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Original Article

Chemoradiotherapy is superior to radiotherapy alone after surgery in advanced squamous cell carcinoma of the head and neck: a systematic review and meta-analysis

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Abstract: Background: To conduct a comprehensive review whether chemotherapy to radiotherapy after surgical resection could improve the loco regional control and survival compared with postoperative radiotherapy alone. Methods: A comprehensive search of PubMed for relevant studies comparing patients with advanced squamous cell carcinoma of the head and neck undergoing chemoradiotherapy or radiotherapy alone after resection was conducted. Results: The meta-analysis demonstrated significant benefits from adding chemotherapy to radiotherapy in local-regional control, disease-free survival and overall survival ($p < 0.00001$). The adverse effects include hematological and non-hematological toxicities. Although the acute and late toxicities occurred more frequently and severely in chemoradiation combined treatment, there was no significant difference compared with radiotherapy alone, but the estimated pooled RR of mucositis or dysphagia was 1.69 ($p < 0.00001$) in favor of radiotherapy regimens. Conclusions: Postoperative chemotherapy adding to radiotherapy is superior to radiotherapy alone. Patients with chemoradiotherapy after surgical resection can achieve the higher LRC, longer DFS and OS.

Keywords: Head and neck neoplasms, chemoradiotherapy, meta-analysis, review

Introduction

Head and neck squamous cell carcinomas (HNSCC) are the eighth most common cause of cancer death worldwide, with the incidence of approximately 8% to 10% in Southeast Asia and Africa particularly [1, 2]. Patients with early stage HNSCC can achieve good curative effect after surgery or radiotherapy alone, with a 5-year overall survival rate of 80% to 90% for a Stage I disease and 65% to 80% for a Stage II [3-6]. However, most patients are present with stage III or IV disease when diagnosed with squamous cell carcinoma [7, 8]. Given the high rate of local/regional failure and distant metastasis after treatment for locally advanced HNSCC, comprehensive therapy plays an important role in the whole treatment, especially postoperative adjuvant treatment. The 5-year survival after surgery followed by radiotherapy was approximately 40% [9], and patients with surgery plus postoperative concurrent chemoradiotherapy achieved the 5-year survival rate of 53% [10]. The previous meta-analysis showed the benefit for chemoradiotherapy in loco regional control (relative risk [RR]: 0.59; 95% confidence interval [CI]: 0.47-0.75; $p < 0.00001$) and overall survival (RR: 0.80; 95% CI: 0.71-0.90; $p = 0.0002$) [11]. Among the included studies in previous meta-analysis, two clinical trials have reported the results of long-term survival based on updated data [12, 13]. This stimulated our interest in performing a systematic review and meta-analysis of available data to further determine if postoperative adjuvant chemoradiotherapy was superior to adjuvant radiotherapy alone in patients with resectable advanced HNSCC.

Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, that provides an evidence-based guideline for reporting the results of systematic

Table 1. Characteristics of included studies

Study	Type of study	Treatment arms	Treatment regimens	No. of patients	Follow-up, median
Bernier et al. 2004	Prospective	CT+RT	66 Gy over a period of $6^{1/2}$ weeks combined with 100 mg/m^2 of cisplatin on days 1, 22, and 43 of radiotherapy.	167	60 months
		RT	66 Gy over a period of $6^{1/2}$ weeks.	167	
Cooper et al. 2012	Prospective	CT+RT	60 to 66 Gy over a period of 6 to 6.6 weeks plus concurrent cisplatin 100 mg/m^2 intravenously on days 1, 22, and 43.	202	9.4 years
		RT	60 to 66 Gy over a period of 6 to 6.6 weeks.	208	
Bachaud et al. 1996	Prospective	CT+RT	1.7 Gy daily for the first 54 Gy and 1.8 to 2 Gy daily or three fractions of 3 Gy per week until a total dose of 65-74, combined with 50 mg cisplatin (7-9 cycles) on the first day of each week of irradiation.	39	5 years
		RT	1.7 Gy daily for the first 54 Gy and 1.8 to 2 Gy daily or three fractions of 3 Gy per week until a total dose of 65-74.	44	
Šmid et al. 2006	Prospective	CT+RT	Irradiated to the total dose of 56-70 Gy, combined with mitomycin C 15 mg/m^2 after 10 Gy and 5 mg of bleomycin twice weekly during RT to the planned total dose of 70 mg.	59	76 months
		RT	Irradiated to the total dose of 56-70 Gy.	55	
Haffty et al. 1993	Prospective	CT+RT	Mean total dose of 58.7-60.1 Gy, with 1.8-2 Gy daily, combined with mitomycin C (15 mg/m^2) following radiation treatment on the 5th day of the radiotherapy course or plus diconmarol (300 mg before mitomycin C and 200 mg on the day of mitomycin C).	55	93 months
		RT	Mean total dose of 58.7-60.1 Gy, with 1.8-2 Gy daily.	58	
Lee et al. 2013	Retrospective	CT+RT	Fractionated dose of 1.8 to 2 Gy each in five weekly sessions until a total dose of 50-65 Gy, combined with 100 mg/m^2 cisplatin on days 1, 22, and 43 of the course of RT or weekly 30 mg/m^2 cisplatin.	45	65 months
		RT	Fractionated dose of 1.8 to 2 Gy each in five weekly sessions until a total dose of 50-65 Gy.	56	

