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ORIGINAL RESEARCH

Evolutionary role of chemotherapy in advanced nasopharyngeal carcinoma: a literature-based network meta-analysis

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Purpose: The role of chemotherapy has evolved greatly in advanced nasopharyngeal carcinoma (NPC). We undertook this network meta-analysis to establish the optimal chemotherapy strategy in advanced NPC.

Materials and methods: This network meta-analysis recruited randomized clinical trials involving patients with advanced NPC randomly allocated to induction chemotherapy plus concurrent chemoradiotherapy (CRT; induction + CRT), CRT plus adjuvant chemotherapy (CRT + adjuvant), CRT or radiotherapy (RT) alone. Pairwise meta-analysis was first conducted, then network meta-analysis was performed using the frequentist approach. Effect size was expressed as HR and 95% CI.

Results: In total, we analyzed 15 studies involving 4,067 patients with 880 (21.6%) patients receiving induction + CRT, 897 (22.1%) receiving CRT + adjuvant, 1,421 (34.9%) receiving CRT, and 869 (21.4%) receiving RT alone. Induction + CRT achieved significantly better distant failure-free survival (HR, 0.67; 95% CI, 0.53–0.86) and locoregional failure-free survival (HR, 0.69; 95% CI, 0.54–0.89) than CRT, and CRT + adjuvant achieved better overall survival than CRT (HR, 0.82; 95% CI, 0.67–1.00). However, no significant survival difference was found between the induction + CRT and CRT + adjuvant groups. Additionally, RT alone is always worse than the other three treatments. In terms of P-score, induction + CRT ranked best for distant and locoregional failure-free survival, while CRT + adjuvant ranked best for overall survival.

Conclusion: Both induction + CRT and CRT + adjuvant were equally effective and feasible choices for patients with advanced NPC.

Keywords: nasopharyngeal carcinoma, advanced, concurrent chemoradiotherapy, induction chemotherapy, adjuvant chemotherapy, network meta-analysis

Introduction

Nasopharyngeal carcinoma (NPC), known as a special kind of head and neck malignancy, is mainly prevalent in East Asia and South China while its incidence in white population is extremely low.[1] According to the recent data on cancer epidemiology, NPC has emerged as the most common head and neck cancer in China.[2,3] Radiotherapy (RT) is the only radical therapy for nonmetastatic disease as a result of complicated anatomy location and high radiation sensitivity of NPC. Also, NPC is highly sensitive to chemotherapy and combined RT with chemotherapy is essential for advanced disease.

The role of chemotherapy in advanced NPC was first established by the Intergroup 0099 study, which revealed concurrent prevalent (CRT) plus adjuvant chemotherapy achieved better overall survival (OS) than RT alone.[4] Later on, many validated trials

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that were carried out in Asia further strengthen the role of CRT plus adjuvant chemotherapy in NPC.[5–7] However, a randomized phase III clinical trial by Chen et al demonstrated that adjuvant chemotherapy additional to CRT may be useless.[8] Consequently, CRT with or without adjuvant chemotherapy has been recommended as the standard treatment for advanced NPC. Although these achievements have been made, the prognosis of advanced disease still remains poor.[9] Therefore, scientists evaluated the efficacy and toxicity of induction chemotherapy additional to CRT in advanced NPC. Thankfully, recent studies found that induction chemotherapy plus CRT was superior to CRT alone,[10–14] making induction chemotherapy a promising treatment for advanced NPC. However, another clinical issue produced: what is the best treatment in advanced NPC? Induction chemotherapy plus CRT (induction + CRT) or CRT plus adjuvant chemotherapy (CRT + adjuvant)? To date, no head-to-head clinical study comparing induction + CRT with CRT + adjuvant has been reported. A network meta-analysis employing individualized patient data (IPD) compared these two treatments indirectly and found no significant difference.[15] Notably, many recent studies were not included in this meta-analysis. Thus, it is worth reanalyzing this issue using the updated data. Given this concern, we conducted this network meta-analysis to establish the optimal treatment in advanced NPC.

Materials and methods

Online literature searching strategy

We searched the online datasets of PubMed, Web of Science, and Cochrane library using the terms of "nasopharyngeal carcinoma or cancer," "radiotherapy," and "induction chemotherapy or neoadjuvant chemotherapy or adjuvant chemotherapy or concurrent chemoradiotherapy" to identify all potential clinical trials. For related Chinese studies, the National Knowledge Infrastructure and WanFang datasets were searched. All studies were restricted to randomized clinical trial. Two investigators completed this process independently, and any discrepancy was solved by consensus. Our network meta-analysis was conducted in accordance with the PRISMA guidelines (PRISMA checklist).

Clinical trial inclusion criteria

The clinical trials published between 1998 and 2018 would be included into this study for analysis if they meet the following criteria: 1) randomized phase II–III clinical trial; 2) recruiting patients with newly diagnosed, nonmetastatic, and advanced NPC; 3) RT was delivered as conventional fraction and total radiation dosage of 66 Gy or more should be scheduled; 4) either experimental or control arm in the trials should contain one of the four treatments (induction + CRT, CRT + adjuvant, CRT alone, RT alone).

Study quality evaluation

In order to select appropriate statistical method and obtain unbiased results, we employed the Jadad/Oxford quality scoring system[16] to assess the study quality. The randomization procedure, sample size calculation, adoption of blinded principle, allocation concealment, and intention-to-treatment analysis of included trials were reviewed and scored according to the standard. Two authors completed this process independently and discrepancies were solved by consensus.

