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Concurrent chemoradiotherapy versus radiotherapy alone for locoregionally advanced nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy: a meta-analysis

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Purpose: In this study, we attempted to compare the efficacy and toxicity of concurrent chemoradiotherapy (CCRT) with radiotherapy alone (RT) for locoregionally advanced nasopharyngeal carcinoma (LANPC) in the era of intensity-modulated radiotherapy (IMRT) by meta-analysis.

Materials and methods: We searched databases, and all randomized controlled trials meeting the inclusion criteria were utilized for a meta-analysis with RevMan 5.3 based on the Cochrane methodology.

Results: Fifteen studies were found suitable based on the inclusion criteria. CCRT not only significantly improved the overall response rate (risk ratio [RR]=0.53, 95% CI 0.43–0.66) and the complete response rate (RR=0.60, 95% CI 0.51–0.71) but also contributed to longer overall survival. The incidence of grade 3–4 adverse events from CCRT group increased in hematologic toxicity (RR 2.25, 95% CI 1.54–3.29), radiation-induced oral mucositis (RR 1.64, 95% CI 1.14–2.35), and radiodermatitis (RR 1.80, 95% CI 1.13–2.88).

Conclusion: Compared with IMRT alone, CCRT provided survival benefit with acceptable toxicity in patients with LANPC. However, we need multicenter randomized controlled trials and long-term follow-up to evaluate the eventual efficacy and toxicity of concurrent chemotherapy plus IMRT.

Keywords: locoregionally advanced nasopharyngeal carcinoma, intensity-modulated radiotherapy, concurrent chemoradiotherapy, meta-analysis

Introduction

Nasopharyngeal carcinoma (NPC) is the most common head and neck malignancy, which is endemic in Southeast Asia.[1] Over 60,600 new cases were diagnosed and almost 34,100 patients were dead in China in 2015.[2] Also, 60%–70% of patients are diagnosed with locoregionally advanced nasopharyngeal carcinoma (LANPC).[3,4] Based on the anatomical location and radiosensitivity, radiotherapy (RT) is the primary therapeutic regimen for NPC. With RT alone, the 5-year overall survival (OS) rate for stage I is >90%. However, the 5-year OS rate is only 67%–77% in LANPC treated with RT alone.[5] In the era of two-dimensional RT (2D-RT), several studies have shown that the addition of concurrent chemotherapy to radiation improves local control and OS.[6–9] Thus, concurrent chemoradiotherapy (CCRT) is the standard therapeutic model recommended by the National Comprehensive Cancer Network guideline.

Intensity-modulated radiotherapy (IMRT) has brought a great progress in the treatment of LANPC. It provides better tumor target coverage with lower

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radiation-associated toxicities than 2D-RT, and thus, the locoregional control has been substantially improved.[10,11] Meanwhile, as reported, IMRT alone can achieve the same or similar treatment effect and significantly decrease the adverse reactions in patients with LANPC, compared with the 2D-RT combined with chemotherapy. The 3-year OS rate was 80.43% for IMRT alone and 74% for 2D-RT combined with chemotherapy.[12] Furthermore, Sun et al reported that by the addition of concurrent chemotherapy to IMRT, no survival benefits were observed in the 5-year disease-specific survival, local recurrence-free survival, regional recurrence-free survival, and distant metastasis-free survival in 603 NPC patients with stage III–IVb.[13] What is more, more treatment-associated toxicities were observed in CCRT group than in IMRT alone group. Similarly, Lin et al found that compared with IMRT alone, CCRT provided no obvious clinical benefit and induced significantly higher grade 3–4 acute toxicities in 370 LANPC patients.[14] On the contrary, Xie et al reported that the addition of concurrent chemotherapy increased the estimated 5-year OS rate from 73.7% (without concurrent chemotherapy) to 81.8% (with concurrent chemotherapy), but was accompanied with increased toxicities.[15] Thus, it is controversial whether the addition of concurrent chemotherapy brings more clinical benefits for LANPC in the era of IMRT.

In this study, we conducted a meta-analysis using available evidence from randomized controlled trials to compare the efficacy and toxicity of CCRT to RT alone for LANPC in the era of IMRT.

Materials and methods

Search strategy and selection criteria

PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, Wanfang Database, Weipu Information Resources System, and Chinese Biomedical Database were searched up to August 2017. References of relevant articles were also searched carefully.

Literatures were screened for eligibility using the following criteria: 1) participating patients with non-metastatic NPC diagnosed as stage III–IVb, 2) studies comparing IMRT combined with current chemotherapy with IMRT alone, and 3) randomized controlled trials.

Reports were excluded by the following criteria: 1) republication of literature; 2) treatment included 2D-RT; 3) no randomized controlled trials or any reviews, comments, and letters; 4) concurrent targeted therapy; 5) induction chemotherapy or adjuvant chemotherapy was applied; and 6) full text was unpublished. Eligibility assessment was performed by two reviewers. Disagreements between reviewers were settled by discussion.

