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Research Paper

Chemoradiotherapy Versus Radiotherapy Alone in Stage II Nasopharyngeal Carcinoma: A Systemic Review and Meta-analysis of 2138 Patients

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Abstract

Background: To explore the value of chemoradiotherapy (CRT) in stage II nasopharyngeal carcinoma (NPC) compared to radiotherapy (RT) alone which includes two-dimensional radiotherapy (2D-RT) and intensity-modulated radiotherapy (IMRT).

Methods: All topic-related comparative articles were identified by a comprehensive search of public databases (MEDLINE, EMBASE, Cochrane Library and CBMdisc). The primary outcomes were overall survival (OS), loco-regional relapse-free survival (LRRFS) and distant metastasis-free survival (DMFS). Secondary outcomes were grade 3-4 acute toxicity events. We performed subgroup analysis of CRT versus 2D-RT/IMRT alone to investigate the optimal modality. Sensitivity analysis focused on CRT versus IMRT alone was used to assess stability of the study results.

Results: Eleven comparative studies (2138 patients) were eligible. CRT had significantly higher OS (HR = 0.67, 95% CI = 0.45-0.98, P = 0.04) and LRRFS (HR = 0.61, 95% CI = 0.46-0.80, P = 0.0003) than RT alone, but no significant difference was observed in DMFS (HR = 0.83, 95% CI = 0.52-1.31, P = 0.41). Meanwhile, CRT was associated with higher frequencies of grade 3-4 leukopenia, mucositis and nausea (P = 0.005, 0.03, < 0.0001, respectively). Subgroup analysis showed that IMRT alone could achieve equivalent OS, LRRFS and DMFS compared to CRT (P = 0.14, 0.06, 0.89, respectively). Significant value was only observed in LRRFS for CRT compared to 2D-RT alone (P = 0.01). Sensitivity analysis for the comparison of CRT and IMRT alone demonstrated generally stable outcomes, in support of the final conclusions.

Conclusions: In the treatment of patients with stage II NPC, CRT was better than 2D-RT alone with significant benefit in LRRFS. IMRT alone was superior to CRT with equivalent survival outcomes and fewer grade 3-4 acute toxicities.

Key words: nasopharyngeal carcinoma; stage II; chemoradiotherapy; radiotherapy; intensity-modulated radiotherapy; meta-analysis.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant head and neck cancer, which has a relatively high incidence of 20–30 per 100000 in endemic areas such as southern China and Southeast Asia [1]. NPC is both radiosensitive and chemosensitive; radiotherapy (RT) and various chemoradiotherapy (CRT) schedules are widely used in clinical practice. Concurrent chemoradiotherapy (CCRT) with or without adjuvant

chemotherapy (AC) is regarded as the first choice for loco-regionally advanced NPC (stage III-IVb), and RT alone is the recommended strategy for stage I NPC [2, 3]. However, there are still a lot of controversies in the treatment of patients with stage II NPC.

Only one randomized controlled trial (RCT) compared CRT with two-dimensional radiotherapy (2D-RT) alone in stage II NPC [4]. This study reported that CRT could significantly improve 5-year overall survival (OS) and distant metastasis-free survival (DMFS), but not loco-regional relapse-free survival (LRRFS). However, data from several retrospective studies comparing CRT with 2D-RT alone in stage II NPC showed conflicting results, with non-significant benefit in all survival outcomes [5] or significant benefit only in LRRFS favoring CRT [6]. Importantly, an individual patient data meta-analysis reported that the addition of chemotherapy should be implemented for loco-regionally advanced NPC but not early stage disease [7].

After the advent of intensity-modulated radiotherapy (IMRT), its therapeutic performance has been demonstrated more efficient than conventional RT, since it provides an adequate dose to the primary tumor while enabling improved sparing of the surrounding normal tissues [8, 9]. It has been reported that patients with early stage NPC treated with IMRT alone can achieve 5-year LRRFS and DMFS of 97.7% and 97.8%, and 3-year OS of 96.2% with tolerable toxicities [10, 11]. However, retrospective studies which compared CRT with IMRT alone in stage II NPC showed inconsistent survival outcomes [12-17]; topic-related RCTs were absent from publication. As such, the benefit of CRT in stage II NPC still remains unclear.

In attempt to address this question, we undertook the first meta-analysis of all topic-related comparative studies to explore the value of CRT compared to RT alone in stage II NPC.

Materials and methods

A prospective protocol was initially planned according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology recommendations for study reporting (MOOSE) [18, 19].

Identification and eligibility of relevant studies

A comprehensive literature search was performed using MEDLINE, EMBASE, Cochrane Library and the CBMdisc database for Chinese articles without restrictions to language or region (last updated on June 29, 2016). The following MeSH terms and their combinations were searched in [Title/Abstract]: stage II/early stage, nasopharyngeal carcinoma/nasopharyngeal cancer/nasopharyngeal neoplasm/NPC. After the initial screening of the title and abstract of retrieved literatures, the full text of relevant articles was independently assessed by two investigators for inclusion (C.X. and L.H.Z.) and any disagreements were resolved by consensus. The related article function and manual searches of reference lists were also carried out to expand the included studies.

The studies included in this meta-analysis complied with all of the following predefined criteria: (1) studies that compared CRT (i.e., CCRT, AC, induction chemotherapy [IC] and their combinations) with 2D-RT/IMRT alone in stage II NPC were included; (2) patients had newly-diagnosed, pathologically-confirmed NPC without previous treatment; (3) at least one of the following outcomes could be extracted directly from the contents of the paper or indirectly by Tierney's Methods: time-to-event data such as OS, LRRFS and DMFS, occurrence of grade 3-4 acute toxicity events [20]; (4) when multiple articles from the same institution were published, articles that examined different populations during non-overlapping time intervals or studies by different authors were included; (5) editorials, letters to editors, reviews, case reports, basic research reports and conference abstracts were excluded.

Data extraction

Two investigators (C.X. and L.H.Z.) independently extracted and summarized the data from all included studies using a standardized data extraction form. For each study, the following items were extracted: first author, year of publication, country of origin, inclusion period, demographic data, study design, median follow-up time and range, staging system (e.g., the 1997/2002/2010 edition of the American Joint Committee on Cancer [AJCC] staging system) and detailed staging data, World Health Organization (WHO) histologic type, description of radiotherapy parameters and chemotherapy regimen, time-to-event data (OS, LRRFS, DMFS) and occurrence of grade 3-4 acute toxicity events.

