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Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

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Abstract

Objectives: Different intrathoracic perfusion therapeutic regimens are available for non-small cell lung cancer with malignant pleural effusion (MPE). Antiangiogenic agents are often used to control MPE, and the results are satisfactory. Here, we performed a network meta-analysis to reveal optimal combinations of antiangiogenic agents and chemical agents and assess their effectiveness and safety.

Design: Systematic review and network meta-analysis.

Data sources: PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database and Chinese National Knowledge Infrastructure were searched from inception to May 2023. Eligible studies were randomized controlled trials that reported on curative effect in MPE.

Data extraction and synthesis: The Cochrane Collaboration tool was used to assess risk of bias. The consistency was evaluated by examining the agreement between direct and indirect effects. Network meta-analysis was performed and the ranking probabilities of being at each possible rank for each intervention were estimated. Comparison-adjusted funnel plots were obtained to assess publication bias.

Results: A total of 46 studies were included in the analysis. Among them, we included a total of 7 interventions. A total of 3026 patients participated in this analysis. According to the results of the network meta-analysis, some antiangiogenic agents combined with chemotherapy regimens improved objective response rate (ORR) and disease control rate (DCR) and quality of life (QOL). The rank probabilities suggested that in terms of ORR, DCR and QOL, Endostar plus lobaplatin was the first-ranked intervention.

Conclusion: Administration of antiangiogenic agents plus chemical agents significantly improved the clinical response and quality of life. In addition, Endostar plus lobaplatin was the most effective combination.

PROSPERO registration number:

CRD42021284786

Keywords: Non-small cell lung cancer · MPE · Antiangiogenic agents · Thoracic perfusion · Network meta-analysis

Strengths and limitations of this study

1. The large number of studies and the considerable sample size enhanced the statistical power of our analysis.

2. The risk of bias tool recommended by Cochrane was used to assess the risk of bias of included RCTs.

3.Meta-regression analysis was performed to determine if potential effect modifiers influence the outcomes.

4. The absence of closed loops within the network prevented a formal assessment of inconsistency.

Introduction

Malignant pleural effusion (MPE) is the accumulation of exudative fluid in the pleural cavity as a result of malignancy; it is usually caused by malignant infiltration of the pleura and often results in dyspnea, chest tightness and shortness of breat [1]. According to Global Cancer Statistics released by GLOBOCAN in 2020, lung cancer is the leading cause of cancer deaths worldwide and accounts for the most common cause (approximately 35.6%) of MPE [2 3]. Studies have revealed that lung cancer combined with MPE has a worse prognosis than other malignant tumors, with a median survival of 3.3 months [4]. Traditional treatments for MPE include pleurodesis, indwelling pleural catheters and thoracic perfusion of chemotherapeutic agents [4]. Currently, with various antiangiogenic agents being approved for cancer treatment, antiangiogenic therapy for MPE has attracted increasing attention.

Vascular endothelial growth factor (VEGF), a proangiogenic factor, has a prominent role in tumor angiogenesis, host vascular endothelial cell activation, malignant proliferation and metastasis [5]. High expression levels of VEGF have been confirmed in the serum of patients with cancer and in malignant pleural effusions. Antiangiogenic agents (bevacizumab and Endostar) have been approved for MPE treatment, and the results are satisfactory.

Bevacizumab, a humanized monoclonal antibody with high binding affinity to VEGF, blocks VEGF signaling and decreases the formation of pleural effusion [6]. Endostar is a modified and recombinant human endostatin (Rh-endostatin). It is now a common angiogenesis antagonist and has been widely used in clinical practice to treat a wide range of tumors [7].

There have been several studies on the efficacy of intrapleural perfusion with antiangiogenic agents combined with chemotherapy in the treatment of malignant pleural effusion [8-11], but comparisons between multiple schemes are lacking, and the results are inconsistent. Network meta-analysis (NMA) allows for the comparison of multiple treatment regimens simultaneously, which is particularly valuable given the lack of direct head-to-head comparisons in the existing literature. Although some meta-

analyses exist on individual treatments, our NMA provides a comprehensive comparative effectiveness analysis across multiple regimens, offering a broader perspective on the optimal treatment strategy for MPE in non-small cell lung cancer (NSCLC). Notably, there are no guidelines for the treatment of MPE; hence, we performed this systematic review and network meta-analysis to identify the optimal combination strategy to aid clinical decision-making.

Materials and methods

Registration and guidelines

The protocol of this systematic review and network meta-analysis has been registered in PROSPERO (CRD42021284786). The reporting of this network meta-analysis follows the Preferred Reporting Items for Systematic Reviews statement for Network Meta-analyses (PRISMA-NMA) (PRISMA NMA Checklist) [12] (Table S1).

Differences Between Protocol and Review

The initial protocol registered in PROSPERO (CRD42021284786) listed a broader range of outcomes, including dyspnea, pain, functional status. However, post data extraction, it was observed that there was insufficient data for these planned outcomes across the included studies, preventing a robust meta-analysis. As a result, we focused on those outcomes for which sufficient data were available: ORR, DCR, QOL, and TRAEs. This adjustment was necessary to maintain the integrity and validity of the analysis.

Search strategy and eligibility criteria

We searched electronic databases, including PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP Database (CQVIP) and Chinese National Knowledge Infrastructure (CNKI), from inception to May 25, 2023, using the following keywords: "Endostar", "recombinant human endostatin", "Rh endostatin", "yh-16"; "Bevacizumab"; "Lung Neoplasms"; "Pleural Effusion, Malignant" and "Drug

Therapy" (Table S2). In this search, there were no restrictions on the language or publication date. In addition to searching electronic databases, we also reviewed relevant systematic reviews to identify primary studies that met our inclusion criteria. Publications were considered eligible based on the following criteria: 1) the study design was a randomized controlled trial (RCT); 2) the study participants were adult patients who had a clear histopathological diagnosis of NSCLC with pleural effusion; and 3) the included studies must compare at least two of the following seven treatments, including pleural perfusion of bevacizumab plus chemical agents, Endostar plus chemical agents or chemical agents alone. Chemical agents including nedaplatin, lobaplatin and cisplatin. During treatment, no patients received systematic chemotherapy, chemoradiotherapy, hyperthermia, or other traditional Chinese medicine injections; and 4) the studies included the objective response rate (ORR) and disease control rate (DCR). Furthermore, nonclinical controlled trials, literature reviews, duplicate publications, case reports, animal research papers, conference abstracts, systematic reviews and meta-analyses, and studies with insufficient information for data extraction were excluded. Title and abstract screening and full-text screening were conducted independently and in duplicate by two reviewers. Discrepancies were resolved through discussion with a third reviewer.

Types of Outcomes

Outcomes included the ORR, DCR, quality of life (QOL), and adverse reaction rate. The included articles were required to have ORR and DCR outcomes. Referring to previous evaluation criteria [13], we defined the clinical response criteria as follows: (1) a complete response (CR) occurred when effusion disappeared for more than four weeks; (2) a partial response (PR) occurred when effusion was reduced >50% for more than four weeks; (iii) stable disease (SD) was defined as reduced effusion <50% or increased effusion <25%; and (4) progressive disease (PD) was effusion increased >25% along with other signs of progression or symptomatic reaccumulation of the fluid requiring repeat treatment. The ORR was defined as the ratio of the total number of

patients experiencing CR and PR to the total number of patients. DCR was defined as the ratio of the total number of patients experiencing CR, PR, and SD to the total number of patients. QOL was measured by the Karnofsky performance score (KPS). Improved (KPS increased by more than 10 points) and stable (KPS changed by less than 10 points) levels were considered to indicate efficacy. The safety outcomes included adverse reactions, such as myelosuppression, hypohepatia and gastrointestinal effects (regardless of the severity (any grade or grade 3 or more)).

Data extraction and quality evaluation

The required data were independently extracted by two reviewers, and the quality assessment of the studies was performed afterward. For eligible studies, the following data were extracted: the first author, study year, proportion of males, mean age, treatment plan, volume of MPE, performance status, ORR, DCR, QOL, incidence of treatment-related adverse events (TRAEs) and grade 3 or higher treatment-related adverse events (≥grade 3 TRAEs) related to treatments. The risk of bias for each trial was assessed using the Cochrane risk of bias method [14], which includes random sequence generation, allocation concealment, blinding to allocated interventions, missing outcome data, selective outcome reporting, and other concerns. A study is classified as low risk only if all evaluated items are deemed low risk. Conversely, if any item is judged high risk, the study is classified as high risk. Studies with any item rated as unclear are classified accordingly. Each study was independently evaluated by two reviewers, and any discrepancies were resolved through discussion with a third reviewer.

Statistical analysis

The primary outcome of this study was the ORR. Secondary outcomes were DCR, QOL and TRAEs (including any grade (AG)-gastrointestinal effect, AG-hypohepatia, AG-myelosuppressive effects, grade 3 or higher (G3)-gastrointestinal effect, G3-hypohepatia, and G3-myelosuppressive effects). The variations in dosing and

scheduling across studies were minimal and consistent enough that we considered them unlikely to significantly influence the therapeutic effects. Thus, the same interventions with the different doses and schedules were grouped together.

Stata 15.0 was used to graphically display the results. The network meta-analysis was performed using the "rjags" and "gemtc" packages in R version 4.2.3. We used non-informative uniform and normal prior distribution. Non-informative uniform priors were used for the heterogeneity parameter (τ), representing the standard deviation of the random effects across studies. This choice was made to allow for a wide range of possible values and to minimize prior influence on the estimation process. Specifically, a uniform prior with a range of U(0, 5) was used for τ.Normal priors were applied to the treatment effects (log-odds ratios) for each intervention comparison. The treatment effects were modeled using $N(0, 10^2)$priors, indicating that we expected the treatment effects to be centered around zero with a wide range of possible values to capture any uncertainty in the effects.

The network meta-analysis model was estimated using the Monte Carlo Markov Chain (MCMC) method. We employed the MCMC method to run 4 MCMC chains simultaneously, setting the number of simulations to 5000 and the number of iterations to 20000. The convergence of the model was assessed by the Brooks-Gelman-Rubin diagnostic and visual inspection of trace plots. The results are shown as odds ratios (ORs) and 95% credible intervals (CrIs). Fixed and random effects models were considered and compared using the deviance information criterion (DIC). For each model, goodness-of-fit to data was evaluated using residual deviance [15].Heterogeneity was assessed using the 'getmc' package. Between-study variance (τ^2) Cochran's Q and I^2 statistic were calculated to quantify heterogeneity. Global and local inconsistencies were unable to be assessed because there were no closed loops in the network. All treatments were ranked according to the surface under the cumulative ranking area curve (SUCRA). Higher SUCRA probabilities indicated better treatment effects [16]. To determine if potential effect modifiers influence the outcomes (ORR and DCR), we conducted a meta-regression analysis. This analysis considered variables such as

sample size (categorized into <50, ≥50 and <100, ≥100), mean age (<60 years, ≥60 years), and sex ratio (male/female <1, male/female ≥1) as potential covariates. Comparison-adjusted funnel plots were employed to assess publication bias. Statistical analyses of the pooled ORRs were performed using R version 4.2.3. We generated forest plots with the use of statistical software R version 4.2.3 to visualize the effect of treatment comparisons. The criteria for selection of comparisons are considered in network meta-analyses, including clinical relevance, data availability and heterogeneity assessment.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Literature search and study characteristics

We identified 5670 records from 7 electronic databases. After removing duplicates, 4442 titles and abstracts were reviewed, and 130 papers were selected for full-text screening. Finally, 46 studies were included in the network meta-analysis (Fig1, Table S3[17-62]). Studies were published between 2012 and 2023 and included a total of 3026 patients. The intrapleural administration therapeutic regimens included Endostar + nedaplatin (Endo + NDP), Endostar + DDP (Endo + DDP), Endostar + lobaplatin (Endo + LBP), Bevacizumab + DDP (Bev + DDP), DDP, nedaplatin (NDP) and lobaplatin (LBP). In particular, 32 studies compared Endostar plus chemical agents versus chemical agents alone, 7 studies compared bevacizumab plus chemical agents versus chemical agents alone, and 7 studies compared the effects of different chemical agents. The general characteristics of the included studies are presented in Table S3.

Quality Assessment

Fig 2 presents our risk of bias assessments for the studies. There were 41 RCTs

among the 46 studies in the unclear risk of bias for random sequence generation. None of the studies reported the processes used for allocation concealment or blinding of outcome assessment; only 1 study mentioned the blinding of participants and personnel. The outcome data of all studies were complete, and no other sources of bias were reported.

NMA

Objective response rate

All included studies with a total of 3026 patients reported the data of ORR, with 1945 patients demonstrating an overall response. The network of studies is presented in Fig S1. Bev+ DDP exhibited a significantly higher ORR than DDP alone, yet it was lower compared to the combinations of Endo+ LBP and Endo+ NDP. DDP alone showed a significantly lower ORR than all evaluated treatment regimens, including Endo+ DDP, Endo+ LBP, Endo+ NDP, LBP, and NDP. Furthermore, Endo+ DDP had a lower ORR compared to both Endo+ LBP and Endo+ NDP, whereas Endo+ LBP and Endo+ NDP each displayed significantly higher ORRs than either LBP or NDP alone (Fig S2; Table 1).

The SUCRA rank and probability value results indicated that Endo + LBP (95%) was the most likely to improve the ORR, followed by Endo + NDP (88%), NDP (48%), Endo + DDP (46%), LBP (40%), Bev + DDP (33%), and DDP (0.002%) (Fig S3; Table 2).

Disease control rate

All included studies with a total of 3026 patients reported the data of DCR, with 2586 patients achieving disease control. The network of studies is presented in Fig S1. Bev+ DDP demonstrated a significantly higher DCR compared to DDP alone. DDP, in turn, exhibited a lower DCR relative to Endo+ DDP, Endo+ LBP, Endo+ NDP, and NDP alone. Among these, Endo+ DDP showed a significantly lower DCR than Endo+ LBP, which itself recorded a higher DCR than Endo+ NDP. Moreover, Endo+ NDP achieved

a significantly higher DCR compared to NDP alone (Fig S2; Table S4). The DCR was ranked for all treatments by estimating the SUCRA value. The results were as follows: Endo + LBP (95%), Endo + NDP (83%), Bev + DDP (51%), Endo + DDP (49%), NDP (41%), LBP (30%), and DDP (1%) (Fig S3; Table 2).

