ORIGINAL RESEARCH

Nimotuzumab combined with concurrent chemoradiotherapy benefits patients with advanced nasopharyngeal carcinoma

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Background: The potential benefits and possible risks associated with combined nimotuzumab and concurrent chemoradiotherapy in patients with advanced nasopharyngeal carcinoma (NPC) have yet to be determined.

Methods: The databases PubMed, Web of Science, China National Knowledge Infrastructure, and Wanfang were systematically searched through February 2017 for studies comparing combined nimotuzumab and chemoradiotherapy versus chemoradiotherapy alone in the treatment of NPC. Primary outcomes were complete and partial responses, and the secondary outcome was adverse reactions. The random-effect model was used to pool relative risks (RRs) and 95% confidence intervals (CIs).

Results: Nine randomized control trials and six cohort studies were included in the final analysis (n=1,015 patients). Compared with chemoradiotherapy alone, chemoradiotherapy combined with nimotuzumab was associated with an increased response rate (RR =1.11, 95% CI: 1.01–1.22). Combined treatment further reduced the occurrence rate of erythropenia (RR =0.11, 95% CI: 0.05–0.28) and neutropenia (RR =0.12, 95% CI: 0.05–0.27). The differences in the rates of other complications were not significant.

Conclusion: Nimotuzumab combined with concurrent chemoradiotherapy is more effective in patients with advanced NPC than chemoradiotherapy alone. Patients receiving combination therapy did not have a higher rate of adverse reactions. Nimotuzumab can thus be recommended as an adjunct therapy in patients with advanced NPC.

Keywords: randomized controlled trial, cohort studies, nasopharyngeal carcinoma, relative risk, radiotherapy, chemoradiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant tumor of the head and neck, especially in China. The World Health Organization estimates that >80% of NPCs occur in China.[1] In recent years, the use of intensity-modulated radiation therapy has increased the efficacy of treatment. The survival rate of patients with stage I or II NPC is 90%, and the rates of recurrence and metastasis are 8.2% and 15.4%, respectively.[2,3] However, the primary lesion of NPC is often occult such that early detection, diagnosis, and treatment are challenging. Thus, at presentation, >70% of NPC patients have stage III or IV disease. The most common form of treatment for these patients with advanced disease is radiotherapy, but its efficacy is poor and severe adverse reactions occur at high rates.[4] Moreover, the rates of local recurrence and distant metastasis are as high as 50%, and the 5-year survival rate for patients treated with radiotherapy alone is only 20%. Indeed, the main reasons for treatment failure are recurrence and

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metastasis. Therefore, patients with advanced NPC are currently treated with concurrent chemotherapy or neoadjuvant therapy.[5] Emerging randomized controlled trials (RCTs) recommend cisplatin, paclitaxel, or both for use in concurrent chemoradiotherapy.[6,7] However, despite the considerable therapeutic benefits, concurrent chemoradiotherapy considerably increases the occurrence of severe toxicities, including nausea and vomiting, gastrointestinal reactions, and skin injury.[8] Thus, there is an urgent need to identify more effective and tolerable agents for the treatment of advanced NPC.

Many types of cancers overexpress growth factors on the tumor cell surface. In the non-keratinizing form of NPC, 90% of the tumor cells are positive for epidermal growth factor receptor (EGFR).[9] Altered EGFR signaling has been widely implicated in processes such as apoptosis, proliferation, metastasis, and invasion.[10,11] Thus, targeted therapy against EGFR has been proposed as an adjunct to radiotherapy to improve the curability of NPC. Nimotuzumab is a humanized anti-EGFR mouse monoclonal antibody that reduces immunoreactivity and promotes radiosensitivity. In clinical trials, nimotuzumab combined with concurrent radiotherapy seemed to facilitate radiosensitivity and thus increase treatment efficacy while maintaining low toxicity.[12,13] These findings indicate a synergistic effect of nimotuzumab combined with radiotherapy. The efficiency of this combined approach versus chemoradiotherapy alone has been examined in several RCTs and cohort studies, but no conclusions were reached regarding the potential benefits and possible risks in patients with advanced NPC. We therefore conducted a meta-analysis of the recent literature to assess the efficacy and safety of combined nimotuzumab with traditional concurrent chemoradiotherapy.

Methods

Ethical approval was not needed for the present study since it was a meta-analysis of previously published studies. The analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement (PRISMA; Figure S1) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. Ethical approval was also not needed for this secondary study.

Literature search

We performed systematic electronic and manual searches of the relevant literature in PubMed, Web of Science, China National Knowledge Infrastructure, and Wanfang databases from their inception to February 28, 2017. The searches were

conducted using the following medical subject headings and key words: "Nimotuzumab OR h-R3" AND "nasopharyngeal carcinoma OR NPC", "targeted therapy" AND "nasopharyngeal carcinoma OR NPC", "nasopharyngeal carcinoma OR NPC" AND "radiotherapy OR chemotherapy". Literature lists of reviews and relevant articles were also retrieved for potentially eligible studies. Only articles published in English and Chinese languages were included.

Inclusion and exclusion criteria

Two investigators independently performed the initial searches, excluding duplicates, and scanning the titles and abstracts of potentially eligible publications. The full text was then obtained for further screening. Any disagreement regarding the appropriateness of the study was solved by discussion and consensus. The criteria for study inclusion were as follows: (1) study design: RCT or cohort study; (2) population: patients with moderate or advanced NPC (stage $\geq$ III) as primarily confirmed by the pathological results (gold standard); (3) intervention: nimotuzumab combined with concurrent chemoradiotherapy in the experimental group and concurrent chemoradiotherapy alone in the control group; and (4) outcome: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or adverse reactions.

Data extraction

The collected data were entered into a standardized Excel sheet, extracted by ZZL, and checked by LFS. The following information was extracted: first author, year of publication, mean ages of the two study groups, numbers of male and female patients, sample size, clinical setting (inclusion criteria for the study population), clinical stage, therapeutic schedules of the trial and control groups, and outcomes. The primary outcomes were CR, PR, SD, and PD, and the secondary outcome was adverse reactions. Any discrepancies were resolved by consensus with the other investigators involved in this study.

Assessment of quality

Our study included RCTs and prospective cohort studies. The Newcastle–Ottawa Scale was used to assess the quality of non-randomized studies based on a "star system" ranking selection, comparability, and outcome. Selection included the exposed cohort, nonexposed cohort, and ascertainment of the exposure and outcome of interest. The outcomes included assessment, length of follow-up, and adequacy of follow-up. Studies with $\geq$7 stars were considered to be of

priority quality, those with ≥5 stars of high quality, and those with ≤5 stars of low quality.[14]

The Cochrane Collaboration's tool was used to assess the risk of bias in the RCTs.[15] The risk was evaluated as high, low, or unclear according to the following items: random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, selective reporting, and other biases. Because blinding of the patients and clinicians in these trials was not possible, the studies were considered to have a high risk of bias when another risk item besides blinding was identified.