The primary outcomes were OS, LRRFS and DMFS. The definition of OS was the time from distribution until death due to any cause or the latest date known to be alive. LRRFS and DMFS were defined as the duration from the date of initiating treatment to local/regional relapse and distant metastasis, respectively. The secondary outcomes were the rates of grade 3-4 acute toxicities, including hematological events (leukopenia, anemia and

thrombocytopenia) and non-hematological events (liver dysfunction, renal impairment, nausea, mucositis and dermatitis).

Quality assessment and data analysis

The methodological quality of RCTs was assessed by the Cochrane risk of bias tool [21]; the methodological quality of retrospective studies was appraised using the modified Newcastle-Ottawa scale, which comprises three items: patient selection, comparability of the study groups, and assessment of outcomes [22]. The quality of each retrospective study was scored on a scale ranging from 0 to 9 by two independent investigators (C.X. and L.H.Z.). Studies with scores ≥ 6 were regarded as high-quality. The level of evidence for each study was assessed according to the criteria published by the Centre for Evidence-Based Medline in Oxford, UK [23].

To evaluate the agreement between the investigators regarding their assessment of study quality, we calculated the *kappa* coefficient for inter-rater reliability; *P*-value < 0.05 indicated a good agreement. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used as summary statistics for time-to-event data. The natural logarithm of HR (lnHR) and standard error of the lnHR (se(lnHR)) were calculated to figure out pooled HRs and 95% CIs for meta-analysis according to the guidelines by Parmar [24]. For dichotomous variables, the risk ratios (RRs) and 95% CIs were used as summary statistics. A HR or RR < 1 represented a survival or safety benefit favoring the CRT group. If the 95% CI was < 1, the benefit of CRT was statistically significant ($P < 0.05$). Statistical heterogeneity between studies was appraised using the Chi-square (χ^2) and I-square (I^2) test, with significance set at $P < 0.10$. Moreover, I^2-value > 25%, 50%, or 75% was considered to have low, moderate, or high heterogeneity [25]. If significant heterogeneity existed, the random-effects model was used; otherwise, the fixed-effects model was used.

Subgroup analyses of CRT versus 2D-RT alone and CRT versus IMRT alone were performed to explore the optimal modality of treatment. Sensitivity analysis of CRT versus IMRT alone was carried out to assess stability of the study results. It was performed by analyzing the results after sequential exclusion of some studies from the meta-analysis according to different matching criteria. Funnel plots and Begg's tests were performed to detect potential publication bias using Stata software 12.0 (StataCorp, College Station, TX, USA) [26]. The meta-analysis and forest plots were produced by Review Manager 5.3 (Cochrane Collaboration, Oxford, UK).

Results

Study identification and description

After the rounds of selection presented in Figure 1, eleven studies assessing 2138 patients (1237 patients treated with CRT and 901 patients treated with RT alone) fulfilled the predefined inclusion criteria and were included in this meta-analysis [4-6, 12-17, 27, 28].

Table 1 presents the baseline characteristics of the eligible studies. Ten of the eleven included articles were retrospective studies [5, 6, 12-17, 27, 28]; the remaining one was an RCT [4]. All studies were performed in Asia, of which, ten studies were published in English [4-6, 12-17, 28], and one was in Chinese with English abstract [27]. All studies recruited patients with stage II NPC; however, two studies also individually included a small proportion of patients with stage I (24.6%: T1N0M0) [13] and stage III (21.4%: T3N0M0) disease [16]. The summary of radiotherapy parameters and chemotherapy regimens of the included studies is shown in Table 2. Seven studies compared CRT with IMRT alone in all or most patients with stage II NPC [12-17, 27]. Four studies compared CRT with 2D-RT alone [4-6, 28].

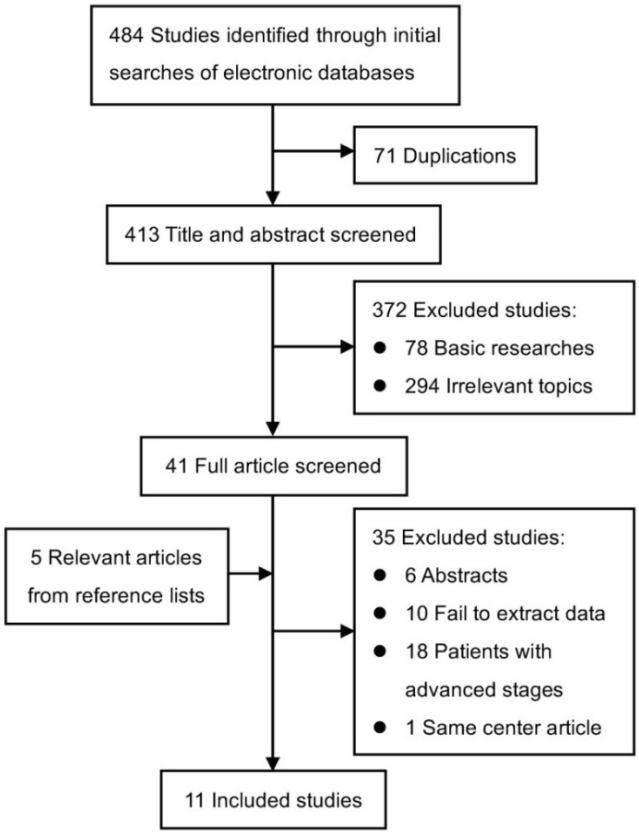

Figure 1. Flow diagram of study identification, exclusion and inclusion.

