The efficacy and safety of concurrent chemoradiotherapy with induction chemotherapy *vs.* concurrent chemoradiotherapy alone for locally advanced nasopharyngeal carcinoma: a systematic-review and meta-analysis

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Background: Although nasopharyngeal carcinoma (NPC) is very sensitive to radiotherapy, patients with advanced NPC still need concurrent chemoradiotherapy (CCRT). The induction chemotherapy (IC) before CCRT can possiblly reduce the distant metastasis rate and improve the survival rate, but the results of studies varied. In this meta-analysis, we included controlled clinical studies to systematically evaluate the gain effect of it.

Methods: The PubMed, Web of Science, Wiley online library, Elsevier, CNKI, and Clinicaltrials. gov databases were electronically searched using keywords "neoadjuvant chemotherapy/induction chemotherapy" and "concurrent chemoradiotherapy" and "nasopharyngeal carcinoma" for articles from the date of establishment of the database to January, 2022. The inclusion criteria was established according to the PICOS principles. The complete response rate, progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) were used as the main efficacy indicators for analysis.

Results: Thirteen articles were included with a total of 7,197 patients, including 3,764 patients who took IC + CCRT and 3,433 patients who received CCRT alone. Two randomized controlled trials (RCTs) included had low risk of bias and 11 cohort studies had some concerns of risk. Meta-analysis showed that IC did not significantly increase the complete response rate [risk ratio (RR) =1.03, 95% confidence interval (CI): 0.96–1.11, P=0.336], the pooled hazard ratio (HR) of IC as a prognostic factor predicting PFS was (HR =0.87, 95% CI: 0.78–0.96, P=0.214), and DMFS (HR =0.76, 95% CI: 0.57–0.96, P=0.004), and OS (HR =0.82, 95% CI: 0.73–0.92, P=0.036). IC increased the adverse effects experienced by patients (RR =1.22, 95% CI: 1.00–1.47, P=0.045).

Discussion: The use of IC before CCRT provided a good effect for NPC patients with tumor, node & metastasis (TNM) stages III and IV, but there was no significant gain for patients with stage II. In addition, the application of IC will increase the toxicity in the oral cavity, digestive tract, and bone marrow, and should be well considered about the toleration of patients. Due to the limitations of this study, more literatures with better quality are needed for further explore into this topic.

Keywords: Local nasopharyngeal carcinoma; concurrent chemoradiotherapy (CCRT); induction chemotherapy

Introduction

Locoregional nasopharyngeal carcinoma (LNC) is a primary malignant tumor of the mucosal epithelium in the nasopharynx, mostly occurring in the parietal and lateral walls of the nasopharynx, especially in the pharyngeal recess site. Its lesion types can be divided into nodular, ulcerative, and submucosal invasive types, with squamous cell carcinoma as the main pathological type and adenocarcinoma representing only a very small number of cases (1,2). Nasopharyngeal carcinoma tends to occur in the yellow race; statistics (3) show that 80% of nasopharyngeal carcinomas occurs in China. Nasopharyngeal carcinoma (NPC) is very sensitive to radiotherapy, and early NPC can be treated with radiotherapy alone. However, advanced NPC usually requires a comprehensive treatment mode of concurrent radiotherapy and chemotherapy to take effect.

Concurrent chemoradiotherapy (CCRT) can significantly improve the survival rate of patients and has become the standard treatment mode for advanced NPC (4). Although, for some patients with large tumors at presentation, CCRT cannot completely eliminate the tumor and may be harmful to the surrounding tissues, so 2–3 cycles of induction chemotherapy (IC) may be performed first followed by CCRT. IC, or neoadjuvant chemotherapy, has the advantages of no radiotherapy-induced fibrosis, which is conducive to the distribution and utilization of chemotherapeutic drugs in the primary nasopharyngeal carcinoma tumor. This increases the sensitivity and tolerance of patients to chemotherapy, and reduces the local and regional tumor burden, thereby improving the local control rate (5).

A previous case-control study by Li *et al.* (6) has reported that the addition of IC prior to CCRT can reduce the rate of distant metastasis and improve the survival rate of patients with nasopharyngeal carcinoma. However, another study by Zhang *et al.* (7) has suggested that for specific patients (NPC with chronic hepatitis B infection), IC does not provide a significant efficacy gain for CCRT, but increases the toxicity and liver burden. A meta-analysis is the best way to resolve the controversies (8). Therefore, we conducted this meta-analysis to further explore the efficacy and safety of IC + CCRT *vs.* CCRT alone, and we also tried to perform subgroup analysis of different stages of LNC, different age levels, and different IC chemotherapy regimens.

We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-604/rc).

Methods

Inclusion of studies

The included studies were limited according to the five aspects of PICOS (participants, interventions, comparisons, outcomes, and study design). (I) Study design: we included randomized controlled trials (RCTs) and observational cohort studies. Case series, case reports, systematic reviews, experience summaries, and expert opinions and consensus were not included in the study. (II) Participants: all of the study subjects were patients with locally advanced nasopharyngeal carcinoma (stage II–IV), without distant metastasis. We did not limit the age or disease stage of the patients, and the subgroup analysis was performed according to the stage of disease, also the age of the patients. (III) Interventions and comparisons: there were at least two cohorts of IC + CCRT and CCRT alone in the included studies (for RCT studies, it was called two groups). Since the IC regimens varied between different studies, we recorded the specific regimen of IC, chemotherapy cycles (circles), time intervals for further analysis. Furthermore, we did not limit the regimen of chemoradiotherapy in CCRT. Studies of combination therapy with other drugs while taking IC, such as the addition of combination therapy with nimotuzumab to IC, were excluded. (IV) Outcomes: we used complete response rate, progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) as the main efficacy indicators, and the incidence of Grade 3 or 4 adverse events or above was the secondary indicator.