Quality of Life

Nineteen studies, involving a total of 1173 patients reported the quality of life, with 654 patients achieving high quality of life. These studies constituted five pairs of direct comparisons involving six interventions (Endo + DDP, Endo + LBP, Bev + DDP, DDP, NDP and LBP). The network diagram is shown in Fig S1. DDP was associated with a lower quality of life compared to Endo + DDP (OR = 0.3, 95% CrI [0.22, 0.39]), Endo + LBP (OR = 0.1, 95% CrI [0.02, 0.57]), and LBP (OR = 0.31, 95% CrI [0.1, 0.93]) (Fig S2; Table S5).

After ranking the six interventions based on the SUCRA values, the results were as follows: Endo + LBP (95%), Endo + DDP (69%), LBP (63%), Bev + DDP (33%), NDP (29%), and DDP (10%), as shown in Fig S3 and Table 2.

Safety and toxicity

Thirty-five studies included 582 patients reported the data of safety profiles. Including a total of 582 patients for any-grade gastrointestinal effect, and 37 patients for grade 3 or higher gastrointestinal effect. A total of 527 patients reported any grade myelosuppressive effect, with 37 patients achieving grade greater than or equal to 3. A total of 122 patients reported any grade hypohepatia, with 9 patients achieving grade greater than or equal to 3. The adverse reactions mainly included myelosuppression, headache, hypohepatia, renal insufficiency, gastrointestinal effects, electrocardiographic abnormalities and fever. Among all types of adverse reactions, the most frequent occurrences were myelosuppressive, hypohepatia and gastrointestinal effects. The NMA included seven therapeutic regimens for TRAEs of any grade and six therapeutic regimens for TRAEs of grade greater than or equal to 3 (Fig S1). We

did not find statistically significant differences in myelosuppression or hypohepatia. A single chemotherapeutic agent caused fewer gastrointestinal reactions (Table S6, Table S7, Table S8, Table S9, Table S10 and Table S11).

The probabilities of adverse events were ranked for all treatments by estimating the SUCRA value. A lower SUCRA value indicated a higher probability of AEs and a poorer treatment regimen. The corresponding ranking of incidences is shown in Fig S3 and Table 2.

Meta-regression analysis

Table 3 showed the results of the meta-regression analysis for demographic and clinical variables (sample size, mean age and sex). Results indicated that none of these variables have significant impact on the ORR and DCR.

Publication bias

The comparison-adjusted funnel plots are presented in Fig S4. Overall, no distinct asymmetry was found in the comparison-adjusted funnel plot on the ORR, DCR, QOL, AG-gastrointestinal effects, AG-myelosuppression, G3-myelosuppression and G3-hypohepatia, indicating no evidence of publication bias. However, the comparison-adjusted funnel plot on AG-gastrointestinal effects, G3-gastrointestinal effects and AG-hypohepatia were not symmetric around the zero line, which revealed that there could be small-study effects.

Discussion

Currently, to the best of our knowledge, intrapleural perfusion with antiangiogenic agents plus chemical agents in controlling MPE conferred satisfying clinical outcomes for patients with NSCLC. Although Endostar/bevacizumab combined with chemotherapy is widely used to treat malignant pleural effusion, there is a lack of head-to-head direct comparisons to determine the best regimen. Hence, we performed a network meta-analysis. In this analysis, two antiangiogenic agents and three chemical

agents formed seven treatment regimens to identify which treatment was optimal in achieving higher clinical responses and QOL and fewer TRAEs. The results suggested the following:

1. Intrapleural administration of Endostar plus lobaplatin was associated with the best ORR and DCR outcomes, followed by Endostar plus nedaplatin.

2. For the ORR, Endo + LBP and Endo + NDP were significantly more favorable than Bev + DDP, while there were no significant differences in the efficacy of Endostar plus chemotherapy or bevacizumab plus chemotherapy with regard to DCR.

Endostar, an endogenous angiogenic inhibitor, can inhibit endothelial cell migration, repress the neovascularization of tumors, block the nutrient supply of tumor cells, and thus prevent tumor proliferation and metastasis. In addition, Endostar reduces the permeability of tumor neovascularization, thereby reducing the production of pleural effusion [63]. In 2022, Yimiao Xia et al. [8] performed a meta-analysis that included 55 RCTs with a total of 3379 patients with lung cancer to investigate the efficacy, safety and cost-effectiveness of Endostar and platinum in controlling MPE. All the studies in the meta-analysis were published in Chinese. This supported the findings in the current network meta-analysis.

Bevacizumab is another frequently studied antiangiogenic agent and plays an important role in the treatment of several types of tumors [7]. It can prevent VEGF-induced vascular permeability and tumor cell migration, thereby reducing MPE [64]. Several studies have demonstrated the efficacy and safety of bevacizumab for the management of MPE. Du et al. [65] compared the efficacy of combined intrapleural therapy with bevacizumab and cisplatin versus cisplatin alone in controlling MPE. The results revealed that bevacizumab plus cisplatin improved the ORR from 50 to 83.3%. However, in our meta-analysis, the pooled ORR of Bev + DDP was 73.8%, and the true efficacy of Bev might have been overestimated. After a literature search, we found no head-to-head comparison between Bev plus other chemical agents and the sole administration of chemical agents other than cisplatin. Therefore, more combination therapeutic regimens still need to be investigated in the future.

MPE is generally considered to be a manifestation of a malignancy in its preterminal stage. Hence, the interventions are palliative in nature. The main goal of treatment is to palliate symptoms and improve quality of life [66]. In our study, we found that intrapleural injection of Endostar combined with DDP was the best in terms of improving QOL, while DDP was the worst.

With regard to the safety profile, although there was no significant difference in the incidence of myelosuppression or hypohepatia between therapeutic regimens in our study, regardless of the severity, the incidence of AG-gastrointestinal effects was significantly more frequent with Endo + DDP and Bev + DDP than with LBP and NDP. Furthermore, in the gastrointestinal effect ranking of the six treatment groups, NDP was the safest, and Endostar plus DDP was the least safe (regardless of the severity (any grade or grade 3 or more)). The results of these analyses suggest that safety considerations may be needed when Endostar plus DDP is administered.

The transitivity assumption, which underlies the validity of network meta-analysis, was assessed by comparing the distribution of key covariates across the included studies. These covariates—mean age, sex ratio, and sample size—were relatively balanced across the different treatment comparisons, suggesting that the assumption of transitivity is plausible. However, it is important to note that unmeasured or inadequately reported effect modifiers could still potentially influence the results. Future studies should aim to collect more homogeneous data and consider additional covariates that may impact treatment effects.

This study had some limitations. First, we utilized only Chinese and English databases, which might have led to retrieval bias, and most of the trials did not report concealment or blinding, which might undermine the validity of the overall findings. Second, all the included RCTs were published in China, and the generalizability of the results is limited. Third, all of the included studies are at unclear risk of bias, and many comparisons rely solely on indirect evidence, as there are no closed loops within the network. This can lead to potentially misleading SUCRA rankings. Therefore, SUCRA rankings should be interpreted with caution. Fourth, although we did not impose

restrictions based on the indexing status of journals during the literature search inclusion criteria, some of these journals are of low quality. The potential influence of journal quality on our results warrants cautious interpretation. Fifth, the absence of closed loops in the network precludes the formal assessment of inconsistency, which is a crucial aspect of NMA. Future studies should aim to include more diverse treatment comparisons to allow for a comprehensive inconsistency evaluation. Sixth, the results in Tables S9-S11 include analyses of all events and are intended to provide a comprehensive perspective. We believe that these results are important in the context of understanding whole-network meta-analyses, although the results for rare events may be subject to greater uncertainty. Because of the rarity of events, the use of informative priors may introduce additional bias, while non-informative priors, although leading to wider CrIs, can more objectively reflect the uncertainty of the data. Therefore, the potential influence on our results should be interpreted with caution.

Conclusions

This network meta-analysis comprehensively compared various treatments for thoracic perfusion of MPE in NSCLC patients and described the QOL and toxicity features. To the best of our knowledge, this is the first comprehensive NMA study of its kind. The results showed that antiangiogenic agents combined with chemotherapy regimens could improve clinical effectiveness and quality of life. In our study, Endo+LBP was the most effective. However, high-quality randomized controlled trials with larger sample sizes are needed to further confirm the evidence.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

YX conducted overall design, data collection, analysis and draft writing. YYC and LMJ were responsible for data collection, partial analysis and partial draft writing. YNY, WS and XHZ were responsible for data collection, YYC and YX revised the manuscript. YX was responsible for the conduct of the study as a guarantor.

Data Availability statement:

All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Conflicts of interest: The authors declare no conflict of interest.

Ethical approval: Not applicable.

Consent for publication: Not applicable

Abbreviations

NSCLC	Non-small cell lung cancer
MPE	Malignant pleural effusion
VEGF	Vascular endothelial growth factor
Rh-endostatin	Recombinant human endostatin
CQVIP	VIP Database
CNKI	Chinese National Knowledge Infrastructure
RCT	Randomized controlled trial
ORR	Objective response rate
DCR	Disease control rate
QOL	Quality of life
CR	Complete response
PR	Partial response

SD	Stable disease
PD	Progressive disease
KPS	Karnofsky performance score
TRAEs	Treatment-related adverse events
≥grade 3 TRAEs	Grade 3 or higher treatment-related adverse events
CrI	Credible intervals
SUCRA	Surface under the cumulative ranking area curve
CI	Confidence intervals
Endo + NDP	Endostar + nedaplatin
Endo + DDP	Endostar + cisplatin
Endo + LBP	Endostar + lobaplatin
Bev + DDP	Bevacizumab + cisplatin
NDP	Nedaplatin
DDP	cisplatin
LBP	lobaplatin

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Table 1 The league table of network meta-analysis for ORR according to all interventions.

OR 95% CrIs						
Bev_DDP						
3.19 (2.11, 4.92)*	DDP					
0.85 (0.53, 1.37)	0.27 (0.22, 0.33)*	Endo_DDP				
0.16 (0.05, 0.53)*	**0.05 (0.02, 0.15)***	**0.19 (0.06, 0.59)***	Endo_LBP			
0.25 (0.09, 0.68)*	**0.08 (0.03, 0.2)***	**0.29 (0.11, 0.75)***	**1.54 (0.35, 6.84)**	Endo_NDP		
0.92 (0.4, 2.03)	0.29 (0.14, 0.56)*	**1.08 (0.52, 2.18)**	5.69 (2.37, 14.65)*	**3.73 (1.17, 12.04)***	LBP	
0.81 (0.38, 1.71)	0.25 (0.13, 0.46)*	**0.95 (0.49, 1.81)**	**5.06 (1.39, 19.02)***	3.28 (1.65, 6.76)*	**0.88 (0.35, 2.24)**	NDP

Abbreviation: *p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate.

Table 2 Rank probabilities of each treatment for different outcome measures based on the network meta-analysis

	BEV_DDP	**DDP**	**Endo_DDP**	**Endo_LBP**	**Endo_NDP**	**LBP**	**NDP**
ORR	0.33	0.00002	0.46	0.95	0.88	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83	0.30	0.41
QOL	0.33	0.10	0.69	0.95	/	0.63	0.29
Gastrointestinal effect	0.32	0.28	0.18	0.47	0.56	0.80	0.89
Myelosuppressive	0.63	0.64	0.58	0.40	0.19	0.59	0.47
Hypohepatia	0.55	0.46	0.35	0.57	0.30	0.65	0.62
G3-gastrointestinal effect	0.40	0.35	0.19	/	0.54	0.71	0.81
G3-myelosuppression	0.39	0.48	0.37	/	0.32	0.64	0.81
G3-hypohepatia	0.21	0.30	0.72	/	0.45	0.57	0.74

Abbreviation: Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, ORR : Objective response rate, DCR: Disease control rate, QOL: quality of life, G3: grade 3 or higher.
The data are listed as SUCRA values (rank) and higher SUCRA values indicate better outcomes.

Table 3 Meta-regression analysis for the impact of potential factors on the outcomes

	Overall response rate		Disease control rate	
	β coefficient (95%CI)	P value	β coefficient (95%CI)	P value
Sample size	-0.65 (-1.91, 0.62)	0.316	-0.73 (-2.47, 1.00)	0.408
Mean age	0.36 (-0.59, 1.31)	0.459	0.18 (-1.28, 1.64)	0.810
Sex	0.12 (-0.84, 1.08)	0.811	-1.26 (-2.72, 0.20)	0.091

Abbreviation: 95%CI: 95% confidence interval.

Figure legends

Fig 1 The flow diagram of the study selection process for the network meta-analysis

Fig 2 Assessment of risk of bias.