Footnotes: No., number; CT, chemotherapy; RT, radiotherapy.

reviews and meta-analyses in a clear, accurate, and reliable manner, was used as the basis for this study [14].

Literature search strategy

The following search strategy was used for searching pubmed: (head and neck squamous cell carcinoma) and (chemoradiotherapy or chemotherapy or radiation) and (resection or surgery). Limits included dates (January 1, 1990 to December 31, 2013), English language, and studies in humans.

Study selection

Eligibility assessment was first performed by screening titles and abstracts identified by the previously described searches and sources. This was performed independently by 2 separated authors in an un-blinded standardized manner. Disagreements between reviewers were resolved by consensus. The full texts of shortlisted studies were reviewed and further assessed. All review authors decided on study inclusion.

Eligibility criteria

Studies containing potentially operable patients with previously untreated advanced HNSCC and comparing postoperative radiotherapy with postoperative chemoradiotherapy were eligible for review. Primary sites included the oral cavity, oropharynx, hypopharynx and larynx. Studies including only nasopharyngeal carcinomas were excluded.

Data collection

Variables for which data were sought included the following: patient-related information (number of patients overall and in each group, diagnosis, etc.) and outcomes (loco regional control, progression-free survival, disease-free survival, overall survival, adverse events). The summary statistics required for these analyses were the log-rank observed minus expected number of relapse and deaths (O-E) or hazard ratio (HRs) and associated variance. When hazard ratios and confidence intervals were not provided, they were extracted from life tables

Table 2. Efficacy data: randomized trials of chemoradiotherapy versus radiotherapy alone

Author. Year	Treatment arms	No. of pts.	Point in time*	Loco-regional recurrence	Disease-free survival	Overall survival	Median survival, mo
Bernier et al. 2004	CT+RT	167	5 y	18%	47%†	53%	72
	RT	167		31%	36%	40%	32
				P = 0.007	P = NR	P = NR	P = NR
			Overall	NR	HR = 0.75, *p* = 0.04	HR = 0.70, *p* = 0.02	
				NR	95% CI = 0.56-0.99	95% CI = 0.52-0.95	
Cooper et al. 2012	CT+RT	202	10 y	22.3%	20.1%	29.1%	NR
	RT	208		28.8%	19.1%	27%	NR
				P = 0.10	P = 0.25	P = 0.31	
			Overall	HR = 0.73,	HR = 0.88	HR = 0.89	
				95% CI = 0.49-1.07	95% CI = 0.71-1.09	95% CI = 0.70-1.12	
Bachaud et al. 996	CT+RT	39	5 y	23%	45%	36%	40
	RT	44		41%	23%	13%	22
				P = 0.08	P < 0.02	P < 0.01	P = NR
			Overall	NR	HR = 2.02	HR = 1.89	
				NR	95% CI = 1.17-3.48	95% CI = 1.07-3.34	
Šmid et al. 2006	CT+RT	59	5 y	12%	53%	55%	68‡
	RT	55		35%	33%	37%	45
				P = 0.026	P = 0.035	P = 0.091	
			Overall	NR	HR = 0.61	HR = 0.66	
				NR	95% CI = 0.37-0.97	95% CI = 0.41-1.07	
Haffty et al. 1993	CT+RT	55	5 y	13%	67%	56%	NR
	RT	58		33%	44%	41%	NR
				P < 0.015	P < 0.03	NS	
			Overall	NR	HR = 0.55	HR = 0.81	
				NR	95% CI = 0.31-1.0	95% CI = 0.48-1.36	
Lee et al. 2013	CT+RT	45	5 y	20%	51.3%	63.2%	NR
	RT	56		30%	41.8%	47.2%	NR
				NR	P = 0.1	P = 0.2	
			Overall	NR	HR = 0.73	HR = 0.78	
				NR	95% CI = 0.43-1.24	95 CI% = 0.44-1.40	