Data extraction

Extraction was performed by two reviewers. Disagreements were resolved by discussion. We contacted the original study researchers for indistinct data and removed the data from stage II NPC patients. The following information was extracted: first author, publication year, patient number, inclusion period, random method, treatment regimen, and outcomes. The efficient outcomes were overall response rate (ORR), complete response rate (CRR), and OS. As for the toxic outcomes, data on grade 3–4 adverse events of hematologic toxicity, gastrointestinal reaction, radiation-induced oral mucositis, and radiodermatitis were extracted. If the study reported relevant adverse events separately, for example, nausea, vomiting, and diarrhea, the higher event rate was used to approximate the overall events. Among the 15 studies, 1 study utilized Common Terminology Criteria for Adverse Events criteria 3.0 for adverse events, and the rest utilized the World Health Organization criteria. However, the evaluation standard is very similar in these two criteria for adverse events. Thus, these data could be combined in this meta-analysis.

Assessment of risk of bias and data analysis

We assessed the risk of bias referring to the guidance of Cochrane Handbook for Systematic Reviews of Interventions (5.1.0).[16] Statistical analysis was performed by Review Manager Software (RevMan 5.3; Cochrane Collaboration, Oxford, UK).

ORR, CRR, OS, and grade 3–4 advent events were analyzed quantitatively by using the risk ratio (RR), and 95% CI was calculated. RR represents the risk ratio of an event which occurred in the CCRT group versus the RT group. An observed RR <1 and a 95% CI which did not overlap 1 with $P<0.05$ indicated that CCRT could offer more benefits to patients with LANPC and would be considered statistically significant. Heterogeneity was used to evaluate the variability in studies by I^2 statistic. If I^2 statistic was <50%, we considered the heterogeneity was acceptable, and we used the fixed-effects model for the meta-analysis. The value of $I^2 \geq 50\%$ was considered to indicate substantial statistical heterogeneity. The causes of heterogeneity among the results of studies were explored. Then, a random-effects model was used.

Results

Search results and characteristics of studies

A total of 1753 citations were searched by PubMed, Embase, the Cochrane Library, China National Knowledge

Infrastructure, Wanfang Database, Weipu Information Resources System and Chinese Biomedical Database (shown in Supplementary materials). Furthermore, possibly useful publications were hand-searched, but eligible studies were not found. One thousand three hundred and twenty citations remained after removing duplicates. After reviewing the titles and abstracts carefully, 1292 citations did not match the inclusion criteria. Finally, 28 citations remained. After reading these 28 studies carefully, 13 studies were removed. These were removed because of the following reasons: three citations were not truly randomized; in three citations, the concurrent drugs were molecular targeted therapy; one citation was a conference abstract; in three citations, adjuvant chemotherapy was administered; and in the remaining three citations, not all patients were treated with IMRT. Collectively, 15 clinical studies were available for this meta-analysis (Figure 1).[17–31]

The characteristics of the 15 studies are summarized in Table 1. We included 1142 patients in the meta-analysis, of whom 573 received CCRT and 569 were allocated to IMRT alone group. Baseline characteristics were balanced in all studies. All patients included in this meta-analysis were LANPC (stage III–IVb). The concurrent chemotherapy drugs reported in these studies included cisplatin, nedaplatin, docetaxel, 5-fluorouracil, xeloda and s-1 (tegafur, gimeracil and oteracil potassium). ORR data were available in 12 studies, CRR data in 13 studies, and OS data in 6 studies. Almost all studies assessed the response rate according to Response Evaluation Criteria in Solid Tumors at 3 months after RT by magnetic resonance imaging.

Risk of bias of eligible studies

Among the selected 15 studies, 9 studies were assessed as low risk of bias because these trials were assigned by the random number table. Two studies were evaluated as high risk because these two trials were assigned by the day on which a patient is admitted to the hospital. It was unclear how to generate random sequence in four studies. Allocation concealment was not clearly reported in all studies. Blinding of participants was not applied in all 15 trials because of intervention measures. Blinding of outcome assessment was not reported in 13 trials and was reported in the remaining 2 trials. Fourteen studies reported complete outcome data. One study reported lost to follow-up, but we assessed this study as low risk because the number of lost to follow-up was balanced in both groups of this study (Liu et al,[20] the number of lost to follow-up in CCRT: 3, RT: 4; Figure 2). The publication bias might exist according to the funnel plots (Figure S1).