Study data extraction

Three investigators reviewed each included study separately to collect and extract related data including study author information, patient recruitment time period, sample size, patient tumor stage, RT and chemotherapy protocol, follow-up duration, and study endpoints. All extracted information and data were reviewed by the fourth investigator to check whether discrepancy existed between the three investigators. Otherwise, discrepancy would be solved by consensus.

Study endpoint

In our current network meta-analysis, we set OS (defined as the time interval between randomization and death from any cause) as the primary endpoint. The other two endpoints were distant failure-free survival (DFFS, defined as time interval between randomization to first distant metastasis) and locoregional failure-free survival (LFFS, defined as time interval between randomization and first local or regional or both recurrence). Given the different definitions of progression-free survival (PFS) or disease-free survival in different clinical trials, we therefore did not perform analysis on this endpoint.

Statistical analysis

Survival data were extracted from trials and expressed in our study as HRs and corresponding CIs since they are the only summary statistic allowed for censoring and time to an event. HRs and corresponding CIs were extracted from original text if they were available, otherwise they were obtained them from a previous meta-analysis[15] or a pooled data analysis.[17]

Pairwise meta-analysis between two treatment arms was conducted first. Pooled HRs and corresponding 95% CIs of direct comparison between two treatment arms were calculated to evaluate the survival difference, and $P<0.05$ was

considered significant. We used the chi-squared test and I^2 statistic to establish the heterogeneity between studies, and the χ^2 P-value <0.1 or an I^2 statistic >50% was considered significant. Stata statistical package 13.0 (StataCorp LP, College Station, TX, USA) was applied to complete this analysis.

For network meta-analysis, multiple treatment comparisons were conducted using netmeta package[18,19] and frequentist approach[18] in R software (version 3.3.5; R Foundation, Vienna, Austria). The logarithmic of HR (logHR) and its variance (selogHR) of each direct comparison were calculated for statistical network meta-analysis. Also, treatment effects of network meta-analysis were estimated by HRs and 95% CIs and presented in forest plots. Inconsistency and heterogeneity between and within different comparisons were evaluated by Q test, which was proposed by Rücker.[19] The P-value of Q test >0.1 indicates no heterogeneity, and vice versa. Random-effect model would be applied and sensitivity analysis would be performed in case of significant heterogeneity. Finally, each treatment would be ranked by a P-score, which was proposed by Rücker and Schwarzer[18] as a frequentist analog to surface under the cumulative ranking curve.[20,21] Briefly, a P-score of 100% indicates the best treatment and 0% for the worst treatment. P<0.05 was considered significant for all analysis.

Results

Basic information of included studies

By the last searching (August 2018), we totally identified 26 potentially eligible clinical trials and the flowchart is presented in Figure S1. The study by Lin et al[22] comparing CRT with RT alone was excluded because HRs and 95% CIs were not provided in the original text. We also excluded two studies which recruited patients with stage II disease.[23,24] Moreover, the study by Lee et al[25] consisting of six treatment arms was not included because HR was not provided for each comparison. Two treatment arms in the study by Lee et al[26,27] receiving accelerated-fraction RT were not included but the other arms were included. Nevertheless, six studies updated their follow-up data: Chen et al comparing CRT + adjuvant with CRT,[28,29] Chan et al comparing CRT with RT,[30,31] Lee et al comparing CRT + adjuvant with RT,[6,32] Chen et al comparing CRT + adjuvant with RT,[33,34] Lee et al comparing CRT + adjuvant with RT,[26,27] and Zhang et al and Wu et al comparing CRT with RT.[35,36] Finally, 15 studies were included for our study[4–8,10–14,35,37–40] and the basic information is shown in Table 1. Overall, these 15 trials recruited 4,067 patients with 880 (21.6%) patients receiving induction + CRT, 897 (22.1%) receiving CRT + adjuvant, 1,421 (34.9%) receiving CRT, and 869 (21.4%) receiving RT alone. The Jadad/Oxford score for each trial is summarized in Table S1. Obviously, most of the trials achieved good quality.

Pairwise meta-analysis between two treatment arms

Figure 1 presents the results of all direct comparisons. As shown by the result, no significant heterogeneity exists between all comparisons for all the endpoints. Therefore, the fixed-effect model was employed for all analysis. Compared with RT alone, CRT + adjuvant achieved significantly better OS (HR, 0.63; 95% CI, 0.53–0.73), DFFS (HR, 0.51; 95% CI, 0.39–0.64), and LFFS (HR, 0.48; 95% CI, 0.32–0.64), while CRT was associated with better OS (HR, 0.77; 95% CI, 0.61–0.93) and DFFS (HR, 0.56; 95% CI, 0.39–0.74) but not LFFS (HR, 0.81; 95% CI, 0.50–1.11). As expected, no significant difference was found between CRT + adjuvant and CRT. Moreover, induction + CRT achieved significantly better OS (HR, 0.74; 95% CI, 0.57–0.91), DFFS (HR, 0.65; 95% CI, 0.50–0.80), and LFFS (HR, 0.66; 95% CI, 0.48–0.84).