Footnotes: No., number; pts., patients; CT, chemotherapy; RT, radiotherapy; NR, not reported; HR, hazard ratio; CI, confidence interval; NS, not statistically significant; Y, years. *Percentiles reflect the point in time that outcomes were measured; overall data reflect hazard ratios from Kaplan-Meier curves, extracted from survival curves. †Date on progression-free survival in this trial. ‡Date extracted from survival curves.

provided by authors, or Kaplan-Meier curves and the maximum follow-up time reported in manuscripts [15].

Statistics

The meta-analysis was performed using Review Manager 5.2 software (provided by Cochrane Collaboration). The results were generated using the fixed-effects model unless otherwise stated. A random-effects model was employed when there was evidence of significant statistical heterogeneity, generating a more conservative estimate. Results are expressed as the RR or HR with 95% CI, where an RR or HR of < 1.0 favors the experimental treatment and an RR or HR of > 1.0 favors control. Statistical heterogeneity was quantified using the I^2 statistics and x^2-based tests.

Results

Trial characteristics

Results of the literature search identified 3592 papers based on the search words in the PubMed. Among those papers, according to the criteria already described, 6 publications [10, 12, 13, 16-18] were eligible for inclusion in this meta-analysis, including 5 randomized control trials (RCTs) and 1 retrospective review (**Tables 1**, **2**).

Loco-regional recurrence

Data on 6 comparisons were available from 6 enrolled studies, including 1155 patients, 567 in the postoperative chemoradiotherapy arms and 588 in the postoperative radiotherapy

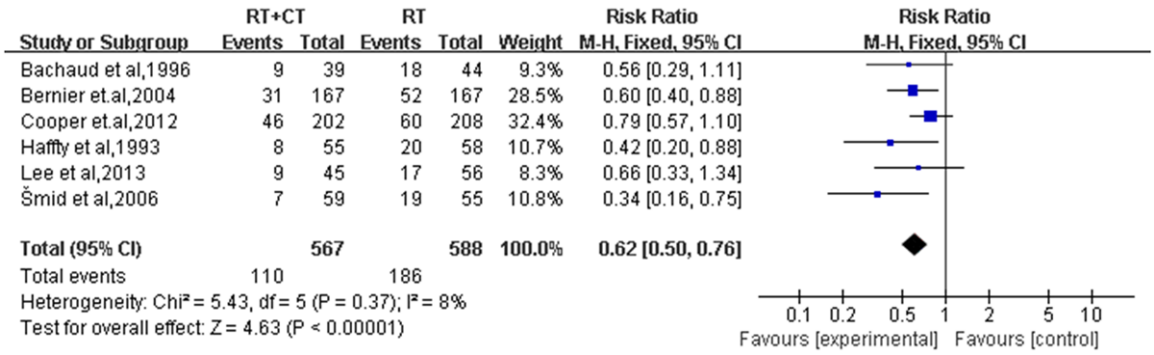

Figure 1. Forest plot of loco-regional recurrence of patients receiving chemoradiotherapy versus radiotherapy alone after surgery. RT, radiotherapy; CT, chemotherapy; CI, confidence interval.