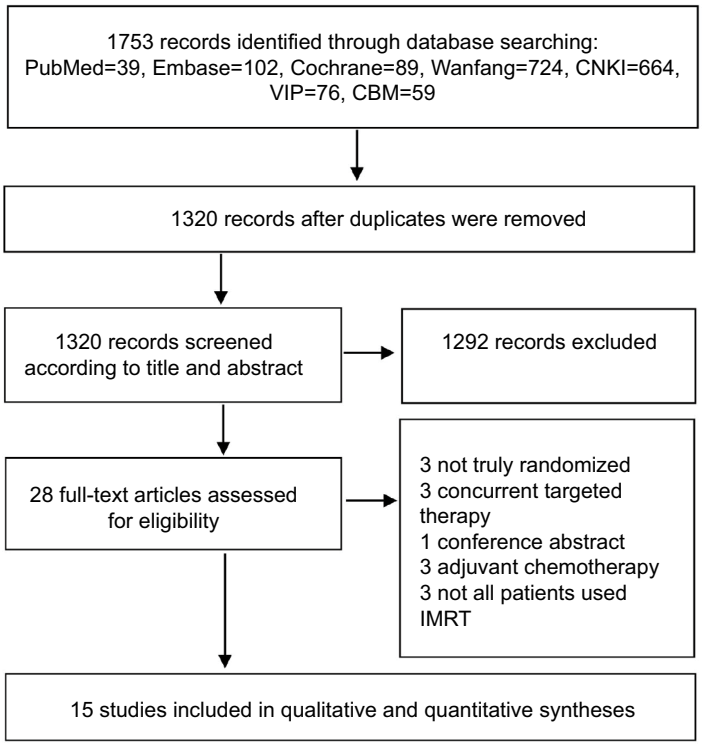

Figure 1 A flow diagram showing the selection of the trials.
Abbreviations: CBM, Chinese Biomedical Database; CNKI, China National Knowledge Infrastructure; IMRT, intensity-modulated radiotherapy; VIP, Weipu Information Resources System.

Table 1 Characteristics of included studies

Studies	Inclusion period	Patients (n)	Mean age	Gender (M:F)	Treatment arm	Stage	Radiotherapy doses	Concurrent chemotherapy
Chen et al,[17] 2017	January 2011 to August 2015	32 34	72.96±2.45 73.27±2. 12	24:8 25:9	RT CCRT	Stage III–IVa	GTVnx: 70–76 Gy/28f GTVnd: 66–70 Gy/28f CTV1: 50.8–60 Gy/28f CTV2: 50.8 Gy/28f	S-1 60 mg/m^2, bid, d1–28, q6w
Li et al,[18] 2010	April 2006 to April 2008	40 40	48 (25–78)	60:20	RT CCRT	Stage III–IVa	GTVnx: 73.9 Gy/33f GTVnd, CTV1: 66 Gy/33f CTV2: 50.4–59.4 Gy/28–33f	DDP 80 mg/m^2, d1, d22, d43
Liu et al,[20] 2012	February 2005 to March 2008	41 44	55 (18–76)	28:13 35:9	RT CCRT	Stage III–IVb	GTV: 70 Gy/32–33f CTV1: 64–66 Gy/32–33f CTV2: 54–56 Gy/30–32f	Xeloda 500 mg/m^2 bid
Tian and You-Ming,[22] 2014	January 2006 to January 2012	24 24	53 (34–74)	27:21	RT CCRT	Stage III	GTV: 68–74 Gy/35–37f CTV: 60–70 Gy/6–7 weeks	Docetaxel 20–25 mg/m^2, 7 weeks
Wang et al,[23] 2008	January 2006 to October 2007	25 25	44 (20–67) 48 (18–68)	18:7 19:6	RT CCRT	Stage III–IVb	GTVnx: 74–78 Gy GTVnd: 70 Gy CTV1: 60–66 Gy CTV2: 51–56 Gy	Xeloda 750–1000 mg/m^2, d1–14, d28–42
Wang et al,[33] 2016	February 2013 to February 2015	47 47	45 (20–60)	59:35	RT CCRT	Stage III–IVb	N/A	Docetaxel 65 mg/m^2 d1, NDP 80 mg/m^2 d1–5
