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Research Paper

Optimal Treatment Modality for Locoregionally Advanced Nasopharyngeal Carcinoma: A Literature-Based Network Meta-Analysis

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Abstract

Background: The standard care for locoregionally advanced nasopharyngeal carcinoma (LA-NPC) has not been well-established: either induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT) or CCRT followed by adjuvant chemotherapy (AC) may be the best treatments. We conducted a network meta-analysis to identity the optimal treatment for LA-NPC.

Methods: We searched electronic databases to identify eligible clinical trials involving patients with NPC randomly allocated to CCRT, CCRT + AC, IC + CCRT, or RT alone. End-points included overall survival (OS), distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS). Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were extracted. Network meta-analysis was performed using the frequentist approach for multiple treatment comparisons.

Results: In total, 11 studies involving 3165 patients were identified. IC + CCRT resulted in significantly better OS (HR, 0.65; 95% CI, 0.43-0.97) and DMFS (HR, 0.47; 95% CI, 0.31-0.73) than CCRT, without significantly increasing toxicities during CCRT. However, no significant differences were observed between IC + CCRT and CCRT + AC, or between CCRT and CCRT + AC for all the endpoints. As expected, RT alone was the least effective treatment. With regards to P-score, IC + CCRT ranked best for OS (95.3%) and DMFS (99.0%), while CCRT + AC ranked best for LRFS (79.1%); CCRT ranked third for all end-points.

Conclusions: IC + CCRT may be the most appropriate treatment for LA-NPC due to its significant OS and DMFS benefits, good compliance and acceptable toxicities.

Key words: nasopharyngeal carcinoma, locoregionally advanced, concurrent chemoradiotherapy; induction chemotherapy; adjuvant chemotherapy; network meta-analysis.

Introduction

The unique head and neck malignancy nasopharyngeal carcinoma (NPC) is rare in most western countries but common in Southern China and Southeast Asia [1, 2]. As a result of anatomical constrains and high radiosensitivity, radiotherapy (RT) is the only curative treatment for non-metastatic NPC. Control of early-stage disease is usually excellent, while the prognosis of advanced disease

remains unsatisfactory [3]. Therefore, improving the survival outcomes of locoregionally advanced NPC (LA-NPC) is a major clinical concern.

Treatment for advanced NPC has changed dramatically over the last two decades. Initially, RT alone was the sole radical therapy. Then, concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy (AC) became the standard treatment after the Intergroup 0099 study demonstrated its positive effect on 3-year overall survival (OS) [4]. Subsequently, the value of AC was proven to be limited [5-7], and CCRT with or without AC was established as the standard of care. Induction chemotherapy (IC), given before radiotherapy, has been widely investigated and used over the last decade as it has better compliance rates and facilitates early eradication of micrometastases. Encouraging results from previous studies [8-10] demonstrated IC followed by CCRT could also be an effective treatment. Given these findings, it may be reasonable to change from concurrent-adjuvant to induction-concurrent chemoradiotherapy to reduce the incidence of toxicities. However, direct trials comparing IC plus CCRT with CCRT plus AC are still lacking. Most recently, a network meta-analysis of individualized data revealed CCRT plus AC provided the highest overall survival benefit while IC plus CCRT resulted in better distant control [11]. However, three recently published articles [8, 10, 12] assessing IC were not included. Therefore, it is necessary to re-conduct the network meta-analysis using up-to-date data to establish the best treatment modality for advanced NPC.

Materials and Methods

Literature search strategy and study selection

We searched the following electronic databases to identify all potentially eligible trials: PubMed, Web of Science, the Cochrane Library, as well as the WangFang database and National Knowledge Infrastructure for Chinese literature. Detailed information on the literature search strategy and study criteria are presented in the *Supplementary Methods*. As a result of the selection criteria, the included studies mainly contained four treatment arms: IC plus CCRT, CCRT alone, CCRT plus AC, and RT alone.

Quality control and data extraction

To assess the quality of the included studies, we examined the randomization procedure, sample size estimation, adoption of blinding in study design, allocation concealment, whether intention-to-treat analysis was followed, loss to follow-up and dropout. The Jadad/Oxford quality scoring system was used to quantify study quality [13]. Three investigators (H.P, B.B.C and R.S) reviewed the published papers and extracted the data independently. Data on study design, study time, number of patients in each arm, staging information, randomization scheme, follow-up duration, treatment protocol, end-points and failure patterns were abstracted. Any discrepancies in quality assessment and data extraction were resolved by consensus.

