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Toxicities of chemoradiotherapy and radiotherapy in nasopharyngeal carcinoma: an updated meta-analysis

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Abstract

Objective: We investigated the risk of acute and late toxicities of concurrent chemoradiotherapy (CCRT) and radiotherapy alone in patients with nasopharynx carcinoma (NPC).

Methods: In this meta-analysis, we searched the PubMed, Embase, Cochrane Library, and Web of Science databases for eligible randomized clinical trials (RCTs). In addition to the incidence of specific toxicities, risk ratios (RRs) or odd ratios (ORs) and 95% confidence intervals (CIs) were obtained using fixed-effect or random-effects models.

Results: In total, 11 RCTs involving 2801 patients with NPC were included in this analysis. For grade $\geq$3 adverse events, patients who received CCRT treatment had a higher proportion of acute mucositis (39.9% vs. 30.5%, RR=1.30, 95%CI, 1.16–1.46) acute nausea and vomiting (RR=6.26, 95% CI: 2.01–19.45), and neutropenia (RR=30.86, 95% CI: 7.36 to 129.35). For late severe toxicities, CCRT treatment was significantly associated with higher incidence of hearing loss (116.56% vs. 411.43%, RR=1.461, 95%CI, 1.043–21.095). The incidence of acute nausea and vomiting was more frequent in patients receiving CCRT.

Conclusion: Compared with radiotherapy alone, CCRT increases the risk of severe acute toxicities (mucositis, nausea/vomiting, and neutropenia) and severe late toxicity (hearing loss) in patients with NPC. However, larger studies are needed to confirm this finding.

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Introduction

Nasopharyngeal carcinoma (NPC) is a rare type of malignant carcinoma that has a specific geographical distribution and a high risk of distant metastases. In Southeast Asia, the annual incidence rate ranges from 0.15% to 0.5%.[1] Radiotherapy is the cornerstone of initial treatment due to the radio-sensitivity of NPC and its deep-seated location. However, although radiotherapy alone is an efficacious treatment option for early-stage NPC, the prognosis of patients with locally advanced NPC remains unsatisfactory.[2,3] Distant metastasis is the main cause of treatment failure in regionally advanced NPC.[4,5] Since the publication of the findings of the 0099 (INT-0099) trial,[6] concurrent chemoradiotherapy (CCRT) has been the standard therapy for locally advanced NPC,[7,8] and further clinical trials have demonstrated that the 5-year overall survival (OS) rate for patients receiving CCRT is 11.7% higher than that for patients receiving radiotherapy alone.[9] Recurrence-free survival and metastasis-free survival have also been shown to be improved in patients with NPC receiving CCRT.[10] In addition, several other studies and meta-analyses have confirmed that CCRT confers additional benefits compared with radiotherapy alone.[11,12]

Equally important is the frequency and type of adverse events associated with combination treatment of concurrent chemotherapy and radiotherapy. Severe toxicities can impair treatment compliance, diminish patient quality of life, and even be life-threatening. During radiotherapy, up to 95% of patients with NPC showed various levels of dosage-dependent acute dermatitis, contributing to increased risk of infection and delayed treatment. Furthermore, the combined activity of anti-neoplastic drugs and radiographic exposure may induce injuries to the oral mucosa and apoptosis of oral epithelial cells approximately 6–15 days after treatment initiation.[13] Although several studies have investigated the toxicities of CCRT and radiotherapy,[3,14–16] no study to date has compared these treatment modalities across almost all categories of acute and late severe (grade 3/4) adverse events in a large patient population.

The objective of the present meta-analysis, which includes almost all eligible randomized controlled trials (RCTs), was to comprehensively compare the incidence and risk of acute and late severe toxicities between CCRT and radiotherapy alone in a large sample size and to provide clinical evidence for the need for increased attention to toxicities in patients with NPC.

Methods and materials

Identification of studies

This meta-analysis was implemented on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[17] Relevant studies were identified by searching the PubMed, Embase, Cochrane Library, and Web of Science databases to a cut-off date of September 30, 2016, regardless of language

or publication status. The search was conducted using the keywords "*nasopharynx cancer or nasopharyngeal carcinoma or nasopharyngeal neoplasms*", "*radiochemotherapy or chemoradiotherapy or chemoradiation or chemo-radiotherapy*" and "*toxicities or adverse event or side effect or adverse reaction or safety issue*," and was limited to human studies and clinical trials. The reference lists of relevant original and review articles were also manually searched to identify additional studies.