Wang et al,[24] 2014	January 2011 to January 2012	30 30	45.45±5.83 45.23±5.67	18:12 20:10	RT CCRT	Stage III–IVb	GTV: 70 Gy/35f	S-1 80 mg/m^2, bid, d1–14, q3w
Wei et al,[25] 2015	April 2012 to March 2014"	39 39	50.6±7.4 51.1±6.8	26:13 25:14	RT CCRT	Stage III–IVb	GTVnx, GTVnd: 65–71 Gy CTV1: 55 Gy CTV2: 53 Gy	Docetaxel d1, NDP d1, q2w
Xie et al,[26] 2011	February 2006 to April 2007	30 30	46 (22–70) 49 (17–71)	19:11 21:9	RT CCRT	Stage III–IVb	GTVnx, GTVnd: 69–76 Gy/32f CTV1: 60–65 Gy/32f CTV2: 50–60 Gy/28f	DDP 60 mg/m^2 d1, 5-FU 750 mg/m^2 d2–4, q3w
Xu,[27] 2014	July 2013 to May 2014	34 35	50.8±17.5 64.2±3.5	20:14 25:10	RT CCRT	Stage III–IVb	GTV: 66–70 Gy/30–33f	DDP 20 mg/m^2, 5-FU 750 mg/m^2
Zhang et al,[34] 2016	January 2013 to January 2014	40 40	63.8±3.1 64.2±3.5	26:14 24:16	RT CCRT	Stage III–IVa	GTVnx: 70–75.9 Gy/30–33f GTVnd: 66–70.4 Gy/30–33f CTV1: 60–64 Gy/30–33f CTV2: 50–54 Gy/30–33f	NDP 80 mg/m^2 d1, d28
Zhen et al,[31] 2015	June 2008 to June 2012	60 60	73.5±2.6 73.6±2.5	31:29 31:29	RT CCRT	Stage III–IVb	N/A	S-1 40–60 mg·m^2
Liu et al,[21] 2015	February 2010 to February 2011	69 69	42.5±15.8 43.1±16.2	35:34 36:33	RT CCRT	Stage III–IVb	GTVnx: 69.96–73.92 Gy GTVnd: 69.96 Gy CTV1: 60.06–66 Gy CTV2: 50.96–56 Gy, 7 weeks	NDP 40 mg/m^2 d1–5
Zheng,[30] 2010	N/A	17 17	40 (20–65)	21:13	RT CCRT	Stage III–IVb	GTVnx: 72.6 Gy GTVnd: 69.96 Gy CTV1: 60.06 Gy CTV2: 50.96 Gy, 7 weeks	DDP 20 mg/m^2, d1–5 5-FU 500 mg/m^2, d1–5
Yuan et al,[29] 2016	May 2012 to June 2015	40 40	51.32±5.29 51.25±5.34	23:17 22:18	RT CCRT	Stage III–IVb	N/A	Docetaxel 60 mg/m^2, Nedaplatin, q2w

