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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

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 metaanalysis.

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%).

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.

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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Review and Meta-Analysis. Annals of the American Thoracic Society. 2019;16(1):124-31.



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

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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.

Tables					BMJ Open		jopen-2023-080703 on 20 De	
Table 1 Characte	ristics of	the included ran	domized co	ontrolled trials.			20 De	
Study	Year	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Enterves related	outcome
Feng C (17)	2016	Endo_DDP:30 DDP:30	39/21	/	Moderate to large	≥60	Endo 48 mg DDP 40mg/m²: 1/week, 3 cycles of the DDP 40mg/m²: 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 45 P DDP 40mg: 2/week, 3 cycles DDP 49mg: 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 45 mg DDP 40mg/m ² : 2/week, 3 cycles DDP 46 mg 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 mg DDP 40mg/m²: 1/week, 4 cycles DDP 40mg/m²: 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 3 mm DDP 30mg: 1/week, 3 cycles DDP 3 mg m l/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 35 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 mg2/week _DDP 50mg 1/week: 2 cccles DDP 50mg /week, 2 cycles	P1,3

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Shuwen L (24)	2020	Endo_DDP:20 DDP:20	24/16	62.3±1.7/ 62.5±1.5	Moderate to large	Un	Endo 4 mg DDP 40mg/m²: 1/week, 3 cycles of DDP 40mg/m²: 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 3 week_DDP 50mg 1/week	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 35 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 60 mg 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 4 mg DDP 40mg/m²: 2/week, 3 cycles DDP 49mg m²: 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 a DDP 50mg L/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 3 mg/m²_DDP 60mg/m²: 2/week, 3 cycleg 2 DDP 60mg/m²: 2/week, DDP 60mg/m²: 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 cccles DDP 40mg 1/week, 3 cycles	P1,2,3

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Ning S (32)	2021	Endo_DDP:30 DDP:30	37/23	61.43±6.45/ 62.05±6.29	Un	Un	Endo 6 mg DDP 40-50mg: 2/week, 2 cycles DDP 4 mg gg: 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 48 mg DDP 40mg/m²: 1/week, 4 cycles DDP 40mg/m²: 1/week, 4	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 3	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 45 DDP 40mg/m²: 2/week, 3 cycles DDP 40mg/m²: 2/week, 3 DDP 40mg/m²: 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 4 DDP 40mg 1/week: 4 cycles DDP 40mg 1/week: 4	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 48 mg DDP 40mg/m²: 2/week, 3 cycles g. DDP 48mg/m²: 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 36 mg_DDP 40mg/m ² : 2/week, 3 cycles DDP 46mg/m ² : 2/week, 3 cycles	P1
Min X (39)	2020	Endo_DDP:20 DDP:20	27/13	/	Large	≥50	Endo 6 mg DDP 40-50mg 2/week: 2 cycles DDP 40-50 g: 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

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							DDP 1 mg kg/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 8 mg DDP 40mg 1/week: 3	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 38 mg DDP 40mg/m²: 2/week, 3 cycles DDP 44mg m²: 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 4 and 2 DDP 30mg 2/week: 2-3 cycles and 2 de 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 3 DDP 30mg 3/6 days: 1-2 cycles DDP 36mg 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 3 mg /week: 3 cycles_LBP: 30mg/m²: 1 week, 1 cycle LBP: 3 mg m²: 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 3 mg LBP: 30mg/m ² : 1/week, 4 cycles LBP: 3 mg mg m ² : 1/week, 4 cycles	P1,3
Shaoxian C (47)	2019	Endo_NDP: 46 NDP:46	45/47	/	Un	Un	Endo 75 mg/m² 7/week,4 cycles _NDP 30mg/m²: 1 week, 2-4 cycles NDP 30mg/m²: 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 /week, 2cycles	P1,3
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M · · · M (40)		Bev_DDP: 29		69.86±11.36/			Bev 30 mg 1,q3w_DDP 40mg d1,8,15,	
Meiqin Y (49)	2021	DDP:29	32/26	67.92±9.83	Un	≥70	q3w: 1 Q ycl g	P1
							DDP: 4 ៉ូច្នេះ d1, 8, 15, q3w: 1 cycle	
		Bev_DDP: 35		65.16 ±9. 34/			Bev 30 g d 1,q3w_DDP 50mg d1,8,15,	
Pengtao C (50)	2022	DDP:35	45/25	65.08± 9.26	Un	Un	q3w: 1 8 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	P1,3
							DDP: 5 d g d1, 8, 15, q3w: 1 cycle	
		Bev_DDP: 34		61.62±2.78/			Bev 36022 DDP 60mg 1/2weeks: 4	
Na Z (51)	2019	DDP:34	33/35	61.38±2.94	Un	>60	cycles and cycles	P1,3
							DDP: இதீ/2weeks, 4 cycles	
		Bev_DDP: 36		58.58±4.45/			Bev 5n DDP 45mg/m ² : 1/week, 3	
Yanhai S (52)	2020	DDP:36	45/27	58.69±4.87	Un	>60	cycles nim m	P1,3
					/ h		DDP: 6 mg/m ² , 1/week, 3 cycles	
		Bev_DDP: 41		58.21±3.25/	(0)		Bev 5ng/kg DDP 60mg: 1/week, 3	
Danfeng X (53) 201	2017	DDP:41	47/35	58.96±3.43	Un	Un	cycles $\frac{\vec{a}}{\vec{b}}$.	P1,3
					1/0.		DDP: dmg 1/week, 3 cycles	
		Bev_DDP: 37		60.28±6.17/			Bev 5n DDP 40mg: 1/week, 3	
Bin H (54)	2016	DDP:36	53/20	61.31±6.05	Moderate to large	>70	cycles v. S	P1,2,3
							DDP: #mg 1/week, 3 cycles	
		Bev_DDP: 24		54.6±7.7			Bev 30mg DDP 60mg: 1/2 weeks, 1	
Tiejun C (55)	2016	DDP:24	31/17		Moderate to large	Un	cycle 50	P1,3
							DDP: mg, 1/2 weeks, 1 cycle	
Maoyu W (56)	2015	NDP: 24	25/23	29-82	Moderate to large	>60	NDP: 🏚 magm²,1/week, 3-4 cycles	P1,2,3
Waoya W (30)	2013	DDP:24	23/23		iviouerate to large	7 00	DDP: 40mg m ² ,1/week, 3-4 cycles	11,2,3
Shu Z (57)	2022	NDP: 40	48/32	56.78±8.92/	Un	Un	NDP: 40mgm ² ,1/week, 4 cycles	P1,3
5114 2 (57)		DDP:40	10/32	57.18±9.12			DDP: 40mgm ² ,1/week, 4 cycles	11,5

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Jiajia B (58)	2019	NDP: 30 DDP:28	38/20	35-75	Moderate to large	≥60	NDP: 20mg/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: 40 m m ² ,1/week, 2-4 cycles DDP: 40 m 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: 3 mg/m ² ,1-2/week, 2-4 cycles DDP: 3 mg/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: 30 mg/n ² ,1-2/week, 2-4 cycles DDP: 30 mg/n 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: 30 m ² ,1/week, 2-4 cycles DDP: 40 m ² ,1/week, 2-4 cycles	P1,2,3

Weiyan G (62) 2019 DDP:31 37/24 Moderate to large 260 DDP: Edward 2017, 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: 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 the complete response and progressive disease; P2: quality of the complet

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

Table 2 Rank probabilities of ea	ch treatment for dit	ferent outcome me	BMJ Open	e network meta-ar			
	BEV_DDP	DDP	Endo_DDP	Endo_LBP	Endo_ND 🕏	LBP	NDP
ORR	0.33	0.00002	0.46	0.95	0.88 em ber 0.83 e.g.	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83 s e e e	0.30	0.41
QOL	0.33	0.10	0.69	0.95	/ 2024. D 0.56	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 and	0.65	0.62
G3-gastrointestinal effect	0.40	0.35	0.19	/	0.54 de de	0.71	0.81
G3-myelosuppression	0.39	0.48	0.37	/	0.32 # A F	0.64	0.81
G3-hypohepatia	0.21	0.30	0.72	/	0.19 Experieur (ABES) 0.32 and data minim	0.57	0.74

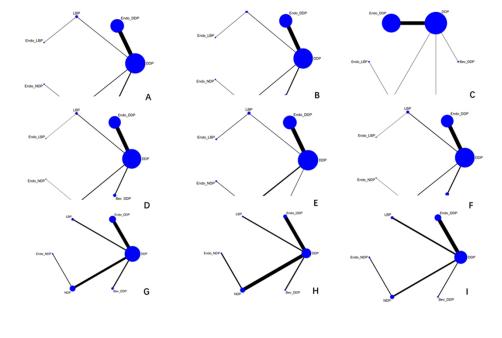
G3-hypohepatia 0.21 0.30 0.72 / 0.45 0.57 0.74

Endo_DDP: Endostar + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + properties of the data are listed as SUCRA values (rank) and higher SUCRA values indicate better outcomes.

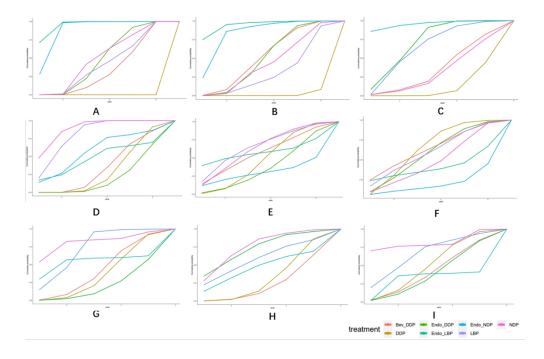
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- Fig 1 Network graph for different outcomes.
- Fig 2 Sequence diagram of the network meta-analysis.
- Fig 3 Funnel plots.

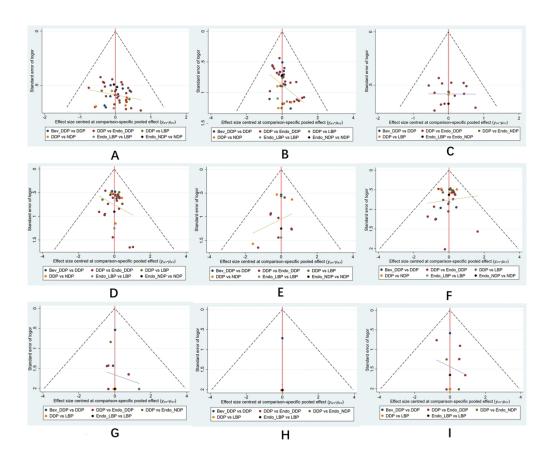




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Section and	Item	NMA Checklist of Items to Include When Reporting a Systematic Review Involvings Network	Location where item is
Topic	#	Checklist item	reported
TITLE		s eig rel	
Title	1	Identify the report as a systematic review.	1
ABSTRACT	<u> </u>	ont &	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTIO	N	d ee da	
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		9. //b AI	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the synthese specific and the	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched 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 esed.	4, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including many reviewers screened each record and each report retrieved, whether they worked independently, and cable, 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 investigates, and if applicable, details of automation tools used in the process.	4,5

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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 company in the each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the each 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 characters). 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) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool(s) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool(s) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool(s) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool(s) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool(s) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool(s) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool(s) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the tool so the tool	4,5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthese essentation 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 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-aralysis 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

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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 regions of the control of	5, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of Describe any methods used to assess the describe and the d	5
RESULTS		nade d c	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified 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 where 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	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6-8
syntheses	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 cemparing groups, describe the direction of the effect.	6-8
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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 results of all sensitivity analyses conducted to assess the robustness of the synthesized results. Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessed to the synthesized results.	6-8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed of each outcome as	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 INFOR	RMATIO	nd s	
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

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Section and	Item	nt, including 2 Location where item	is
Topic	#	Checklist item 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 college growns; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the grown which of the following are publicly available and where they can be found: template data college growns; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the grown which of the following are publicly available and where they can be found: template data college growns; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the grown which of the following are publicly available and where they can be found: template data college growns; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the grown which is the grown whi	
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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)*		(0.35, 2.24)	NDP
*p<0.05		700			fro (AE		
ORs between the inclu	ided interventions accord	ding to the results of netwo	ork meta-analysis.		nini SES		
Endo_DDP: Endostar	+ cisplatin, DDP: cispl	latin, Endo_LBP: Endosta	ır + lobaplatin, LBP: lobap	latin, Endo_NDP: Endo	gar 🗧 ned	aplatin, NDP:	nedaplatin, Bev_DDl
Bevacizumab + cispla	tin, ORR : Objective resp	ponse rate.			//bmjop Al train		
Table S4 The l	eague table of netw	ork meta-analysis fo	r DCR according to al	l interventions.	en.		
			OR 95%CI	11.	an		_

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0.15 (0.01, 1.03)	$0.04(0, 0.27)^*$	$0.15~(0.02,0.93)^*$	Endo_LBP	chn		
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 o 11		
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, 28.9 %) 2025	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

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Bevacizumab + cisplatin, DCR: Disease control rate.

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

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1.56 (0.52, 4.94)	DDP			d to	
0.47 (0.15, 1.52)	0.3 (0.22, 0.39)*	Endo_DDP		t Su	
0.16 (0.02, 1.26)	0.1 (0.02, 0.57)*	0.34 (0.05, 1.95)	Endo_LBP	nloa t an	
0.49 (0.1, 2.39)	0.31 (0.1, 0.93)*	1.05 (0.31, 3.25)	3.06 (0.82, 12.66)	a in the P	
1.09 (0.21, 5.56)	0.7 (0.21, 2.22)	2.35 (0.69, 7.75)	6.93 (0.85, 60.14)	a ⊋25 (0.45, 11.58)	NDP
*p<0.05		N		min T	
ORs between the include	d interventions according to the	e results of network meta-analy	rsis.	ing,	
Endo_DDP: Endostar +	cisplatin, DDP: cisplatin, End	o_LBP: Endostar + lobaplatir	n, LBP: lobaplatin, Endo_NDP:	Endosar nedaplatin, NDP: neda	aplatin, Bev_D
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		OR 9	5%CI	<u>a</u> <u>o</u>	
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	9	v 1 1				
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0.68 (0.1, 4.32)	0.69 (0.11, 4.01)	0.71 (0.11, 4.25)	Endo_LBP	olog		
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 es 2025		
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
				<u> </u>		•

^{*}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 + loba	BMJ Open aplatin, LBP: lobaplatin,	Jopen-2023-080703 on polytight, includings Bridger Polytight, includings Endo NDP: Endo	edaplatin, NDP: nedaplatir	a, Bev DDP:
Bevacizumab + cisplatin Table S7 League	e tables of all grades g	gastrointestinal effect ev	vent comparison of a	O December for uses results interventions a		
			OR 95%CI	202 Inem later		
Bev_DDP				4. Downloaded nent Superieur d to text and da		
0.93 (0.58, 1.49)	DDP			text		
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP		nload perie t and		
1.58 (0.04, 24.01)	1.7 (0.05, 24.68)	1.86 (0.05, 27.49)	Endo_LBP	wnloaded uperieur xt and da		
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 2 2 2 2		
4 (1.82, 8.94)*	4.29 (2.3, 8.26)*	4.69 (2.36, 9.59)*	2.52 (0.19, 83.76)	Endo_NDP and Toom 1.87 (0.25, 187)	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, 20025)	1.26 (0.53, 2.99)	NDP
*p<0.05		4	<u> </u>	//bmjo		
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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

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ORs between the included inter	rventions according to the results	s of network meta-analysis.		for		
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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 + Good 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.

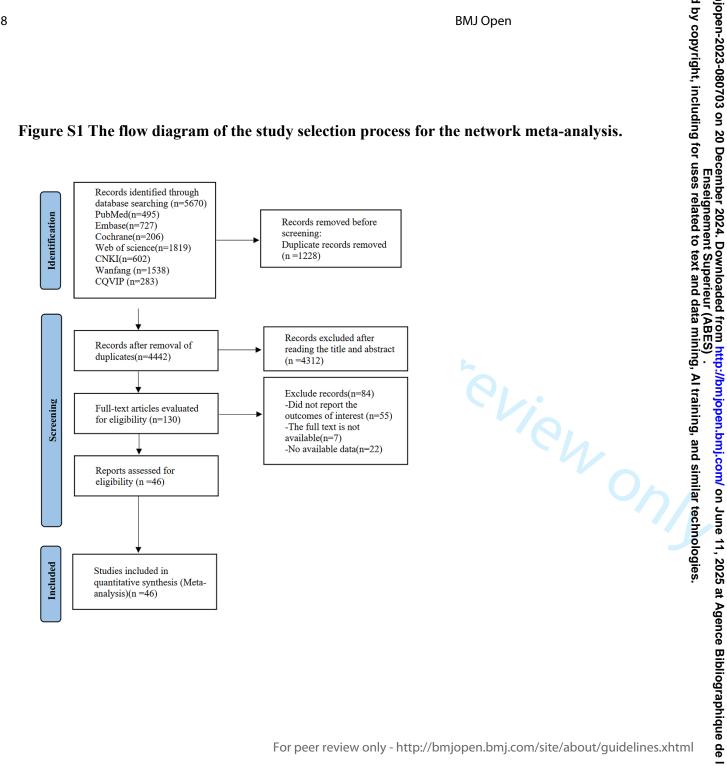
OR 95%CI

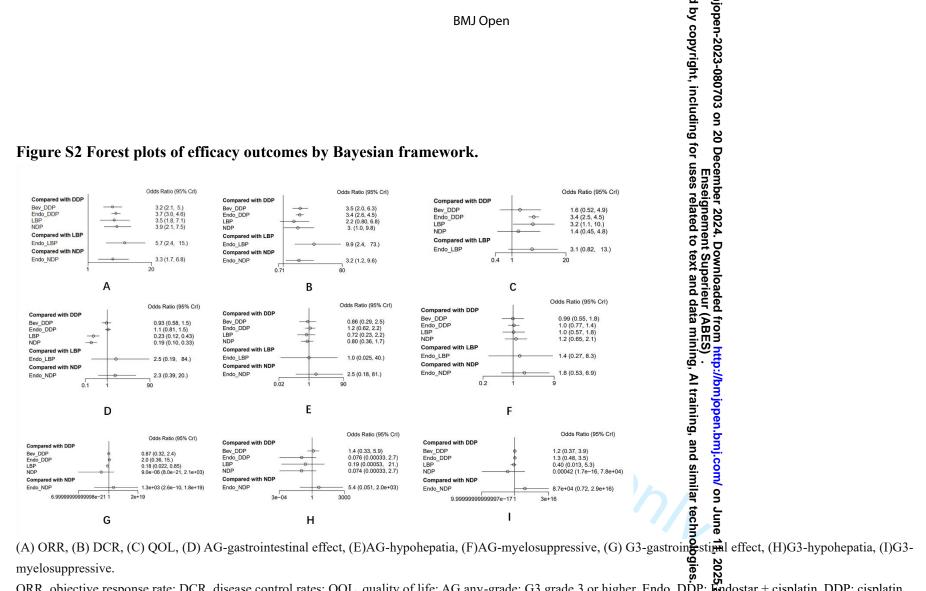
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Endo_DDP: Endostar + cispl Bevacizumab + cisplatin, G3:	grade 3 or higher.	: Endostar + lobaplatin, LBP: lob	inioaded uperieur tand da	nedaplatin, NDP: nedaplatin, E	Bev_DDP:
Table S11 League tab	les of G3-hypohepatia ever	it comparison of all interve		•	
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Roy DDD			n T		

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7.15 (0.05, 5005.72)				<u> </u>		
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Figure S1 The flow diagram of the study selection process for the network meta-analysis.





