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REVIEW

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Survival after induction chemotherapy in locoregional advanced nasopharyngeal carcinoma: An updated systematic review and meta-analysis

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Abstract

Background: Induction chemotherapy (ICT) augmentation is a common strategy for standard concurrent chemoradiotherapy (CCRT) of locoregionally advanced nasopharyngeal carcinoma (NPC). The survival condition is a crucial issue for patients with locoregionally advanced NPC. The survival of ICT patients with CCRT treatment versus standard CCRT alone should be elucidated via a systemic review and meta-analysis of randomized clinical trials.

Methods: We compared ICT with CCRT and CCRT alone treatment to determine if ICT with CCRT can be associated with a significant benefit of survival conditions versus CCRT. Different survival indicators were analyzed for the ICT with CCRT. Twelve studies with a total of 3711 patients with locoregionally advanced NPC were enrolled. The focused outcome was the overall survival, progression-free survival, distant metastasis-free survival, and locoregional recurrence-free survival.

Results: Our results showed that ICT with CCRT is associated with a significant benefit for the overall survival status versus CCRT treatment. Similar significant benefits in the survival condition were seen in progression-free survival, distant metastasis-free survival, and locoregional recurrence-free survival.

Conclusions: The updated meta-analysis results suggest that the ICT with CCRT might be associated with significant benefits of survival in overall, progression-free, distant metastasis-free, as well as locoregional recurrence-free dimensions versus CCRT treatment. However, the bias of different kinds, doses, and regimens of chemotherapy agents and radiotherapy should not be ignored.

KEYWORDS
concurrent chemoradiotherapy, induction chemotherapy, locoregionally advanced, meta-analysis, nasopharyngeal carcinoma, survival

1 | INTRODUCTION

Nasopharyngeal cancer (NPC) is relatively rare with a distribution pattern different than other kinds of cancers. It is very common in South China, North Africa, Southeast Asia, etc.[1–3] It is usually difficult to detect due to the anatomical origin of this cancer. NPC is also associated with a decrease of 13–15 age-standardized years of lifespan.[4–6] 70% of NPC cases are locoregionally advanced,[7] and this type of NPC might be easier to be controlled locally. However, the undifferentiated carcinoma characteristics of this type of NPC is associated with a greater possibility of metastasis.[8] Treatment of NPC might include surgery, chemotherapy, radiotherapy, etc. The effect of surgery is limited, and the NPC is relatively sensitive to chemotherapy and radiotherapy. However, even with the modern radiotherapy, the failure of distant control is still a concern for NPC.[9] Therefore, concurrent chemoradiotherapy (CCRT) is important in the treatment of NPC. However, the CCRT still has limitations in terms of treatment effects. Therefore, another kind of treatment combination is evolved under the need for higher treatment effects and better survival profiles.

According to the National Comprehensive Cancer Network (NCCN) guidelines of 2018 (https://www.nccn.org/professionals/physician_gls/default.aspx), CCRT alone or followed by adjuvant chemotherapy or induction chemotherapy (ICT) followed by CCRT are treatment options for locoregionally advanced NPC (T1, N1–3; T2–4, any N). ICT can improve quality of life and decrease the need for morbid surgery. In an individual patient data network meta-analysis, the results suggest that ICT with CCRT might be related to better progression-free survival (PFS), locoregional control, and distant control than CCRT treatment alone.[10] A meta-analysis of nine randomized trials suggest that ICT with CCRT might improve the overall survival (OS) and PFS versus CCRT treatment alone. The results also altered the pattern of standard care of locoregionally advanced NPC.[11] Other than OS and PFS, recent randomized trials of ICT with CCRT demonstrated the ability to improve distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRRFS).[12–19] Therefore, ICT with CCRT is an important treatment option for locoregionally advanced NPC.

This meta-analysis evaluates the survival profiles of randomized clinical trials of ICT with CCRT versus CCRT alone in terms of treatment of locoregionally advanced NPC patients. The literature led to our hypothesis that ICT with CCRT might reveal a superior effect on survival profiles such as OS, PFS, DMFS, and LRRFS. ICT with CCRT might improve the survival profiles of locoregionally advanced NPC patients versus CCRT treatment alone.

2 | METHODS

2.1 | Literature selection criteria

We applied a set of keywords to search and collect the related prospective RCT articles in the PubMed, ScienceDirect, EmBase, Web of Science. and the Cochrane Central Register of Controlled Trials (CENTRAL). The keywords included "induction chemotherapy," "neoadjuvant chemotherapy," "nasopharyngeal carcinoma," "locally," "local," "locoregional," "locoregionally," "advanced," "trials," "randomized," "clinical," "controlled," "treatment," "therapy," "survival" or "outcome," "comparison," "versus," "concurrent," and "chemoradiotherapy." We only recruited articles published or e-published online before August 2022.