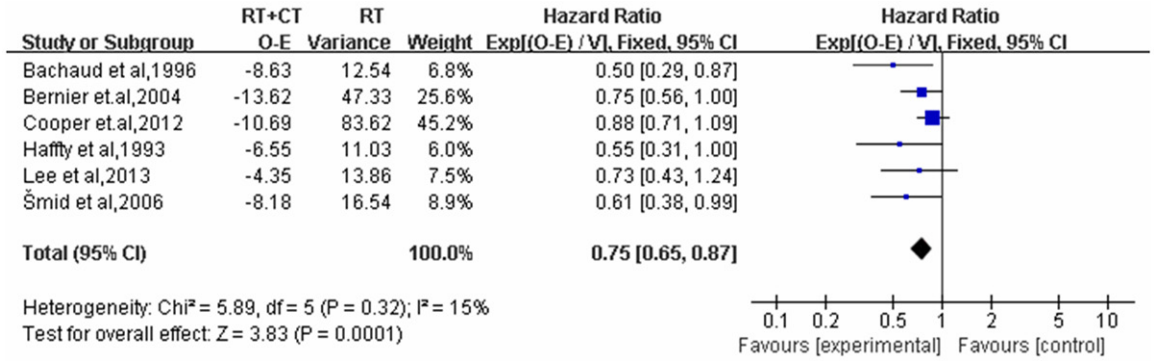

Figure 2. Forest plot of disease-free survival of patients receiving chemoradiotherapy versus radiotherapy alone after surgery. RT, radiotherapy; CT, chemotherapy; CI, confidence interval.

arms. Three of the 5 RCTs reported patients who received chemoradiotherapy achieved significantly improved loco-regional control compared to those who received radiotherapy alone [10, 13, 17] (**Table 1**). The other two trials and the retrospective review also showed a benefit with the addition of chemotherapy, but the difference was not statistically significant [12, 16] or reported [18]. The estimated proportion of between-study variability (I^2) was 8% for the risk ratio for loco-regional recurrence of postoperative radiotherapy versus postoperative chemoradiotherapy. Based on the x^2 test, no significant statistical heterogeneity was found (**Figure 1**). A summary of individual trials and overall pooled results from the primary analysis of loco-regional recurrence is shown in **Figure 1**. The estimated pooled RR for loco-regional recurrence in all studies was 0.62 (95% CI: 0.50-0.76, $p < 0.00001$) in favor of chemoradiotherapy regimens. The corresponding absolute benefit is a 38% relative reduction in the risk of loco-regional recurrence with the addition of chemotherapy to radiotherapy.

Progression-free or disease-free survival

Data on 6 comparisons were available from 6 enrolled studies, including 1155 patients, 567 in the postoperative chemoradiotherapy arms and 588 in the postoperative radiotherapy arms. Only 1 trial reported progression-free survival as an outcome of interest [10], with a significant progression-free survival difference favoring chemoradiotherapy (HR: 0.75; 95% CI: 0.56-0.99; $p = 0.04$). Three RCTs reported patients who received chemoradiotherapy achieved significantly better DFS compared to those who received radiotherapy alone [13, 16, 17] (**Table 1**). One trial and the retrospective review also showed a benefit with the addition of chemotherapy, but the difference was not statistically significant [12, 18]. Progression-free survival (PFS) was defined as the time from randomization to any type of progression or death from any cause. Disease-free survival (DFS) was measured from the time of randomization to the time of discovery of the first evidence after treatment of any tumor (local, regional, meta-

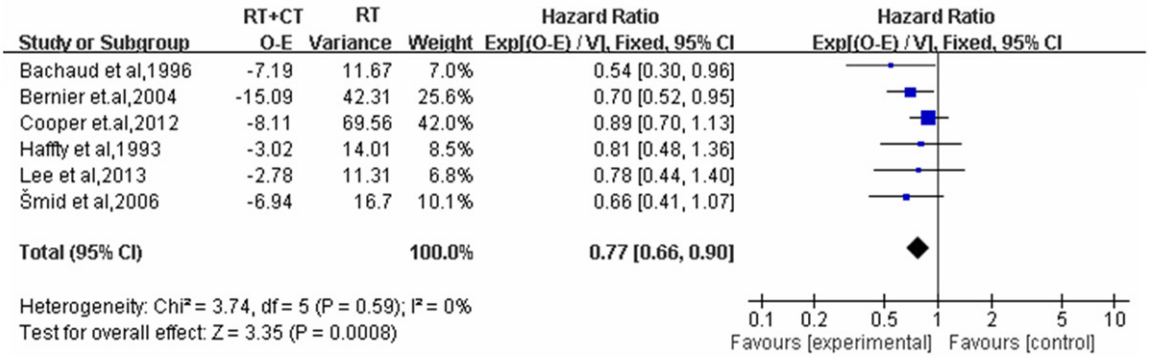

Figure 3. Forest plot of overall survival of patients receiving chemoradiotherapy versus radiotherapy alone after surgery. RT, radiotherapy; CT, chemotherapy; CI, confidence interval.

