

# Which neoadjuvant chemotherapy regimen should be recommended for patients with advanced nasopharyngeal carcinoma?

## A network meta-analysis

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### Abstract

**Background:** The clinical application has widespread disagreement on the different regimens of neoadjuvant chemotherapy (NCT) in the treatment of locoregionally advanced nasopharyngeal carcinoma (NPC). We conducted a network meta-analysis (NMA) to evaluate the efficacy of the different NCT regimens in the treatment of NPC.

**Methods:** A systematic literature search was performed using PubMed, Embase, and Cochran Library. Totally, 31 randomized controlled trials (RCTs) (n=4062) met study selection criteria and were incorporated in this NMA study.

**Results:** Our study showed that certain NCT regimens improved the prognosis of patients, and found out the relative best solution for each endpoint, such as paclitaxel, carboplatin, and gemcitabine for 1-year overall survival (OS) rate, cisplatin, calcium folinate, and 5-fluorouracil for 2-year OS rate, vinorelbine and cisplatin (NP) for 3-year OS rate, cyclophosphamide, cisplatin, and 5-fluorouracil for 5-year OS rate, NP for complete remission rate, cisplatin and gemcitabine for overall remission rate of the primary tumor. In addition, for certain grade 3 and above toxicity, the results of the NMA reflected certain NCT regimens can reduce toxicity of chemoradiotherapy (CRT) to a minimum, such as NP for anemia, mucositis, and thrombocytopenia, paclitaxel, epirubicin, and cisplatin for neutropenia and skin toxicity.

**Conclusion:** Our NMA showed that certain cisplatin-based NCT regimens improved the prognosis of patients with NPC and reduced the toxicity of CRT. However, in view of survival rate and response rate, the best NCT regimen is not entirely consistent. Therefore, which NCT regimen will benefit most patients will need further explored.

**Abbreviations:** BCE = bleomycin, epirubicin, and cisplatin, BFC = bleomycin, 5-fluorouracil, and cisplatin, CEP = paclitaxel, epirubicin, and cisplatin, CI = confidence interval, CPF = cyclophosphamide, cisplatin, and 5-fluorouracil, CR = complete remission, CRT = chemoradiotherapy, CT = chemotherapy, DF = docetaxel and cisplatin, EBV = Epstein-Barr virus, GCP = paclitaxel, carboplatin, and gemcitabine, NCCN = National Comprehensive Cancer Network, NMA = network meta-analysis, NP = vinorelbine and cisplatin, NPC = nasopharyngeal carcinoma, OR = overall remission, ORs = odds ratios, OS = overall survival, PE = cisplatin and epirubicin, PF = cisplatin and 5-fluorouracil, PFP = carboplatin, 5-fluorouracil, and pingyangmycin, PFS = progression-free survival, PG = cisplatin and gemcitabine, PLF = cisplatin, calcium folinate, and 5-fluorouracil, RCT = randomized controlled trial, RT = radiotherapy, TP = docetaxel and cisplatin, TPF = docetaxel, cisplatin, and 5-fluorouracil.

**Keywords:** nasopharyngeal carcinoma, neoadjuvant chemotherapy, network meta-analysis

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CY, SWL, and LW contributed equally to this work.

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## 1. Introduction

Nasopharyngeal carcinoma (NPC), linked to Epstein–Barr virus (EBV), is the most common malignant tumor in head and neck, mainly distributing in southeast Asia, southern China, Hong Kong, and Taiwan.<sup>[1]</sup> Due to the abundant lymphatic network under the nasopharyngeal mucosa, NPC has a tendency to metastasize to lymph nodes early. Radiotherapy (RT) is used to be the recommended option for these patients; however, only 30% to 50% patients with NPC with RT are able to survive for 5 years, and if RT is not delivered timely, the recurrence rate of lymph nodes will be as high as 40%.<sup>[2]</sup> As a result, the combination of chemotherapy (CRT) and RT is hypothesized to be an effective therapy to improve the survival status of patients with NPC. But even so, the 5-year survival rate is only 40% to 50%.<sup>[3,4]</sup>

Neoadjuvant chemotherapy (NCT) was usually regarded as no benefit at first glance in the past, due to triggering an accelerated repopulation and even cross resistance after treatment. A recent meta-analysis demonstrated that NCT followed by concurrent chemoradiotherapy (CCRT) or RT could improve both overall survival (OS) and progression-free survival (PFS) for patients with locoregionally advanced NPC, compared with CCRT or RT.<sup>[5]</sup>

The clinical application has widespread disagreement on the different regimens of NCT in the treatment of locoregionally advanced NPC. Consequently, it remains unclear which NCT regimen benefits patients with NPC better. As such, the pairwise comparison meta-analysis is difficult to determine the superiority of a NCT regimen. It is more and more popular for network meta-analysis (NMA) to assess medical interventions, especially, although the head-to-head comparisons are lacking, NMA could provide an effective way to evaluate the relative effectiveness among all interventions and rank ordering of the interventions. Therefore, in the present study, we conducted an NMA to evaluate the efficacy of the different NCT regimens in the treatment of NPC.

## 2. Methods

### 2.1. Search strategy and selection criteria

Literature search was conducted in electronic databases by 2 independent reviewers. Multiple resources were searched accordingly for the purpose of preventing selection bias: the Cochrane Library, PubMed, and Embase. The following terms were applied: “nasopharyngeal neoplasm,” “NPC,” “neoadjuvant chemotherapy,” “induction chemotherapy,” “randomized controlled trial,” and “RCT.” The searching results were updated in May 2017. Studies were included if they were RCT combined with at least 1 NCT regimen with chemotherapy or RT. The reference lists of the included studies were reviewed as a supplement. No language limits were applied to literature search. Besides that patients in the included studies were diagnosed with NPC (stages I–IV) according to the criteria set by the American Joint Committee on Cancer, the World Health Organization, the International Union against Cancer, and the tumor node metastasis staging system.

### 2.2. Data extraction and quality assessment

Two investigators independently reviewed the articles and disagreements were resolved by discussion and consensus. We extracted the following information from each study: first author’s surname, publication year, stages, number of patients, median age, and median follow-up; treatment regimens for each study; reported outcomes, including complete remission rate (CRR) or overall remission rate (ORR) of the primary tumor, OS

and grade 3 and above toxicities. If the same study had been published for more than once, the one with longer follow-up duration would be preferred.

