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Concurrent cisplatin or cetuximab with radiotherapy in patients with locally advanced head and neck squamous cell carcinoma

A meta-analysis

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Abstract

Background: Concurrent cisplatin with radiotherapy (CRT) or concurrent cetuximab with radiotherapy (BRT) improves outcomes in locally advanced head and neck squamous cell carcinoma (HNSCC) compared with radiotherapy alone. Nevertheless, a detailed comparison between CRT and BRT in locally advanced HNSCC is required due to inconclusive results.

Methods: A comprehensive literature search was conducted on PubMed, Web of Science, Cochrane databases, and EMBASE. Studies that evaluated CRT vs BRT in locally advanced HNSCC were included. The primary outcome that was overall survival (OS), whereas the secondary outcomes were progression-free survival (PFS), locoregional control (LRC), and distant metastasis-free survival (DMFS). Pooled hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were used to evaluate prognosis. All the analyses were performed using Stata Statistical Software 12.0.

Results: Twenty-three studies, with a total of 8701 patients, were considered eligible and included in this meta-analysis. Our results revealed that patients treated with CRT had longer OS (HR = 0.51, 95%CI, 0.41–0.64, $P < .001$), PFS (HR = 0.37, 95%CI, 0.23–0.60, $P < .001$), LRC (HR = 0.46, 95%CI, 0.37–0.57, $P < .001$), and DMFS (HR = 0.56, 95%CI, 0.40–0.77, $P < .001$) than those treated with BRT. Furthermore, the results of the subgroup analyses were consistent with the primary analysis.

Conclusions: CRT has a better OS, PFS, LRC, and DMFS than BRT in locally advanced HNSCC, and should be the preferred treatment for patients with the disease.

Abbreviations: − = negative, + = positive, BRT = concurrent cetuximab with radiotherapy, CIs = confidence intervals, CRT = concurrent cisplatin with radiotherapy, DMFS = distant metastasis-free survival, EGFR = epidermal growth factor receptor, HNC = head and neck cancer, HNSCC = head and neck squamous cell carcinomas, HPV = human papillomavirus, HR = hazard ratio, LRC = locoregional control, NCCN = National Comprehensive Cancer Network, OS = overall survival, PFS = progression-free survival, RT = radiotherapy.

Keywords: head and neck carcinoma, cisplatin, cetuximab, radiation therapy, outcome

1. Introduction

Head and neck cancers (HNC) are relatively common carcinomas, with approximately 600,000 new cases and 320,000 deaths annually.[1,2] The head and neck squamous cell carcinoma (HNSCC) have the highest morbidity, accounting for 85% death among all HNC.[3] Most patients have advanced locoregional disease at diagnosis and require combined treatment of radiotherapy (RT), surgery and systemic therapy.[4]

The established standard treatment for patients, which are unsuitable for surgical treatment is concurrent systemic therapy with RT. There are currently 2 common treatment strategies supported by guidelines, concurrent platinum, or cetuximab with RT. Platinum-based chemoradiotherapy is the standard of care for locally advanced HNSCC in many countries, and concurrent high-dose cisplatin is the preferred systemic agent recommended by National Comprehensive Cancer Network Guideline, which is used most widely in the world. Many large phase 3 trials and meta-analysis have shown that concurrent cisplatin with radiotherapy (CRT) improves overall survival (OS) compared with RT alone. However, CRT leads to numerous toxicities.[5–7] As patients may might

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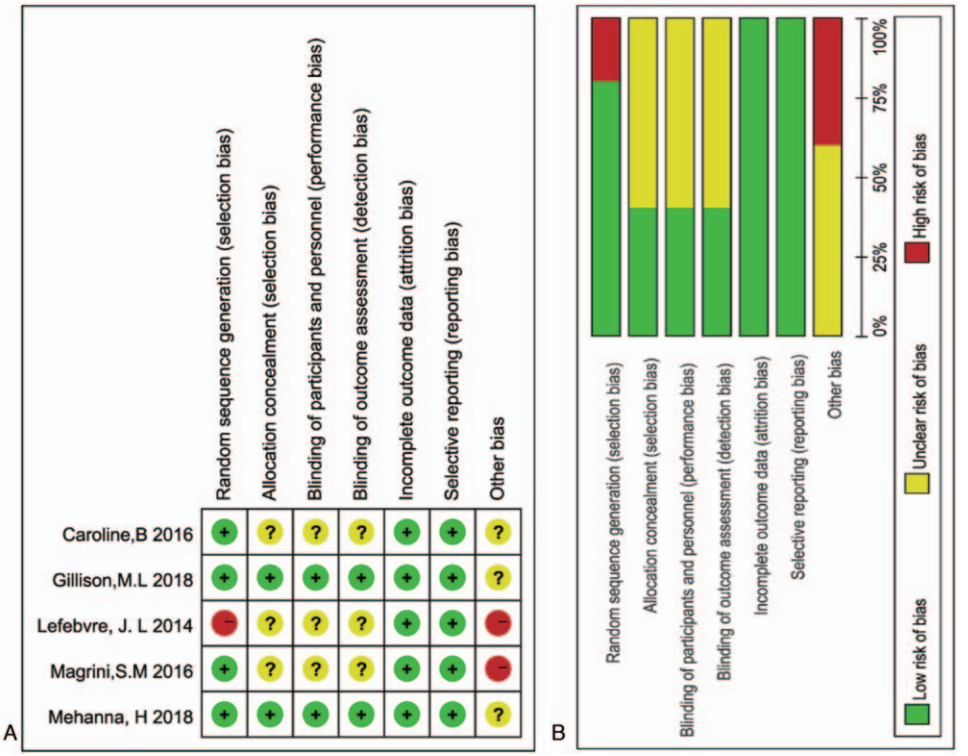

Figure 1. Flow chat of study selection.

develop serious toxicity of cisplatin, which could persist for a long time, and could affect their quality of life. Radiotherapy can induce the expression of epidermal growth factor receptor (EGFR) in HNC, leading to acquired resistance.[8] Cetuximab, a monoclonal antibody that targets the EGFR, is the first targeted treatment that shows therapeutic efficacy in HNC and may help to overcome this resistance. Similarly, some phase 3 trials have demonstrated that concurrent cetuximab with radiotherapy (BRT) improves OS, locoregional control (LRC), and the quality of life compared with RT alone.[9,10] Cetuximab has been increasingly used to treat patients who concern about the toxicity of platinum chemotherapy, such as elderly or frail patients. Recently, 2 randomized studies showed that BRT was inferior to CRT for patients with human papillomavirus (HPV) positive (+) oropharyngeal carcinoma.[9,10] However, except for its highly selected group, there are no randomized clinical trials to compare the efficacy of cisplatin and cetuximab head to head in patients with HPV negative (−) tumors, which comprises the majority in HNSCC. Furthermore, several studies suggest that EGFR inhibition might be more effective in HPV (−) disease than in HPV (+) disease.[13,14] Therefore, it is still unclear if the efficacy of BRT is similar to CRT in HPV (−) HNSCC.