Study inclusion and exclusion criteria

Only RCTs in which CCRT was compared with radiotherapy alone in patients with NPC and in which detailed data on acute or late toxicities were reported were eligible for inclusion in the meta-analysis. Studies meeting the following additional standards were included: (1) endpoints regarding acute toxicities of CCRT and radiotherapy covering at least one of dysphagia, dermatitis, hearing loss, peripheral neuropathy, constipation, mucositis, and nausea and vomiting; (2) endpoints concerning late toxicities including at least one of xerostomia, dysphagia, mucositis, nasopharyngeal mucosal necrosis, otitis, hearing loss, brachial plexopathy, bone necrosis, temporal lobe necrosis, symptomatic brain damage, radiation-induced brain damage, radiation encephalopathy, endocrine dysfunction, visual toxicity, radiation-induced malignancy, secondary tumor, subcutaneous fibrosis, torrential bleeding, trismus, and spinal damage. Additionally, studies were excluded if they (1) were case reports, meeting abstracts, or editorial materials; or (2) were duplicated, incomplete, or outside of the range of the research topic.

Data extraction

Two reviewers independently extracted the data on study characteristics of CCRT and radiotherapy groups (e.g. sample size, ethnicity, and mean age of the study subjects), publication year, treatment arms, number of patients who suffered from acute or late toxicities, duration of follow up, and counts of acute and late toxicities. Where there was disagreement between the two reviewers, the opinion of a third reviewer was obtained.

Statistical analysis

The software R 3.3.1 (www.r-project.org) including the meta package was used for direct meta-analysis.[18] First, a frequency table was generated to describe each toxicity item based on counts of toxic events or number of subjects with reported toxic events. The distinctions of dichotomous variables were statistically evaluated with the use of the risk ratio (RR) according to event frequency or odds ratio (OR) according to subject frequency with a two-tailed 95% confidence interval (CI).One fixed-effect model was established for consistent studies while a random-effects model was fitted for studies with heterogeneous results. Two-tailed P values <0.05 were considered statistically significant. Heterogeneity between the studies was evaluated by means of I^2 (if $I^2>50\%$)[19] and the Q test of Cochran (if $P<0.10$).[20] Both indices assess the percentage of variability across studies that is attributable to heterogeneity rather than to chance.

Results

Search results and study characteristics

Eleven eligible RCTs[6,10,21–29] involving 2801 patients were included in the meta-analysis after excluding reviews, irrelevant studies, and duplicates. Figure 1 shows the details of the study selection process. Among the included studies, only two used intensity-modulated radiation therapy, while conventional irradiation was used in

