original article

Clinical efficacy of neoadjuvant chemotherapy with platinum-based regimen for patients with locoregionally advanced head and neck squamous cell carcinoma: an evidence-based meta-analysis

Hui Chen,[a] Liang Zhou,[a] Dongbin Chen,[b] Jianfeng Luo[c]

From the [a]Department of Otolaryngology-Head and Neck Surgery, Affiliated with the Eye and ENT Hospital of Fudan University, Shanghai, China; [b]Reference Department, Library of Fudan University, Shanghai, China; [c]Department of Health Statistics and Social Medicine, School of Public Health, Fudan University, Shanghai, China

Correspondence: Dr. Liang Zhou · Department of Otolaryngology-Head and Neck Surgery, Affiliated with the Eye and ENT Hospital of Fudan University, #83, Fenyang Road, Shanghai, China · T: +86-21-64377134 · zhlwc@online.sh.cn · Accepted: October 2010

BACKGROUND AND OBJECTIVES: As a vital chemotherapeutic modality, the clinical benefits of neoadjuvant chemotherapy still remain uncertain and controversial. The purpose of this meta-analysis was to evaluate the efficacy of neoadjuvant chemotherapy with a platinum-based regimen for patients with locoregional stage III or IV squamous cell carcinoma of the head and neck.

DESIGN AND SETTING: Meta-analysis of randomized, controlled trials.

METHODS: Relevant randomized controlled trials (RCTs) were identified through systematic search and selected according to the inclusion and exclusion criteria. Eligible RCTs were further analyzed by systematic meta-analysis. Statistical analysis was performed by Review Manager 5.0.21.0 software.

RESULTS: A total of 6 RCTs were identified. Pooling effects revealed that there was no statistical significance in locoregional recurrence [relative risk (RR)= 1.06; 95% CI (confidence interval= 0.91-1.24; P>.05], distant metastasis (RR= 0.6; 95% CI= 0.28-1.30; P>.05), disease-free survival (RR= 0.93; 95% CI= 0.75-1.15; P>.05) or overall survival (RR= 0.98; 95% CI= 0.89-1.09; P>.05). More of the common hematological adverse effects were reported with a cisplatin-based regimen. All the studies analyzed in this meta-analysis were individual RCTs with adequate follow-up and relatively narrow confidence intervals, which were classified to the 1b level, and this meta-analysis was classified to the 1a level, according to the Levels of Evidence (March 2009) of Oxford Center for Evidence-based Medicine.

CONCLUSIONS: The meta-analysis indicates there is a non-significant difference between neoadjuvant chemotherapeutic treatment and conventional locoregional modality for patients at high risk of recurrence, with regard to overall survival, disease-free survival, distant metastases, and locoregional recurrence. However, well-performed studies of identical platinum-based combinations as neoadjuvant chemotherapeutic regimen are needed for further evaluation.

Head and neck squamous cell carcinomas (HNSCCs) are the eighth most common cause of cancer deaths worldwide.[1] About 500 000 cases of HNSCC are diagnosed worldwide annually,[2] of which 60% patients are stage III or IV on presentation,[3] with a high probability of recurrence.[4] Surgery with radiotherapy is the main modality for locoregional treatment and is often followed by chemotherapy, especially for locally advanced stages, as adjuvant treatment.[5] Nevertheless, the 5-year overall survival rate for patients with advanced disease is no better than 50%, even with the combination of surgery, postoperative radiotherapy and chemotherapy.[6] This poor prognosis mostly attributes to suboptimal cancer control[7]

and a low probability of successful salvage surgery.[8]

For patients with resectable disease, surgery with radiotherapy is the conventional locoregional treatment, which also reduces the risk of postoperative locoregional recurrence. More recently, chemotherapy is incorporated into the combined-modality treatment, particularly for patients with clinical characteristics portending a high risk of locoregional recurrence. Chemotherapy is capable of improving the prognosis by three means: neoadjuvant chemotherapy; concomitant or concurrent chemoradiotherapy; and adjuvant chemotherapy, which is actually not a curative treatment by itself.[9] Compared with the other modalities, neoadjuvant chemotherapy has several benefit potentials, such as demonstrating a higher organ-preservation rate, facilitating surgical resection by controlling primary tumor status and increasing the overall survival rate theoretically by providing a better locoregional control. In a randomized controlled trial reported by Lefebvre,[10] the use of neoadjuvant chemotherapy followed by radiation was conducize to larynx preservation without jeopardizing survival.