Statistical analysis

Relative risks (RRs) and 95% confidence intervals (CIs) were used to calculate estimates of dichotomous outcomes. A value of 1 was considered to indicate beneficial effects for patients because the primary outcome was either CR or PR. The heterogeneity of the studies was assessed using the Cochran Q and I^2 statistics.[16] For the I^2 statistic, a value >50% was considered to indicate a high level of heterogeneity.

The outcome data were pooled using the random-effect model for significant heterogeneity. The fixed-effect model was used for less significant heterogeneity. The risk of occurrence of 15 adverse reactions was also determined: nausea and vomiting, gastrointestinal reactions, skin injury, leucopenia, radiation dermatitis, mucosa reaction, declining hemoglobin, erythropenia, thrombocytopenia, liver injury, renal injury, neutropenia, myelosuppression, hair loss, and fever. A sensitivity analysis was performed by sequentially excluding individual studies to assess the stability of the results. Publication bias was assessed by visually inspecting a funnel plot and using Egger's linear regression test.[17–20] All statistical analyses were performed using Stata 14.0 (Stata Corp., College Station, TX, USA) and Review Manager 5.3 (Cochrane Center). P-value <0.05 was considered to indicate statistical significance.

Results
Study selection
A flow chart of the study selection process is presented in Figure 1. Our initial search returned 386 results. No record
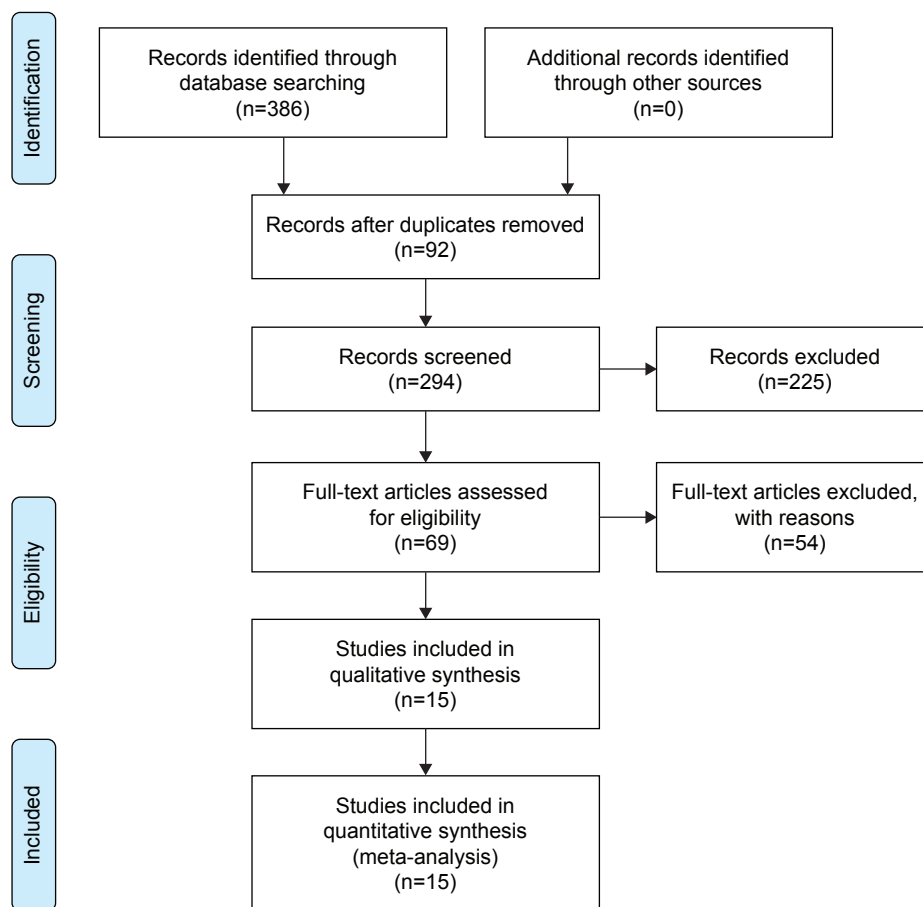
Figure 1 Flow diagram of studies selection process.

was obtained from additional sources. After the removal of 92 duplicate records, 294 articles were screened for their titles and abstracts. After the full text of 69 articles eligible for inclusion was reviewed, nine RCTs and six cohort studies were finally included in the meta-analysis.[4,21–34]

General characteristics of the included studies

The general characteristics of the included studies are summarized in Table 1. The studies were published from 2012 to 2016, and the sample sizes ranged from 31 to 183, with a total of 1,015 patients. In three of the 15 studies, nimotuzumab was combined with cisplatin and paclitaxel, in six studies with cisplatin and radiotherapy, in three studies with nedaplatin and radiotherapy, in two studies with paclitaxel and radiotherapy, and in one study with carboplatin and radiotherapy. All studies were conducted in adult patients. All outcomes were assessed within 1 year. Consistent with the finding of the World Health Organization that 80% of NPCs occur in China, all of the included studies were from this location.[35]

Quality assessment

Quality was assessed based on an assessment of the risk of bias (Figures S2 and S3). Among the nine RCTs, three were considered to have a low risk of bias, five an unclear risk, and one a high risk. The main sources of bias were related to allocation concealment, the blinding of participants and personnel, and outcome assessment. Each of the six cohort studies received >5 stars. The overall quality of the cohort studies was high (Table 2).

Nimotuzumab and chemoradiotherapy versus chemoradiotherapy alone

Fourteen studies with 877 NPC patients provided data on CRs and PRs. Compared with chemoradiotherapy alone, patients treated with nimotuzumab combined with chemoradiotherapy had a significantly improved response rate (RR =1.11, 95% CI: 1.01–1.22). The heterogeneity of the studies was 75% (Figure 2).

Figures 3–5 present the pooled results for adverse reactions. Compared with chemoradiotherapy alone, the combination of nimotuzumab and chemoradiotherapy did not lower the occurrence rate of nausea and vomiting (RR =0.74, 95% CI: 0.39–1.42), gastrointestinal reactions (RR =1.04, 95% CI: 0.42–2.36), skin injury (RR =0.82, 95% CI: 0.39–1.70),

Table 1 Characteristics of included study comparing nimotuzumab combined with three-dimensional radiotherapy for nasopharyngeal carcinoma