The quality was evaluated by the Jadad composite scale. This scale included the method of randomization (0–2 points), double blinding (0–2 points), and the description of dropouts (0–1 points).

### 2.3. Statistical analysis

The primary endpoint of this NMA was OS, defined as the time from random assignment to death. Secondary endpoints were grade 3 and above toxicities and CRR or ORR of the primary tumor.

The NMA was performed by STATA 13.1 (Stata Corporation, College Station, TX). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the random-effects model or fixed-effects model for investigating treatment effects. Z test was conducted to assess the significance of overall effect size. A *P*-value of <.05 was considered statistically significant.

After constructing a heterogeneity matrix, the frequentist method was applied to the fitted meta-regression model. The model covariates as the basic parameters and assumed that heterogeneity is independent of the comparison between effect sizes from multi-arm studies. Inconsistency refers to the differences between direct and various indirect effects estimated for the same comparison. We estimated the probability of a treatment being ranked at a specific place according to the outcome using “network rank.” The publication bias was evaluated by a “comparison-adjusted” funnel plots whose horizontal axis presents the difference between study-specific effect sizes and the corresponding comparison-specific summary effect. The funnel plot should be symmetrical near the zero line if there is no publication bias.

## 3. Results

### 3.1. Baseline characteristics of included studies

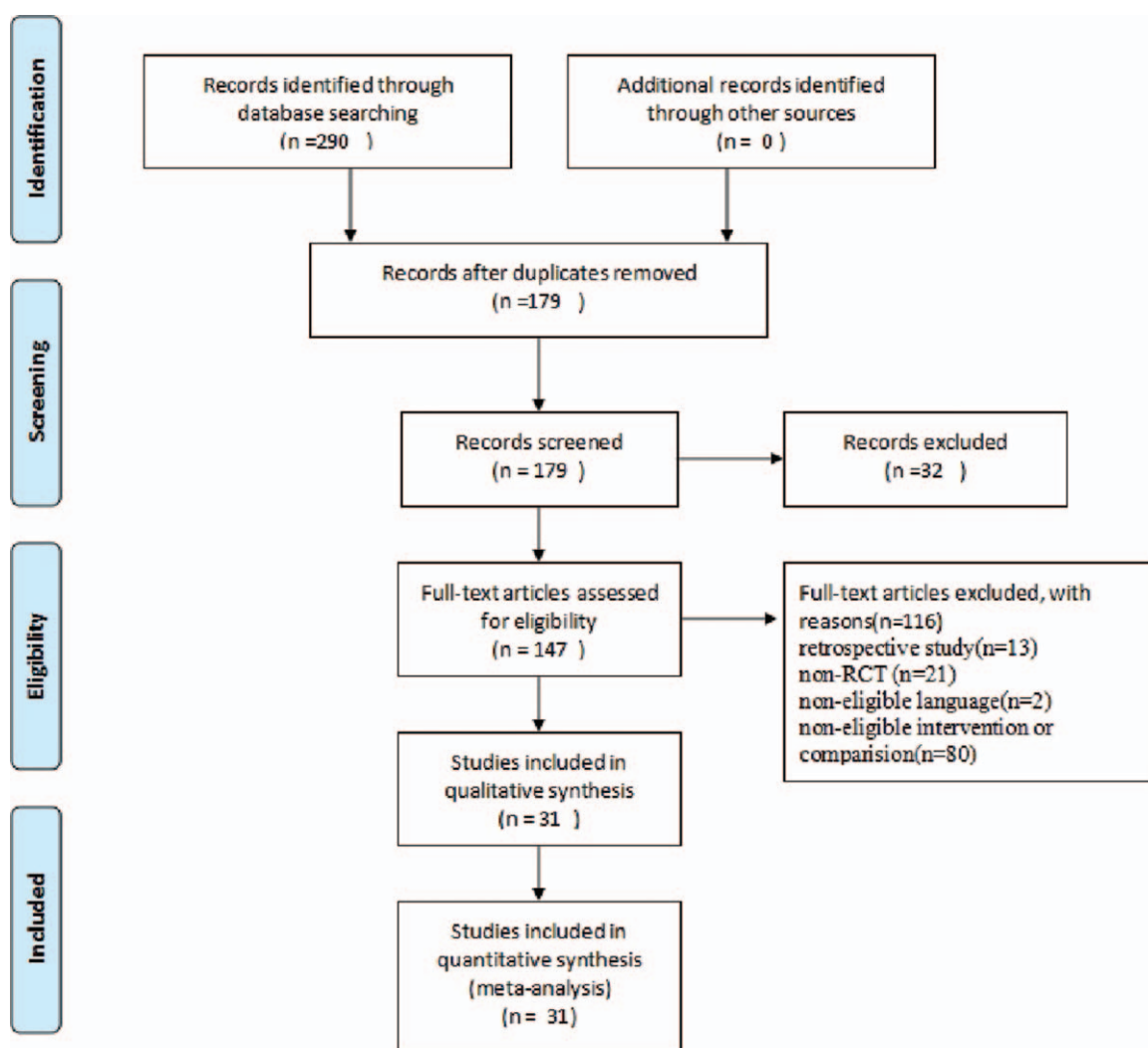
The initial database search broadly identified 290 studies. After reviewing the title and abstract, duplicate search results (*n* = 111), letters or reviews (31), and nonhuman studies (1) were excluded. From the remaining *n* = 147 full-text articles, non-RCT (*n* = 21), articles not associated with NPC or not related to the research topic (*n* = 80), retrospective study (*n* = 13), and not English or Chinese (*n* = 2) were further eliminated by the screening process. Ultimately, 31 RCTs<sup>[6–36]</sup> (*n* = 4062) met study selection criteria and were incorporated in this NMA study. Among the 31 RCTs, we summarized 16 NCT regimens. The screening and inclusion process is presented in Figure 1, and the baseline characteristics of the 31 included studies are summarized in Table 1.

### 3.2. Evidence network

The evidence network is displayed in Figures 2 and 3. Connecting lines indicated direct comparison between the 2 interventions, and pairs of interventions without connection can be compared indirectly through NMA. The width of lines represents the number of trials. The size of nodes suggests the overall sample size of intervention.