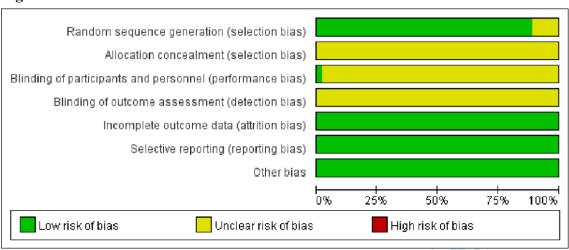
myelosuppressive.

ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG,any-grade; G3,grade 3 or higher, Endo_DDP: Landostar + cisplatin, DDP: cisplatin,

Endo LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev DDP: Bevacizuma + cisplatin.

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Figure S3 Assessment of risk of bias

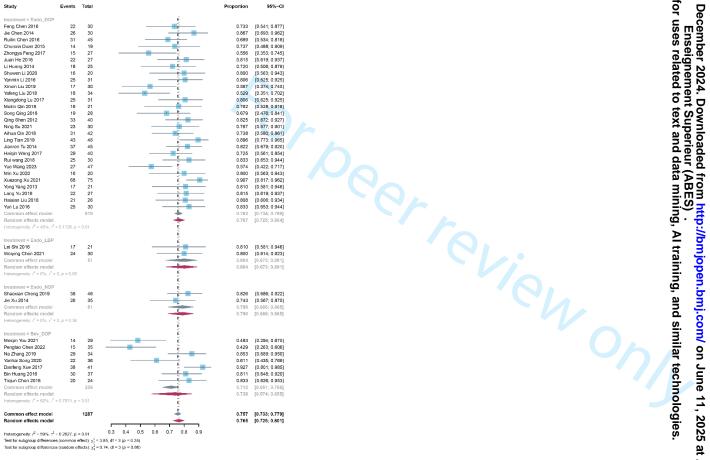


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Figure S4 Bias risk summary of the included studies.

Xinxin Liu2019 Xuezong Xu2021 Yafeng Liu2018 Yanhai Song2020 Yanhai Song2020 Yanmin Li2016 Yong Yang2013 Yue Wang2023 Yun Lu 2016 Zhinong Sheng2017	Qing Shen2012 Qiurong Huang2017 Ruilin Chen 2016 Rui Wang2018 Shaoxian Cheng2019 Shuwen Ll2020 Shu Zhu2022 Song Qing2018 Trejun Chen2016 Weiyan Gao2019 Weiying Chen2021 Xiangdong Lu2017 Xiangdong Lu2017	Lang Yu2016 Lei Shi2016 Li Huang2014 Ling Tian2019 Maoyu Wang2015 Meilin Oin2016 Meiqin You2021 Min Xu2020 Na Zhang2019 Ning Su2021 Pengtao Chen2022	Tor uses related to the haidin Wangzon? Haidin Wangzon? Haidin Baizon ? Jianren Tuzon4 Jie Chenzon4 Jie Xuzon4 Juan Hezon6 3	Bin Huang 2011 6 Random sequence generation (selection bias)
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BMJ Open BMJ Open BMJ Open 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 + nedapatin; Bev_DDP: Bevacizumab + cisplatin.

BMJ Open

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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Manuscript ID	bmjopen-2023-080703.R1
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Date Submitted by the Author:	04-Jul-2024
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Primary Subject Heading :	Oncology
Secondary Subject Heading:	Oncology
Keywords:	Clinical Decision-Making, Respiratory tract tumours < ONCOLOGY, Systematic Review

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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 breat¹. 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

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 (egrade 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 "gemte" 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 I² 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 $<50, \ge 50$ and $<100, \ge 100$), 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 S3¹⁷⁻⁶²). 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 or higher (G3)-gastrointestinal effect, G3-hypohepatia, and G3-myelosuppressive effects). The analyses are presented separately for ORRs, DCRs, QOL, TRAEs and \geq 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).

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, insufficiency, renal gastrointestinal effects, electrocardiographic abnormalities and fever. Among all types of adverse reactions, the most frequent occurrences were myelosuppressive, hypohepatia 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.



 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

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

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) De	
Bev_DDP					cember 2024. Do Enseignement uses related to t	
3.19 (2.11, 4.92)*	DDP				nber seig	
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0.16 (0.05, 0.53)*	0.05 (0.02, 0.15)*	0.19 (0.06, 0.59)*	Endo_LBP		nen d to	
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	t Su t Su	
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)*	n DLBP	
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)*	$\frac{1}{2}$ $\frac{1}$	NDP
Abbreviation: *p<0	.05. Data bolded in black	indicate they are from an i	ndirect comparison.		ata A	

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

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 + 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_NQP	LBP	NDP
ORR	0.33	0.00002	0.46	0.95	0.88 nilar	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83 fg Ju	0.30	0.41
QOL	0.33	0.10	0.69	0.95	hnc	0.63	0.29
Gastrointestinal effect	0.32	0.28	0.18	0.47	0.56 9 7, 2	0.80	0.89
Myelosuppressive	0.63	0.64	0.58	0.40	2025	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

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	uses related to text and data min				Table 3 Meta-re
β coefficient (95%CI) P value $β$ coefficient (95%CI) P value ample size -0.65 (-1.91, 0.62) 0.316 -0.73 (-2.47, 1.00) 0.408 dean age 0.36 (-0.59, 1.31) 0.459 0.18 (-1.28, 1.64) 0.810 ex 0.12 (-0.84, 1.08) 0.811 -1.26 (-2.72, 0.20) 0.091	alue day	Disease control r	e rate	Overall magnenes	
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Mean age 0.36 (-0.59, 1.31) 0.459 0.18 (-1.28, 1.64) 0.810 ex 0.12 (-0.84, 1.08) 0.811 -1.26 (-2.72, 0.20) 0.091	08 <u>a</u> <u>a</u>	-0.73 (-2.47, 1.00)	0.316	-0.65 (-1.91, 0.62)	Sample size
ex 0.12 (-0.84, 1.08) 0.811 -1.26 (-2.72, 0.20) 0.091	10 min				_
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 Fig 1 The flow diagram of the study selection process for the network meta-analysis

Fig 2 Assessment of risk of bias.

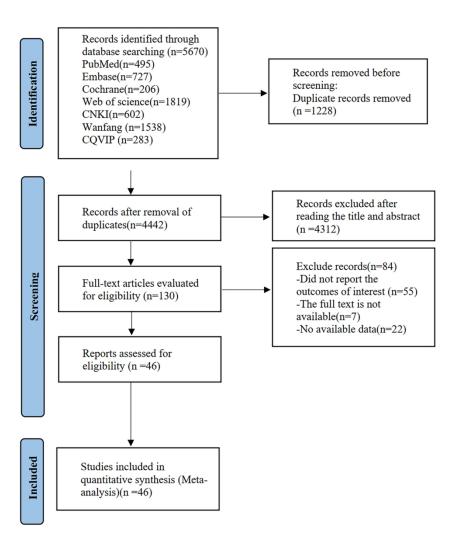
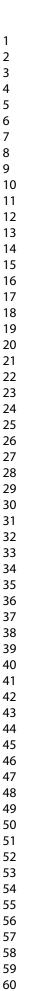


Fig 1 149x171mm (300 x 300 DPI)



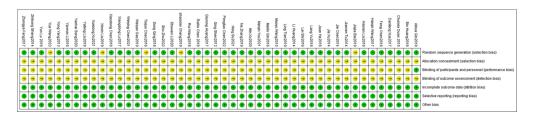


Fig 2 455x93mm (300 x 300 DPI)

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Table ST PRISMA NMA Checklist of Items to Include when Reporting a Systematic Review Involving Network M					
Section and	Item	Checklist item	Location where item is		
Topic	#	IS IT	reported		
TITLE		ber s reig			
Title	1	Identify the report as a systematic review.	1		
ABSTRACT		to mit to			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2		
INTRODUCTIO	N	nd da			
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		9. b			
Eligibility	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the synthese	5, 6		
criteria		pen			
Information	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched except consulted to	5		
sources		identify studies. Specify the date when each source was last searched or consulted.			
Search	7	Present the full search strategies for all databases, registers and websites, including any filters and limits gsed.	5, Supplementary Table		
strategy		Jur	S2		
Selection	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including many	5, 6		
process		reviewers screened each record and each report retrieved, whether they worked independently, and capital retrieved.			
		details of automation tools used in the process.			
Data	9	Specify the methods used to collect data from reports, including how many reviewers collected data from chargest report,	7		
collection		whether they worked independently, any processes for obtaining or confirming data from study investigators, and if			
process		applicable, details of automation tools used in the process.			

Section and	Item	BMJ Open BMJ Open Checklist item	Location where item is
Торіс	#		reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible of the control outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the control outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the control outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the control outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the control outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the control outcome domain in each study were sought (e.g. for all measures).	7, 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characters to 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) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the 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 esentation 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 sing 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-aratiys 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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	8

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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 region be region at the control of the c	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of supplied to a specific supplied to specific supplied to	8
RESULTS	•	nd c	
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 with 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	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
syntheses	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
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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 results of all investigations of possible causes of heterogeneity among study results. Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results of results of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessed to the synthesized results (arising from reporting biases) for each synthesized results assessed to the synthesized results (arising from reporting biases) for each synthesized results assessed to the synthesized results (arising from reporting biases) for each synthesized results assessed to the synthesized results (arising from reporting biases) for each synthesized results assessed to the synthesized results (arising from reporting biases) for each synthesized results (arising from reporting biases).	9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence for each outcome assessed and confidence of the body of evidence of the	11
DISCUSSION	<u>.</u>	¬ 60 0	
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 INFOR	RMATIO	n nj. o	
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		5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the	14
Competing nterests	26	Declare any competing interests of review authors. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	14

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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 college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and where they can be found: template data college of the following are publicly available and the following are publicly avail	
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Table S2 Literature Search Strategy

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Table S3 Characteristics of the included randomized controlled trials.

Study	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Intervention December uses re	outcome
F. Chen et al. 2016 ¹⁷	Endo_DDP:30 DDP:30	39/21	/	Moderate to large	≥60	Endo 45 mg_DDP 40ng/eng 1/week, 3 cycles	P1,2,3
Chen et al.	Endo_DDP:30		54.3±5.6/			DDP 40mg/m ² : 1/week 2 40 5 cles Endo 45 mg_DDP 40m 2 5 o o o o o o o o o o o o o o o o o o	
2014 ¹⁸	DDP:30	44/16	55.6±4.5	NR	NR	cycles DDP 40mg: 2/week, 3 20 20 20 20 20 20 20 20 20 20 20 20 20	P1,3
R. Chen et	Endo_DDP:45		60.6±7.2/			Endo 45 mg_DDP 40mg2/week,	
al. 2016 ¹⁹	DDP:45	53/37	60.8 ± 7.5	Moderate to large	≥60	3 cycles $\mathbf{G} \cdot \mathbf{f}$	P1,2,3
Duan et al. 2015 ²⁰	Endo_DDP:19 DDP:19	23/15	61.4	Moderate to large	≥60	DDP 40mg/m²: 2/week 3 cocles Endo 40 mg_DDP 40ng/mg 1/week, 4 cycles DDP 40mg/m²: 1/week 4 cocles	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 loweek, 3 cycles DDP 30mg: 1/week, 3 gycles	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/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 2 0mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

	Endo_DDP:20		62.3±1.7/			Endo 45 mg DDP 40ng/mg/1/week,	
Li 2020 ²⁴	DDP:20	24/16	62.5 ± 1.5	Moderate to large	NR	3 cycles of D	P1,3
				_		DDP 40mg/m²: 1/week 22 23 cles	
	Endo_DDP:31		42.22±6.92/			Endo 30 mg 2/week D	
Li 2016 ²⁵	DDP:31	35/27	42.14±6.89	NR	>60	1/week: 2 cycles	P1,3
						1/week: 2 cycles and 2002 to 2	
T' 4 1	Endo_DDP:30		52.64±6.55/			Endo 45 mg/m ² _DDP 2/week,	
Liu et al.	DDP:30	36/24	53.31±7.56	NR	≥60	2-3 cycles	P1,3
2019^{26}						DDP 30mg: 2/week, 2-2 Eyeles	
Liu et al.	Endo_DDP:34	20/20	63.19±4.73/		> (0	Endo 60 mg _DDP 60mg	D1 2 2
2018^{27}	DDP:34	38/30	65.55±5.28	Moderate to large	≥60	DDP 60mg: 2/week	P1,2,3
Lu and	Endo_DDP:31		46.3±10.6/			Endo 45 mg_DDP 40ngg/m 2/week,	
Zhang	DDP:31	35/27	45.7±11.3	Moderate to large	≥60	3 cycles	P1,2,3
2017^{28}						DDP 40mg/m²: 2/week 23 cociles	
	Endo_DDP:21		59.6			Endo 60 mg_DDP 50ng: 12week, 3	
Qin 2016 ²⁹	DDP:21	24/18		Moderate to large	≥60	cycles an a	P1,3
						DDP 50mg: 1/week, 3 wycles	
Qing et al.	Endo_DDP:28		68.2±4.6/			Endo 35 mg/m ² _DDP mg/m ² :	
2018 ³⁰	DDP:23	22/27	68.2 ± 4.6	NR	NR	2/week, 3 cycles	P1,2,3,4
2016						DDP 60mg/m ² : 2/week 3 ckcles	
Shen et al.	Endo_DDP:40		37-79			Endo 30 mg 2/week_D P 40 mg:	
2012 ³¹	DDP:40	42/38		Moderate to large	≥60	1/week, 3 cycles	P1,2,3
2012						DDP 40mg: 1/week, 3 cycles	
Su et al.	Endo_DDP:30		61.43±6.45/			Endo 60 mg_DDP 40-50m 2/week,	
2021 ³²	DDP:30	37/23	62.05 ± 6.29	NR	NR	2 cycles	P1,3
2021						DDP 40-50mg: 2/week, 2 celes	
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	Endo_DDP:42		56.84±7.03/			Endo 40 mg_DDP 40næ/m g 1/week,	
Qin 2018 ³³	DDP:42	43/41	57.19 ± 8.25	NR	NR	4 cycles	P1,2
						DDP 40mg/m²: 1/week 💆 450 Geles	
Tian et al.	Endo_DDP:48		59.26±2.43/			Endo 30 mg 4/week_D	
2019 ³⁴	DDP:48	57/39	61.54±2.32	Moderate to large	≥60	40mg/m ² : 2/week, 1 cy يو آم کې	P1
2019						40mg/m ² : 2/week, 1 cycle DDP 30-40mg/m ² : 2/wgc2, 1 cycle	
Tu et al.	Endo_DDP:45		46.5±11.5/			Endo 45 mg_DDP 40mg 2/week, 3 cycles DDP 40mg/m²: 2/week 2/week	
2014 ³⁵	DDP:45	48/42	47.5±10.5	Moderate to large	≥60	3 cycles and of	P1,2,3
2014**						DDP 40mg/m ² : 2/week 2 cles	
W/	Endo_DDP:40		55.5±2.2/			Endo 40 mg_DDP 40mg	
Wang et al. 2017 ³⁶	DDP:40	41/39	55.8 ± 2.9	Large	≥60	cycles	P1,2,3
20175						DDP 40mg: 1/week, 4 gycl	
	Endo_DDP:30		61.28±6.32/			Endo 45 mg_DDP 40n / 2/week,	
Wang 2018 ³⁷	DDP:30	35/25	60.54 ± 5.65	NR	≥60	3 cycles	P1,3
						DDP 40mg/m ² : 2/week 3 cocles	
	Endo_DDP:47		53.47±3.25/			Endo 30 mg_DDP 40n\(\) /m\(\) 2/week,	
Wang 2023 ³⁸	DDP:47	51/43	54.09±3.38	NR	≥80	3 cycles $\underline{\omega}$	P1
						DDP 40mg/m ² : 2/week 3 cycles	
T 1	Endo_DDP:20		/			Endo 60 mg_DDP 40-\$\frac{1}{2}\text{pmg_2}/week:	
Xu et al.	DDP:20	27/13		Large	≥50	2 cycles	P1,2,3,4
20239						DDP 40-50mg: 2/week 2 cycles	
	Endo_DDP:75		63.65±5.11/			Endo 45 mg_DDP 10ng 1/Reek: 3	
Xu et al.	DDP:75	79/71	63.87±5.38	NR	NR	cycles w	P1,3
202140						DDP 10mg: 1/week, 3 cycl	
(Yang et al.	Endo_DDP:21		41.5±7.6	_		Endo 30 mg DDP 40mg 1/Freek: 3	
(rang et ai.	DDP:21	27/15		Large	NR	cycles Billographique graphique de /about/guidelines.xhtml	P1,2,3,4