In addition, there is overwhelming evidence confirming that a platinum-based regimen is the most common and effective modality of treatment for HNSCC,[11] yet its toxicity and high cost, along with controversial overall survival, disease-free survival, distant metastases, and locoregional recurrence, challenge its widespread application. It is therefore important to clarify whether neoadjuvant chemotherapy with a platinum-based regimen leads to clinical benefits, especially for patients in advanced stage with poor prognosis. Additionally, controlled trials with disparate results have created further controversy about the difference between the addition of neoadjuvant chemotherapy with a platinum-based regimen and conventional therapy alone for patients with advanced locoregional HNSCC. While Kohno[12] suggested improvement in locoregional control, other investigators[10,13-16] found opposite results. While several articles[12,15,17-19] reported benefits in distant metastasis, Richard[14] found it be insignificant, and while certain trials[12,13,19,20] indicated augmentation in overall survival, others[14-16,18,21,22] supported the conventional locoregional treatment. However, the population of each study was too small to make a reliable conclusion with statistical significance. These important trials presented the feasibility and potential efficacy of neoadjuvant chemotherapy with a platinum-based regimen for patients with advanced HNSCC and provided a strong rationale for further study of these randomized controlled trials (RCTs) with this approach. Thus to better understand the discordant data and to gain insight into the overall magnitude of the efficacy of neoadjuvant che-

motherapy to advanced HNSCC patients, we undertook this systematic review with meta-analysis of the updated literatures.

Literature-search strategy and data extraction
We conducted a systematic search, restricted to the English language, using PubMed, limited to randomized controlled trials; MEDLINE (OVID: from 1950 to July 2009); Cochrane Central Register of Controlled Trials (OVID: from 1980 to July 2009); EMBASE (OVID: from 1980 to July 2009); and Web of Science with Conference Proceedings (1898 to July 2009). Article references were also searched for evidence relevant to this meta-analysis. The study search of the electronic databases combined disease-specific terms with treatment-specific terms. The following terms were used as primary search items: "head and neck" or laryngeal or pharyngeal or oral or maxillofacial, carcinoma or neoplasm or cancer or tumor, neoadjuvant or induction or preoperative. All terms were further expanded to include all the secondary headings. Two authors, including a professional librarian, retrieved the data independently. For conflicting evaluations, a consensus was reached following a discussion.

Study selection criteria
We evaluated potentially relevant reports by checking their titles and abstracts and then procured the most relevant publications for a closer examination. The following criteria were used to include studies for the meta-analysis:

1) The officially published data were randomized controlled trials. Phase I or II clinical trials were excluded. The papers clearly demonstrated the clinical benefits of neoadjuvant chemotherapy with a platinum-based regimen for advanced HNSCC patients.

2) Patients were eligible only if they were diagnosed previously as "untreated locoregional stage III or IV squamous cell carcinoma of larynx, oral cavity, oropharynx, hypopharynx, and maxillofacial sinus without distant metastasis or locoregional recurrence." Nasopharyngeal carcinoma was excluded due to its unique characteristics with regard to epidemiology, histology and treatment methods.[23] The carcinomas were resectable or unresectable. Some clinical trials containing stage II HNSCC patients were excluded.

3) Treatment arm was confined to neoadjuvant or induction chemotherapy plus conventional locoregional treatment (including surgery plus radiotherapy, surgery or radiotherapy alone), and the control arm was conventional locoregional treatment alone. Concurrent radiochemotherapy or adjuvant chemotherapy was excluded.

4) A platinum-based regimen had to be administered in a treatment arm.

5) The patient consent had to be obtained and the outcomes of interest, including locoregional control, distant metastases, disease-free survival, overall survival, adverse events or aspects related to prognosis, had to be demonstrated as well.

6) Articles in English only were included.

The following criteria were used to exclude studies from the meta-analysis:

1) Controlled trials that were not randomized.

2) The goals were obviously different from those of the selected articles.

3) Insufficient or unclearly described data used in the calculation of the predetermined variables in the meta-analysis.

4) Reviews and duplicate data were excluded.

5) Not published in English.

All papers were closely reviewed, both electronically and manually, in accordance with the criteria stated above for further meta-analysis. Each study was scrutinized with respect to its evaluation of toxicity effects as well.

Statistical analysis

Once all the original studies were identified, the population of the treatment and control arms, adverse events and outcomes related to the prognosis were identified. The methodological quality of the eligible studies was assessed by the Jadad scoring method,[24] which graded RCTs with a 5-point scale (1-2 points indicating trials with low methodological quality; 3-5 points referring to high-quality trials).[25,26] Data were obtained directly from the articles or on the basis of the calculated percentages of identified variables of individual studies. Otherwise, we used the intention-to-treat method to analyze events in both experimental and control arms. Cases of patients who dropped out or were lost to follow-up were considered treatment failures. Provided that the clinical trials were relatively homogeneous with regard to populations, interventions and outcome of interest, pooling had stronger power and improved the reliability and confidence of the point estimates; hence we used this approach to assess the efficacy of neoadjuvant chemotherapy. A chi-square-based Q statistic test was performed to assess heterogeneity.[27] Theoretically, if the database from each article was homogeneous, a fixed-effects model was utilized for the difference of variables was only caused by sampling error; otherwise, a randomized-effect model was preferred, which provided more conservative estimates of treatment effects than the fixed-effects model.[28] For a more rigid comparison and necessary sensitivity