The inclusion criteria for the articles were as follows: (1) Randomized clinical trials. (2) Comparisons between ICT with CCRT and CCRT alone for the treatment of locoregionally advanced NPC patients. (3) Outcome profiles at baseline and post-treatment status for the survival including OS, PFS, DMFS, and LRRFS. (4) Containing detailed outcome from the perspective of survival such as the 95% confidence interval (CI) and hazard ratio (HR). (5) Published in journals in the science citation index database and in the English language.

2.2 | Data quality evaluation and collection

We applied the Cochrane Handbook for Systematic Reviews and Interventions to perform the systematic review and meta-analysis study. We also followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[20] to report the results. Five factors were used to evaluate the risk of bias for each study. The factors included the bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The following data were collected from the enrolled articles. First, the HR, 95% CI, and patient number for the OS after ICT with CCRT and CCRT alone for treatment of locoregionally advanced NPC. Second, the HR, 95% CI, and patient number for the PFS after ICT with CCRT and CCRT alone for treatment of locoregionally advanced NPC. Third, the HR, 95% CI, and patient number for the DMFS after ICT with CCRT and CCRT alone for treatment of locoregionally advanced NPC. Fourth, the HR, 95% CI, and patient number for the LRRFS after ICT with CCRT and CCRT alone for treatment of locoregionally advanced NPC.

2.3 | Critical appraisal of data

The abstracts were reviewed by two reviewers to screen out the articles. An independent assessment of the full text version of the selected citations was performed by each reviewer. Extraction of clinical outcome data from text, tables, and figures of the enrolled articles were performed by the two reviewers independently. The enrolled articles had data of OS, PFS, DMFS, or LRRFS in the full text content. A collaborative review was performed by all reviewers to resolve any discrepancies leading to strong agreement (kappa = 0.9). The final results were then reviewed by all authors.

2.4 | Meta-analysis and statistical analysis

For the OS, PFS, DMFS, and LRRFS, pooled estimates of HR were generated with the associated 95% CI. We searched the summary statistics for each trial by extracting the reported HRs and 95% CIs due to the lack of patient-level data. The Cochrane Collaboration Review Manager Software Package (Rev Man Version 5.4) was used to perform the meta-analyses. The log-HRs was obtained by transforming the HR, and the start of the 95% CIs in the Rev Man calculation function. The inverse variance weighted averages of log HRs were combined to evaluate the risk estimates of individual studies in the fixed-effects model.

ICT with CCRT and CCRT treatment alone were compared to determine if ICT with CCRT could improve the OS, PFS, DMFS, and LRRFS. Heterogeneity between the enrolled studies was assessed by the Chi-square tests. We used the derived I^2 statistic to evaluate the statistical heterogeneity of enrolled studies in the meta-analysis. We applied the cut-off value for the Higgins I^2 index according to the Cochrane Handbook for Systematic Reviews of Interventions (2nd edition).[21] The derived p-values were two-sided. A funnel plot was used to assess the publication bias to see if there was a symmetric distribution of pooled studies.

3 | RESULTS

3.1 | Description of studies

The selection process was presented according to the PRISMA flow chart (Figure 1). Qualitative analysis of the residual 12 articles was performed and the residual 12 studies were included in the quantitative analysis.[12–19,22–25] The PRISMA flow diagram of the meta-analysis is presented as Figure 1. The characteristics and related study design of the 12 enrolled studies are summarized in Table 1. The risk of bias assessment showed that two studies have overall high bias and three studies have some concerns for the overall bias assessment (Figure 2). A symmetric distribution is shown in the funnel plot of enrolled studies.

3.2 | Log HR of OS of the ICT with CCRT versus CCRT treatment for locoregionally advanced NPC

The I^2 was 44%, which indicated moderate heterogeneity. The test for overall effect was $Z = 4.67$ ($p < .00001$), and the meta-analysis results showed significant difference of log HR of OS events between ICT