Author	Year of publication	Age (T/C)	Sex (M/F)	Sample size (T/C)	Clinical setting	Stage	Treatment		Outcomes (within 1 year)
							Trial	Control	
Li[28]	2016	56.9/56.5	29/19	24/24	Expected lifetime >6 months; KPS ≧60; no severe heart, lung, liver, or renal diseases; no metastasis	III–IVa	IMRT: 70–80 Gy (lesion); cisplatin: 60 mg/m²; paclitaxel: 175 mg/m²; nimotuzumab: 100 mg/250 mL saline, once a week for 8 weeks before radiation	IMRT: 60–80 Gy; cisplatin: 60 mg/m²; paclitaxel: 175 mg/m²	CR, PR, SD, PD, adverse reactions
Hu et al[31]	2013	49.3/49.2	40/28	36/32	Expected lifetime >6 months; no severe heart, lung, liver, or renal diseases	III–IVa	IMRT: 70–80 Gy (lesion); cisplatin: 80 mg/m²; docetaxel: 70 mg/m²; nimotuzumab: 100 mg/250 mL saline, once a week	IMRT: 70–80 Gy (lesion); cisplatin: 80 mg/m²; docetaxel: 70 mg/m²	CR, PR, SD, PD, adverse reactions
He et al[32]	2013	–/–	27/27	20/20	Expected lifetime >6 months; KPS ≧70; no severe infection or hemorrhagic, endocrine, heart, lung, liver, or renal diseases; no metastasis	III–IVa	IMRT: 70–76 Gy (lesion); carboplatin: 300 mg/m²; 5-fluorouracil: 500 mg/m²; nimotuzumab: 100 mg/250 mL saline, once a week for 6–8 weeks	IMRT: 70–76 Gy (lesion); carboplatin: 300 mg/m²; 5-fluorouracil: 500 mg/m²	CR, PR, SD, PD, adverse reactions
Chen et al[34]	2016	45.6/44.9	37/29	33/33	Expected lifetime >6 months; KPS ≧800; no metastasis; no severe heart, lung, liver, or renal diseases	III–IVa	IMRT: 60–78 Gy; cisplatin: 60 mg/m²; 5-fluorouracil: 500 mg/m²; calcium foliate: 200 mg/m²; nimotuzumab: 100 mg/250 mL saline, once a week for 6–7 weeks	IMRT: 60–78 Gy; cisplatin: 60 mg/m²; 5-fluorouracil: 500 mg/m²; calcium foliate: 200 mg/m²	CR, PR, SD, PD, median survival time, adverse reactions

Study	Year				Inclusion criteria	Stage	Treatment (experimental)	Treatment (control)	Outcomes
Lu et al[26]	2014	39.2/39.3	28/26	27/27	KPS ≧80, no metastasis	III–IVa	IMRT: 60–70 Gy (lesion); cisplatin: 40 mg/m²; nimotuzumab: 100 mg/250 mL saline, once a week for 8 weeks	IMRT: 60–70 Gy (lesion); cisplatin: 40 mg/m²	CR, PR, SD, PD, adverse reactions
Cheng et al[33]	2016	49.8/50.6	50/30	40/40	Expected lifetime >6 months; KPS ≧70; no severe infection or hemorrhagic, endocrine, heart, brain, liver, or renal diseases; no metastasis	III–IV	3D-CRT: 70–75 Gy (lesion); cisplatin: 20 mg/m²; paclitaxel: 175 mg/m²; nimotuzumab: 100 mg/250 mL saline for 7 weeks	3D-CRT: 70–75 Gy (lesion); cisplatin: 20 mg/m²; paclitaxel: 175 mg/m²	CR, PR, SD, PD, adverse reactions
Tu[4]	2013	–/–	19/12	14/17	Expected lifetime >6 months; no severe infection, or hemorrhagic, endocrine, heart, brain, liver, or renal diseases; no metastasis; PS: 0–1	III–IV	IMRT: 68–72 Gy (lesion); cisplatin: 20 mg/m²; nimotuzumab: 100 mg/250 mL saline for 6 weeks	IMRT: 68–72 Gy (lesion); cisplatin: 20 mg/m²	CR, PR, SD, PD, adverse reactions
Yu et al[23]	2014	–/–	29/15	20/24	Expected lifetime >6 months; PS: 0–1; no liver, renal, or heart diseases; no metastasis	III–IV	IMRT: 66–70 Gy; cisplatin: 20 mg/m²; nimotuzumab: 100 mg/250 mL saline for 6 weeks	IMRT: 66–70 Gy; cisplatin: 20 mg/m²	CR, PR, SD, PD, adverse reactions
Tang et al[24]	2012	54.2/55.2	79/44	63/60	Expected lifetime >6 months; KPS ≧60; no metastasis; no serious organic disease	III–IVa	IMRT: 70–76 Gy; cisplatin: 60 mg/m²; paclitaxel: 175 mg/m²; nimotuzumab 100 mg/250 mL saline	IMRT: 70–76 Gy; cisplatin: 60 mg/m²; paclitaxel: 175 mg/m²	CR, PR, SD, PD, adverse reaction
Zhou and Liao[22]	2013	–/–	–/–	16/16	No metastasis; no serious organic disease	III–IVa	IMRT: 60–70 Gy; cisplatin: 60 mg/m²; nimotuzumab: 100 mg/250 mL	IMRT: 60–70 Gy; cisplatin: 60 mg/m²	CR, PR, SD, PD, adverse reactions
Shao et al[25]	2014	47/50	35/13	24/24	Expected lifetime >6 months; KPS ≧70; no metastasis; no serious organic disease	III–IV	IMRT: 72–76 Gy; nedaplatin; nimotuzumab: 100 mg/250 mL	IMRT: 72–76 Gy; nedaplatin	CR, PR, SD, PD, adverse reactions
Li et al[30]	2015	57.3/54.6	38/22	30/30	Expected lifetime >6 months; KPS ≧70; no liver, renal, or heart diseases	III–IVb	IMRT: 60–70 Gy; nedaplatin: 40 mg/500 mL saline; nimotuzumab: 100 mg/250 mL	IMRT: 60–70 Gy; nedaplatin: 40 mg/500 mL saline	CR, PR, SD, PD, adverse reactions
Lou et al[27]	2016	–/–	–/–	161/22	Expected lifetime >6 months; KPS ≧60; no liver, renal, or heart diseases	III–IV	IMRT: 60–70 Gy; nedaplatin: 40 mg/m²; paclitaxel: 135 mg/m²; nimotuzumab: 100 mg/250 mL	IMRT: 60–70 Gy; nedaplatin: 40 mg/m²; paclitaxel: 135 mg/m²	CR, PR, SD, PD, adverse reactions
Zhuang et al[21]	2016	65.8	37/5	18/15	Expected lifetime >6 months; KPS ≧60	III–IVa	IMRT: 72–80 Gy; cisplatin: 30 mg/m²; 5-fluorouracil: 500 mg/m²; nimotuzumab: 100 mg/250 mL	IMRT: 72–80 Gy; cisplatin: 30 mg/m²; 5-fluorouracil: 500 mg/m²	CR, PR, SD, PD, adverse reactions
Li et al[29]	2016	–/–	78/26	52/52	Expected lifetime >6 months; KPS ≧60	III–IVa	IMRT: 70–74 Gy; cisplatin: 25 mg/m²; nimotuzumab: 200 mg/250 mL; 5-fluorouracil: 600 mg/m²	IMRT: 70 or 74 Gy; cisplatin: 30 mg/m²; 5-fluorouracil: 600 mg/m²	CR, PR, SD, PD, adverse reactions

Abbreviations: KPS, Karnofsky Performance Scale; IMRT, intensity-modulated radiation therapy; CR, complete response; PR, partial disease; SD, stable disease; PD, progressive disease; 3D-CRT, three-dimensional conformal radiotherapy; PS, performance status.