Statistical analysis

The primary end-point was OS, defined as the duration from randomization to death from any cause. Other end-points included distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS). Survival data were expressed as hazard ratios (HRs). Traditional pairwise meta-analysis was initially conducted using Stata 13.0 (StataCorp LP, College Station, TX, USA). HRs and corresponding variance were used directly if reported in the original studies; otherwise, we extracted these data from the previous meta-analysis based on individualized data [14] using the method of Parmar et al. [15]. Heterogeneity across studies was examined using the χ^2 test and I^2 statistic. Statistically significant heterogeneity was defined as a χ^2 P-value < 0.1 or an I^2 statistic > 50%.

Network meta-analysis was performed with R software (version 3.3.3; R Foundation, Vienna, Austria) using the *netmeta* package [16, 17] and a frequentist approach [16]. Treatment effects were estimated by calculating HRs with corresponding 95% confidence intervals (CIs). Heterogeneity or inconsistency between and within designs was assessed using the Q test, which was proposed to be a generalization of Cochran's test by Rücker et al. [16]. If no heterogeneity existed (P > 0.1), a fixed-effects model was used. In case of significant heterogeneity, use of a random-effects model and sensitivity analysis were considered. The P-score, proposed by Rücker and Schwarzer [18] as a frequentist analog to surface under the cumulative ranking curve [19, 20], was adopted to rank treatment arms. The P-score of the best treatment is 100%, and the worst, 0%. Grade 3 or 4 toxicities in different treatment arms were compared using the χ^2 test. A two-sided P-value of < 0.05 was considered significant. More details of the network meta-analysis are presented in the *Supplementary Methods*.

Results

Included studies

Up to April 2017, we identified 23 potentially eligible studies in total (*Supplementary Figure S1*). The studies by Chen et al. [21] and Fountzilas et al. [22]

involving stage II NPC were excluded. Since uracil + tegafur was used as the concurrent chemotherapy regimen, the study by Kwong et al. [23] was also excluded but would be included in the sensitivity analysis. We excluded the study by Lin et al. [24] as it did not meet the inclusion criterion of unpredictable treatment allocation. The studies by Tan et al. [12] reporting only one-side 95% CI, and that by Lee et al. [25] not providing HR for each comparison were excluded. We therefore excluded this study. Moreover, updates have been made to six studies: Chan et al. [26, 27], Lee et al. [28, 29], Lee et al. [30, 31], Chen et al. [32, 33], Chen et al. [6, 34] and Zhang et al. [35, 36]. Therefore, 11 studies [4, 8-10, 26, 29, 30, 33-35, 37] were eligible for this network meta-analysis. Notably, two treatment arms receiving accelerated-fraction radiotherapy in the study by Lee et al. [30, 31] were excluded as they did not meet the inclusion criterion of conventional-fraction radiotherapy. The baseline characteristics of the 11 studies are summarized in Table 1. In total, 3165 patients were randomly assigned: 513 received IC + CCRT, 840 received CCRT + AC, 998 received CCRT, and 814 received RT alone. HR and variance were obtained from two previous meta-analysis based on individualized data [11, 14] or directly from the original text. Quality assessment of all eligible studies is presented in *Supplementary Table S1*.

Direct meta-analysis

Supplementary Figure S2 presents the results of all direct meta-analysis. Notably, between-study effect size heterogeneity only existed in the comparison of CCRT vs. RT for DMFS (I^2 = 55.9%), therefore a random-effects model was used. Compared to RT alone, CCRT + AC (OS: HR, 0.63; 95% CI, 0.53-0.74; DMFS: HR, 0.51; 95% CI, 0.39-0.64) and CCRT (OS: HR, 0.75; 95% CI, 0.58-0.91; DMFS: HR, 0.63; 95% CI, 0.34-0.92) resulted in significantly better OS and DMFS. Moreover, CCRT + AC significantly reduced locoregional recurrence compared to RT alone (HR, 0.48; 95% CI, 0.32-0.64). Compared to CCRT, IC + CCRT was associated with significantly improved OS (HR, 0.68; 95% CI, 0.46-0.91), DMFS (HR, 0.57; 95% CI, 0.39-0.76) and LRFS (HR, 0.70; 95% CI, 0.40-1.00). No significant differences in OS, DMFS or LRFS were observed between CCRT + AC and CCRT alone.