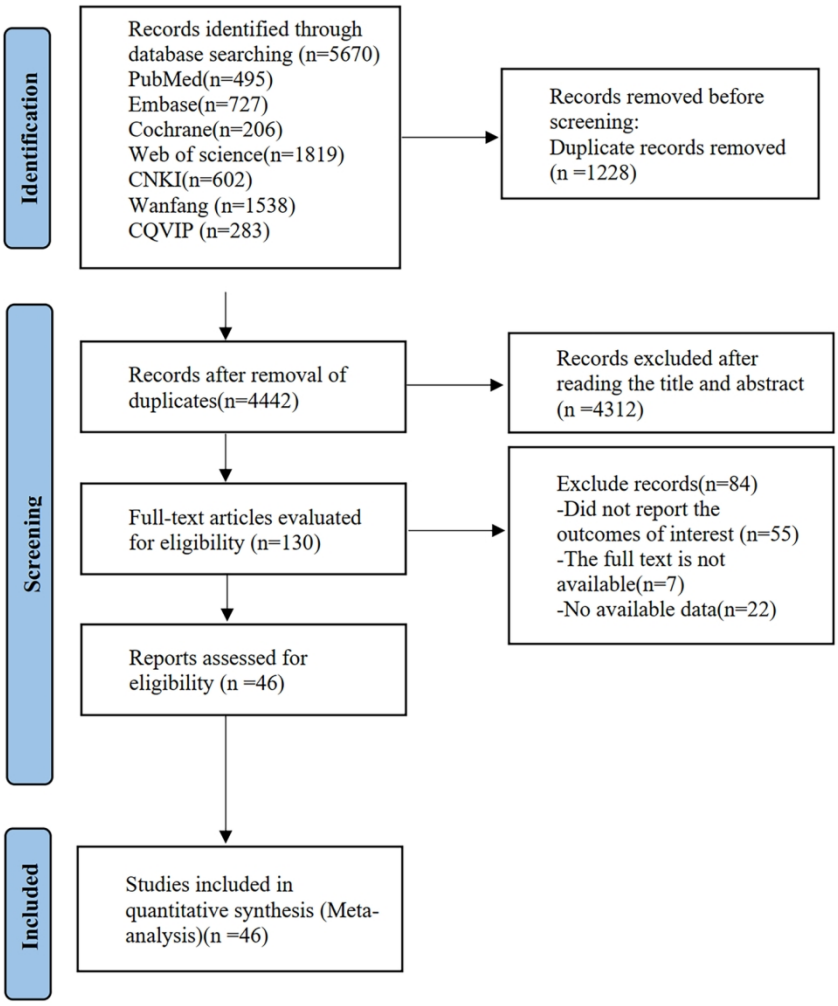

Fig 1

149x171mm (300 x 300 DPI)

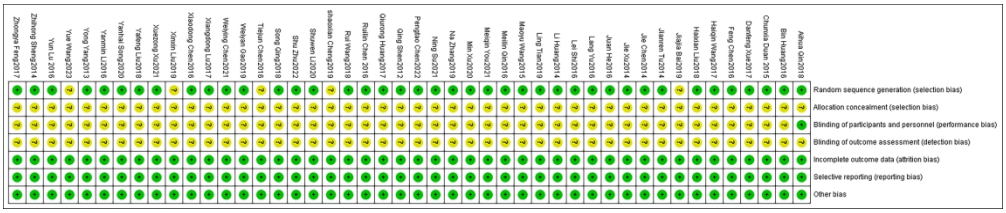

Fig 2

455x93mm (300 x 300 DPI)

Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

Supplementary Materials

Table of Contents

Table S1 PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3, 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5, 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7, 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7, 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8-9, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8-9
Study characteristics	17	Cite each included study and present its characteristics.	9, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9, Fig.2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-12

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	12-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	14

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S2 Literature Search Strategy

Database and Search strategy	5670
CNKI	
(主题=肺癌 + 肺恶性肿瘤 + 原发性支气管癌 + 支气管癌) AND (主题=恶性胸腔积液 + 恶性胸腔积液 + 癌性胸水 + 癌性胸腔积液 + 恶性胸膜腔积液 + 恶性胸水 + 恶性胸腹水 + 恶性胸腹水 + 恶性胸腔液) AND (主题=贝伐珠单抗 + 恩度 + 重组人血管内皮抑制素 + 化疗 + 化学疗法 + 化学药物治疗 + 化学治疗)	602
CQVIP	
(((((题名或关键词=肺癌 OR 题名或关键词=肺恶性肿瘤) OR 题名或关键词=原发性支气管癌) OR 题名或关键词=支气管癌) AND ((((((题名或关键词=恶性胸腔积液 OR 题名或关键词=癌性胸水) OR 题名或关键词=癌性胸腔积液) OR 题名或关键词=恶性胸腔积液) OR 题名或关键词=恶性胸水) OR 题名或关键词=恶性胸腹水) OR 题名或关键词=恶性胸腔液)) AND ((((((题名或关键词=贝伐珠单抗 OR 题名或关键词=恩度) OR 题名或关键词=重组人血管内皮抑制素) OR 题名或关键词=化疗) OR 题名或关键词=化学疗法) OR 题名或关键词=化学药物治疗) OR 题名或关键词=化学治疗))	283
Wanfang	
主题:(肺癌 OR 肺恶性肿瘤 OR 原发性支气管癌 OR 支气管癌) and 主题:(恶性胸腔积液 OR 癌性胸水 OR 癌性胸腔积液 OR 恶性胸膜腔积液 OR 恶性胸水 OR 恶性胸腹水 OR 恶性胸腔液) and 主题:(贝伐珠单抗 OR 恩度 OR 重组人血管内皮抑制素 OR 化疗 OR 化学疗法 OR 化学药物治疗 OR 化学治疗)	1538
PubMed	
((((("Drug Therapy"[Mesh]) OR (((((((Drug Therapy[Title/Abstract]) OR (Therapy, Drug[Title/Abstract])) OR (Drug Therapies[Title/Abstract])) OR (Therapies, Drug[Title/Abstract])) OR (Chemotherapy[Title/Abstract])) OR (Chemotherapies[Title/Abstract])) OR (Pharmacotherapy[Title/Abstract])) OR (Pharmacotherapies[Title/Abstract]))) OR (("Bevacizumab"[Mesh]) OR (((((((((Bevacizumab[Title/Abstract]) OR (Mvasi[Title/Abstract])) OR (Bevacizumab-awwb[Title/Abstract])) OR (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) OR (Endostar[Title/Abstract])) OR (recombinant human endostatin[Title/Abstract])) OR (Rh endostatin[Title/Abstract])) OR (yh-16[Title/Abstract])))) AND (("Lung Neoplasms"[Mesh])	495

OR ((((((((((((((((Lung Neoplasms[Title/Abstract]) OR (Pulmonary Neoplasms[Title/Abstract])) OR (Neoplasms, Lung[Title/Abstract])) OR (Lung Neoplasm[Title/Abstract])) OR (Neoplasm, Lung[Title/Abstract])) OR (Neoplasms, Pulmonary[Title/Abstract])) OR (Neoplasm, Pulmonary[Title/Abstract])) OR (Pulmonary Neoplasm[Title/Abstract])) OR (Lung Cancer[Title/Abstract])) OR (Cancer, Lung[Title/Abstract])) OR (Cancers, Lung[Title/Abstract])) OR (Lung Cancers[Title/Abstract])) OR (Pulmonary Cancer[Title/Abstract])) OR (Cancer, Pulmonary[Title/Abstract])) OR (Cancers, Pulmonary[Title/Abstract])) OR (Pulmonary Cancers[Title/Abstract])) OR (Cancer of Lung[Title/Abstract])) OR (Cancer of the Lung[Title/Abstract])) OR (Cancer of Lung[Title/Abstract]))))) AND (("Pleural Effusion, Malignant"[Mesh]) OR ((((((Pleural Effusion, Malignant[Title/Abstract]) OR (Malignant Pleural Effusion[Title/Abstract])) OR (Effusion, Malignant Pleural[Title/Abstract])) OR (Effusions, Malignant Pleural[Title/Abstract])) OR (Malignant Pleural Effusions[Title/Abstract])) OR (Pleural Effusions, Malignant[Title/Abstract]))))		
Embase		
#1	'lung tumor'/exp	727
#2	'lung tumor':ab,ti	
#3	'pulmonary neoplasms':ab,ti	
#4	'neoplasms, lung':ab,ti	
#5	'lung neoplasm':ab,ti	
#6	'neoplasm, lung':ab,ti	
#7	'neoplasms, pulmonary':ab,ti	
#8	'neoplasm, pulmonary':ab,ti	
#9	'pulmonary neoplasm':ab,ti	

#10	'lung cancer':ab,ti	
#11	'cancer, lung':ab,ti	
#12	'cancers, lung':ab,ti	
#13	'lung cancers':ab,ti	
#14	'pulmonary cancer':ab,ti	
#15	'cancer, pulmonary':ab,ti	
#16	'cancers, pulmonary':ab,ti	
#17	'pulmonary cancers':ab,ti	
#18	'cancer of the lung':ab,ti	
#19	'cancer of lung':ab,ti	
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	
#21	'malignant pleura effusion'/exp	
#22	'malignant pleura effusion':ab,ti	
#23	'effusion, malignant pleural':ab,ti	

#24	'effusions, malignant pleural':ab,ti	
#25	'malignant pleural effusions':ab,ti	
#26	'pleural effusions, malignant':ab,ti	
#27	'pleural effusion, malignant':ab,ti	
#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	
#29	'bevacizumab'/exp	
#30	'bevacizumab':ab,ti	
#31	'mvasi':ab,ti	
#32	'bevacizumab-awwb':ab,ti	
#33	'bevacizumab awwb':ab,ti	
#34	'avastin':ab,ti	
#35	'endostar':ab,ti	
#36	'recombinant human endostatin':ab,ti	
#37	'rh endostatin':ab,ti	

#38	'yh-16':ab,ti	
#39	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	
#40	'drug therapy'/exp	
#41	'drug therapy':ab,ti	
#42	'therapy, drug':ab,ti	
#43	'drug therapies':ab,ti	
#44	'therapies, drug':ab,ti	
#45	'chemotherapy':ab,ti	
#46	'chemotherapies':ab,ti	
#47	'pharmacotherapy':ab,ti	
#48	'pharmacotherapies':ab,ti	
#49	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	
#50	#39 OR #49	
#51	#20 AND #28 AND #50	

Cochrane		
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	206
#2	(Lung Neoplasms):ti,ab,kw OR (Pulmonary Neoplasms):ti,ab,kw OR (Neoplasms, Lung):ti,ab,kw OR (Lung Neoplasm):ti,ab,kw OR (Neoplasm, Lung):ti,ab,kw	
#3	(Neoplasms, Pulmonary):ti,ab,kw OR (Neoplasm, Pulmonary):ti,ab,kw OR (Pulmonary Neoplasm):ti,ab,kw OR (Lung Cancer):ti,ab,kw OR (Cancer, Lung):ti,ab,kw	
#4	(Cancers, Lung):ti,ab,kw OR (Lung Cancers):ti,ab,kw OR (Pulmonary Cancer):ti,ab,kw OR (Cancer, Pulmonary):ti,ab,kw OR (Cancers, Pulmonary):ti,ab,kw	
#5	(Pulmonary Cancers):ti,ab,kw OR (Cancer of the Lung):ti,ab,kw OR (Cancer of Lung):ti,ab,kw	
#6	#1 or #2 or #3 or #4 or #5	
#7	MeSH descriptor: [Pleural Effusion, Malignant] explode all trees	
#8	(Pleural Effusion, Malignant):ti,ab,kw OR (Malignant Pleural Effusion):ti,ab,kw OR (Effusion, Malignant Pleural):ti,ab,kw OR (Effusions, Malignant Pleural):ti,ab,kw OR (Malignant Pleural Effusions):ti,ab,kw 725 #9 (Pleural Effusions, Malignant):ti,ab,kw	
#9	(Pleural Effusions, Malignant):ti,ab,kw	
#10	#7 or #8 or #9	
#11	MeSH descriptor: [Bevacizumab] explode all trees	
#12	(Bevacizumab):ti,ab,kw OR (Mvasi):ti,ab,kw OR (Bevacizumab-awwb):ti,ab,kw OR (Bevacizumab awwb):ti,ab,kw OR (Avastin):ti,ab,kw 7448 #13 (Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#13	(Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#14	#11 or #12 or #13	
#15	MeSH descriptor: [Drug Therapy] explode all trees	
#16	(Drug Therapy):ti,ab,kw OR (Therapy, Drug):ti,ab,kw OR (Drug Therapies):ti,ab,kw OR (Therapies, Drug):ti,ab,kw OR (Chemotherapy):ti,ab,kw	

#17	(Chemotherapies):ti,ab,kw OR (Pharmacotherapy):ti,ab,kw OR (Pharmacotherapies):ti,ab,kw	
#18	#15 or #16 or #17	
#19	#14 or #18	
#20	#19 and #6 and #10	
Web of science		
#1	TS=(Lung Neoplasms) OR TS=(Pulmonary Neoplasms) OR TS=(Neoplasms, Lung) OR TS=(Lung Neoplasm) OR TS=(Neoplasm, Lung) OR TS=(Neoplasms, Pulmonary) OR TS=(Neoplasm, Pulmonary) OR TS=(Pulmonary Neoplasm) OR TS=(Lung Cancer) OR TS=(Cancer, Lung) OR TS=(Cancers, Lung) OR TS=(Lung Cancers) OR TS=(Pulmonary Cancer) OR TS=(Cancer, Pulmonary) OR TS=(Cancers, Pulmonary) OR TS=(Pulmonary Cancers) OR TS=(Cancer of the Lung) OR TS=(Cancer of Lung) and 预印本 (排除 – 数据库)	1819
#2	TS=(Pleural Effusion, Malignant) OR TS=(Malignant Pleural Effusion) OR TS=(Effusion, Malignant Pleural) OR TS=(Effusions, Malignant Pleural) OR TS=(Malignant Pleural Effusions) OR TS=(Pleural Effusions, Malignant) and 预印本 (排除 – 数据库)	
#3	TS=(Bevacizumab) OR TS=(Mvasi) OR TS=(Bevacizumab-awwb) OR TS=(Bevacizumab awwb) OR TS=(Avastin) OR TS=(Endostar) OR TS=(recombinant human endostatin) OR TS=(Rh endostatin) OR TS=(yh-16) and 预印本 (排除 – 数据库)	
#4	TS=(Drug Therapy) OR TS=(Therapy, Drug) OR TS=(Drug Therapies) OR TS=(Therapies, Drug) OR TS=(Chemotherapy) OR TS=(Chemotherapies) OR TS=(Pharmacotherapy) OR TS=(Pharmacotherapies) and 预印本 (排除 – 数据库)	
#5	#4 OR #3 and 预印本 (排除 – 数据库)	
#6	#5 AND #2 AND #1 and 预印本 (排除 – 数据库)	

Table S3 Characteristics of the included randomized controlled trials.