Table 2 Methodological quality assessment (risk of bias) of included studies by Newcastle–Ottawa Scale

Study	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Li et al[29]	*	*	*	*	**	*	–	–	7
Chen et al[34]	*	*	*	*	*	*	–	–	6
Lu et al[26]	*	*	*	*	**	*	–	–	7
Li et al[30]	*	*	*	*	**	*	–	–	7
Lou et al[27]	*	*	*	*	**	*	*	–	8
Li[28]	*	*	*	*	*	*	–	–	6

Note: *1 point; **2 points.

leucopenia (RR =1.43, 95% CI: 0.79–2.57), radiation dermatitis (RR =1.08, 95% CI: 0.15–7.74), mucosal reactions (RR =0.79, 95% CI: 0.31–2.02), declining hemoglobin (RR =0.99, 95% CI: 0.62–1.59), thrombocytopenia (RR =0.72, 95% CI: 0.36–1.45), liver injury (RR =1.12, 95% CI: 0.54–2.30), renal injury (RR =0.97, 95% CI: 0.39–2.41), myelosuppression (RR =1.14, 95% CI: 0.30–4.24), hair loss (RR =0.39, 95% CI: 0.02–9.73), or fever (RR =0.80, 95% CI: 0.21–3.12). The results of the overall effect test were not significant ($P>0.05$). However, the occurrence rates of erythropenia and neutropenia were significantly lower in the combined nimotuzumab group than in the chemoradiotherapy-alone group (RR =0.11, 95% CI: 0.05–0.28; RR =0.12, 95% CI: 0.05–0.27).

Sensitivity analyses were conducted by sequentially excluding one study at a time. Figure 5 shows that the pooled estimation was not altered; therefore, the results were statistically robust.

Begg's and Egger's tests were used to test for publication bias. Begg's test did not detect publication bias ($Z=1.480$, $P=0.155$), but Egger's test was based on an inspection of the funnel plot and formal statistical tests ($t=2.17$, $P=0.050$). A trim-and-fill analysis showed that four studies were required to balance the asymmetry of the funnel plot (Figure 6).

Discussion

A comprehensive and systematic literature retrieval and meta-analysis of the eligible articles suggested that nimotuzumab combined with concurrent chemoradiotherapy benefits patients with advanced NPC and is better than chemoradiotherapy alone. The two treatment methods did not differ significantly in the occurrence rates of most of the adverse reactions. However, combined therapy lowered the occurrence rates of erythropenia and neutropenia compared with chemoradiotherapy alone.

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Risk ratio IV, random, 95% CI
Chen et al[34]	38	40	33	40	10.8	1.15 (0.98, 1.35)
Cheng et al[33]	28	33	20	33	5.9	1.40 (1.03 1.91)
He et al[32]	19	20	18	20	10.1	1.06 (0.88, 1.26)
Hu et al[31]	35	36	30	32	13.0	1.04 (0.93, 1.15)
Li et al[30]	16	24	22	24	5.9	0.73 (0.53, 0.99)
Li[28]	21	30	12	30	3.0	1.75 (1.06, 2.88)
Lou et al[27]	22	22	159	161	14.5	0.99 (0.93, 1.06)
Lu et al[26]	26	27	20	27	8.0	1.30 (1.03, 1.64)
Shao et al[25]	21	45	16	40	3.0	1.17 (0.71, 1.91)
Tang et al[24]	62	63	49	60	12.3	1.21 (1.06, 1.36)
Tu[4]	11	14	6	17	1.7	2.23 (1.11, 4.48)
Yu et al[23]	15	20	12	24	3.2	1.50 (0.93, 2.41)
Zhou and Liao[22]	8	16	7	16	1.5	1.14 (0.54, 2.40)
Zhuang et al[21]	19	26	15	16	7.1	0.78 (0.60, 1.02)
Total (95% CI)		**416**		**540**	**100**	**1.11 (1.01, 1.22)**
Total events	341		419			

Heterogeneity: $\tau^2=0.02$; $\chi^2=36.59$, $df=13$ ($P=0.0005$); $I^2=64\%$
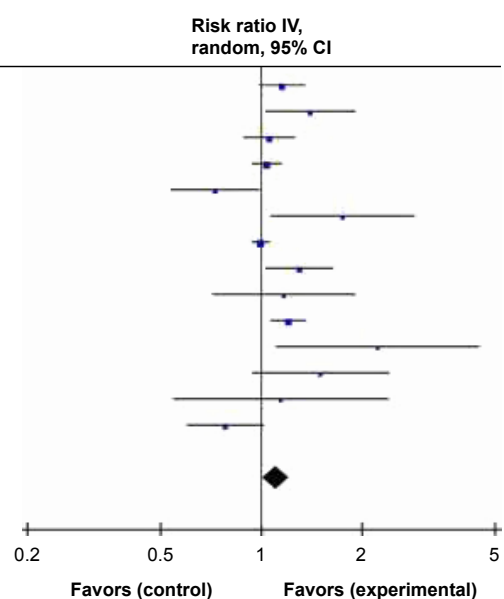Test for overall effect: $Z=2.08$ ($P=0.04$)