Literature search strategy

The PubMed, Web of Science, Wiley online library, Elsevier databases, and Chinese National Knowledge Infrastructure (CNKI) were searched by computer to include the latest clinical research. We also searched for literature on this topic on Clinicaltrials.gov. The search method was a keyword rapid search, and the input keywords were as follows: "neoadjuvant chemotherapy/induction chemotherapy" and "concurrent chemoradiotherapy" and "nasopharyngeal carcinoma". We did not limit the period of literature publication, and searched the above databases from the date of establishment of the database to January, 2022.

Literature selection and data extraction

After obtaining the full texts of the articles, two researchers

independently completed the inclusion and screening of the studies. Any inconsistencies in this process were resolved through agreement by negotiation with a third researcher. Excel 2020 (released by Microsoft Corp). was used to extract the data, which included the following contents: (I) basic study data: publication time, author, and region; (II) characteristics of the study subjects: age, gender, disease stage, smoking history, T stage, and N stage; (III) study intervention methods: IC cycle, concurrent cycle, drug type, drug dose, and radiotherapy regimen and dose; and (IV) outcome data: Complete response rate, PFS, DMFS, OS, and adverse events. The PFS, DMFS, OS should be manifested by hazard ratio (HR), we pooled the HR of studies to perform the meta-analysis. In the process of data extraction, if no specific data was provided in the literature, the data were obtained according to the address specified in the literature. If the data could not be obtained, the original author of the study was contacted, and if the data still could not be obtained, the literature was excluded. We did not consider it possible to derive data from the graphical (Kaplan-Meier) presentation of data trends, unless otherwise indicated on the graphical presentation.

Risk of bias

We used the Cochrane risk of bias 2.0 scale (9) to assess the quality of RCTs and cohort studies, with an overall bias assessment of "low risk of bias", "some concerns", and "high risk of bias". We consider the study with "high risk of bias" as with low quality and excluded it.

Statistical methods

I^2 test analysis and Q test were used to assess the heterogeneity between different studies. $I^2<50\%$ or $P\geq0.1$ indicated that the heterogeneity was not statistically significant, signifying that there was no (or acceptable) heterogeneity between the literatures. The outcome indicators of complete response rate and adverse events rate in this study were pooled with risk ratio (RR) effect size, and PFS, DMFS, OS with the HR effect size, all with 95% confidence interval (CI) calculated, and $P<0.05$ (both sided) indicating the difference statistically significant. If there was no statistical heterogeneity in the included studies, the fixed-effect model was used, and if there was heterogeneity, the random-effects model was used. In this study, STATA 16.0 software (released by StataCorp LLC, TX77845, USA) was used as the analysis tool to present the

analysis results in the form of a forest plot. We eliminated the studies one-by-one to perform the heterogeneity investigation and sensitivity analysis. Subgroup analysis was introduced to investigate the heterogeneity also. The publication bias analysis was conducted by Egger's test.

Results

Literature screening results

This study initially retrieved 797 articles, and 13 studies were finally included (6-7,10-20). The selection flow chart is shown in *Figure 1*. Some studies (21,22) were single-arm studies, which could not provide comparison between the two groups of data, and therefore excluded. One study (23) was a systematic review, which could not provide data, and was excluded. Moreover, some studies (24,25) provided a comparison of efficacy using different chemotherapeutic drug regimens in IC + CCRT, but could not provide a comparison of the efficacy between IC + CCRT and CCRT alone, and were also excluded. We did not list all of the excluded articles, but only listed five representative studies.

Basic characteristics of literatures

As shown in *Table 1*, a total of 7,197 patients were included in this study, including 3,764 patients who received IC + CCRT and 3,433 patients who received CCRT alone. The TNM grade was II–IV, and the average follow-up time was 15–76.8 months. The included 2 RCTs all with low risk of bias, and 11 cohort studies with some concerns of risk.

Meta-analysis results

Complete response rate

Five studies (10-11,13-14,16) reported the complete response rate of IC + CCRT and CCRT alone, and there was no statistical heterogeneity between the articles ($I^2=0\%$, P=0.514), and thus, fixed-effect mode analysis was used. As shown in *Figure 2*, there was no significant difference in the complete response rate between IC + CCRT and CCRT alone in NPC patients (RR =1.03, 95% CI: 0.96–1.11, P=0.336).