Hence, this meta-analysis was conducted to comprehensively compare concurrent cisplatin or cetuximab with radiotherapy in locally advanced HNSCC, towards providing direction in decision making for treatment.

2. Methods

2.1. Search strategy

We performed a comprehensive literature search in PubMed, Web of Science, Cochrane databases, and EMBASE, up to 1st May 2019 using the following keywords "head and neck squamous cell carcinoma," "cancers of the larynx," "HNSCC," "cancer of oropharynx," "opc," "cancer of hypopharynx," "cancer of tongue," "radiotherapy," "cisplatin" and "cetuximab." We also reviewed conference abstracts of the unpublished articles and searched the references list of relevant studies to find other potential studies. This meta-analysis was registered in PROSPERO (registration number: CRD42019123560), and the research was conducted according to the recommended items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[15]

2.2. Selection criteria

Studies were included in this meta-analysis if they fulfilled the following criteria: Studies

1. that evaluated the efficacy of CRT and compared it with BRT in locally advanced HNSCC;
2. with one or more outcomes, including OS, progression-free survival (PFS), LRC or distant metastasis-free survival (DMFS);
3. that provided hazard ratio (HR) and its 95% confidence intervals (CI) or that can obtain the HR and 95% CI by statistical extraction; and
4. that published latest data or largest data was included if a particular center published the same study severally.

Exclusion criteria:

1. studies that patients were treated with cisplatin-based double or multiple concurrent agents;
2. studies that included patients with nasopharyngeal carcinoma, and

Table 1

Characteristics of studies included in the meta-analysis.

Author	Year	Region	Type	Study period	Therapy regimens	No. pts. (N) CRT/BRT	Mean/median age (years) CRT/BRT	Cancer sites (%)	Stage (%)	IT	HPV (+)(N) CRT/ BRT	Follow up* CRT/BRT	Outcome for analysis
Gillison	2018	American	P	2011–2014	IMRT-CIS IMRT-CET	406/399	58/58	Oropharynx	III-IV	N	406/399	54	5-yr OS 5-yr PFS 5-yr LFC 5-yr DMFS
Mehanna	2018	United Kingdom	P	2012–2016	RT-CIS RT-CET	166/168	57/57	Oropharynx	NA	N	166/168	25.9	2-yr OS
Bauml	2018	American	R	2000–2016	RT-CIS RT-CET	3737/783	61/66.8	Oral cavity 8.2/6.9 Oropharynx 68.6/ 65.7 Hypopharynx/ larynx 23.2/27.5	III-IV	NA	NA	36	OS
Amini	2018	American	R	2006–2011	RT-CIS RT-CET	348	NA	Oropharynx	NA	NA	NA	NA	2-yr OS
Onita	2018	American	R	2006–2016	IMRT-CIS IMRT-CET	251/40	57/70	Oropharynx	I-III	N	251/40	40	3-yr LRC 3-yr DMFS
Rawat	2017	India	R	2006–2008	IMRT-CIS IMRT-CET	30/23	53/61	Oral cavity 16.7/13 Oropharynx 56.7/ 52.2 Larynx 16.7/13 Hypopharynx 10/ 21.7	III-IV	Y	NA	32.93/ 25.90	3-yr OS
Stokes	2017	American	R	2004–2015	RT-CIS RT-CET	125/34	58/63	Oropharynx 74.4/58.8 Larynx 25.6/ 41.2	III-IV	N	71/12	27.2	OS LRF DMFS
Caroline	2016	United Kingdom	P	2006–2014	RT-CIS RT-CET	10/10	59.5 60	Oropharynx 80/80 Larynx/hypopharynx 20/20	III-IV	N	NA	NA	21-mo OS
Riaz	2016	American	R	2006–2008	IMRT-CIS IMRT-CET	125/49	NA	Oropharynx 78.4/69.4 Hypopharynx/ larynx 21.6/30.6	NA	N	16/10	47	3-yr OS 3-yr LRF
Law	2016	Hong Kong	R	2008–2014	IMRT-CIS IMRT-CET	21/21	65/67	Larynx 61.9/52.4 Hypopharynx 33.3/ 33.3 Oropharynx 4.8/14.3	II-IV	NA	NA	16/21	OS LRC
Magrini	2016	Italy	P	2011–2014	RT-CIS RT-CET	35/35	67.5/61	Oropharynx 46/49 Oral cavity 14/14 Hypopharynx 23/17 Supraglottic larynx 17/20	III-IV	N	NA	19.3	2-yr OS 2-yr LC
Ou	2016,	France	R	2006–2012	RT-CIS RT-CET	194/71	58/60	Oral cavity 4/4 Oropharynx 70/65 Hypopharynx 11/17 Larynx 15/14	I-IV	N	63/25	54.5	5-yr OS 5-yr PFS 5-yr LRC 5-yr DMFS
Onita	2016	American	R	2006–2014	IMRT-CIS IMRT-CET	151/35	56/70	Oropharynx	III-IV	N	104	43.4	3-yr OS 3-yr PFS 3-yr LRC
Weller	2015	American	R	2002–2013	RT-CIS RT-CET	267/43	NA	Oropharynx	III-IV	NA	267/43	44	2,5-yr DMFS
Strom	2015	American	R	2006–2011	IMRT-CIS IMRT-CET	241/38	58/62	Oropharynx 81.3/89.5 Oral Cavity 2.9/0 Larynx 12.0/7.9 Hypopharynx 3.7/2.6	III-IV	N	85/14	27	2-yr OS 2-yr LRC 2-yr DMFS
Peddi	2015	American	R	2006–2011	RT-CIS RT-CET	45/24	55/61	Oral cavity 20.0/33.3 Oropharynx 37.8/ 33.3 larynx 35.5/20.9 Hypopharynx 6.67/12.5	III-IV	N	3/1	NA	2-yr OS 2-yr PFS
Kanakamedala	2014	American	R	2005–2011	IMRT-CIS IMRT-CET	57/66	53	NA	NA	NA	NA	36	LRC DMFS
Borchiellini	2014	France	R	2005–2010	RT-CIS RT-CET	113/51	56/57	Larynx 23/27 No Larynx 77/73	NA	Y	NA	24	OS PFS
Lefebvre	2014	France	P	2006–2008	RT-CIS RT-CET	60/56	57.5/ 57.8	Larynx 43.3/35.7 Hypopharynx 56.7/ 64.3	II-IV	Y	NA	36	18-mo OS 36-mo OS
Ley	2013	American	R	2005–2010	IMRT-CIS IMRT-CET	18/29	55/62	Oropharynx 55.6/44.8 Oral Cavity 0./ 10.3 Larynx 38.9/24.1 Hypopharynx 0/ 13.8 Other 5.6/6.9	III-IV	N	8/8	19/23	OS
Ye	2013	Canada	R	2007–2010	RT-CIS RT-CET	262/87	57/62	Oropharynx 72/59 Hypopharynx 8/5 Larynx 8/16 Oral cavity 7/8 paranasal sinuses 2/0 Salivary gland 1/1 Unknown primary 4/10	III-IV	N	NA	20/16	1-yr OS 1-yr LRC
Chew	2011	Canada	R	2007–2010	RT-CIS RT-CET	118/72	56.5/63.1	NA	NA	NA	NA	NA	DMFS
Galper	2009	American	R	2005–2008	IMRT-CIS IMRT-CET	9/15	58/71	NA	NA	NA	NA	11/12	1-yr LRF