Figure 2 Forest plot of nimotuzumab combined with concurrent chemoradiotherapy versus chemoradiotherapy alone in advanced NPC.
Abbreviations: NPC, nasopharyngeal carcinoma; IV, inverse variance; CI, confidence interval.
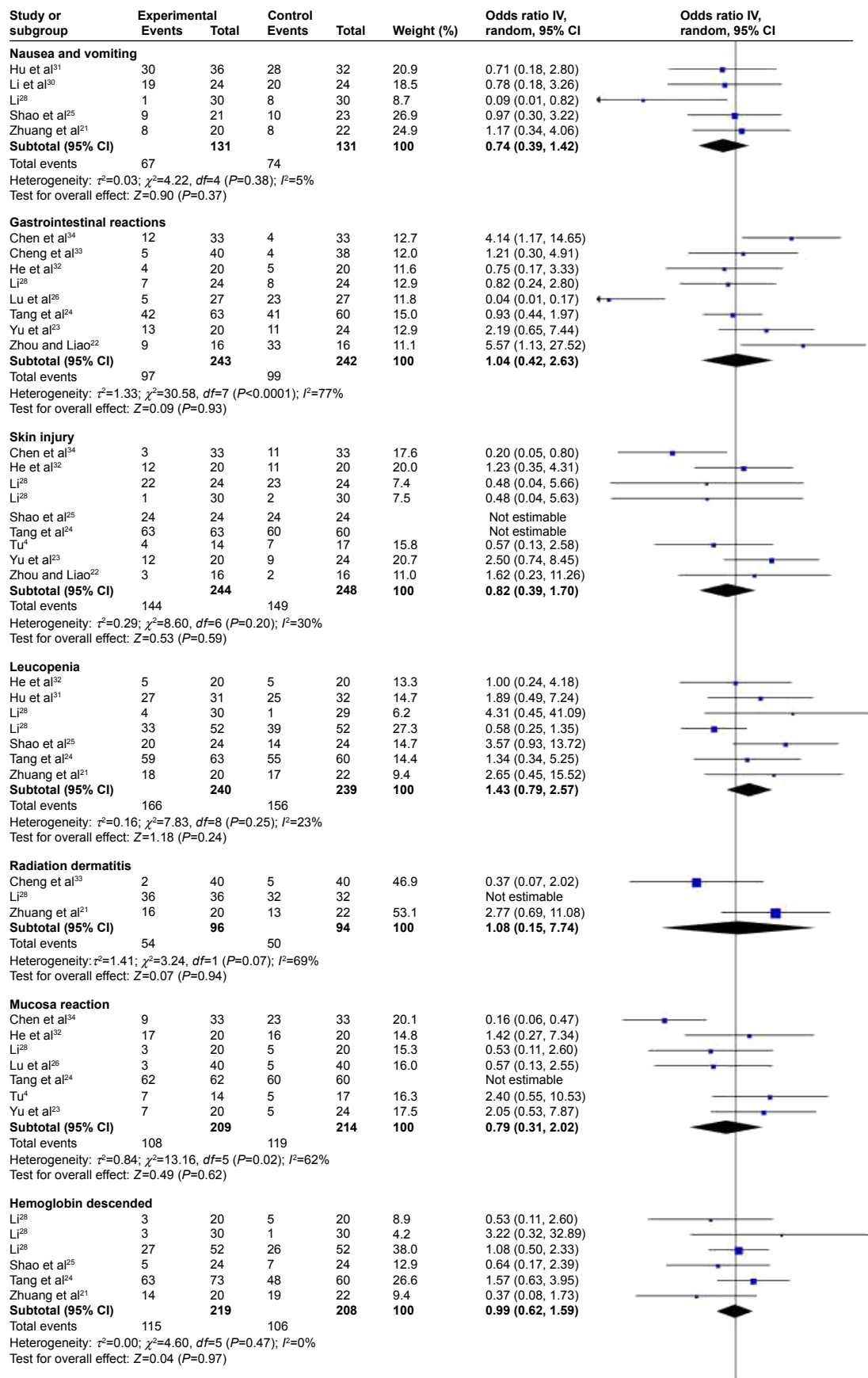
Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio IV, random, 95% CI	Odds ratio IV, random, 95% CI
Nausea and vomiting							
Hu et al[31]	30	36	28	32	20.9	0.71 (0.18, 2.80)	
Li et al[30]	19	24	20	24	18.5	0.78 (0.18, 3.26)	
Li[28]	1	30	8	30	8.7	0.09 (0.01, 0.82)	
Shao et al[25]	9	21	10	23	26.9	0.97 (0.30, 3.22)	
Zhuang et al[21]	8	20	8	22	24.9	1.17 (0.34, 4.06)	
Subtotal (95% CI)		**131**		**131**	**100**	**0.74 (0.39, 1.42)**	
Total events	67		74				
Heterogeneity: τ^2=0.03; χ^2=4.22, df=4 (P=0.38); I^2=5%							
Test for overall effect: Z=0.90 (P=0.37)							
Gastrointestinal reactions							
Chen et al[34]	12	33	4	33	12.7	4.14 (1.17, 14.65)	
Cheng et al[33]	5	40	4	38	12.0	1.21 (0.30, 4.91)	
He et al[32]	4	20	5	20	11.6	0.75 (0.17, 3.33)	
Li[28]	7	24	8	24	12.9	0.82 (0.24, 2.80)	
Lu et al[26]	5	27	23	27	11.8	0.04 (0.01, 0.17)	
Tang et al[24]	42	63	41	60	15.0	0.93 (0.44, 1.97)	
Yu et al[23]	13	20	11	24	12.9	2.19 (0.65, 7.44)	
Zhou and Liao[22]	9	16	33	16	11.1	5.57 (1.13, 27.52)	
Subtotal (95% CI)		**243**		**242**	**100**	**1.04 (0.42, 2.63)**	
Total events	97		99				
Heterogeneity: I^2=1.33; χ^2=30.58, df=7 (P<0.0001); I^2=77%							
Test for overall effect: Z=0.09 (P=0.93)							
Skin injury							
Chen et al[34]	3	33	11	33	17.6	0.20 (0.05, 0.80)	
He et al[32]	12	20	11	20	20.0	1.23 (0.35, 4.31)	
Li[28]	22	24	23	24	7.4	0.48 (0.04, 5.66)	
Li[28]	1	30	2	30	7.5	0.48 (0.04, 5.63)	
Shao et al[25]	24	24	24	24		Not estimable	
Tang et al[24]	63	63	60	60		Not estimable	
Tu[4]	4	14	7	17	15.8	0.57 (0.13, 2.58)	
Yu et al[23]	12	20	9	24	20.7	2.50 (0.74, 8.45)	
Zhou and Liao[22]	3	16	2	16	11.0	1.62 (0.23, 11.26)	
Subtotal (95% CI)		**244**		**248**	**100**	**0.82 (0.39, 1.70)**	
Total events	144		149				
Heterogeneity: τ^2=0.29; χ^2=8.60, df=6 (P=0.20); I^2=30%							
Test for overall effect: Z=0.53 (P=0.59)							
Leucopenia							
He et al[32]	5	20	5	20	13.3	1.00 (0.24, 4.18)	
Hu et al[31]	27	31	25	32	14.7	1.89 (0.49, 7.24)	
Li[28]	4	30	1	29	6.2	4.31 (0.45, 41.09)	
Li[28]	33	52	39	52	27.3	0.58 (0.25, 1.35)	
Shao et al[25]	20	24	14	24	14.7	3.57 (0.93, 13.72)	
Tang et al[24]	59	63	55	60	14.4	1.34 (0.34, 5.25)	
Zhuang et al[21]	18	20	17	22	9.4	2.65 (0.45, 15.52)	
Subtotal (95% CI)		**240**		**239**	**100**	**1.43 (0.79, 2.57)**	
Total events	166		156				
Heterogeneity: τ^2=0.16; χ^2=7.83, df=8 (P=0.25); I^2=23%							
Test for overall effect: Z=1.18 (P=0.24)							
Radiation dermatitis							
Cheng et al[33]	2	40	5	40	46.9	0.37 (0.07, 2.02)	
Li[28]	36	36	32	32		Not estimable	
Zhuang et al[21]	16	20	13	22	53.1	2.77 (0.69, 11.08)	
Subtotal (95% CI)		**96**		**94**	**100**	**1.08 (0.15, 7.74)**	
Total events	54		50				
Heterogeneity: τ^2=1.41; χ^2=3.24, df=1 (P=0.07); I^2=69%							
Test for overall effect: Z=0.07 (P=0.94)							
Mucosa reaction							
Chen et al[34]	9	33	23	33	20.1	0.16 (0.06, 0.47)	
He et al[32]	17	20	16	20	14.8	1.42 (0.27, 7.34)	
Li[28]	3	20	5	20	15.3	0.53 (0.11, 2.60)	
Lu et al[26]	3	40	5	40	16.0	0.57 (0.13, 2.55)	
Tang et al[24]	62	62	60	60		Not estimable	
Tu[4]	7	14	5	17	16.3	2.40 (0.55, 10.53)	
Yu et al[23]	7	20	5	24	17.5	2.05 (0.53, 7.87)	
Subtotal (95% CI)		**209**		**214**	**100**	**0.79 (0.31, 2.02)**	
Total events	108		119				
Heterogeneity: τ^2=0.84; χ^2=13.16, df=5 (P=0.02); I^2=62%							
Test for overall effect: Z=0.49 (P=0.62)							
Hemoglobin descended							
Li[28]	3	20	5	20	8.9	0.53 (0.11, 2.60)	
Li[28]	3	30	1	30	4.2	3.22 (0.32, 32.89)	
Li[28]	27	52	26	52	38.0	1.08 (0.50, 2.33)	
Shao et al[25]	5	24	7	24	12.9	0.64 (0.17, 2.39)	
Tang et al[24]	63	73	48	60	26.6	1.57 (0.63, 3.95)	
Zhuang et al[21]	14	20	19	22	9.4	0.37 (0.08, 1.73)	
Subtotal (95% CI)		**219**		**208**	**100**	**0.99 (0.62, 1.59)**	
Total events	115		106				
Heterogeneity: τ^2=0.00; χ^2=4.60, df=5 (P=0.47); I^2=0%							
Test for overall effect: Z=0.04 (P=0.97)							