PFS

PFS indicators were reported in 10 of the included studies (6-7,10-11,14-18,20), and there was statistical heterogeneity between the articles ($I^2=39.4\%$, P=0.086). Therefore,
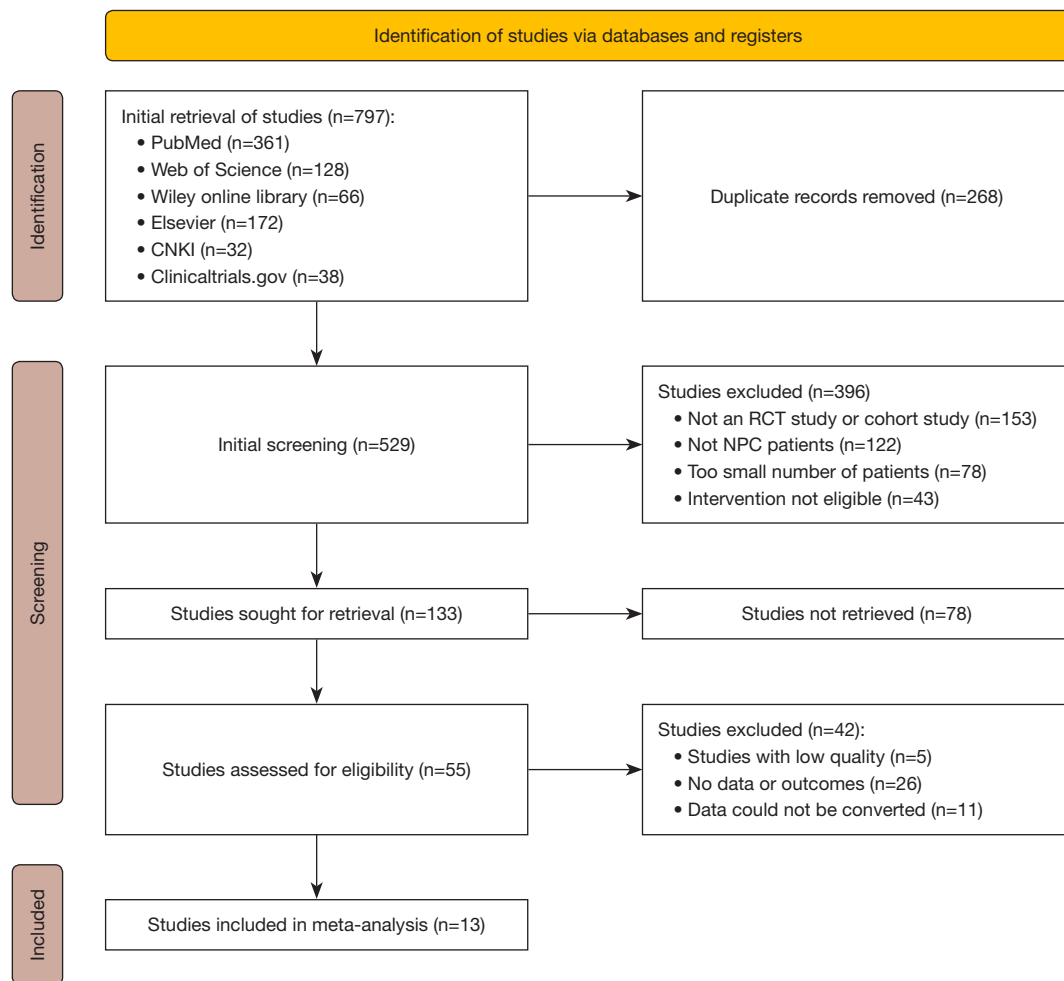
Figure 1 Literature selection flow chart. NPC, nasopharyngeal carcinoma.

by using fixed-effect mode, the pooled HR of IC as a prognostic factor predicting PFS for NPC patients was (HR =0.87, 95% CI: 0.78–0.96, P=0.214), as shown in *Figure 3*.

DMFS

DMFS indicators were reported in 9 studies (6-7,10,12,14-17,20). There was statistical heterogeneity between the articles (I^2=53.9%, P=0.026). As shown in *Figure 4*, by using random-effect mode, the pooled HR showed that IC was an independent prognostic factor predicting better for NPC patients (HR =0.76, 95% CI: 0.57–0.96, P=0.004).

OS

OS indicators were reported in 12 of the included studies (6-7,10-12,14-20), and there was statistical heterogeneity

between the articles (I^2=35.6%, P=0.106). Therefore, using fixed-effect mode combined analysis the pooled HR of OS was HR =0.82 (95% CI: 0.73–0.92, P=0.036).

The studies were divided into stage II, stage III, stage IV, and stage III–IV according to TNM stage. As shown in *Figure 5*, the HR of OS between IC + CCRT and CCRT alone were as follows: stage II (HR =1.06, 95% CI: 0.45–1.67, P= 0.375); stage III (HR =1.23, 95% CI: 0.96–1.49, P=0.068); stage IV (HR =0.80, 95% CI: 0.67–0.93, P=0.018); and stage III–IV (HR =0.71, 95% CI: 0.55–0.86, P=0.002).

According to the study type, the included studies were divided into two subgroups: RCTs and cohort studies. As shown in *Figure 6*, the HR of IC for different study types were HR =0.75 (95% CI: 0.54–0.96, P=0.114) for RCTs, while HR =0.84 (95% CI: 0.74–0.94, P=0.110) for cohort studies.

Table 1 Basic study characteristics, patient characteristics, intervention measures, outcome indicators, and quality scores of the included literatures

| Author	Year of publication	Type of study	TNM stage	Age (years)	Population (E/C)	Induction chemotherapy regimen	Median follow-up time (months)	Outcome indicators	RoB 2.0
Li et al. (6)	2018	Retro	Stage III–IV	17.28 [8–21]	43:43	TPF	51.5	b, c, d, e	Some concerns of risk
Zhang et al. (7)	2017	Retro	Stage III–IV	44 [39–55]	70:70	TPF or PF or TP	61	b, c, d	Some concerns of risk
Sun et al. (10)	2016	RCT	Stage III–IV	44 [39–50]	241:239	TPF	45	a, b, c, d	Low risk of bias
Ou et al. (11)	2016	Retro	Stage III–IV	49 [18–75]	58:48	TPF	76.8	a, b, c, d	Some concerns of risk
Lan et al. (12)	2016	Retro	Stage IV	46 [13–78]	406:196	TPF	52.3	c, d	Some concerns of risk
Kawahira et al. (13)	2017	Retro	Stage III–IV	57 [18–92]	12:16	TPF	36.4	a, e	Some concerns of risk
Hong et al. (14)	2018	RCT	Stage IV	53.1 [30–80]	239:240	TPF	72.0	a, b, c, d, e	Low risk of bias
Jin et al. (15)	2020	Retro	Stage II	54.3 [33–67]	195:250	PF or TP or TPF	15	b, d, e	Some concerns of risk
Zhang et al. (16)	2017	Retro	Stage III–IV	47.30±10.42	178:84	PF or TP or TPF	29.02	a, b, c, d	Some concerns of risk
Li et al. (17)	2018	Retro	Stage II	48.6	78:95	TPF	64.7	b, c, d, e	Some concerns of risk
Xia et al. (18)	2019	Retro	Stage III	48 [37–62]	1,416:986	TPF	67	b, d	Some concerns of risk
Xia et al. (18)	2019	Retro	Stage IV	48 [35–60]	676:902	TPF or PF or TP	67	b, d	Some concerns of risk
Wang et al. (19)	2017	Retro	Stage III–IV	67.6±5.3	82:82	TP	52.5	e	Some concerns of risk
Wang et al. (20)	2020	Retro	Stage III–IV	35–58	38:92	TPF	59	b, c, d, e	Some concerns of risk