Table 1. Baseline characteristics of included studies

First author/ year	Country of origin	Study language	Time range	Study design	No. of patients (M/F)	Mean age	Matching items[c]	Median follow-up time (range), mo.	Detailed data of staging	Histologic type (WHO)	High quality	Level of evidence
Guo/2016 [14]	Mainland, China	English	2005-2010	R	311 (220/91)	NR	NR	57.0 (5.0-105.0)	AJCC-2010 II	I-III	No	4
Zhang/2015 [16]	Mainland, China	English	2009-2012	R	305[a] (222/83)	NR	1, 2, 3, 4, 5, 6, 7, 8	37.3 (8.0-58.8)	AJCC-2010 II+T3N0M0 (21.4%)	I-III	Yes	2b
Xu/2015 [15]	Mainland, China	English	2009-2011	R	86 (63/23)	50.5	1, 2, 3, 4, 7, 9	37.4 (4.8-66.2)	AJCC-2002 II	NR	Yes	2b
Su/2015 [17]	Mainland, China	English	2005-2010	R	249 (178/71)	NR	1, 2, 3, 4, 10, 11	59.4 (4.0-115.7)	AJCC-2010 II	II-III	Yes	4
Kang/2015 [12]	South Korea	English	2004-2011	R	138 (98/40)	NR	1, 2, 3, 4	48.0 (7.0-79.0)	AJCC-2002 II	I-III	No	4
Luo/2014 [13]	Mainland, China	English	2006-2010	R	69 (38/31)	42.0	NR	34.0 (12.0-64.0)	AJCC-2002 II+T1N0M0 (24.6%)	II-III	No	4
Xu/2011 [6]	Mainland, China	English	2000-2003	R	392 (293/99)	48.0	1, 2, 3, 4, 7, 12	66.0 (2.4-117.1)	AJCC-2002 II	I-III	Yes	2b
Song/2008 [5]	South Korea	English	1986-2004	R	43[b] (30/13)	50.0	1, 2, 3, 4, 5, 6	124.5 (5.0-239.0)	AJCC-1997 IIb	I-III	No	4
Chua/2006 [28]	Hong Kong, China	English	1989-1994	R	208 (145/63)	43.6	1, 2, 4, 5, 6	67.0 (NR)	AJCC-1997 IIb	I-III	Yes	2b
Chen/2011 [4]	Mainland, China	English	2003-2007	RCT	230 (166/64)	42.5	1, 2, 3, 4, 5, 6, 9	60.0 (5.0-87.0)	Chinese-1992 II	II-III	Yes	2b
Chen/2015 [27]	Mainland, China	Chinese	2007-2014	R	107 (NR)	NR	1, 2, 3, 4, 5, 6, 7	47.0 (6.0-89.0)	AJCC-2010 II	III	Yes	2b

Abbreviations: AJCC: American Joint Committee on Cancer; WHO: World Health Organization; R: retrospective; RCT: randomized controlled trial; M: male; F: female; mo.: months; NR: not reported.

[a] This study enrolled 440 patients, but only 305 patients were analyzed using propensity score matching.

[b] This study enrolled 60 patients with AJCC-1997 stage I-II NPC; we extracted the available data of 43 patients with stage IIb NPC.

[c] Matching items: 1 = age; 2 = sex; 3 = pathology; 4 = T stage; 5 = N stage; 6 = stage; 7 = Karnofsky score; 8 = pre-treatment plasma Epstein-Barr Virus DNA; 9 = retropharyngeal lymph node involvement; 10 = cigarette smoking; 11 = alcohol consumption; 12 = lactate dehydrogenase level.

Table 2. Summary of radiotherapy parameters and chemotherapy regimens of included studies

First author /year	No. of patients		Radiotherapy	Chemotherapy	
	RT	CRT		Concurrent chemotherapy	Induction and/or adjuvant chemotherapy
Guo/2016 [14]	66	245	IMRT: 69.75 Gy (2.25 Gy/fx/d, 5 fx/wk)	(1-6)*DDP 80 mg/m² (d1-3); DDP and PTX	IC and/or AC (55.8%): (1-6)*DDP 80 mg/m² (d1-3) and PTX 135 mg/m2 (d1); GEM 1000 mg/m² (d1, d8)
Zhang/2015 [16]	112	193	IMRT: 66-72 Gy (2.27 Gy/fx/d, 5 fx/wk); additional intracavitary irradiation for local tumor persistence	(≥2)*DDP or Nedaplatin 80-100 mg/m², 3-weekly; (≥5)*DDP 30-50 mg/m² or Nedaplatin 20-30 mg/m² or CBP 100 mg/m²; (3-6)*DOC 15-35 mg/m², weekly	IC and AC (28%): NR
Xu/2015 [15]	43	43	IMRT: 66 Gy (2.2 Gy/fx, 5 fx/wk); local dose boost for residual primary lesion or neck LN+	(5-6)*DDP 40 mg/m², weekly	None
Su/2015 [17]	106	143	IMRT: 68 Gy (2.26 Gy/fx/d, 5 fx/wk); 50 Gy (2 Gy/fx/d) for lower neck and supraclavicular fossae	(2-6)*Platinum single-agent, 3-weekly or weekly; PTX or PF or TP regime	None
Kang/2015 [12]	41	97	IMRT+2D-RT (2%): 64-74.2 Gy (2.12 Gy/fx/d, 5 fx/wk)	DDP weekly or 3-weekly or 4-weekly; PF regime	IC (17%): DDP+5-FU or DOC or both
Luo/2014 [13]	25	44	IMRT: 68-72 Gy (2.2 Gy/fx/d, 5 fx/wk); 66-70 Gy for neck LN+	DDP 80-100 mg/m² (d1-3), 3-weekly	None
Xu/2011 [6]	211	181	2D-RT: 70Gy (2.0 Gy/fx/day, 5 fx/wk); 66-70 Gy for neck LN+	3*DDP 100 mg/m² (d1, d22, d43); 2*DDP 100 mg/m² (d1, d22)	None
Song/2008 [5]	22	21	2D-RT: 66.6-72 Gy (1.8-2.0 Gy/fx/day, 5 fx/wk); 54-72 Gy for neck LN+	None	IC: 3*DDP 100 mg/m² (d1); 3*5-FU 1000 mg/m² (d1-5)
Chua/2006 [28]	110	98	2D-RT: 66-74 Gy (2.0 Gy/fx/day, 5 fx/wk); 60-76 Gy for neck LN+	None	IC: (2-3)*DDP 60 mg/m² (d1) and EPI 110 mg/m² (d1); DDP 100 mg/m² (d1) and 5-FU 800 mg/m² (d1-5) and BLM 10 mg/m² (d1, d5), 3-weekly
Chen/2011 [4]	114	116	2D-RT: 68-70 Gy (2.0 Gy/fx/day, 5 fx/wk); 60-62 Gy for neck LN+	(6-8)*DDP 30 mg/m² (d1), weekly	None
Chen/2015 [27]	51	56	IMRT+2D-RT (45.8%): 66-70 Gy (2.0 Gy/fx/day, 5 fx/wk); 60-70 Gy for neck LN+	(2-3)*DDP 80 mg/m² or 100 mg/m² (d1-3), 3-weekly	None