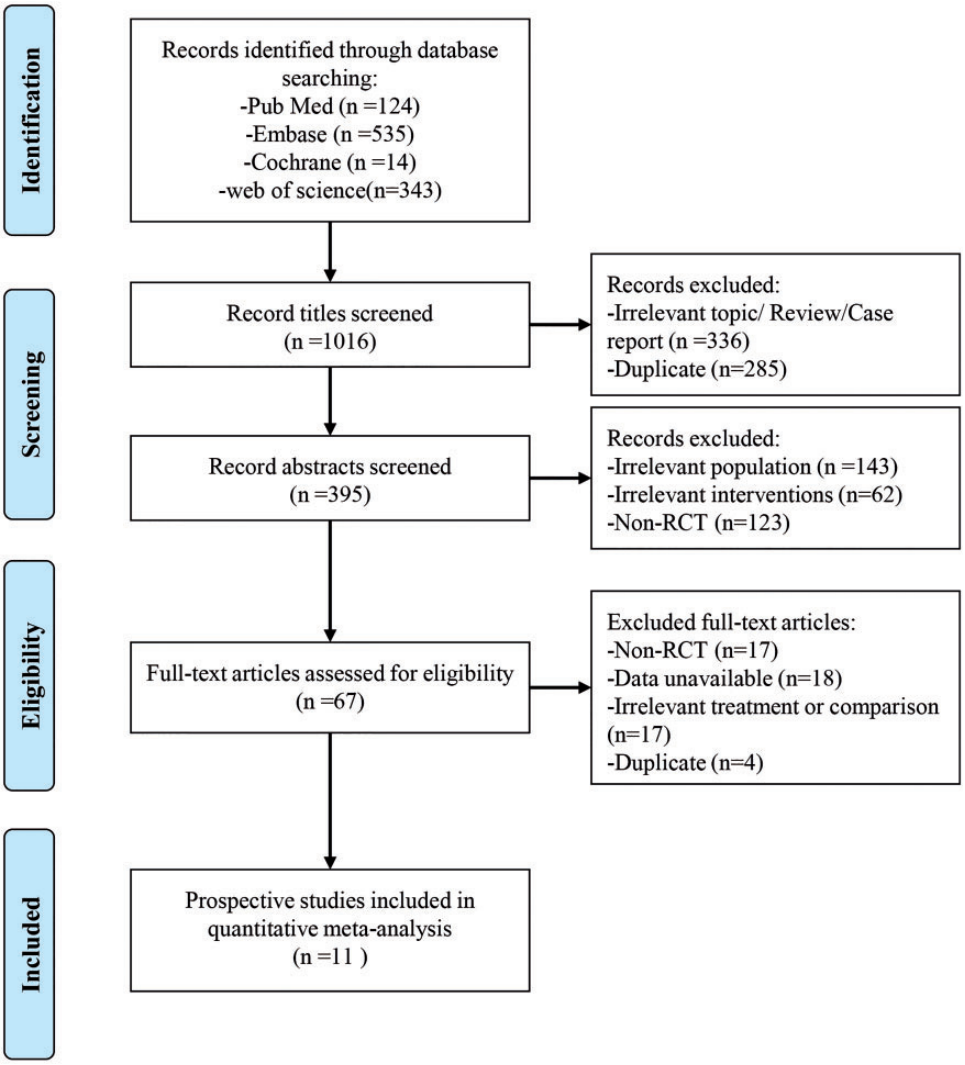

Figure 1. PRISMA flow chart.

the remaining studies. The main characteristics of the included studies are presented in Table 1. Patients were recruited between 1989 and 2008, and the median follow-up period was 35 months–7.3 years. The mean age of patients in the CCRT group in all studies was 42–50 years, while patients in the radiotherapy group were aged 44.3–52 years. The CCRT group received treatment including cisplatin, cisplatin complexes, 5-fluorouracil, oxaliplatin, and carboplatin, although the administration duration and dosage varied among the included studies. The prescribed dose among patients in the radiotherapy group was generally in the range of 60–70 Gy. Publication bias was not assessed in this meta-analysis as there were as many as ten toxicity endpoints with varying sample sizes included. The selected studies all featured

Table 1. Characteristics of randomized clinical trials included in the meta-analysis.

First author/ year [ref]	Inclusion period/ stage/ median follow-up	Group description/ patients, n	Mean age, years	Treatment 1	Treatment 2
Chen/2013[24]	2002–2005/AJCC stage III–IVB/70 months	RT/158 CRT/158	46 46		
Huang/ 2012[25]	2002–2005/Chinese 1992 staging system stage III or IV/7.3 years	IC+CCRT/201 IC+RT/199	42.7 43.3	RT: carboplatin (AUC = 6) on days 7, 28, and 49	IC: two cycles of floxuridine (FuDR) + carboplatin (FuDR, 750 mg/m^2, days 1–5; carboplatin, AUC = 6) RT: 36–40 Gy in the first course and 66–78 Gy to the primary tumor and 60–70 Gy to the neck in the second course. Conventional fractionated radiotherapy (2 Gy once daily, 5 times per week)
Lee/2010[26]	1999–2004/AJCC stage T1–4 N2–3 M0/5 years	CCRT/172 RT/176	46 47	CCRT: cisplatin (100 mg/m^2) given intravenously every 3 weeks for three cycles starting with commencement of radiotherapy, followed by a combination of cisplatin (80 mg/m^2) plus fluorouracil (1000 mg/m^2 per day by 96-hour infusion) every 4 weeks for three cycles	RT: ≥66 Gy (2 Gy/Fx/day, 5 Fx/week)
Chen/2007[28]	2002–2005/AJCC stage T3–4 Nx M0 or Tx N2–3 M0/ 29 months	RT/158 CRT/158	46 46	CCRT: cisplatin (40 mg/m^2 on day 1) for 7 weeks during the RT phase; combination of cisplatin (80 mg/m^2 intravenously) on day 1 and fluorouracil	RT: 68–70 Gy to the primary tumor, 60–62 Gy to involved areas of the neck, and 50 Gy to uninvolved areas

(continued)