Outcome indicators: a, complete response; b, progression-free survival; c, distant metastasis-free survival; d, overall survival; e, any grade 3 or 4 adverse events. TNM, tumor node and metastases; E/C, experimental group/control group; RCT, randomized controlled trial; TPF, docetaxel, cisplatin, and fluorouracil chemotherapy; PF, cisplatin and fluorouracil; TP, docetaxel and cisplatin; Retro, retrospective study, RoB, risk of bias.

Serious adverse reactions

A total of six studies (6,13-15,17,19) reported any grade 3 or 4 adverse events, and there was statistical heterogeneity between the articles (I^2=64.8%, P=0.014). Therefore, using random-effect mode combined analysis, we found that there was a statistically significant difference in the incidence rate of serious adverse reactions between IC + CCRT and CCRT alone in NPC patients (RR =1.22, 95% CI: 1.00–1.47, P=0.045), as shown in *Figure 7*.

Heterogeneity investigation and sensitivity analysis

In the analysis of OS outcome indicators, no statistically significant heterogeneity was found between the included studies. We introduced subgroups by study type to investigate if risk of bias played a role in the analysis of effect sizes. However, the result showed there was no difference between the two subgroups, which suggested the risk of bias played little effect on the results. The sensitivity analysis also showed no sign of impact on the effect sizes by
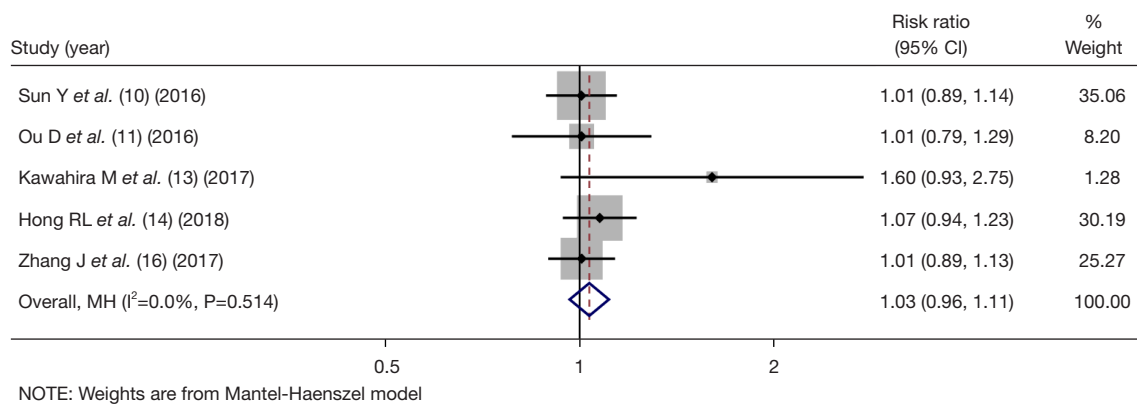
Figure 2 Comparison of the effect of IC + CCRT and CCRT alone on the complete response rate in patients. IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy.
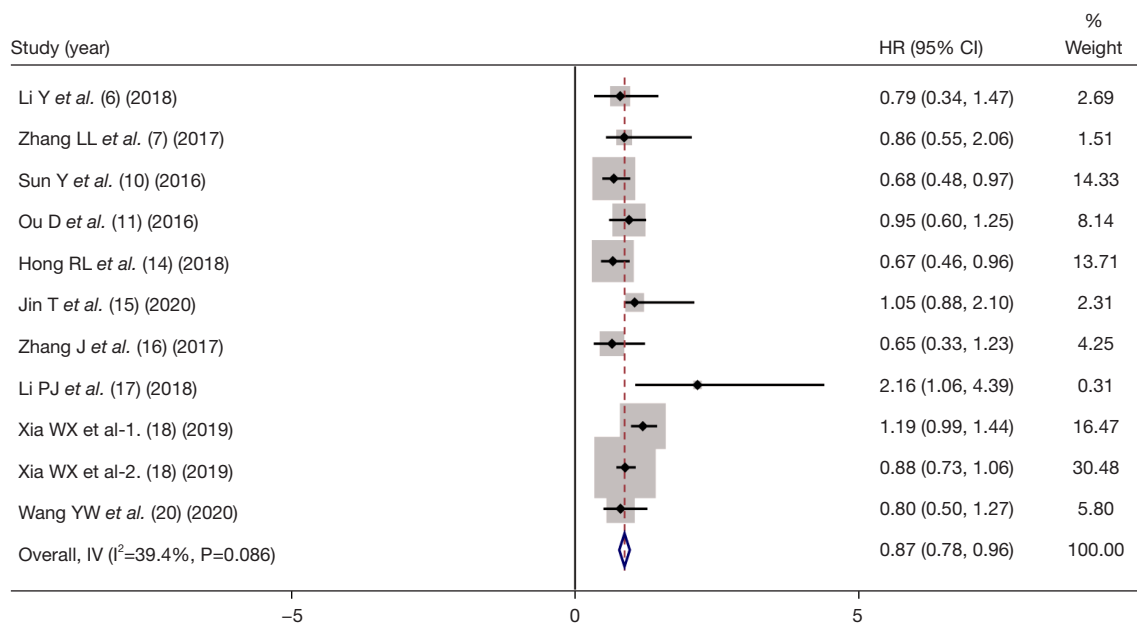
Figure 3 Pooled HR of IC as an prognostic factor predicting PFS for NPC patients. IC, induction chemotherapy; NPC, nasopharyngeal carcinoma; PFS, progression-free survival; HR, hazard ratio.