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	E. 1. DDD.27		(0.29+(.17/			Endo 30 mg_DDP 40mg/mg 2/week, 3 cycles	
N. 201642	Endo_DDP:27	22/20	60.28±6.17/	M 1 4 4 1	> 70	Endo 30 mg_DDP 40mg/mg 2/week,	D1 2 2
Yu 2016 ⁴²	DDP:25	32/20	61.31 ± 6.05	Moderate to large	≥70	3 cycles s s b	P1,2,3
	E 1 DDD 26		41 75/20 75			DDP 40mg/m ² : 2/week	
Liu and Tan	Endo_DDP:26	22/20	41-75/39-75	M 1 4 4 1	ND	Endo 45mg_DDP 30mg_#veek: 2-3	D1 2
2018^{43}	DDP:26	23/29		Moderate to large	NR	cycles of Sulface	P1,3
	E 1 DDD 20					DDP 30mg: 2/week: 2 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	
Lu et al.	Endo_DDP:30	20/22		No. 1 1	NID	Endo 30mg_DDP 30mg 30mg 20mg 21-2	D1 0
201644	DDP:30	28/32		Moderate to large	NR	cycles DDP 30mg: 3/6 days: 52 20 20 cles	P1,2
	E 1 IDD 21		12 2 5 6			=: :::: ⊃	
Shi et al.	Endo_LBP:21	05/17	42.3±5.6		NID	Endo 30mg 2/week: 3 5 LBP:	D1 2 4
2016^{45}	LBP:21	25/17		Moderate to large	NR	30mg/m ² : 1/3 week, 1 Eycle	P1,2,4
	E 1 IDD 20		50.21+4.27/			LBP: 30mg/m ² : 1/3 weak, Ecycle	
C1 202146	Endo_LBP: 30	20/21	50.31±4.27/	M 1 4 4 1	ND.	Endo 30mg_LBP: 30mg/mg 1/week,	D1 2
Chen 2021 ⁴⁶	LBP:30	39/21	50.16±4.35	Moderate to large	NR	4 cycles	P1,3
	E 1 NDD 46		1			LBP: 30mg/m ² : 1/weel 4 wcles	
Cheng et al.	Endo_NDP: 46	45/45	/	NID.	NID	Endo 7.5mg/m² 7/weel 4 cycles	Di
2019^{47}	NDP:46	45/47		NR	NR	_NDP 30mg/m ² : 1/wee x , 2 9 cycles	P1
	E 1 NDD 25		62.515.5			NDP 30mg/m ² : 1/week 2-4 cycles	
Xu et al.	Endo_NDP: 35	42/27	62.5±5.5	M. 1 1	NID	Endo 60mg_NDP 60mg. 1/week, 2	D1 2
2014^{48}	NDP:35	43/27		Moderate to large	NR	cycles NDP 60mg: 1/week, 26ycles	P1,3
	D DDD 20		(0.06, 11.26)				
You et al.	Bev_DDP: 29	22/25	69.86±11.36/			Bev 300mg, d1,q3w_D \(\bar{Q}\)P 40mg	
2021 ⁴⁹	DDP:29	32/26	67.92 ± 9.83	NR	≥70	d1,8,15, q3w: 1 cycle	P1
						DDP: 40mg d1, 8, 15, q3w: cycle	
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Chen and Ai	Bev_DDP: 35		65.16 ± 9.34			Bev 300mg, d1,q3 \(\overline{\partial} D\)\(\overline{\partial} P\) 50mg	
2022 ⁵⁰	DDP:35	45/25	65.08 ± 9.26	NR	NR	d1,8,15, q3w: 1 cycle	P1,3
022						DDP: 50mg d1, 8, 15, 50mg cycle	
Chang et al.	Bev_DDP: 34		61.62±2.78/			Bev 300mg_DDP 60mg 4 weeks: 4	
2019 ⁵¹	DDP:34	33/35	61.38±2.94	NR	>60	cycles an en 202	P1,3
.019						DDP: 60mg 1/2weeks,	
	Bev_DDP: 36		58.58±4.45/			Bev 5mg/kg_DDP 45ng 202 1/week,	
Song 2020 ⁵²	DDP:36	45/27	58.69±4.87	NR	>60	3 cycles	P1,3
						DDP: 45mg/m², 1/week ar ar archivel	
Kue and	Bev_DDP: 41		58.21±3.25/			Bev 5mg/kg_DDP 60n 2 Aveek, 3	
Zhao 2017 ⁵³	DDP:41	47/35	58.96 ± 3.43	NR	NR	cycles nim m	P1,3
LIIau 2017						DDP: 60mg, 1/week, 36cycles	
Huang	Bev_DDP: 37		60.28 ± 6.17			Bev 5mg/kg_DDP 40n 2: 1 week, 3	
2016 ⁵⁴	DDP:36	53/20	61.31 ± 6.05	Moderate to large	>70	cycles \overline{a} \overline{b}	P1,2,
2010						DDP: 40mg, 1/week, 3 ycles	
Γ. Chen et	Bev_DDP: 24		54.6±7.7			Bev 300mg_DDP 60m g : 1/ 2 weeks, 1	
al. 2016 ⁵⁵	DDP:24	31/17		Moderate to large	NR	cycle <u>s</u> <u>o</u>	P1,3
11. 2010						DDP: 60mg, 1/2 weeks 1 cocle	
Wang et al.	NDP: 24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m ² ,1/week 3-4 cycles	P1,2,
2015^{56}	DDP:24	23123		Wioderate to large	> 00	DDP: 40mg/m ² ,1/week 2 3-4 5 cycles	1 1,2,
Zhu et al.	NDP: 40	48/32	56.78±8.92/	NR	NR	NDP: 40mg/m ² ,1/weekg4 cycles	P1,3
2022^{57}	DDP:40	40/32	57.18 ± 9.12	TVIX	IVIX	DDP: 40mg/m ² ,1/week 4 c cles	11,5
Bai 2019 ⁵⁸	NDP: 30	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m ² ,1/week, 2-3xcycles	P1,3
Dai 2017	DDP:28	30/20		wioderate to large	_00	DDP: 40mg/m ² ,1/week, 2- 2 cycles	11,5
	NDP: 39	43/36	55.8±8.1/	Large	≥60	NDP: 40mg/m ² ,1/week, 2-4 g cycles	P1,3,4
X. Chen et al. 2016 ⁵⁹		13/30	58.2 ± 7.3	Large	_00	DDP: 40mg/m ² ,1/week, 2-4 cycles	11,5,

						<u>a</u> 0	
Huang et al.	LBP: 38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m ² ,1-2/we 2 k, 2 2 cycles	P1.3
2017^{60}	DDP:38	41/33		NK NK	NK	DDP: 30mg/m^2 , $1-2/\text{we}$, $2\sqrt{2}$ 4 cycles	г1,3
Sheng	LBP: 30	20/40	38-74	Madagata ta lagga	>60	LBP: 30mg/m²,1-2/wekkpp34 cycles	D1 2
2014^{61}	DDP:30	20/40	Moderate to large		≥60	DDP: 30mg/m²,1-2/wegk²,254 cycles	P1,3
Gao et al.	LBP: 30	27/24	57-69/54-68	M		LBP: 30mg/m²,1/week 2548 ycles	
2019 ⁶²	DDP:31	37/24	Moderate to large	≥60	DDP: 40mg/m ² ,1/week 24 cycles	P1,2,3	

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Engley or + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cispleta. NR, not reported.

Endostar + lobaplatin, EBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + classified (1968) NR, not reported.

Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quining, Al training, and similar technologies.

A training and similar technologies.

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Table S4	The league table of network meta-anal	lysis for DCR according to all interventions.
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			OR 95% CrIs	for		
Bev_DDP				cemt Ens uses		
3.51 (2.03, 6.28)*	DDP			ber seig s re		
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP		oer 2024 eignem related		
0.15 (0.01, 1.03)	0.04 (0, 0.27)*	0.15 (0.02, 0.93)*	Endo_LBP	24. D nent d to		
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 of the		
1.59 (0.46, 5.15)	0.45 (0.15, 1.26)	1.54 (0.48, 4.47)	9.99 (2.38, 76.59)*	$4.39 (0.7, 28.9) = \frac{1}{2}$	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 a) $\frac{1}{2}$	0.74 (0.16, 3.45)	NDP
+ 005 B : 1 11 12				# C -		

^{*}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 + finedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

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

		OR 95	% CrIs	ano	<u> </u>	
Bev_DDP				Si	con	_
1.56 (0.52, 4.94)	DDP			milar	0	
0.47 (0.15, 1.52)	$0.3 (0.22, 0.39)^*$	Endo_DDP		Ę	ے	
0.16 (0.02, 1.26)	0.1 (0.02, 0.57)*	0.34 (0.05, 1.95)	Endo_LBP	chno	ne e	
0.49 (0.1, 2.39)	$0.31 (0.1, 0.93)^*$	1.05 (0.31, 3.25)	3.06 (0.82, 12.66)	olog	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)	yies	25 (0.45, 11.58)	NDP

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

*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.

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

		OR 95% CrIs	De or		
			cem En use		
DDP			nber seig s re		
0.96 (0.72, 1.3)	Endo_DDP		202 Jner late		
0.69 (0.11, 4.01)	0.71 (0.11, 4.25)	Endo_LBP	24. E d to		
0.47 (0.11, 1.84)	0.49 (0.11, 1.98)	0.68 (0.07, 6.89)	Endo_NDP 💆 🛱 🗸		
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	
0.86 (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
_	0.96 (0.72, 1.3) 0.69 (0.11, 4.01) 0.47 (0.11, 1.84) 0.98 (0.54, 1.74)	0.96 (0.72, 1.3) Endo_DDP 0.69 (0.11, 4.01) 0.71 (0.11, 4.25) 0.47 (0.11, 1.84) 0.49 (0.11, 1.98) 0.98 (0.54, 1.74) 1.01 (0.53, 1.94)	0.96 (0.72, 1.3) Endo_DDP 0.69 (0.11, 4.01) 0.71 (0.11, 4.25) Endo_LBP 0.47 (0.11, 1.84) 0.49 (0.11, 1.98) 0.68 (0.07, 6.89) 0.98 (0.54, 1.74) 1.01 (0.53, 1.94) 1.42 (0.27, 8.33)	DDP 0.96 (0.72, 1.3) Endo_DDP 0.69 (0.11, 4.01) 0.71 (0.11, 4.25) Endo_LBP 0.47 (0.11, 1.84) 0.49 (0.11, 1.98) 0.68 (0.07, 6.89) Endo_NDP tryon is a construction of the construction o	DDP 0.96 (0.72, 1.3) Endo_DDP 0.69 (0.11, 4.01) 0.71 (0.11, 4.25) Endo_LBP 0.47 (0.11, 1.84) 0.49 (0.11, 1.98) 0.68 (0.07, 6.89) Endo_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 + finedaplatin, NDP: nedaplatin, Bev_DDP: + cisplatin.

League tables of all grades gastrointestinal effect event comparison of all interventions Bevacizumab + cisplatin.

Table S7

			OR 95% CrIs	ano		_
Bev_DDP				com/ (_
0.93 (0.58, 1.49)	DDP			nilar		
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP		te J		
1.58 (0.04, 24.01)	1.7 (0.05, 24.68)	1.86 (0.05, 27.49)	Endo_LBP	chn		
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 6 3		
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, 18578)	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.

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

			OR 95% CrIs	ber seig s rel		
Bev_DDP				2024. Do gnement lated to t		
0.86 (0.29, 2.5)	DDP			24. E d to		
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP		t Sur t ext		
1.2 (0.02, 64.26)	1.39 (0.03, 65.71)	1.63 (0.03, 80.3)	Endo_LBP	nload and NDD		
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, ₺) 🛱	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) E G	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 + onedaplatin, NDP: nedaplatin, Bev_DDP:

Bevacizumab + cisplatin.

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

OR 95% CrIs

		OR 95% CrIs	iia		
Bev_DDP			r teo		
1.19 (0.37, 3.93)	DDP		chn		
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP	olog		
0.02 (0, 1158726093196.45)	0.02 (0, 946584795528.83)	$0.02\ (0,1200464612598)$	Endo_NDP gie s. 2025		
3.03 (0.17, 114.1)	2.48 (0.19, 79.56)	3.18 (0.2, 112.91)	179.3 (0, 13158904182927350)g	LBP	
2806.8 (0,	2358.54 (0,	3012.84 (0,	86977.28 (0.72,	877.08 (0,	NDD
7080696058054300)	5857536555380624)	7540937082788929)	28713088892365632)	2259231168436329)	NDP

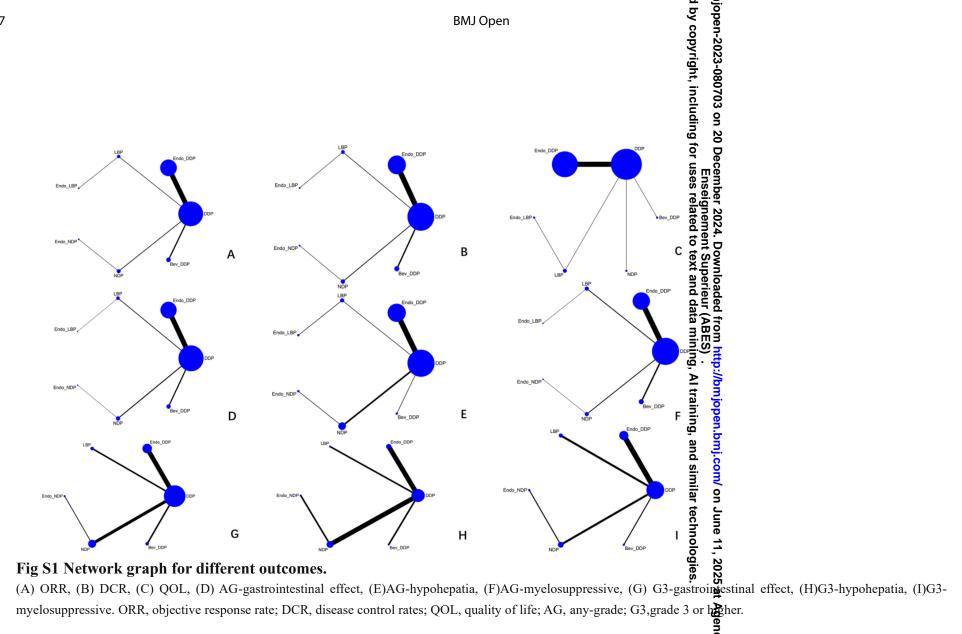
^{*}p<0.05. Data bolded in black indicate they are from an indirect comparison.

ORs between the included into	erventions according to the results	BMJ Open of network meta-analysis.	by copyright, including	en-2023-080	
			platin, Endo NDP: Endos	n - ⊋nedaplatin, NDP: nedaplatin, B	Bev DDP:
Bevacizumab + cisplatin, G3:	grade 3 or higher.		uses re	cembe Ensei	
Table S10 League table	les of G3-gastrointestinal e	ffect event comparison of all	l interventions.	gne	
Table S10 League tab	les of G3-gastrointestinal e	ffect event comparison of all OR 95% CrIs	l interventions.	r 2024. gnemer	
Table S10 League table Bev_DDP 0.87 (0.32, 2.38)	les of G3-gastrointestinal es	*	ä. S	### ### ### ##########################	
Bev_DDP	70,	*	ä. S	### ### ### ##########################	
Bev_DDP 0.87 (0.32, 2.38)	DDP	OR 95% CrIs	d to text and data	24. Downloaded f	
Bev_DDP 0.87 (0.32, 2.38) 0.43 (0.05, 3.16) 146.72 (0,	DDP 0.5 (0.06, 2.74) 170.13 (0,	OR 95% CrIs Endo_DDP 346.11 (0,	d to text and data	24. Downloaded f	
Bev_DDP 0.87 (0.32, 2.38) 0.43 (0.05, 3.16) 146.72 (0, 2.25957982568521e+21)	DDP 0.5 (0.06, 2.74) 170.13 (0, 2.60852595759042e+21)	OR 95% CrIs Endo_DDP 346.11 (0, 5.58712188787727e+21)	d to text and data	24. Downloaded from http://bnment Superieur (ABES) .	ND

77133.10 (0,	110057.40 (0,	250540.57 (0,	1347.03 (0,	₹ ₹	10057.20 (0,	ND
1.05993280385622e+20)	1.25474480157232e+20)	2.61196338258981e+20)	182291206742938		21936173709446430720)	P
*p<0.05. Data bolded in blac	k indicate they are from an indirect	comparison.		an,		
ORs between the included in	terventions according to the results	of network meta-analysis.		d si		
Endo_DDP: Endostar + cisp	olatin, DDP: cisplatin, Endo_LBP:	Endostar + lobaplatin, LBP:	lobaplatin, Endo_NDP: E	ndos z ar 🕏 1	nedaplatin, NDP: nedaplatin, B	ev_DDP
Bevacizumab + cisplatin, G3	grade 3 or higher.			n Ju		
				chn		
Table S11 League tal	oles of G3-hypohepatia even	t comparison of all inter	ventions.	11, olog		
		OR 95% CrIs		202! gies		
Bev_DDP				at		
1.36 (0.33, 5.91)	DDP			Age		
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP		nce		
3.64 (0, 4662.71)	2.67 (0, 2952.95)	0.17 (0, 561.64)	Endo_NDP	Bibl		

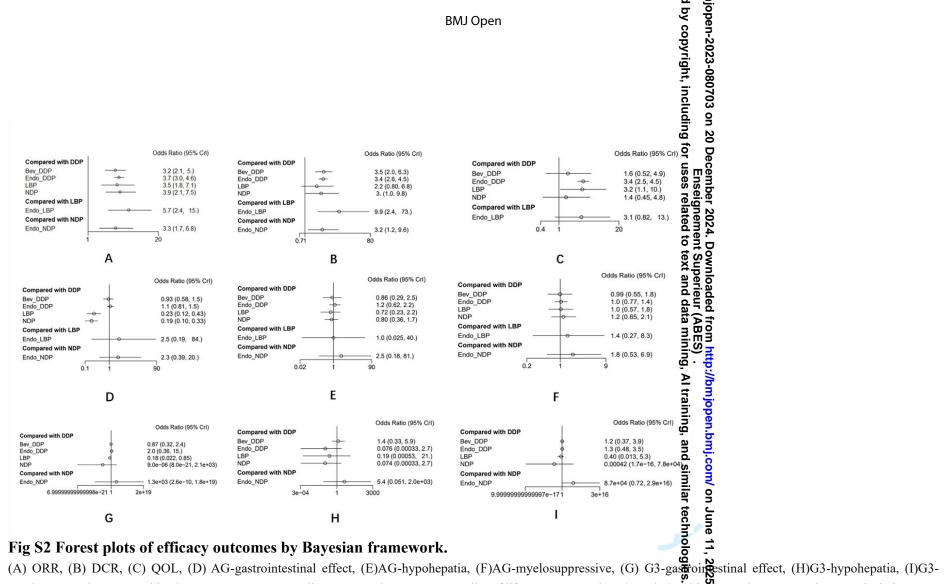
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7.15 (0.05, 3005.42)	5.2 (0.05, 1901.09)	0.37 (0, 382.55)	2.15 (0, 16410.56)	ocluding	
18.95 (0.38, 4882.5)	13.51 (0.37, 3023.28)	1.03 (0, 666.32)	5.38 (0.05, 2025.4)	2.79 (0, 310	2.18) NDP
ORs between the included in Endo_DDP: Endostar + cisp Bevacizumab + cisplatin, G3	5.2 (0.05, 1901.09) 13.51 (0.37, 3023.28) ek indicate they are from an indirect aterventions according to the results of platin, DDP: cisplatin, Endo_LBP: By grade 3 or higher.	of network meta-analysis. Endostar + lobaplatin, LBP:	lobaplatin, Endo_NDP: En	n, and a similar technologies. seignement Superieur (ABES) . s related to text and data mining, Al training, and similar technologies.	NDP: nedaplatin, Bev_DDP:
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myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or header.

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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: Beacizumab + cisplatin.

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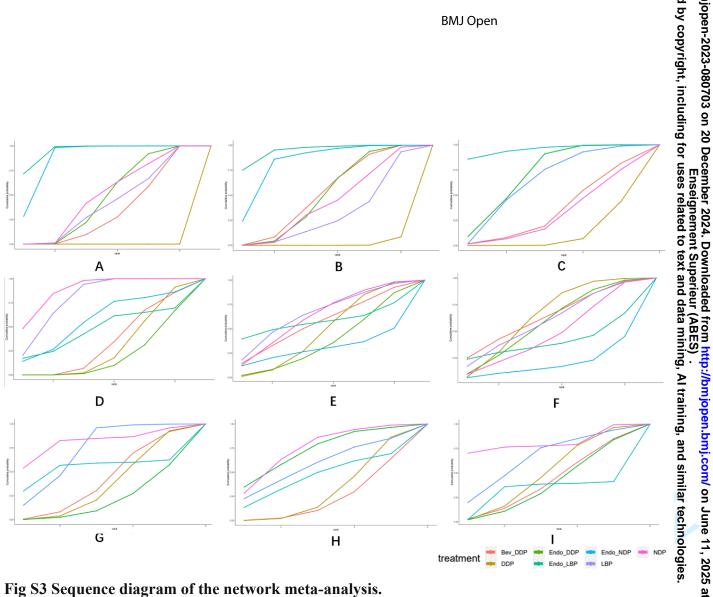


Fig S3 Sequence diagram of the network meta-analysis.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or has her.