Network meta-analysis

The network analysis of the four treatment arms (CCRT, CCRT + AC, IC + CCRT, and RT) is represented in Figure 1. The CCRT arm was established as the reference group. The results of multiple treatment meta-analysis are summarized in Table 2. Inconsistency or heterogeneity were not found either within or between studies for any end-point (P > 0.1). Therefore, a fixed-effects model was adopted. The forest plot of OS, DMFS and LRFS in the network meta-analysis with different reference groups is presented in Figure 2.

Compared to CCRT, IC + CCRT resulted in significantly better OS (HR, 0.65; 95% CI, 0.43-0.97) and RT alone led to significantly poorer OS (HR, 1.32; 95% CI, 1.05-1.65). However, no differences were observed between CCRT + AC and CCRT, and CCRT + AC and IC + CCRT (*Supplementary Table S2*). The corresponding P-scores for CCRT, CCRT + AC, IC + CCRT, and RT were 38.0%, 66.4%, 95.3%, and 0.3%, indicating IC + CCRT has a higher probability of being the best treatment in terms of OS.

With regards to DMFS, the HRs for CCRT + AC, IC + CCRT, and RT compared to CCRT were 0.80 (0.58-1.11), 0.47 (0.31-0.73), and 1.26 (0.95-1.68), respectively. No significant difference in DMFS was observed between CCRT + AC and IC + CCRT (*Supplementary Table S3*), and IC + CCRT achieved the highest P-score of 99.0% for DMFS. For LRFS, a significant difference was only observed between CCRT + AC and RT alone (HR, 1.55; 95% CI, 1.17-2.06; *Supplementary Table S4*), and the P-scores for CCRT, CCRT + AC, IC + CCRT, and RT were 29.2%, 79.5%, 78.8%, and 12.6%. Therefore, IC + CCRT resulted in best OS and DMFS, and CCRT + AC, best LRFS.

Grade 3-4 acute toxicities

Due to data limitations, it was not possible to compare toxicities between the four treatment arms. Therefore, we only compared grade 3-4 acute toxicities during CCRT between the initial (CCRT and CCRT + AC treatments) and subsequent (IC + CCRT treatment) phases (*Supplementary Table S5*). Generally, patients in the subsequent phase experienced a lower rate of grade 3-4 skin (P < 0.001) and mucositis toxicities (P < 0.001) compared with those in the initial phase. Additionally, most toxicities were comparable between the two phases. Therefore, IC did not significantly increase severe toxicities during CCRT.

Sensitivity analysis

To test the stability of our results, we conducted sensitivity analysis after including the study by Kwong et al. [23]; and the results are described in the *Supplementary Results*. Notably, the conclusions remained valid after including this study. Moreover, IC + CCRT was even found to be superior to CCRT + AC for DMFS. Similarly, IC + CCRT still provided the highest OS and DMFS benefits, while CCRT + AC provided highest LRFS benefit.

Discussion

Based on all available information extracted from the included studies and two previous meta-analysis with individualized data, we conducted multiple comparisons between CCRT, CCRT + AC, IC + CCRT and RT alone to assess the optimal treatment modality for LA-NPC. IC + CCRT provided the largest OS and DMFS benefits while CCRT + AC provided the largest LRFS benefit. Sensitivity analysis after including the study by Kwong et al. [23] also obtained similar outcomes. Good consistency and heterogeneity were observed between the direct and network meta-analysis for all end-points, indicating these findings are robust.