Figure 3 Forest plot of adverse reactions between nimotuzumab group and chemoradiotherapy alone.
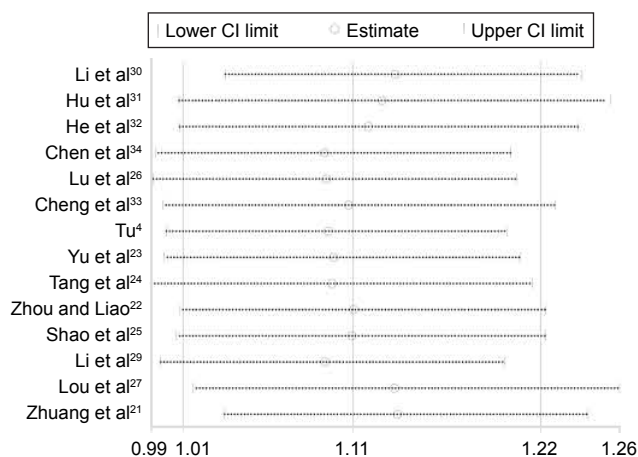**Abbreviations:** IV, inverse variance; CI, confidence interval.

Figure 4 Forest plot of adverse reactions between nimotuzumab group and chemoradiotherapy alone.

Several studies have examined the efficacy of combined nimotuzumab therapy, but ours is the first to comprehensively evaluate the efficacy of nimotuzumab combined with chemoradiotherapy. In previous studies of head and neck carcinomas and NPC, concurrent chemoradiotherapy was shown to be more effective than radiotherapy or chemotherapy alone. However, these cases are rare, as most patients with these cancers do not need concurrent chemoradiotherapy. The 5-year overall survival rate of patients with stage II NPC treated with concurrent chemoradiotherapy is 94.5%, and the treatment plan is effective and feasible. The addition of nimotuzumab to the standard treatment protocol increases the CR rate without increasing the occurrence of adverse reactions. Our results support these findings.

Platinum has always been the main chemotherapeutic agent used to treat NPC, serving as a sensitizer during chemotherapy, radiotherapy, or both. Although patients with NPC greatly benefit from concurrent chemoradiotherapy, relapses and metastases are frequent, especially for patients with advanced NPC.[6] Thus, there is an urgent need for adjunct therapies for advanced disease. Nimotuzumab is a human monoclonal antibody that specifically recognizes EGFR-binding sites and blocks other factors from binding to them. The Chinese government approved clinical trials of nimotuzumab in 2002. By binding to extracellular segments of EGFR, nimotuzumab blocks its activation pathways, including those linked to tumor angiogenesis factors, and potently inhibits tumor proliferation and metastasis.[36,37] Our results suggest that nimotuzumab synergizes with chemoradiotherapy,

as reported in clinical populations. In the study of Nabid et al, the CR of patients treated with nimotuzumab for locally advanced squamous cell cancer of the head and neck after radiotherapy was 70%.[38] Crombet et al reported a 3-year survival rate for nimotuzumab combined with radiotherapy of 66.7%, which is significantly higher than that for radiotherapy alone, and fewer adverse reactions.[39] The Chinese Academy of Medical Sciences conducted a multicenter Phase II RCT to assess the efficacy and adverse reactions of nimotuzumab combined with radiotherapy in patients with advanced NPC. In that study, the 3-year survival rate was significantly higher in the treated than in the control group (84.3% versus 77.6%), a result attributed to the binding ability of nimotuzumab.[40] The affinity of nimotuzumab for EGFR is several times higher than that for the endogenous ligand. Moreover, the occurrence of erythropenia and neutropenia was lower.[31] However, these results were specifically reported in only two studies and remain to be confirmed.

A major strength of our meta-analysis is that it was conducted in accordance with PRISMA guidelines and the recommendations outlined in the Cochrane Center handbook. Another strength is the study population, which consisted of first-visit patients with advanced NPC. Our sensitivity analyses confirmed the findings of the included studies. However, there are several limitations that still need to be addressed. First, the studies included in our meta-analysis were performed in different clinical settings, and the standard treatment plans were different (nimotuzumab was combined with cisplatin, paclitaxel, or nedaplatin). This potential heterogeneity must be taken into account in interpreting the results of our analysis. Second, most of the included RCTs were not blinded, which may have caused performance and detection biases. Third, some adverse reactions were examined in only two or three studies; thus, the results may be unstable. Finally, the included studies used experimental arms, including cisplatin and paclitaxel, as the control arms. While their findings address these patients, for others the results remain to be determined.