Network comparison between multiple treatment arms

The network plot of multiple treatment comparisons is presented in Figure 2. No significant between-study or within-study heterogeneity was found between all comparisons (Table 2), and the fixed-effect model was therefore applied. The forest plot of multiple treatment comparisons in the network meta-analysis is shown in Figure 3.

Compared with CRT, CRT + adjuvant achieved significantly better OS (HR, 0.82; 95% CI, 0.67–1.00), while RT alone achieved significantly worse OS (HR, 1.25; 95% CI, 1.05–1.49). However, no statistical difference was found between induction + CRT and CRT (HR, 0.83; 95% CI, 0.67–1.03). After changing the reference group, CRT + adjuvant did not significantly differ from induction + CRT (HR, 1.02; 95% CI, 0.76–1.36); while RT alone was poorer than both CRT + adjuvant (HR, 1.53; 95% CI, 1.32–1.77) and induction + CRT (HR, 1.50; 95% CI, 1.14–1.98). The P-scores for CRT, CRT + adjuvant, induction + CRT, and RT alone were 35.3%, 84.1%, 80.3%, and 0.3%, respectively (Table 2), suggesting that CRT + adjuvant achieved the higher possibility of becoming the best treatment for OS.

For the endpoint of DFFS, induction + CRT was better than CRT (HR, 0.67; 95% CI, 0.53–0.86), while no significant difference was found between CRT and CRT + adjuvant (HR, 0.94; 95% CI, 0.70–1.28) or between CRT + adjuvant and induction + CRT (HR, 0.71; 95% CI, 0.48–1.05). Notably, RT

Table 1 Basic information of the 15 clinical trials included

Author	Recruitment time	Sample size (experimental/control)	Tumor stage	Median follow-up	Radiotherapy protocol
CRT + adjuvant vs RT					
Al-Sarraf et al[4]	1989–1995	78/69[a]	III–IV	32.4 m	66–70 Gy at 1.8–2.0 Gy/f/day (5 f/qw)
Kwong et al[38b]	1995–2001	57/55	II–IV	37 m	66–68 Gy at 2.0 or 2.5 Gy/f/daily (4 or 5 f/qw)+ 10 Gy boost dose to parapharyngeal extension or residual neck node
Wee et al[7]	1997–2003	111/110	III–IV, T3-4Nx or TxN2-3	38.4 m	70 Gy/35 f at 2 Gy/f/day (5 f/qw) for 7 weeks
Lee et al[6]	1999–2004	172/178	III–IV, N2-3	70.8 m	≥66 Gy at 2.0 Gy/f/day (5 f/qw)+ additional boosts to parapharyngeal space, primary or nodal sites when indicated not exceeding 20 Gy
Lee et al[26]	1999–2004	51/42	III–IV, T3-4N0-1	75.6 m	≥66 Gy at 2.0 Gy/f/day (5 f/qw) + additional boosts to parapharyngeal space, primary or nodal sites when indicated not exceeding 20 Gy
Chen et al[5]	2002–2005	158/158	III-IV, T1-4 or N0-3	70 m	≥68 Gy at 2.0 Gy/f/day (5 f/qw) for 7 weeks + additional boost in case of parapharyngeal extension, residual neck and/or nasopharyngeal tumor
CRT vs RT					
Chan et al[30]	1994–1997	174/176	Ho's N2-3 or N1 with nodal size ≥4 cm	66 m	66 Gy + additional boost in case of parapharyngeal extension, residual neck or nasopharyngeal tumor
Kwong et al[38b]	1995–2001	56/55	II–IV	37 m	66–68 Gy at 2.0 or 2.5 Gy/f/daily (4 or 5 f/qw) + 10 Gy boost dose to parapharyngeal extension or residual neck node
Zhang et al[36]	2001–2003	59/56	III–IV, N2-3	114 m	70–74 Gy at 2 Gy/f/day (5 f/qw) + additional boost in case of parapharyngeal extension, residual neck or nasopharyngeal tumor
Induction + CRT vs CRT					
Hui et al[13]	2002–2004	34/31	III–IVB, T1-4, N0-3	51.6 m	66 Gy/33 f at 2 Gy/f/day (5 f/qw) + additional boost of 20 Gy/10 f to parapharyngeal
Tan et al[40]	2004–2012	86/86	III–IVB, T1-4, N0-3	40.8 m	2D-RT: 70 Gy/35 f at 2 Gy/f/day (5 f/qw) IMRT: 69.96 Gy/33 f at 2.12 Gy/f/day (5 f/qw)
Sun et al[11]	2011–2013	241/239	III–IVB, except T3-4N0	45 m	≥66 Gy at 2.00–2.35 Gy/f/day for 6–7 weeks
Cao et al[10]	2008–2015	476	III–IVB, except T3N0-1	50 m	≥66 Gy at 2.0–2.33 Gy/f/day
Frikha et al[12]	2009–2012	42/41	T2b-4 and/or N1-3	43.1 m	70 Gy at 2 Gy/f/day (5 f/qw)
Hong et al[14]	2003–2009	239/240	IVA–IVB	72.0 m	At least 70 Gy at 1.8–2.0 Gy/f/day (5 f/qw) for 33–39 f
CRT + adjuvant vs CRT					
Kwong et al[38b]	1995–2001	57/56	II-IV	37 m	66–68 Gy at 2.0 or 2.5 Gy/f/daily (4 or 5 f/qw) + 10 Gy boost dose to parapharyngeal extension or residual neck node
Chen et al[8]	2006–2010	251/257	III–IVB except T3-4N0	68.4 m	≥66 Gy at 2.0–2.27 Gy/f/day (5 f/qw) for 6–7 weeks

Notes: [a]One hundred ninety-three patients were registered, but only 147 patients were analyzed. [b]The study by Kwong et al consisted of four treatment arms.
Abbreviations: 2D-RT, two-dimensional radiotherapy; AUC, area under concentration-time curve; CRT, concurrent chemoradiotherapy; DDP, cisplatin; *f*, fraction; Fu, fluorouracil; IMRT, intensity-modulated radiotherapy; q3w, every 3 weeks; q4w, every 4 weeks; RT, radiotherapy.