Follow up*: mean or median duration months.

CET = cetuximab, CIS = cisplatin, DMFS = distant metastasis-free survival, F = female, IMRT = Intensity Modulated Radiation Therapy, IT = induction chemotherapy, LRC = locoregional control, LRF = locoregional failure, M = male, N = = no, NA = not applicable, OS = overall survival, P = prospective, PFS = progression-free survival, pts = patients, R = retrospective, RT = Radiation Therapy, T = Total, Y = yes,

Table 2

Ottawa Quality Assessment Scale: cohort studies.

	Selection					Outcome			
Study/Year	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not presenting at the start	Comparability	Assessment of outcome	Enough follow-up duration	Adequate follow-up	Total score
Bauml /2018	0	1	1	1	1	1	1	0	6
Amini /2018	1	1	1	1	1	1	0	0	6
Onita /2018	1	1	1	1	1	1	1	0	7
Rawat /2017	1	1	1	1	1	1	1	1	8
Stokes /2017	1	1	1	1	1	1	1	0	7
Riaz /2016	1	1	1	1	1	1	1	0	7
Law /2016	1	1	1	1	1	1	1	0	7
Ou /2016	1	1	1	1	1	1	1	0	7
Onita /2016	1	1	1	1	1	1	1	0	7
Weller /2015	1	1	1	1	1	1	1	0	7
Strom /2015	1	1	1	1	1	1	1	0	7
Peddi /2015	1	1	1	1	1	1	0	0	6
Kanakam-edala /2014	1	1	1	1	1	1	1	0	7
Borchiell-ini /2014	1	1	1	1	1	1	1	0	8
Ley/2013	1	1	1	1	1	1	1	1	8
Ye /2013	1	1	1	1	1	1	1	0	7
Chew /2011	1	1	1	1	1	1	0	0	6
Galper /2009	1	1	1	1	1	1	0	0	6