Table 1. Summary of the 11 studies included in this network meta-analysis

Study	No. of patients	Study time	Median follow-up duration months)	Patient stage	Radiotherapy	Induction	Chemotherapy	
							Concurrent	Adjuvant
CCRT + AC vs. RT								
Al-Sarraf et al. [5]	193[a]	1989-1995	32.4	AJCC III-IV	66-70 Gy at 1.8-2.0 Gy/f/day (5f/qw)	None	DDP 100 mg/m² d1 q3w × 3	DDP 80 mg/m² d1 + Fu 1000 mg/m²/day d1-4 civ q3w × 4
Wee et al. [30]	221	1997-2003	38.4	AJCC III-IV, T3-4Nx or TxN2-3	70 Gy/35f at 2 Gy/f/day (5f/qw) for 7 weeks	None	DDP 25 mg/m²/day for 4 days or 30/30/40 mg/m²/day for 3 days q3w × 3	DDP 20 mg/m²/day for 4 days + Fu 1000 mg/m²/day d1-4 q3w × 3
Lee et al. [20,21]	348	1999-2004	70.8	AJCC III-IV, any T, N2-3	≥ 66 Gy at 2.0 Gy/f/day (5f/qw) + additional boosts to parapharyngeal space, primary or nodal sites when indicated not exceeding 20 Gy	None	100 mg/m² d1 q3w × 3	DDP 80 mg/m² d1 + 1000 mg/m²/day d1-d4 civ q4w × 3
Lee et al. [22,23]	93	1999-2004	75.6	AJCC III-IV, T3-4N0-1	≥ 66 Gy at 2.0 Gy/f/day (5f/qw) + additional boosts to parapharyngeal space, primary or nodal sites when indicated not exceeding 20 Gy	None	100 mg/m² d1 q3w × 3	DDP 80 mg/m² d1 + 1000 mg/m²/day d1-d4 civ q4w × 3
Chen et al. [24,25]	316	2002-2005	70	AJCC III-IV, T1-4, N0-3	≥ 68 Gy at 2.0 Gy/f/day (5f/qw) for 7 weeks + additional boost in case of parapharyngeal extension, residual neck and/or nasopharyngeal tumor	None	100 mg/m² d1 q3w × 3	DDP 80 mg/m² d1 + Fu 800 mg/m²/day d1-5 civ q3w × 3
CCRT vs. RT								
Chan et al. [18,19]	350	1994-1997	66	Ho's N2-3 or N1 with nodal size ≥ 4cm	66 Gy + additional boost in case of parapharyngeal extension, residual neck or nasopharyngeal tumor	None	DDP 40 mg/m² d1 weekly for 8 weeks	None
Zhang et al. [27,28]	115	2001-2003	114	AJCC III-IV, any T, N2-3	70-74 Gy at 2 Gy/f/day (5f/qw) + additional boost in case of parapharyngeal extension, residual neck or nasopharyngeal tumor	None	Oxaliplatin 70 mg/m² d1 weekly for 6 weeks	None
IC + CCRT vs. CCRT								
Hui et al. [10]	65	2002-2004	51.6	AJCC III-IVB, T1-4, N0-3	66 Gy/33f at 2 Gy/f/day (5f/qw) + additional boost of 20 Gy/10f to parapharyngeal	Docetaxel 75 mg/m² d1 + DDP 75 mg/m² d1 q3w × 2	40 mg/m² d1 qw × 8	None
Sun et al. [11]	480	2011-2013	45	AJCC III-IVB, except T3-4N0	≥ 66 Gy at 2.00-2.35 Gy/f/day for 6-7 weeks	Docetaxel 60 mg/m² d1 + DDP 60 mg/m² d1 + Fu 600 mg/m²/day d1-5 civ q3w × 3	100 mg/m² d1 q3w × 3	None
Cao et al. [9]	476	2008-2015	50	AJCC III-IVB, except T3N0-1	≥ 66 Gy at 2.0-2.33 Gy/f/day	DDP 80 mg/m² d1 + Fu 800 mg/m²/day d1-5 civ q3w × 3	80 mg/m² d1 q3w × 3	None
CCRT + AC vs. CCRT								
Chen et al. [7,26]	508	2006-2010	68.4	AJCC III-IVB except T3-4N0	≥ 66 Gy at 2.0-2.27 Gy/f/day (5f/qw) for 6-7 weeks	None	DDP 40 mg/m² d1 weekly for up to 7 weeks	DDP 80 mg/m² d1 + Fu 800 mg/m²/day d1-5 civ q4w × 3

Abbreviations: CCRT = concurrent chemoradiotherapy; IC = induction chemotherapy; AC = adjuvant chemotherapy; RT = radiotherapy; AJCC = American Joint Committee on cancer; f = fraction; DDP = cisplatin; Fu = fluorouracil; civ = continuous i.v.; q3w = every 3 weeks; q4w = every 4 weeks; AUC = area under concentration-time curve. 2D-RT = two-dimensional radiotherapy; IMRT = intensity-modulated radiotherapy.