Chemotherapy protocol		
Induction phase	**Concurrent phase**	**Adjuvant phase**
None	DDP 100 mg/m^2 d1 q3w×3	DDP 80 mg/m^2 d1 + Fu 1,000 mg/m^2/day d1–4 civ q3w×4
None	UFT 200 mg TID, 7 days per week for 5–8 weeks	DDP 100 mg/m^2 d1 + 5-FU 1,000 mg/m^2/d d1–3 civ, q3w×6 or vincristine 2 mg d1 + bleomycin 30 mg d1 + methotrexate 150 mg/m^2 d1, q3w×6
None	DDP 25 mg/m^2/day for 4 days or 30/30/40 mg/m^2/day for 3 days q3w×3	DDP 20 mg/m^2/day for 4 days + Fu 1,000 mg/m^2/day d1–4 q3w×3
None	100 mg/m^2 d1 q3w×3	DDP 80 mg/m^2 d1 + 1,000 mg/m^2/day d1–4 civ q4w×3
None	100 mg/m^2 d1 q3w×3	DDP 80 mg/m^2 d1 + 1,000 mg/m^2/day d1–4 civ q4w×3
None	100 mg/m^2 d1 q3w×3	DDP 80 mg/m^2 d1 + Fu 800 mg/m^2/day d1–5 civ q3w×3
None	DDP 40 mg/m^2 d1 weekly for 8 weeks	None
None	UFT 200 mg TID, 7 days per week for 5–8 weeks	None
None	Oxaliplatin 70 mg/m^2 d1 weekly for 6 weeks	None
Docetaxel 75 mg/m^2 d1 + DDP 75 mg/m^2 d1 q3w×2	40 mg/m^2 d1 qw×8	None
Paclitaxel 70 mg/m^2 d1,d8 + Carboplatin AUC=2.5 d1,d8 + Gemcitabine 1,000 mg/m^2 d1,d8 q3w×3	DDP 40 mg/m^2 weekly for 8 weeks	None
Docetaxel 60 mg/m^2 d1 + DDP 60 mg/m^2 d1 + Fu 600 mg/m^2/day d1-5 civ q3w×3	100 mg/m^2 d1 q3w×3	None
DDP 80 mg/m^2 d1 + Fu 800 mg/m^2/day d1-5 civ q3w×3	80 mg/m^2 d1 q3w×3	None
Docetaxel 75 mg/m^2 d1 + DDP 75 mg/m^2 d1 + 5-Fu 750 mg/m^2/day d1-d5	DDP 40 mg/m^2/weekly	None
Mitomycin 8 mg/m^2 d1 + epirubicin 60 mg/m^2 d1 + DDP 60 mg/m^2 d1 + 5-Fu 450 mg/m^2 d8 + leucovorin 30 mg/m^2 d8	DDP 30 mg/m^2/weekly	None
None	UFT 200 mg TID, 7 days per week for 5–8 weeks	DDP 100 mg/m^2 d1 + 5-FU 1,000 mg/m^2/d d1–3 civ, q3w×6 or vincristine 2 mg d1 + bleomycin 30 mg d1 + methotrexate 150 mg/m^2 d1, q3w×6
None	DDP 40 mg/m^2 d1 weekly for up to 7 weeks	DDP 80 mg/m^2 d1 + Fu 800 mg/m^2/day d1–5 civ q4w×3