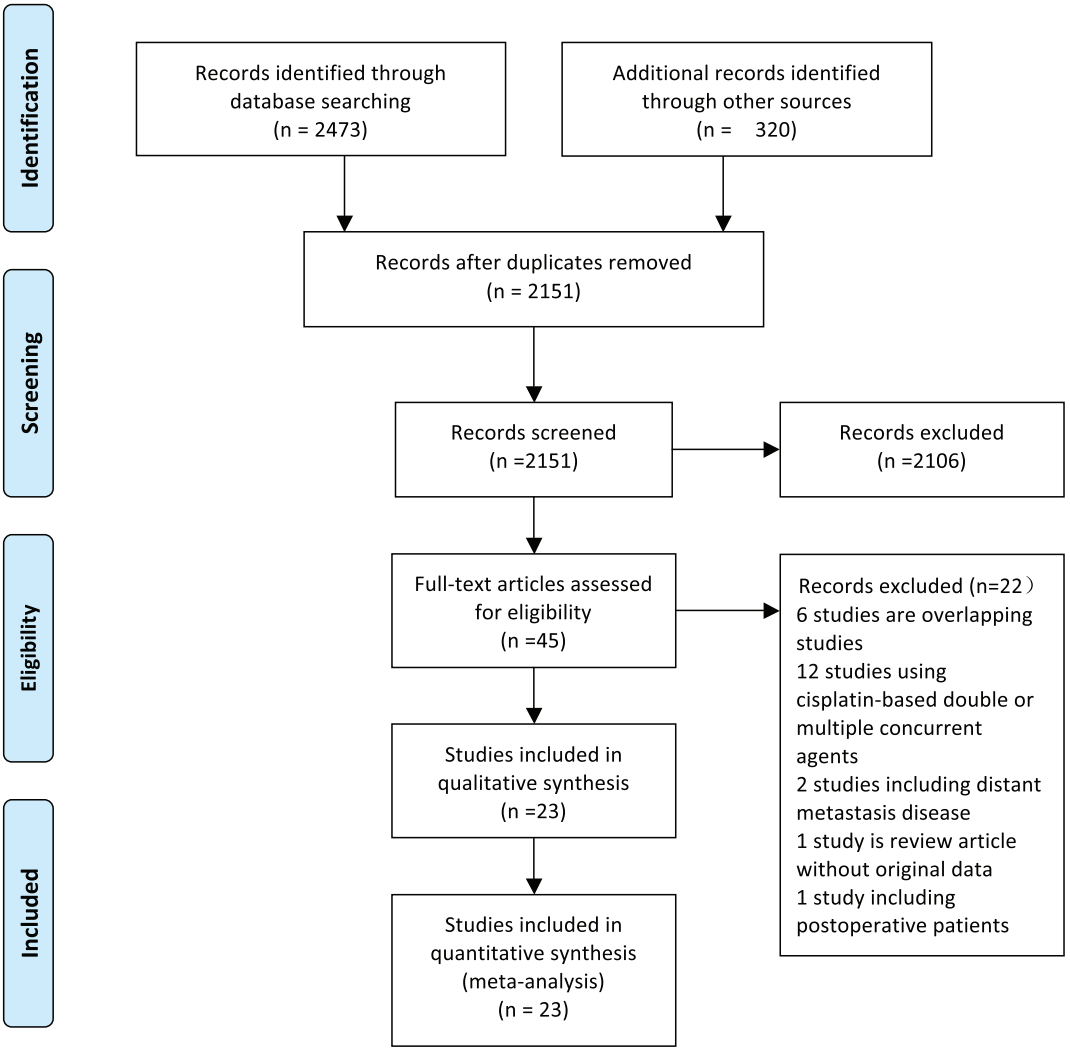

Figure 2. Cochrane Collaboration's risk of bias: randomized clinical trial.

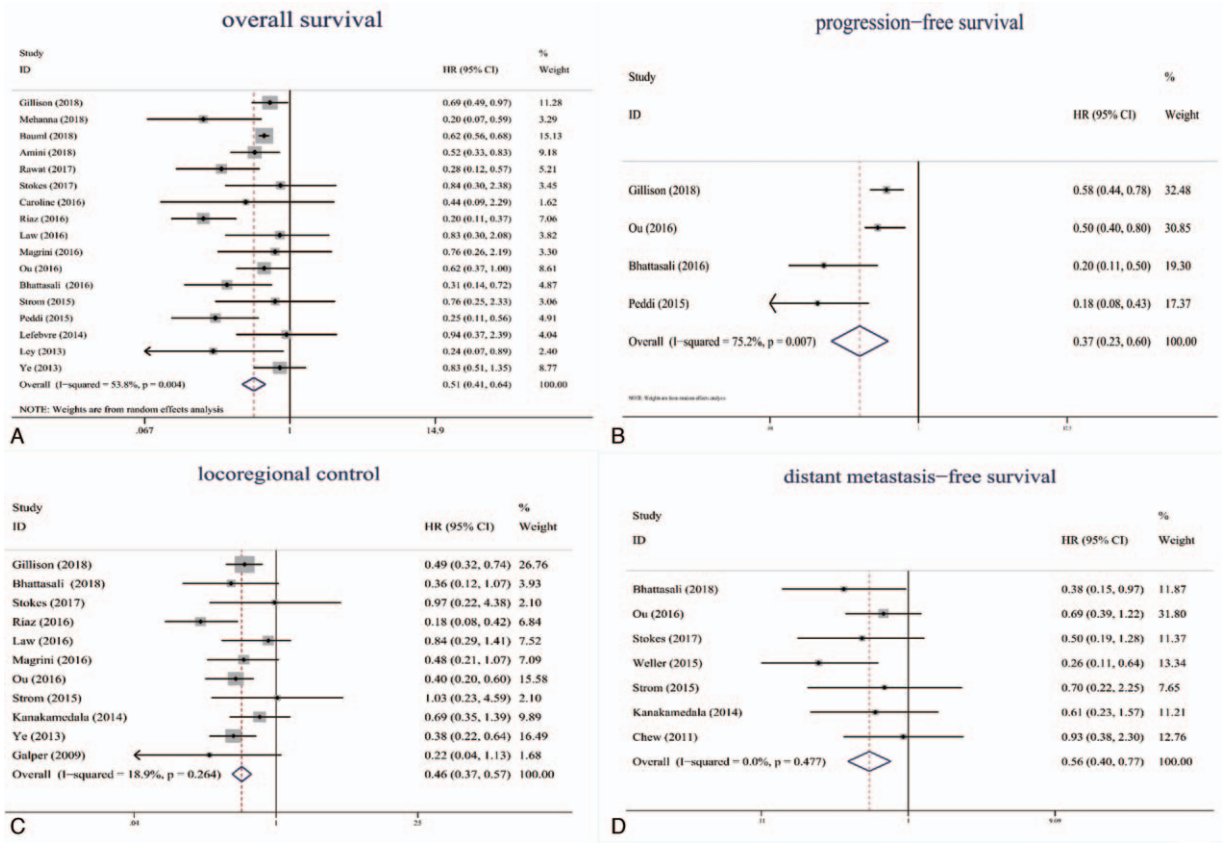

Figure 3. Forrest plot of HR assessing the risk of cisplatin-based chemoradiotherapy vs cetuximab-based bioradiotherapy for locally advanced HNSCC. A, Forrest plot for 18 studies considering overall survival (OS). B, Forrest plot for 4 studies considering progression-free survival. C Forrest plot for 11 studies considering locoregional control. D, Forrest plot for 8 studies considering distant metastasis-free survival. CI = confidence interval, HR = hazard ratio.

3. review articles.

No ethical review is needed in this study.

2.3. Data extraction

The following data was extracted from the included studies: first author's last name, publication year, country of origin, type of study, study period, therapy regimens, number of patients, number of both sexes, median age, cancer types, stage, median follow-up time, and survival data (HR and its 95% CI for OS, PFS, LRC, DMFS). If HR and the corresponding 95% CI could not be extracted directly from the text, then methods proposed by Tierney[16] and Parmar[17] were applied to calculate these statistical variables by using the available numerical data. Any disagreements were settled by consulting with the third author.

2.4. Study quality assessment

Three authors independently evaluated the quality of the included studies. The Newcastle-Ottawa Scale was used to evaluate the cohort studies,[18] and scores of 6 or greater showed the high quality of the study. The Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate the randomized clinical trial.[19] Three categories, including "low risk," "high risk" or "unclear" for bias, were performed judging from the risk of bias in the included studies for each domains.