Table 1. Continued

First author/ year [ref]	Inclusion period/ stage/ median follow-up	Group description/ patients, n	Mean age, years	Treatment 1	Treatment 2
				(800 mg/m^2 intravenously) on days 1–5 by 120-h infusion for 3 cycles	
Zhang/ 2005[10]	2001–2003/AJCC stage T1–4 N0–3/24 months	RT/56 CCRT/59	46.3 45.7	CCRT: oxaliplatin 70 mg/m^2 weekly for six doses from the first day of RT	RT: five times a week at 2 Gy/ day on Monday through Friday
Wee/2005[29]	1997–2003/T3–4 Nx M0 or Tx N2–3 M0/3.2 years	RT/110 CCRT/111	46 49	CCRT: cisplatin (25 mg/m^2 on days 1–4) on weeks 1, 4, and 7 of RT AC: cisplatin (20 mg/m^2 on days 1–4) and fluorouracil (1000 mg/m^2 on days 1–4) every 4 weeks (weeks 11, 15, and 19) for three cycles after completion of RT	Standard-course RT: 70 Gy in 35 fractions (2 Gy per fraction)
Lin/2003[31]	1993–1999/AJCC stage T1–4 N0–3 overall III–IV (M0)/ 65 months	CCRT/141 RT/143	45 48	CCRT: cisplatin 20 mg/m^2/d in normal saline with fluorouracil (FU) 400 mg/m^2/d as a 96-hour continuous infusion during weeks 1 and 5 of RT	RT: 70–74 Gy/7–8 weeks to the primary tumor and positive neck region and 50–60 Gy/5–6 weeks to the negative neck region
Chan/2002[32]	1994–1997/Ho's N2 or N3 stage or N1 stage with nodal size $\geq$4 cm/ 2.71 years	RT/176 CCRT/174	45.5 44	CCRT: cisplatin 40 mg/m^2 in 1 L of normal saline over 2 hours on a weekly basis during external radiotherapy, starting on the first day of radiotherapy	RT: 66 Gy in 33 fractions per 6.5 weeks

(continued)

Table 1. Continued

First author/ year [ref]	Inclusion period/ stage/ median follow-up	Group description/ patients, n	Mean age, years	Treatment 1	Treatment 2
Al-Sarraf/ 1998[6]	1989–1995/stage III and IV/ 2.7 years	Control/69	52		RT: 1.8–2.0 Gy/day fractions, Monday to Friday for 35 to 39 fractions for a total dose of 70 Gy
		CCRT/78	50	CCRT: cisplatin 100 mg/m^2 on days 1, 22, and 43 during radiotherapy; postradiotherapy, chemotherapy with cisplatin 80 mg/m^2 on day 1 and fluorouracil 1000 mg/m^2/d on days 1–4 administered every 4 weeks for three courses	
Wu/2013[23]	2001–2003/AJCC stage T1–4 N0–3; WHO subtype II, or III NPC/114 months	Control/56	–		RT: The accumulated radiation doses to the primary tumor were 70–74 Gy. The accumulated doses were 60–64 Gy to the involved areas of the neck
		CCRT/59	–	CCRT: oxaliplatin 70 mg/m^2 delivered via intravenous infusion 1 h on day 1 every week	
Lee/2011[27]	1999–2004/T3–4 N0–1 M0/ 6.3 years	CF/42	49		RT: 2 Gy/Fx/day, 5 Fx/week
		AF/51	48		RT: 2 Gy/Fx/day, 6 Fx/week
		CF+C/52	47	CRT: cisplatin 100 mg/m^2 intravenously every 3 weeks for 3 cycles starting with the commencement of RT, followed by a combination of cisplatin 80/ m^2 plus fluorouracil 1000 mg/ m^2/day by 96-h infusion every 4 weeks for 3 cycles	RT: 2 Gy/Fx/day, 5 Fx/week
		AF+C/44	50		RT: 2 Gy/Fx/day, 6 Fx/week

randomization to treatment arm, indicating that the data were likely to be robust (Table 2).

Incidence and risk of specific acute toxicities

For grade ≥3 toxicities, CCRT was significantly associated with higher incidence of mucositis (36.6% vs. 29%), nausea and vomiting (14.6% vs. 0.2%), and neutropenia (22.8% vs. 0.3%). According to subject frequency, all patients experienced any grade toxicities, and more patients experienced grade ≥3 nausea and vomiting in the CCRT group. In the radiotherapy alone group, no patient experienced grade ≥3 nausea and vomiting (Table 3).