### 3.3. Evaluating and presenting assumptions of NMA

The present NMA consisted of 1 triangular loop (RT/CRT-cisplatin and 5-fluorouracil [PF]-docetaxel and cisplatin [TP]



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

**Figure 1.** Flow chart shows the detailed procedures of study screening and exclusion criteria. Thirty-one studies were included in this network meta-analysis. RCT= randomized controlled trial.

loop). For indirect comparisons, node-splitting model was performed to estimated degree of inconsistency. Then we found inconsistency was not statistically significant ( $P > .05$ ).

### 3.4. CRR and ORR of primary tumor

Nineteen RCTs reported CRR of primary tumor. In these RCTs, 1912 patients were involved, and 12 NCT regimens were included. The results of NMA found RT/CRT followed by TP, vinorelbine and cisplatin (NP), and cisplatin and gemcitabine (PG) regimens can improve CRR of the primary tumor. The ranking probabilities of the 3 regimens for the effects on CRR of the primary tumor were: 37.2% for NP regimen, 18.1% for DF regimen, and 16.4% for PG regimen. In addition, 14 RCTs reported ORR of primary tumor further. PG regimen improved CRR of the primary tumor significantly and the value of ranking probabilities was 37%. The ranking for CRR and ORR of primary tumor is illustrated in Figure 4.

### 3.5. Overall survival rate

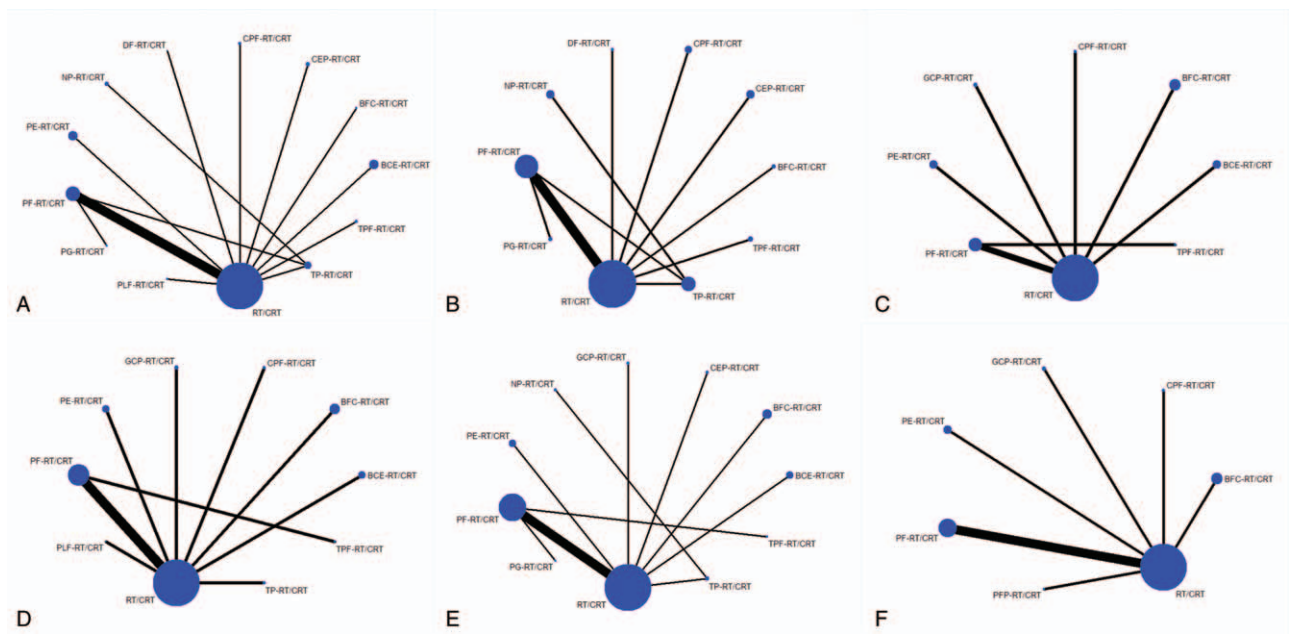
Data available regarding the survival outcomes were limited. Although certain literatures reported the results of metastasis-free survival, PFS, disease-free survival, and recurrence-free survival, the reporting and occurrence of these events were rare. Therefore, we could only choose the results of OS to evaluate the survival outcomes.

A total of 1916 patients in 8 RCTs containing 7 NCT regimens (cyclophosphamide, cisplatin, and 5-fluorouracil [CPF], TPF, bleomycin, 5-fluorouracil, and cisplatin [BFC], bleomycin, epirubicin, and cisplatin [BCE], cisplatin and epirubicin [PE], PF, and paclitaxel, carboplatin, and gemcitabine [GCP]) were included to compare the 1-year OS rate. All the NCT regimens except PF can improve 1-year OS rate. The results of probability ranking of the 8 interventions revealed that GCP regimen group was significantly higher than other 7 groups (ranking probabilities was 53.4%, Fig. 5A). The CIs of estimates for 1-year OS rate are shown in Table 2.