Abbreviations: 5-FU, 5-fluorouracil; bid, twice daily; CCRT, concurrent chemoradiotherapy; CTV, clinical target volume; DDP, cisplatin; d, day; F, female; GTV gross tumor volume; IMRT, intensity-modulated radiotherapy; M, male; N/A, not available; NDP, nedaplatin; q2w, every 2 weeks; q3w, every 3 weeks; q6w, every 6 weeks; RT, intensity-modulated radiotherapy alone.

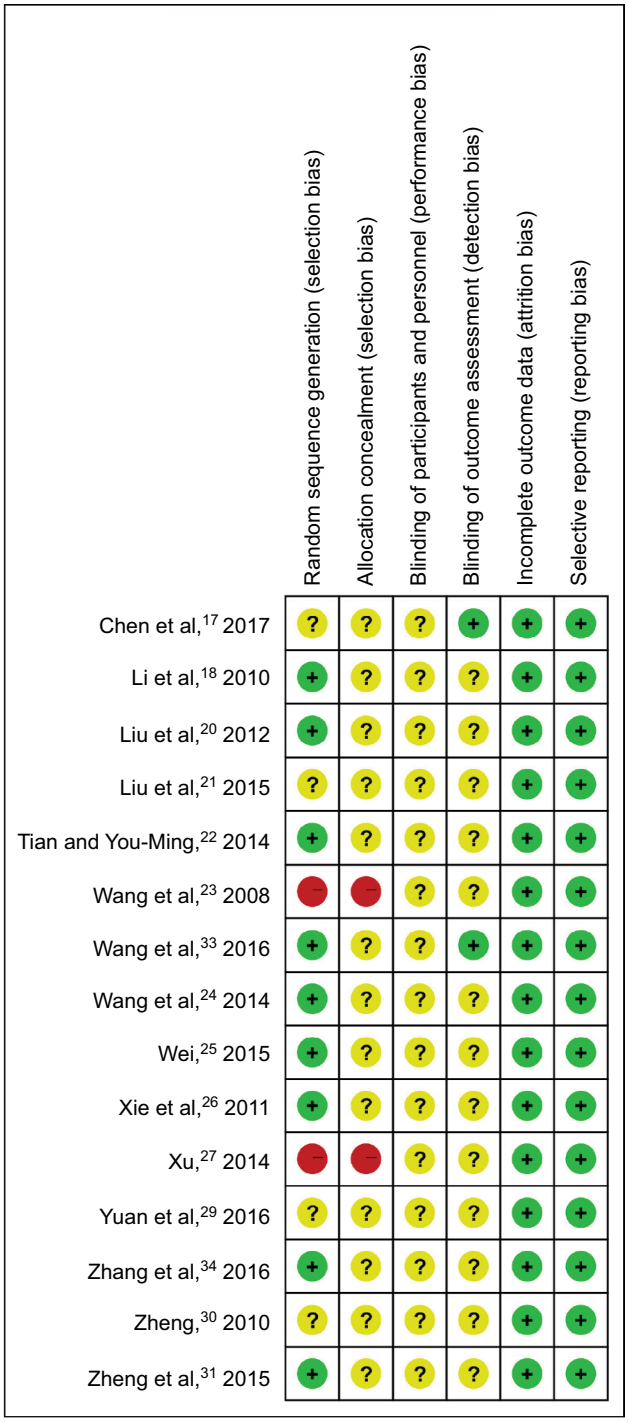

Figure 2 Risk of bias summary.

Efficacy and toxicity

Compared with RT alone group, ORR (RR 0.53, 95% CI 0.43–0.66, $P<0.00001$; participants=946 [CCRT:474, RT:472]; studies=12; $I^2=46\%$) and CRR (RR 0.60, 95% CI 0.51–0.71, $P<0.00001$; participants=968 [CCRT:486, RT:482]; studies=13; $I^2=23\%$) were significantly improved in CCRT group (Figure 3). CCRT also obviously prolonged 1-year OS (RR 0.44, 95% CI 0.26–0.77, $P=0.004$; participants=507 [CCRT: 256, RT: 251]; studies=6; $I^2=0\%$), when compared with IMRT alone. Furthermore, results showed that 3-year OS (RR 0.61, 95% CI 0.39–0.95, $P=0.03$; participants=223 [CCRT: 113, RT: 110]; studies=2; $I^2=12\%$) and 5-year OS (RR 0.64, 95% CI 0.45–0.91, $P=0.01$; participants=154 [CCRT: 78, RT: 76]; studies=2; $I^2=0\%$) were significantly prolonged in CCRT group (Figure 4). Among these 15 papers, 3 reported distant metastasis rate, and all