As shown in Figure 2, CCRT significantly increased the risk of acute mucositis, whether assessed by event frequency (RR=1.26, 95% CI: 1.10–1.44, $P<0.001$) or subject frequency (RR=1.62, 95% CI: 1.05–2.50, $P=0.029$). Furthermore, CCRT significantly increased the risk of acute nausea/vomiting (RR=31.28, 95% CI: 7.70–127.06, $P<0.001$) and acute neutropenia (RR=55.85, 95% CI: 11.20–278.58, $P<0.001$) when compared with radiotherapy alone. No significant differences were observed between the groups in the risk of acute dermatitis and acute hepato-renal dysfunctions.

Incidence and risk of specific late toxicities

For late grade ≥3 toxicities, the event frequency of hearing loss (20.6% vs. 13.5%), mucositis (45.4% vs. 31.0%), and neutropenia (13.5% vs. 0%) was significantly higher in the CCRT group (Table 4). Our meta-analysis showed that CCRT was significantly associated with elevated risk of late severe hearing loss (RR=1.52, 95% CI: 1.03–2.25, $P=0.037$) compared with radiotherapy (Figure 3). For grade ≥3 xerostomia, the incidence in the CCRT group and the radiotherapy alone group was 5.8% and 2.4%, respectively, and the difference between the groups was not significant.

Discussion

To the best of our knowledge, this is the first meta-analysis that comprehensively compares the incidence and risk of severe acute and late toxicities associated with CCRT versus radiotherapy alone in a large population of patients with NPC. This meta-analysis included 11 RCTs,

Table 2. Risk for bias assessment in selected randomized controlled trials

Authors/year	Concealed randomization	Stopped early	Participants blinded	Health-care providers blinded	Data collectors blinded	Outcome assessors blinded
Chen/2013	Yes	No	Yes	Yes	Yes	Yes
Huang/2012	Yes	No	Not specified	Not specified	Not specified	Not specified
Lee/2010	Yes	No	Not specified	Not specified	Not specified	Not specified
Chen/2007	Yes	No	Not specified	Not specified	Not specified	Yes
Zhang/2005	Not specified	No	Not specified	Not specified	Not specified	Not specified
Wee/2005	Yes	No	Not specified	Not specified	Not specified	Not specified
Lin/2003	Not specified	No	Not specified	Not specified	Not specified	Not specified
Chan/2002	Yes	No	Not specified	Not specified	Not specified	Not specified
Al-Sarraf/1998	Not specified	No	Not specified	Not specified	Not specified	Not specified
Lee/2011	Not specified	No	No	No	Not specified	Not specified
Wu/2013	Not specified	No	Not specified	Not specified	Not specified	Not specified

Table 3. Summary of acute toxicities (grade 3/4 and any grade)

	No. of studies	Treatment group				P value for ≥3 grade
		Concurrent chemoradiotherapy		Radiotherapy alone		
		≥3 grade	Any grade	≥3 grade	Any grade	
By event frequency						
Mucositis[4,5,26,27]	4	229/626 (36.6%)	–	182/627 (29.0%)	–	0.0047
Dysphagia[24]	1	1/158 (0.6%)	–	0/158	–	>0.9999
Ear deafness[27]	1	4/95 (4.2%)	–	0/94	–	0.1210
Liver and kidney dysfunction[26,27]	2	4/277 (1.4%)	–	0/270	–	0.1238
Nausea and vomiting[24,26,27]	3	62/425 (14.6%)	–	1/428 (0.2%)	–	<0.0001
Neutropenia[24,26]	2	82/334 (22.8%)	–	1/334 (0.3%)	–	<0.0001
Peripheral neuropathy[27]	1	0/95		1/94 (1.1%)	–	0.4974
Radioactive skin reaction[24,26,27]	3	64/425 (15.1%)	–	50/428 (11.7%)	–	0.1473
By subject frequency						
Mucositis[10,31]	3	76/259 (29.3%)	259/259 (100.0%)	56/255 (22.0%)	255/255 (100.0%)	0.0289
Dysphagia[10]	2	0/118	118/118 (100.0%)	0/112	112/112 (100.0%)	-
Nausea and vomiting[31,32]	2	27/315 (8.6%)	315/315 (100.0%)	0/319	319/319 (100.0%)	< 0.0001