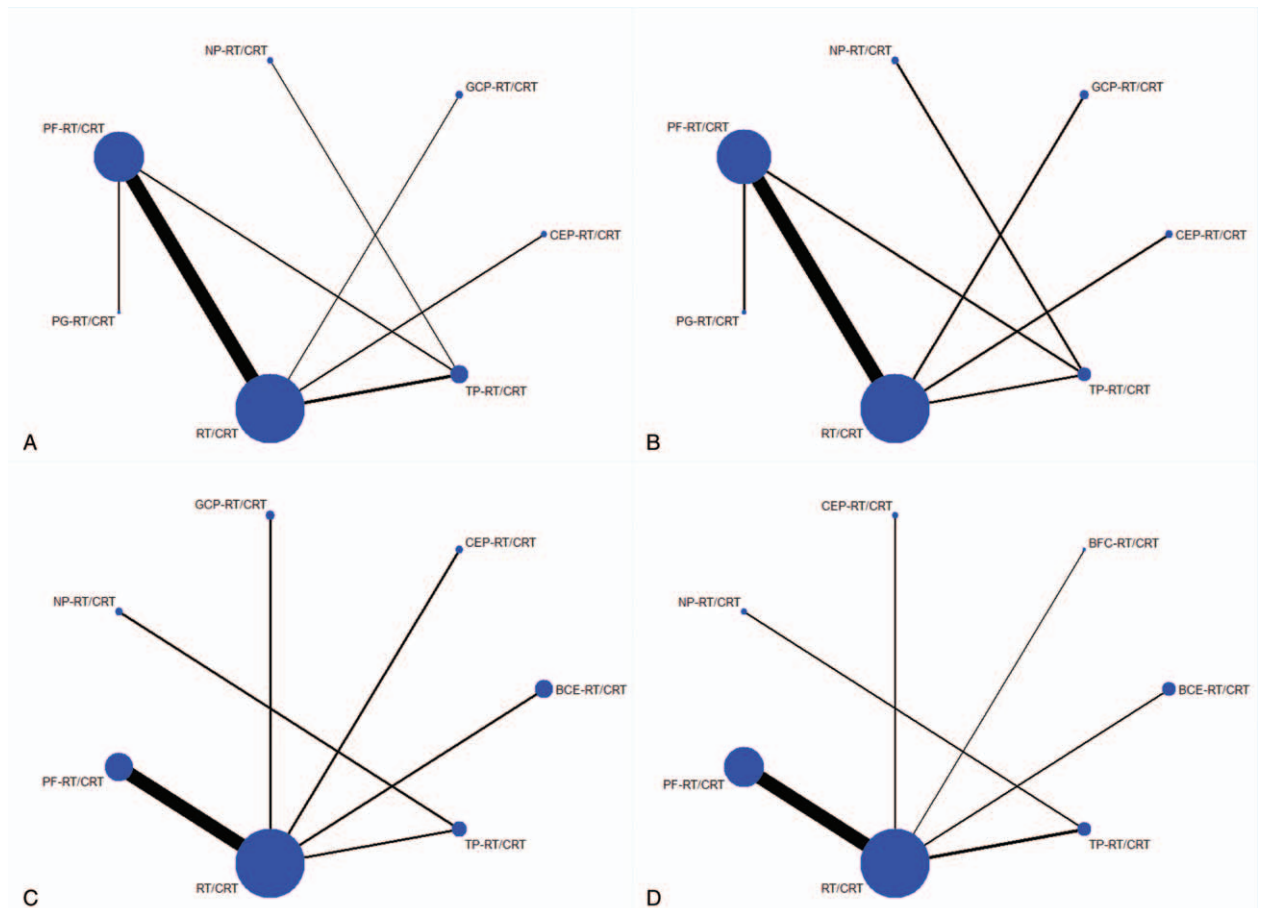
**Table 1**  
**Characteristics of published studies included in this network meta-analysis.**

Study	Year	No of patients	Median age, y	Median follow-up, mo	Stage	Neoadjuvant chemotherapy regimens	Evaluation index	Jadad
Anonymous <sup>[6]</sup>	1996	339	42; 44	49	I-II	BCE (bleomycin, epirubicin, and cisplatin)	CR 1-y OS rate, 2-y OS rate, Mucositis toxicities,	3
Casanova et al <sup>[7]</sup>	2016	75	16; 16	39.6	IIb-IV	TPF (docetaxel, cisplatin, and 5-fluorouracil)	1-y OS rate, 2-y OS rate and 3-y OS rate	4
Chakrabandhu et al <sup>[8]</sup>	2015	94	-	25	-	TPF (docetaxel, cisplatin, and 5-fluorouracil)	CR, OR	4
Chan et al <sup>[10]</sup>	1995	77	44; 44	28.5	II-III	PF (cisplatin and 5-fluorouracil)	CR, OR 2-y OS rate, anemia, thrombocytopenia, neutropenia, and mucositis toxicities	4
Chan et al <sup>[9]</sup>	2005	53	48	-	III-IV	DF (docetaxel and cisplatin)	CR, OR	3
Changqing et al <sup>[11]</sup>	1999	86	54; 55	-	III-IV	PF (cisplatin and 5-fluorouracil)	CR 1-y OS rate, 2-y OS rate, and 3-y OS rate	2
Chen <sup>[12]</sup>	2003	68	47.5; 46.8	-	I-III	PF (cisplatin and 5-fluorouracil)	Anemia, thrombocytopenia, neutropenia, skin toxicity, and mucositis toxicity	2
Chua et al <sup>[13]</sup>	2002	334	47; 46	71	II-IV	PE (cisplatin and epirubicin)	CR; 1-, 2-, 3-, and 5-y OS rate	2
Fan et al <sup>[14]</sup>	2008	48	-	-	II-III	PF (cisplatin and 5-fluorouracil)	CR, OR	3
Fountzilas et al <sup>[15]</sup>	2012	141	49; 51	55	IIb-IVb	CEP (paclitaxel, epirubicin, and cisplatin)	CR, OR; 3-y OS rate; anemia, thrombocytopenia, neutropenia, skin toxicity and mucositis toxicity	4
Gao et al <sup>[29]</sup>	2013	112	-	42	III-IVa	PF (cisplatin and 5-fluorouracil)	3-y OS rate; anemia, thrombocytopenia, neutropenia, skin toxicity, and mucositis toxicity	3
Geara et al <sup>[16]</sup>	1997	122	47; 49	58.8	III-IV	PF (cisplatin and 5-fluorouracil)	5-y OS rate	4
Han et al <sup>[17]</sup>	2013	146	45.6; 42	45	III-IV	NP (vinorelbine and cisplatin); TP (docetaxel and cisplatin)	CR, OR; 3-y OS rate; anemia, thrombocytopenia, neutropenia, skin toxicity, and mucositis toxicity	3
Hareyama et al <sup>[18]</sup>	2002	80	-	49	I-IV	PF (cisplatin and 5-fluorouracil)	5-y OS rate	4
Hu et al <sup>[19]</sup>	2002	78	-	-	III-IVa	PFP (carboplatin, 5-fluorouracil and pin- gyangmycin)	5-y OS rate	3
Huang et al <sup>[20]</sup>	2012	200	-	46.8	III-IV	PF (cisplatin and 5-fluorouracil)	3-y OS rate; anemia, thrombocytopenia, neutropenia, skin toxicity, and mucositis toxicity	2
Hui et al <sup>[21]</sup>	2009	64	-	51.6	III-IVb	TP (docetaxel and cisplatin)	CR, OR; 3-y OS rate; anemia, thrombocytopenia, neutropenia, and mucositis toxicity	2
Li et al <sup>[23]</sup>	2002	43	46; 48	10	I-III	PF (cisplatin and 5-fluorouracil)	CR, OR; anemia, thrombocytopenia, neutropenia, skin toxicity, and mucositis toxicity	2
Ling et al <sup>[24]</sup>	2008	60	33.4; 34.2	-	III-IVa	PLF (cisplatin, calcium folinate, and 5- fluorouracil)	CR; 1-y OS rate	3
Liu et al <sup>[25]</sup>	2002	64	55; 55	-	III-IVa	BFC (bleomycin, 5-fluorouracil, and cisplati- num)	CR, OR; mucositis toxicity	2
Long et al <sup>[26]</sup>	2012	144	-	-	III-IV	TP (docetaxel and cisplatin)	2-y OS rate; thrombocytopenia, neutropenia, skin toxicity, and mucositis toxicity	2
Ma et al <sup>[27]</sup>	2001	456	46; 47	59	III-IV	BFC (bleomycin, 5-fluorouracil, and cisplatin)	1-, 2-, 3-, and 5-y OS rate	2
Pan et al <sup>[28]</sup>	2000	207	45.8; 45.6	-	I-IV	PF (cisplatin and 5-fluorouracil)	5-y OS rate	3
Ruste et al <sup>[30]</sup>	2011	30	-	-	III-IVb	PF (cisplatin and 5-fluorouracil)	CR, OR; 3-y OS rate; anemia, neutropenia, skin toxicity, and mucositis toxicity	3
Tan et al <sup>[31]</sup>	2015	172	48.5; 51.6	40.8	III-IV	GCP (paclitaxel, carboplatin, and gemcita- bine)	1-, 2-, 3-, and 5-y OS rate; anemia, thrombocytopenia, neutropenia, and skin toxicity	2
Wu et al <sup>[32]</sup>	2002	116	42.3; 42.3	-	III-IVa	CPF (cyclophosphamide, cisplatin, and 5- fluorouracil)	CR, OR; 1-, 2-, 3-, and 5-y OS rate	2
Xie et al <sup>[33]</sup>	2007	40	45; 44	-	III-IV	TP (docetaxel, cisplatin); PF (cisplatin and 5-fluorouracil)	CR, OR; anemia, thrombocytopenia, and neutropenia	3
Xu et al <sup>[34]</sup>	2014	338	48	60	III-IVb	PF (cisplatin and 5-fluorouracil)	1-, 2-, 3-, and 5-y OS rate; anemia, thrombocytopenia, neutropenia, and mucositis toxicity	3
Yang et al <sup>[35]</sup>	2002	34	56; 55	-	IV	PF (cisplatin and 5-fluorouracil)	CR; 3-y OS rate; neutropenia and mucositis toxicity	3
Yau et al <sup>[36]</sup>	2006	75	50.3; 49.4	43.2	IV	PF (cisplatin and 5-fluorouracil); PG (cisplatin and gemcitabine)	CR, OR; 3-y OS rate; anemia, thrombocytopenia, and neutropenia	3
Li et al <sup>[22]</sup>	2004	90	-	-	III-IV	PF (cisplatin and 5-fluorouracil);	OR; neutropenia, skin toxicity, and mucositis	2