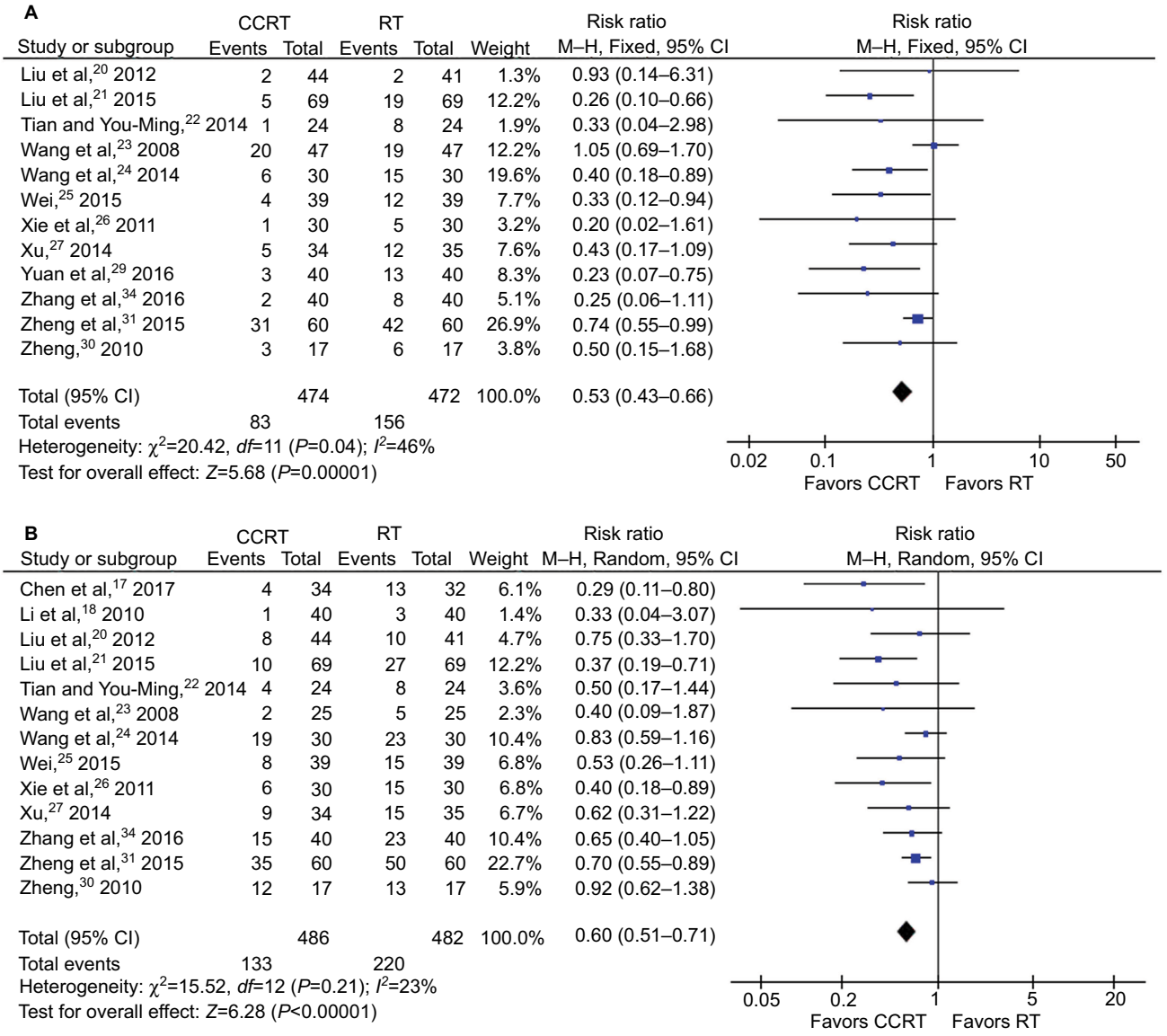

Figure 3 Forest plot of the comparison between CCRT and IMRT alone for (**A**) overall response rate and (**B**) complete response rate.
Abbreviations: CCRT, concurrent chemoradiotherapy; *df*, degrees of freedom; IMRT, intensity-modulated radiotherapy; M–H, the Mantel–Haenszel method; RT, radiotherapy alone.

showed that the addition of concurrent chemotherapy contributed to a significant decrease in distant metastasis rate, compared with IMRT alone.[21,25,29]

In CCRT group, higher grade 3–4 adverse reaction was observed in hematologic toxicity (RR 2.25, 95% CI 1.54–3.29, $P<0.0001$; participants=627 [CCRT: 316, RT: 311]; studies=9; $I^2=42\%$), radiation-induced oral mucositis (RR 1.64, 95% CI 1.14–2.35, $P=0.007$; participants=469 [CCRT: 237, RT: 232]; studies=7; $I^2=8\%$) and radiodermatitis (RR 1.80, 95% CI 1.13–2.88, $P=0.01$; participants=469 [CCRT: 237, RT: 232]; studies=7; $I^2=14\%$), as shown in Figure 5. Only grade 3–4 gastrointestinal reaction (RR 1.19, 95% CI 0.14–9.82, $P=0.87$; participants=579 [CCRT: 292, RT: 287]; studies=8; $I^2=86\%$) was not significantly different between these two groups. We observed that grade 3–4 gastrointestinal reaction had obvious heterogeneity. Subgroup analyses were conducted (Figure S2), and results showed that heterogeneity was obviously decreased in the subgroup using different chemotherapy regimens. Cisplatin-based concurrent chemotherapy indicated higher grade 3–4 gastrointestinal reaction in CCRT group than in RT group, while no obvious increase of grade 3–4 gastrointestinal reaction was found in nedaplatin-based studies.

We performed a sensitivity analysis by excluding each study once in all of the genetic models. No obvious influence on final results, including ORR, CRR, OS and grade