Abbreviations: RT: radiotherapy; CRT: chemoradiotherapy; IMRT: intensity modulated radiotherapy; 2D-RT: two-dimensional radiotherapy; IC: induction chemotherapy; AC: adjuvant chemotherapy; fx: fraction; wk: week; d: day; LN+: lymph node positive; DDP: cisplatin; PTX: paclitaxel; GEM: gemcitabine; CBP: carboplatin; DOC: docetaxel; 5-FU: 5-fluorouracil; EPI: epirubicin; BLM: bleomycin; PF: cisplatin combined with 5-fluorouracil; TP: docetaxel combined with cisplatin; NR: not reported.

Assessment of the included studies

The two investigators showed a good agreement in their assessment of the study quality of ten retrospective studies, with a *kappa* coefficient of 0.912 ($P < 0.001$) (Supplementary Table S1). The general quality of the ten retrospective studies was fair. Six of the ten studies had scores ≥ 6 [6, 15-17, 27, 28]. Five studies reached evidence level 2b, of which, one study used the propensity score matching method with two well-matched cohorts to mimic a randomized trial [16], and one study implemented the 1-to-1 paired comparison method [15]. The remaining five studies (level of evidence: 4) consisted of four typically-designed retrospective studies [5, 13, 14, 17], and one study with a complicated design compromising its reliability [12]. As for the only one RCT, the study quality was good (Supplementary Table S2) [4]. This study complied with the intention-to-treat principle, avoided selective outcome reporting and assessed each outcome adequately. All patients were randomly assigned to two groups with allocation concealment. However, it was unclear whether the blind method was used.

CRT versus RT alone

The overall meta-analysis of primary outcomes is summarized in Table 3. Pooling the data assessing OS for 2138 patients from all included studies revealed marginally significant difference between CRT and RT alone (HR = 0.67, 95% CI = 0.45-0.98, $P = 0.04$) and significant between-study heterogeneity ($P = 0.09$). Ten studies assessed LRRFS in 2069 patients, and one study reported local relapse-free survival as outcome [13]. The pooled data revealed a significantly improved LRRFS for CRT compared to RT alone (HR = 0.61, 95% CI = 0.46-0.80, $P = 0.0003$). Between-study heterogeneity was non-significant ($P = 0.10$). In pooled analysis of 2138 patients across the included studies, DMFS was not statistically different between CRT and RT alone (HR = 0.83, 95% CI = 0.52-1.31, $P = 0.41$), while the between-study heterogeneity was significant ($P = 0.01$).

Secondary outcomes could be extracted from three to five studies, representing 640 to 1262 cases with grade 3-4 acute toxicities (Table 3) [4, 6, 15-17]. The pooled outcomes indicated that CRT has higher frequencies of leukopenia (RR = 6.40, 95% CI = 1.77-23.15, $P = 0.005$), mucositis (RR = 1.41, 95% CI = 1.03-1.93, $P = 0.03$) and nausea (RR = 10.61, 95% CI = 3.49-32.27, $P < 0.0001$) than RT alone.

CRT versus IMRT alone and CRT versus 2D-RT alone

Two RT subgroups, 2D-RT alone and IMRT alone, were generated to compare with CRT in subgroup analyses. Seven retrospective studies enrolling 1265 patients compared CRT with IMRT alone [12-17, 27]. Unlike the overall meta-analysis, CRT did not obtain improved OS (HR = 0.69, 95% CI = 0.41-1.13, $P = 0.14$; Figure 2A), LRRFS (HR = 0.49, 95% CI = 0.24-1.02, $P = 0.06$; Figure 3A) or DMFS (HR = 1.03, 95% CI = 0.66-1.61, $P = 0.89$; Figure 4A) compared to IMRT alone. Moreover, non-significant between-study heterogeneity was observed in OS ($P = 0.18$, $I^2 = 32\%$) and DMFS ($P = 0.21$, $I^2 = 29\%$); moderate between-study heterogeneity was reported in LRRFS ($P = 0.07$, $I^2 = 52\%$). Three of the seven studies also investigated secondary outcomes among 640 patients [15-17]. The result showed that CRT could obtain higher frequencies of grade 3-4 leukopenia ($P < 0.0001$) and thrombocytopenia ($P = 0.02$) than IMRT alone.

Table 3. Results of the meta-analysis for the comparison of CRT and RT alone

Outcome	No. of studies	No. of RT pts	No. of CRT pts	No. of all pts	HR/RR (95% CI)	*P*-value[b]	Study heterogeneity			
							χ^2	*df*	I^2 (%)	*P*-value[b]
Primary outcomes										
Overall survival	11	901	1237	2138	0.67 [0.45, 0.98][a]	**0.04**	16.34	10	39	**0.09**
Loco-regionally relapse-free survival	10	876	1193	2069	0.61 [0.46, 0.80][a]	**0.0003**	14.81	9	39	0.10
Distant metastasis-free survival	11	901	1237	2138	0.83 [0.52, 1.31][a]	0.41	23.14	10	57	**0.01**
Secondary outcomes										
Leukopenia	5	586	676	1262	6.40 [1.77, 23.15]	**0.005**	10.17	4	61	**0.04**
Anemia	3	261	379	640	0.96 [0.16, 5.79]	0.97	0.06	2	0	0.81
Thrombocytopenia	5	586	676	1262	1.67 [0.91, 3.06]	0.10	5.27	4	24	0.26
Liver dysfunction	4	375	495	870	1.74 [0.87, 3.48]	0.12	1.93	3	0	0.38
Renal impairment	4	375	495	870	4.51 [0.79, 25.66]	0.09	0.09	3	0	0.77
Mucositis	5	586	676	1262	1.41 [1.03, 1.93]	**0.03**	11.34	4	65	**0.02**
Dermatitis	5	586	676	1262	1.37 [0.84, 2.23]	0.21	1.87	4	0	0.60
Nausea	4	543	633	1176	10.61 [3.49, 32.27]	**< 0.0001**	0.88	3	0	0.83

Abbreviations: CRT: chemoradiotherapy; RT: radiotherapy; pts: patients; HR: hazard ratio; RR: risk ratio; CI: confidence interval; *df*: degrees of freedom.