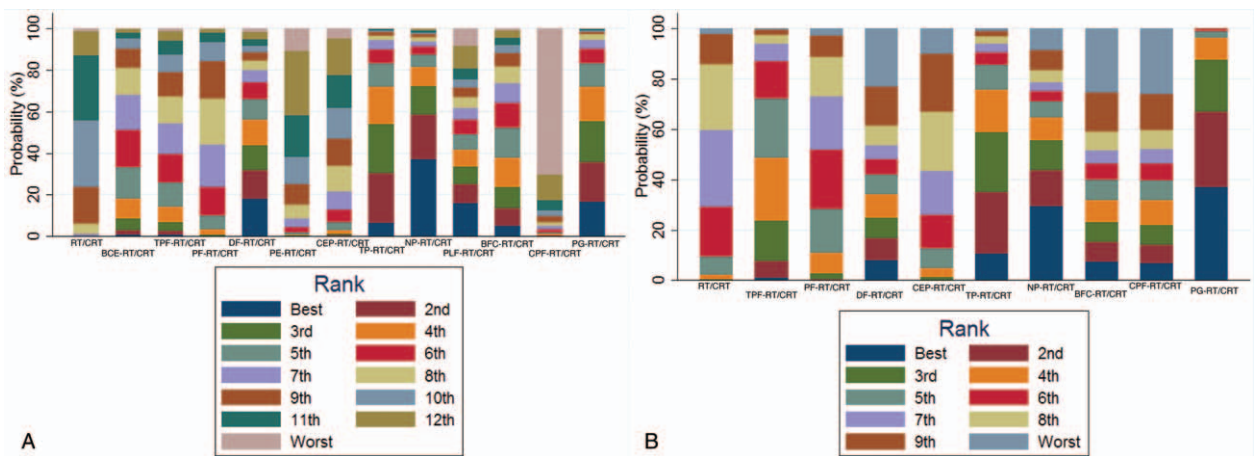
CR = complete remission, No = number, OR = overall remission, OS = overall survival.



**Figure 2.** Evidence network of all enrolled studies in relation to short-term effects and survival outcomes in this network meta-analysis. (A) Network plot of complete remission rate (CRR) of primary tumor. (B) Network plot of overall remission rate (ORR) of primary tumor. (C) Network plot of 1-year overall survival (OS) rate. (D) Network plot of 2-year OS rate. (E) Network plot of 3-year OS rate. (F) Network plot of 5-year OS rate.