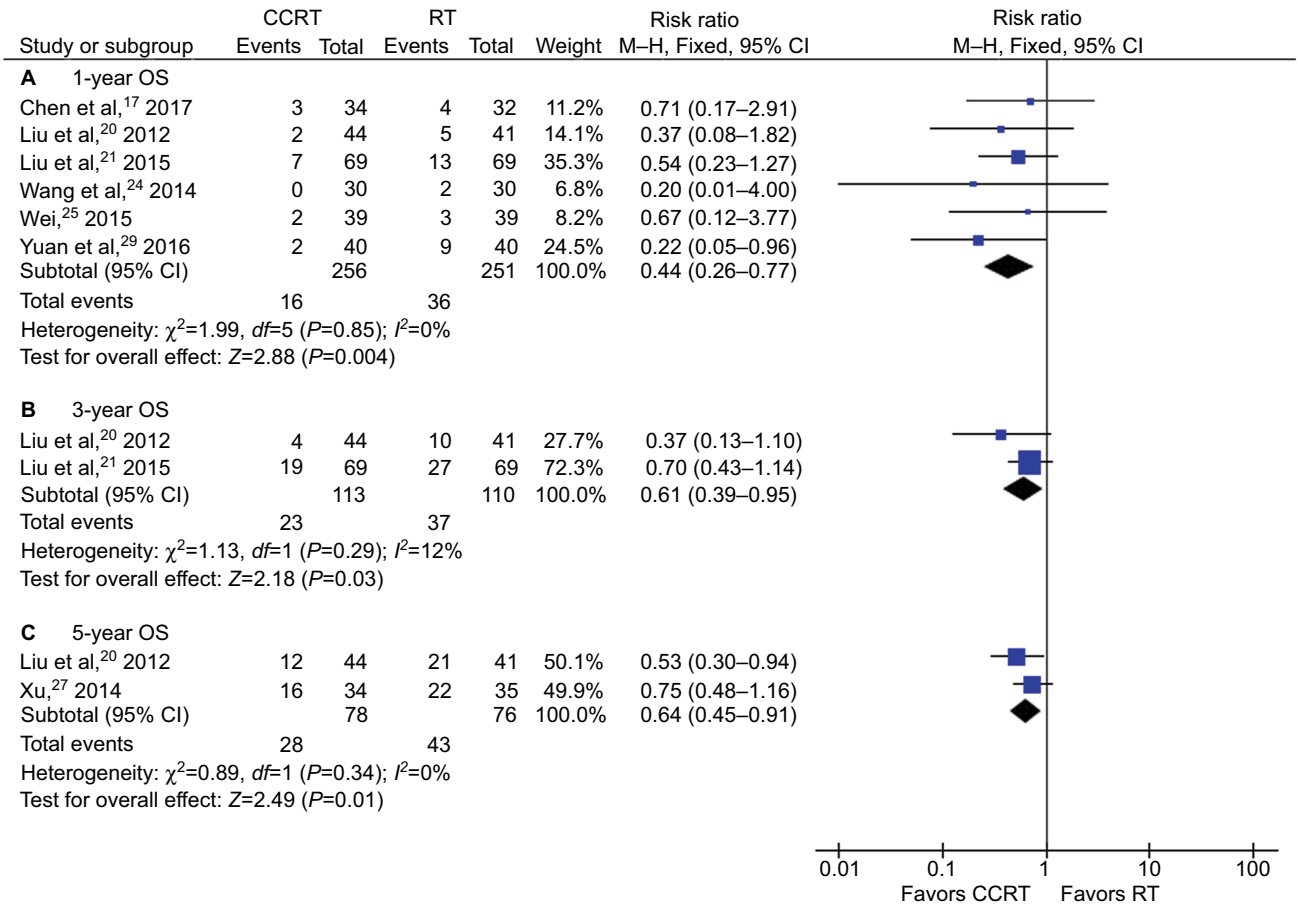

Figure 4 Forest plot of the comparison between CCRT and IMRT alone for OS.
Note: (**A**) 1-year OS, (**B**) 3-year OS, and (**C**) 5-year OS.
Abbreviations: CCRT, concurrent chemoradiotherapy; *df*, degrees of freedom; IMRT, intensity-modulated radiotherapy; M–H, the Mantel–Haenszel method; OS, overall survival; RT, radiotherapy.

3–4 adverse reaction, was observed after excluding each study.

Discussion

NPC has an uneven worldwide distribution and a high incidence rate is found in Southeast Asia.[1] RT is the main treatment for NPC. However, the 5-year OS rate for LANPC is only 67%–77% by utilizing 2D-RT.[3] With the development of RT technology, IMRT is recommended to treat NPC because it brings better tumor target coverage and less radiation-associated toxicities.[6,7,32] In the era of IMRT, it is unclear whether adding concurrent chemotherapy provides additional benefits for LANPC.

In this meta-analysis, all included studies were prospective randomized controlled studies. The analysis results pooling 15 clinical studies indicated that concurrent chemotherapy plus IMRT contributed to better prognosis than IMRT alone. CCRT significantly improved ORR, CRR, and OS. As for the treatment-associated toxicities, CCRT led to more tolerated adverse events compared with IMRT alone.

Previous published meta-analyses showed that the addition of concurrent chemotherapy improved prognosis in LANPC patients in the era of 2D-RT. For example, it was reported that the 5-year OS was significantly improved after the addition of concurrent chemotherapy in a meta-analysis from 16 trials involving 2576 patients with LANPC, when compared with RT alone.[33] Furthermore, a meta-analysis, pooling the data of NPC in endemic areas, showed that CCRT group also improved the 5-year OS, compared with RT alone.[34] In terms of toxicities, the addition of concurrent chemotherapy is associated with higher incidences of acute and late toxicities. It was shown that cisplatin-based chemotherapy combined with RT increased the risk of treatment-related death and acute toxicities, and the overall incidence rates of treatment-related mortality in CCRT and RT alone were 1.7% and 0.8%, respectively.[35] Moreover, the overall