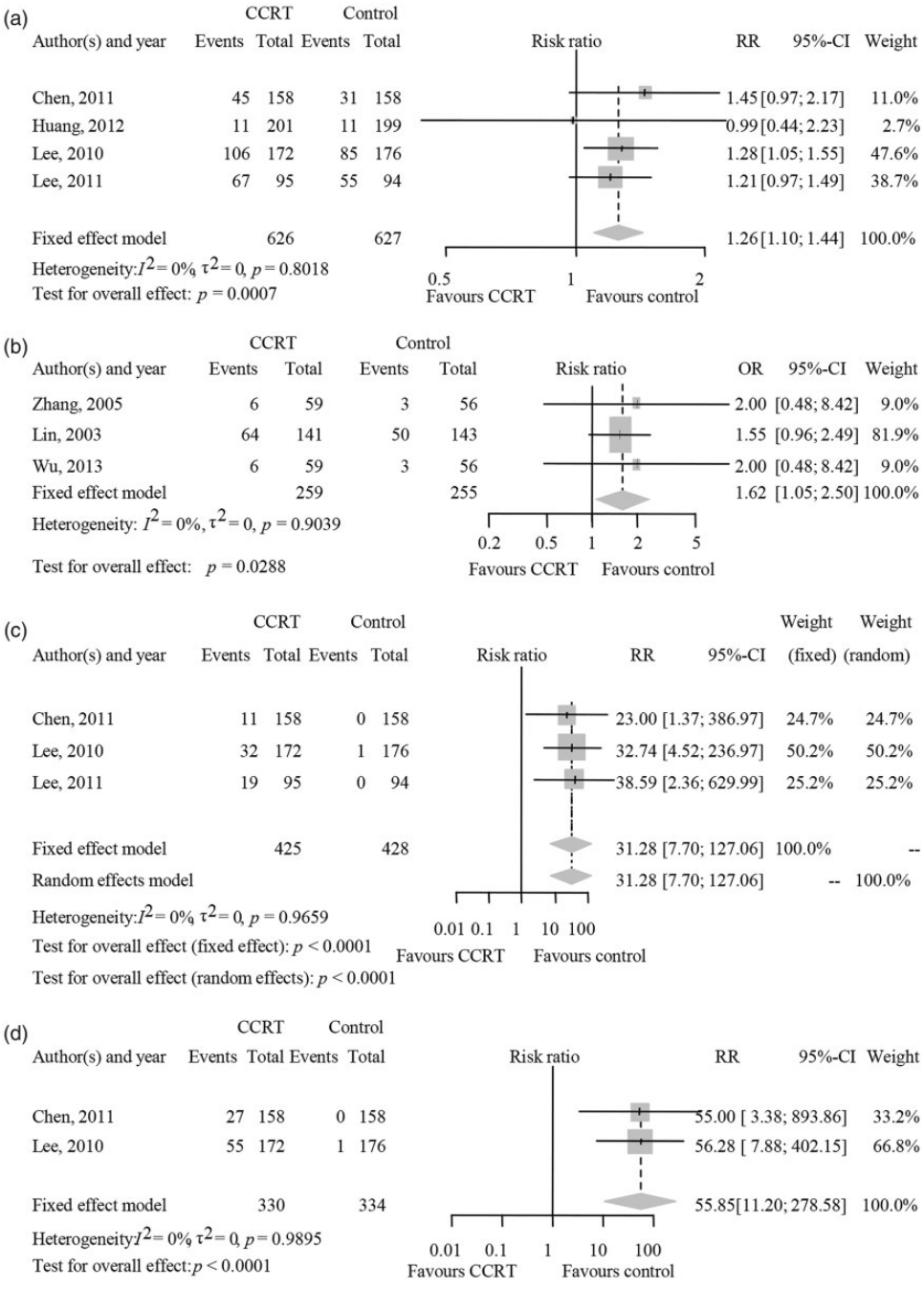

Figure 2. Forest plot comparing acute toxicities between CCRT and radiotherapy alone according to event frequency of grade 3/4 mucositis (a); subject frequency of grade 3/4 mucositis (b); event frequency of grade 3/4 nausea and vomiting (c); and event frequency of grade 3/4 neutropenia (d). Size of the data square marker indicates the weight of each study in this analysis. The diamond represents the overall estimated effects in the model. CCRT: concurrent chemoradiotherapy; CI: confidence interval; OR: odds ratio; RR: risk ratio.