2.5. Statistical analysis

The primary outcome was evaluated by the OS, defined as the time from diagnosis of locally advanced HNSCC to death from any cause. Other outcomes were evaluated by PFS, defined as the time from diagnosis of locally advanced HNSCC to tumor progression in any aspect or death from any cause; LRC, defined as the time from completion of RT to locoregional recurrence; and DMFS, defined as the time from completion of RT to distant metastasis. HR and its 95% CI were applied to investigate the treatment efficacy of CRT or BRT. The overall HR, integrated from individual HR, was shown with a forest plot. Pooled HR <1, and 1 not included in the corresponding 95% CI ($P<.05$), was described as a better survival for the CRT group. Heterogeneity was assessed using the Cochran Q test and the Higgins I^2 statistic test. When the case of I^2 value $\geq$50% or P-value $\leq$.1 was considered as substantial heterogeneity,[20] a random effect model was applied; otherwise, a fixed-effect model was employed. Subgroup analyses were based on cancer types, HPV infection status, study types, and the type of therapy (induction chemotherapy or none induction chemotherapy). The funnel plot and Egger test[21] were used to identify potential publication biases. P-values $<.05$ were recognized as statistically significant, and all analyses were calculated using Stata Statistical Software 12.0. (Stata Corporation, College Station, TX).

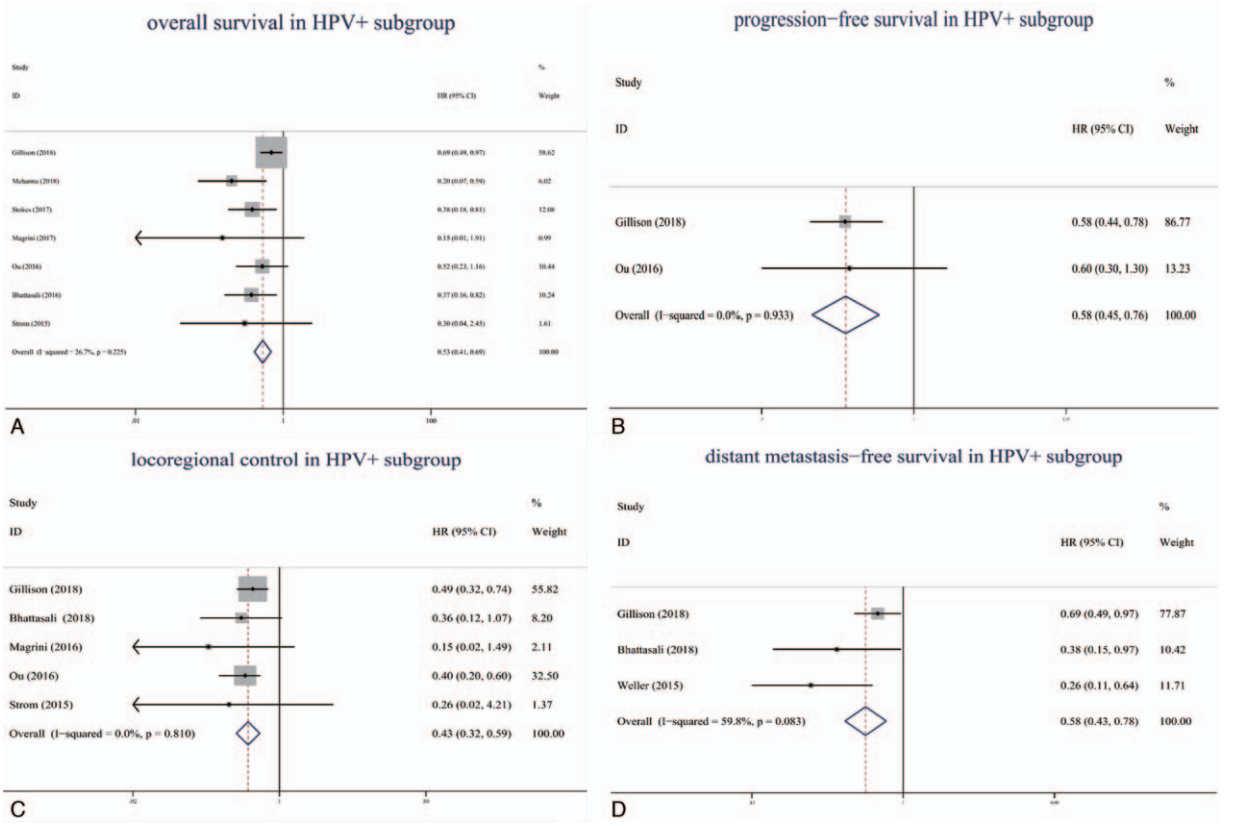

Figure 4. Forrest plot of HR assessing the risk of cisplatin-based chemoradiotherapy vs cetuximab-based bioradiotherapy for HPV positive (+) HNSCC. A, Forrest plot for 7 studies considering overall survival. B, Forrest plot for 2 studies considering progression-free survival. C, Forrest plot for 5 studies considering locoregional control. D, Forrest plot for 3 studies considering distant metastasis-free survival. CI = confidence interval, HPV = human papillomavirus, HR = hazard ratio.

3. Results

3.1. Literature selection and screening

As illustrated in Figure 1, a total of 2473 studies were identified based on the initial literature search, and 45 studies remained after screening the titles and abstracts. Subsequently, 22 studies were excluded after reading the full-text or abstracts, based on the following reasons: overlap with others studies (6), use of cisplatin-based double or multiple concurrent agents (12), inclusion of distant metastasis patients (2), a review article without original data (1), and inclusion of postoperative patients (1).

3.2. Characteristics of included studies and quality assessment

Twenty-three studies with a total of 8701 patients were enrolled in this meta-analysis; and Table 1 summarizes the major characteristics of the enrolled studies. The eligible studies consisted of 18 retrospective trials[22–40] and 5 prospective studies,[11,12,41–43] including 2 randomized, multicenter, and phase 3 trials.[11,12] For the median age, patients treated with CRT were generally older than patients treated with BRT. All studies used the same cetuximab schedule with a loading dose of 400 mg/m^2 and, subsequently, administration of 250 mg/m^2 weekly. Regarding the therapeutic schedule, some studies included patients that received induction chemotherapy while others did not. Eighteen studies with 8007 patients were pooled to assess the impact of the treatment with OS. To evaluate the PFS, LRC, and DMFS, 4, 11, and 8 studies were pooled, respectively. The results of the quality assessment for the cohort studies are presented in Table 2. Five, 10, and 3 studies had quality scores of 6, 7, and 8, respectively. Each included randomized clinical trial and its quality score was shown in Figure 2. Most of them had low risk of bias.