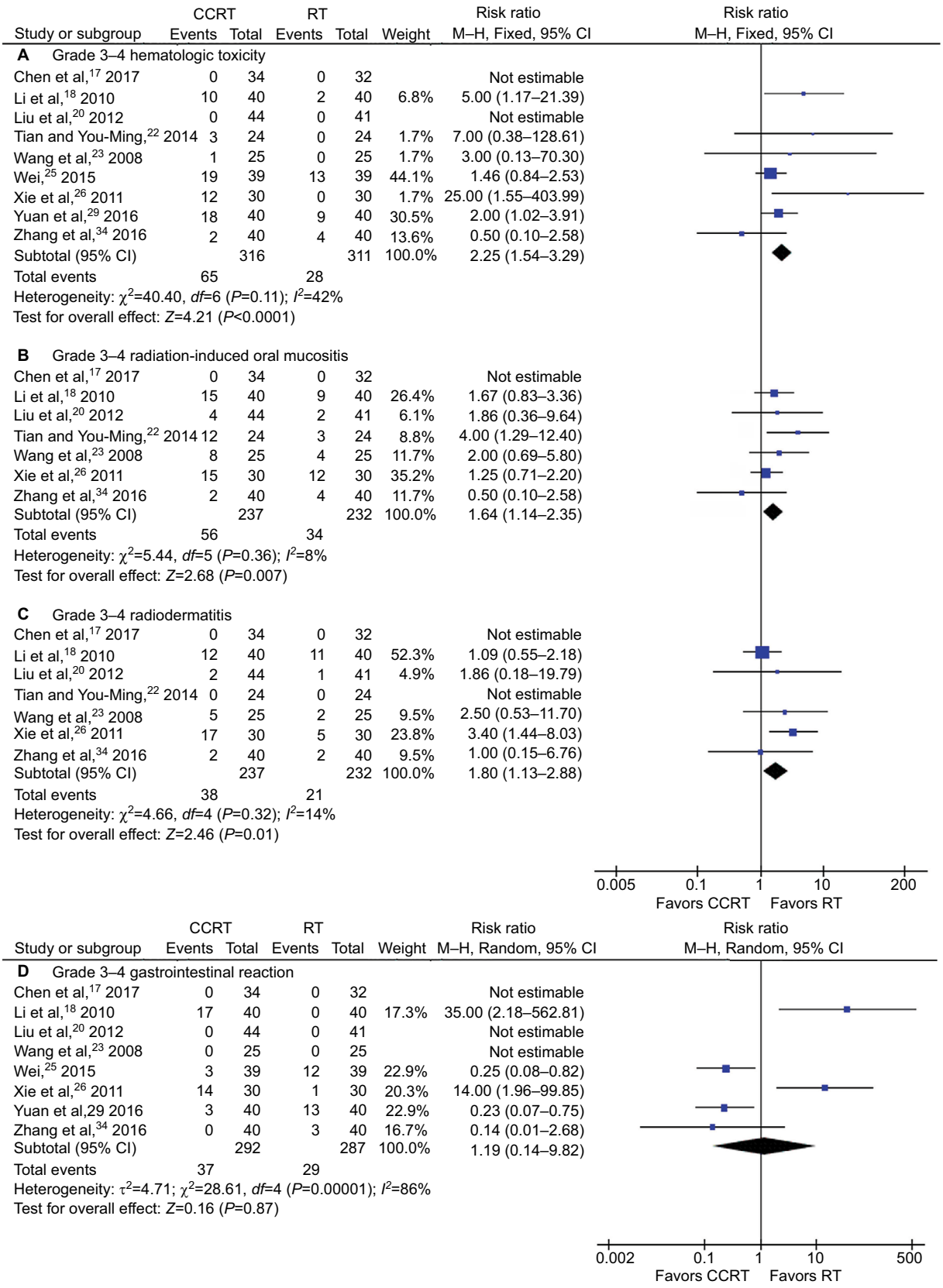

Figure 5 Forest plot of the comparison between CCRT and IMRT alone for grade 3–4 advent events.
Note: (**A**) Hematologic toxicity, (**B**) radiation-induced oral mucositis, (**C**) radiodermatitis, and (**D**) gastrointestinal reaction.
Abbreviations: CCRT, concurrent chemoradiotherapy; *df*, degrees of freedom; IMRT, intensity-modulated radiotherapy; M–H, the Mantel–Haenszel method; RT, radiotherapy.

incidence of late toxicities was 30.7% in CCRT group, while it was 21.7% in RT alone group.[36] In these meta-analyses, the radiation mainly utilized 2D-RT methods, and a very small group of patients were treated with IMRT. These data are consistent with our conclusions that concurrent chemotherapy improves OS in LANPC, compared with IMRT alone.

To our knowledge, this is the first meta-analysis focusing on comparing the efficacy and toxicity of CCRT to IMRT alone for LANPC. This meta-analysis has several limitations. First, randomization method and allocation concealment were not reported in all included studies. Second, the recruited patient population was small in these included studies. Third, the median follow-up time is not long enough in some trials. Thus, we need multicenter randomized controlled trials and long-term follow-up to evaluate the eventual efficacy and toxicity of concurrent chemotherapy plus IMRT.

In conclusion, in the era of IMRT, current evidences show that compared with RT alone, CCRT still brings clinical benefit in LANPC with acceptable toxicities.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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