Table 4. Summary of late toxicities (grade 3/4 and any grade)

	No. of studies	Treatment group				P value for ≥3 grade
		Concurrent chemoradiotherapy		Radiotherapy alone		
		≥3 grade	Any grade	≥3 grade	Any grade	
By event frequency						
Hearing loss[24,27]	2	52/253 (20.6%)	–	34/252 (13.5%)	–	0.0438
Dysphagia[26,27]	2	2/267 (0.7%)	–	0/270	–	0.2467
Mucositis[28,29]	2	122/269 (45.4%)	–	83/268 (31.0%)	–	0.0006
Mucositis[26]	1	4/172 (2.3%)		1/176 (0.5%)	–	0.2108
Otitis[26]	1	37/172 (21.5%)	–	27/176 (15.3%)	–	0.1374
Peripheral neuropathy[25–27]	3	7/425 (1.6%)	–	2/428 (0.5%)	–	0.1065
Cranial neuropathy[24,26,27]	3	15/425 (3.5%)	–	15/428 (4.3%)	–	>0.9999
Brachial plexopathy[26,27]	2	0/267	–	2/270 (0.7%)		0.4991
Bone necrosis[24,26]	2	2/330 (18.2%)	–	0/334	–	0.2466
Temporal lobe Necrosis[24,27]	1	6/253 (2.3%)	–	9/252 (3.5%)	–	0.4271
Fibrosis[24,26,27]	3	19/425 (4.5%)	–	15/428 (35.0%)	–	0.4709
Symptomatic brain damage[24]	1	1/158 (0.6%)	–	1/158 (0.6%)	–	>0.9999
Endocrine dysfunction[26,27]	2	16/267 (59.9%)	–	13/270 (4.8%)	–	0.5460
Visual toxicity[24,27]	2	3/253 (1.2%)	–	2/252 (0.8%)	–	>0.9999
Radiation-induced malignancy[24,26]	2	0/330	–	1/334 (0.3%)	–	>0.9999
Spinal damage[24]	1	0/158	–	0/158	–	–
Neutropenia[29]	1	15/111 (13.5%)	–	0/110	–	<0.0001
Nausea and vomiting[29]	1	1/111 (0.9%)	–	0/110	–	>0.9999
Brainstem damage[26]	1	0/172	–	1/176 (0.6%)	–	>0.9999
Vascular occlusion[26]	1	1/172 (0.6%)	–	0/176	–	0.4943
By subject frequency						
Mucositis[10]	1	0/59	59/59 (100.0%)	0/56	56/56 (100.0%)	–
Hearing loss[6]	1	9/78 (11.5%)	61/78 (78.2%)	3/69 (4.3%)	54/69 (78.3%)	0.1120
Nausea and vomiting[6]	1	14/78 (17.9%)	39/78 (50.0%)	5/69 (7.2%)	46/69 (66.7%)	0.0536
Total late toxicities[10]	1	17/59 (28.8%)	59/59 (100.0%)	11/56 (19.6%)	56/56 (100.0%)	0.2521

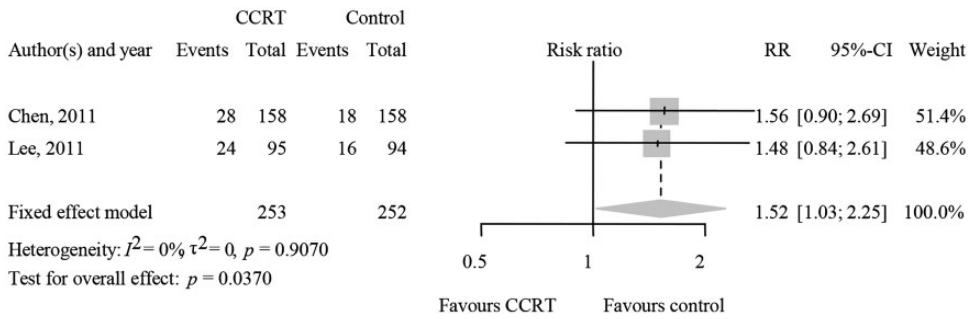

Figure 3. Forest plot comparing late toxicities between CCRT and radiotherapy alone by event frequency of late grade 3/4 hearing loss. Size of the data square marker indicates the weight of each study in this analysis. The diamond represents the overall estimated effects in the model. CCRT: concurrent chemo-radiotherapy; CI: confidence interval; RR: risk ratio.

with 2801 patients in total, to compare the toxicities associated with these two treatment modalities. By evaluating the incidence of five subtypes of acute toxicity (mucositis, nausea and vomiting, neutropenia, dermatitis, and hepato-renal function) and four subtypes of late toxicity (cranial neuropathy, hearing loss, peripheral neuropathy, and fibrosis of the neck), we showed that CCRT was associated with more severe acute mucositis, acute nausea/vomiting, acute neutropenia, and late hearing loss than radiotherapy alone. Among the enrolled studies, the median follow-up varied from 35 months to 7.3 years, durations which were appropriate for the analysis of late toxicities. In the present study, toxicities were the primary endpoint, and data on acute, late, and severe toxicities associated with CCRT and radiotherapy were recorded and analyzed to produce a comprehensive analysis of the types and severity of toxicities associated with CCRT and radiotherapy.