3.3. Survival analysis

The OS, PFS, LRC, and DMFS, were used as outcomes in this study. As regards OS, the pooled HR was 0.51 (95%CI, 0.41–0.64, $P < .001$, Fig. 3A), indicating that patients treated with CRT compared with BRT had a longer OS in locally advanced HNSCC. Similarly, this study demonstrated that patients treated with CRT had better PFS (HR = 0.37, 95%CI 0.23–0.60, $P < .001$, Fig. 3B), LRC (HR = 0.46, 95%CI, 0.37–0.57, $P < .001$ Fig. 3C) and DMFS (HR = 0.56, 95%CI, 0.40–0.77, $P < .001$, Fig. 3D).

3.4. Subgroup analysis

Further subgroup analyses also had similar results to those of the primary analysis. In the subgroup of HPV (+) HNSCC, the combined HR for OS was 0.53 (95%CI, 0.41–0.69, $P < .001$, Fig. 4A). Similarly, we observed that HPV (+) HNSCC treated

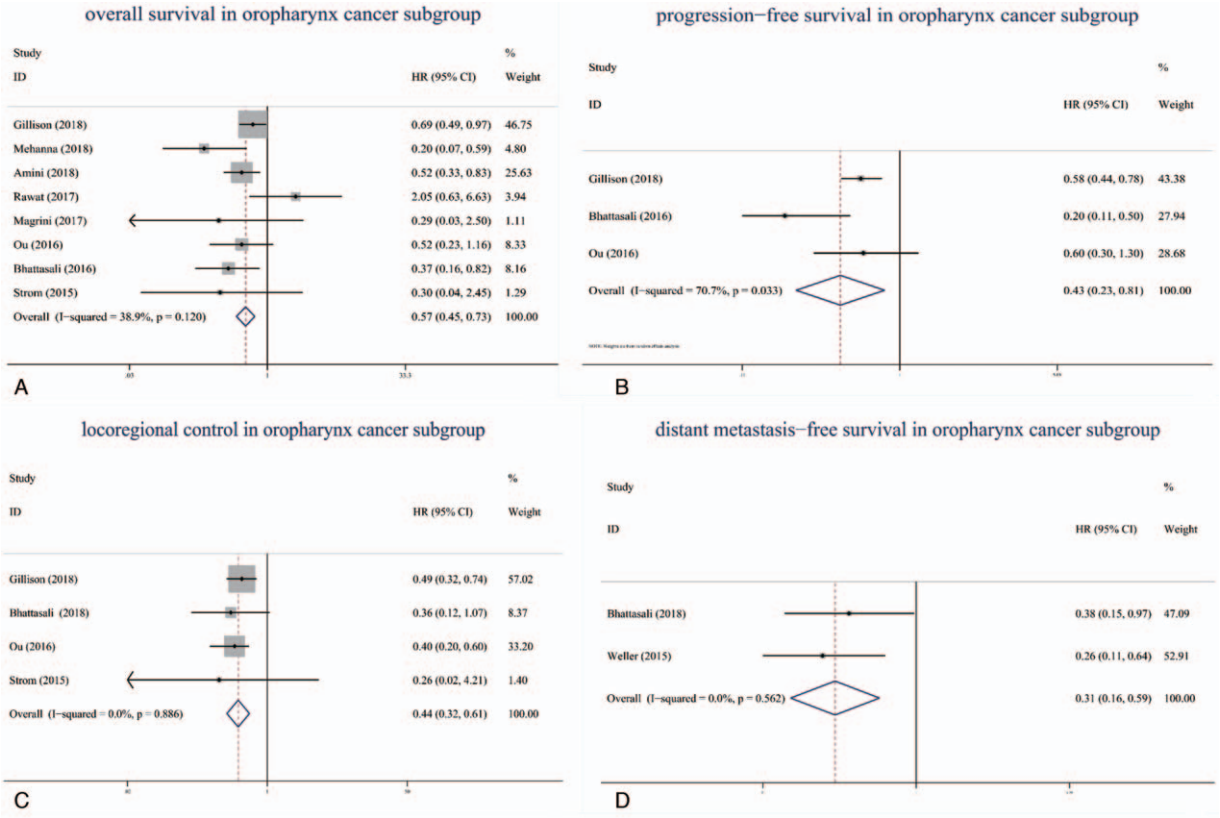

Figure 5. Forrest plot of HR assessing the risk of cisplatin-based chemoradiotherapy vs cetuximab-based bioradiotherapy for human papillomavirus positive (+) HNSCC. A, Forrest plot for 8 studies considering overall survival. B, Forrest plot for 3 studies considering progression-free survival. C, Forrest plot for 4 studies considering locoregional control. D, Forrest plot for 2 studies considering distant metastasis-free survival. CI = confidence interval, HR = hazard ratio.

with CRT had better PFS (HR = 0.58, 95%CI, 0.47–0.76, $P < .001$, Fig. 4B), LRC (HR = 0.43, 95%CI, 0.32–0.59, $P < .001$, Fig. 4C) and DMFS (HR = 0.46, 95%CI, 0.24–0.86, $P < .001$, Fig. 4D). For oropharynx cancer regardless of HPV condition, CRT showed better OS (HR = 0.46, 95%CI, 0.37–0.57, $P < .001$, Fig. 5A), PFS (HR = 0.37, 95%CI, 0.23–0.60, $P = .009$, Fig. 5B), LRC (HR = 0.46, 95%CI, 0.37–0.57, $P < .001$, Fig. 5C) and DMFS (HR = 0.51, 95%CI, 0.41–0.64, $P < .001$, Fig. 5D) than BRT. Furthermore, as shown in Table 3, we also observed longer OS in patients treated with CRT than in patients treated with BRT, irrespective of the study type, retrospective or prospective, and the type of therapy (induction chemotherapy or none induction chemotherapy).

Table 3

Subgroup analyses overall survival.

subgroup	Adjusted HR (95% CI, *P*-value)	I^2
Study type		
Retrospective study	0.50 (0.39–0.65, $P < .001$)	59.4
Prospective study	0.53 (0.30–0.93, $P < .001$)	40.2
Induction chemotherapy		
Yes	0.54 (0.33–0.90, $P = .180$)	58.7
No	0.46 (0.33–0.65, $P < .001$)	59.4

CI = confidence interval, HR = hazard ratio.