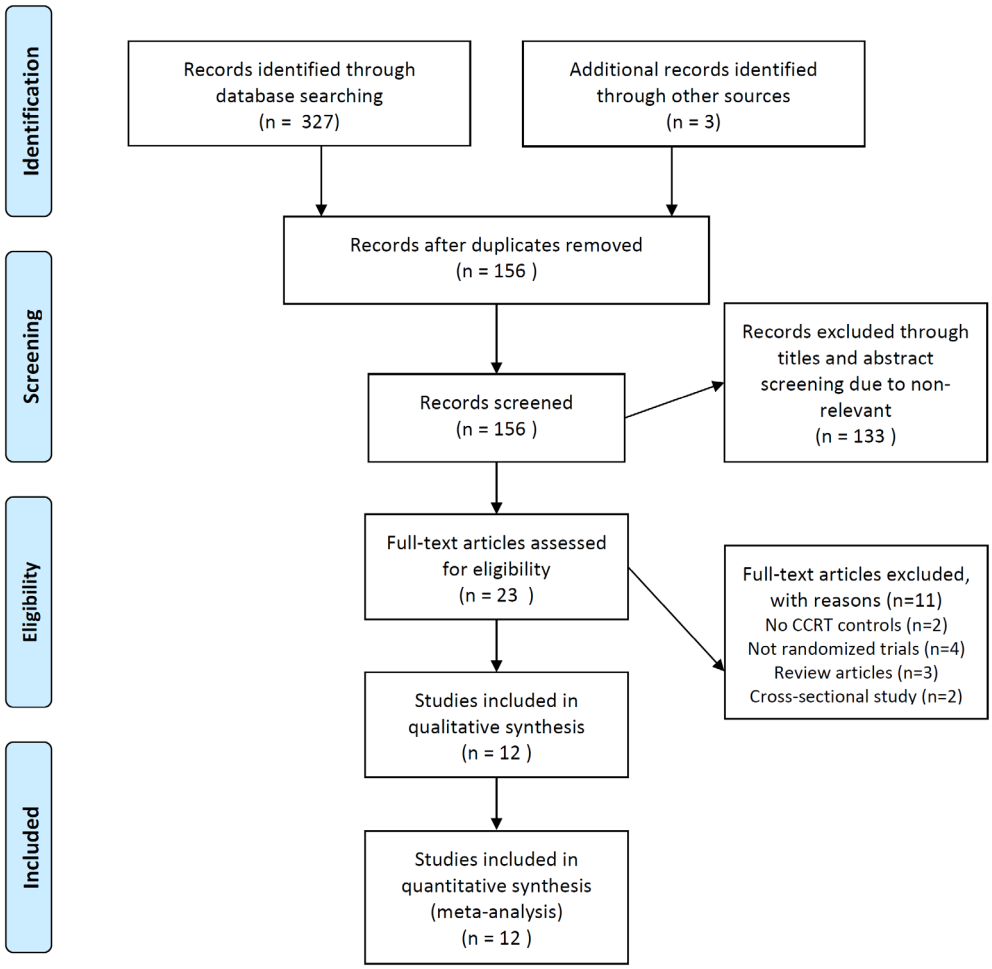

FIGURE 1 PRISMA flow chart for the selection of enrolled randomized trials. The identification of the potentially relevant literature and the screening of the identified literature using abstract and title selection were adherent to the PRISMA guideline. The assessment of the full text of screened literature was to find the eligible studies. Then the suitable studies were enrolled for the final meta-analysis.

TABLE 1 Summary of enrolled studies.