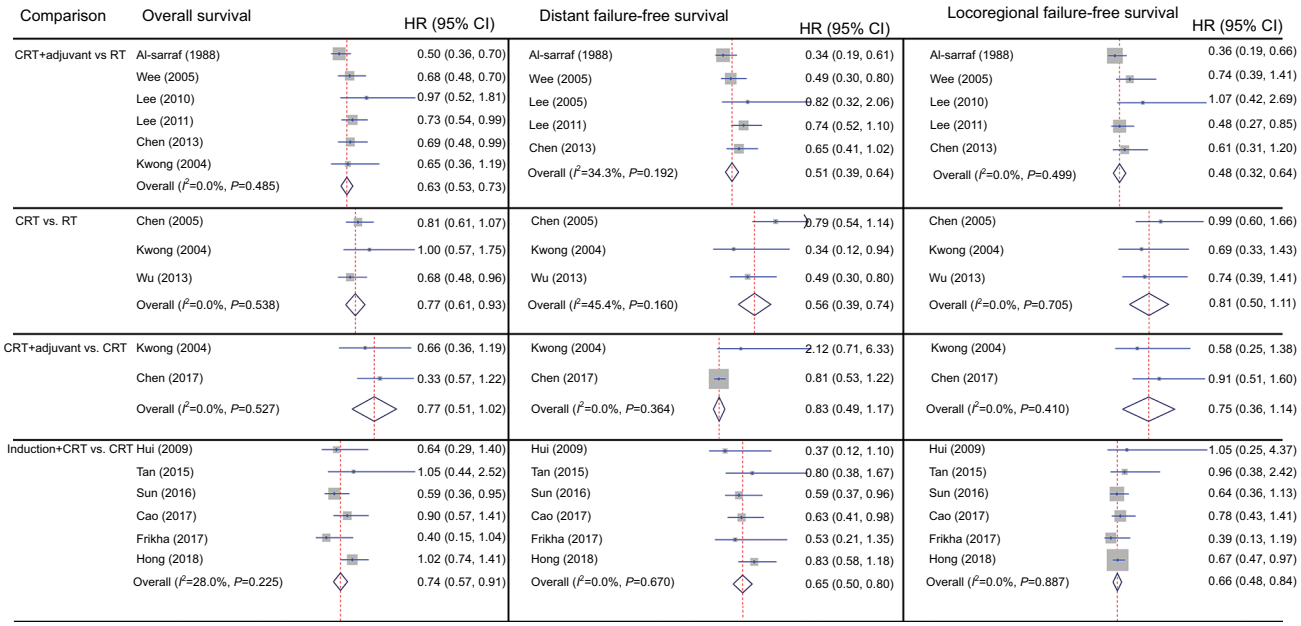

Figure 1 Forest plot of pairwise meta-analysis.
Abbreviations: civ, continuous intravenous injection; CRT, concurrent chemoradiotherapy; RT, radiotherapy; UFT, uracil-FT-207.

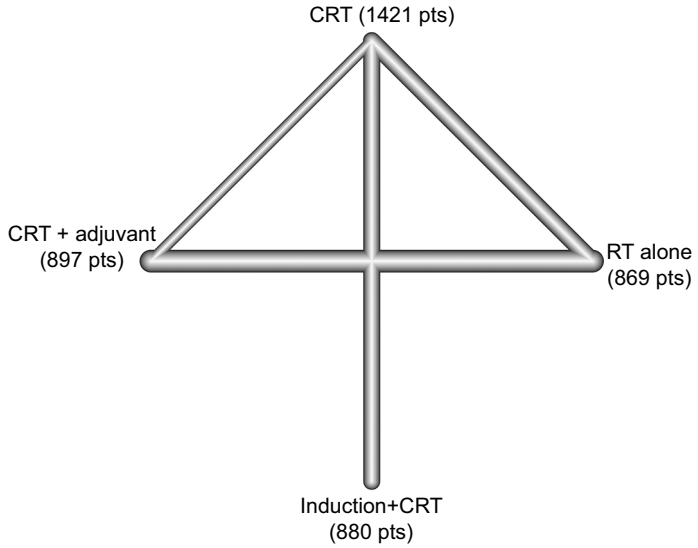

Figure 2 Graph of the network comparisons for overall survival.
Abbreviations: CRT, concurrent chemoradiotherapy; RT, radiotherapy.

alone was worse than the other three treatments. Undoubtedly, induction + CRT achieved highest P-score of 98.6% (Table 2), indicating that induction + CRT may be the best choice for reducing distant failure.

With regard to LFFS, induction + CRT was better than CRT (HR, 0.69; 95% CI, 0.54–0.89) and RT alone (HR, 0.55; 95% CI, 0.37–0.81). Moreover, CRT + adjuvant was also better than RT (HR, 0.58; 95% CI, 0.44–0.75). Otherwise, no significant difference was identified between other comparisons. Similarly, induction + CRT still achieved the highest P-score of 86.2% (Table 2).

Given these findings, CRT + adjuvant may be a better treatment for improving OS, while induction + CRT was better in reducing distant failure and locoregional failure.

Sensitivity analysis

To validate the stability of our findings, we performed sensitivity analysis after excluding the study by Kwong et al[38]

Table 2 Results of network multiple comparisons

Treatment arms	OS	DFFS	LRFS
P-value of total heterogeneity/inconsistency	0.51	0.27	0.79
P-value of within-study heterogeneity	0.44	0.21	0.75
P-value of between-study heterogeneity	0.69	0.94	0.62
CRT (reference group)			
Hazard ratio	1.00	1.00	1.00
P-score	35.3%	42.7%	32.1%
CRT + adjuvant			
Hazard ratio (95% CI)	0.82 (0.67–1.00)	0.94 (0.70–1.28)	0.73 (0.52–1.01)
P-score	84.1%	58.7%	79.4%
Induction + CRT			
Hazard ratio (95% CI)	0.83 (0.67–1.03)	0.67 (0.53–0.86)	0.69 (0.54–0.89)
P-score	80.3%	98.6%	86.2%
RT alone			
Hazard ratio (95% CI)	1.25 (1.05–1.49)	1.63 (1.23–2.14)	1.25 (0.93–1.69)
P-score	0.3%	<0.1%	2.3%

Notes: Fixed-effects model was used for OS, DFFS, and locoregional failure-free survival.
Abbreviations: CRT, concurrent chemoradiotherapy; DFFS, distant failure-free survival; LRFS, locoregional recurrence-free survival; OS, overall survival.