[a] 193 patients were registered, but only 147 were analyzed.

Table 2. Summary of network meta-analysis for the three end-points

Treatment arm	OS	DMFS	LRFS
P value for overall heterogeneity/inconsistency	0.44	0.84	0.52
P value for heterogeneity (within designs)	0.37	0.76	0.45
P value for heterogeneity (between designs)	0.63	0.76	0.59
CCRT			
HR	1.00	1.00	1.00
P-score (%)	38.0	34.5	29.2
CCRT + AC			
HR (95% CI)	0.86 (0.66-1.12)	0.80 (0.58-1.11)	0.72 (0.46-1.13)
P-score (%)	66.4	64.7	79.5
IC + CCRT			
HR (95% CI)	0.65 (0.43-0.97)	0.47 (0.31-0.73)	0.69 (0.40-1.19)
P-score (%)	95.3	99.0	78.8
RT			
HR (95% CI)	1.32 (1.05-1.65)	1.26 (0.95-1.68)	1.12 (0.75-1.66)
P-score (%)	0.3	1.8	12.6

Abbreviations: OS = overall survival; DMFS = distant metastasis-free survival; LRFS = locoregional recurrence-free survival; CCRT = concurrent chemoradiotherapy; AC = adjuvant chemotherapy; IC = induction chemotherapy; RT = radiotherapy. HR = hazard ratio; CI = confidence interval.
A fixed-effects model was used for overall survival, distant metastasis-free survival and locoregional recurrence-free survival.

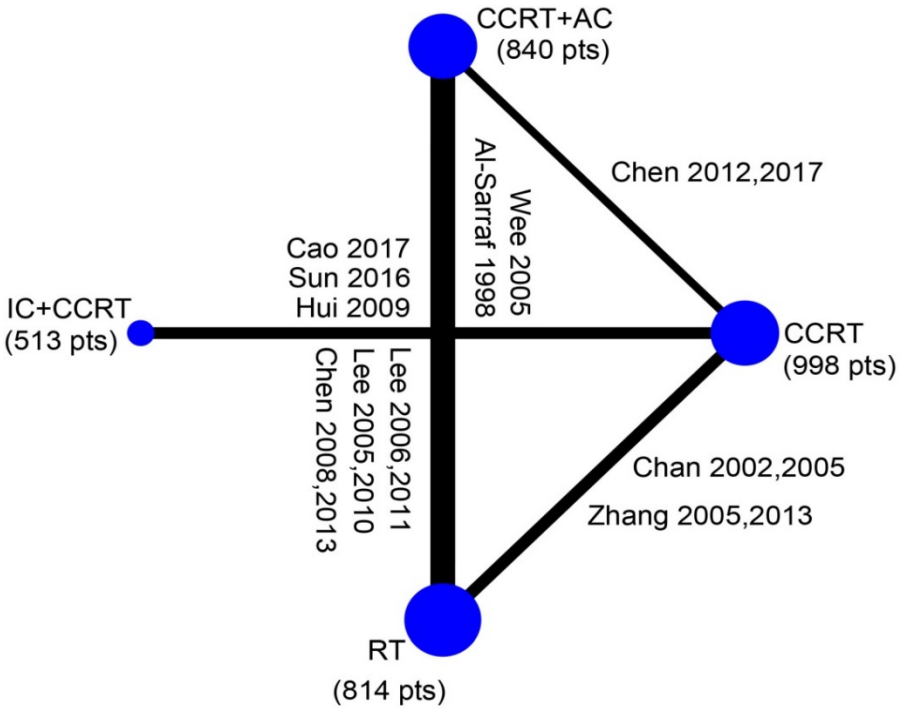

Figure 1. Graphical presentation of the trial network for overall survival. The sizes of the blue nodes represent the number of patients in each treatment arm. The width of the lines between nodes is proportional to the number of comparisons. Only two treatment arms receiving conventional-fraction radiotherapy in the study by Lee et al. (2011) were included in this study. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; RT, radiotherapy.