	Subjects (ICT + CCRT vs. CCRT treatment)	ICT + CCRT vs. CCRT treatment content	Radiotherapy	Outcome of interest
Fountzilas 2012 (Greece, Romania)	72 (51 M, 21 F, median age: 49 years old) vs. 69 (48 M, 21 F, median age: 51 years old) Stage IIB–IVB	Cisplatin 75 mg/m^2 (d2); paclitaxel 175 mg/m^2 (d1); epirubicin 75 mg/m^2 (d1) (3*q3wk) vs. cisplatin 40 mg/m^2 weekly (8 weeks)	3D-radiotehrapy, 2D-radiotherapy 66–70 Gy/33–35 fx, 6.5–7 weeks	Overall response rate, acute toxicity, PFS, rate of distant metastases and OS
Frikha 2018 (France, Tunisia)	39 (17 M, 12 F, median age: 46 years old) vs. 41 (32 M, 9 F, median age: 48 years old) Stage IIB–IVB	Cisplatin 75 mg/m^2 (d1); docetaxel 75 mg/m^2 (d1); 5FU 750 mg/m^2 (d1 to d5) (3*q3wk) vs. cisplatin 40 mg/m^2 weekly (7 weeks)	Intensity modulation radiotherapy; non-intensity modulation radiotherapy; 70 Gy/35 fx	PFS, OS, LRRFS, DMFS
Hong 2018 (Taiwan)	239 (176 M, 63 F, median age: 45 years old) vs. 240 (179 M, 61 F, median age: 47 years old) Stage IVA–IVB	Mitomycin 8 mg/m^2 (d1); epirubicin 60 mg/m^2 (d1); Cisplatin 60 mg/m^2 (d1); 5FU 450 mg/m^2 (d8); leucovorin 30 mg/m^2 (d8) (3*q3wk) vs. cisplatin 30 mg/m^2 weekly (7 weeks)	Intensity modulation radiotherapy; 3D-radiotherapy ≥70 Gy; 1.8–2.2 Gy/fx per day; 5 fx/week	PFS, OS, LRRFS, DMFS
Hui 2009 (Hong Kong)	34 (21 M, 13 F, median age: 50 years old) vs. 31 (24 M, 7 F, median age: 45 years old) Stage III–IVB	Cisplatin 75 mg/m^2 (d1), docetaxel 75 mg/m^2 (d1) (2*q3wk) vs. cisplatin 40 mg/m^2 weekly (8 weeks)	Intensity modulation radiotherapy; 2D-radiotherapy 66–86 Gy/33–43 fx; 2 Gy/fx per day; 8.6 wk + 18 Gy brachyboost if persistent tumor at 6th week	OS, PFS
Jin 2017 (China)	242 (173 M, 69 F, median age: 46 years old) vs. 238 (150 M, 88 F, median age: 46 years old) Stage III–IVB	Cisplatin 5-fluorouracil vs. cisplatin 40 mg/m^2 weekly (8 weeks)	3D-radiotehrapy, 2D-radiotherapy 66–70 Gy/33–35 fx, 6.5–7 weeks	OS, LRRFS, DMFS
Li 2019 (China)	241 (193 M, 48 F, median age: 42 years old) vs. 239 (174 M, 65 F, median age: 44 years old) Stage III–IVB (except T3–4N0)	Cisplatin 60 mg/m^2 (d1); docetaxel 60 mg/m^2 (d1); 5FU 600 mg/m^2 (d1–d5) (3*q3wk) vs. cisplatin 100 mg/m^2 (3*q3wk)	Intensity modulation radiotherapy 66–74 Gy; 2.0–2.35 Gy/fx per day; 5 fx/week; 6–7 weeks	OS, PFS, LRRFS, DMFS
Miao 2022 (China)	90 (73 M, 17 F, median age: 46 years old) vs. 90 (70 M, 20 F, median age: 48 years old) Stage III–IVB	8 cycles of oral capecitabine at a dosage of 1000 mg/m^2 twice daily for 14 days every 21 days vs. cisplatin 100 mg/m^2 every 3 weeks for 2 to 3 cycles depending on the duration of radiotherapy	Intensity modulation radiotherapy 68 to 72 Gy, 60 to 68 Gy, 60 to 64 Gy, and 54 to 58 Gy in 30 to 32 fractions to the primary planning target volume, lymph node planning target volume, high-risk planning target volume, and low-risk planning target volume, respectively.	OS, PFS, LRRFS, DMFS, adverse events
Tan 2015 (Singapore)	86 (71 M, 15 F, median age: 48.5 years old) vs. 86 (63 M, 23 F, median age: 51.6 years old) Stage III–IVB	Carboplatin AUC 2.5; gemcitabin 1000 mg/m^2; paclitaxel 70 mg/m^2 (d1 and d8) (3*q3wk) vs. cisplatin 40 mg/m^2 weekly (8 weeks)	Intensity modulation radiotherapy 69.96 Gy/33 fx; 2.12 Gy/fx per day; 6.6 weeks; 2D-radiotherapy: 70 Gy/35 fx; 2 Gy/fx per day; 7 weeks	OS, DMFS, toxicities, quality of life
Yang 2019 (China)	238 (173 M, 65 F, median age: 44 years old) vs. 238 (190 M, 48 F, median age: 42 years old) Stage III–IVB (except T3N0–1)	Cisplatin 80 mg/m^2 (d1); 5FU 800 mg/m^2; (d1 to d5) (2*q3wk) vs. cisplatin 80 mg/m^2 (3*q3wk) months	Intensity modulation radiotherapy ≥66 Gy 2–2.33 Gy/fx per day; 2D-radiotherapy: 64–72 Gy; 2 Gy/fx per day; 5 fx/week	DMFS, OS, LRFFS, long-term toxicities
Yang 2021 (China)	99 (75 M, 24 F, median age: 51 years old) vs. 99 (75 M, 24 F, median age: 50 years old) Stage III–IVB	Docetaxel 75 mg/m^2 on Day 1 and cisplatin 25 mg/m^2 per day from Day 1 to 3 vs. cisplatin 25 mg/m^2 per day from Day 1 to 3, given intravenously with an interval of 3 weeks.	Intensity modulation radiotherapy A total of 7000 cGy/30–33 F to the planning target volume of the nasopharynx, 6600–6800 cGy/30–33 F to the enlarged lymph nodes, 6000 cGy/30–33 F to the high-risk planning target volume and	Treatment response OS, PFS, LRRFS, DMFS, living status, failure pattern, toxicity

TABLE 1 (Continued)