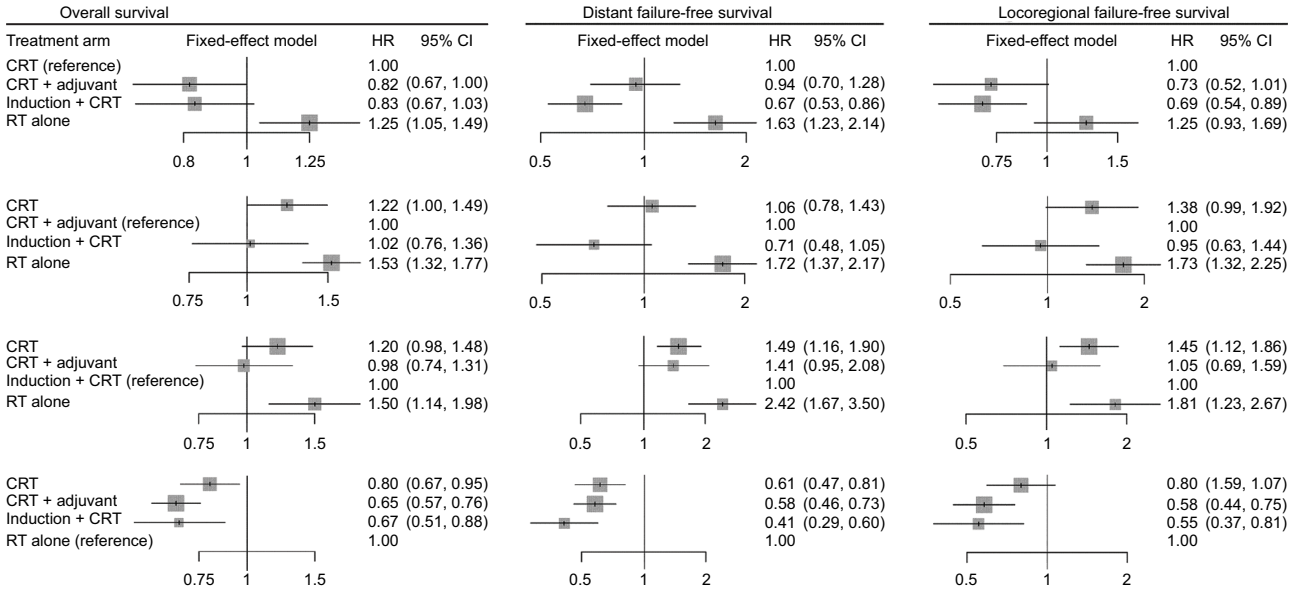

Figure 3 Forest plot of network meta-analysis.
Abbreviations: CRT, concurrent chemoradiotherapy; RT, radiotherapy.

because the chemotherapeutic agent used during RT is not platinum. The network plot was shown in Figure S2. As indicated by the results (Figure 4, Table 3), induction + CRT was still better than CRT in terms of DFFS (HR, 0.68; 95% CI, 0.54–0.85) and LFFS (HR, 0.69; 95% CI, 0.54–0.89), while no significant difference between CRT + adjuvant and CRT, or between induction + CRT and CRT + adjuvant was found. RT alone was still worse than the other treatments. Intriguingly, induction + CRT achieved the highest P-score on OS, DFFS, and LFFS. Taken these together, our results remained valid in sensitivity analysis.

Discussion

Our current network meta-analysis compared four treatment arms (CRT, CRT + adjuvant, induction + CRT, and RT alone) in advanced NPC and found that induction + CRT was better than CRT in reducing distant metastasis and locoregional recurrence, while CRT + adjuvant was superior to CRT in improving OS. Notably, induction + CRT did not significantly differ from CRT + adjuvant. RT alone was always worse than the other three treatments. Further, sensitivity analysis after excluding the study by Kwong et al[38] also confirmed these findings.