Study	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Intervention	outcome
F. Chen et al. 2016 [17]	Endo_DDP:30 DDP:30	39/21	/	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,2,3
Chen et al. 2014[18]	Endo_DDP:30 DDP:30	44/16	54.3±5.6/ 55.6±4.5	NR	NR	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg: 2/week, 3 cycles	P1,3
R. Chen et al. 2016[19]	Endo_DDP:45 DDP:45	53/37	60.6±7.2/ 60.8±7.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Duan et al. 2015[20]	Endo_DDP:19 DDP:19	23/15	61.4	Moderate to large	≥60	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Feng 2017[21]	Endo_DDP:27 DDP:27	32/22	59.15±10.26/ 58.71±10.04	Moderate to large	NR	Endo 30 mg_DDP 30mg: 1/week, 3 cycles DDP 30mg: 1/week, 3 cycles	P1
He et al. 2016[22]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2
Huang 2014[23]	Endo_DDP:25 DDP:25	30/20	41. 5 ± 7. 6	Moderate to large	>60	Endo 30 mg 2/week _DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

Li 2020[24]	Endo_DDP:20 DDP:20	24/16	62.3±1.7/ 62.5±1.5	Moderate to large	NR	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,3
Li 2016[25]	Endo_DDP:31 DDP:31	35/27	42.22±6.92/ 42.14±6.89	NR	>60	Endo 30 mg 2/week_DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3
Liu et al. 2019[26]	Endo_DDP:30 DDP:30	36/24	52.64±6.55/ 53.31±7.56	NR	≥60	Endo 45 mg/m^2_DDP 30mg: 2/week, 2-3 cycles DDP 30mg: 2/week, 2-3 cycles	P1,3
Liu et al. 2018[27]	Endo_DDP:34 DDP:34	38/30	63.19±4.73/ 65.55±5.28	Moderate to large	≥60	Endo 60 mg _DDP 60mg: 2/week DDP 60mg: 2/week	P1,2,3
Lu and Zhang 2017[28]	Endo_DDP:31 DDP:31	35/27	46.3±10.6/ 45.7±11.3	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Qin 2016[29]	Endo_DDP:21 DDP:21	24/18	59.6	Moderate to large	≥60	Endo 60 mg_DDP 50mg: 1/week, 3 cycles DDP 50mg: 1/week, 3 cycles	P1,3
Qing et al. 2018[30]	Endo_DDP:28 DDP:23	22/27	68.2±4.6/ 68.2±4.6	NR	NR	Endo 35 mg/m^2_DDP 60mg/m^2: 2/week, 3 cycles DDP 60mg/m^2: 2/week, 3 cycles	P1,2,3,4
Shen et al. 2012[31]	Endo_DDP:40 DDP:40	42/38	37-79	Moderate to large	≥60	Endo 30 mg 2/week_DDP 40mg: 1/week, 3 cycles DDP 40mg: 1/week, 3 cycles	P1,2,3
Su et al. 2021[32]	Endo_DDP:30 DDP:30	37/23	61.43±6.45/ 62.05±6.29	NR	NR	Endo 60 mg_DDP 40-50mg: 2/week, 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,3

Qin 2018[33]	Endo_DDP:42 DDP:42	43/41	56.84±7.03/ 57.19±8.25	NR	NR	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Tian et al. 2019[34]	Endo_DDP:48 DDP:48	57/39	59.26±2.43/ 61.54±2.32	Moderate to large	≥60	Endo 30 mg 4/week_DDP 30-40mg/m^2: 2/week, 1 cycle DDP 30-40mg/m^2: 2/week, 1 cycle	P1
Tu et al. 2014[35]	Endo_DDP:45 DDP:45	48/42	46.5±11.5/ 47.5±10.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Wang et al. 2017[36]	Endo_DDP:40 DDP:40	41/39	55.5±2.2/ 55.8±2.9	Large	≥60	Endo 40 mg_DDP 40mg/week: 4 cycles DDP 40mg: 1/week, 4 cycles	P1,2,3
Wang 2018[37]	Endo_DDP:30 DDP:30	35/25	61.28±6.32/ 60.54±5.65	NR	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,3
Wang 2023[38]	Endo_DDP:47 DDP:47	51/43	53.47±3.25/ 54.09±3.38	NR	≥80	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1
Xu et al. 202[39]	Endo_DDP:20 DDP:20	27/13	/	Large	≥50	Endo 60 mg_DDP 40-50mg: 2/week: 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,2,3,4
Xu et al. 2021[40]	Endo_DDP:75 DDP:75	79/71	63.65±5.11/ 63.87±5.38	NR	NR	Endo 45 mg_DDP 10mg: 1/week: 3 cycles DDP 10mg: 1/week, 3 cycles	P1,3
(Yang et al. 2013[41]	Endo_DDP:21 DDP:21	27/15	41.5±7.6	Large	NR	Endo 30 mg_DDP 40mg 1/week: 3 cycles	P1,2,3,4

						DDP 40mg: 1/week, 3 cycles	
Yu 2016[42]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Liu and Tan 2018[43]	Endo_DDP:26 DDP:26	23/29	41-75/39-75	Moderate to large	NR	Endo 45mg_DDP 30mg: 2/week: 2-3 cycles DDP 30mg: 2/week: 2-3 cycles	P1,3
Lu et al. 2016[44]	Endo_DDP:30 DDP:30	28/32	/	Moderate to large	NR	Endo 30mg_DDP 30mg: 3 days: 1-2 cycles DDP 30mg: 3/6 days: 1-2 cycles	P1,2
Shi et al. 2016[45]	Endo_LBP:21 LBP:21	25/17	42.3±5.6	Moderate to large	NR	Endo 30mg 2/week: 3 cycles_LBP: 30mg/m^2: 1/3 week, 1 cycle LBP: 30mg/m^2: 1/3 week, 1 cycle	P1,2,4
Chen 2021[46]	Endo_LBP: 30 LBP:30	39/21	50.31±4.27/ 50.16±4.35	Moderate to large	NR	Endo 30mg_LBP: 30mg/m^2: 1/week, 4 cycles LBP: 30mg/m^2: 1/week, 4 cycles	P1,3
Cheng et al. 2019[47]	Endo_NDP: 46 NDP:46	45/47	/	NR	NR	Endo 7.5mg/m^2 7/week, 4 cycles _NDP 30mg/m^2: 1/week, 2-4 cycles NDP 30mg/m^2: 1/week, 2-4 cycles	P1
Xu et al. 2014[48]	Endo_NDP: 35 NDP:35	43/27	62.5±5.5	Moderate to large	NR	Endo 60mg_NDP 60mg: 1/week, 2 cycles NDP 60mg: 1/week, 2cycles	P1,3
You et al. 2021[49]	Bev_DDP: 29 DDP:29	32/26	69.86±11.36/ 67.92±9.83	NR	≥70	Bev 300mg, d1,q3w_DDP 40mg d1,8,15, q3w: 1 cycle DDP: 40mg d1, 8, 15, q3w: 1 cycle	P1

Chen and Ai 2022[50]	Bev_DDP: 35 DDP:35	45/25	65.16 ±9. 34/ 65.08± 9.26	NR	NR	Bev 300mg, d1,q3w_DDP 50mg d1,8,15, q3w: 1 cycle DDP: 50mg d1, 8, 15, q3w: 1 cycle	P1,3
Zhang et al. 2019[51]	Bev_DDP: 34 DDP:34	33/35	61.62±2.78/ 61.38±2.94	NR	>60	Bev 300mg_DDP 60mg, 2weeks: 4 cycles DDP: 60mg 1/2weeks, 4cycles	P1,3
Song 2020[52]	Bev_DDP: 36 DDP:36	45/27	58.58±4.45/ 58.69±4.87	NR	>60	Bev 5mg/kg_DDP 45mg/m^2, 1/week, 3 cycles DDP: 45mg/m^2, 1/week, 3cycles	P1,3
Xue and Zhao 2017[53]	Bev_DDP: 41 DDP:41	47/35	58.21±3.25/ 58.96±3.43	NR	NR	Bev 5mg/kg_DDP 60mg, 1/week, 3 cycles DDP: 60mg, 1/week, 3cycles	P1,3
Huang 2016[54]	Bev_DDP: 37 DDP:36	53/20	60.28±6.17/ 61.31±6.05	Moderate to large	>70	Bev 5mg/kg_DDP 40mg: 1/week, 3 cycles DDP: 40mg, 1/week, 3cycles	P1,2,3
T. Chen et al. 2016[55]	Bev_DDP: 24 DDP:24	31/17	54.6±7.7	Moderate to large	NR	Bev 300mg_DDP 60mg: 1/2 weeks, 1 cycle DDP: 60mg, 1/2 weeks, 1 cycle	P1,3
Wang et al. 2015[56]	NDP: 24 DDP:24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m^2,1/week,3-4 cycles DDP: 40mg/m^2,1/week,3-4cycles	P1,2,3
Zhu et al. 2022[57]	NDP: 40 DDP:40	48/32	56.78±8.92/ 57.18±9.12	NR	NR	NDP: 40mg/m^2,1/week,4 cycles DDP: 40mg/m^2,1/week,4 cycles	P1,3
Bai 2019[58]	NDP: 30 DDP:28	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3
X. Chen et al. 2016[59]	NDP: 39 DDP:40	43/36	55.8±8.1/ 58.2±7.3	Large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3,4

Huang et al. 2017[60]	LBP: 38 DDP:38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Sheng 2014[61]	LBP: 30 DDP:30	20/40	38-74	Moderate to large	≥60	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Gao et al. 2019[62]	LBP: 30 DDP:31	37/24	57-69/54-68	Moderate to large	≥60	LBP: 30mg/m^2,1/week, 2-4 cycles DDP: 40mg/m^2,1/week, 2-4 cycles	P1,2,3

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin. NR, not reported.
Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quality of life (QOL); P3: treatment-related adverse events (TRAEs); P4: survivals.

Table S4 The league table of network meta-analysis for DCR according to all interventions.

OR 95% CrIs						
Bev_DDP						
3.51 (2.03, 6.28)*	DDP					
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP				
0.15 (0.01, 1.03)	**0.04 (0, 0.27)***	**0.15 (0.02, 0.93)***	Endo_LBP			
0.36 (0.07, 1.73)	**0.1 (0.02, 0.44)***	**0.35 (0.07, 1.54)**	**2.37 (0.21, 33.93)**	Endo_NDP		
1.59 (0.46, 5.15)	0.45 (0.15, 1.26)	**1.54 (0.48, 4.47)**	9.99 (2.38, 76.59)*	**4.39 (0.7, 28.93)**	LBP	
1.18 (0.32, 3.88)	0.34 (0.1, 0.95)*	**1.14 (0.33, 3.36)**	**7.62 (0.87, 91.12)**	3.21 (1.22, 9.5)	**0.74 (0.16, 3.45)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

Table S5 The league table of network meta-analysis for QOL according to all interventions.

OR 95% CrIs						
Bev_DDP						
1.56 (0.52, 4.94)	DDP					
0.47 (0.15, 1.52)	0.3 (0.22, 0.39)*	Endo_DDP				
0.16 (0.02, 1.26)	**0.1 (0.02, 0.57)***	**0.34 (0.05, 1.95)**	Endo_LBP			
0.49 (0.1, 2.39)	0.31 (0.1, 0.93)*	**1.05 (0.31, 3.25)**	3.06 (0.82, 12.66)	LBP		
1.09 (0.21, 5.56)	0.7 (0.21, 2.22)	**2.35 (0.69, 7.75)**	**6.93 (0.85, 60.14)**	**2.25 (0.45, 11.58)**	NDP	

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, QOL: quality of life.

Table S6 League tables of all grades myelosuppressive event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.99 (0.55, 1.76)	DDP					
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP				
0.68 (0.1, 4.32)	**0.69 (0.11, 4.01)**	**0.71 (0.11, 4.25)**	Endo_LBP			
0.46 (0.1, 2.05)	**0.47 (0.11, 1.84)**	**0.49 (0.11, 1.98)**	**0.68 (0.07, 6.89)**	Endo_NDP		
0.96 (0.42, 2.18)	0.98 (0.54, 1.74)	**1.01 (0.53, 1.94)**	1.42 (0.27, 8.33)	**2.08 (0.47, 9.88)**	LBP	
0.85 (0.37, 1.93)	0.86 (0.48, 1.54)	**0.89 (0.46, 1.71)**	**1.25 (0.2, 8.81)**	1.83 (0.53, 6.94)	**0.88 (0.39, 2.02)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S7 League tables of all grades gastrointestinal effect event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.93 (0.58, 1.49)	DDP					
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP				
1.58 (0.04, 24.01)	**1.7 (0.05, 24.68)**	**1.86 (0.05, 27.49)**	Endo_LBP			
2.15 (0.22, 15.02)	**2.31 (0.25, 15.24)**	**2.52 (0.27, 17.04)**	**1.37 (0.04, 70.76)**	Endo_NDP		
4 (1.82, 8.94)*	4.29 (2.3, 8.26)*	**4.69 (2.36, 9.59)***	2.52 (0.19, 83.76)	**1.87 (0.25, 18.78)**	LBP	
5.01 (2.37, 10.84)*	5.39 (3.02, 9.89)*	**5.89 (3.07, 11.51)***	**3.19 (0.2, 113.19)**	2.32 (0.39, 20.25)	**1.26 (0.53, 2.99)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP:

Bevacizumab + cisplatin.

Table S8 League tables of all grades hypohepatia e event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.86 (0.29, 2.5)	DDP					
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP				
1.2 (0.02, 64.26)	**1.39 (0.03, 65.71)**	**1.63 (0.03, 80.3)**	Endo_LBP			
0.43 (0.01, 8)	**0.5 (0.01, 7.53)**	**0.58 (0.02, 9.69)**	**0.34 (0, 38.81)**	Endo_NDP		
1.2 (0.25, 5.83)	1.39 (0.45, 4.41)	**1.62 (0.44, 6.12)**	1 (0.03, 40.32)	**2.82 (0.14, 112.78)**	LBP	
1.09 (0.29, 4.08)	1.26 (0.58, 2.74)	**1.47 (0.54, 4.05)**	**0.91 (0.02, 45.55)**	2.5 (0.18, 81.39)	**0.91 (0.22, 3.56)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S9 League tables of G3-myelosuppressive event comparison of all interventions.

OR 95% CrIs					
Bev_DDP					
1.19 (0.37, 3.93)	DDP				
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP			
0.02 (0, 1158726093196.45)	**0.02 (0, 946584795528.83)**	**0.02 (0, 1200464612598)**	Endo_NDP		
3.03 (0.17, 114.1)	2.48 (0.19, 79.56)	**3.18 (0.2, 112.91)**	**179.3 (0, 13158904182927350)**	LBP	
2806.8 (0, 7080696058054300)	2358.54 (0, 5857536555380624)	**3012.84 (0, 7540937082788929)**	86977.28 (0.72, 28713088892365632)	**877.08 (0, 2259231168436329)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.
Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S10 League tables of G3-gastrointestinal effect event comparison of all interventions.

OR 95% CrIs					
Bev_DDP					
0.87 (0.32, 2.38)	DDP				
0.43 (0.05, 3.16)	0.5 (0.06, 2.74)	Endo_DDP			
146.72 (0, 2.25957982568521e+21)	**170.13 (0, 2.60852595759042e+21)**	**346.11 (0, 5.58712188787727e+21)**	Endo_NDP		
4.96 (0.76, 48.98)	5.6 (1.18, 45.11)*	**11.87 (1.1, 198.58)***	**0.04 (0, 1389506420906047 84)**	LBP	
97135.18 (0, 1.05993280385622e+20)	110659.48 (0, 1.25474480157232e+20)	**230346.59 (0, 2.61196338258981e+20)**	1349.63 (0, 1822912067429389107)	**18857.28 (0, 21936173709446430720)**	ND P

*p<0.05. Data bolded in black indicate they are from an indirect comparison.
ORs between the included interventions according to the results of network meta-analysis.
Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S11 League tables of G3-hypohepatia event comparison of all interventions.