	Subjects (ICT + CCRT vs. CCRT treatment)	ICT + CCRT vs. CCRT treatment content	Radiotherapy	Outcome of interest
			5400 cGy/30–33 F to the low-risk planning target volume were prescribed.	
Zhang 2019 (China)	242 (182 M, 60 F, median age: 46 years old) vs. 238 (164 M, 74 F, median age: 45 years old) Stage III–IVB (except bulky primary tumor N0)	Gemcitabin 1000 mg/m^2 (d1 and d8); CDDP 80 mg/m^2 (d1) (3*q3wk) vs. Cisplatin 100 mg/m^2 (3*q3wk)	Intensity modulation radiotherapy 66–70 Gy; 30–33 fx	OS, PFS, LRRFS, DMFS
Zhang 2022 (China)	242 (182 M, 60 F, median age: 46 years old) vs. 238 (164 M, 74 F, median age: 45 years old) Stage III–IVB (excluding T3-4N0)	Gemcitabin 1000 mg/m^2 (d1 and d8); CDDP 80 mg/m^2 (d1) (3*q3wk) vs. Cisplatin 100 mg/m^2 (3*q3wk)	Intensity modulation radiotherapy 66–70 Gy; 30–33 fx	OS, late toxicities, prognostic value of tumor response to induction chemotherapy, predictive value of cell-free Epstein–Barr virus DNA for induction chemotherapy

with CCRT and CCRT treatment, which suggested a significant benefit of OS for the ICT with CCRT treatment (Figure 3).

3.3 | Log HR of PFS of the ICT with CCRT versus CCRT treatment for locoregionally advanced NPC

The I^2 was 20%, which indicated low heterogeneity. The test for overall effect was $Z = 5.47$ ($p < .00001$), and the meta-analysis results showed significant difference of log HR of PFS events between ICT with CCRT and CCRT treatment, which suggested a significant benefit of PFS for ICT with CCRT treatment (Figure 4).

3.4 | Log HR of PFS of the DMFS with CCRT versus CCRT treatment for locoregionally advanced NPC

The I^2 was 0% suggesting extremely low heterogeneity. The test for overall effect was $Z = 4.17$ ($p < .0001$), and the meta-analysis results showed significant difference of log HR of DMFS events between ICT with CCRT and CCRT treatment, which suggested a significant benefit of DMFS for the ICT with CCRT treatment (Figure 5).

3.5 | Log HR of PFS of the LRRFS with CCRT versus CCRT treatment for locoregionally advanced NPC

The I^2 was 14% suggesting low heterogeneity. The test for overall effect was $Z = 3.60$ ($p = .0003$), and the meta-analysis results showed a significant difference of log HR of LRRFS events between ICT with CCRT and CCRT treatment suggesting a significant benefit of LRRFS for the ICT with CCRT treatment (Figure 6).

4 | DISCUSSION

This meta-analysis focused on the survival of ICT with CCRT combination treatment for locoregionally advanced NPC patients. The results showed significant benefits for OS, PFS, DMFS, and LRRFS. The results suggested superior effects of ICT for improving the OS, PFS, DMFS, and LRRFS on patients with locoregionally advanced NPC. Our meta-analysis enrolled the latest studies evaluating ICT with CCRT for patients with locoregionally advanced NPC.[18,19,24] The results might be more updated than previous meta-analyses.[26–31] We also analyzed more survival indicators than the previous meta-analyses.[27–29] In addition, our meta-analysis purely focused on randomized controlled trials, which minimizes bias from retrospective studies or cohort studies as found in other meta-analyses.[32–34] The consistent and significant benefits of the OS, PFS, DMFS, and LRRFS seen here underscore the advantages of applying ICT for locoregionally advanced NPC patients. However, different regiments of