[a] Hazard ratio.

[b] Statistically significant results are shown in **bold.**

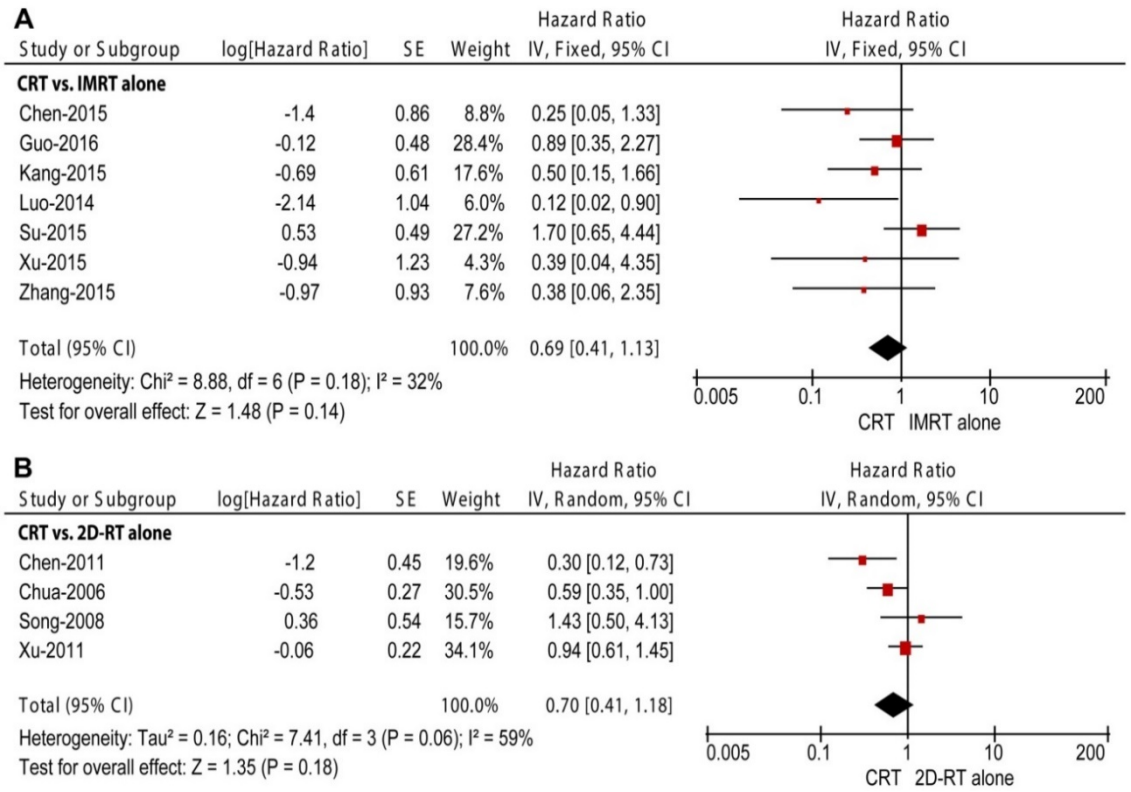

Figure 2. Forest plot and meta-analysis of overall survival (OS) in subgroup analysis. **(A)** CRT versus IMRT alone; **(B)** CRT versus 2D-RT alone. Squares are the point estimates of the HRs with the 95% CIs indicated by horizontal bars. Diamonds are the summary estimates and 95% CIs from the pooled studies. CRT: chemoradiotherapy; IMRT: intensity modulated radiotherapy; 2D-RT: two-dimensional radiotherapy; CI: confidence interval; SE: standard error; IV: inverse variance method.