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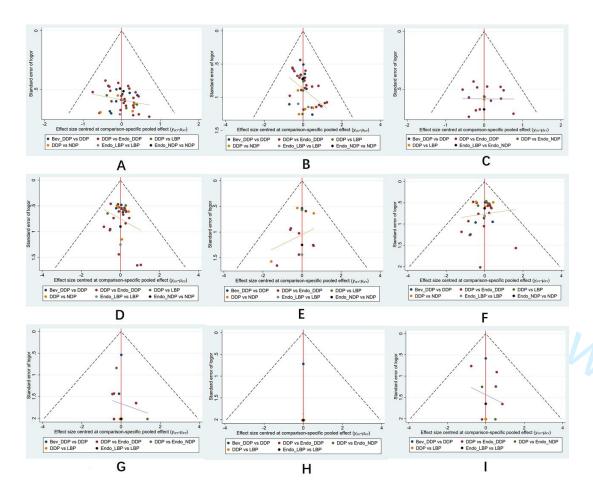


Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3myelosuppressive. ce Bibliographique de l

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

- **Objectives:** Different intrathoracic perfusion therapeutic regimens are available for
- 3 non-small cell lung cancer with malignant pleural effusion (MPE). Antiangiogenic
- 4 agents are often used to control MPE, and the results are satisfactory. Here, we
- 5 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.
- 8 Data sources: PubMed/Medline, Embase, Cochrane, Web of Science, Wanfang, VIP
- 9 Database and Chinese National Knowledge Infrastructure were searched from
- 10 inception to May 2023. Eligible studies were randomized controlled trials that
- 11 reported on curative effect in MPE.
- 12 Data extraction and synthesis: The Cochrane Collaboration tool was used to assess
- risk of bias. The consistency was evaluated by examining the agreement between
- 14 direct and indirect effects. Network meta-analysis was performed and the ranking
- probabilities of being at each possible rank for each intervention were estimated.
- 16 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
- 19 analysis. According to the results of the network meta-analysis, some antiangiogenic
- 20 agents combined with chemotherapy regimens improved objective response rate
- 21 (ORR) and disease control rate (DCR) and quality of life (QOL). The rank
- 22 probabilities suggested that in terms of ORR, DCR and QOL, Endostar plus lobaplatin
- was the first-ranked intervention.
- 24 Conclusion: Administration of antiangiogenic agents plus chemical agents
- significantly improved the clinical response and quality of life. In addition, Endostar
- 26 plus lobaplatin was the most effective combination.

PROSPERO registration number:

29 CRD42021284786

1	Keywords : Non-small cell lung cancer · MPE · Antiangiogenic agents · Thoracio
2	perfusion · Network meta-analysis
3	
4	Strengths and limitations of this study
5	1. The large number of studies and the considerable sample size enhanced the
6	statistical power of our analysis.

- 7 2. The risk of bias tool recommended by Cochrane was used to assess the risk of bias
- 8 of included RCTs.
- 9 3.Meta-regression analysis was performed to determine if potential effect modifiers
- 10 influence the outcomes.
- 4. The absence of closed loops within the network prevented a formal assessment of
- 12 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 breat¹. 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

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,

 1 G3-hypohepatia, and G3-myelosuppressive effects). The variations in dosing and

2 scheduling across studies were minimal and consistent enough that we considered

them unlikely to significantly influence the therapeutic effects. Thus, the same

4 interventions with the different doses and schedules were grouped together.

5 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

8 priors were used for the heterogeneity parameter (τ) , representing the standard

9 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 I² 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

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

Patient and public involvement

- 9 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

17 (Fig1, Table S3¹⁷⁻⁶²). Studies were published between 2012 and 2023 and included a

total of 3026 patients. The intrapleural administration therapeutic regimens included

19 Endostar + nedaplatin (Endo + NDP), Endostar + DDP (Endo + DDP), Endostar +

20 lobaplatin (Endo + LBP), Bevacizumab + DDP (Bev + DDP), DDP, nedaplatin (NDP)

and lobaplatin (LBP). In particular, 32 studies compared Endostar plus chemical

22 agents versus chemical agents alone, 7 studies compared bevacizumab plus chemical

23 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.

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

NMA

Objective response rate

- 8 All included studies with a total of 3026 patients reported the data of ORR, with
- 9 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
- 11 lower compared to the combinations of Endo+ LBP and Endo+ NDP. DDP alone
- showed a significantly lower ORR than all evaluated treatment regimens, including
- 13 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+
- 15 LBP and Endo+ NDP each displayed significantly higher ORRs than either LBP or
- NDP alone (Fig S2; Table 1).
- 17 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
- 19 (48%), Endo + DDP (46%), LBP (40%), Bev + DDP (33%), and DDP (0.002%) (Fig.
- 20 S3; Table 2).

Disease control rate

- All included studies with a total of 3026 patients reported the data of DCR, with
- 24 2586 patients achieving disease control. The network of studies is presented in Fig S1.
- 25 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
- 27 NDP alone. Among these, Endo+ DDP showed a significantly lower DCR than
- 28 Endo+ LBP, which itself recorded a higher DCR than Endo+ NDP. Moreover, Endo+
- 29 NDP achieved a significantly higher DCR compared to NDP alone (Fig S2; Table

- 2 results were as follows: Endo + LBP (95%), Endo + NDP (83%), Bev + DDP (51%),
- 3 Endo + DDP (49%), NDP (41%), LBP (30%), and DDP (1%) (Fig S3; Table 2).

Quality of Life

- 6 Nineteen studies, involving a total of 1173 patients reported the quality of life, with
- 7 654 patients achieving high quality of life. These studies constituted five pairs of
- 8 direct comparisons involving six interventions (Endo + DDP, Endo + LBP, Bev +
- 9 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,
- 12 95% CrI [0.1, 0.93]) (Fig S2; Table S5).
- After ranking the six interventions based on the SUCRA values, the results were as
- 14 follows: Endo + LBP (95%), Endo + DDP (69%), LBP (63%), Bev + DDP (33%),
- 15 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

 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

6 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

- 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

- 2 potential influence of journal quality on our results warrants cautious interpretation.
- 3 Fifth, the absence of closed loops in the network precludes the formal assessment of
- 4 inconsistency, which is a crucial aspect of NMA. Future studies should aim to include
- 5 more diverse treatment comparisons to allow for a comprehensive inconsistency
- 6 evaluation.

Conclusions

- This network meta-analysis comprehensively compared various treatments for
- 10 thoracic perfusion of MPE in NSCLC patients and described the QOL and toxicity
- 11 features. To the best of our knowledge, this is the first comprehensive NMA study of
- 12 its kind. The results showed that antiangiogenic agents combined with chemotherapy
- 13 regimens could improve clinical effectiveness and quality of life. In our study,
- 14 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

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

Author Contributions

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

1 Data Availability statement:

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

- 5 Declarations
 - **Conflicts of interest:** The authors declare no conflict of interest.
- *Ethical approval:* Not applicable.
- 8 Consent for publication: Not applicable

- 10 Abbreviations
- 11 NSCLC Non-small cell lung cancer
- 12 MPE Malignant pleural effusion
- 13 VEGF Vascular endothelial growth factor
- 14 Rh-endostatin Recombinant human endostatin
- 15 CQVIP VIP Database
- 16 CNKI Chinese National Knowledge Infrastructure
- 17 RCT Randomized controlled trial
- 18 ORR Objective response rate
- 19 DCR Disease control rate
- 20 QOL Quality of life
- 21 CR Complete response
- 22 PR Partial response
- 23 SD Stable disease
- 24 PD Progressive disease
- 25 KPS Karnofsky performance score
- 26 TRAEs Treatment-related adverse events
- 27 ≥grade 3 TRAEs Grade 3 or higher treatment-related adverse events
- 28 CrI Credible intervals
- 29 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		

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

			OR 95% CrIs		for	De	
Bev_DDP					Ense	C C C C C	
3.19 (2.11, 4.92)*	DDP				seig s rel	ber	
0.85 (0.53, 1.37)	0.27 (0.22, 0.33)*	Endo_DDP			gnem lated	20	
0.16 (0.05, 0.53)*	0.05 (0.02, 0.15)*	0.19 (0.06, 0.59)*	Endo_LBP		nen d to	24. E	
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	t Su	Ow W	
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)*	Superi text and	<u>D</u> 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)*	ieur d d	0.88 (0.35, 2.24)	NDP
Abbreviation: *p<0	.05. Data bolded in black in	dicate they are from an	indirect comparison.		(AE	# fro	
ORs between the inc	luded interventions according	ng to the results of netw	ork meta-analysis.		mini	<u> </u>	
Endo_DDP: Endosta	ar + cisplatin, DDP: cisplat	tin, Endo_LBP: Endos	tar + lobaplatin, LBP: lo	baplatin, Endo_NDP: End	oggar -	nedaplatin, NDP: r	nedaplatin, Bev_DDl
Bevacizumab + cispl	latin, ORR: Objective respo	nse rate.			<u> </u>	//br	
					rain	<u>n</u> .	
					ing	en.	
Гable 2 Rank proba	abilities of each treatment	for different outcome	measures based on the	network meta-analysis	, an	<u>b</u> <u>3</u> .	
	BEV_DDP	DDP	Endo_DDP	Endo_LBP Endo_1	Ν <mark>δ</mark> Β	LBP	NDP
)DD	0.22	0.00002	0.46	0.05	⊒:	0.40	0.48

	BEV_DDP	DDP	Endo_DDP	Endo_LBP	Endo_NQP	LBP	NDP
ORR	0.33	0.00002	0.46	0.95	0.88 nilar	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83 وأق	0.30	0.41
QOL	0.33	0.10	0.69	0.95	hno)	0.63	0.29
Gastrointestinal effect	0.32	0.28	0.18	0.47	0.56 g 7,	0.80	0.89
Myelosuppressive	0.63	0.64	0.58	0.40	0.19 iii ?025	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

	uses related to text and data min				Table 3 Meta-re
β coefficient (95%CI) P value $β$ coefficient (95%CI) P value ample size -0.65 (-1.91, 0.62) 0.316 -0.73 (-2.47, 1.00) 0.408 dean age 0.36 (-0.59, 1.31) 0.459 0.18 (-1.28, 1.64) 0.810 ex 0.12 (-0.84, 1.08) 0.811 -1.26 (-2.72, 0.20) 0.091	alue	Disease control r	e rate	Overall magnenes	
Mean age 0.36 (-0.59, 1.31) 0.459 0.18 (-1.28, 1.64) 0.810 ex 0.12 (-0.84, 1.08) 0.811 -1.26 (-2.72, 0.20) 0.091		β coefficient (95%CI)			
Mean age 0.36 (-0.59, 1.31) 0.459 0.18 (-1.28, 1.64) 0.810 ex 0.12 (-0.84, 1.08) 0.811 -1.26 (-2.72, 0.20) 0.091	08 <u>a</u> <u>a</u>	-0.73 (-2.47, 1.00)	0.316	-0.65 (-1.91, 0.62)	Sample size
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- Fig 1 The flow diagram of the study selection process for the network meta-analysis
- Fig 2 Assessment of risk of bias.

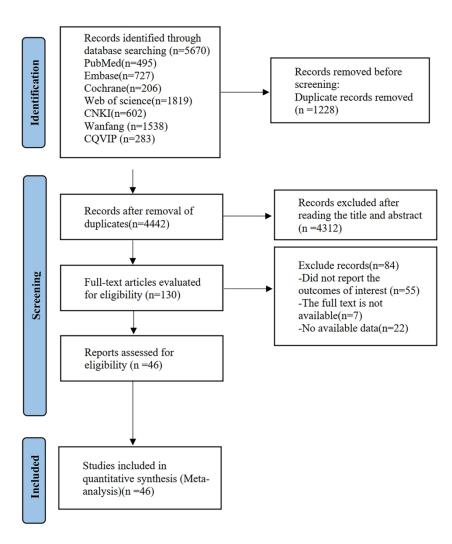


Fig 1 149x171mm (600 x 600 DPI)

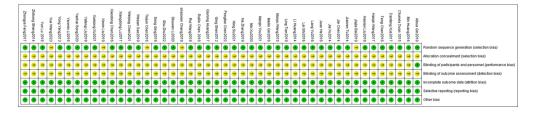


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Title	Content	Page
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Section and Topic	Item #	Checklist item Checklist item	Location where item is reported
TITLE	<u>'</u>		
Title	1	Identify the report as a systematic review.	1
ABSTRACT		to to	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTIO	N	rieur d da	
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	<u>.</u>	ÿ · p Α //	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the synthms of the	5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched 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 esed.	5, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including many reviewers screened each record and each report retrieved, whether they worked independently, and contains 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 cach 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
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Topic	#	Checklist item	reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible in the each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the each 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 characters to 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) how many reviewers assessed each study and whether they worked independently, and if applicable, details of the 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 esentation of results.	7, 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating to be 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 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-aralysia 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

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Section and	Item	BMJ Open BMJ Open	Location where item is
Topic	#	Checklist item 20 De	reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from region biases).	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of supplied in the body of evidence for an outcome of supp	8
RESULTS	-	nd e	
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 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	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the surpary 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
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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 results of all sensitivity analyses conducted to assess the robustness of the synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessed.	9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed of each outcome as	11
DISCUSSION		ta n	
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 INFOR	RMATIO	n d.	
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

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Table S2	Literature	Search	Strategy
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Table S3 Characteristics of the included randomized controlled trials.

Study	Sample size	Gender (M/F)	Mean age(years)	Volume of MPE	KPS scores	Intervention December	outcome
F. Chen et al. 2016 ¹⁷	Endo_DDP:30 DDP:30	39/21		Moderate to large	≥60	Endo 45 mg_DDP 40ng/mp21/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	DDP 40mg/m ² : 1/week 2 2 cles Endo 45 mg_DDP 40mg 2 o o o o o o o o o o o o o o o o o o	P1,3
R. Chen et	Endo_DDP:45	52/27	60.6±7.2/	964	> (0	DDP 40mg: 2/week, 3 2/week, Endo 45 mg_DDP 40mg	D1 2 2
al. 2016 ¹⁹	DDP:45 Endo_DDP:19	53/37	60.8±7.5 61.4	Moderate to large	≥60	3 cycles DDP 40mg/m ² : 2/week 3 cycles Endo 40 mg_DDP 40ng/mg 1/week,	P1,2,3
Duan et al. 2015 ²⁰	DDP:19	23/15		Moderate to large	≥60	4 cycles DDP 40mg/m²: 1/weeka czcles	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 gycles	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 40ng/m 2/week, 3 cycles DDP 40mg/m ² : 2/weekg 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 \$0mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