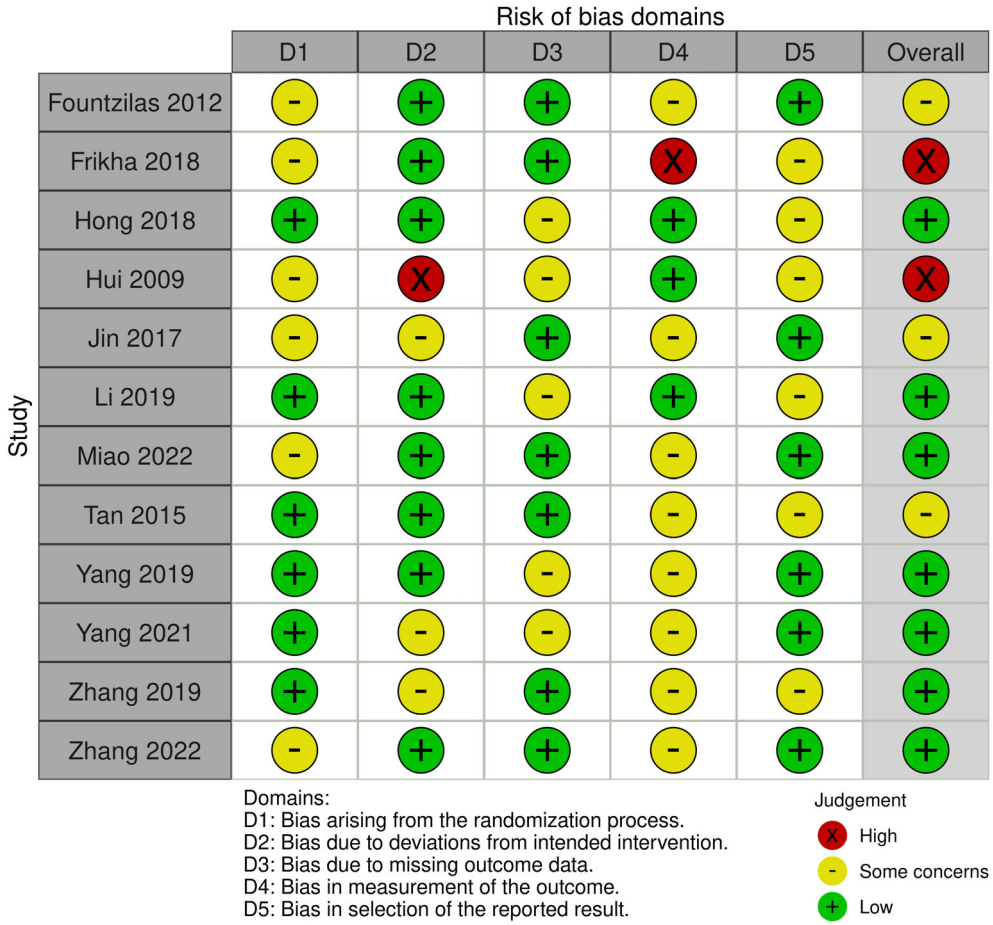

FIGURE 2 Risk of bias assessment. The risk of bias assessment updated version (ROB v2) was used to assess the risk of bias for the enrolled articles.

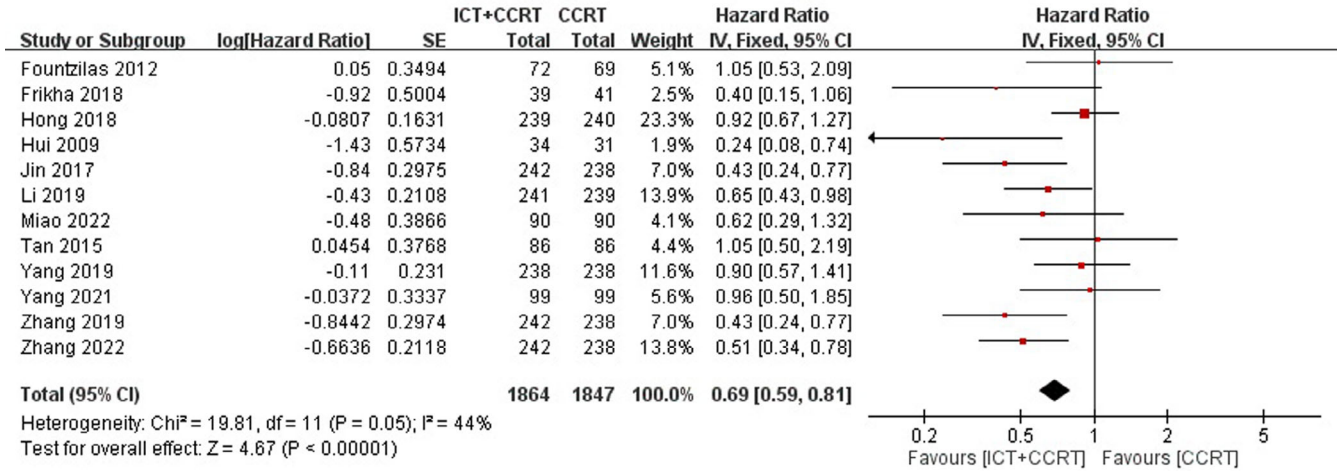

FIGURE 3 The forest plot of log HR for the meta-analysis results of OS [ICT + CCRT vs. CCRT]. The ICT + CCRT treatment showed a significantly benefit of improved OS when compared to the CCRT (statistically significant).

ICT in these studies should be considered when interpreting the meta-analysis results. We pooled all kinds of ICT regimens of enrolled randomized trials in the meta-analysis. The bias from the different regimens of ICT in each trial should not be ignored. In addition, the current meta-analysis just focused on the survival conditions of locoregionally advanced NPC patients. Therefore, the treatment side effects and other related profiles are not revealed in the results. However, the current meta-analytic results reconfirmed the significant benefits for survival of patients with locoregionally advanced NPC seen in previous meta-analyses.[26–35] Therefore, the benefits of ICT for the survival condition of locoregionally advanced NPC might be consistent and persuasive.