analysis, we performed both models simultaneously in this meta-analysis. Results were expressed in terms of the relative risk (RR) with 95% confidence intervals (CIs), which indicated that the experimental arm was better if RR was <1.0. The primary endpoint assessed in this meta-analysis was overall survival, and the minor outcomes of interest consisted of locoregional recurrence, distant metastasis, disease-free survival and chemotherapy-related adverse effects. Sensitivity analysis was performed for the purpose of investigating the influence of one particular study on the stability of the pooled results; that is, one study was focused upon at a time, and the combined effect of the remaining studies was calculated. In this meta-analysis, we performed a sensitivity analysis on each predetermined variable, respectively, excluding studies with small populations, which had an influence on the quality of the studies. Forest plots were constructed for visual display of relative risk of an individual study;[29] if necessary, a funnel plot was constructed to evaluate publication bias.[30] All statistical analyses were performed spontaneously using the Review Manager 5.0.21.0 software, available through the Cochrane Collaboration.

RESULTS

Literature search and meta-analysis databases

The search strategy yielded 175 potential citations, from which 22 original studies were identified as being potentially appropriate for the meta-analysis (**Figure 1**). Evaluation of these 22 studies found that 8 studies included patients not only with stage III or IV disease but also patients with stage II disease; 4 studies did not clearly describe the tumor status and there was lack of information about the treatment of patients; one study administered chemotherapeutic combinations other than a platinum-based regimen, and two studies were not published in English. Therefore, 7 studies were considered eligible for inclusion in the systematic review and meta-analysis.[12-15,17,20,21] Among the 7 studies, data from 2 studies[13,17] had to be combined because the latter reported continuous results of the previously published article due to long-term follow-up.

Characteristics of RCTs

As highlighted in **Table 1**, the patients in the seven studies had typical clinical characteristics. To be eligible to participate in the RCTs, adult patients had histologically confirmed advanced (stage III or IV) squamous cell carcinoma of the head and neck. Primary tumor sites within the head and neck were well presented, and all patients had advanced tumor stage. Most RCTs[12,13,15,20,21] comprised patients with HNSCC of

original article

Table 1. Eligible studies and patient characteristics.

Author	Year	Treatment arms	No. of patients	Regimen	Primary tumor site (%)					Clinical stage (%)		Tumor status (%)			
					Oral cavity	Oro-pharynx	Hypo-pharynx	Larynx	Maxillary sinus	III	IV	Well differentiated	Moderate	Poor	Un-differentiated
Zorat et al[17] Paccagnella et al[13]*	2004; 1994	CT+Sur+RT	118	P+F	15.3	59.3	25.4	0	0	35.6	64.4	24.6	61	12.7	1.7
		Sur+RT	119		16	54.6	28.6	0	0	37	63	28.6	58.8	10.1	2.5
Kohno et al[12]	2000	CT+Sur	13	P+E+M	30.8	30.8	38.5	0	0	46.2	53.8	NR	NR	NR	NR
		Sur	11		45.5	18.2	36.4	0	0	63.6	36.4	NR	NR	NR	NR
Richard et al[14]	1998	CT+Sur/RT	36	P+F	0	0	0	100	0	88.9	11.1	NR	NR	NR	NR
		Sur+RT	32		0	0	0	100	0	96.9	3.1	NR	NR	NR	NR
Maipang et al[21]	1995	CT+Sur+RT	30	P+B+Meth	80	6.7	10	0	3.3	26.7	73.3	NR	NR	NR	NR
		Sur+RT	24		70.8	12.5	16.7	0	0	33.3	66.7	NR	NR	NR	NR
Tejedor et al[20]	1992	CT+RT	19	Car+Ftorafur	26.3	36.8	10.5	15.8	0	26.3	73.3	NR	NR	NR	NR
		RT	17		35.3	35.3	0	17.6	0	35.3	64.7	NR	NR	NR	NR
Schuller et al[15]	1988	CT+Sur+RT	82	P+B+Meth+V	35	28	15	22	0	35	65	NR	NR	NR	NR
		Sur+RT	76		36	28	17	20	0	39	61	NR	NR	NR	NR

CT: chemotherapy; RT: radiotherapy; Sur: surgery; NR: not reported; P: cisplatin; F: fluorouracil; E: etoposide; M: mitomycin; B: bleomycin; Meth: methotrexate; Car: carboplatin; V: vincristine
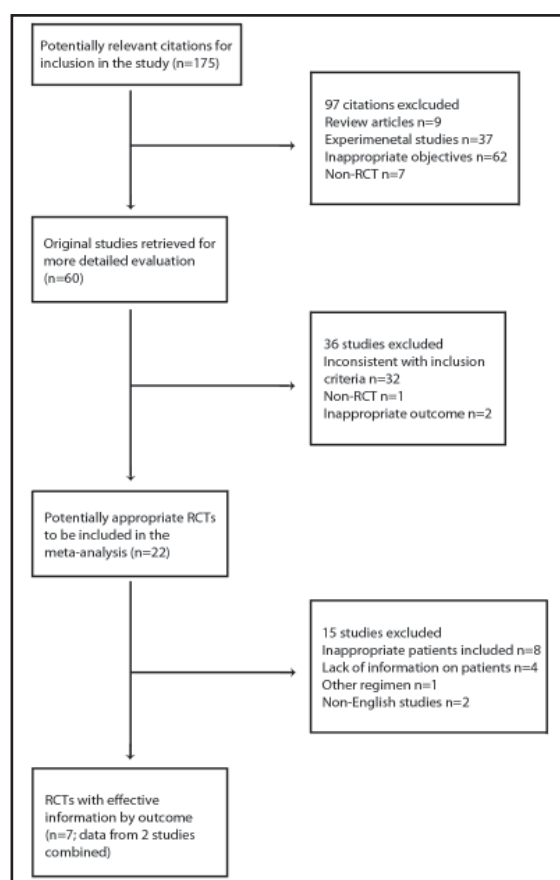* Data from the two studies were combined for results from the same RTC.