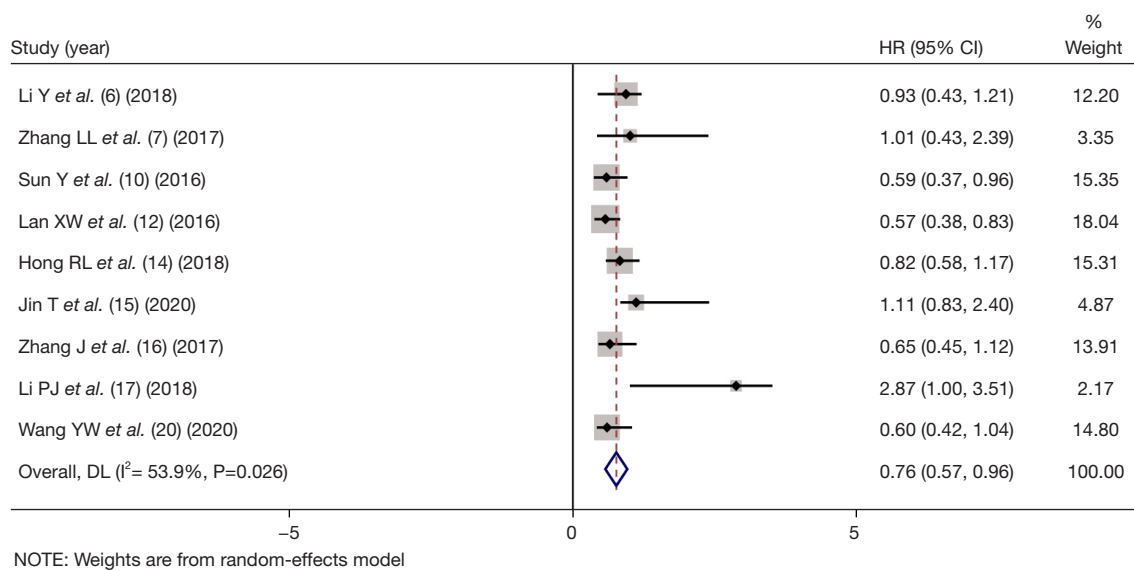eliminating studies one by one, as shown in *Figure 8*.

Analysis of publication bias

In the analysis of OS indicators, the Egger's test showed that both sides were evenly distributed, and P=0.891, suggesting that there was no publication bias, as shown in *Figure 9*.
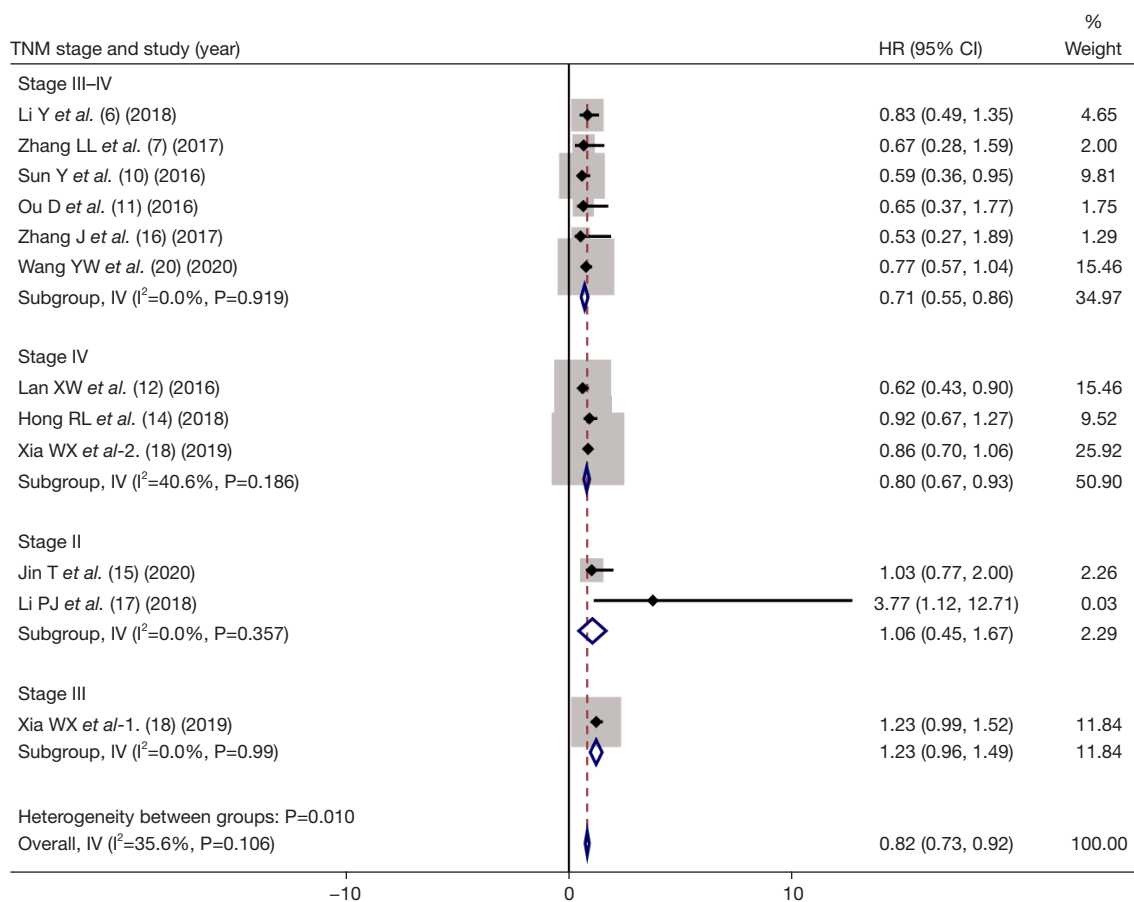
Discussion