Compared to CCRT, CCRT + AC did not result in significantly better OS, DMFS or LRFS, indicating the value of adding AC to CCRT may be limited. Notably, the recommended AC regimen, cisplatin with fluorouracil (PF)–which was first proven in the Intergroup Study 0099–was used in all included studies [4]. However, a randomized phase III trial conducted in head and neck cancer showed this combined AC regimen did not improve survival outcomes compared with either single-agent regimen individually [38]. Therefore, it is reasonable to infer the adjuvant PF regimen is insufficiently effective in terms of preventing distant failure and improving survival in both head and neck cancers and NPC. The rates of compliance to three cycles of AC range from approximately 52-63% [4, 6, 28, 32, 37], and many patients also require dose reductions. Therefore, the actual benefits of AC are reduced by severe toxicities and poor compliance. Furthermore, the favorable survival outcomes of CCRT may also dilute the benefit of AC.

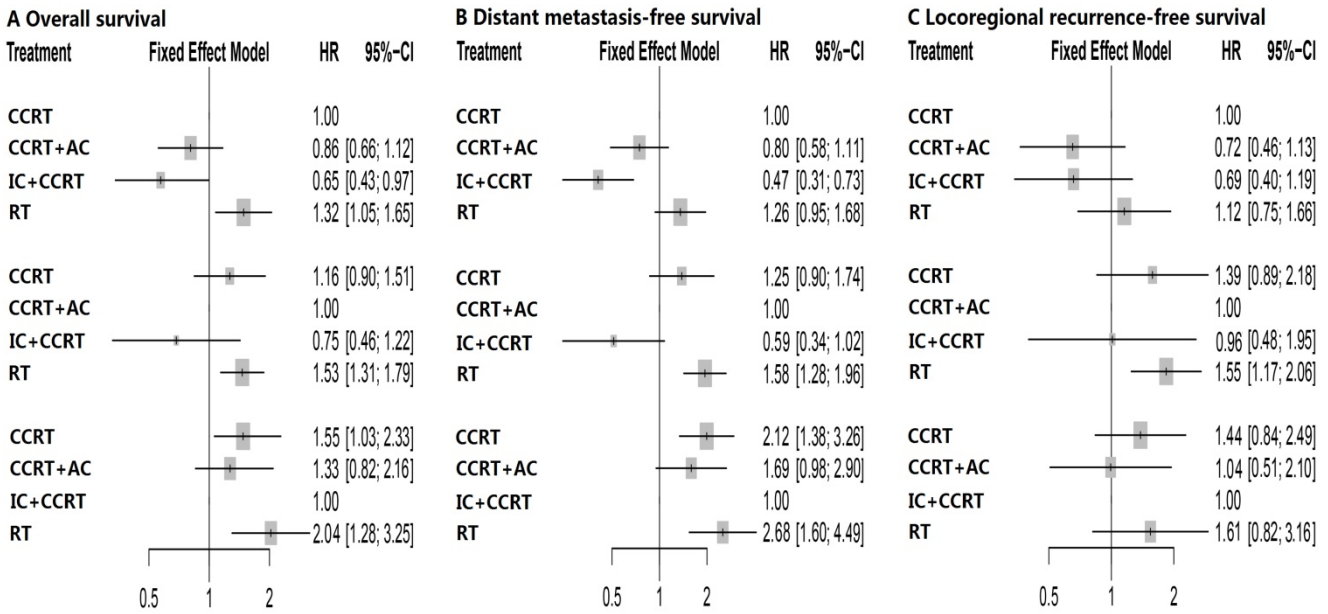

Figure 2. Forest plot of network meta-analysis for overall survival, distant metastasis-free survival and locoregional recurrence-free survival with different reference groups. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; RT, radiotherapy.