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	Endo_DDP:20		62.3 ± 1.7			Endo 45 mg_DDP 40ng/mg 1/week,	
Li 2020 ²⁴	DDP:20	24/16	62.5 ± 1.5	Moderate to large	NR	3 cycles	P1,3
						DDP 40mg/m²: 1/week 💆 📆 💃 cles	
	Endo_DDP:31		42.22 ± 6.92			Endo 30 mg 2/week_D	
Li 2016 ²⁵	DDP:31	35/27	42.14±6.89	NR	>60	1/week: 2 cycles ted 1024 DDP 50mg: 1/week, 2 50245	P1,3
						DDP 50mg: 1/week, 2 5/2165	
Liu et al.	Endo_DDP:30		52.64±6.55/			Endo 45 mg/m ² _DDP Deg 2/week,	
2019 ²⁶	DDP:30	36/24	53.31±7.56	NR	≥60	2-3 cycles	P1,3
2019						DDP 30mg: 2/week, 2-2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	
Liu et al.	Endo_DDP:34	38/30	63.19±4.73/	Moderate to large	≥60	Endo 60 mg _DDP 60mg 22 week	P1,2,3
2018^{27}	DDP:34	30/30	65.55 ± 5.28	wioderate to large	≥00	DDP 60mg: 2/week	1 1,2,3
Lu and	Endo_DDP:31		46.3±10.6/			Endo 45 mg_DDP 40mg/m 2/week,	
Zhang	DDP:31	35/27	45.7±11.3	Moderate to large	≥60	3 cycles $\stackrel{\triangleright}{=}$	P1,2,3
2017^{28}						DDP 40mg/m ² : 2/week 3 cocles	
	Endo_DDP:21		59.6			Endo 60 mg_DDP 50ng : 12week, 3	
Qin 2016 ²⁹	DDP:21	24/18		Moderate to large	≥60	cycles an J.	P1,3
						DDP 50mg: 1/week, 3 wycles	
Qing et al.	Endo_DDP:28		68.2±4.6/			Endo 35 mg/m ² _DDP d mg/m ² :	
2018 ³⁰	DDP:23	22/27	68.2 ± 4.6	NR	NR	2/week, 3 cycles	P1,2,3,4
2010						DDP 60mg/m ² : 2/week 3 cocles	
Shen et al.	Endo_DDP:40		37-79			Endo 30 mg 2/week_D P 40 mg:	
2012 ³¹	DDP:40	42/38		Moderate to large	≥60	1/week, 3 cycles gives 2025	P1,2,3
2012						DDP 40mg: 1/week, 3 cycl	
Su et al.	Endo_DDP:30		61.43±6.45/			Endo 60 mg_DDP 40-50m	
2021 ³²	DDP:30	37/23	62.05 ± 6.29	NR	NR	2 cycles	P1,3
2021						DDP 40-50mg: 2/week, 2 celes	
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	Endo_DDP:42		56.84±7.03/			Endo 40 mg_DDP 40ng/mg/1/week,	
Qin 2018 ³³	DDP:42	43/41	57.19 ± 8.25	NR	NR	4 cycles	P1,2
						DDP 40mg/m²: 1/week 25cles	
Tian et al.	Endo_DDP:48		59.26±2.43/			Endo 30 mg 4/week_D	
2019 ³⁴	DDP:48	57/39	61.54±2.32	Moderate to large	≥60	40mg/m ² : 2/week, 1 cy a lag 20	P1
2017						DDP 30-40mg/m ² : 2/wge 2 , 1 cycle	
Tu et al.	Endo_DDP:45		46.5 ± 11.5 /			Endo 45 mg_DDP 40mg 42/week,	
2014 ³⁵	DDP:45	48/42	47.5±10.5	Moderate to large	≥60	3 cycles and	P1,2,3
						DDP 40mg/m ² : 2/weeka for the control of the contr	
Wang et al.	Endo_DDP:40		55.5±2.2/			Endo 40 mg_DDP 40m 🕏 🔭 eek: 4	
2017^{36}	DDP:40	41/39	55.8±2.9	Large	≥60	cycles in temperature cycles	P1,2,3
						DDP 40mg: 1/week, 4 dycl	
	Endo_DDP:30		61.28±6.32/			Endo 45 mg_DDP 40ng/mg 2/week,	
Wang 2018 ³⁷	DDP:30	35/25	60.54 ± 5.65	NR	≥60	3 cycles	P1,3
	E 1 DDD 15		50 45 2 05/			DDP 40mg/m ² : 2/week 3 cycles	
M. 202238	Endo_DDP:47	51/40	53.47±3.25/	NID	. 00	Endo 30 mg_DDP 40n\(\frac{1}{2} \)/m\(\frac{1}{2} \)/week,	D1
Wang 2023 ³⁸	DDP:47	51/43	54.09±3.38	NR	≥80	3 cycles	P1
	E 1 DDD 20		,			DDP 40mg/m ² : 2/week 3 cycles	
Xu et al.	Endo_DDP:20	27/12	/	Laura	>50	Endo 60 mg_DDP 40-30mg_2/week:	D1 2 2 4
202^{39}	DDP:20	27/13		Large	≥50	2 cycles DDP 40-50mg: 2/week 2 cycles	P1,2,3,4
	Endo_DDP:75		63.65±5.11/			Endo 45 mg_DDP 10ng 1/Reek: 3	
Xu et al.	DDP:75	79/71	63.87±5.38	NR	NR	, vi	P1,3
202140	DDI ./3	19/11	03.87±3.36	IVIX	INIX	cycles a DDP 10mg: 1/week, 3 cycles	1 1,5
(Yang et al.	Endo_DDP:21		41.5±7.6			Endo 30 mg DDP 40mg 1/8 eek: 3	
2013 ⁴¹	DDP:21	27/15	41.527.0	Large	NR		P1,2,3,4
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						DDP 40mg: 1/week, 3 dycles Endo 30 mg_DDP 40mg/mg 2/week, 3 cycles DDP 40mg/m²: 2/week	
	Endo_DDP:27		60.28±6.17/			Endo 30 mg DDP 40mg/mg 2/week.	
Yu 2016 ⁴²	DDP:25	32/20	61.31±6.05	Moderate to large	≥70	3 cycles	P1,2,3
14 2010	551.23	32,20	01.51=0.05	Wederate to large	_/0	DDP 40mg/m ² : 2/week 2 cycles	11,2,5
	Endo_DDP:26		41-75/39-75			Endo 45mg_DDP 30mg_20xek: 2-3	
Liu and Tan	DDP:26	23/29	(1 /6/65 /6	Moderate to large	NR	cycles cycles	P1,3
2018^{43}	<i>DD1</i> .20	23,29		Wiederate to large	111	DDP 30mg: 2/week: 2 5 5 sles	1 1,5
	Endo_DDP:30					Endo 30mg_DDP 30mg Heddays: 1-2	
Lu et al.	DDP:30	28/32		Moderate to large	NR	cycles dat c	P1,2
2016 ⁴⁴	<i>BB</i> 1.30	20/32		Wiederate to large	111	DDP 30mg: 3/6 days: \(\frac{1}{2}\)\	1 1,2
	Endo_LBP:21		42.3±5.6			Endo 30mg 2/week: 3	
Shi et al.	LBP:21	25/17		Moderate to large	NR	30mg/m ² : 1/3 week, 1 cycle	P1,2,4
2016^{45}						LBP: 30mg/m ² : 1/3 weak, Ecycle	, ,
	Endo_LBP: 30		50.31±4.27/			Endo 30mg_LBP: 30mg/mg 1/week,	
Chen 2021 ⁴⁶	LBP:30	39/21	50.16±4.35	Moderate to large	NR	4 cycles	P1,3
				C		LBP: 30mg/m ² : 1/weel 4 wcles	
~	Endo_NDP: 46		/			Endo 7.5mg/m² 7/week 4 cycles	
Cheng et al.	NDP:46	45/47		NR	NR	NDP 30mg/m ² : 1/weex, 2 9 cycles	P1
2019^{47}						NDP 30mg/m ² : 1/week g 2-4 cycles	
37 . 1	Endo_NDP: 35		62.5±5.5			Endo 60mg_NDP 60mg 1/week, 2	
Xu et al.	NDP:35	43/27		Moderate to large	NR	cycles	P1,3
2014 ⁴⁸						NDP 60mg: 1/week, 20ycles	
37 . 1	Bev_DDP: 29		69.86±11.36/			Bev 300mg, d1,q3w_D P 40mg	
You et al.	DDP:29	32/26	67.92±9.83	NR	≥70	d1,8,15, q3w: 1 cycle	P1
2021 ⁴⁹						DDP: 40mg d1, 8, 15, q3w 2 cycle	
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Chen and Ai	Bev_DDP: 35		65.16 ± 9.34			Bev 300mg, d1,q3 DP 50mg	
2022 ⁵⁰	DDP:35	45/25	65.08 ± 9.26	NR	NR	d1,8,15, q3w: 1 cycle	P1,3
						DDP: 50mg d1, 8, 15, 📆 🖺 cycle	
Zhang et al.	Bev_DDP: 34		61.62±2.78/			Bev 300mg_DDP 60ng	
2019^{51}	DDP:34	33/35	61.38±2.94	NR	>60	cycles ated	P1,3
						DDP: 60mg 1/2weeks,	
	Bev_DDP: 36		58.58±4.45/			Bev 5mg/kg_DDP 45ng 2 1/week,	
Song 2020 ⁵²	DDP:36	45/27	58.69 ± 4.87	NR	>60	3 cycles apperi	P1,3
						DDP: 45mg/m², 1/week a d d d d d d	
Xue and	Bev_DDP: 41		58.21±3.25/			Bev 5mg/kg_DDP 60n aboveek, 3	
Zhao 2017 ⁵³	DDP:41	47/35	58.96 ± 3.43	NR	NR	cycles nim m	P1,3
Z11a0 2017						DDP: 60mg, 1/week, 36 yees	
Huang	Bev_DDP: 37		60.28±6.17/			Bev 5mg/kg_DDP 40n 2: 1 week, 3	
2016 ⁵⁴	DDP:36	53/20	61.31 ± 6.05	Moderate to large	>70	cycles $\frac{\vec{a}}{\vec{b}}$	P1,2,3
2010						DDP: 40mg, 1/week, 3 yces	
T. Chen et	Bev_DDP: 24		54.6 ± 7.7			Bev 300mg_DDP 60m g : 1/ 2 weeks, 1	
al. 2016 ⁵⁵	DDP:24	31/17		Moderate to large	NR	cycle <u>s</u> c	P1,3
al. 2010						DDP: 60mg, 1/2 weeks 1 cocle	
Wang et al.	NDP: 24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m ² ,1/week 3-4 cycles	P1,2,3
2015^{56}	DDP:24	23/23		Moderate to large	~00	DDP: 40mg/m ² ,1/week 2 3-4 cycles	F1,2,3
Zhu et al.	NDP: 40	48/32	56.78±8.92/	NR	NR	NDP: 40mg/m ² ,1/weel 4 cycles	P1,3
202257	DDP:40	46/32	57.18 ± 9.12	NK	NK	DDP: 40mg/m ² ,1/week 4 cacles	P1,5
Bai 2019 ⁵⁸	NDP: 30	29/20	35-75	M. J	>60	NDP: 40mg/m ² ,1/week, 2-3 cycles	D1 2
Bai 2019**	DDP:28	38/20		Moderate to large	≥60	DDP: 40mg/m ² ,1/week, 2-2cycles	P1,3
X. Chen et	NDP: 39	12/26	55.8±8.1/	I	>60	NDP: 40mg/m ² ,1/week, 2-4 cycles	D1 2 4
al. 2016 ⁵⁹	DDP:40	43/36	58.2±7.3	Large	≥60	DDP: 40mg/m ² ,1/week, 2-4 cycles	P1,3,4

						<u>ā</u> o	
Huang et al.	LBP: 38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m ² ,1-2/weak, 2 cycles	D1 2
2017^{60}	DDP:38	41/33		INK	NK	DDP: 30mg/m^2 , $1-2/\text{we}$ k, $2\sqrt{6}$ 4 cycles	P1,3
Sheng	LBP: 30	20/40	38-74	Madamata ta lama	≥60	LBP: 30mg/m²,1-2/wekkppg4 cycles	D1 2
2014^{61}	DDP:30	20/40		Moderate to large	≥00	DDP: 30mg/m²,1-2/wegk2.54 cycles	P1,3
Gao et al.	LBP: 30	37/24	57-69/54-68	Madamata ta lama		LBP: 30mg/m²,1/week 2548 ycles	P1,2,3
2019^{62}	DDP:31	3//24		Moderate to large	≥60	DDP: 40mg/m²,1/week 24 cycles	r1,2,3

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Engley or + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, EBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + classified (1968) NR, not reported.

Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quining, Al training, and similar technologies.

A training and similar technologies.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Endostar + lobaplatin, LBP: lobaplatin, Endo NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev DDP: Bevacizumab + cisple 2. NR, not reported.

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Table S4	The league table of network meta-anal	ysis for DCR according to all interventions.
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			OR 95% CrIs) De for		
Bev_DDP				cemb Ens uses		
3.51 (2.03, 6.28)*	DDP			nber seig s re		
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP		ber 2024 seignem s related		
0.15 (0.01, 1.03)	0.04 (0, 0.27)*	0.15 (0.02, 0.93)*	Endo_LBP	24. D nent d to		
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, 28.9) ਹੈ ਨੂੰ ਨੂੰ	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) (1.22)	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 + cisplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

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

		OR 95	% CrIs	an <u>ă</u>		
Bev_DDP				com/ od simil		
1.56 (0.52, 4.94)	DDP			n/ on		
0.47 (0.15, 1.52)	$0.3 (0.22, 0.39)^*$	Endo_DDP		te _		
0.16 (0.02, 1.26)	0.1 (0.02, 0.57)*	0.34 (0.05, 1.95)	Endo_LBP	une chn		
0.49 (0.1, 2.39)	$0.31 (0.1, 0.93)^*$	1.05 (0.31, 3.25)	3.06 (0.82, 12.66)	O 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)	gi 25 (0.45,	, 11.58)	NDP

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

*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.

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Table S6	League tables of all g	grades myelosuppressive even	t comparison of all interventions.
	Deague tubies of all a		t companion of an interventions.

			OR 95% CrIs	De		
Bev_DDP				cemb Ens uses		
0.99 (0.55, 1.76)	DDP			ıber 2 seign s relai		
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP		2024 Jnem lated		
0.68 (0.1, 4.32)	0.69 (0.11, 4.01)	0.71 (0.11, 4.25)	Endo_LBP	nent d to		
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 + finedaplatin, NDP: nedaplatin, Bev_DDP: + cisplatin.

League tables of all grades gastrointestinal effect event comparison of all interventions Bevacizumab + cisplatin.

Table S7

			OR 95% CrIs	an j		
Bev_DDP				com/ d simil		
0.93 (0.58, 1.49)	DDP			nilar		
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP		te Ju		
1.58 (0.04, 24.01)	1.7 (0.05, 24.68)	1.86 (0.05, 27.49)	Endo_LBP	chn		
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 6		
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, 18778)	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

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Bevacizumab + cisplatin.

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

			OR 95% CrIs	nber Iseig Is re		
Bev_DDP				202 jner late		
0.86 (0.29, 2.5)	DDP			nen d to		
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP		Jow t Su tex		
1.2 (0.02, 64.26)	1.39 (0.03, 65.71)	1.63 (0.03, 80.3)	Endo_LBP	nloa t an		
0.43 (0.01, 8)	0.5 (0.01, 7.53)	0.58 (0.02, 9.69)	0.34 (0, 38.81)	Endo_NDP die e		
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. Data bolded	in black indicate they are fro	om an indirect comparison.	k	ng,		
ORs between the inclu	ided interventions according	to the results of network me	eta-analysis.	Al t		
Endo_DDP: Endostar	+ cisplatin, DDP: cisplatin	n, Endo_LBP: Endostar + le	obaplatin, LBP: lobaplati	n, Endo_NDP: Endosaar 👼 ne	daplatin, NDP: nedaplati	n, Bev_DDI
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Table S9 Leag	ue tables of G3-myelos	suppressive event com	parison of all interve	entions. $\underline{\underline{\varphi}}$		
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		OR 95% CrIs	iia		
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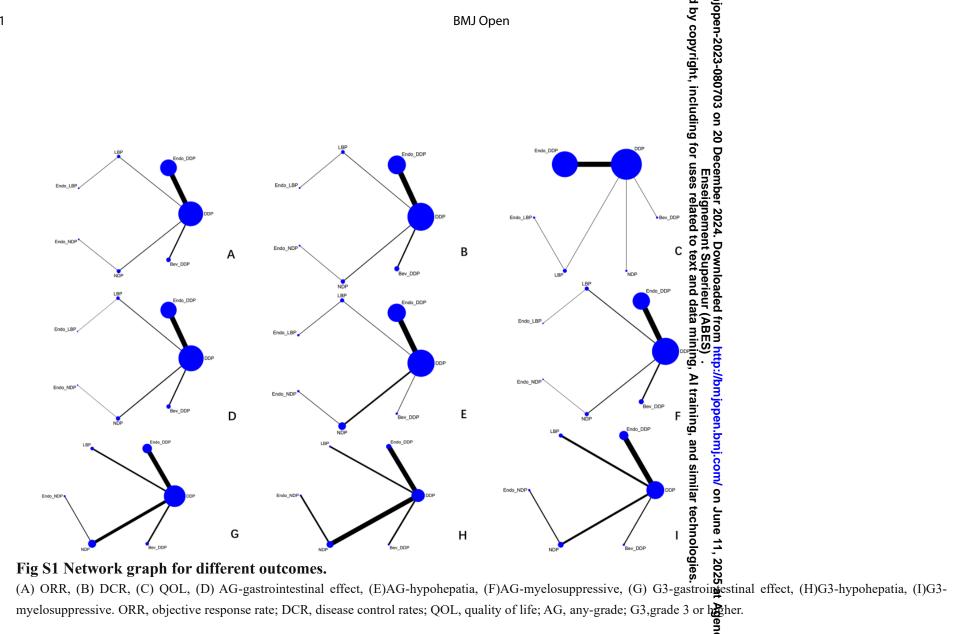
^{*}p<0.05. Data bolded in black indicate they are from an indirect comparison.

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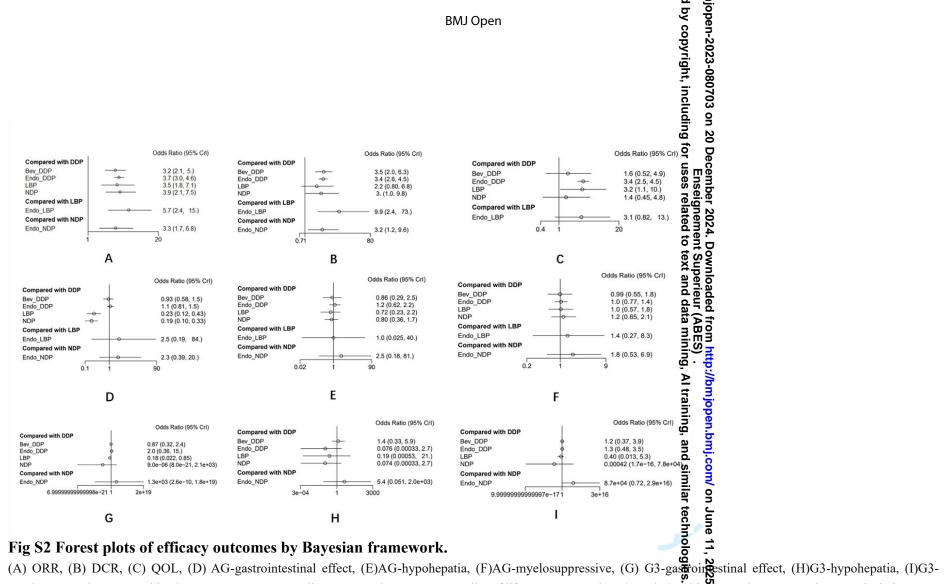
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myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or header.

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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: Beacizumab + cisplatin.

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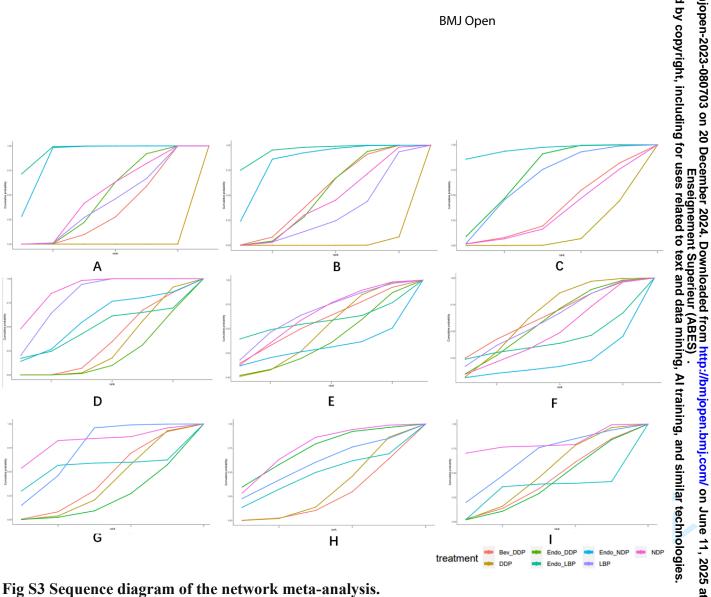


Fig S3 Sequence diagram of the network meta-analysis.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or has her.

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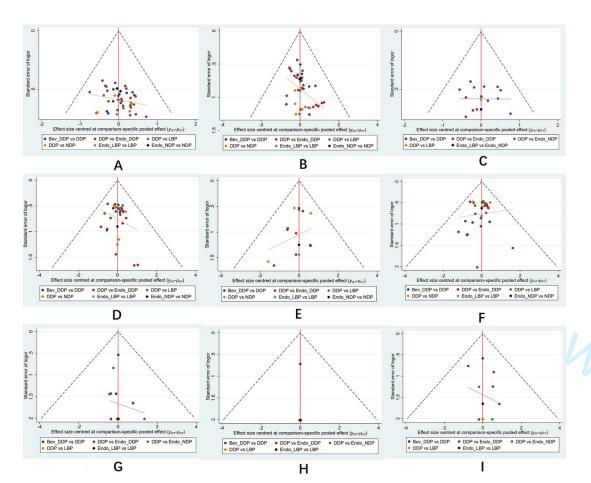


Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3myelosuppressive. ce Bibliographique de l

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

BMJ Open

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:

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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 (egrade 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 S3¹⁷⁻⁶²). 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

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

- 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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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.

	BEV_DDP	DDP	Endo_DDP	Endo_LBP	Endo_NI	LBP	NDP
ORR	0.33	0.00002	0.46	0.95	0.88 nilar	0.40	0.48
DCR	0.51	0.01	0.49	0.95	0.83 fe Ju	0.30	0.41
QOL	0.33	0.10	0.69	0.95	/ hnc	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 gies.	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

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Mean age	0.36 (-0.59, 1.31)	0.459	0.18 (-1.28, 1.64)	0.810	ninir	
Sex	0.12 (-0.84, 1.08)	0.811	-1.26 (-2.72, 0.20)	0.091	ල්. සු	
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- Fig 1 The flow diagram of the study selection process for the network meta-analysis
- Fig 2 Assessment of risk of bias.