In conclusion, the use of nimotuzumab combined with concurrent chemoradiotherapy was shown to benefit patients with advanced NPC and was better than chemoradiotherapy alone. Moreover, combined therapy did not increase the rates of adverse reactions. Nimotuzumab can therefore be recommended as adjunct therapy in patients with advanced NPC.
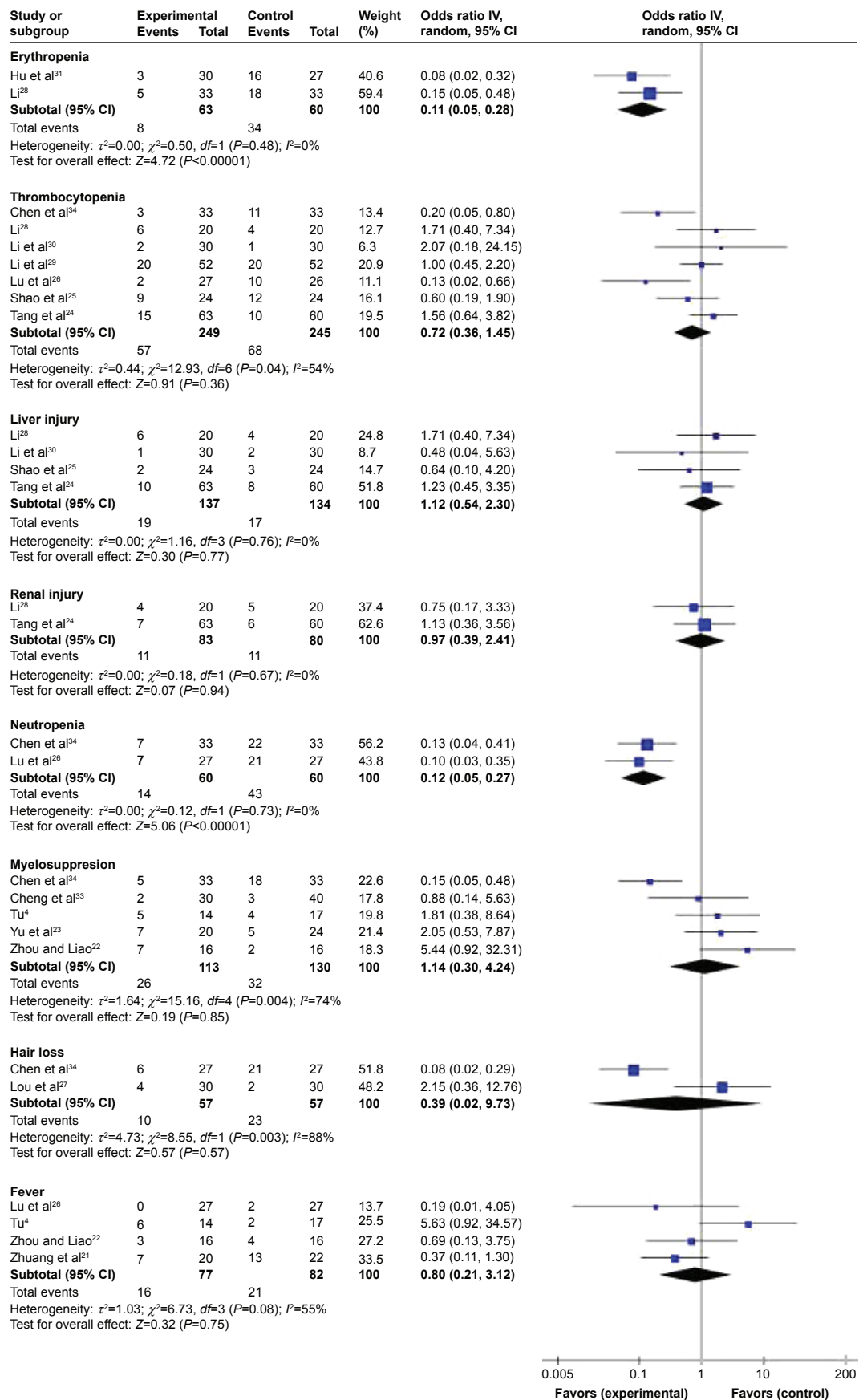
Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio IV, random, 95% CI	Odds ratio IV, random, 95% CI
Erythropenia							
Hu et al[31]	3	30	16	27	40.6	0.08 (0.02, 0.32)	
Li[28]	5	33	18	33	59.4	0.15 (0.05, 0.48)	
Subtotal (95% CI)		63		60	100	**0.11 (0.05, 0.28)**	
Total events	8		34				
Heterogeneity: τ^2=0.00; χ^2=0.50, df=1 (P=0.48); I^2=0%							
Test for overall effect: Z=4.72 (P<0.00001)							
Thrombocytopenia							
Chen et al[34]	3	33	11	33	13.4	0.20 (0.05, 0.80)	
Li[28]	6	20	4	20	12.7	1.71 (0.40, 7.34)	
Li et al[30]	2	30	1	30	6.3	2.07 (0.18, 24.15)	
Li et al[29]	20	52	20	52	20.9	1.00 (0.45, 2.20)	
Lu et al[26]	2	27	10	26	11.1	0.13 (0.02, 0.66)	
Shao et al[25]	9	24	12	24	16.1	0.60 (0.19, 1.90)	
Tang et al[24]	15	63	10	60	19.5	1.56 (0.64, 3.82)	
Subtotal (95% CI)		249		245	100	**0.72 (0.36, 1.45)**	
Total events	57		68				
Heterogeneity: τ^2=0.44; χ^2=12.93, df=6 (P=0.04); I^2=54%							
Test for overall effect: Z=0.91 (P=0.36)							
Liver injury							
Li[28]	6	20	4	20	24.8	1.71 (0.40, 7.34)	
Li et al[30]	1	30	2	30	8.7	0.48 (0.04, 5.63)	
Shao et al[25]	2	24	3	24	14.7	0.64 (0.10, 4.20)	
Tang et al[24]	10	63	8	60	51.8	1.23 (0.45, 3.35)	
Subtotal (95% CI)		137		134	100	**1.12 (0.54, 2.30)**	
Total events	19		17				
Heterogeneity: τ^2=0.00; χ^2=1.16, df=3 (P=0.76); I^2=0%							
Test for overall effect: Z=0.30 (P=0.77)							
Renal injury							
Li[28]	4	20	5	20	37.4	0.75 (0.17, 3.33)	
Tang et al[24]	7	63	6	60	62.6	1.13 (0.36, 3.56)	
Subtotal (95% CI)		83		80	100	**0.97 (0.39, 2.41)**	
Total events	11		11				
Heterogeneity: τ^2=0.00; χ^2=0.18, df=1 (P=0.67); I^2=0%							
Test for overall effect: Z=0.07 (P=0.94)							
Neutropenia							
Chen et al[34]	7	33	22	33	56.2	0.13 (0.04, 0.41)	
Lu et al[26]	7	27	21	27	43.8	0.10 (0.03, 0.35)	
Subtotal (95% CI)		60		60	100	**0.12 (0.05, 0.27)**	
Total events	14		43				
Heterogeneity: τ^2=0.00; χ^2=0.12, df=1 (P=0.73); I^2=0%							
Test for overall effect: Z=5.06 (P<0.00001)							
Myelosuppresion							
Chen et al[34]	5	33	18	33	22.6	0.15 (0.05, 0.48)	
Cheng et al[33]	2	30	3	40	17.8	0.88 (0.14, 5.63)	
Tu[4]	5	14	4	17	19.8	1.81 (0.38, 8.64)	
Yu et al[23]	7	20	5	24	21.4	2.05 (0.53, 7.87)	
Zhou and Liao[22]	7	16	2	16	18.3	5.44 (0.92, 32.31)	
Subtotal (95% CI)		113		130	100	**1.14 (0.30, 4.24)**	
Total events	26		32				
Heterogeneity: τ^2=1.64; χ^2=15.16, df=4 (P=0.004); I^2=74%							
Test for overall effect: Z=0.19 (P=0.85)							
Hair loss							
Chen et al[34]	6	27	21	27	51.8	0.08 (0.02, 0.29)	
Lou et al[27]	4	30	2	30	48.2	2.15 (0.36, 12.76)	
Subtotal (95% CI)		57		57	100	**0.39 (0.02, 9.73)**	
Total events	10		23				
Heterogeneity: τ^2=4.73; χ^2=8.55, df=1 (P=0.003); I^2=88%							
Test for overall effect: Z=0.57 (P=0.57)							
Fever							
Lu et al[26]	0	27	2	27	13.7	0.19 (0.01, 4.05)	
Tu[4]	6	14	2	17	25.5	5.63 (0.92, 34.57)	
Zhou and Liao[22]	3	16	4	16	27.2	0.69 (0.13, 3.75)	
Zhuang et al[21]	7	20	13	22	33.5	0.37 (0.11, 1.30)	
Subtotal (95% CI)		77		82	100	**0.80 (0.21, 3.12)**	
Total events	16		21				
Heterogeneity: τ^2=1.03; χ^2=6.73, df=3 (P=0.08); I^2=55%							
Test for overall effect: Z=0.32 (P=0.75)							