Figure 1. Flow chart displaying the process of study selection for the meta-analysis.

various primary tumor sites, including the oral cavity, oropharynx, hypopharynx, larynx and maxillary sinus; while patients involved in one RCT[14] all suffered from laryngeal cancer. In all the RCTs, only one RCT[13] reported the differentiation status of HNSCC, which revealed a more specific comparison as to the application of neoadjuvant chemotherapy. In all eligible RCTs, a cisplatin-based regimen was administered, except for one RCT,[20] which was carboplatin-based. In four trials,[13-15,21] patients received both surgery and radiotherapy as conventional locoregional treatment; and in the remaining two RCTs, patients only underwent surgery[12] or radiotherapy[20] as the control arm.

Quality assessment of studies

The quality assessment for each paper was carried out in accordance with the Jadad scale.[24] Overall scores ranged from 2 to 3 out of a maximum of 5; among the RCTs, four RCTs[12-14,20] received 2 points as all of them illustrated in detail the reasons for the patients being dropped out and lost to follow-up, and mentioned the

randomization without a precise random series; and two RCTs[15,21] received 3 points because both of these further described the randomization. All RCTs executed randomization and illustrated the reasons for the loss to follow-up, yet seldom mentioned double blinding, which definitely lowered the quality of trials and influenced the power of meta-analysis.

Test of heterogeneity

We analyzed the heterogeneity of eligible studies, and the value of chi-square test was 7.96 with 5 degrees of freedom ($P>.05$) in the meta-analysis of overall survival; 3.39 with 3 degrees of freedom ($P>.05$) in the meta-analysis of locoregional recurrence; 9.69 with 3 degrees of freedom ($P<.05$) in the meta-analysis of distant metastasis; and 3.65 with 3 degrees of freedom ($P>.05$) in the meta-analysis of disease-free survival, which indicated that data for the evaluation of overall survival, locoregional recurrence and disease-free survival were homogeneous; in contrast, the data for the evaluation of distant metastasis had significant heterogeneity.

Quantitative data synthesis

For evaluation of the locoregional recurrence, the data available for our meta-analysis were obtained from four studies[12-15] of 249 experimental patients and 238 controls, of which 134 experimental patients and 123 controls appeared to have locoregional recurrence. Only one RCT[12] reported a benefit with the addition of neoadjuvant chemotherapy, and three RCTs showed a negative result.[13-15] However, the results of two of the four RCTs were not statistically significant, and two studies did not report the *P* value (**Table 2**). Since the eligible data for locoregional recurrence appeared homogeneous ($P>.05$), we utilized a fixed-effects model to evaluate the effect of neoadjuvant chemotherapy in cases of locoregional recurrence. A random-effects model was applied to compare the differences in the results between both models and to evaluate sensitivity. As shown in **Figure 2**, the overall RR was 1.06 (95% CI= 0.91-1.24) and the test for overall effect was 0.79 ($P>.05$) in the Mantel-Haenzal (M-H) fixed-effects model; and the result from M-H random-effects model was identical, which proved the homogeneity of the studies statistically (data not shown). The RR of 1.06 indicated there was nearly no reduction; rather there was 6% increase in the risk of locoregional recurrence when neoadjuvant chemotherapy was added; and *P* value indicated that there was no statistical significance in locoregional recurrence in favor of patients who received neoadjuvant chemotherapy versus those who re-

Table 2. Efficacy data: randomized trials of neoadjuvant chemotherapy versus local treatment.