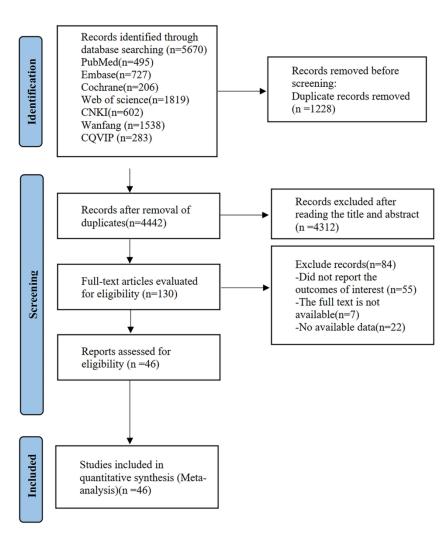


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Section and Topic	Item #	Checklist item	Location where item is reported
TITLE	'	s eig reig	
Title	1	Identify the report as a systematic review.	1
ABSTRACT		to to	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTIO	N	nd d	
Rationale	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	<u>.</u>	9 · β Α ://	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the synthms of the	5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched 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 esed.	5, Supplementary Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including many reviewers screened each record and each report retrieved, whether they worked independently, and catalla 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 cach 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
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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 compatible 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 characters). 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(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool(specific by the methods used to assess risk of bias in the included studies, including details of the tool (specific by the methods used to assess risk of bias in the included studies, including details of the tool (specific by the methods used to assess risk of the tool (specific by the method to assess risk of the tool (specific by the methods used to assess risk of the tool (specific by the methods used to assess risk of the tool (specific by the methods used to assess risk of the tool (specific by the methods used to assess risk of the tool (7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis esentation of results.	7, 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating budy 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 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. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses conducted to assess robustness of the synthesized results. Solitor Describe any sensitivity analyses Describe any sensitivity analyses Describe any sensitivity Describe a	8

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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 region be region at the control of the c	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of supplied to a specific supplied to specific supplied to	8
RESULTS	•	nd c	
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 with 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	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
syntheses	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
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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 results of all sensitivity analyses conducted to assess the robustness of the synthesized results. Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessed to the synthesized results.	9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed of end of end of each outcome assessed of end of end of end of each outcome assessed of end	11
DISCUSSION		ia n	
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 INFOR	RMATIO		
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	ing for	n 20 De	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 extracted from included studies; data used for all analyses; analytic code; any other materials used for all analyses.	collegs related to t	Peview. 2024.	15
From: Page MJ, N	McKe nzie	Checklist item Report which of the following are publicly available and where they can be found: template data extracted from included studies; data used for all analyses; analytic code; any other materials used. JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guide. For more information, visit: http://www.prisma-statement.org/ For peer review only - http://bmjopen.bmj.com/site/about/guidelines/	Seperieur (ABES) . 321 and data mining, Al training, and similar technologies. 6 ein	wing systemation of the system	c reviews. BMJ 2021;372:n71. doi
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Table S2 Literature Search Strategy

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Table S3 Characteristics of the included randomized controlled trials.

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Table S3 Ch Study	aracteristics of Sample size	the includ Gender (M/F)	led randomize Mean age(years)	d controlled trials. Volume of MPE	KPS scores	1703 on 20 December Enseig including for uses re	outcome
F. Chen et al. 2016 ¹⁷	Endo_DDP:30 DDP:30	39/21		Moderate to large	≥60	Endo 45 mg_DDP 40mg 70 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	DDP 40mg/m ² : 1/week 2 Cles Endo 45 mg_DDP 40mg 2 Coveek, 3 cycles DDP 40mg: 2/week, 3	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/m² 2/week, 3 cycles DDP 40mg/m²: 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 40ng/mg 1/week, 4 cycles DDP 40mg/m²: 1/weekg4 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: 12 week, 3 cycles DDP 30mg: 1/week, 3 gycles	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/mb 2/week, 3 cycles DDP 40mg/m²: 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 \(\frac{9}{20}\)mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

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	Endo_DDP:20		62.3±1.7/			Endo 45 mg_DDP 40ng/mg/1/week,	
Li 2020 ²⁴	DDP:20	24/16	62.5 ± 1.5	Moderate to large	NR	3 cycles	P1,3
						DDP 40mg/m ² : 1/week 23 37 32 32 32 cles	
	Endo_DDP:31		42.22 ± 6.92			Endo 30 mg 2/week_Dp. mg	
Li 2016 ²⁵	DDP:31	35/27	42.14±6.89	NR	>60	1/week: 2 cycles de	P1,3
						DDP 50mg: 1/week, 2 50 2 65	
Liu et al.	Endo_DDP:30		52.64±6.55/			Endo 45 mg/m²_DDP 2/week,	
2019 ²⁶	DDP:30	36/24	53.31±7.56	NR	≥60	2-3 cycles	P1,3
2019						DDP 30mg: 2/week, 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	
Liu et al.	Endo_DDP:34	38/30	63.19±4.73/	Moderate to large	≥60	Endo 60 mg _DDP 601	P1,2,3
2018^{27}	DDP:34	36/30	65.55 ± 5.28	Wioderate to large	≥00	DDP 60mg: 2/week	11,2,3
Lu and	Endo_DDP:31		46.3±10.6/			Endo 45 mg_DDP 40ngg/m 2/week,	
Zhang	DDP:31	35/27	45.7±11.3	Moderate to large	≥60	3 cycles	P1,2,3
2017^{28}						DDP 40mg/m ² : 2/week 3 controls	
	Endo_DDP:21		59.6			Endo 60 mg_DDP 50ng; 12week, 3	
Qin 2016 ²⁹	DDP:21	24/18		Moderate to large	≥60	cycles	P1,3
						DDP 50mg: 1/week, 3 gycl	
Oina at al	Endo_DDP:28		68.2±4.6/			Endo 35 mg/m ² _DDP mg/m ² :	
Qing et al. 2018 ³⁰	DDP:23	22/27	68.2±4.6	NR	NR	2/week, 3 cycles	P1,2,3,4
2016						DDP 60mg/m ² : 2/week 3 c c cles	
Shen et al.	Endo_DDP:40		37-79			Endo 30 mg 2/week_D P 40 mg:	
2012 ³¹	DDP:40	42/38		Moderate to large	≥60	1/week, 3 cycles	P1,2,3
2012						DDP 40mg: 1/week, 3 cycles	
Su et al.	Endo_DDP:30		61.43±6.45/			Endo 60 mg_DDP 40-50m 2/week,	
2021 ³²	DDP:30	37/23	62.05 ± 6.29	NR	NR	2 cycles	P1,3
2021						DDP 40-50mg: 2/week, 2 celes	
						- Jliog	
						Jrap	
						liographique de /about/guidelines.xhtml	
			For peer review	only - http://bmjopen.bn	ni.com/site	/about/quidelines.xhtml •	
				,	,	<u>•</u>	

	Endo_DDP:42		56.84±7.03/			Endo 40 mg_DDP 40mg/mg/1/week,	
Qin 2018 ³³	DDP:42	43/41	57.19±8.25	NR	NR	4 cycles	P1,2
						DDP 40mg/m ² : 1/week 475 scles	,-
	Endo DDP:48		59.26±2.43/			Endo 30 mg 4/week_D	
Tian et al.	_ DDP:48	57/39	61.54±2.32	Moderate to large	≥60		P1
2019^{34}				C		40mg/m ² : 2/week, 1 cy a 2 8 8 8 DDP 30-40mg/m ² : 2/wge 2 , 1 cycle	
	Endo_DDP:45		46.5±11.5/			Endo 45 mg_DDP 40n 2/week,	
Tu et al.	DDP:45	48/42	47.5±10.5	Moderate to large	≥60	3 cycles and	P1,2,3
2014 ³⁵						DDP 40mg/m ² : 2/week = Ecceles	
OV7 4 1	Endo_DDP:40		55.5±2.2/			Endo 40 mg_DDP 40mg	
Wang et al. 2017 ³⁶	DDP:40	41/39	55.8±2.9	Large	≥60	cycles	P1,2,3
201750						DDP 40mg: 1/week, 4 ycl	
	Endo_DDP:30		61.28±6.32/			Endo 45 mg_DDP 40n 2/week,	
Wang 2018 ³⁷	DDP:30	35/25	60.54 ± 5.65	NR	≥60	3 cycles	P1,3
						DDP 40mg/m ² : 2/week 3 cccles	
	Endo_DDP:47		53.47±3.25/			Endo 30 mg_DDP 40n\(\) /m\(\) 2/week,	
Wang 2023 ³⁸	DDP:47	51/43	54.09 ± 3.38	NR	≥80	3 cycles	P1
						DDP 40mg/m^2 : $2/\text{week} = 3$ cocles	
Xu et al.	Endo_DDP:20		/			Endo 60 mg_DDP 40-30 mg_2/week:	
202 ³⁹	DDP:20	27/13		Large	≥50	2 cycles	P1,2,3,4
202						DDP 40-50mg: 2/week 2 cycles	
Xu et al.	Endo_DDP:75		63.65±5.11/			Endo 45 mg_DDP 10mg 1/Reek: 3	
2021 ⁴⁰	DDP:75	79/71	63.87 ± 5.38	NR	NR	cycles	P1,3
2021						DDP 10mg: 1/week, 3 cycl	
	Endo_DDP:21	27/15	41.5±7.6	Large	NR	Endo 30 mg_DDP 40mg 1/ Reek: 3	P1,2,3,4
(Yang et al.	Endo_BB1.21			Large	1110	cycles Bibliographique de e/about/guidelines.xhtml	1 1,2,5,

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						-202; оругі	
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						0703	
						DDP 40mg: 1/week, 3 dycles	
			50.50.51.			ā ī	
TT 2016/12	Endo_DDP:27	22/20	60.28±6.17/		. 50	Endo 30 mg_DDP 40mg/mg 2/week,	D1 0 0
Yu 2016 ⁴²	DDP:25	32/20	61.31 ± 6.05	Moderate to large	≥70	3 P A	P1,2,3
	E 1 DDD 46		A11 55/00 55			DDP 40mg/m ² : 2/week	
Liu and Tan	Endo_DDP:26	22/22	41-75/39-75			Endo 45mg_DDP 30mg_#\delta ek: 2-3	21.0
2018 ⁴³	DDP:26	23/29		Moderate to large	NR	· ave	P1,3
						DDP 30mg: 2/week: 2 \$\frac{1}{2} \frac{1}{2} \frac{1}{	
Lu et al.	Endo_DDP:30	00/00				Endo 30mg_DDP 30mg #@days: 1-2	21.0
2016 ⁴⁴	DDP:30	28/32		Moderate to large	NR	cycles DDP 30mg: 3/6 days: 2 Pcles	P1,2
	E 1 1DD 01		10.2.5.6			=· · · · · >	
Shi et al.	Endo_LBP:21	25/17	42.3±5.6		NID	Endo 30mg 2/week: 3 Endo 30mg 2/week: 3 Endo 30mg 2/week: 3	D1 2 4
2016^{45}	LBP:21	25/17		Moderate to large	NR		P1,2,4
	E 1 IDD 20		50.21 : 4.25/			LBP: 30mg/m ² : 1/3 weatk, Ecycle	
C1 202146	Endo_LBP: 30	20/21	50.31±4.27/	36.1	VID	Endo 30mg_LBP: 30mg/mg/1/week,	D1 2
Chen 2021 ⁴⁶	LBP:30	39/21	50.16±4.35	Moderate to large	NR	<u> </u>	P1,3
	E 1 NDD 46		,			LBP: 30mg/m ² : 1/weel 4 cycles	
Cheng et al.	Endo_NDP: 46	45/47	/	NID	NID	Endo 7.5mg/m² 7/weel 4 cycles	D1
2019^{47}	NDP:46	45/47		NR	NR		P1
	E 1 NDD 25		(2.5.5.5			NDP 30mg/m ² : 1/week 2-4 cycles	
Xu et al.	Endo_NDP: 35	42/27	62.5±5.5	M 1 4 4 1	NID	Endo 60mg_NDP 60mg: 1/week, 2	D1 2
2014^{48}	NDP:35	43/27		Moderate to large	NR	cycles	P1,3
	D DDD, 20		(0.96+11.26/				
You et al.	Bev_DDP: 29 DDP:29	22/26	69.86±11.36/	NID	>70	Bev 300mg, d1,q3w_DDP 40mg d1,8,15, q3w: 1 cycle	D1
2021 ⁴⁹	DDF:29	32/26	67.92±9.83	NR	≥70	DDP: 40mg d1, 8, 15, q3w. 1 cycle	P1
							
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						угар	
						ibliographique aphique de	
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			, p. 22. 12.12.	,	j ,	<u>o</u>	

Chen and Ai	Bev_DDP: 35		65.16 ± 9.34			Bev 300mg, d1,q3 DP 50mg		
2022 ⁵⁰	DDP:35	45/25	65.08 ± 9.26	NR	NR	d1,8,15, q3w: 1 cycle 즉	P1,3	
2022						DDP: 50mg d1, 8, 15, 🛱 🖫 🖺 cycle		
Zhang et al.	Bev_DDP: 34		61.62 ± 2.78			Bev 300mg_DDP 60ng 4 kgweeks: 4		
2019 ⁵¹	DDP:34	33/35	61.38±2.94	NR	>60	cycles lain 20	P1,3	
2019						DDP: 60mg 1/2weeks,		
	Bev_DDP: 36		58.58±4.45/			Bev 5mg/kg_DDP 45ng 202 1/week,		
Song 2020 ⁵²	DDP:36	45/27	58.69±4.87	NR	>60	3 cycles and	P1,3	
						DDP: 45mg/m², 1/week a gycles		
Xue and	Bev_DDP: 41		58.21±3.25/			Bev 5mg/kg_DDP 60m		
Zhao 2017 ⁵³	DDP:41	47/35	58.96 ± 3.43	NR	NR	cycles	P1,3	
ZHao Zui /**						DDP: 60mg, 1/week, 3 yces		
Huang	Bev_DDP: 37		60.28±6.17/			Bev 5mg/kg_DDP 40n : 1 week, 3		
nuang 2016 ⁵⁴	DDP:36 53/20	53/20	61.31 ± 6.05	Moderate to large	>70	cycles an op	P1,2,3	
2010						DDP: 40mg, 1/week, 3 yces		
Γ. Chen et	Bev_DDP: 24		54.6±7.7	Moderate to large		Bev 300mg_DDP 60m g : 1/ 2 weeks, 1		
al. 2016 ⁵⁵	DDP:24	DDP:24 31/17			NR	cycle <u>v</u> . S	P1,3	
11. 2010						DDP: 60mg, 1/2 week 1 cycle		
Wang et al.	NDP: 24	3 29-82	Moderate to large >	>60	NDP: 40mg/m ² ,1/week 3-4 cycles	P1,2,3		
2015^{56}	DDP:24	23123		Woderate to large	>00	DDP: 40mg/m ² ,1/weel 3-4 cycles	1 1,2,.	
Zhu et al.	NDP: 40	48/32	56.78±8.92/	NR	NR	NDP: 40mg/m ² ,1/weel 4 cycles	P1,3	
2022^{57}	DDP:40	40/32	57.18 ± 9.12	INIX	NIX	DDP: 40mg/m ² ,1/week 4 cecles	11,5	
Rai 2010 ⁵⁸	NDP: 30	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m ² ,1/week, 2-32cycles	P1,3	
Bai 2019 ⁵⁸	DDP:28	36/20		Wioderate to large	≥00	DDP: 40mg/m ² ,1/week, 2-2cycles	11,5	
	NIDD 20		55.8 ± 8.1	Large	≥60	NDP: 40mg/m ² ,1/week, 2-4 cycles	P1,3,4	
X. Chen et	NDP: 39	43/36		Laige	≥00	DDP: 40mg/m ² ,1/week, 2-4 cycles	11,5,-	

						₫ 0	
Huang et al.	LBP: 38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m²,1-2/week, 25 cycles	P1.3
2017^{60}	DDP:38	41/33	INK INK		DDP: 30mg/m ² ,1-2/we k, 2 cycles	Г1,3	
Sheng	LBP: 30	20/40	38-74	Moderate to large	≥60	LBP: 30mg/m²,1-2/we 🖟 🕰 cycles	P1.3
2014^{61}	DDP:30	20/40	Moderate to la		≥00	DDP: 30mg/m ² ,1-2/wegk ² ,34 cycles	P1,3
Gao et al.	LBP: 30	27/24	57-69/54-68	M-1		LBP: 30mg/m²,1/week 2548 ycles	
2019^{62}	DDP:31	37/24	Moderate to large		≥60	DDP: 40mg/m²,1/week 24 cycles	P1,2,3

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: Engley or + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev DDP: Bevacizumab + cisple 2. NR, not reported.

Endostar + lobaplatin, EBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + classified (1968) NR, not reported.

Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quining, Al training, and similar technologies.

A training and similar technologies.

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			OR 95% CrIs) De for		
Bev_DDP				cemb Ens uses		
3.51 (2.03, 6.28)*	DDP			re eic		
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP		2024 Jinem lated		
0.15 (0.01, 1.03)	0.04 (0, 0.27)*	0.15 (0.02, 0.93)*	Endo_LBP	24. D nent d to		
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, 28.9) 0 0	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 a) $\frac{1}{2}$	0.74 (0.16, 3.45)	NDP
* .0.05 D . 1.11 1:	11 1 1 1 1 1 1			3t (-)		

^{*}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 + cisplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

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

		OR 95	% CrIs	an	<u> </u>	
Bev_DDP				SIMI		_
1.56 (0.52, 4.94)	DDP			nllar	: ?	
0.47 (0.15, 1.52)	$0.3 (0.22, 0.39)^*$	Endo_DDP		e e		
0.16 (0.02, 1.26)	0.1 (0.02, 0.57)*	0.34 (0.05, 1.95)	Endo_LBP	Chn	. In e	
0.49 (0.1, 2.39)	$0.31 (0.1, 0.93)^*$	1.05 (0.31, 3.25)	3.06 (0.82, 12.66)	olog	· 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)	gies	225 (0.45, 11.58)	NDP

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

*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.

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

			OR 95% CrIs	for		
Bev_DDP				cemb Ens uses		
0.99 (0.55, 1.76)	DDP			nber seig s rel		
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP		2024 gnem lated		
0.68 (0.1, 4.32)	0.69 (0.11, 4.01)	0.71 (0.11, 4.25)	Endo_LBP	neni d to		
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 + finedaplatin, NDP: nedaplatin, Bev DDP: + cisplatin.

League tables of all grades gastrointestinal effect event comparison of all interventions Bevacizumab + cisplatin.

Table S7

			OR 95% CrIs	ano		
Bev_DDP				com/ simil		
0.93 (0.58, 1.49)	DDP			nilar		
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP		te Ju		
1.58 (0.04, 24.01)	1.7 (0.05, 24.68)	1.86 (0.05, 27.49)	Endo_LBP	chn		
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 6		
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) ကို	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

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Bevacizumab + cisplatin.