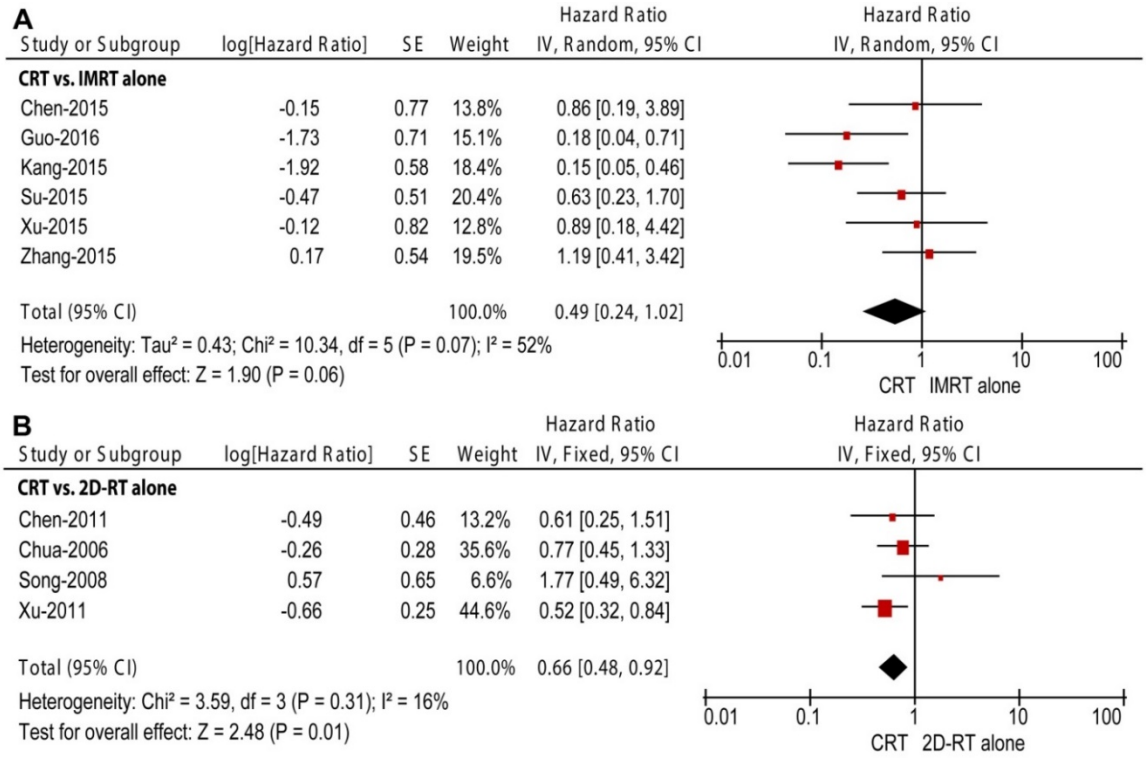

Figure 3. Forest plot and meta-analysis of loco-regional relapse-free survival (LRRFS) in subgroup analysis. **(A)** CRT versus IMRT alone; **(B)** CRT versus 2D-RT alone. Squares are the point estimates of the HRs with the 95% CIs indicated by horizontal bars. Diamonds are the summary estimates and 95% CIs from the pooled studies. CRT: chemoradiotherapy; IMRT: intensity modulated radiotherapy; 2D-RT: two-dimensional radiotherapy; CI: confidence interval; SE: standard error; IV: inverse variance method.

Four studies enrolling 873 patients were included in the subgroup of CRT versus 2D-RT alone, including three retrospective studies and one RCT [4-6, 28]. The pooled data revealed non-significant differences in OS and DMFS (HR = 0.70, 95% CI = 0.41-1.18, P = 0.18, Figure 2B; HR = 0.69, 95% CI = 0.30-1.59, P = 0.39, Figure 4B, respectively) between the two modalities. The pooled OS and DMFS were accompanied with moderate and high between-study heterogeneity (P = 0.06, I^2 = 59%; P = 0.003, I^2 = 78%, respectively). Moreover, CRT showed significantly higher LRRFS than 2D-RT alone (HR = 0.66, 95% CI = 0.48-0.92, P = 0.01, Figure 3B); no significant between-study heterogeneity was observed (P = 0.31, I^2 = 16%).

Sensitivity analysis and assessment of publication bias

Sensitivity analysis was carried out to assess stability of the study results of CRT versus IMRT alone (Table 4). The sensitivity analysis that individually excluded one study published in Chinese [27], two studies enrolling less than one hundred patients [13, 15], and three studies with relatively low-quality [12-14], yielded no changes in the significance of any survival outcome as the original subgroup analysis of CRT versus IMRT alone. Meanwhile, I^2-values of all pooled outcomes in the sensitivity analysis of high-quality studies were 0%. Considering that different CRT schedules were used in comparison to IMRT alone, we individually included four studies using CCRT [13, 15, 17, 27] and three studies using CCRT plus IC and/or AC [12, 14, 16] in sensitivity analysis. All pooled survival outcomes still remained non-significant. Thus, the results of CRT versus IMRT alone were of high stability.

As for the overall meta-analysis, no significant publication bias was observed in OS, LRRFS or DMFS (P = 0.186, 0.967, 0.774, respectively). A funnel plot was created for OS; all studies were located inside the 95% CIs with a symmetric distribution (Figure 5).

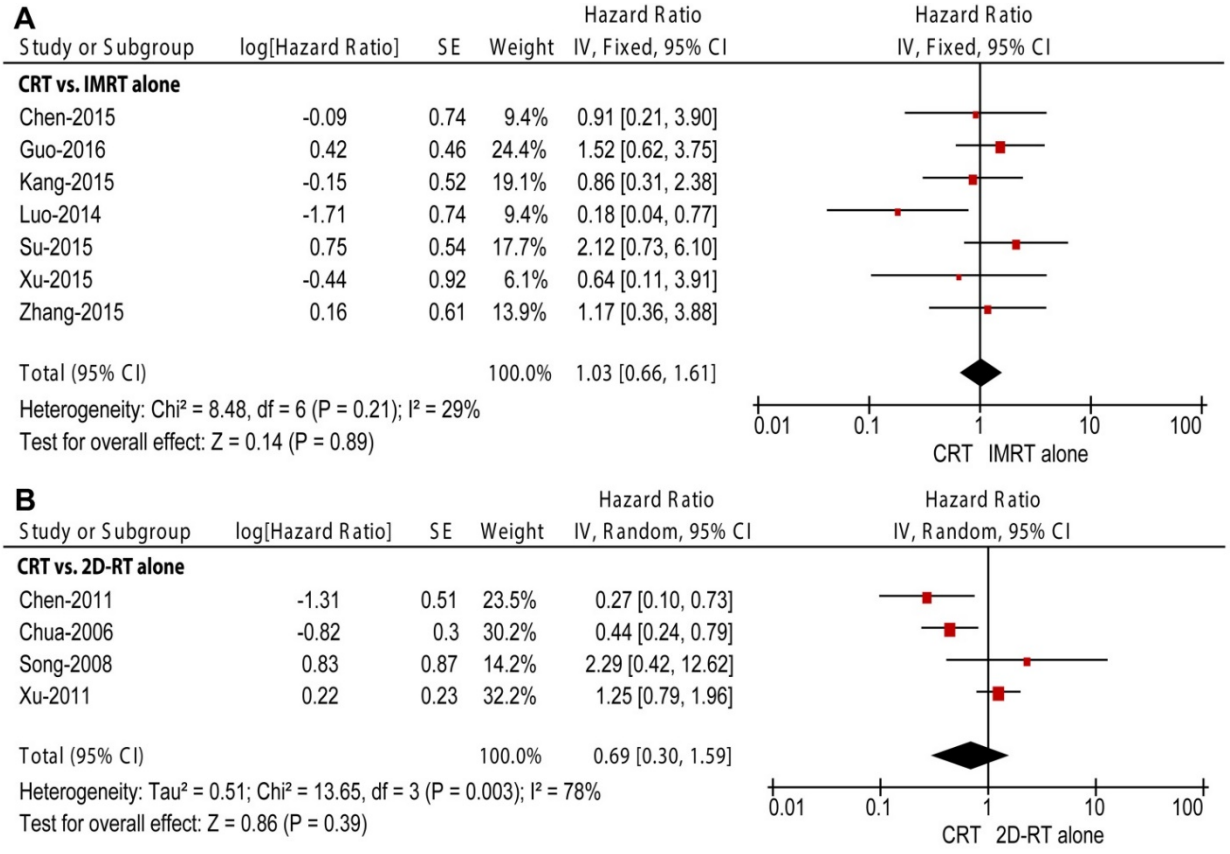

Figure 4. Forest plot and meta-analysis of distant metastasis-free survival (DMFS) in subgroup analysis. **(A)** CRT versus IMRT alone; **(B)** CRT versus 2D-RT alone. Squares are the point estimates of the HRs with the 95% CIs indicated by horizontal bars. Diamonds are the summary estimates and 95% CIs from the pooled studies. CRT: chemoradiotherapy; IMRT: intensity modulated radiotherapy; 2D-RT: two-dimensional radiotherapy; CI: confidence interval; SE: standard error; IV: inverse variance method.