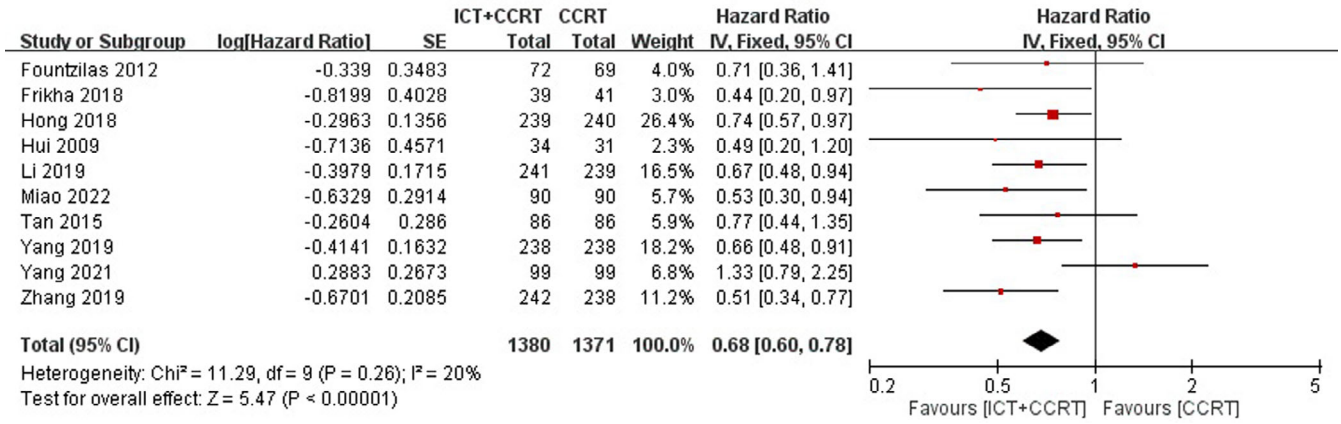

FIGURE 4 The forest plot of log HR for the meta-analysis results of PFS [ICT + CCRT vs. CCRT]. The ICT + CCRT treatment showed a significantly benefit of improved PFS when compared to the CCRT (statistically significant).

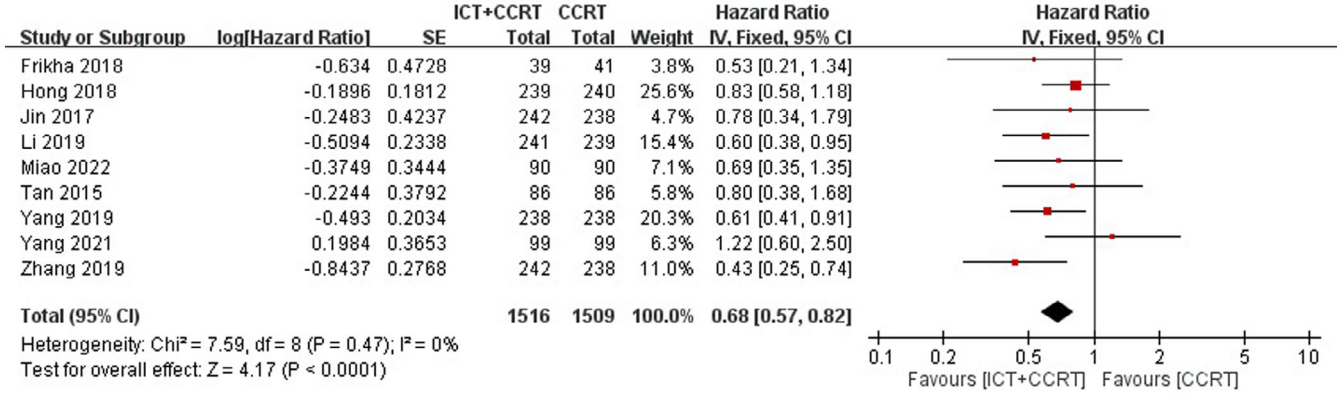

FIGURE 5 The forest plot of log HR for the meta-analysis results of DMFS [ICT + CCRT vs. CCRT]. The ICT + CCRT treatment showed a significantly benefit of improved DMFS when compared to the CCRT (statistically significant).