Although NPC is highly sensitive to radiotherapy, 70%

of NPC patients are at an advanced stage at the time of diagnosis, with strong tumor invasiveness and risk of metastasis to the hematologic and lymphatic systems. Only CCRT can inhibit the primary lesion, control distant metastasis of the tumor, and improve the efficacy of treatment (26). IC refers to chemotherapy used before radiotherapy, and its role is to inhibit the implantation of tumor cells, thereby killing these tumor cells in the systemic circulation and reducing subclinical metastases. The use of chemotherapy in untreated patients has good compliance

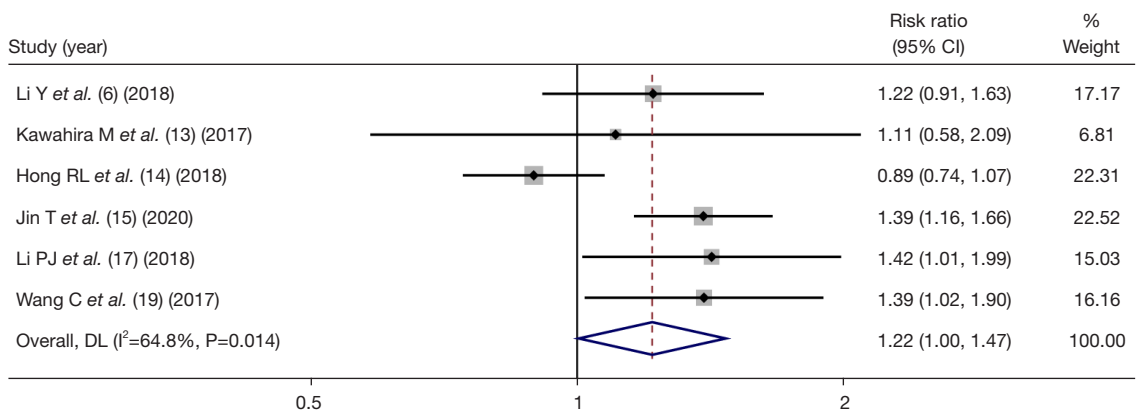| Study (year)		HR (95% CI)	% Weight
Li Y *et al.* (6) (2018)		0.93 (0.43, 1.21)	12.20
Zhang LL *et al.* (7) (2017)		1.01 (0.43, 2.39)	3.35
Sun Y *et al.* (10) (2016)		0.59 (0.37, 0.96)	15.35
Lan XW *et al.* (12) (2016)		0.57 (0.38, 0.83)	18.04
Hong RL *et al.* (14) (2018)		0.82 (0.58, 1.17)	15.31
Jin T *et al.* (15) (2020)		1.11 (0.83, 2.40)	4.87
Zhang J *et al.* (16) (2017)		0.65 (0.45, 1.12)	13.91
Li PJ *et al.* (17) (2018)		2.87 (1.00, 3.51)	2.17
Wang YW *et al.* (20) (2020)		0.60 (0.42, 1.04)	14.80
Overall, DL (I^2= 53.9%, P=0.026)		0.76 (0.57, 0.96)	100.00

NOTE: Weights are from random-effects model

Figure 4 Pooled HR of IC as a prognostic factor predicting DMFS for NPC patients. IC, induction chemotherapy; NPC, nasopharyngeal carcinoma; DMFS, distant metastasis-free survival; HR, hazard ratio.

TNM stage and study (year)		HR (95% CI)	% Weight
Stage III–IV			
Li Y *et al.* (6) (2018)		0.83 (0.49, 1.35)	4.65
Zhang LL *et al.* (7) (2017)		0.67 (0.28, 1.59)	2.00
Sun Y *et al.* (10) (2016)		0.59 (0.36, 0.95)	9.81
Ou D *et al.* (11) (2016)		0.65 (0.37, 1.77)	1.75
Zhang J *et al.* (16) (2017)		0.53 (0.27, 1.89)	1.29
Wang YW *et al.* (20) (2020)		0.77 (0.57, 1.04)	15.46
Subgroup, IV (I^2=0.0%, P=0.919)		0.71 (0.55, 0.86)	34.97
Stage IV			
Lan XW *et al.* (12) (2016)		0.62 (0.43, 0.90)	15.46
Hong RL *et al.* (14) (2018)		0.92 (0.67, 1.27)	9.52
Xia WX *et al*-2. (18) (2019)		0.86 (0.70, 1.06)	25.92
Subgroup, IV (I^2=40.6%, P=0.186)		0.80 (0.67, 0.93)	50.90
Stage II			
Jin T *et al.* (15) (2020)		1.03 (0.77, 2.00)	2.26
Li PJ *et al.* (17) (2018)		3.77 (1.12, 12.71)	0.03
Subgroup, IV (I^2=0.0%, P=0.357)		1.06 (0.45, 1.67)	2.29
Stage III			
Xia WX *et al*-1. (18) (2019)		1.23 (0.99, 1.52)	11.84
Subgroup, IV (I^2=0.0%, P=0.99)		1.23 (0.96, 1.49)	11.84
Heterogeneity between groups: P=0.010			
Overall, IV (I^2=35.6%, P=0.106)		0.82 (0.73, 0.92)	100.00