Author	Year	Treatment arms	No. of patients	CT Response CR (%)	CT Response PR (%)	Point in time[a] (y)	Local recurrence (%)	Distant metastasis (%)	Progression-free survival (%)	Disease-free survival	Overall survival	Median survival (mo)
Zorat et al[17] Paccagnella et al[13b]	2004; 1994	CT+Sur/RT	118	31	49	10	72	14	NR	37%	19%	15.4
		Sur/RT	119	-	-		71 P=.77	38 P=.002	NR	33% P=.22	9% P=.14	15.3
Kohno et al[12]	2000	CT+Sur	13	31	23	5	15	0	83	NR	83%	NR
		Sur	11	-	-		36 P=.15	18 P=NR	53 P=.15	NR	62% P=.33	NR
Richard et al[14]	1998	CT+Sur/RT	36	39	33	2	17	25	NR	60%[c]	69%	48
		Sur+RT	32	-	-		9 P=NR	3 P=NR	NR	78% P=.02	84% P=.006	NR
Maipang et al[21]	1995	CT+Sur+RT	30	23.3	53.3	4	NR	NR	NR	NR	45%	NR
		Sur+RT	24	-	-		NR	NR	NR	NR	57% P=.736	NR
Tejedor et al[20]	1992	CT+RT	19	31.5	37	3.5	NR	NR	NR	55%	47%	NR
		RT	17	-	-		NR	NR	NR	52% P=NS	34% P=NS	NR
Schuller et al[15]	1998	CT+Sur+RT	82	19	51	4	48	28	NR	23%	28%	shorter
		Sur+RT	76	-	-		40 P=NS	49 P=.07	NR	31% P=NS	31.6% P=NS	longer

CT: chemotherapy; RT: radiotherapy; Sur: surgery; NR: not reported; NS: not statistically significant; y: years; CR: complete response; PR: partial response
[a]Percentage indicates the point in time when outcomes were measured. [b]Data extracted from disease-free survival curve by reviewer. [c]Data from the two studies were combined for resulted from the same RTC.

Table 3. Sensitivity analysis of locoregional recurrence.*

Excluding	Heterogeneity, P value	Relative risk, 95% CI	Pooled effect, z value
Kohno et al.[12]	.34	1.06 (0.90-1.25)	.66 (P=.51)
Richard et al.[14]	.34	1.03 (0.88-1.22)	.39 (P=.69)

*Pooled relative risk and corresponding confidence interval after stepwise removal of individual studies.

Table 4. Sensitivity analysis of distant metastasis.*

Excluding	Heterogeneity, P value	Relative risk, 95% CI	Pooled effect, z value
Kohno et al.[12]	.01	0.66 (0.29-1.53)	.96 (P=.33)
Richard et al.[14]	.36	0.47 (0.34-0.65)	4.59 (P<.00001)

*Pooled relative risk and corresponding confidence interval after stepwise removal of individual studies.

Table 5. Sensitivity analysis of disease-free survival.*

Excluding	Heterogeneity, P value	Relative risk, 95% CI	Pooled effect, z value
Richard et al.[14]	.40	1.00 (0.77-1.29)	.02 (P=.99)
Tejedor et al.[20]	.24	0.88 (0.68-1.14)	.96 (P=.34)

*Pooled relative risk and corresponding confidence interval after stepwise removal of individual studies.

Table 6. Sensitivity analysis of overall survival.*

Excluding	Heterogeneity, P value	Relative risk, 95% CI	Pooled effect, z value
Kohno et al.[12]	.12	1.00 (0.83-1.21)	.04 (P=.97)
Maipang et al.[21]	.22	0.96 (0.81-1.13)	.53 (P=.59)
Richard et al.[14]	.30	0.95 (0.84-1.09)	.70 (P=.48)
Tejedor et al.[20]	.09	1.02 (0.82-1.26)	.18 (P=.85)

*Pooled relative risk and corresponding confidence interval after stepwise removal of individual studies.

ceived locoregional treatment alone. Results were similar when two RCTs[12,14] with smaller populations were assessed, respectively, for sensitivity analysis, as shown in **Table 3**.

Distant metastasis
Data for the analysis of distant metastasis was extracted from four RCTs,[12-15] from which three RCTs[12,13,15] indicated that adding neoadjuvant chemotherapy had a positive effect on preventing distant metastasis when compared with locoregional treatment alone; and one RCT[14] had a negative result without statistical significance. Owing to the significant heterogeneity of the effect of neoadjuvant chemotherapy in distant metastasis across these trials (χ^2= 9.69 with 3 degrees of freedom; P=.02), we used the preferred random-effects model to calculate pooled relative risk,[31] as the random-effects model provides a more conservative estimate by incorporating both intra- and inter-study variation,[32] and a fixed-effects model was also applied for comparison. On the basis of the random-effects model, as shown in **Figure 3**, the pooled RR was 0.6 (95% CI= 0.28-1.30) and the test for overall effect was 1.30 (P>.05), which indicated the administration of neoadjuvant chemotherapy could reduce the risk of distant metastasis by 40%, yet it had no statistical significance (P>.05). On the basis of the fixed-effects model, RR was 0.54 (95% CI= 0.40-0.73; P<.0001). This difference in RR further confirmed the heterogeneity among the studies, since both fixed-effects and random-effects RR would be identical in an analysis of homogeneous studies.[29] Through sensitivity analysis of the distant metastasis, we excluded two RCTs[12,14] with smaller populations, respectively, and observed that in the condition of excluding one particular RCT,[14] the data turned homogeneous; the pooled relative risk had positive 95% confidence interval (0.34-0.65), and the overall effect became statistically significant (P<.00001) (**Table 4**).