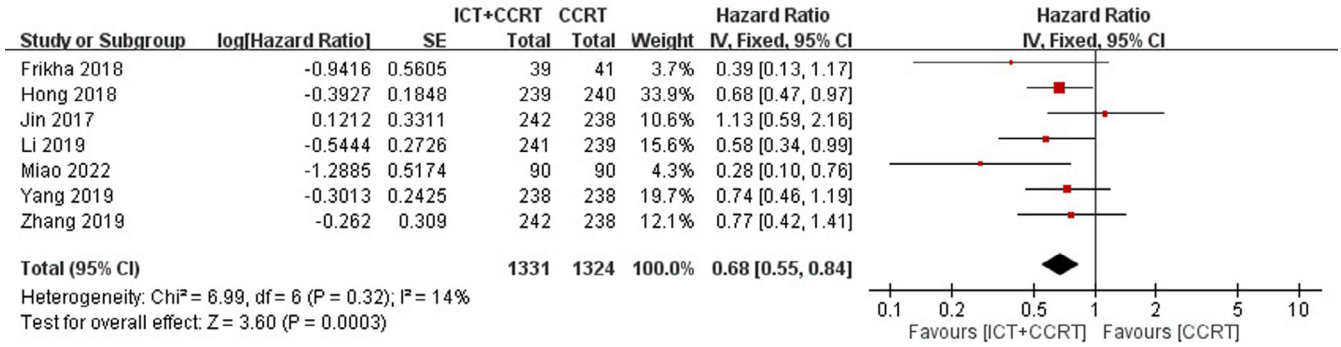

FIGURE 6 The forest plot of log HR for the meta-analysis results of LRRFS [ICT + CCRT vs. CCRT]. The ICT + CCRT treatment showed a significantly benefit of improved LRRFS when compared to the CCRT (statistically significant).

Despite the high sensitivity of NPC to radiotherapy, NPC patients often have advanced disease at the time of diagnosis. The invasiveness of the tumor and the risk of metastasis might be harmful to the hematologic and lymphatic systems. CCRT might inhibit the primary tumor and control distant metastasis of the tumor, which can thus improve treatment efficacy. The benefits of the OS, PFS, DMFS, and LRRFS might be related to role of ICT in eliminating micro-metastases at the initial treatment. they can enhance the local control of locoregionally advanced NPC through a combination of CCRT.[31] In addition, ICT might inhibit the implantation of tumor cells and kill the tumor

cells in systemic circulation. ICT might reduce subclinical metastases and strengthen the sensitivity of subsequent radiotherapy while reducing the toxicity caused by radiotherapy such as fibrosis of cervical and mandibular joints.[33] Different kinds of regimens and chemotherapeutic agents might also influence the meta-analysis results.

The previous meta-analysis mentioned that gemcitabine-based ICT might be different from taxane-based ICT from the perspective of improving the OS.[32] Another meta-analysis suggested that the cisplatin might be related to more toxicities than other platinum compounds. The authors recommended substituting cisplatin with other platinum compounds.[35] Our meta-analysis found that cisplatin was still popularly used in the ICT or CCRT. Therefore, toxicities and treatment side effects should be considered when we looked at such consistent benefits on the OS, PFS, DMFS, and LRRFS. Therefore, future randomized trials might use treatment with other platinum compounds to optimize therapy safety. Ideal regimens of ICT are still not clear. More randomized studies comparing different regimens of ICT are needed to determine which kind of ICT regimen would be the most appropriate under the balance of clinical outcomes and treatment toxicities.[36]

There were several limitations in the current meta-analysis. First, most patients recruited in the enrolled randomized trials were in stage III-IV. Therefore, it is difficult to understand if the positive effects can be replicated in stage II patients. A previous meta-analysis suggested that the ICT might be beneficial for the distant control of NPC.[31] However, the efficacy of the ICT regimen in patients with stage II NPC is still unclear. Second, the age and gender variances of enrolled studies might influence the interpretations of our study results. More consistent age and gender distribution patterns might be needed in future randomized clinical trials to decrease the bias from the different age and gender distributions. Third, variations of ICT regimens might also bias our meta-analysis results. The more consistent ICT regiments might be helpful for improving the accuracy of the meta-analytic results. More enrollment of less-toxic ICT regimen compounds might be needed for patient-centered treatment. Fourth, the different techniques, doses, regimens, and durations of radiotherapy might also influence the interpretations of our results. 2D- and 3D-radiotherapy as well as intensity modulation radiotherapy were used in the enrolled trials. Better consistency of radiotherapy techniques, doses, regimens, and durations can help clinicians and scientists determine the real impacts on the survival conditions of ICT. Fifth, the different regimens, doses, and durations of CCRT might be another concern in this meta-analysis. However, group comparisons of the same CCRT regimen in the same individual enrolled study might reduce the bias impact from the different regiments, doses, and durations of CCRT. Sixth, the lack of meta-analysis on the treatment adverse events, toxicities, and compliance seen here might prevent detailed conclusions. However, our current meta-analysis focused on the survival condition of the most recent randomized clinical trials. Seventh, most enrolled studies were from Asia (China, Singapore, and Taiwan). The demographic or ethnicity issue should be kept in mind when we interpreted the meta-analysis results.

5 | CONCLUSION

This updated systematic review and meta-analysis of the latest randomized trials showed that ICT with CCRT treatment might improve OS, PFS, DMFS, and LRRFS versus CCRT treatment. More consistent ICT, radiotherapy, and CCRT regimens might be warranted in future studies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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