Figure 5 Pooled HR of IC as a prognostic factor predicting OS for NPC patients grouped by TNM stage. IC, induction chemotherapy; NPC, nasopharyngeal carcinoma; OS, overall survival; HR, hazard ratio; TNM, tumor node and metastases.
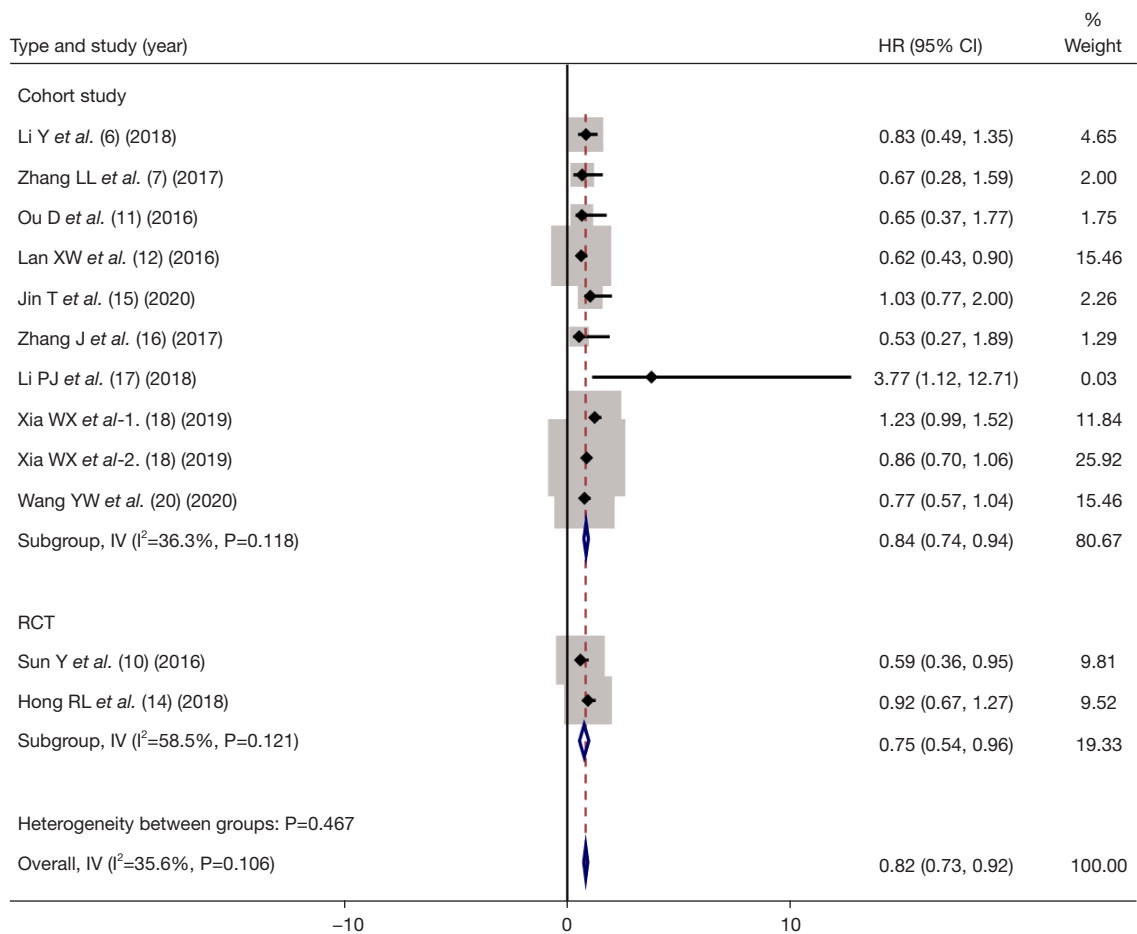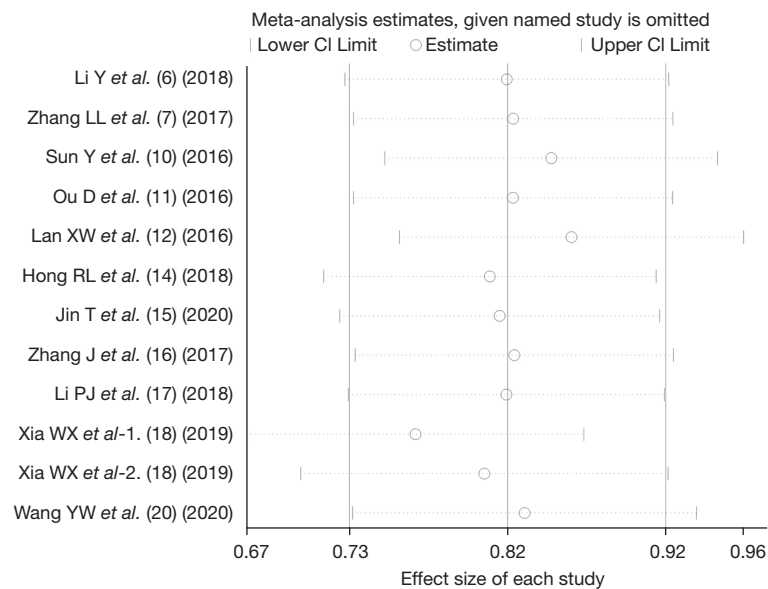
Figure 6 Pooled HR of IC as a prognostic factor predicting OS for NPC patients grouped by study type. IC, induction chemotherapy; NPC, nasopharyngeal carcinoma; OS, overall survival; HR, hazard ratio.
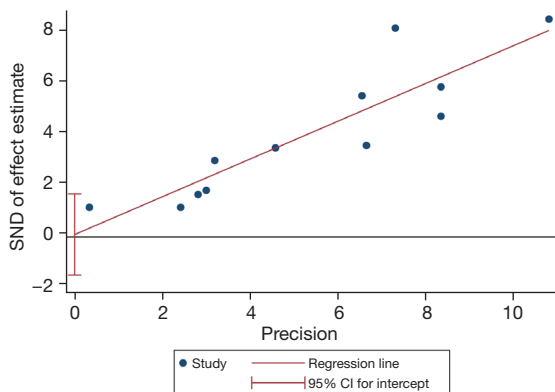