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

			OR 95% CrIs	nber Iseig Is re		
Bev_DDP				202 Iner late		
0.86 (0.29, 2.5)	DDP			nen d to		
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP		Tow tex		
1.2 (0.02, 64.26)	1.39 (0.03, 65.71)	1.63 (0.03, 80.3)	Endo_LBP	nloa t an		
0.43 (0.01, 8)	0.5 (0.01, 7.53)	0.58 (0.02, 9.69)	0.34 (0, 38.81)	Endo_NDP Q. T. a.d.		
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. Data bolded	in black indicate they are from	om an indirect comparison.	/	ng,		
ORs between the inclu	ided interventions according	to the results of network me	eta-analysis.	AI t		
Endo_DDP: Endostar	+ cisplatin, DDP: cisplatin	n, Endo_LBP: Endostar + lo	obaplatin, LBP: lobaplati	in, Endo_NDP: Endosar 5 ne	daplatin, NDP: nedaplati	n, Bev_DDl
Bevacizumab + cisplat	tin.			ing		
				, an		
Table S9 Leag	ue tables of G3-myelo	suppressive event comp	parison of all interve	entions.		
			OR 95% CrIs	mila		
				<u> </u>		

		OR 95% CrIs	iia		
Bev_DDP			r teo		
1.19 (0.37, 3.93)	DDP		chno.		
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP	olog 11		
0.02 (0, 1158726093196.45)	0.02 (0, 946584795528.83)	$0.02\ (0, 1200464612598)$	Endo_NDP gies 2025		
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,	2358.54 (0,	3012.84 (0,	86977.28 (0.72, §	877.08 (0,	NDD
7080696058054300)	5857536555380624)	7540937082788929)	28713088892365632)	2259231168436329)	NDP
		•			

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

	erventions according to the results	BMJ Open of network meta-analysis. Endostar + lobaplatin, LBP: loba	uding :	iopen-2023-080703 on 20 Enadaplatin NDP: nadaplatin P	tov DDD:
Bevacizumab + cisplatin, G3:		Endostai + iooapiatiii, LBF. iooaj			DEV_DDF.
Devacizamao - Cispianii, G5.	grade 5 of migner.		Enseig uses rel	Б	
Table S10 League tabl	les of G3-gastrointestinal e	ffect event comparison of all	interventions.	가 20	
		OR 95% CrIs	d mer	\$ 4 -	
Bev_DDP					
Dev_DDF			tex	□ o v	
0.87 (0.32, 2.38)	DDP		t Super text an	Downlos	
	DDP 0.5 (0.06, 2.74)	Endo_DDP	text and d	©ownloadec	
0.87 (0.32, 2.38)		Endo_DDP 346.11 (0,	a (⊋	Downloaded fro	
0.87 (0.32, 2.38) 0.43 (0.05, 3.16)	0.5 (0.06, 2.74)		Endo_NDP	from	
0.87 (0.32, 2.38) 0.43 (0.05, 3.16) 146.72 (0, 2.25957982568521e+21)	0.5 (0.06, 2.74) 170.13 (0, 2.60852595759042e+21)	346.11 (0, 5.58712188787727e+21)	Endo_NDP	from	
0.87 (0.32, 2.38) 0.43 (0.05, 3.16) 146.72 (0,	0.5 (0.06, 2.74) 170.13 (0,	346.11 (0,	Endo_NDP	from	
0.87 (0.32, 2.38) 0.43 (0.05, 3.16) 146.72 (0, 2.25957982568521e+21)	0.5 (0.06, 2.74) 170.13 (0, 2.60852595759042e+21)	346.11 (0, 5.58712188787727e+21)	Endo_NDP	from http	ND

1.05993280385622e+20)

1.25474480157232e+20)

2.61196338258981e+20)

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

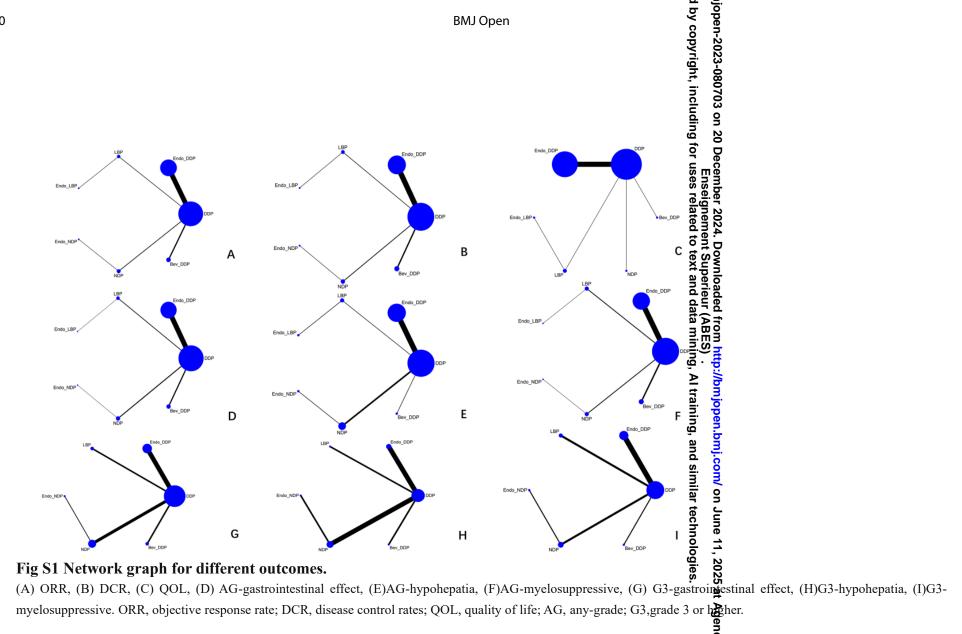
ORs between the included interventions according to the results of network meta-analysis.

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

Bevacizumab + cisplatin, G3: grade 3 or higher.

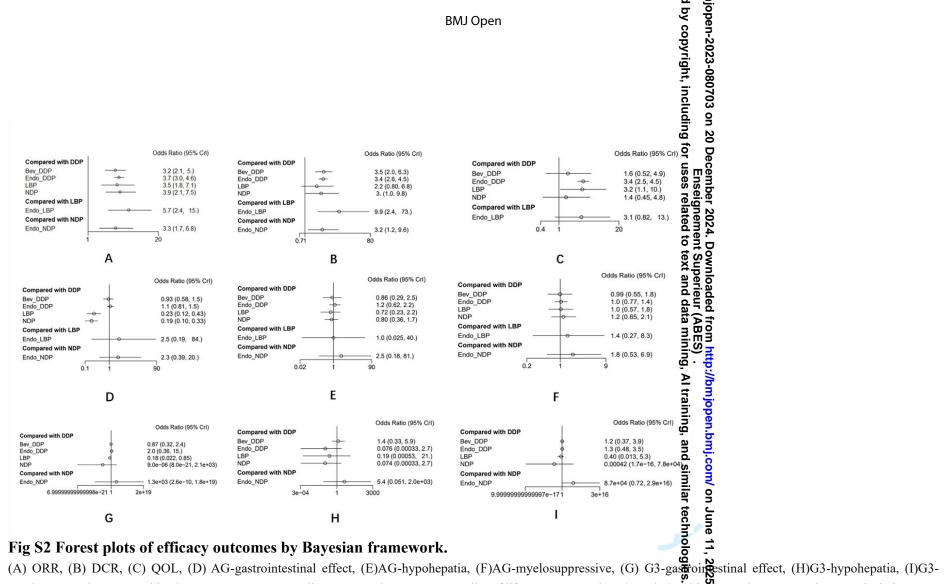
		OR 95% CrIs		ies	.02!	
Bev_DDP				•	5 at	
1.36 (0.33, 5.91)	DDP				Age	
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP			nce	
3.64 (0, 4662.71)	2.67 (0, 2952.95)	0.17 (0, 561.64)	Endo_NDP		Bib	
					ō	

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7.15 (0.05, 3005.42)	5.2 (0.05, 1901.09)	0.37 (0, 382.55)	2.15 (0, 16410.56)	ocluding	
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, 310	2.18) NDP
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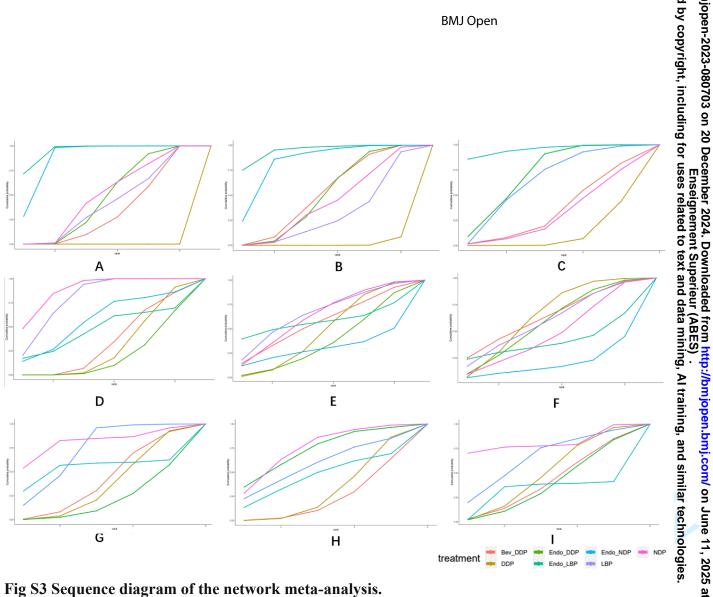


Fig S3 Sequence diagram of the network meta-analysis.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or has her.

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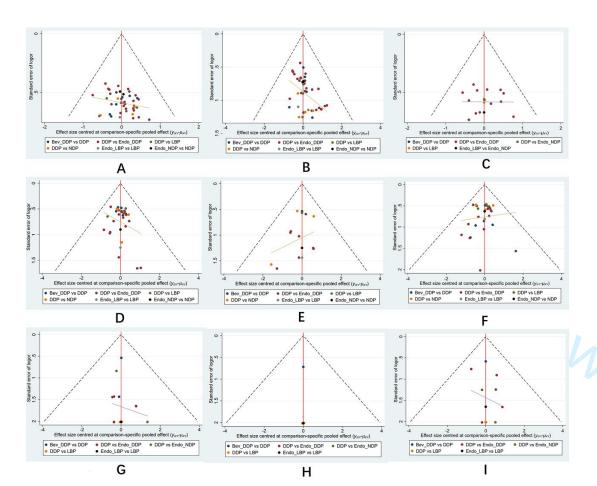


Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3myelosuppressive. ce Bibliographique de l

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Supplementary Materials

Supplementary Materials

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Section and	Item	NMA Checklist of Items to Include When Reporting a Systematic Review Involving so Network	Location where item is
Topic	#	Checklist item	reported
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Title	1	Identify the report as a systematic review.	1
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Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
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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	1	9. † A ://r	
Eligibility	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the synths see	5, 6
criteria		ning	
Information	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched except consulted to	5
sources		identify studies. Specify the date when each source was last searched or consulted.	
Search	7	Present the full search strategies for all databases, registers and websites, including any filters and limits ged.	5, Supplementary Table
strategy		Jur	S2
Selection	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including many	5, 6
process		reviewers screened each record and each report retrieved, whether they worked independently, and Pappicable,	
		details of automation tools used in the process.	
Data	9	Specify the methods used to collect data from reports, including how many reviewers collected data from ach report,	7
collection		whether they worked independently, any processes for obtaining or confirming data from study investigators, and if	
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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 compared in the each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the each 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 characters, 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(specify, how many reviewers assessed each study and whether they worked independently, and if applicable, details of	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis esentation of results.	7, 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating dudy 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 similar 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-aralyse 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
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Section and	Item	<u>5</u>	Location where item is
Topic	#	Checklist item 20 De	reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from region biases).	9, Fig.2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome of supplied to a specific supplied to specific supplied to	8
RESULTS		nd e	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the review 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 with 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	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9-12
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the sunymary 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
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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 results of all investigations of possible causes of heterogeneity among study results. Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results of results of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results assessments of risk of bias due to missing results (arising from reporting biases) for each synthesized results as a second results (arising from reporting biases) for each synthesized results are also because the result	sessed. 9-12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed of carried	11
DISCUSSION		ta m	
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 INFOR	RMATIO	N d.	
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	he 14
Competing interests	26	Declare any competing interests of review authors.	14
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	TS=(Endostar) OR TS=(recombinant human endostatin) OR TS=(Rh endostatin) OR TS=(yh-16) and Preparation (Excluded -	
	database)	
#4	TS=(Drug Therapy) OR TS=(Therapy, Drug) OR TS=(Drug Therapies) OR TS=(Therapies, Drug) 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)	
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Table S3 Characteristics of the included randomized controlled trials.

			BMJ Open			jopen-2023-080703 on 20 Decemt Ens by copyright, including for uses Intervention	
Table S3 Ch	aracteristics of Sample size	Gender	Mean	ed controlled trials. Volume of MPE	KPS	າg	outcome
		(M/F)	age(years)		scores	Intervention for uses re	
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/m²: 1/week 2 2 cles	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. Doveek, 3 cycles DDP 40mg: 2/week, 3	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 40ng/m² 2/week, 3 cycles DDP 40mg/m²: 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/mg 1/week, 4 cycles DDP 40mg/m²: 1/week34 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: 18week, 3 cycles DDP 30mg: 1/week, 3 gycles	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/mg 2/week, 3 cycles DDP 40mg/m²: 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 \$ 0mg 1/week: 2 cycles DDP 50mg: 1/week, 2 cycles	P1,3

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	Endo_DDP:20		62.3 ± 1.7			Endo 45 mg_DDP 40n 1/week,	
Li 2020 ²⁴	DDP:20	24/16	62.5 ± 1.5	Moderate to large	NR	3 cycles	P1,3
						DDP 40mg/m²: 1/week 💆 ፲፱፻월cles	
	Endo_DDP:31		42.22 ± 6.92			Endo 30 mg 2/week_D	
Li 2016 ²⁵	DDP:31	35/27	42.14±6.89	NR	>60	1/week: 2 cycles	P1,3
						1/week: 2 cycles	
Liu et al.	Endo_DDP:30		52.64±6.55/			Endo 45 mg/m ² _DDP 2 2/week,	
2019 ²⁶	DDP:30	36/24	53.31±7.56	NR	≥60	2-3 cycles	P1,3
2019						DDP 30mg: 2/week, 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	
Liu et al.	Endo_DDP:34	38/30	63.19±4.73/	Moderate to large	>60	Endo 60 mg _DDP 60mg	P1,2,3
2018^{27}	DDP:34	36/30	65.55 ± 5.28	Moderate to large	≥60	DDP 60mg: 2/week	P1,2,3
Lu and	Endo_DDP:31		46.3±10.6/			Endo 45 mg_DDP 40ngg/m 2/week,	
Zhang	DDP:31	35/27	45.7±11.3	Moderate to large	≥60	3 cycles	P1,2,3
2017^{28}						DDP 40mg/m ² : 2/week 3 cocles	
	Endo_DDP:21		59.6			Endo 60 mg_DDP 50ng.: 12week, 3	
Qin 2016 ²⁹	DDP:21	24/18		Moderate to large	≥60	cycles	P1,3
						DDP 50mg: 1/week, 3 wycles	
Oin a at al	Endo_DDP:28		68.2±4.6/			Endo 35 mg/m ² _DDP mg/m ² :	
Qing et al. 2018 ³⁰	DDP:23	22/27	68.2±4.6	NR	NR	2/week, 3 cycles	P1,2,3,4
2018						DDP 60mg/m²: 2/week 3 c c cles	
Cl 1	Endo_DDP:40		37-79			Endo 30 mg 2/week_D P 40 mg:	
Shen et al. 2012 ³¹	DDP:40	42/38		Moderate to large	≥60	1/week, 3 cycles	P1,2,3
2012						DDP 40mg: 1/week, 3 cycles	
C4 -1	Endo_DDP:30		61.43±6.45/			Endo 60 mg_DDP 40-50m 2/week,	
Su et al.	DDP:30	37/23	62.05±6.29	NR	NR	2 cycles	P1,3
202132						DDP 40-50mg: 2/week, 2 cueles	

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	Endo_DDP:42		56.84±7.03/			Endo 40 mg_DDP 40ng/mg/1/week,	
Qin 2018 ³³	DDP:42	43/41	57.19 ± 8.25	NR	NR	4 cycles f O	P1,2
						DDP 40mg/m²: 1/week 25 45 Scles	
Tian et al.	Endo_DDP:48		59.26±2.43/			Endo 30 mg 4/week_D	
2019 ³⁴	DDP:48	57/39	61.54±2.32	Moderate to large	≥60	40mg/m ² : 2/week, 1 cy 200	P1
2017						DDP 30-40mg/m ² : 2/wgc 2 , 1 cycle	
Tu et al.	Endo_DDP:45		46.5 ± 11.5 /			Endo 45 mg_DDP 40ng / 2/week,	
2014 ³⁵	DDP:45	48/42	47.5±10.5	Moderate to large	≥60	3 cycles and	P1,2,3
						DDP 40mg/m ² : 2/weeka #ccles	
Wang et al.	Endo_DDP:40		55.5±2.2/			Endo 40 mg_DDP 40m	
2017^{36}	DDP:40	41/39	55.8±2.9	Large	≥60	cycles inin	P1,2,3
	E 1 DDD 20		(1.20) (.22)			DDP 40mg: 1/week, 4	
W 201037	Endo_DDP:30	25/25	61.28±6.32/	NID	>(0)	Endo 45 mg_DDP 40mg/mg 2/week,	D1 2
Wang 2018 ³⁷	DDP:30	35/25	60.54 ± 5.65	NR	≥60	3 cycles	P1,3
	Endo DDD:47		53.47±3.25/			DDP 40mg/m ² : 2/week 3 cycles Endo 30 mg DDP 40n 2/week,	
Wang 2023 ³⁸	Endo_DDP:47 DDP:47	51/43	54.09±3.38	NR	≥80	3 cycles ω	P1
wang 2023	DDI .47	31/43	34.09±3.36	NK	≥80	DDP 40mg/m ² : 2/week 3 cycles	11
	Endo_DDP:20		/			Endo 60 mg_DDP 40-50 mg_2/week:	
Xu et al.	DDP:20	27/13	,	Large	≥50	2 cycles	P1,2,3,4
202^{39}	221.20	27710		Zuige	_6 0	DDP 40-50mg: 2/week 2 cycles	11,2,0,
	Endo_DDP:75		63.65±5.11/			Endo 45 mg_DDP 10mg 1/Reek: 3	
Xu et al.	_ DDP:75	79/71	63.87±5.38	NR	NR	cycles & S	P1,3
202140						DDP 10mg: 1/week, 3 cycl	•
(Yang et al.	Endo_DDP:21	27/15	41.5±7.6	.	ND	Endo 30 mg_DDP 40mg 1/g/eek: 3	D1 2 2 4
201341	DDP:21	27/15		Large	NR	cycles 🖳	P1,2,3,4
						cycles B: Ographique de	
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						DDP 40mg: 1/week, 3 dycles	
	Endo_DDP:27		60.28±6.17/			Endo 30 mg_DDP 40mg/mg 2/week,	
Yu 2016 ⁴²	DDP:25	32/20	61.31±6.05	Moderate to large	≥70	3 cycles & means	P1,2,3
						3 cycles $\frac{1}{2}$ $\frac{1}{2$	
T ' 170	Endo_DDP:26		41-75/39-75			Endo 45mg_DDP 30m	
Liu and Tan 2018 ⁴³	DDP:26	23/29		Moderate to large	NR	cycles to the cycles	P1,3
2018						DDP 30mg, DDP 30mg 76 days: 1-2	
Lu et al.	Endo_DDP:30					Endo 30mg_DDP 30mg & Qdays: 1-2	
2016 ⁴⁴	DDP:30	28/32		Moderate to large	NR	cycles data	P1,2
2010						DDP 30mg: 3/6 days:	
Shi et al.	Endo_LBP:21		42.3±5.6			Endo 30mg 2/week: 3 Endo 20mg LBP:	
2016 ⁴⁵	LBP:21	25/17		Moderate to large	NR	30mg/m ² : 1/3 week, 1 sycl	P1,2,4
2010						LBP: 30mg/m ² : 1/3 westk, Ecycle	
	Endo_LBP: 30		50.31±4.27/			Endo 30mg_LBP: 30mg/mg 1/week,	
Chen 2021 ⁴⁶	LBP:30	39/21	50.16 ± 4.35	Moderate to large	NR	4 cycles	P1,3
						LBP: 30mg/m ² : 1/weel 4 cycles	
Cheng et al.	Endo_NDP: 46		/			Endo 7.5mg/m² 7/weel 4 c cles	
2019 ⁴⁷	NDP:46	45/47		NR	NR	_NDP 30mg/m ² : 1/wee x , 2 9 cycles	P1
2017						NDP 30mg/m ² : 1/week 22-45 cycles	
Xu et al.	Endo_NDP: 35		62.5±5.5			Endo 60mg_NDP 60mg: 1/week, 2	
2014 ⁴⁸	NDP:35	43/27		Moderate to large	NR	NDP 60mg: 1/week, 26ycles	P1,3
						NDP 60mg: 1/week, 26%cless	
You et al.	Bev_DDP: 29		69.86±11.36/			Bev 300mg, d1,q3w_DDP 40mg	
2021 ⁴⁹	DDP:29	32/26	67.92 ± 9.83	NR	≥70	d1,8,15, q3w: 1 cycle	P1
						DDP: 40mg d1, 8, 15, q3w 2 cycle	