3.5. Publication bias

We evaluated publication bias by assessing the asymmetry of the funnel plot visually and quantitatively performing Egger test. No apparent asymmetry was observed from the visual evaluation of the funnel plot, and there was no publication bias using the Egger test ($P = .127$ for OS, $P = .089$ for PFS, $P = .79$ for LRC, $P = .609$ for DMFS) as illustrated in Figure 6.

4. Discussion

CRT and BRT are both the standard of treatment for patients with inoperable locally advanced HNSCC. Since there were no randomized phase 3 trials to compare these two strategies for a long time, the opinion that BRT was comparable to CRT has been challenged all the time. Some clinical studies and meta-analyses that have addressed this issue have conflicting conclusions. Fausto et al conducted a meta-analysis to evaluate the efficacy of platinum-based chemoradiotherapy compared with cetuximab-based bioradiotherapy in locally advanced HNSCC,[44] and they found cisplatin had better OS and PFS. However, the risk ratio was defined as the primary measurement of treatment outcome in this study, but the outcome of time-to-event was not considered. A meta-analysis by Huang et al observed a better OS in patients with HPV (+) HNSCC and better PFS in patients with oropharyngeal cancer treated with BRT than in patients treated with CRT,[45] including studies containing patients treated with cisplatin-based dual or multiple concurrent

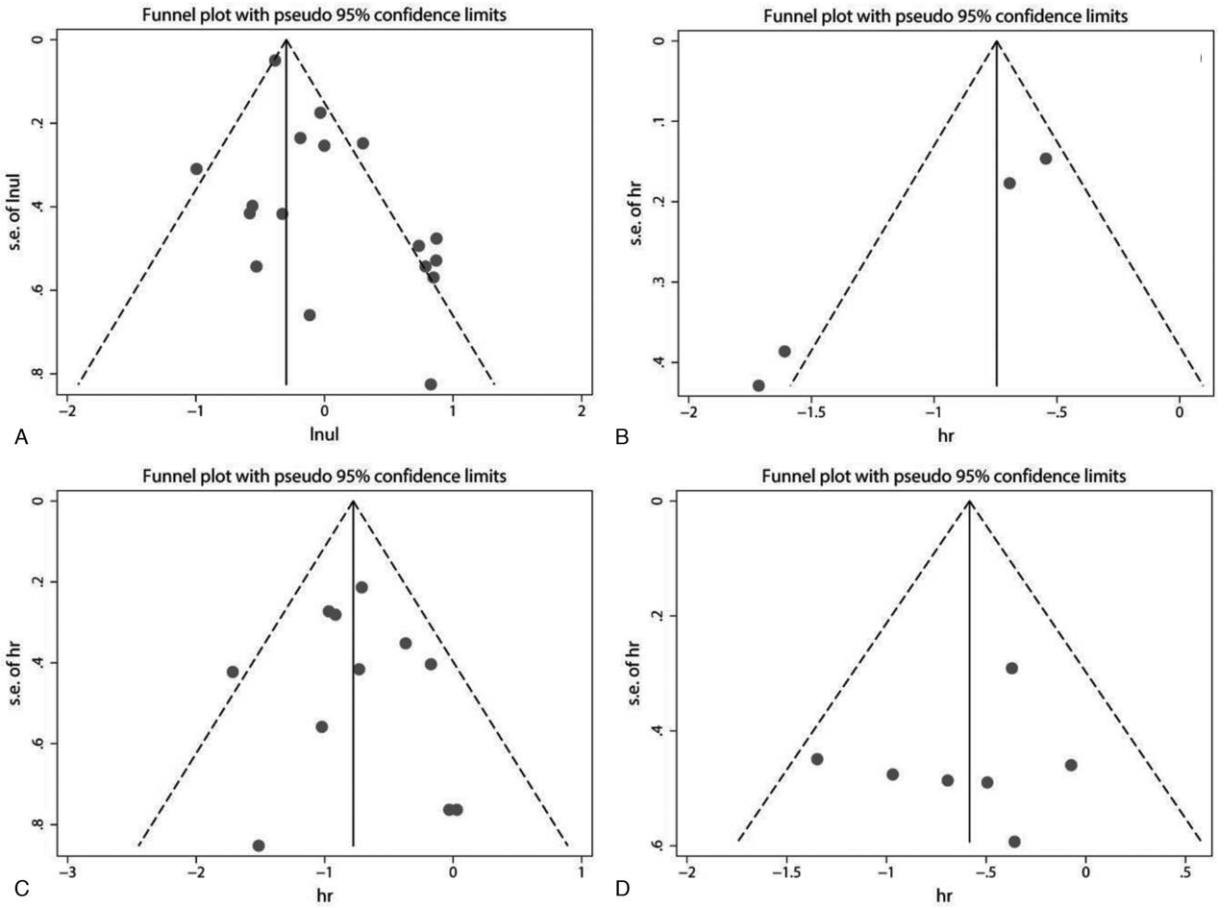

Figure 6. Funnel plot for the assessment of publication bias in this study. A, Funnel plot for 18 studies considering overall survival. B, Funnel plot for 4 studies considering progression-free survival. C, Funnel plot for 11 studies considering locoregional control. D, Funnel plot for 8 studies considering distant metastasis-free survival.

drugs. A pivotal limitation of this study was that negative numbers were included when calculating the HR in some included studies. The HR in survival analysis is described as the ratio of the hazard rate, and the hazard rates correspond to the conditions that are described by 2 levels of an explanatory variable. The negative numbers are often not included. Thus, we observed that there were different conclusions in the two meta-analyses as regards the OS of HPV (+) HNSCC patients and the PFS of patients with oropharyngeal cancer. Hence, we conducted this meta-analysis employing the latest researches to settle the dispute. The studies included in this meta-analysis were selected based on strict selected criteria. Since concurrent high-dose cisplatin is the preferred systemic agent recommended by National Comprehensive Cancer Network Guideline and has been used most commonly in clinic, our meta-analysis compared concurrent cetuximab with concurrent cisplatin only, excluding studies using other platinum-based chemoradiotherapy such as carboplatin plus paclitaxel, cisplantin plus 5-fluorouracil and cisplantin plus 5-fluorouracil/hydorxyurea,[46–50] the studies were excluded. Moreover, the latest updated results of some duplicate studies were accepted and the previous reports were excluded.[51–58] Eighteen studies were included in this analysis to assess the impact of treatment on OS. The combined HR for OS was 0.53 (95%CI, 0.41–0.69, $P < .001$), suggesting that patients treated with CRT compared with BRT had a longer OS in locally advanced HNSCC. Moreover, patients treated with CRT also had better PFS (HR = 0.37, 95%CI 0.23–0.60, $P < .001$), LRC (HR = 0.46, 95%CI, 0.37–0.57, $P < .001$) and DMFS (HR = 0.56, 95%CI, 0.40–0.77, $P < .001$). These results indicated that cetuximab could not replace the role of cisplatin in locally advanced HNSCC.