Figure 7 Comparison of incidence of adverse reactions between IC + CCRT and CCRT. IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy.

Figure 8 Sensitivity analysis of pooled HR of IC as a prognostic factor predicting OS . OS, overall survival; IC, induction chemotherapy; HR, hazard ratio.

Figure 9 Egger' test for pooled HR of IC as a prognostic factor predicting OS. OS, overall survival; IC, induction chemotherapy; HR, hazard ratio; SND, standard normal deviation.

and can accomplish the treatment as planned, enhance subsequent radiotherapy sensitivity, and reduce the toxicity caused by radiotherapy in some patients, such as limited mouth opening caused by cervical fibrosis and mandibular joint fibrosis (27).

In this meta-analysis, 13 clinical studies (including two RCTs and 11 retrospective cohort studies) involving a total of 7,197 patients were included. According to the overall pooled results, there were no significant differences between the two groups for the outcome of complete response rate,

the pooled HR for IC as a predictor for better PFS showed no significant too, but the pooled HRs for IC as a predictor for DMFS and OS were statistically significant, which meant that IC could be a prognostic factor predicting better DMFS and OS. After subgrouping the patients according to TNM stage II, stage III, and stage IV, the P value of HR for OS showed no significant for patients with stage II, which indicated that IC + CCRT treatment could be more suitable for patients with stage III or IV. A study by He *et al.* (28) has reported that for stage II nasopharyngeal carcinoma, intensity modulated radiation therapy (IMRT) alone can achieve better results, and that IC or CCRT do not provide additional benefits.

Since no fixed induction chemotherapy regimen was applied for most of the studies, so we could not perform subgroup analysis according to the chemotherapy regimen. Zeng *et al.* (29) compared the two regimens of TPF (cisplatin, fluorouracil, and Docetaxel) with GP (gemcitabine and cisplatin) for IC, and it was found that there was no significant difference in the improvement of patient survival between these two regimens during IC. A previous mesh meta-analysis (30) revealed that the docetaxel-platinum-5-fluorouracil (5FU) regimen had better efficacy than other regimens. Choi *et al.*'s reticular meta-analysis (31) included nine controlled studies with a total of eight induction chemotherapy regimens, and concluded that the docetaxel + cisplatin (DC), gemcitabine

+ cisplatin (GP), and cisplatin + capecitabine (PX) regimens were the most effective for improving patient survival.

The side effects of radiotherapy manifest as radiation mucosal injury and radiation dermatitis, and chemotherapeutic drugs cause significant gastrointestinal symptoms and hematological toxicity. When the two are synchronized, the side effects are superimposed and may be enhanced by each other, such as significant mucosal reactions, resulting in decreased patient tolerance (32). The present meta-analysis showed that IC + CCRT had more serious adverse reactions than CCRT alone, which indicated that IC increased the toxicity in concurrent chemotherapy, especially that in the oral cavity, digestive tract, and bone marrow. This resulted in some patients having to reduce the chemotherapeutic drug dosage or use segmented radiotherapy, and even some having to suspend chemoradiotherapy due to severe toxicity.

In this study, although no heterogeneity among the included articles was observed in the analysis of PFS, and OS, it should be noted that there were some variations between different studies, which may affect the accuracy of our results. For example, the chemotherapy and radiotherapy regimens differed among the included studies, with some studies using the three-dimensional conformal or intensity-modulated radiotherapy, and others utilized the traditional two-dimensional conformal radiotherapy. Moreover, although docetaxel, cisplatin, and fluorouracil (TPF) was used in the majority of included studies, other regimens were also applied which could be one source of the heterogeneity. Lastly, there were only two RCTs included in this study, the cohort studies included were non-RCTs with lower quality. Therefore, more RCTs with better quality are still needed to compare the efficacy and safety of IC + CCRT and CCRT alone.

Conclusions

Before CCRT for locally advanced nasopharyngeal carcinoma, the use of IC shows a positive effect for patients with TNM stage III and IV, but there is no significant gain for patients with stage II. In addition, when IC is applied, it will significantly increase the toxicity of the oral cavity, digestive tract, and bone marrow, and thus, it should be considered whether patients can tolerate it.

Acknowledgments

Footnote

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