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Chen and Ai	Bev_DDP: 35		65.16 ±9. 34/			Bev 300mg, d1,q3 2 DDP 50mg	
2022 ⁵⁰	DDP:35	45/25	65.08 ± 9.26	NR	NR	d1,8,15, q3w: 1 cycle 9	P1,3
2022						DDP: 50mg d1, 8, 15, 褒項警 cycle	
Zhang et al.	Bev_DDP: 34		61.62±2.78/			Bev 300mg_DDP 60ng 4 weeks: 4	
2019 ⁵¹	DDP:34	33/35	61.38±2.94	NR	>60	cycles at ec	P1,3
2019						DDP: 60mg 1/2weeks,	
	Bev_DDP: 36		58.58±4.45/			Bev 5mg/kg_DDP 45ng 42 1/week,	
Song 2020 ⁵²	DDP:36	45/27	58.69±4.87	NR	>60	3 cycles and series	P1,3
						DDP: 45mg/m², 1/week a d o d o d o d o d o d o d o d o d o d	
Xue and	Bev_DDP: 41		58.21±3.25/			Bev 5mg/kg_DDP 60n	
Zhao 2017 ⁵³	DDP:41	47/35	58.96±3.43	NR	NR	cycles Di H	P1,3
21140 2017						DDP: 60mg, 1/week, 3 gryces	
Huang	Bev_DDP: 37		60.28±6.17/			Bev 5mg/kg_DDP 40n 2: 1 week, 3	
2016 ⁵⁴	DDP:36	53/20	61.31 ± 6.05	Moderate to large	>70	cycles a s	P1,2,3
2010						DDP: 40mg, 1/week, 3 yces	
T. Chen et	Bev_DDP: 24		54.6 ± 7.7			Bev 300mg_DDP 60m g : 1/ 2 weeks, 1	
al. 2016 ⁵⁵	DDP:24	31/17		Moderate to large	NR	cycle g. S	P1,3
ai. 2010						DDP: 60mg, 1/2 weeks 1 cocle	
Wang et al.	NDP: 24	25/23	29-82	Moderate to large	>60	NDP: 40mg/m ² ,1/week 3-4 cycles	P1,2,3
2015^{56}	DDP:24	23123		wioderate to large	- 00	DDP: 40mg/m ² ,1/week 2 3-4 5 cycles	1 1,2,3
Zhu et al.	NDP: 40	48/32	56.78±8.92/	NR	NR	NDP: 40mg/m ² ,1/week 4 cycles	P1,3
2022 ⁵⁷	DDP:40	40/32	57.18±9.12	NK	INIX	DDP: 40mg/m²,1/week 4 c cles	11,5
Bai 2019 ⁵⁸	NDP: 30	38/20	35-75	Moderate to large	≥60	NDP: 40mg/m ² ,1/week, 2-3xcycles	P1,3
Bai 2019	DDP:28	36/20		Woderate to large	≥00	DDP: 40mg/m ² ,1/week, 2- 2 cycles	11,5
X. Chen et	NDP: 39	43/36	55.8 ± 8.1	Large	≥60	NDP: 40mg/m ² ,1/week, 2-4 cycles	P1,3,4
al. 2016 ⁵⁹	DDP:40	73/30	58.2±7.3	Darge	_00	DDP: 40mg/m ² ,1/week, 2-4 cycles	11,5,7

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Huang et al.	LBP: 38	41/35	54±7/ 54±7	NR	NR	LBP: 30mg/m ² ,1-2/week, 2 8 cycles	P1,3
2017^{60}	DDP:38	41/33		INK	NK	DDP: 30mg/m^2 , $1-2/\text{we}$, $2 \frac{1}{8}$ 4 cycles	F1,3
Sheng	LBP: 30	20/40	38-74	Moderate to large	≥60	LBP: 30mg/m²,1-2/we	P1,3
2014^{61}	DDP:30	20/40		Wioderate to large	≥00	DDP: 30mg/m ² ,1-2/we	F1,3
Gao et al.	LBP: 30	37/24	57-69/54-68	Madagata ta laga	>60	LBP: 30mg/m²,1/week 2548 ycles	D1 2 2
2019 ⁶²	DDP:31	37/24		Moderate to large	≥60	DDP: 40mg/m ² ,1/week 24 cycles	P1,2,3

Abbreviation: M: male, F: female, MPE: malignant pleural effusion, KPS: Karnofsky performance score, Endo_DDP: English + cisplatin, DDP: cisplatin, Endo_LBP: Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + classified (1968) NR, not reported.

Outcomes: P1: clinical responses including complete response, partial response, stable disease and progressive disease; P2: quining, Al training, and similar technologies.

A training and similar technologies.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Endostar + lobaplatin, LBP: lobaplatin, Endo_NDP: Endostar + nedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cispleta. NR, not reported.

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

			OR 95% CrIs	De		
Bev_DDP				cemt Ens uses		
3.51 (2.03, 6.28)*	DDP			ıber 2 seign s relat		
1.03 (0.56, 1.97)	0.29 (0.22, 0.39)*	Endo_DDP		2024 ynem lated		
0.15 (0.01, 1.03)	0.04 (0, 0.27)*	0.15 (0.02, 0.93)*	Endo_LBP	24. D nent d to		
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, 28.9) ਹ ਨੂੰ ਨੂੰ	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 a) a a	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 + finedaplatin, NDP: nedaplatin, Bev_DDP: Bevacizumab + cisplatin, DCR: Disease control rate.

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

		OR 95	% CrIs	an j	
Bev_DDP				Sir Con	
1.56 (0.52, 4.94)	DDP			n/ on	
0.47 (0.15, 1.52)	$0.3 (0.22, 0.39)^*$	Endo_DDP		t _	
0.16 (0.02, 1.26)	0.1 (0.02, 0.57)*	0.34 (0.05, 1.95)	Endo_LBP	une 1	
0.49 (0.1, 2.39)	$0.31 (0.1, 0.93)^*$	1.05 (0.31, 3.25)	3.06 (0.82, 12.66)	ō L∄P	
1.09 (0.21, 5.56)	0.7 (0.21, 2.22)	2.35 (0.69, 7.75)	6.93 (0.85, 60.14)	g. 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	Lagrana tables of all grades	myologunnroggiyo oyont o	comparison of all interventions.
Table So	League tables of all grades	myelosuppressive event c	comparison of an interventions.

			OR 95% CrIs) De for		
Bev_DDP				cember 2024. Do Enseignement uses related to t		
0.99 (0.55, 1.76)	DDP			ber seig s re		
0.95 (0.5, 1.83)	0.96 (0.72, 1.3)	Endo_DDP		202 gner late		
0.68 (0.1, 4.32)	0.69 (0.11, 4.01)	0.71 (0.11, 4.25)	Endo_LBP	94. E d to		
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 text		
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 + finedaplatin, NDP: nedaplatin, Bev_DDP: League tables of all grades gastrointestinal effect event comparison of all interventions Bevacizumab + cisplatin.

Table S7

			OR 95% CrIs	an ji		
Bev_DDP				com/ d simil		
0.93 (0.58, 1.49)	DDP			n/ on		
0.85 (0.49, 1.49)	0.92 (0.69, 1.23)	Endo_DDP		n Ju		
1.58 (0.04, 24.01)	1.7 (0.05, 24.68)	1.86 (0.05, 27.49)	Endo_LBP	chn		
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 6		
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, 18778)	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

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

			OR 95% CrIs	nber seig s re		
Bev_DDP				202 jnem lated		
0.86 (0.29, 2.5)	DDP			nen d to		
0.74 (0.21, 2.55)	0.85 (0.45, 1.62)	Endo_DDP		t Su		
1.2 (0.02, 64.26)	1.39 (0.03, 65.71)	1.63 (0.03, 80.3)	Endo_LBP	nloa It an		
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, 20) 🛱 🛨	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 fr	om an indirect comparison.	<i>k</i>	ng,		
ORs between the inclu	ided interventions according	g to the results of network m	eta-analysis.	Al t		
Endo_DDP: Endostar	+ cisplatin, DDP: cisplatin	n, Endo_LBP: Endostar +	lobaplatin, LBP: lobaplati	n, Endo_NDP: Endosar 💆 ne	daplatin, NDP: nedaplati	n, Bev_DD
Bevacizumab + cisplat	tin.			ing		
				, an		
Table S9 Leag	ue tables of G3-myelo	suppressive event com	parison of all interv	entions. $\underline{\underline{\omega}}$		
			OR 95% CrIs	mila		
Bev_DDP				r te		

		OR 95% CrIs	villa		
Bev_DDP			n Jur		
1.19 (0.37, 3.93)	DDP		chno		
0.95 (0.2, 4.43)	0.79 (0.29, 2.1)	Endo_DDP	olog		
0.02 (0, 1158726093196.45)	$0.02 \ (0,946584795528.83)$	0.02 (0, 1200464612598)	Endo_NDP gie s. 2025		
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,	2358.54 (0,	3012.84 (0,	86977.28 (0.72,	877.08 (0,	NDP
7080696058054300)	5857536555380624)	7540937082788929)	28713088892365632)	2259231168436329)	NDP

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

Bevacizumab + cisplatin.

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	erventions according to the results	· · · · · · · · · · · · · · · · · · ·	anlatia Enda NIDD. En	on 20 uding 1	nadanlasia NDD nadanlasia D	DDD.
Bevacizumab + cisplatin, G3:		: Endostar + lobaplatin, LBP: lob	apiaun, endo_NDP: En	Decemb Enso Struses	nedapiatin, NDF: nedapiatin, B	ev_DDP:
				7 W A		
Table S10 League tabl	les of G3-gastrointestinal e	ffect event comparison of a	ll interventions.	elated to		
Bev_DDP	704	*	ll interventions.	ment d to		
Bev_DDP 0.87 (0.32, 2.38)	DDP	OR 95% CrIs	ll interventions.	24. Downloa ment Superi ad to text an		
Bev_DDP 0.87 (0.32, 2.38) 0.43 (0.05, 3.16) 146.72 (0,	DDP 0.5 (0.06, 2.74) 170.13 (0,	OR 95% CrIs Endo_DDP 346.11 (0,	Il interventions. Endo_NDP	ment d to		
Bev_DDP 0.87 (0.32, 2.38) 0.43 (0.05, 3.16)	DDP 0.5 (0.06, 2.74)	OR 95% CrIs Endo_DDP		24. Downloaded from http:/ ment Superieur (ABES) . ad to text and data mining, .	LBP	
Bev_DDP 0.87 (0.32, 2.38) 0.43 (0.05, 3.16) 146.72 (0, 2.25957982568521e+21)	DDP 0.5 (0.06, 2.74) 170.13 (0, 2.60852595759042e+21)	OR 95% CrIs Endo_DDP 346.11 (0, 5.58712188787727e+21)	Endo_NDP 0.04 (0,	24. Downloaded from http:/ ment Superieur (ABES) . ad to text and data mining, .	LBP 18857.28 (0,	ND

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

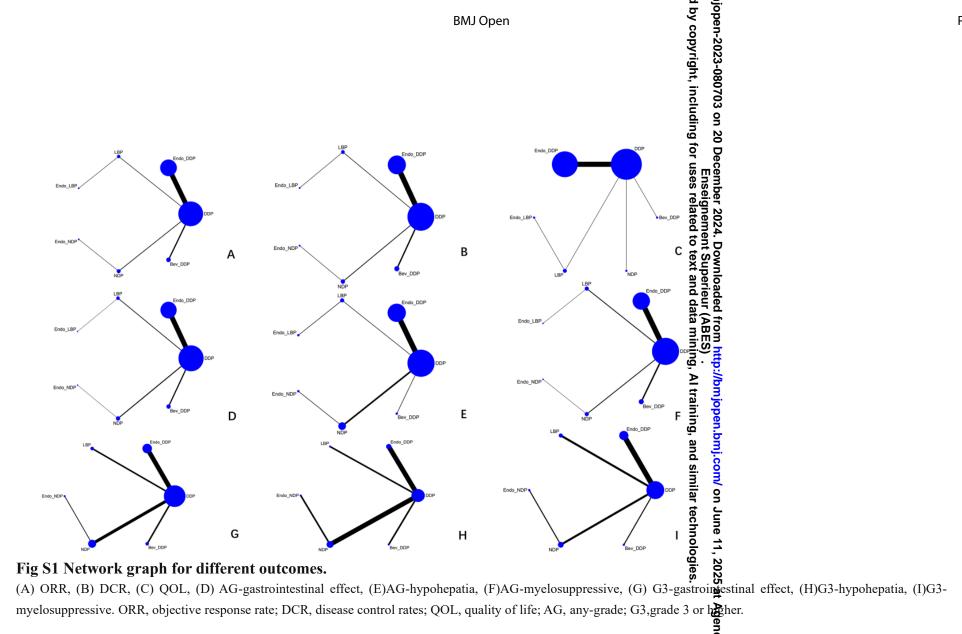
ORs between the included interventions according to the results of network meta-analysis.

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

		OR 95% Crls		es)2!	
Bev_DDP				. 5 at	
1.36 (0.33, 5.91)	DDP			Age	
18.4 (0.37, 4951.17)	13.12 (0.37, 3043.87)	Endo_DDP		nce	
3.64 (0, 4662.71)	2.67 (0, 2952.95)	0.17 (0, 561.64)	Endo_NDP	Bib	
				Į. O	

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7.15 (0.05, 3005.42) 18.95 (0.38, 4882.5)	5.2 (0.05, 1901.09) 13.51 (0.37, 3023.28)	0.37 (0, 382.55) 1.03 (0, 666.32)	2.15 (0 , 16410.56) 5.38 (0.05, 2025.4)	including LBP for D 2.79 (0, 3102.18)	NDP
*p<0.05. Data bolded in blace ORs between the included in Endo_DDP: Endostar + cis Bevacizumab + cisplatin, G3	5.2 (0.05, 1901.09) 13.51 (0.37, 3023.28) ek indicate they are from an indirect aterventions according to the results of platin, DDP: cisplatin, Endo_LBP: 3: grade 3 or higher.	comparison. of network meta-analysis. Endostar + lobaplatin, LBP:	lobaplatin, Endo_NDP: End	P: ned platin, NDP: NDP: NDP: NDP: NDP: NDP: NDP: NDP:	daplatin, Bev_DDP:
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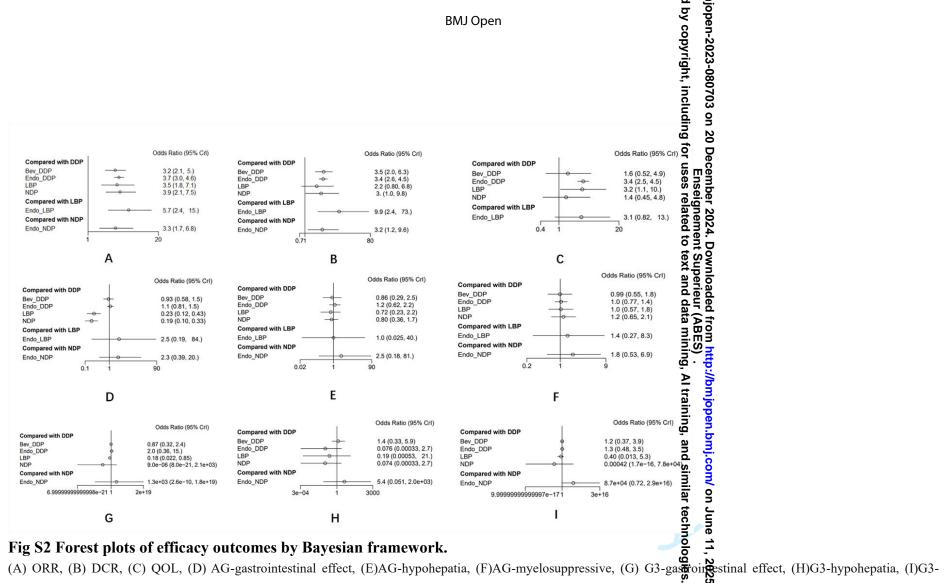
myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or header.

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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)G3myelosuppressive. ORR, objective response rate; DCR, disease control rates; QOL, quality of life; AG, any-grade; G3,grade 3 or hasher.

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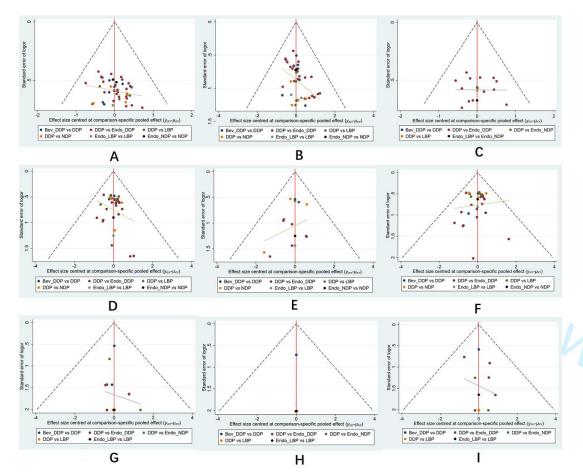


Fig S4 Funnel plots.

(A) ORR, (B) DCR, (C) QOL, (D) AG-gastrointestinal effect, (E)AG-hypohepatia, (F)AG-myelosuppressive, (G) G3-gastrointestinal effect, (H)G3-hypohepatia, (I)G3myelosuppressive. ce Bibliographique de l

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