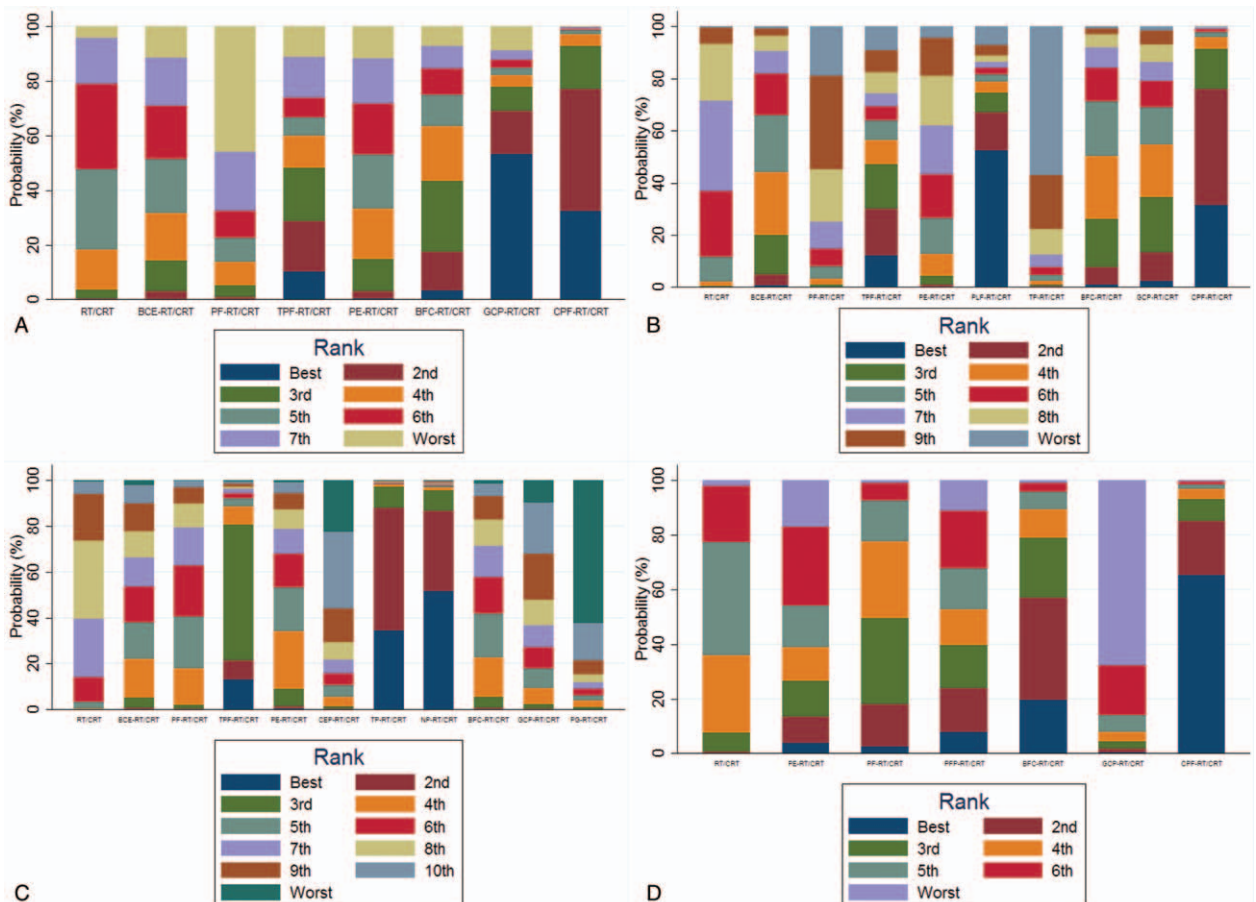
**Figure 3.** Evidence network of all enrolled studies in relation to toxicities (≥grade 3) in this network meta-analysis. (A) Network plot of anemia. (B) Network plot of neutropenia. (C) Network plot of skin toxicity. (D) Network plot of mucositis toxicity.



**Figure 4.** Ranking for the short-term effects in this network meta-analysis. (A) Complete remission rate (CRR) of primary tumor. (B) Overall remission rate (ORR) of primary tumor.

Eleven studies reported 2-year OS rate, and 9 NCT regimens (BCE, PFT, PF, PE, cisplatin, calcium folinate, and 5-fluorouracil [PLF], TP, BFC, GCP, and CPF) were included. In addition to PF and TP regimens, other 7 NCT regimens improved 2-year OS rate. Probability ranking revealed that the 2-year OS rate of PLF

regimen group was significantly higher than other groups (ranking probabilities were 52.9% for PLF, 31.6% for CPF, 11.7% for TPF, 2.3% for GCP, 1.0% or BFC, 0.3% for BCE and 0.1% for PE, Fig. 5B). The CIs of estimates for 2-year OS rate are shown in Table 3.



**Figure 5.** Ranking for the survival outcomes in this network meta-analysis. (A) 1-year overall survival (OS) rate. (B) 2-year OS rate. (C) 3-year OS rate. (D) 5-year OS rate.

**Table 2**

**Combined odds ratio and 95% confidence interval for 1-year overall survival (OS) rate from network meta-analysis.**

	GCP-RT/CRT	BFC-RT/CRT	PE-RT/CRT	TPF-RT/CRT	PF-RT/CRT	BCE-RT/CRT	RT/CRT
CPF-RT/CRT	0.7 (0.03–18.66)	2.48 (0.52–11.75)	3.47 (0.94–12.85)	2.42 (0.25–23.35)	5.31 (1.02–27.75)	3.51 (0.95–5.09)	3.59 (1.18–10.95)
GCP-RT/CRT		3.53 (0.13–93.01)	4.95 (0.21–116.65)	3.45 (0.09–134.37)	7.56 (0.27–208.82)	5.00 (0.21–117.74)	5.12 (0.23–111.94)
BFC-RT/CRT			1.40 (0.39–5.05)	0.98 (0.10–9.27)	2.14 (0.42–10.96)	1.42 (0.39–5.09)	1.45 (0.49–4.28)
PE-RT/CRT				0.70 (0.09–5.62)	1.53 (0.38–6.20)	1.01 (0.39–2.65)	1.03 (0.52–2.05)
TPF-RT/CRT					2.19 (0.47–10.30)	1.45 (0.18–11.65)	1.48 (0.21–10.65)
PF-RT/CRT						0.66 (0.16–2.67)	0.68 (0.20–2.30)
BCE-RT/CRT							1.02 (0.52–2.02)

BCE = bleomycin, epirubicin, and cisplatin, BFC = bleomycin, 5-fluorouracil, and cisplatin, CPF = cyclophosphamide, cisplatin, and 5-fluorouracil, CRT = chemoradiotherapy, GCP = paclitaxel, carboplatin, and gemcitabine, PE = cisplatin and epirubicin, PF = cisplatin and 5-fluorouracil, RT = radiotherapy, TPF = docetaxel, cisplatin, and 5-fluorouracil.