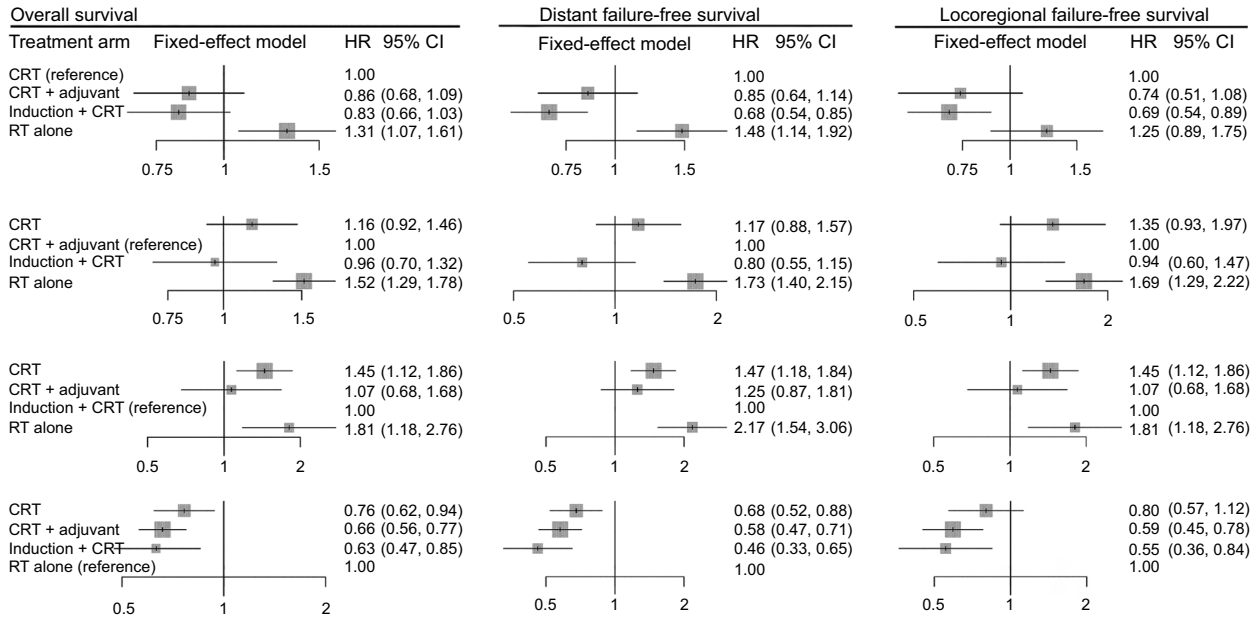

Figure 4 Forest plot of sensitivity analysis.
Abbreviations: CRT, concurrent chemoradiotherapy; RT, radiotherapy.

Table 3 Results of network multiple comparisons after excluding the study by Kwong et al[38]

Treatment arms	OS	DFFS	LRFS
P-value of total heterogeneity/inconsistency	0.37	0.40	0.69
P-value of within-study heterogeneity	0.30	0.32	0.69
P-value of between-study heterogeneity	0.82	0.75	0.35
CRT (reference group)			
Hazard ratio	1.00	1.00	1.00
P-score	37.7%	37.6%	32.0%
CRT + adjuvant			
Hazard ratio (95% CI)	0.86 (0.68–1.09)	0.85 (0.64–1.14)	0.74 (0.51–1.08)
P-score	77.3%	66.1%	77.6%
Induction + CRT			
Hazard ratio (95% CI)	0.83 (0.66–1.03)	0.68 (0.54–0.85)	0.69 (0.54–0.89)
P-score	84.8%	96.3%	87.0%
RT alone			
Hazard ratio (95% CI)	1.31 (1.07–1.61)	1.48 (1.14–1.92)	1.25 (0.89–1.75)
P-score	0.1%	<0.1%	3.4%

Notes: Fixed-effects model was used for OS, DFFS, and locoregional failure-free survival.
Abbreviations: CRT, concurrent chemoradiotherapy; DFFS, distant failure-free survival; LRFS, locoregional recurrence-free survival; OS, overall survival.

As intensity-modulated radiotherapy has become the predominant treatment for patients with NPC, locoregional control of advanced disease has improved greatly and distant metastasis has become the main failure pattern.[41,42] Therefore, combined strategies of chemotherapy with radiotherapy have been intensively investigated. A possible and feasible strategy is additional cycles of chemotherapy, such as adjuvant chemotherapy and induction chemotherapy, to CRT. In fact, both CRT + adjuvant and induction + CRT have been recommended as the standard cure for patients with advanced NPC by the National Comprehensive Cancer Network (NCCN) guidelines. However, this produces another question: which one is better? CRT + adjuvant or induction + CRT? As far as we know, there are no head-to-head clinical trials comparing CRT + adjuvant with induction + CRT being reported yet. Given this concern, we performed this network meta-analysis to provide preliminary answer for this question. Our findings indicated that CRT + adjuvant and induction + CRT were equally effective.

A recent individual patient data pooled analysis of four randomized clinical trials comparing induction + CRT with CRT revealed that induction + CRT was superior over CRT in reducing distant metastasis and improving OS.[17] Similar to these findings, our study also demonstrated that induction + CRT was better than CRT both in direct and network meta-analysis. However, when comparing induction + CRT with CRT + adjuvant, no significant difference was found in both original and sensitivity analysis for all endpoints, which was consistent with the findings in an individual patient data network meta-analysis.[15] Obviously, the incorporation of new evidence[11,12,14] about induction + CRT into the network meta-analysis still failed to demonstrate the superiority of induction + CRT over CRT + adjuvant. One possible explanation is that previous value regarding CRT + adjuvant is too strong since RT alone was the control arm,[4–7,39] therefore increasing the weight of CRT + adjuvant in the network comparison. Given these findings and concerns, head-to-head randomized clinical trials comparing induction + CRT with CRT + adjuvant are urgently warranted. Possibly, only results from such trials could be conclusive.

To validate the results of original analysis, we performed sensitivity analysis after excluding the study by Kwong et al[38] because a standard concurrent chemotherapy regimen of cisplatin was not used in that trial. Generally, the results of sensitivity remained valid, indicating that our meta-analysis was reliable. Of note, CRT + adjuvant was better than CRT for OS in original analysis, while they were comparable in sensitivity analysis. The reason being only one trial comparing CRT + adjuvant with CRT existed[8] after excluding the study by Kwong et al.[38] Actually, no significant difference between CRT + adjuvant and CRT was found in the original text.[8] Undoubtedly, a lack of such trials would affect the final results of network meta-analysis. Therefore, future meta-analysis should include more trials.

It should be pointed out that we could not only rely on the P-score to select treatment although we employed it to rank treatment. A treatment ranking probability would still be generated without definitive statistical significance even if differences of effect size between treatments were small and nonsignificant. Thus, we should not overinterpret the P-score in network meta-analysis.