OR 95% CrIs			
Bev_DDP			
1.36 (0.33, 5.91)	DDP		
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP	
3.64 (0, 4662.71)	**2.67 (0, 2952.95)**	**0.17 (0, 561.64)**	Endo_NDP

7.15 (0.05, 3005.42)	5.2 (0.05, 1901.09)	**0.37 (0, 382.55)**	**2.15 (0, 16410.56)**	LBP	
18.95 (0.38, 4882.5)	13.51 (0.37, 3023.28)	**1.03 (0, 666.32)**	5.38 (0.05, 2025.4)	**2.79 (0, 3102.18)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

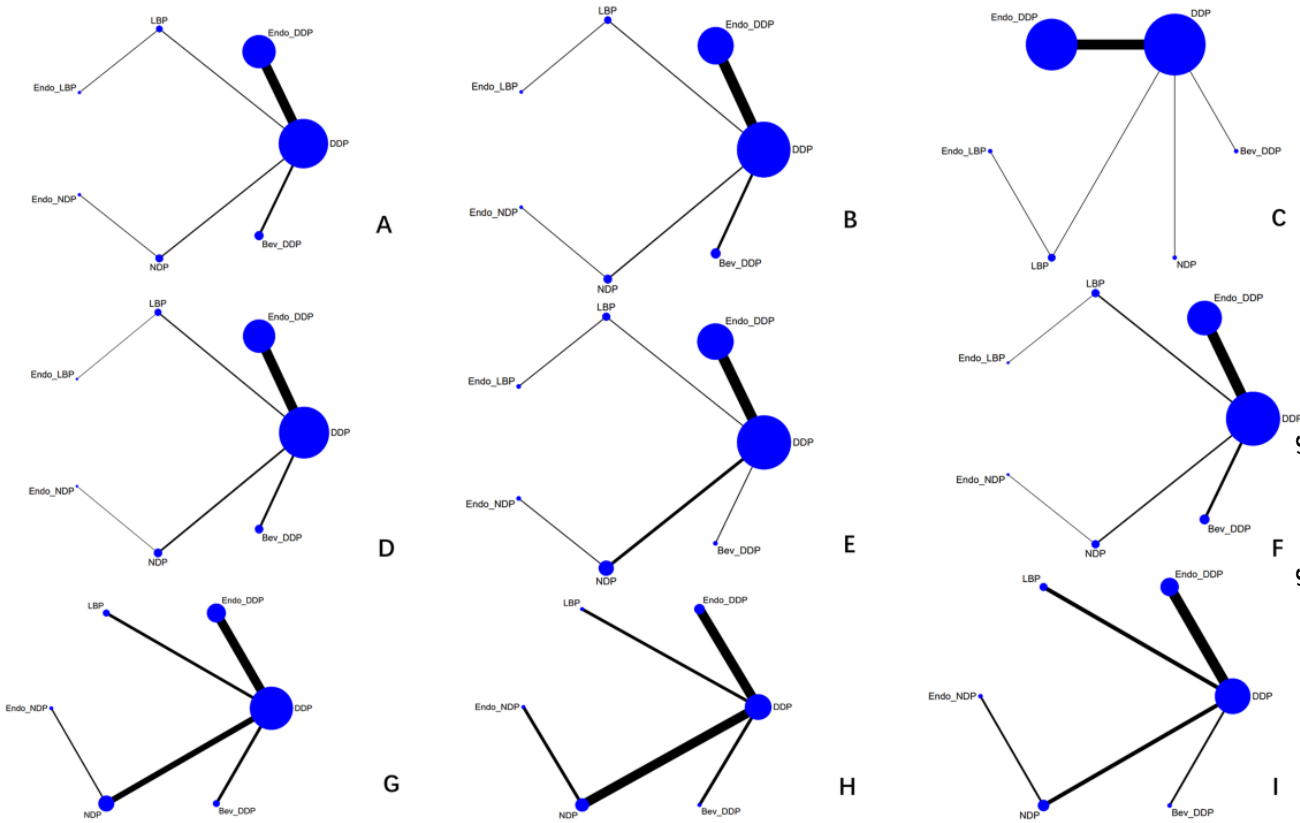

Fig S1 Network graph for different outcomes.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

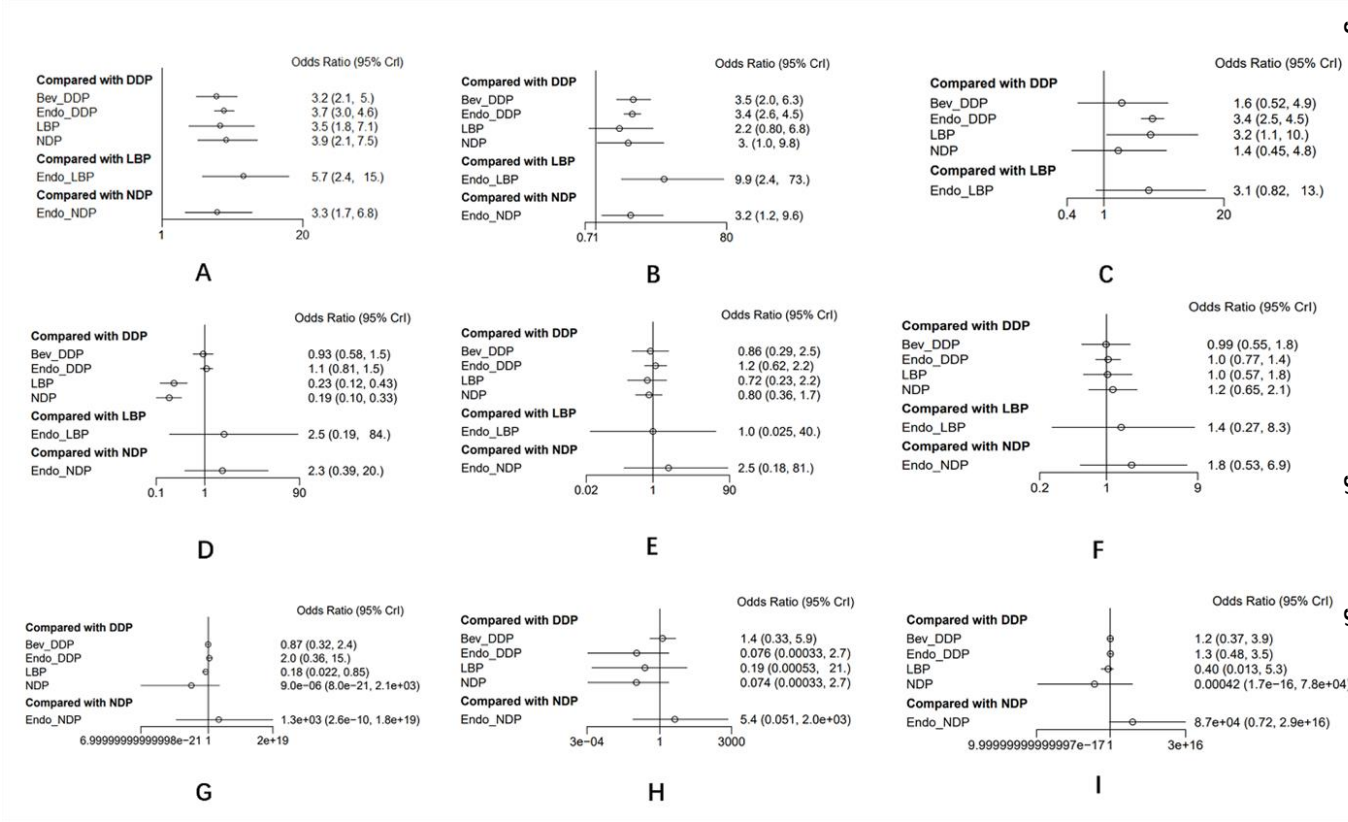

Fig S2 Forest plots of efficacy outcomes by Bayesian framework.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

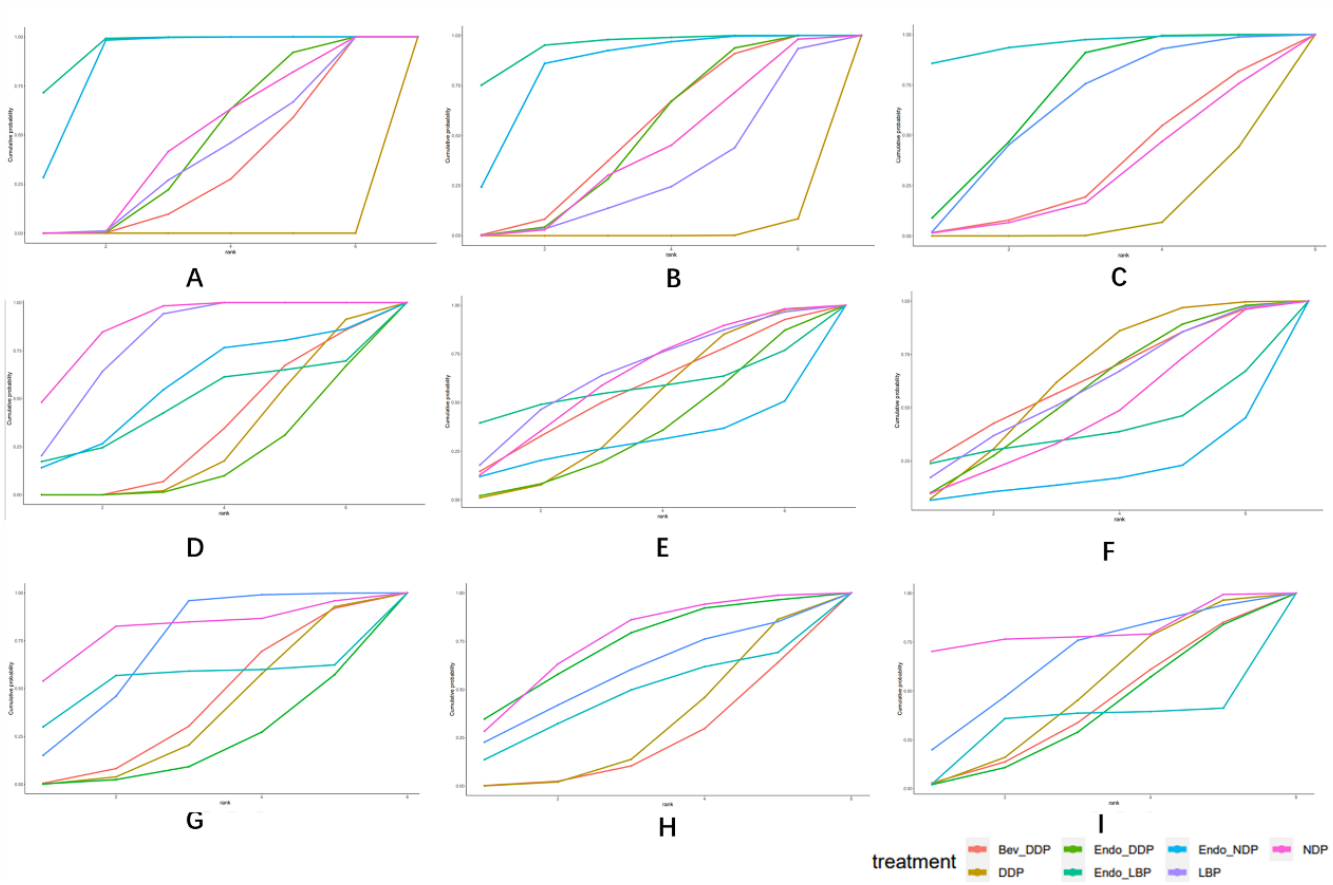

Fig S3 Sequence diagram of the network meta-analysis.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

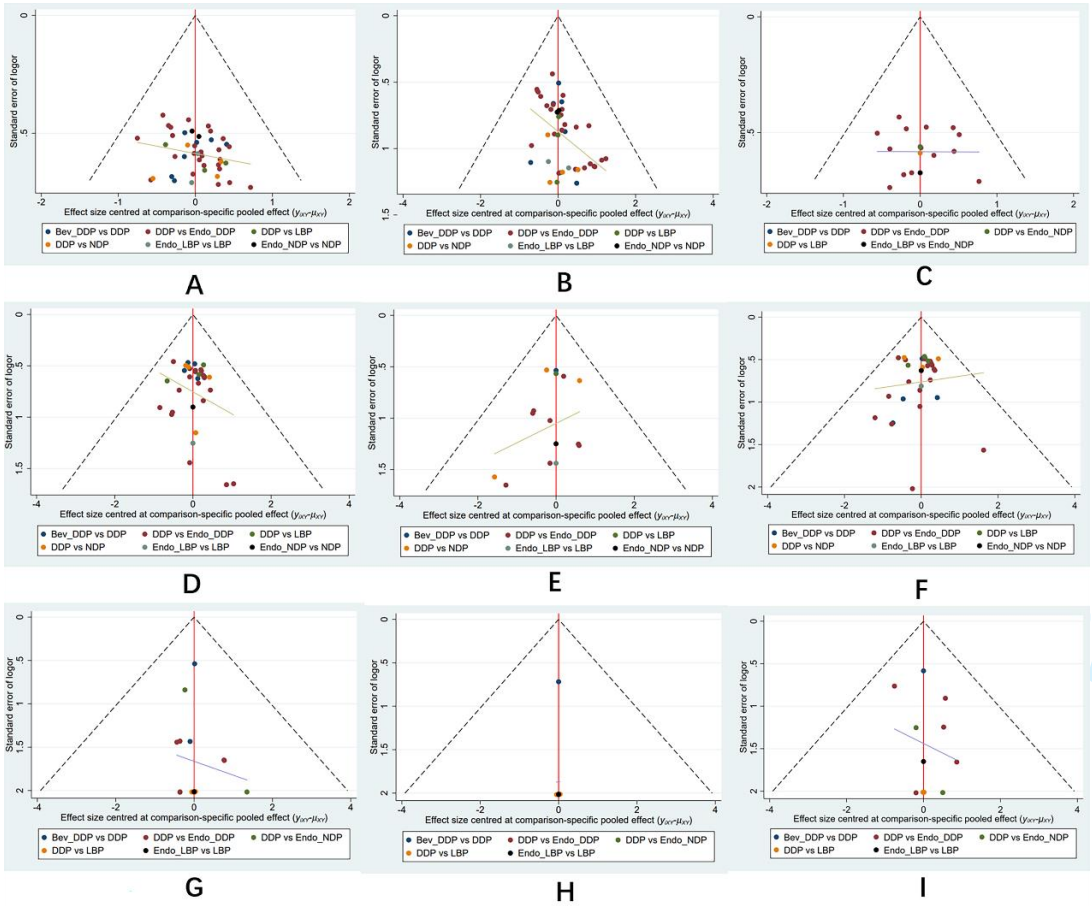

Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive.

ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: A network meta-analysis

Supplementary Materials

Table of Contents

Table S1 PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3, 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5, 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7, 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7, 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8-9, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8-9
Study characteristics	17	Cite each included study and present its characteristics.	9, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9, Fig.2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-12

Section and Topic	Item #	Checklist item	Location where item is reported
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	12-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	14

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table S2 Literature Search Strategy

Database and Search strategy	5670
CNKI	
(Theme = lung cancer + primary bronchial cancer + bronchial cancer) AND (Theme = malignant pleural effusion) AND (Theme = bevacizumab + endostar + recombinant human endostatin + chemotherapy)	602
CQVIP	
(((((title OR key words = lung cancer OR title OR key words = lung malignant tumor) OR title OR key words = primary bronchial carcinoma) AND ((((((title OR key words = malignant pleural effusion OR title OR key words = cancerous pleural effusion) OR Title OR key words = malignant pleural effusion) AND ((((((title OR keywords = bevacizumab OR Endostar (OR) OR recombinant human endostatin (OR) chemotherapy (OR)	283
Wanfang	
Subject :(lung cancer OR lung malignancy OR primary bronchial cancer OR bronchial cancer) and subject :(malignant pleural effusion OR malignant pleural ascites OR malignant pleural fluid) and subject :(bevacizumab) OR endostar OR recombinant human endostatin OR chemotherapy)	1538
PubMed	
((((("Drug Therapy"[Mesh]) OR (((((((Drug Therapy[Title/Abstract]) OR (Therapy, Drug[Title/Abstract])) OR (Drug Therapies[Title/Abstract])) OR (Therapies, Drug[Title/Abstract])) OR (Chemotherapy[Title/Abstract])) OR (Chemotherapies[Title/Abstract])) OR (Pharmacotherapy[Title/Abstract])) OR (Pharmacotherapies[Title/Abstract]))) OR (("Bevacizumab"[Mesh]) OR (((((((((Bevacizumab[Title/Abstract]) OR (Mvasi[Title/Abstract])) OR (Bevacizumab-awwb[Title/Abstract])) OR (Bevacizumab awwb[Title/Abstract])) OR (Avastin[Title/Abstract])) OR (Endostar[Title/Abstract])) OR (recombinant human endostatin[Title/Abstract])) OR (Rh endostatin[Title/Abstract])) OR (yh-16[Title/Abstract])))) AND (("Lung Neoplasms"[Mesh])	495

OR ((((((((((((((((Lung Neoplasms[Title/Abstract]) OR (Pulmonary Neoplasms[Title/Abstract])) OR (Neoplasms, Lung[Title/Abstract])) OR (Lung Neoplasm[Title/Abstract])) OR (Neoplasm, Lung[Title/Abstract])) OR (Neoplasms, Pulmonary[Title/Abstract])) OR (Neoplasm, Pulmonary[Title/Abstract])) OR (Pulmonary Neoplasm[Title/Abstract])) OR (Lung Cancer[Title/Abstract])) OR (Cancer, Lung[Title/Abstract])) OR (Cancers, Lung[Title/Abstract])) OR (Lung Cancers[Title/Abstract])) OR (Pulmonary Cancer[Title/Abstract])) OR (Cancer, Pulmonary[Title/Abstract])) OR (Cancers, Pulmonary[Title/Abstract])) OR (Pulmonary Cancers[Title/Abstract])) OR (Cancer of Lung[Title/Abstract])) OR (Cancer of the Lung[Title/Abstract])) OR (Cancer of Lung[Title/Abstract]))))) AND (("Pleural Effusion, Malignant"[Mesh]) OR ((((((Pleural Effusion, Malignant[Title/Abstract]) OR (Malignant Pleural Effusion[Title/Abstract])) OR (Effusion, Malignant Pleural[Title/Abstract])) OR (Effusions, Malignant Pleural[Title/Abstract])) OR (Malignant Pleural Effusions[Title/Abstract])) OR (Pleural Effusions, Malignant[Title/Abstract]))))	
Embase		
#1	'lung tumor'/exp	727
#2	'lung tumor':ab,ti	
#3	'pulmonary neoplasms':ab,ti	
#4	'neoplasms, lung':ab,ti	
#5	'lung neoplasm':ab,ti	
#6	'neoplasm, lung':ab,ti	
#7	'neoplasms, pulmonary':ab,ti	
#8	'neoplasm, pulmonary':ab,ti	
#9	'pulmonary neoplasm':ab,ti	

#10	'lung cancer':ab,ti	
#11	'cancer, lung':ab,ti	
#12	'cancers, lung':ab,ti	
#13	'lung cancers':ab,ti	
#14	'pulmonary cancer':ab,ti	
#15	'cancer, pulmonary':ab,ti	
#16	'cancers, pulmonary':ab,ti	
#17	'pulmonary cancers':ab,ti	
#18	'cancer of the lung':ab,ti	
#19	'cancer of lung':ab,ti	
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	
#21	'malignant pleura effusion'/exp	
#22	'malignant pleura effusion':ab,ti	
#23	'effusion, malignant pleural':ab,ti	

#24	'effusions, malignant pleural':ab,ti	
#25	'malignant pleural effusions':ab,ti	
#26	'pleural effusions, malignant':ab,ti	
#27	'pleural effusion, malignant':ab,ti	
#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	
#29	'bevacizumab'/exp	
#30	'bevacizumab':ab,ti	
#31	'mvasi':ab,ti	
#32	'bevacizumab-awwb':ab,ti	
#33	'bevacizumab awwb':ab,ti	
#34	'avastin':ab,ti	
#35	'endostar':ab,ti	
#36	'recombinant human endostatin':ab,ti	
#37	'rh endostatin':ab,ti	

#38	'yh-16':ab,ti	
#39	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	
#40	'drug therapy'/exp	
#41	'drug therapy':ab,ti	
#42	'therapy, drug':ab,ti	
#43	'drug therapies':ab,ti	
#44	'therapies, drug':ab,ti	
#45	'chemotherapy':ab,ti	
#46	'chemotherapies':ab,ti	
#47	'pharmacotherapy':ab,ti	
#48	'pharmacotherapies':ab,ti	
#49	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	
#50	#39 OR #49	
#51	#20 AND #28 AND #50	

Cochrane		
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	206
#2	(Lung Neoplasms):ti,ab,kw OR (Pulmonary Neoplasms):ti,ab,kw OR (Neoplasms, Lung):ti,ab,kw OR (Lung Neoplasm):ti,ab,kw OR (Neoplasm, Lung):ti,ab,kw	
#3	(Neoplasms, Pulmonary):ti,ab,kw OR (Neoplasm, Pulmonary):ti,ab,kw OR (Pulmonary Neoplasm):ti,ab,kw OR (Lung Cancer):ti,ab,kw OR (Cancer, Lung):ti,ab,kw	
#4	(Cancers, Lung):ti,ab,kw OR (Lung Cancers):ti,ab,kw OR (Pulmonary Cancer):ti,ab,kw OR (Cancer, Pulmonary):ti,ab,kw OR (Cancers, Pulmonary):ti,ab,kw	
#5	(Pulmonary Cancers):ti,ab,kw OR (Cancer of the Lung):ti,ab,kw OR (Cancer of Lung):ti,ab,kw	
#6	#1 or #2 or #3 or #4 or #5	
#7	MeSH descriptor: [Pleural Effusion, Malignant] explode all trees	
#8	(Pleural Effusion, Malignant):ti,ab,kw OR (Malignant Pleural Effusion):ti,ab,kw OR (Effusion, Malignant Pleural):ti,ab,kw OR (Effusions, Malignant Pleural):ti,ab,kw OR (Malignant Pleural Effusions):ti,ab,kw 725 #9 (Pleural Effusions, Malignant):ti,ab,kw	
#9	(Pleural Effusions, Malignant):ti,ab,kw	
#10	#7 or #8 or #9	
#11	MeSH descriptor: [Bevacizumab] explode all trees	
#12	(Bevacizumab):ti,ab,kw OR (Mvasi):ti,ab,kw OR (Bevacizumab-awwb):ti,ab,kw OR (Bevacizumab awwb):ti,ab,kw OR (Avastin):ti,ab,kw 7448 #13 (Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#13	(Endostar):ti,ab,kw OR (recombinant human endostatin):ti,ab,kw OR (Rh endostatin):ti,ab,kw OR (yh-16):ti,ab,kw	
#14	#11 or #12 or #13	
#15	MeSH descriptor: [Drug Therapy] explode all trees	
#16	(Drug Therapy):ti,ab,kw OR (Therapy, Drug):ti,ab,kw OR (Drug Therapies):ti,ab,kw OR (Therapies, Drug):ti,ab,kw OR (Chemotherapy):ti,ab,kw	

#17	(Chemotherapies):ti,ab,kw OR (Pharmacotherapy):ti,ab,kw OR (Pharmacotherapies):ti,ab,kw	
#18	#15 or #16 or #17	
#19	#14 or #18	
#20	#19 and #6 and #10	
Web of science		
#1	TS=(Lung Neoplasms) OR TS=(Pulmonary Neoplasms) OR TS=(Neoplasms, Lung) OR TS=(Lung Neoplasm) OR TS=(Neoplasm, Lung) OR TS=(Neoplasms, Pulmonary) OR TS=(Neoplasm, Pulmonary) OR TS=(Pulmonary Neoplasm) OR TS=(Lung Cancer) OR TS=(Cancer, Lung) OR TS=(Cancers, Lung) OR TS=(Lung Cancers) OR TS=(Pulmonary Cancer) OR TS=(Cancer, Pulmonary) OR TS=(Cancers, Pulmonary) OR TS=(Pulmonary Cancers) OR TS=(Cancer of the Lung) OR TS=(Cancer of Lung) and Preprint (Excluded - database)	1819
#2	TS=(Pleural Effusion, Malignant) OR TS=(Malignant Pleural Effusion) OR TS=(Effusion, Malignant Pleural) OR TS=(Effusions, Malignant Pleural) OR TS=(Malignant Pleural Effusions) OR TS=(Pleural Effusions, Malignant) and Preprint (Excluded - database)	
#3	TS=(Bevacizumab) OR TS=(Mvasi) OR TS=(Bevacizumab-awwb) OR TS=(Bevacizumab awwb) OR TS=(Avastin) OR TS=(Endostar) OR TS=(recombinant human endostatin) OR TS=(Rh endostatin) OR TS=(yh-16) and Preprint (Excluded - database)	
#4	TS=(Drug Therapy) OR TS=(Therapy, Drug) OR TS=(Drug Therapies) OR TS=(Therapies, Drug) OR TS=(Chemotherapy) OR TS=(Chemotherapies) OR TS=(Pharmacotherapy) OR TS=(Pharmacotherapies) and Preprint (Excluded - database)	
#5	#4 OR #3 and Preprint (Excluded - database)	
#6	#5 AND #2 AND #1 and Preprint (Excluded - database)	

Table S3 Characteristics of the included randomized controlled trials.

Study	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Intervention	outcome
F. Chen et al. 2016 [17]	Endo_DDP:30 DDP:30	39/21	/	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,2,3
Chen et al. 2014[18]	Endo_DDP:30 DDP:30	44/16	54.3±5.6/ 55.6±4.5	NR	NR	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg: 2/week, 3 cycles	P1,3
R. Chen et al. 2016[19]	Endo_DDP:45 DDP:45	53/37	60.6±7.2/ 60.8±7.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Duan et al. 2015[20]	Endo_DDP:19 DDP:19	23/15	61.4	Moderate to large	≥60	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Feng 2017[21]	Endo_DDP:27 DDP:27	32/22	59.15±10.26/ 58.71±10.04	Moderate to large	NR	Endo 30 mg_DDP 30mg: 1/week, 3 cycles DDP 30mg: 1/week, 3 cycles	P1
He et al. 2016[22]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2
Huang 2014[23]	Endo_DDP:25 DDP:25	30/20	41. 5 ± 7. 6	Moderate to large	>60	Endo 30 mg 2/week _DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

Li 2020[24]	Endo_DDP:20 DDP:20	24/16	62.3±1.7/ 62.5±1.5	Moderate to large	NR	Endo 45 mg_DDP 40mg/m^2: 1/week, 3 cycles DDP 40mg/m^2: 1/week, 3 cycles	P1,3
Li 2016[25]	Endo_DDP:31 DDP:31	35/27	42.22±6.92/ 42.14±6.89	NR	>60	Endo 30 mg 2/week_DDP 40mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3
Liu et al. 2019[26]	Endo_DDP:30 DDP:30	36/24	52.64±6.55/ 53.31±7.56	NR	≥60	Endo 45 mg/m^2_DDP 30mg: 2/week, 2-3 cycles DDP 30mg: 2/week, 2-3 cycles	P1,3
Liu et al. 2018[27]	Endo_DDP:34 DDP:34	38/30	63.19±4.73/ 65.55±5.28	Moderate to large	≥60	Endo 60 mg _DDP 60mg: 2/week DDP 60mg: 2/week	P1,2,3
Lu and Zhang 2017[28]	Endo_DDP:31 DDP:31	35/27	46.3±10.6/ 45.7±11.3	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Qin 2016[29]	Endo_DDP:21 DDP:21	24/18	59.6	Moderate to large	≥60	Endo 60 mg_DDP 50mg: 1/week, 3 cycles DDP 50mg: 1/week, 3 cycles	P1,3
Qing et al. 2018[30]	Endo_DDP:28 DDP:23	22/27	68.2±4.6/ 68.2±4.6	NR	NR	Endo 35 mg/m^2_DDP 60mg/m^2: 2/week, 3 cycles DDP 60mg/m^2: 2/week, 3 cycles	P1,2,3,4
Shen et al. 2012[31]	Endo_DDP:40 DDP:40	42/38	37-79	Moderate to large	≥60	Endo 30 mg 2/week_DDP 40mg: 1/week, 3 cycles DDP 40mg: 1/week, 3 cycles	P1,2,3
Su et al. 2021[32]	Endo_DDP:30 DDP:30	37/23	61.43±6.45/ 62.05±6.29	NR	NR	Endo 60 mg_DDP 40-50mg: 2/week, 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,3