Table 4. Sensitivity analysis for the comparison of CRT and IMRT alone.

Outcome	No. of studies	No. of IMRT pts	No. of CRT pts	No. of all pts	HR (95% CI)	*P*-value[a]	Study heterogeneity			
							χ^2	*df*	I^2 (%)	*P*-value[a]
English publications										
Overall survival	6	393	765	1158	0.76 [0.45, 1.28]	0.30	7.33	5	32	0.20
Loco-regionally relapse-free survival	5	368	721	1089	0.45 [0.19, 1.04]	0.06	9.76	4	59	**0.04**
Distant metastasis-free survival	6	393	765	1158	1.05 [0.66, 1.67]	0.85	8.45	5	41	0.13
Sample size > 100 patients										
Overall survival	5	376	734	1110	0.79 [0.47, 1.35]	0.39	5.51	4	27	0.24
Loco-regionally relapse-free survival	5	376	734	1110	0.45 [0.19, 1.03]	0.06	9.78	4	59	**0.04**
Distant metastasis-free survival	5	376	734	1110	1.30 [0.80. 2.11]	0.29	1.82	4	0	0.77
High-quality studies										
Overall survival	4	312	435	747	0.63 [0.22, 1.81]	0.39	5.21	3	42	0.16
Loco-regionally relapse-free survival	4	312	435	747	0.85 [0.47, 1.57]	0.61	0.75	3	0	0.86
Distant metastasis-free survival	4	312	435	747	1.29 [0.67, 2.47]	0.44	1.65	3	0	0.65
Studies using CCRT										
Overall survival	4	225	286	511	0.45 [0.11, 1.75]	0.25	7.90	3	62	**0.05**
Loco-regionally relapse-free survival	3	200	242	442	0.73 [0.35, 1.52]	0.40	0.19	2	0	0.91
Distant metastasis-free survival	4	225	286	511	0.74 [0.25, 2.23]	0.59	7.33	3	59	**0.06**
Studies using CCRT plus IC and/or AC										
Overall survival	3	219	535	754	0.65 [0.33, 1.29]	0.22	0.94	2	0	0.63
Loco-regionally relapse-free survival	3	219	535	754	0.32 [0.08, 1.31]	0.11	8.26	2	76	**0.02**
Distant metastasis-free survival	3	219	535	754	1.18 [0.66, 2.13]	0.58	0.67	2	0	0.71

Abbreviations: CRT: chemoradiotherapy; CCRT: concurrent chemoradiotherapy; IMRT: intensity modulated radiotherapy; IC: induction chemotherapy; AC: adjuvant chemotherapy; pts: patients; HR: hazard ratio; CI: confidence interval; *df*: degrees of freedom.

[a] Statistically significant results are shown in **bold**.

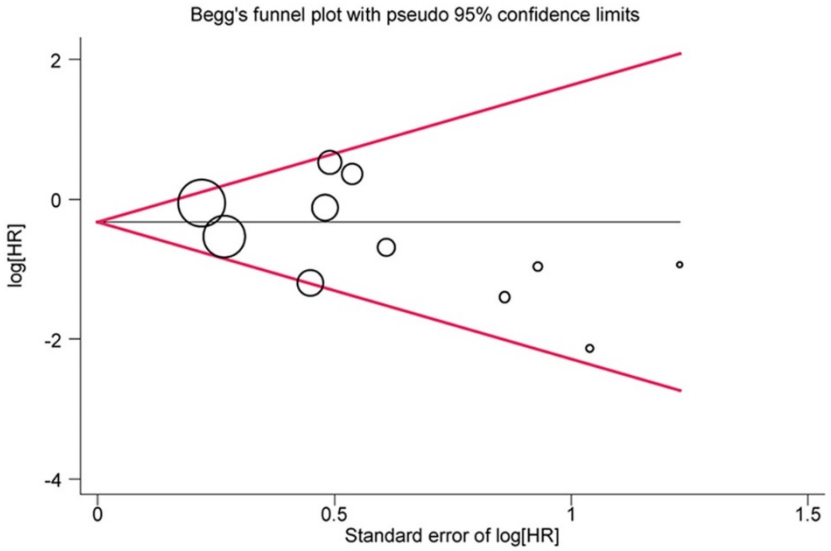

Figure 5. Begg's funnel plot for assessing publication bias of overall survival (OS) in overall meta-analysis. The size of the circles indicates the weight of each study. HR: hazard ratio.

Discussion

This meta-analysis enrolling 2138 patients with stage II NPC showed that CRT has significantly higher OS and LRRFS than RT alone. The improved LRRFS is due mainly to the superiority of CRT over 2D-RT alone. When it comes to the improved OS for CRT, drawing the conclusion should be discreet because of the marginal significance (P = 0.04) and obvious between-study heterogeneity. Besides, although both RT subgroups reported non-significant difference in OS compared to CRT, the result of IMRT alone was of high reliability, while the result of 2D-RT alone was accompanied with significant between-study heterogeneity. The inconsistence between studies comparing CRT and 2D-RT alone might be caused by different CRT schedules (CCRT, IC plus 2D-RT). Given the lack of number of studies and obvious heterogeneity, we did not perform further investigation (e.g., sensitivity analysis) for the subgroup of CRT versus 2D-RT alone. For the comparison of CRT and IMRT alone, the sensitivity analysis showed similar survival outcomes as the original analysis with excellent stability, which

indicated the superiority of IMRT alone.