Progression-free survival and disease-free survival
Only one trial reported progression-free survival as an outcome of interest[12] (**Table 2**). The 5-year progression-free survival for the patients in neoadjuvant chemotherapy arm was 83%, while it was 53% in the locoregional treatment arm; however, the difference was not significant (P>.05) in favor of neoadjuvant chemotherapy. Four trials reported results of disease-free survival,[13-15,20] of which two RCTs[13,20] favored the addition of neoadjuvant chemotherapy, while others[14,15] supported conventional treatment. A statistically significant difference in disease-free survival between the neoadjuvant chemotherapy arm and locoregional treatment arm was illustrated in one RCT,[14] with the result favoring locoregional treatment (P=.02), while two RCTs[13,20] revealed no statistically significant difference and one RCT[15] did not report a P value. With homogeneous data across the trials as shown in **Figure 4**, the

pooled RR was 0.93 (95% CI=0.75-1.15) and the overall effect was 0.68, there being no statistical significance (P>.05) in the fixed-effects model. The random-effects model presented similar results (data not shown), and the results were also similar in the sensitivity analysis when two smaller RCTs[14,20] were excluded (**Table 5**).

Overall survival
All included studies reported data of overall survival (**Table 2**). Only one RCT[14] demonstrated a significant difference in overall survival (P=.006), in favor of patients who only received conventional locoregional treatment when compared with patients treated with neoadjuvant chemotherapy (neoadjuvant arm versus conventional arm 69% vs. 84%), whereas others reported there was an insignificant difference in overall survival between the two treatment arms. Among the other five RCTs, three RCTs[12,17,20] revealed the results with regard to effect favored adding neoadjuvant chemotherapy, and the improvement in overall survival ranged from 10% to 21%; in contrast, the remaining two RCTs[15,21] favored locoregional treatment alone. In all six RCTs, 298 patients of the treatment arm and 279 patients of the control arm were eligible for the meta-analysis. All the data for assessment of overall survival were extracted from the actual values in the published articles. Across all the trials, no RCT with significant heterogeneity was detected, and the pooled RR was 0.98 (95% CI= 0.89-1.09) on the basis of a fixed-effects model, which indicated a 2% relative reduction in the risk of death when neoadjuvant chemotherapy was added to locoregional treatment; however, the results were not statistically significant (P>.05) (**Figure 5**). For a more scrupulous comparison, we conducted a random-effects model as well, the results of which also indicated that there was no significant difference in overall survival between the two treatment arms (data not shown). The outcomes of the sensitivity analysis confirmed the stability of the pooled effect of overall survival when 4 RCTs with smaller sample size were excluded in a stepwise fshion (**Table 6**).

The median survival was reported in three RCTs.[13-15] One RCT[13] indicated kind of longer median survival in patients treated with neoadjuvant chemotherapy when compared with patients who received conventional treatment alone; one RCT[14] only reported that median survival of the neoadjuvant chemotherapy arm was 48 months, and the other published RCT[15] reported that the median survival of locoregional treatment arm was longer than that of neoadjuvant chemotherapy arm. However, the statistical basis for comparisons between treatment and control arms was not consistently report-

Table 7. Adverse events associated with neoadjuvant chemotherapy.

| Author | Year | Regimen | No. of patients of neoadjuvant-CT arm | Nausea/vomiting (%) | Anemia (%) | Grade 3/4 adverse effects | | | | | | | |
						Leukopenia (%)	Thrombo-cytopenia (%)	Mucositis/Stromatitis (%)	Digestive tract (%)	Renal toxicity (%)	Cardio-toxicity (%)	Death, CT related (%)
Zorat et al[17] Paccagnella et al[13a]	2004; 1994	P+F	118	9	3	7	2	7	NR	2	7	0
Kohno et al[12]	2000	P+E+M	13	0	8	0	8	0	0	0	0	0
Richard et al[14]	1998	P+F	36	NR		3[b]		NR	6	0	NR	0
Maipang et al[21]	1995	P+B+Meth	30	0		27[b]		7	NR	NR	0	4
Tejedor et al[20]	1992	Car+Ftorafur	19	0	0	0	0	0	0	NR	NR	0
Schuller et al[15]	1998	P+B+Meth+V	82	4	2	3	5	4	0	0	NR	5

P: cisplatin; F: fluorouracil; E: etoposide; M: mitomycin; B: bleomycin; Meth: methotrexate; Car: carboplatin; V: vincristine; CT: chemotherapy; NR: not reported
[a]Data from the two studies were combined for results from the same RTC; [b]Specific hematological adverse events were not specified.
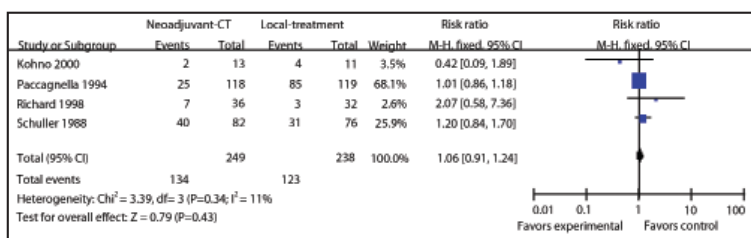
Figure 2. Pooling effect of locoregional recurrence with fixed-effect model
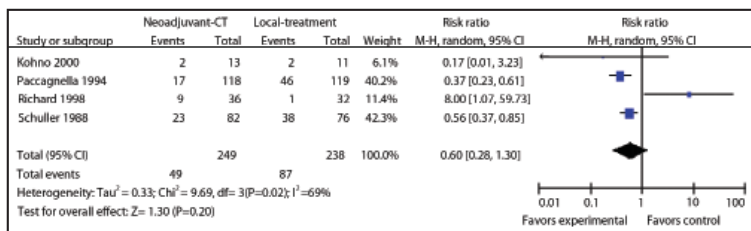