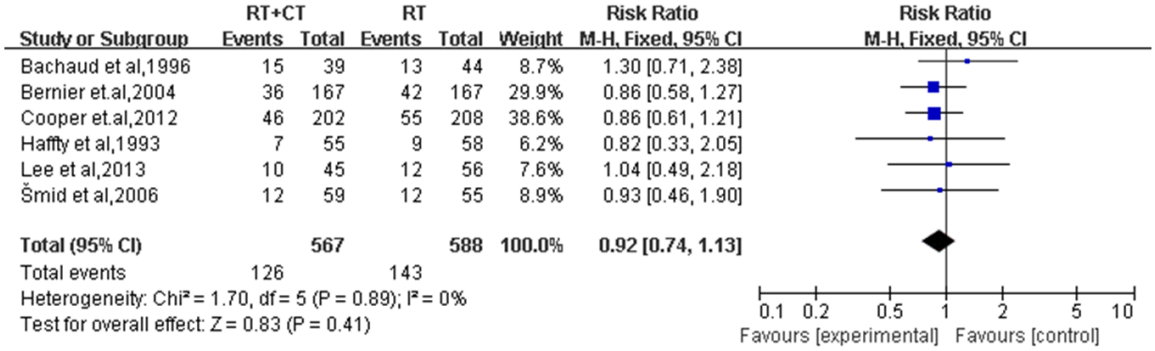

Figure 4. Forest plot of distant metastasis of patients receiving chemoradiotherapy versus radiotherapy alone after surgery. RT, radiotherapy; CT, chemotherapy; CI, confidence interval.

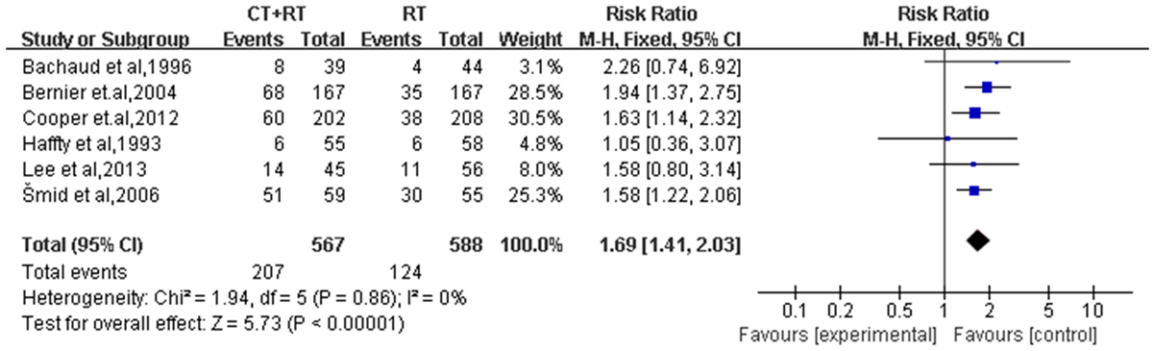

Figure 5. Forest plot of mucositis/dysphagia of patients receiving chemoradiotherapy versus radiotherapy alone after surgery. RT, radiotherapy; CT, chemotherapy; CI, confidence interval.

static, or second primary) or death from any cause. As the similar definition of DFS and PFS, data on them were pooled from all 6 included studies. The estimated proportion of between-study variability (I^2) was 15% for the hazard ratio for DFS of postoperative radiotherapy versus postoperative chemoradiotherapy. Based on the x^2 test, no significant statistical heterogeneity was found (**Figure 2**). A summary of individual trials and overall pooled results from the primary analysis of DFS is shown in **Figure 2**. The estimated pooled HR for DFS in all studies was 0.75 (95% CI: 0.65-0.87, $p = 0.0001$) in favor of chemoradiotherapy regimens.

Overall survival

Data on 6 comparisons were available from 6 enrolled studies, including 1155 patients, 567 in the postoperative chemoradiotherapy arms

and 588 in the postoperative radiotherapy arms. Only two RCTs reported patients who received chemoradiotherapy achieved significantly better OS compared to those who received radiotherapy alone [10, 16] (**Table 1**). Other studies also showed a benefit with the addition of chemotherapy, but the difference was not statistically significant [12, 13, 17, 18]. The estimated proportion of between-study variability (I^2) was 0% for the hazard ratio for OS of postoperative radiotherapy versus postoperative chemoradiotherapy. Based on the x^2 test, no significant statistical heterogeneity was found (**Figure 3**). A summary of individual trials and overall pooled results from the primary analysis of OS is shown in **Figure 3**. The estimated pooled HR for OS in all studies was 0.77 (95% CI: 0.66-0.80, p = 0.0008) in favor of postoperative chemoradiotherapy. The HR of 0.77 indicates a 23% relative reduction in the risk of death when chemotherapy is added to radiotherapy.