Qin 2018[33]	Endo_DDP:42 DDP:42	43/41	56.84±7.03/ 57.19±8.25	NR	NR	Endo 40 mg_DDP 40mg/m^2: 1/week, 4 cycles DDP 40mg/m^2: 1/week, 4 cycles	P1,2
Tian et al. 2019[34]	Endo_DDP:48 DDP:48	57/39	59.26±2.43/ 61.54±2.32	Moderate to large	≥60	Endo 30 mg 4/week_DDP 30-40mg/m^2: 2/week, 1 cycle DDP 30-40mg/m^2: 2/week, 1 cycle	P1
Tu et al. 2014[35]	Endo_DDP:45 DDP:45	48/42	46.5±11.5/ 47.5±10.5	Moderate to large	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Wang et al. 2017[36]	Endo_DDP:40 DDP:40	41/39	55.5±2.2/ 55.8±2.9	Large	≥60	Endo 40 mg_DDP 40mg/week: 4 cycles DDP 40mg: 1/week, 4 cycles	P1,2,3
Wang 2018[37]	Endo_DDP:30 DDP:30	35/25	61.28±6.32/ 60.54±5.65	NR	≥60	Endo 45 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,3
Wang 2023[38]	Endo_DDP:47 DDP:47	51/43	53.47±3.25/ 54.09±3.38	NR	≥80	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1
Xu et al. 202[39]	Endo_DDP:20 DDP:20	27/13	/	Large	≥50	Endo 60 mg_DDP 40-50mg: 2/week: 2 cycles DDP 40-50mg: 2/week, 2 cycles	P1,2,3,4
Xu et al. 2021[40]	Endo_DDP:75 DDP:75	79/71	63.65±5.11/ 63.87±5.38	NR	NR	Endo 45 mg_DDP 10mg: 1/week: 3 cycles DDP 10mg: 1/week, 3 cycles	P1,3
(Yang et al. 2013[41]	Endo_DDP:21 DDP:21	27/15	41.5±7.6	Large	NR	Endo 30 mg_DDP 40mg 1/week: 3 cycles	P1,2,3,4

						DDP 40mg: 1/week, 3 cycles	
Yu 2016[42]	Endo_DDP:27 DDP:25	32/20	60.28±6.17/ 61.31±6.05	Moderate to large	≥70	Endo 30 mg_DDP 40mg/m^2: 2/week, 3 cycles DDP 40mg/m^2: 2/week, 3 cycles	P1,2,3
Liu and Tan 2018[43]	Endo_DDP:26 DDP:26	23/29	41-75/39-75	Moderate to large	NR	Endo 45mg_DDP 30mg: 2/week: 2-3 cycles DDP 30mg: 2/week: 2-3 cycles	P1,3
Lu et al. 2016[44]	Endo_DDP:30 DDP:30	28/32	/	Moderate to large	NR	Endo 30mg_DDP 30mg: 3 days: 1-2 cycles DDP 30mg: 3/6 days: 1-2 cycles	P1,2
Shi et al. 2016[45]	Endo_LBP:21 LBP:21	25/17	42.3±5.6	Moderate to large	NR	Endo 30mg 2/week: 3 cycles_LBP: 30mg/m^2: 1/3 week, 1 cycle LBP: 30mg/m^2: 1/3 week, 1 cycle	P1,2,4
Chen 2021[46]	Endo_LBP: 30 LBP:30	39/21	50.31±4.27/ 50.16±4.35	Moderate to large	NR	Endo 30mg_LBP: 30mg/m^2: 1/week, 4 cycles LBP: 30mg/m^2: 1/week, 4 cycles	P1,3
Cheng et al. 2019[47]	Endo_NDP: 46 NDP:46	45/47	/	NR	NR	Endo 7.5mg/m^2 7/week, 4 cycles _NDP 30mg/m^2: 1/week, 2-4 cycles NDP 30mg/m^2: 1/week, 2-4 cycles	P1
Xu et al. 2014[48]	Endo_NDP: 35 NDP:35	43/27	62.5±5.5	Moderate to large	NR	Endo 60mg_NDP 60mg: 1/week, 2 cycles NDP 60mg: 1/week, 2cycles	P1,3
You et al. 2021[49]	Bev_DDP: 29 DDP:29	32/26	69.86±11.36/ 67.92±9.83	NR	≥70	Bev 300mg, d1,q3w_DDP 40mg d1,8,15, q3w: 1 cycle DDP: 40mg d1, 8, 15, q3w: 1 cycle	P1

Chen and Ai 2022[50]	Bev_DDP: 35 DDP:35	45/25	65.16 ±9. 34/ 65.08± 9.26	NR	NR	Bev 300mg, d1,q3w_DDP 50mg d1,8,15, q3w: 1 cycle DDP: 50mg d1, 8, 15, q3w: 1 cycle	P1,3
Zhang et al. 2019[51]	Bev_DDP: 34 DDP:34	33/35	61.62±2.78/ 61.38±2.94	NR	>60	Bev 300mg_DDP 60mg_2weeks: 4 cycles DDP: 60mg 1/2weeks, 4cycles	P1,3
Song 2020[52]	Bev_DDP: 36 DDP:36	45/27	58.58±4.45/ 58.69±4.87	NR	>60	Bev 5mg/kg_DDP 45mg/m^2, 1/week, 3 cycles DDP: 45mg/m^2, 1/week, 3cycles	P1,3
Xue and Zhao 2017[53]	Bev_DDP: 41 DDP:41	47/35	58.21±3.25/ 58.96±3.43	NR	NR	Bev 5mg/kg_DDP 60mg, 1/week, 3 cycles DDP: 60mg, 1/week, 3cycles	P1,3
Huang 2016[54]	Bev_DDP: 37 DDP:36	53/20	60.28±6.17/ 61.31±6.05	Moderate to large	>70	Bev 5mg/kg_DDP 40mg: 1/week, 3 cycles DDP: 40mg, 1/week, 3cycles	P1,2,3
T. Chen et al. 2016[55]	Bev_DDP: 24 DDP:24	31/17	54.6±7.7	Moderate to large	NR	Bev 300mg_DDP 60mg: 1/2 weeks, 1 cycle DDP: 60mg, 1/2 weeks, 1 cycle	P1,3
Wang et al. 2015[56]	NDP: 24 DDP:24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m^2,1/week,3-4 cycles DDP: 40mg/m^2,1/week,3-4cycles	P1,2,3
Zhu et al. 2022[57]	NDP: 40 DDP:40	48/32	56.78±8.92/ 57.18±9.12	NR	NR	NDP: 40mg/m^2,1/week,4 cycles DDP: 40mg/m^2,1/week,4 cycles	P1,3
Bai 2019[58]	NDP: 30 DDP:28	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3
X. Chen et al. 2016[59]	NDP: 39 DDP:40	43/36	55.8±8.1/ 58.2±7.3	Large	≥60	NDP: 40mg/m^2,1/week, 2-4cycles DDP: 40mg/m^2,1/week, 2-4cycles	P1,3,4

Huang et al. 2017[60]	LBP: 38 DDP:38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Sheng 2014[61]	LBP: 30 DDP:30	20/40	38-74	Moderate to large	≥60	LBP: 30mg/m^2,1-2/week, 2-4 cycles DDP: 30mg/m^2,1-2/week, 2-4 cycles	P1,3
Gao et al. 2019[62]	LBP: 30 DDP:31	37/24	57-69/54-68	Moderate to large	≥60	LBP: 30mg/m^2,1/week, 2-4 cycles DDP: 40mg/m^2,1/week, 2-4 cycles	P1,2,3

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin. NR, not reported.
Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quality of life (QOL); P3: treatment-related adverse events (TRAEs); P4: survivals.

Table S4 The league table of network meta-analysis for DCR according to all interventions.

OR 95% CrIs						
Bev_DDP						
3.51 (2.03, 6.28)*	DDP					
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP				
0.15 (0.01, 1.03)	**0.04 (0, 0.27)***	**0.15 (0.02, 0.93)***	Endo_LBP			
0.36 (0.07, 1.73)	**0.1 (0.02, 0.44)***	**0.35 (0.07, 1.54)**	**2.37 (0.21, 33.93)**	Endo_NDP		
1.59 (0.46, 5.15)	0.45 (0.15, 1.26)	**1.54 (0.48, 4.47)**	9.99 (2.38, 76.59)*	**4.39 (0.7, 28.93)**	LBP	
1.18 (0.32, 3.88)	0.34 (0.1, 0.95)*	**1.14 (0.33, 3.36)**	**7.62 (0.87, 91.12)**	3.21 (1.22, 9.52)	**0.74 (0.16, 3.45)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

Table S5 The league table of network meta-analysis for QOL according to all interventions.

OR 95% CrIs					
Bev_DDP					
1.56 (0.52, 4.94)	DDP				
0.47 (0.15, 1.52)	0.3 (0.22, 0.39)*	Endo_DDP			
0.16 (0.02, 1.26)	**0.1 (0.02, 0.57)***	**0.34 (0.05, 1.95)**	Endo_LBP		
0.49 (0.1, 2.39)	0.31 (0.1, 0.93)*	**1.05 (0.31, 3.25)**	3.06 (0.82, 12.66)	LBP	
1.09 (0.21, 5.56)	0.7 (0.21, 2.22)	**2.35 (0.69, 7.75)**	**6.93 (0.85, 60.14)**	**2.25 (0.45, 11.58)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, QOL: quality of life.

Table S6 League tables of all grades myelosuppressive event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.99 (0.55, 1.76)	DDP					
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP				
0.68 (0.1, 4.32)	**0.69 (0.11, 4.01)**	**0.71 (0.11, 4.25)**	Endo_LBP			
0.46 (0.1, 2.05)	**0.47 (0.11, 1.84)**	**0.49 (0.11, 1.98)**	**0.68 (0.07, 6.89)**	Endo_NDP		
0.96 (0.42, 2.18)	0.98 (0.54, 1.74)	**1.01 (0.53, 1.94)**	1.42 (0.27, 8.33)	**2.08 (0.47, 9.88)**	LBP	
0.85 (0.37, 1.93)	0.86 (0.48, 1.54)	**0.89 (0.46, 1.71)**	**1.25 (0.2, 8.81)**	1.83 (0.53, 6.94)	**0.88 (0.39, 2.02)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S7 League tables of all grades gastrointestinal effect event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.93 (0.58, 1.49)	DDP					
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP				
1.58 (0.04, 24.01)	**1.7 (0.05, 24.68)**	**1.86 (0.05, 27.49)**	Endo_LBP			
2.15 (0.22, 15.02)	**2.31 (0.25, 15.24)**	**2.52 (0.27, 17.04)**	**1.37 (0.04, 70.76)**	Endo_NDP		
4 (1.82, 8.94)*	4.29 (2.3, 8.26)*	**4.69 (2.36, 9.59)***	2.52 (0.19, 83.76)	**1.87 (0.25, 18.78)**	LBP	
5.01 (2.37, 10.84)*	5.39 (3.02, 9.89)*	**5.89 (3.07, 11.51)***	**3.19 (0.2, 113.19)**	2.32 (0.39, 20.25)	**1.26 (0.53, 2.99)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP:

Bevacizumab + cisplatin.

Table S8 League tables of all grades hypohepatia e event comparison of all interventions.

OR 95% CrIs						
Bev_DDP						
0.86 (0.29, 2.5)	DDP					
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP				
1.2 (0.02, 64.26)	**1.39 (0.03, 65.71)**	**1.63 (0.03, 80.3)**	Endo_LBP			
0.43 (0.01, 8)	**0.5 (0.01, 7.53)**	**0.58 (0.02, 9.69)**	**0.34 (0, 38.81)**	Endo_NDP		
1.2 (0.25, 5.83)	1.39 (0.45, 4.41)	**1.62 (0.44, 6.12)**	1 (0.03, 40.32)	**2.82 (0.14, 112.7)**	LBP	
1.09 (0.29, 4.08)	1.26 (0.58, 2.74)	**1.47 (0.54, 4.05)**	**0.91 (0.02, 45.55)**	2.5 (0.18, 81.39)	**0.91 (0.22, 3.56)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

Table S9 League tables of G3-myelosuppressive event comparison of all interventions.

OR 95% CrIs					
Bev_DDP					
1.19 (0.37, 3.93)	DDP				
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP			
0.02 (0, 1158726093196.45)	**0.02 (0, 946584795528.83)**	**0.02 (0, 1200464612598)**	Endo_NDP		
3.03 (0.17, 114.1)	2.48 (0.19, 79.56)	**3.18 (0.2, 112.91)**	**179.3 (0, 13158904182927350)**	LBP	
2806.8 (0, 7080696058054300)	2358.54 (0, 5857536555380624)	**3012.84 (0, 7540937082788929)**	86977.28 (0.72, 28713088892365632)	**877.08 (0, 2259231168436329)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S10 League tables of G3-gastrointestinal effect event comparison of all interventions.

OR 95% CrIs					
Bev_DDP					
0.87 (0.32, 2.38)	DDP				
0.43 (0.05, 3.16)	0.5 (0.06, 2.74)	Endo_DDP			
146.72 (0, 2.25957982568521e+21)	**170.13 (0, 2.60852595759042e+21)**	**346.11 (0, 5.58712188787727e+21)**	Endo_NDP		
4.96 (0.76, 48.98)	5.6 (1.18, 45.11)*	**11.87 (1.1, 198.58)***	**0.04 (0, 1389506420906047 84)**	LBP	
97135.18 (0, 1.05993280385622e+20)	110659.48 (0, 1.25474480157232e+20)	**230346.59 (0, 2.61196338258981e+20)**	1349.63 (0, 1822912067429389107)	**18857.28 (0, 21936173709446430720)**	ND P

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

Table S11 League tables of G3-hypohepatia event comparison of all interventions.

OR 95% CrIs			
Bev_DDP			
1.36 (0.33, 5.91)	DDP		
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP	
3.64 (0, 4662.71)	**2.67 (0, 2952.95)**	**0.17 (0, 561.64)**	Endo_NDP

7.15 (0.05, 3005.42)	5.2 (0.05, 1901.09)	**0.37 (0, 382.55)**	**2.15 (0, 16410.56)**	LBP	
18.95 (0.38, 4882.5)	13.51 (0.37, 3023.28)	**1.03 (0, 666.32)**	5.38 (0.05, 2025.4)	**2.79 (0, 3102.18)**	NDP

*p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included interventions according to the results of network meta-analysis.