Figure 3. Pooling effect of distant metastasis with random-effect model
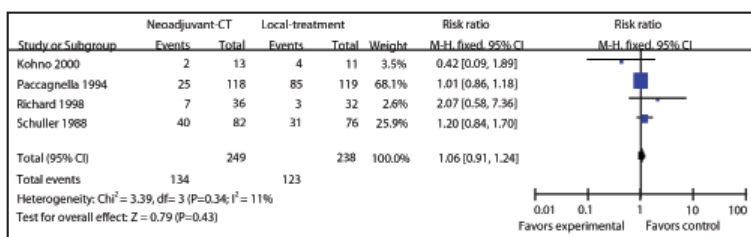

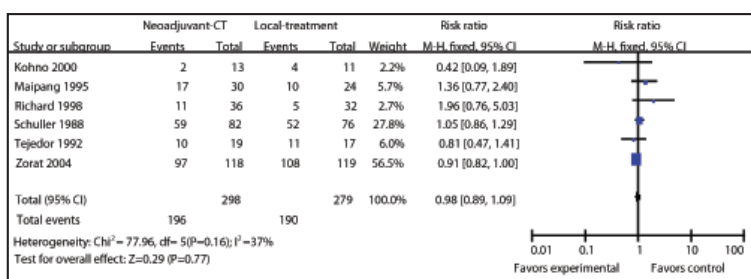**Figure 4.** Pooling effect of disease-free survival with fixed-effect model

Figure 5. Pooling effect of overall number of deaths with fixed-effect model

ed for that outcome, and three RCTs did not report P values for that outcome.

Toxicity

The common acknowledged adverse events related to neoadjuvant chemotherapy are listed in **Table 7**. Statistical comparisons were not reported. Generally, the cisplatin-based regimen had the most common hematological adverse effects like anemia, leucopenia and thrombocytopenia, followed by mucositis or stro-

matitis and nausea and vomiting; comparing with other cisplatin-based combinations, the regimen of cisplatin plus fluorouracil had the trend of more severe nausea, vomiting and digestive tract events (**Table 7**), yet it had better chemotherapeutic response, including complete response and partial response (**Table 2**). Two RCTs[15,21] reported chemotherapy-related deaths, in both of which cisplatin plus bleomycin and methotrexate were used.

DISCUSSION

Since the stage of HNSCC and the regimen of neoadjuvant chemotherapy have direct influence on clinical efficacy, we performed a stringent selection of publications considering both these two aspects, for an accurate clinical evaluation. Evidence from 6 randomized controlled trials investigating 517 patients revealed that the addition of neoadjuvant chemotherapy to conventional locoregional treatment, including surgery with or without radiotherapy, resulted in no statistically significant improvement in overall survival, locoregional recurrence and disease-free survival in previously untreated locoregional stage III or IV HNSCC patients. This estimate was based on both the fixed-effects model and a more conservative random-effects model of pooled relative risk, which incorporated both interstudy and intra-study variation in the model, and the conclusions made from both models were coherent. Pooling of published data from the RCTs identified the results, and the progression-free survival from one RCT[12] was consistent with the findings. Further, sensitivity analysis of locoregional recurrence, disease-free survival and overall survival also demonstrated similar results when smaller RCTs with impact on the quality of studies were stepwise removed from the database for meta-analysis. The results indicated that the relative risk was not unduly influenced by any single study, but was moderately sensitive to each of them based on the percentage effective weights.

However, we observed that the data for the analysis of distant metastasis were statistically significantly heterogeneous in the test of heterogeneity. The preferred random-effects model was assessed to analyze the data, and fixed-effects model was applied to compare the difference between the results of two models. The pooled result by random-effects model indicated that there was no significant difference in distant metastasis between the neoadjuvant chemotherapy arm and conventional locoregional treatment arm. Nevertheless, the overall effect showed an opposite result when one RCT[14] with small population was removed in the sensitivity analysis; on the contrary, the pooled result indicated stability when the other smaller RCT[12] was removed from the database.