Distant metastasis

Date on distant metastasis was available from 6 enrolled studies, including 1155 patients, 567 in the postoperative chemoradiotherapy arms and 588 in the postoperative radiotherapy arms. There were no studies demonstrating that adding chemotherapy to radiotherapy significantly reduced the occurrence of distant metastases. The estimated proportion of between-study variability (I^2) was 0% for the risk ratio for distant metastasis of postoperative radiotherapy versus postoperative chemoradiotherapy. Based on the x^2 test, no significant statistical heterogeneity was found (**Figure 4**). A summary of individual trials and overall pooled results from the primary analysis of distant metastasis is shown in **Figure 4**. The estimated pooled RR for distant metastasis in all studies was 0.92 (95% CI: 0.74-1.13), and there was no significant difference in the probability of occurrence of distant metastases between chemoradiotherapy group and radiotherapy group (p = 0.41).

Toxicity

The hematological and non-hematological toxicities related to treatment are outlined in **Table 3**. As anticipated, toxicities were more common with chemoradiotherapy than with radiotherapy alone. Only one trial reported that chemoradiotherapy was significantly associated with the higher rate of acute severe adverse events compared with radiotherapy alone (77% vs. 34%, p < .001) [19]. The major grade 3/4 adverse events were mucositis or dysphagia, followed by various hematologic events and nausea and vomiting. Significant differences in late adverse events were not found between treatment groups in 4 trials [10, 12, 13, 16], and two studies did not report data on that outcome [17, 18]. Data on mucositis or dysphagia were pooled from the all 6 studies (**Figure 5**). The estimated pooled RR was 1.69 (95% CI: 1.41-2.03, p < 0.00001) in favor of radiotherapy regimens. The corresponding absolute benefit is a 69% relative increase in the risk of mucositis or dysphagia with the addition of chemotherapy to radiotherapy.

Discussion

It is widely accepted that surgery or radiotherapy alone is the most optimal treatment for HNSCC patients with stages I and II, with excellent outcome. However, a majority of patients were firstly diagnosed with locally-advanced stage (stages III and IV) disease, and local-regional recurrence and distant metastasis are common after surgical treatment in these patients, especially with inadequate resection margins, extranodal spread, or multiple involved lymph nodes [20-23]. Thereby, postoperative adjuvant treatment is necessary for patients with stages III and IV disease. Before the EORTC report, the standard treatment for locally advanced HNSCC was total resection of all visible and palpable disease, followed by adjuvant radiotherapy [24]. A number of retrospective studies have demonstrated that loco-regional control and survival were significantly better after surgery followed by radiotherapy compared to after surgery alone [25-27]. Based on these results, indications for postoperative radiotherapy include positive (< 1 mm) or close (1-5 mm) surgical margins, lymph node metastases with extranodal spread, 2 or more positive lymph nodes, invasion of the soft tissues and/or skin of the neck, more than 5 mm subglottic extension and perineural growth [28].

Despite such a relatively aggressive bimodality treatment, the prognosis of locally advanced HNSCC is poor, with loco-regional recurrence, distant metastasis and 5-year survival rates of 30%, 25%, and 40%, respectively [23, 24]. Consequently, more intensive treatment is

Table 3. Adverse events associated with chemoradiotherapy versus radiotherapy alone