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, G3: grade 3 or higher.

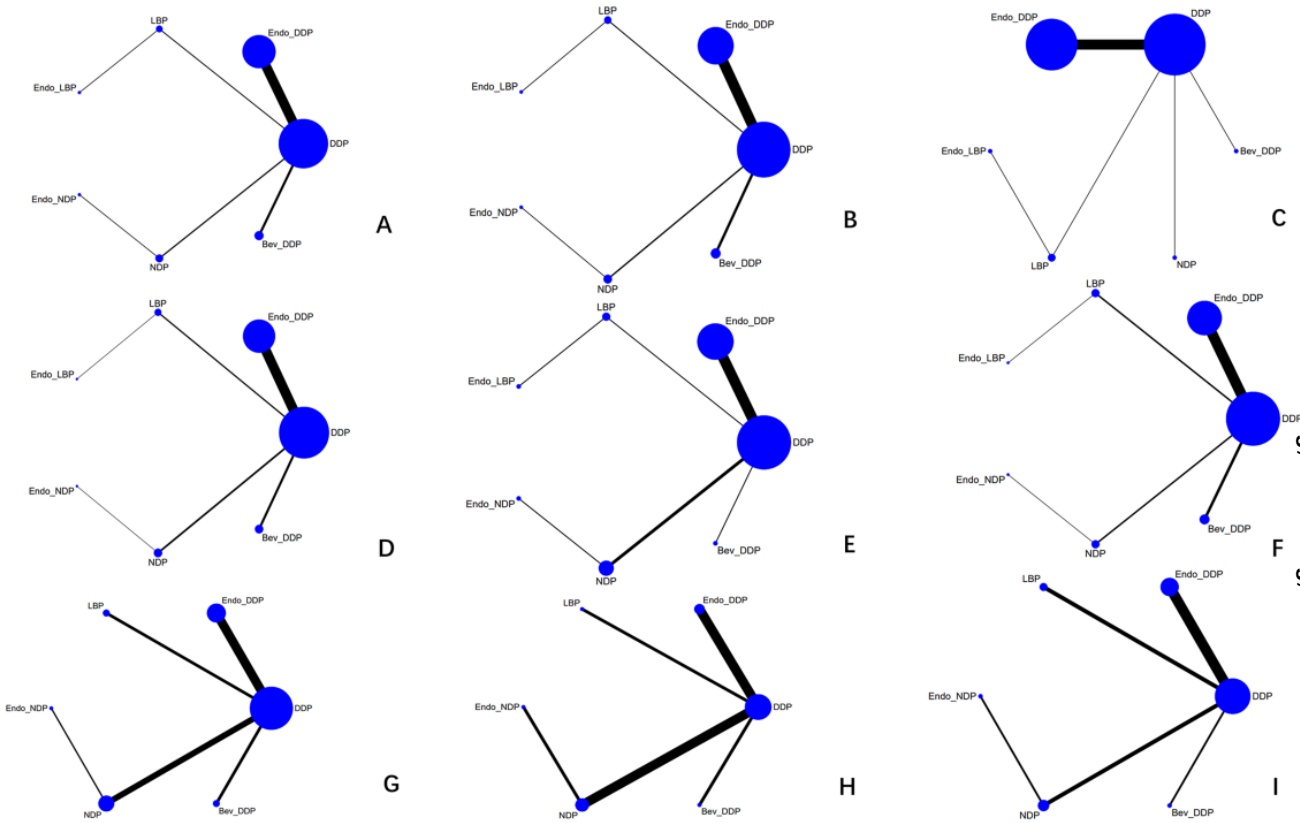

Fig S1 Network graph for different outcomes.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

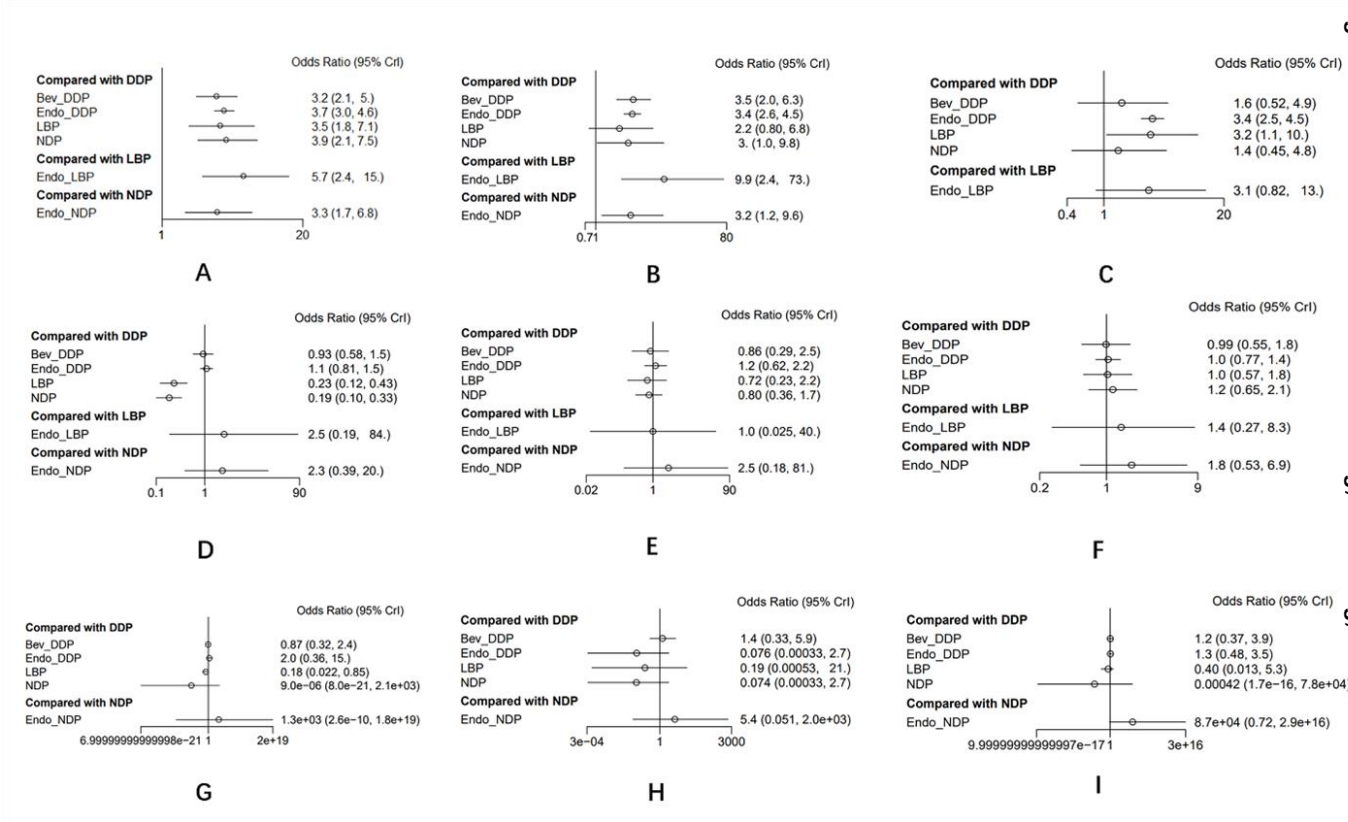

Fig S2 Forest plots of efficacy outcomes by Bayesian framework.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher, Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin.

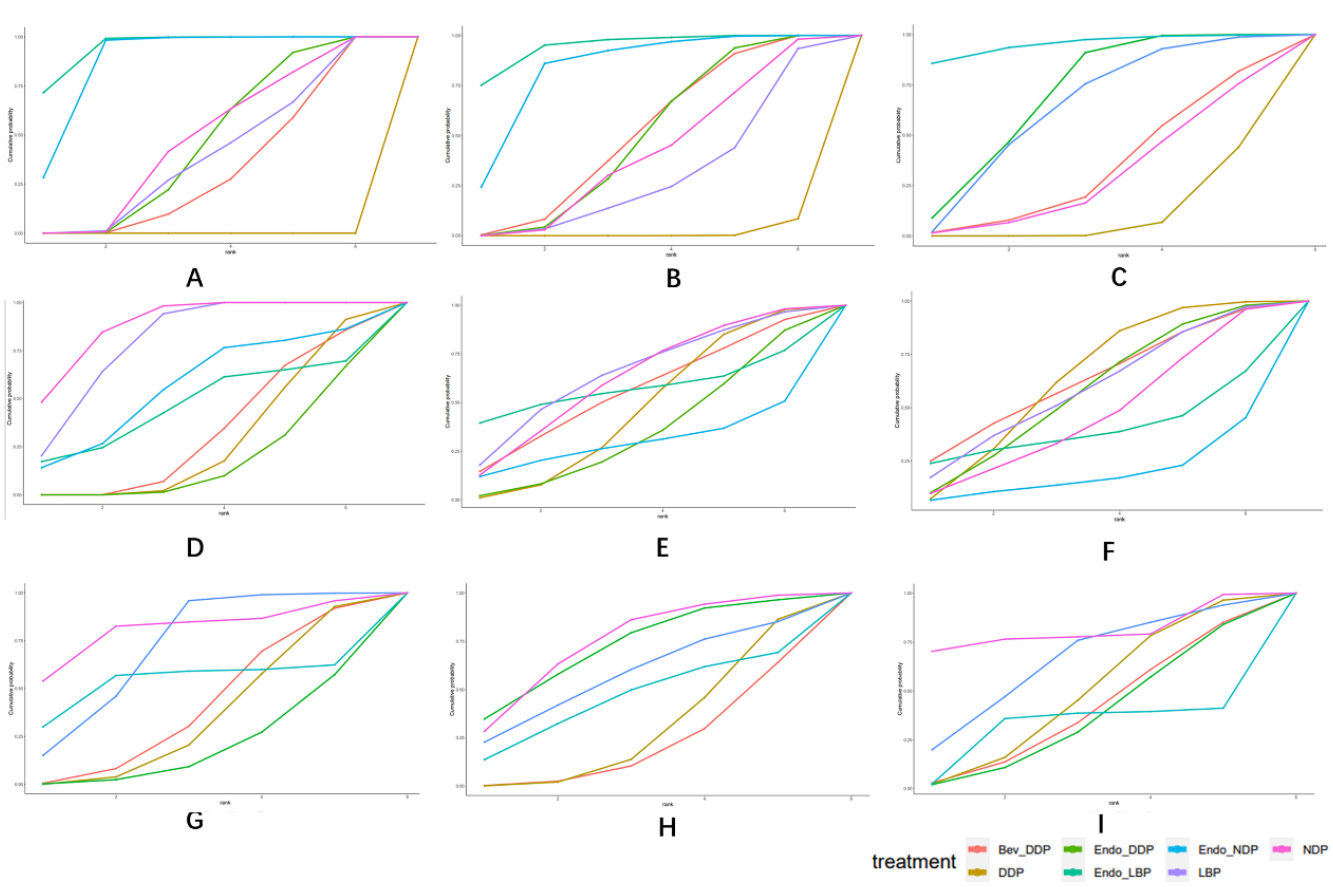

Fig S3 Sequence diagram of the network meta-analysis.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.

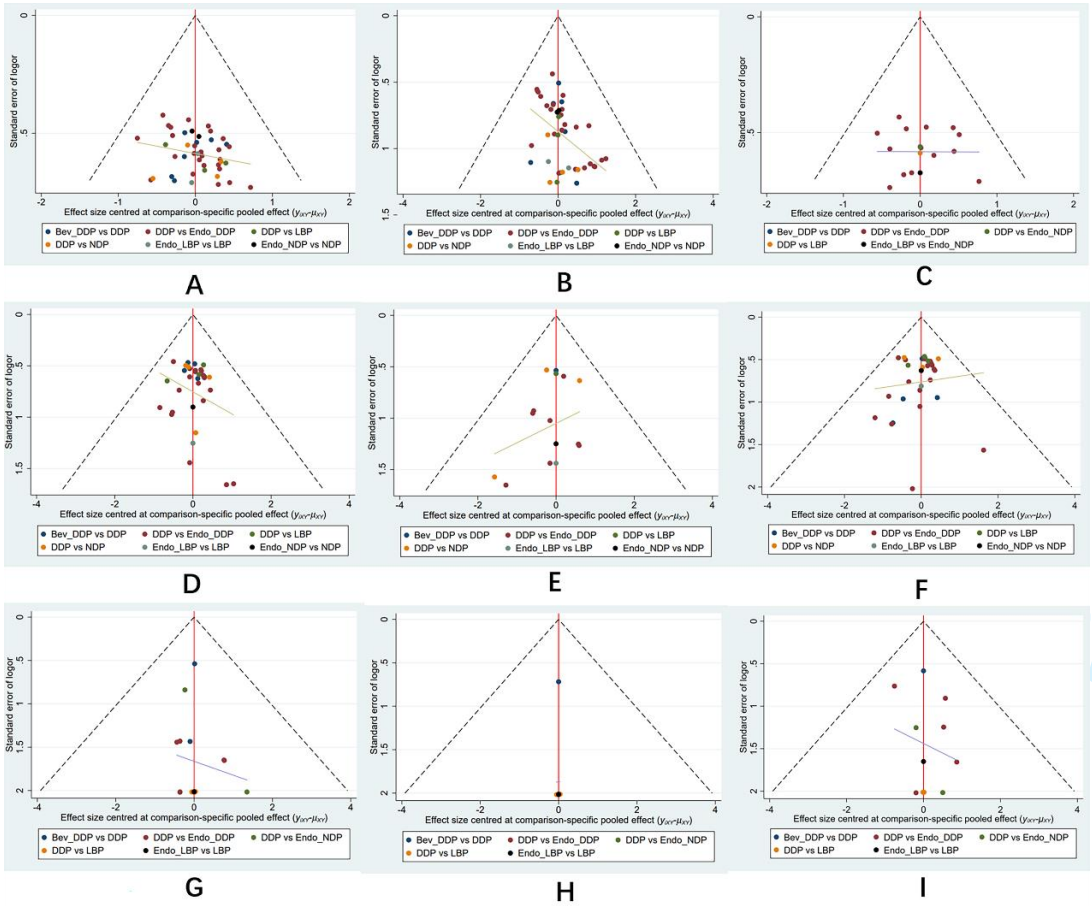

Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3-myelosuppressive.

ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or higher.