We should also address the limitations of this study. Since we have no access to individual patient data, potentially reporting bias could be produced. To minimize such bias, we set strict criteria for study inclusion to reduce heterogeneity between studies. Another important issue should be the application of different radiotherapy technique (intensity-modulated radiotherapy vs conventional radiotherapy) across different trials which may affect the results. Moreover, we did not evaluate the endpoint of PFS because the definition of PFS varied greatly across trials. Of course, these limitations should be addressed in future studies.

Conclusion

Overall, our current study showed the indirect results of comparing CRT + adjuvant with induction + CRT in locoregionally advanced NPC and found that they were equally effective but both better than CRT alone. Future head-to-head clinical trials were needed to provide more conclusive evidence for optimal treatment strategy in advanced NPC.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Jadad/Oxford score for the 15 clinical trials

Clinical trial	Randomization method	Allocation concealment	Blinding principle	Patient dropout	Jadad score
CRT + adjuvant vs RT					
Al-Sarraf et al (1998)[1]	No	No	No	Yes	1
Kwong et al (2004)[2]	Yes	No	No	Yes	3
Wee et al (2005)[3]	Yes	Yes	No	Yes	4
Lee et al (2010)[4]	Yes	Yes	No	Yes	4
Lee et al (2011)[5]	Yes	Yes	No	Yes	4
Chen et al (2013)[6]	Yes	Yes	Yes	Yes	6
CRT vs RT					
Chan et al (2005)[7]	Yes	Yes	No	Yes	5
Kwong et al (2004)[2]	Yes	No	No	Yes	3
Zhang et al (2005)[8]	No	No	No	Yes	1
Induction + CRT vs CRT					
Hui et al (2009)[9]	Yes	Yes	No	Yes	5
Tan et al (2015)[10]	Yes	Yes	No	Yes	4
Sun et al (2016)[11]	Yes	Yes	No	Yes	5
Cao et al (2017)[12]	Yes	Yes	No	Yes	5
Frikha et al (2018)[13]	Yes	Yes	No	Yes	5
Hong et al (2018)[14]	Yes	Yes	No	Yes	5
CRT + adjuvant vs CRT					
Kwong et al (2004)[2]	Yes	No	No	Yes	3
Chen et al (2017)[15]	Yes	Yes	No	Yes	5

Abbreviations: CRT, concurrent chemoradiotherapy; RT, radiotherapy.

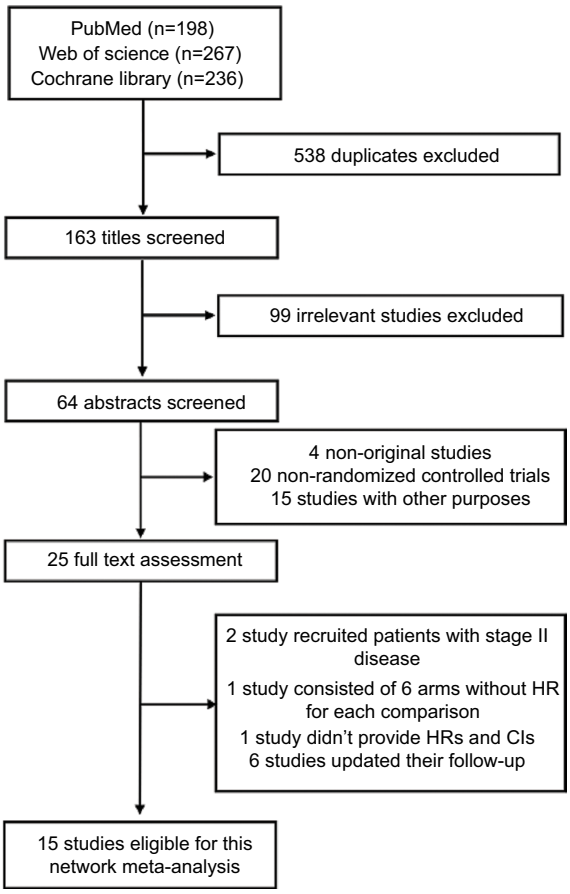

Figure S1 Flowchart of study inclusion.

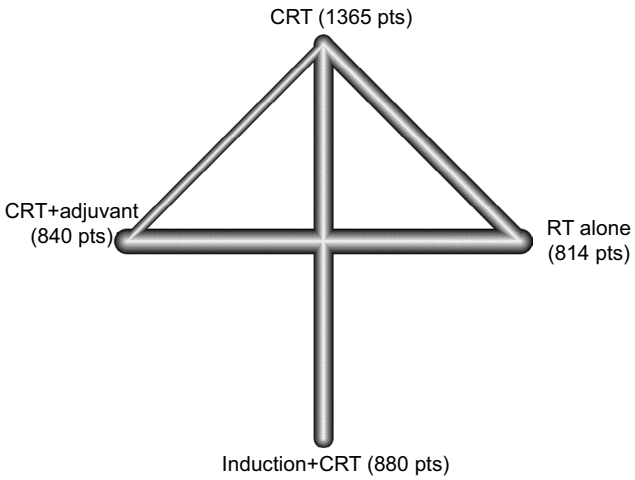

Figure S2 Graph of network comparison for overall survival in sensitivity analysis.
Abbreviations: CRT, concurrent chemoradiotherapy; RT, radiotherapy.

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