**Table 3**

**Combined odds ratio and 95% confidence interval for 2-year overall survival (OS) rate from network meta-analysis.**

	GCP-RT/CRT	BFC-RT/CRT	TP-RT/CRT	PLF-RT/CRT	PE-RT/CRT	TPF-RT/CRT	PF-RT/CRT	BCE-RT/CRT	RT/CRT
CPF-RT/CRT	1.91 (0.69–5.33)	1.98 (0.80–4.88)	4.18 (1.45–12.05)	0.80 (0.07–9.25)	2.58 (1.07–6.22)	1.78 (0.36–8.84)	3.27 (1.28–8.33)	2.07 (0.86–4.96)	2.58 (1.20–5.55)
GCP-RT/CRT		1.04 (0.45–2.39)	2.19 (0.80–5.96)	0.42 (0.04–4.73)	1.35 (0.60–3.03)	0.93 (0.20–4.46)	1.71 (0.72–4.08)	1.08 (0.48–2.42)	1.35 (0.68–2.68)
BFC-RT/CRT			2.11 (0.88–5.06)	0.40 (0.04–2.34)	1.30 (0.69–2.48)	0.90 (0.20–3.98)	1.65 (0.80–3.39)	1.04 (0.55–1.98)	1.30 (0.81–2.10)
TP-RT/CRT				0.19 (0.02–2.19)	0.62 (0.26–1.45)	0.43 (0.09–2.08)	0.78 (0.31–1.94)	0.49 (0.21–1.15)	0.62 (0.30–1.29)
PLF-RT/CRT					3.22 (0.30–34.22)	2.22 (0.15–33.59)	4.07 (0.38–44.24)	2.58 (0.24–27.33)	3.22 (0.32–32.89)
PE-RT/CRT						0.69 (0.16–3.00)	1.26 (0.63–2.52)	0.80 (0.44–1.47)	1.00 (0.65–1.54)
TPF-RT/CRT							1.83 (0.50–6.72)	1.16 (0.27–5.04)	1.45 (0.36–5.92)
PF-RT/CRT								0.63 (0.32–1.26)	0.79 (0.46–1.36)
BCE-RT/CRT									1.25 (0.82–1.92)

BCE = bleomycin, epirubicin, and cisplatin, BFC = bleomycin, 5-fluorouracil, and cisplatin, CPF = cyclophosphamide, cisplatin, and 5-fluorouracil, CRT = chemoradiotherapy, GCP = paclitaxel, carboplatin, and gemcitabine, PE = cisplatin and epirubicin, PF = cisplatin and 5-fluorouracil, PLF = cisplatin, calcium folinate, and 5-fluorouracil, RT = radiotherapy, TP = docetaxel and cisplatin.

Fifteen studies also reported 3-year OS rate, and 7 NCT regimens were considered to be able to improve 3-year OS rate of patients. NMA results demonstrated that NP regimens may be the patients' 3-year OS rate of maximum benefit (ranking probability was 51.7%, Fig. 5C).

Nine RCTs reported 5-year OS rate, involving 6 NCT regimens and 1903 patients. We found 4 NCT regimens (CPF, BFC, PFP, PE, and PF regimen) improved the 5-year OS rate of patients with advanced NPC in different degree. Then the results of probability ranking revealed that the 5-year OS rate of CPF regimen group was significantly higher than other groups (ranking probability was 65.4%, Fig. 5D). The CIs of estimates for 5-year OS rate are shown in Table 4.

**3.6. Grade 3 and above toxicity**

Toxicities are the important indicators of drug evaluation. To address severe acute toxicities (≥grade 3), we compared toxicity

rates among NCT groups and RT/CRT alone groups. This NMA evaluated the following most reported toxicities: anemia, thrombocytopenia, neutropenia, skin toxicity, and mucositis toxicity.

Six NCT regimens were included compared the incidence rate of anemia. Two regimens (TP and NP) were considered to decrease the incidence rate of anemia, while other 4 regimens (PF, paclitaxel, epirubicin, and cisplatin [CEP], GCP, and PG) increased the rate. Incidence rate was lowest in NP regimen (ranking probability was 75.4%).

Sixteen studies (n=1774) provided data about neutropenia which occurred during the entire treatment and 6 NCT regimens (PF, CEP, TP, NP, GCP, and PG) were reported. The pooled incidence rates of neutropenia from 16 studies reflected CEP regimen had the lowest incidence rate (ranking probability was 55.8%).

The pooled incidence rates of thrombocytopenia for each treatment regimen from 13 studies, including 6 NCT regimens

**Table 4**

**Combined odds ratio and 95% confidence interval for 5-year overall survival (OS) rate from network meta-analysis.**

	GCP-RT/CRT	BFC-RT/CRT	PFP-RT/CRT	PF-RT/CRT	PE-RT/CRT	RT/CRT
CPF-RT/CRT	5.45 (1.18–25.15)	1.58 (0.42–5.98)	2.44 (0.51–11.63)	2.15 (0.67–6.87)	2.95 (0.65–13.45)	2.71 (0.95–7.74)
GCP-RT/CRT		0.29 (0.07–1.15)	0.45 (0.09–2.23)	0.39 (1.12–1.33)	0.54 (0.11–2.58)	0.50 (0.16–1.51)
BFC-RT/CRT			1.55 (0.37–6.40)	1.36 (0.52–3.57)	1.87 (0.48–7.37)	1.72 (0.76–3.91)
PFP-RT/CRT				0.88 (0.25–3.11)	1.21 (0.25–5.95)	1.11 (0.35–3.53)
PF-RT/CRT					1.38 (0.41–4.58)	1.26 (0.78–2.08)
PE-RT/CRT						0.92 (0.31–2.74)

BFC = bleomycin, 5-fluorouracil, and cisplatin, CPF = cyclophosphamide, cisplatin, and 5-fluorouracil, CRT = chemoradiotherapy, GCP = paclitaxel, carboplatin, and gemcitabine, PE = cisplatin and epirubicin, PF = cisplatin and 5-fluorouracil, PFP = carboplatin, 5-fluorouracil and pingyangmycin, RT = radiotherapy.

(PF, CEP, TP, NP, GCP, and PG). We found only NP regimen could reduce the risk of thrombocytopenia (ORs = -0.36, 95% CI -2.43 to 1.70).

In addition, we evaluated incidence rate of mucositis by comparing 6 NCT regimens (BCE, PF, CEP, TP, NP, and BFC). BCE, CEP, and NP regimens reduced the risk of mucositis. And NP regimen had the lowest incidence rate (ranking probability was 46.2%). Eleven studies reported incidence rate of skin toxicity, involving 6 NCT regimens (BCE, PF, CEP, TP, NP, and GCP). CEP regimen had the lowest incidence rate (ranking probability was 81.5%).

**3.7. Publication bias**

Figure 6 presented the funnel plot for the network. All the included studies symmetrically distribute around the vertical line ( $x=0$ ), indicating no significant publication bias in this NMA.