For acute toxicities, including grade 3/4 acute toxicities, this meta-analysis showed that CCRT was associated with higher risk of acute mucositis and nausea compared with radiotherapy, consistent with previous reports.[32] The duration and severity of mucositis caused by radiotherapy have been closely correlated with the integrated action of accumulated dose, radioactive source, irradiation volume of mucosa, dose intensity, and xerostomia.[31,32] Endothelial tissues and epithelium of connective tissues are damaged during radiotherapy, and the release of inflammatory factors such as prostaglandins, tumor necrosis factor, and interleukin-1 can aggravate tissue injury.[33] Somewhat distinct from radiotherapy, mucositis induced by chemotherapy is mainly attributable to the route of administration, dose intensity, duration of therapy, and chemotherapeutic drug used. Normal DNA synthesis can be affected by chemotherapy, and the repeated and continuous usage of low-dose cytotoxic agents can further exacerbate the risk of mucositis.[34] Therefore, CCRT appeared to promote the development of oral mucositis to a greater extent than radiotherapy alone. In clinical practice, anti-neoplastic drugs are typically administered 1 week after initiation of radiotherapy, leading to further injury to the oral mucous epithelium and associated formation of anabrosis.[35]

For late toxicities, our meta-analysis showed that CCRT was significantly associated with late grade 3/4 hearing loss, consistent with previous reports.[15,36] The inclusion of studies that used discrepant chemotherapeutic regimens for treating patients with NPC might have affected the

credibility of this association. Thus, the meta-analysis considered only the general outcomes of chemotherapy and the findings may therefore be inapplicable to specific medications. Any one of these chemotherapeutic studies may inevitably have over- or underestimated the association between CCRT and risk of late hearing loss.

Two of the included RCTs reported cases of bone necrosis when comparing CCRT with radiotherapy ($1:0^4$ and $1:1^7$). No further evaluation of this finding was carried out because of the small number of RCTs included. Furthermore, a study by Lee et al.[37] in 2013 found that concurrent chemotherapy was not associated with a significant increase in the risk of bone necrosis. Future studies in larger populations are needed to further explore these observations.

This study was limited by a lack of heterogeneity as all included studies enrolled only subjects of Chinese Han ethnicity, meaning that it may be difficult to generalize the results to other populations. In addition, there might be potential mutations that could affect the efficacy of CCRT. For instance, it was reported that non-small-cell lung cancer (NSCLC) patients who carried epidermal growth factor receptor (EGFR) mutations (e.g. exon 19 deletions and the L858R point mutation) could achieve better efficacy after treatment of gefitinib than those with normal EGFR genotypes.[38,39] As a result, further molecular studies should be explored to discover potential mutations that might influence NPC patients' responses to different drugs.

There is increasing evidence that, compared with radiotherapy alone, CCRT may improve survival among patients with locally advanced NPC, and CCRT is thus commonly used in clinical practice. For patients at high risk of developing severe toxicities associated with CCRT such as mucositis, nausea and vomiting, and hearing loss should therefore be followed more closely when receiving CCRT.

Conclusions

The current study is the first meta-analysis to comprehensively and intensively analyze and compare acute and late toxicities between CCRT and radiotherapy alone. The findings indicate that CCRT is more likely to induce certain acute severe toxicities (e.g. acute mucositis and acute nausea and vomiting) and late severe toxicity (i.e. hearing loss) than radiotherapy. However, larger studies in more diverse populations are required to stratify patients with NPC by disease grade and specific mutations, and to subsequently compare the incidences of acute and late toxicities after treatment with CCRT or radiotherapy alone.

List of abbreviations

CCRT: concurrent chemoradiotherapy; CI: confidence interval; EGFR: epidermal growth factor receptor; NPC: nasopharynx carcinoma; NSCLC: non-small-cell lung cancer; OR: odd ratio; OS: overall survival; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; RCT: randomized clinical trial; RR: risk ratio

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Availability of data and material

The data extracted and analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Ethical approval

This article does not contain data from any studies with human participants or animals performed

by any of the authors. As the present study was a meta-analysis of published literatures, the study was exempt from Ethics Committee approval.

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