The above 2 meta-analyses drew inconsistent conclusions regarding OS in HPV (+) HNSCC patients and the PFS in patients with oropharyngeal cancer. Our subgroup analysis, limited to the HPV (+) HNSCC patients, showed that the CRT group had better OS (HR = 0.53, 95%CI, 0.41–0.69, $P < .001$), PFS (HR = 0.58, 95%CI, 0.47–0.76, $P < .001$), LRC (HR = 0.43, 95%CI, 0.32–0.59, $P < .001$) and DMFS (HR = 0.46, 95%CI, 0.24–0.86, $P < .001$). Similarly, when limited to oropharynx cancer, we found that CRT was associated with better OS (HR = 0.46, 95% CI, 0.37–0.57, $P < .001$), PFS (HR = 0.37, 95%CI, 0.23–0.60, $P = .009$), LRC (HR = 0.46, 95%CI, 0.37–0.57, $P < .001$) and DMFS (HR = 0.51, 95%CI, 0.41–0.64, $P < .001$). Conclusively, this analysis suggests that HPV (+) HNSCC and oropharyngeal cancer patients could benefit much more from concurrent cisplatin than BRT.

Given that in the clinical stages, radiotherapy regimens, and patients receiving induction chemotherapy is related to a patient's

survival, we designed subgroup analyses in our study. Considering the nine studies that focused on stage III-IV patients and other studies that included all the clinical stages, we could not perform subgroup analysis on clinical stages. Similarly, subgroup analysis of the radiotherapy technique was not performed also because intensity-modulated radiation therapy was used in ten studies, the radiotherapy technology was not given in other studies. The combined HR for OS was 0.54 (95%CI, 0.33–0.90, $P = .180$) for three studies that employed induction chemotherapy, and 0.46 (95%CI, 0.33–0.65, $P < .001$) in the fourteen studies without induction chemotherapy. The OS and PFS cox model analysis from a phase II-III trial found that after induction, concurrent chemoradiotherapy had a similar survival to BRT. However, BRT had a better OS after induction chemotherapy than concurrent chemoradiotherapy, indicating that induction chemotherapy could cause different effect to the subsequent concomitant strategy.[47] After 3 cycles of intensive TPF induction chemotherapy, the patients could tolerate concurrent cetuximab more easily than concurrent high-dose cisplatin-based chemotherapy. Therefore, concurrent cetuximab could achieve a better survival by avoiding the severe toxicity caused by concurrent chemotherapy. But the interaction test did not reach the statistical significance ($P = .088$). Similarly, in the subgroup analyses stratified by study types, the combined HR for OS was 0.50 (95%CI, 0.39–0.65, $P < .001$) in the 19 retrospective studies, and 0.53 (95%CI, 0.30–0.93, $P < .001$) in the 5 prospective studies. The results of the subgroup and pooled analysis were similar, demonstrating that patients treated with CRT had a better outcome in locally advanced HNSCC.

HPV (+) and HPV (−) HNSCC are different groups with different treatment strategies. HPV (+) HNSCC has higher chemosensitivity and radiosensitivity with a better prognosis, in which de-intensification is being investigated widely. Previous studies reported that HPV infection and EGFR status were inversely associated.[59] Therefore, EGFR inhibition may be inferior to chemotherapy in HPV (+) HNSCC; however, the studies had inconsistent conclusions regarding this. Some studies reported better outcomes with cetuximab than with cisplatin in HPV (+) HNSCC.[45,60] Recently, 2 randomized studies demonstrated that cetuximab was inferior to cisplatin for patients in terms of OS. Furthermore, cetuximab also caused severe toxicity similar to cisplatin. Similarly, our meta-analysis, also showed that cisplatin had better survival in HPV (+) HNSCC.[11,12] Hence, cisplatin should remain the standard of care for HPV (+) HNSCC patients. As is known to all, HPV (+) OPC is genetically different from HPV (−) HNSCC. Activating mutations in downstream genes of the EGFR pathway might cause anti-EGFR resistance in HPV (+) OPC. Amplification, overexpression of EGFR, and downstream signal transduction are more frequent in HPV (−) HNSCC.[61] Retrospective study suggested that EGFR inhibition might be more effective in HPV (−) disease than in HPV (+) disease.[13,14] Considering the effect of cetuximab in two different groups might be different, it is not appropriate to ratiocinate the results of this meta-analysis to HPV(−) HNSCC. Additionally, we conducted subgroup analyses to explore the potential areas of bias. A reduced heterogeneity was found when we included prospective studies suggesting that the differences in study types could be a source of heterogeneity. Moreover, heterogeneity might partly result from different administration and doses of cisplatin. Cisplatin was given at 40 mg/m^2 weekly in some studies,[25,28,35,41,42] while 100 mg/m^2 was administered every 3 weeks in others studies. The heterogeneity may be reduced after the standardization of the issues in the future. In terms of publication bias, Egger test demonstrated that there was no publication bias. Moreover, there is no need to worry about the publication bias in this meta-analysis. Also, it is clinically meaningful and highly publishable no matter CRT or BRT is better.

However, this meta-analysis has some limitations. Firstly, the data were extracted from prospective or retrospective studies with different inclusion criteria, which might bring bias. Furthermore, the choice of CRT or BRT might be on account of the patients' characteristics and clinical condition in the retrospective studies. Also, this meta-analysis lacks individual data. Furthermore, we excluded studies that had no adequate data to calculate HR. Finally, the sample size of each study varied widely.

5. Conclusion

In this meta-analysis, we observed that CRT had better OS, PFS, LRC, and DMFS in locally advanced HNSCC than BRT. Thus, concurrent cisplatin should remain the standard of treatment for patients in this setting. Concurrent cetuximab may still be administered to patients who cannot tolerate cisplatin.

Author contributions

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Methodology: Wei Sun, Wen-Hua Tang.
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Supplementary Digital Content, http://links.lww.com/MD/E724.

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