Study	No. of pts	Treatment arms	Rate of adverse events		Grade 3/4 adverse effects					
			Acute	Late	Mucositis/dysphagia	Thrombocytopenia	Leukopenia	Granulocytopenia	Nausea/vomiting	Xerostomia
Bernier et al. 2004	167	CT+RT	NR	38%	41%	NR	16%	13%	11%	14%
	167	RT	NR	49%	21%	NR	0%	0%	0%	20%
				P = NS	P = 0.001		P = NR	P = NR	P = NR	P = NR
Cooper et al.[§] 2012	202	CT+RT	77%	24.9%[¶]	30%	38%*			20%	NR
	208	RT	34%	20.5%	18%	< 1%			0%	NR
			P < 0.001	P = 0.34	P = NR	P = NR			P = NR	
Bachaud et al.[§] 1996	39	CT+RT	41%	20%[‡]	21%	10%[†]			23%	NR
	44	RT	16%	15%	9%	0%			0%	NR
			P = NR	P = NR	P = NR	P = NR			P = NR	
Šmid et al.[§] 2006	59	CT+RT	NR	26%	86%	7%	7%	NR	NR	NR
	55	RT	NR	19%	55%	0%	0%	NR	NR	NR
				P = 0.52	P < 0.001	P = NR	P = NR			
Haffty et al. 1993	55	CT+RT	NR	NR	11%	9%	7%	NR	0%	NR
	58	RT	NR	NR	10%	0%	0%	NR	0%	NR
					P = NR	P = NR	P = NR		P = NR	
Lee et al. 2013	45	CT+RT	NR	NR	31.1%	37.7%*			4.4%	15.5%
	56	RT	NR	NR	19.6%	1.7%			0%	7.1%
					P = 0.21	P = 0.01			P = NR	P = 0.14

Abbreviations: CT, chemotherapy; RT, radiotherapy; NR, not reported; NS, not statistically significant. *Specific hematological adverse events not specified. †Neutrophils < 1000/mm^3. ‡Percentage based on 26 patients in the radiotherapy group and 30 patients in the chemoradiotherapy group. ¶Percentage based on 205 patients in the radiotherapy group and 193 patients in the chemoradiotherapy group. §Most adverse events for these trials were reported in the earlier publications [19, 29, 30].

needed to improve the outcome of the patients who have resectable and locally advanced HNSCC. The role of chemotherapy added to radiotherapy after surgery has been extensively investigated. There were 4 small size studies [13, 16-18] and 2 large scale RCTs [10, 19] to evaluate the value of concomitant chemotherapy with radiation therapy in the postoperative setting for patients with locally advanced HNSCC. In addition to radiotherapy, the administration of chemotherapy included cisplatin or mitomycin C or mitomycin C plus bleomycin. Despite the various types of drugs to be combined concomitantly with radiotherapy, the reported outcomes demonstrated that the addition of chemotherapy resulted in the benefits of local-regional control, disease-free survival and overall survival. The previous meta-analysis by Eric Winquist et al. [11] showed that postoperative adjuvant chemoradiotherapy was superior to radiotherapy alone in the terms of loco-regional recurrence and overall survival.

As two studies added [17, 18] and the follow-up increased [12, 13], we performed this updated individual patient data meta-analysis to further clarify the value of chemotherapy in locally advanced head and neck cancer. Adding new data did not change loco-regional control (RR: 0.62, 95% CI: 0.50-0.76, $p < 0.00001$) and overall survival (HR: 0.77, 95% CI: 0.66-0.90, $p = 0.0008$) benefits resulting from the addition of chemotherapy. Furthermore, this updated meta-analysis demonstrated that the addition of chemotherapy to postoperative radiotherapy improved disease-free survival over radiotherapy alone (HR: 0.75, 95% CI: 0.65-0.87, $p = 0.0001$). However, adding chemotherapy to radiotherapy did not significantly reduce the occurrence of distant metastasis (RR: 0.92, 95% CI: 0.74-1.13, $p = 0.41$).

Regardless of the pronounced benefit of loco-regional control and survival from more aggressive treatment with concurrent postoperative chemotherapy and radiotherapy, patients may pay the cost with a significant increase in severe adverse effects. This increase resulted largely from an increased incidence of hematologic, mucous membrane, and gastrointestinal adverse effects related to chemotherapy. Mucositis or dysphagia was the most common grade 3/4 adverse event. We pooled the data on mucositis or dysphagia and found that patients with concurrent postoperative chemoradiotherapy experienced it more frequently than those with radiotherapy alone (RR: 1.69; 95% CI: 1.41-2.03, $p < 0.00001$).

Conclusion

In conclusion, the addition of chemotherapy to postoperative radiotherapy significantly improved overall survival and disease-free survival of patients with resectable Stage III and IV head and neck carcinomas. The increased loco-regional control seems to be the main benefit of the combined modality. Because of the limited included studies and the small size of the series, additional randomized studies are necessary to further confirm these results. Furthermore, adjuvant treatment should be modified to minimize the adverse effects, as well as improve the disease control and survival.

Disclosure of conflict of interest

None.

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