There are three possible explanations for the non-significant difference in survival outcomes between CRT and IMRT alone. Firstly, IMRT provides a higher local tumor control rate than conventional RT [29, 30]; therefore, this advanced technique may narrow the potential therapeutic gains of CRT. The positive conclusion for CRT reached in the overall meta-analysis was associated with the relative efficacy of CRT compared to the sub-optimal treatment effects of 2D-RT alone [28]. Secondly, the increased frequencies of severe adverse reactions among patients treated with CRT may compromise the survival benefit of chemotherapy and result in more favorable outcomes for IMRT alone [31]. In the subgroup analysis of CRT versus IMRT alone, one study showed that IMRT alone could significantly improve OS [17]; this effect was associated with a higher incidence of grade 3-4 acute toxicities in the group of patients receiving CRT, especially non-hematological events such as liver dysfunction and renal impairment, compared to other included studies. Thirdly, it should be noted that patients with T2N1M0 NPC represent a special group at high risk of distant metastasis [4, 10, 13]. There is evidence that patients with T2N1M0 disease experience significantly poorer OS (P = 0.044) and DMFS (P = 0.010) than those with T1N1M0 disease [14]. Moreover, some studies have indicated that it is difficult to eradicate micro-metastatic lesions using cisplatin-based regimens [32-34]. Therefore, assessment of patients with stage II NPC without precise population stratification may reduce the benefits of CRT to a non-significant effect.

Apart from the equivalent survival outcomes compared to CRT, IMRT also had fewer grade 3-4 hematological toxicities, which suggest better patient compliance and lower medical cost. Moreover, Tham et al. reported that IMRT alone had comparable survival outcomes with acceptable toxicities compared to CRT in stage IIb NPC [11]. Therefore, it seems that IMRT alone may be more suitable than CRT for patients with stage II NPC. Nonetheless, the benefit of CRT in LRRFS still calls for special attention and further discussion. Even though non-significant differences were observed for LRRFS between CRT and IMRT alone, the potential trend towards increased LRRFS for CRT and moderate between-study heterogeneity indicated a number of factors might contribute to and affect the results. Kang et al. reported that CRT could significantly improve LRRFS [12]; however, the OS, LRRFS and DMFS in this study were generally poor (88.2%, 86.2%, 85.5%) compared to other included studies in which these rates generally exceed at least 90%. Thus, objectively sub-optimal loco-regional control may be one possible factor that increased the apparent value of CRT. Moreover, the studies included in this meta-analysis adopted different regimens, recruited patients from different areas (endemic and non-endemic regions), and matched patients using different criteria. These variations could contribute to the between-study heterogeneity and discrepancies in survival outcomes. After the sequential exclusion of some studies in sensitivity analyses based on different matching criteria, IMRT alone was proved to be superior to CRT with excellent stability. Therefore, we can conclude on the basis of the stable outcomes that IMRT alone is better than CRT for patients with stage II NPC. Currently, several phase II-III trials are undertaking to confirm the efficacy of IMRT alone in stage II NPC compared to CRT (e.g., NCT02116231, NCT02610010), and the final results are awaiting to be reported.

The present meta-analysis has several limitations that must be taken into account. First, the main limitation is the inferior level of evidence. Only one study was RCT [4]; the remaining ten studies were retrospective observational articles with different designs, including a study by Kang et al. with a complicated design at the cost of reliability [12]. Second, the inclusion criteria for the meta-analysis need to be strictly amended to avoid inaccurate information. Two of the eleven studies individually included additional patients with T1N0M0 disease (24.6%; AJCC-2002) [13] and T3N0M0 disease (21.4%; AJCC-2010) [16]. As stage II NPC in the study including T1N0M0 disease overlapped with part of stage I NPC when patients were re-staged based on AJCC-2010, and the T3N0M0 subgroup was reported to have similar survival outcomes to patients with stage II [35, 36], we included the two studies in our meta-analysis. However, the inaccurate information could induce noticeable heterogeneity between studies and obscure conclusions of this meta-analysis. Third, several studies have suggested that the size of lymph node and pre-treatment Epstein-Barr virus (EBV)-deoxyribonucleic acid (DNA) levels are probably more important factors to show a difference with the addition of chemotherapy [37-39]. Thus, appropriate stratification of NPC patients should be established by incorporating lymph node classification, EBV-DNA and other biological/ molecular markers [40, 41]. In the absence of detailed data of individuals, we cannot stratify patients with stage II NPC and failed to obtain the accurate conclusion. Further studies restricted to IMRT alone with individual patient data are awaited. Finally, only five studies directly reported survival data as HRs and the associated CIs [4, 5, 15, 16, 27]. Even though we calculated these values using the same methods

designed by Tierney in all remaining studies, this may also result into bias and error [20].

Conclusion

The present meta-analysis showed that CRT is better than 2D-RT alone in stage II NPC with significant benefit in LRRFS. IMRT alone is superior to CRT with equivalent survival outcomes and fewer grade 3-4 acute toxicities. This meta-analysis is the first attempt to compare CRT with 2D-RT/IMRT alone in stage II NPC. In the future, well-designed RCTs comparing CRT and IMRT alone in stage II NPC and patient stratification based on lymph node classifications and pre-treatment EBV-DNA levels are needed.

Supplementary Material

Supplementary Figures.
http://www.jcancer.org/v08p0287s1.pdf

Abbreviations

NPC: nasopharyngeal carcinoma; RCT: randomized controlled trial; CRT: chemoradiotherapy; RT: radiotherapy; 2D-RT: two-dimensional radiotherapy; IMRT: intensity-modulated radiotherapy; CCRT: concurrent chemoradiotherapy; AC: adjuvant chemotherapy; IC: induction chemotherapy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; MOOSE: Meta-analysis of Observational Studies in Epidemiology recommendations for study reporting; OS: overall survival; LRRFS: loco-regional relapse-free survival; DMFS: distant metastasis-free survival; AJCC: American Joint Committee on Cancer; WHO: World Health Organization; HR: hazard ratio; RR: risk ratio; CI: confidence interval; χ^2: Chi-square; I^2: I-square; EBV: Epstein-Barr virus; DNA: deoxyribonucleic acid.

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Competing Interests

The authors have declared that no competing interest exists.

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