0.005   0.1   1   10   200
Favors (experimental)   Favors (control)

Figure 5 Sensitivity analysis of the pooled estimation.
Abbreviations: IV, inverse variance; CI, confidence interval.

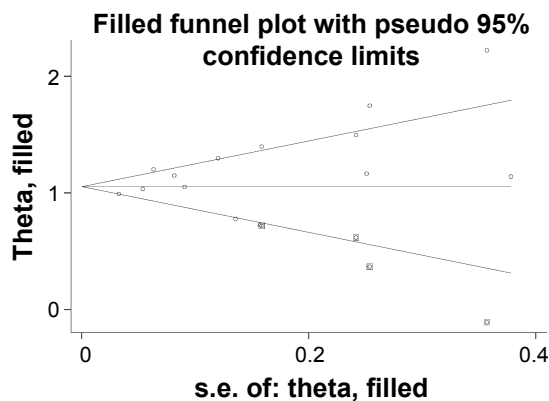**Figure 6** Deek's funnel plot to evaluate the publication bias.
Abbreviation: s.e., standard error.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2–3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	5–6
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	6–7
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6–7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6–7
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	7–8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	7–8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	9–14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15

Figure S1 (*Continued*)

PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	16–17
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	17
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	17–19
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	Declared on online PLoS submission system

Figure S1 PRISMA checklist.
Notes: Reproduced from Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(6):e1000097.[10] For more information, visit: www.prisma-statement.org.
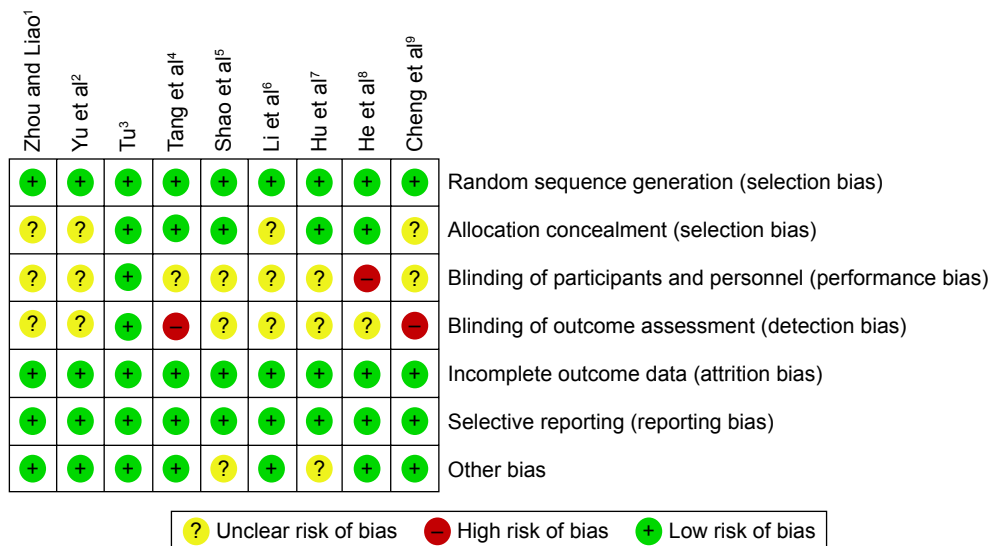
Figure S2 Risk of bias and applicability concerns graph: review authors' judgments about each domain presented as percentages across included studies.
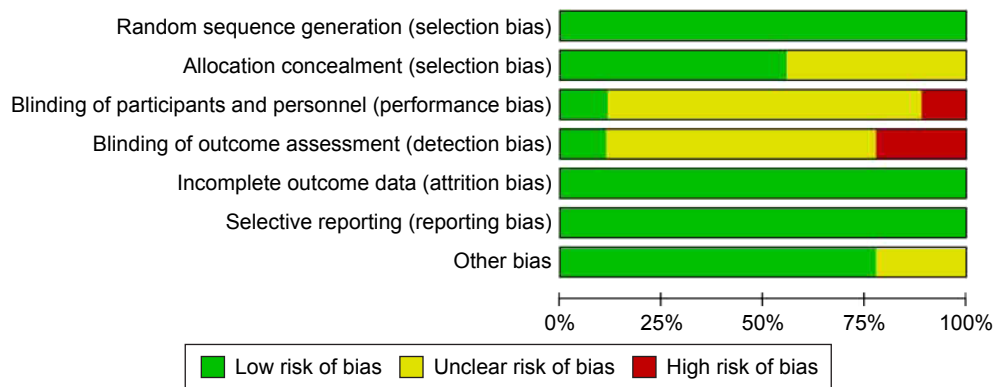
Figure S3 Risk of bias and applicability concerns summary: review authors' judgments about each domain for each included study.

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