In the last decade, intensity-modulated radiotherapy (IMRT) has revolutionized the management of NPC, and distant metastasis has become the predominant failure pattern for advanced disease [39, 40]. Consequently, IC has attracted much attention as it can eradicate micrometastases during early treatment and shrink tumor volume to improve radiation dose coverage. In this study, IC + CCRT achieved significantly better OS and DMFS than CCRT in both the direct and network meta-analyses, while LRFS was comparable between arms. This conclusion was different from the study by Ribassin-Majed et al. [41], and that is because the evidence for IC in our study was stronger since two trials [8, 10] regarding IC were included. Therefore, IC effectively improves survival outcomes, and does not significantly increase acute toxicities during CCRT. However, we can also learn two key points from previously negative studies [12, 22, 42, 43]. First, it is possible that only high-risk patients benefit from IC. In studies achieving positive results [8, 10, 44], patients with T3-4N0 or T3N1 were usually excluded, or only patients with stage IV disease were included. However, Tan et al. [12] and Fountzilas et al. [22] obtained negative results since low-risk patients (stage IIB or T3-4N0) were included. Secondly, it is critical to select an effective induction regimen, such as docetaxel plus cisplatin with fluorouracil (TPF), which has been proven to be superior to PF in head and neck cancer [45-47]. Moreover, gemcitabine with cisplatin (GP) has been proven superior to PF in recurrent or metastatic NPC [48]. Thus, selection of effective chemotherapy regimens for appropriate patients should be a priority. Pre-treatment plasma Epstein-Barr virus (EBV) DNA has recently been confirmed to be an effective indicator of the response to IC [49, 50], although randomized trials are warranted.

CCRT is inadequate for high-risk patients with LA-NPC; additional induction or adjuvant chemotherapy is a reasonable approach [51]. Therefore, either CCRT + AC or IC + CCRT is potentially the most appropriate treatment. However, clinical trials directly comparing CCRT + AC with IC + CCRT are lacking. In this study, survival outcomes did not differ significantly between CCRT + AC and IC + CCRT for any end-point. However, after including the study by Kwong et al. [23], IC + CCRT was more effective than CCRT + AC for reducing distant metastasis. Therefore, our findings indicate IC + CCRT may be slightly superior to, or at least as efficacious as, CCRT + AC. Given its lower toxicities and better compliance, it is reasonable to recommend IC + CCRT as the preferred treatment for LA-NPC.

RT was poorer than CCRT, CCRT + AC and IC + CCRT and for all end-points. Therefore, RT alone should not be recommended whenever possible. However, while clinical treatment outcomes are indicated by the P-score of each treatment arm, if differences in effect size between treatments were small and non-significant, a treatment ranking probability would still have been generated without definitive statistical meaning. Compared to previous network meta-analyses [7, 52-54], the main strength of this work is inclusion of studies comparing IC + CCRT with CCRT alone [8, 10]. Though the NCCN

guidelines consider only level III evidence is available for IC + CCRT at present, our findings provided stronger evidence in favor of this treatment.

The limitations of this study should be addressed: HRs and corresponding 95% CIs were mainly extracted from the original studies without access to individualized data, except for two studies [10, 34], which could produce reporting bias. Moreover, progression-free survival (PFS) could not be assessed as the definitions of PFS varied between studies. To minimize these limitations, we set strict inclusion criteria and three investigators independently reviewed and extracted data. Furthermore, sensitivity analysis confirmed the findings were valid.

Conclusion

In summary, this network meta-analysis demonstrates IC + CCRT is superior to CCRT provides highest OS and DMFS benefits while CCRT + AC provides highest LRFS benefit. Therefore, IC + CCRT may be the most appropriate treatment for LA-NPC. Our ongoing trial (NCT01872962) may be more informative.

Abbreviations

NPC: nasopharyngeal carcinoma; RT: radiotherapy; LA-NPC: locoregionally advanced nasopharyngeal carcinoma; CCRT: concurrent chemoradiotherapy; AC: adjuvant chemotherapy; OS: overall survival; IC: induction chemotherapy; DMFS: distant metastasis-free survival; LRFS: locoregional relapse-free survival; HRs: hazard ratios; CIs: confidence intervals; IMRT: intensity-modulated radiotherapy; PF: cisplatin with fluorouracil; TPF: docetaxel plus cisplatin with fluorouracil; GP: gemcitabine with cisplatin; EBV: Epstein-Barr virus; PFS: progression-free survival.

Supplementary Material

Supplementary methods, figures and tables.
http://www.jcancer.org/v09p0540s1.pdf

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Author contributions

H.P, B.B.C and L.L.T contributed to study design and conception. H.P, B.B.C and R.S searched the electronic database and extracted data independently. H.P, X.L, R.G, Y.Z, Y.P.M and A.H.L analyzed and interpreted the data. H.P and B.B.C contributed to manuscript editing. R.S, G.Q.Z and W.H.H contributed to quality control and review of the data and manuscript. All authors have read and approved the final version of the submitted manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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