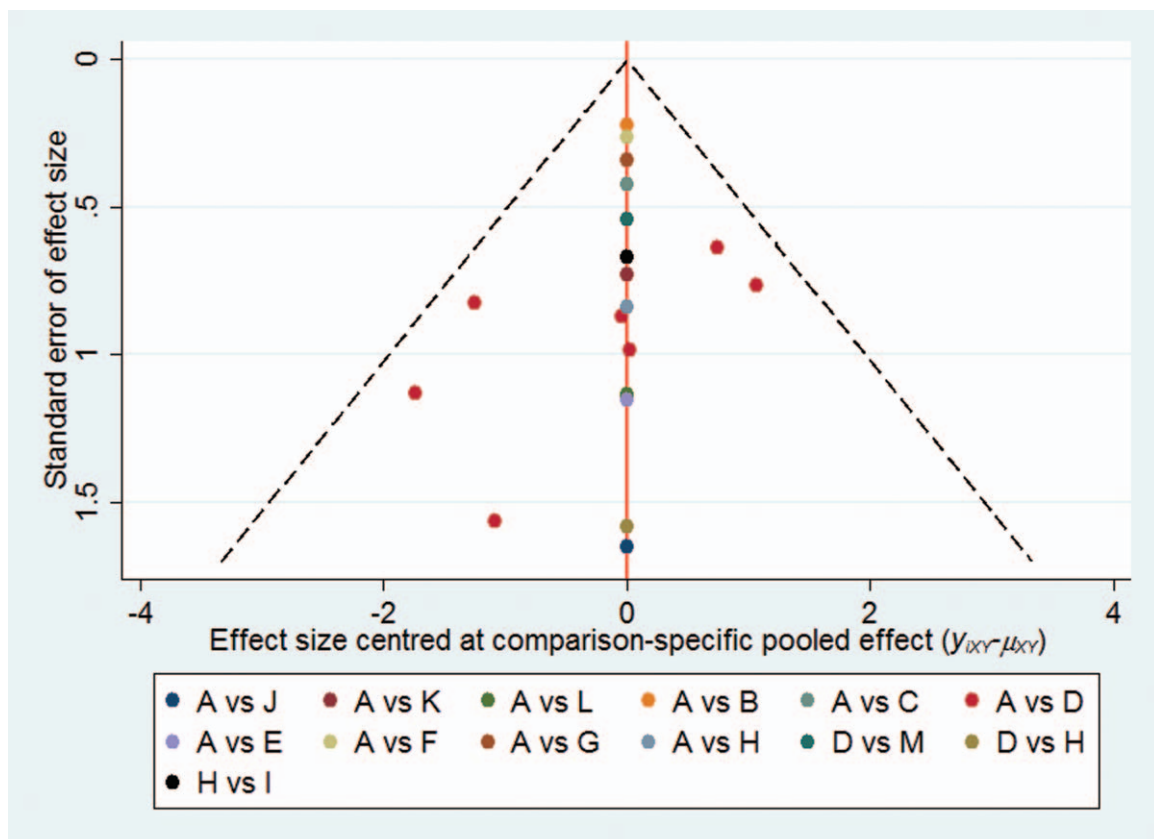
**4. Discussion**

This NMA is the first study to evaluate the efficacy of the different NCT regimens in the treatment of NPC through direct and indirect statistical comparisons based on all available information from the

included RCTs. Compared with RT/CRT alone, most of the NCT regimens can improve the long-term survival rate (1-year, 2-year, 3-year, and 5-year OS rate) of patients and CRR and ORR of primary tumor in different degrees. Meanwhile certain NCT regimens do not improve patient prognosis, and even cause serious toxicity.

As far as this research is concerned, we still not able to confirm the best NCT regimen, because the best regimen for various outcomes and toxicity is not entirely consistent. In spite of this, the NMA identified the relatively optimal NCT regimen based different prognostic indicators, such as GCP for 1-year OS rate, PLF for 2-year OS rate, NP for 3-year OS rate, CPF for 5-year OS rate, NP for CRR, and PG for ORR. In addition, for certain grade 3 and above toxicity, we found certain NCT regimens can reduce toxicity to a minimum, such as NP for anemia, mucositis, and thrombocytopenia, CEP for neutropenia and skin toxicity.

National Comprehensive Cancer Network recommends CCRT for locoregionally advanced NPC. On the contrary, according to clinical practice guidelines of European Society of Oncology, cisplatin-based NCT regimens are recommended for patients with advanced NPC.<sup>[37]</sup> And our NMA results also confirm and support the conclusion.



**Figure 6.** Comparison-adjusted funnel plot for assessing publications bias. The red line suggests the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors represent different comparisons. (A) RT/CRT, (B) BCE-RT/CRT, (C) TPF-RT/CRT, (D) PF-RT/CRT, (E) DF-RT/CRT; (F) PE-RT/CRT, (G) CEP-RT/CRT, (H) TP-RT/CRT, (I) NP-RT/CRT, (J) PLF-RT/CRT, (K) BFC-RT/CRT, (L) CPF-RT/CRT, (M) PG-RT/CRT. BCE = bleomycin, epirubicin, and cisplatin, BFC = bleomycin, 5-fluorouracil, and cisplatin, CEP = paclitaxel, epirubicin, and cisplatin, CPF = cyclophosphamide, cisplatin, and 5-fluorouracil, CRT = chemoradiotherapy, DF = docetaxel and cisplatin, NP = vinorelbine and cisplatin, PE = cisplatin and epirubicin, PF = cisplatin and 5-fluorouracil, PG = cisplatin and gemcitabine, PLF = cisplatin, calcium folinate, and 5-fluorouracil, RT = radiotherapy, TP = docetaxel and cisplatin, TPF = docetaxel, cisplatin, and 5-fluorouracil.



But the study limitations also should be acknowledged: only English and Chinese language studies were included might have led to potential publication bias; the exclusion of unpublished data was generally associated with an overestimation of the true effect; prognosis indexes failed to incorporate all of the NCT regimens, so that it is difficult to determine which regimen is optimal for the patients.

In conclusion, our NMA showed that certain cisplatin-based NCT regimens improved the prognosis of patients with NPC and reduced the toxicity of CRT. However, in view of survival rate and response rate, the best NCT regimen is not entirely consistent. Therefore, which NCT regimen will benefit most patients will need further explored.

## Author contributions

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