Each study in the meta-analysis of distant metastasis contributed significantly to the pooled relative risk by random-effects model, and the percentage weight of individual studies on the overall effect ranged from 6.1% to 42.3% (**Figure 3**), which indicated that without unduly influencing the overall effect, this pooled RR is a reasonable estimate of all the studies included in this meta-analysis. Three studies[13-15] had positive confidence intervals; but since all of the 4 RCTs had significant weight on the overall model, removal of any positive study should result in the loss of significance in the confidence intervals of the pooled RR. Yet since only one RCT[14] had a negative effect while the other three RCTs[12,13,15] all demonstrated a positive effect, removal of this one[14] led to a statistically significant overall effect (P<.00001) and positive confidence interval (0.34-0.65), which could be an explanation for heterogeneity with respect to statistics. Moreover, from the clinical characteristics of the eligible patients (**Table 1**), we observed that all patients included in the negative RCT[14] had only the larynx as the primary tumor site; in contrast, others[12,13,15] consisted of HNSCC patients with the primary site in the oral cavity, oropharynx, hypopharynx, larynx and maxillary sinus. Although the histopathological diagnosis confirmed all eligible patients were suffering from squamous cell carcinoma, the primary sites being different might be a reason for heterogeneity in assessment of distant metastasis; however, further investigations are needed to evaluate the validity of this reason. Varying clinical characteristics of eligible patients in RCTs and the relative shorter-term follow-up of 2 years might lead to the variation in RR, which might result in a positive effect compared to others in distant metastasis (**Table 2**). Further, the sample size of the clinical trials could also contribute to the statistically insignificant overall effect in the random-effects model. the RCTs might be too underpowered to demonstrate positive results. However, from RCTs[12,13,15] in which suffered from HNSCC at various primary sites, we could see the trend of the advantage of neoadjuvant chemotherapy with platinum-based regimen in improving distant metastasis, which was also consistent with the previous findings of Pignon.[6]

In all 6 RCTs, some evidence was worth paying more attention to. Two trials revealed statistically significant results; one indicated an improvement in terms of reducing distant metastasis,[17] which was convincing evidence from a large population and long duration of follow-up; the other showed the advantage of conventional locoregional treatment in overall survival with statistical significance,[14] although the sample size was very small. The comparison between neoadjuvant chemotherapy and locoregional treatment alone for locore-gional stage III or IV HNSCC was best demonstrated in two randomized trials, both of which had a relatively larger sample size and were more compelling.[15,17] Of the two RCTs, both experimental arms employed neoadjuvant chemotherapy plus a comprehensive conventional locoregional modality, including surgery and radiotherapy, and both carried out long-term follow-up: one was 10 years[17]; the other had median follow-up of 5 years.[15]

Despite all this evidence, some fundamental issues remain unresolved due to the various combinations of chemotherapeutic pharmaceuticals. Administrating different platinum-based regimens meant a variability in doses and chemotherapeutic response, and also the severity of chemotherapy-related adverse effects. In the eligible studies, the complete chemotherapeutic response ranged from 19% to 39%, and partial response ranged from 23% to 53.3% with regard to various platinum-based regimens. However, better sensitivity to chemotherapy did not lead to higher overall survival.[14] Moreover, two RCTs[15,21] reported deaths attributable to treatment in 4% to 5% of the patients receiving neoadjuvant chemotherapy. Even though the RCTs showed that the worse the adverse effects were the better was the response to chemotherapy, the correlation between certain outcomes (such as overall survival, locoregional recurrence, distant metastasis) and a particular platinum-based combination is still uncertain. A previous meta-analysis[33] revealed a small but significant benefit in reducing distant metastasis and improving the overall survival with the cisplatin and fluorouracil regimen, but the eligible patients in the meta-analysis were not restricted to those in advanced stage III or IV with a poorer prognosis. Since the therapeutic effects could be alterable because of difference in clinical status, the efficacy of certain platinum-based regimens for advanced HNSCC patients remains a concern.

One of the strengths of this meta-analysis is the distinctive analysis of individual studies and the reliable and stable results with regard to the pooled effects, which were further confirmed in the sensitivity analysis. Despite this robustness of pooled relative risk, the limitations of the present meta-analysis of published data are well recognized.[34] It is possible that some related or unpublished studies which might meet the inclusion criteria were missed, leading to inevitable biases in the results. A funnel plot was not created for evaluating the publication bias because there is lack of efficacy when the number of studies is small,[35,36] but publication bias might still exist. Although our results are primarily based on homogeneous RCTs with adequate follow-up and would further remind surgeons to consider the magnitude of the overall benefits in disease control, overall survival and toxicity, this meta-analysis is still

limited by lack of power, with small numbers of patients and poorer quality based on the Jadad scale.

In conclusion, this meta-analysis revealed that there were insignificant effects in applying neoadjuvant chemotherapy with platinum-based regimens for the purpose of achieving better locoregional or distant disease control or survival outcomes in comparison with conventional locoregional treatment, with respect to HNSCC patients with locoregional advanced stage III or IV, who were at a high risk of recurrence due to

general accepted characteristics, including microscopically involved mucosal margins of resection, histological evidence of metastases in two or more regional lymph nodes and extracapsular extension of nodal disease.[37] Since the addition of chemotherapy increases toxicity and influences potential long-term effects, it is obligatory to have close monitoring and optimal supportive care. Well-performed studies of identical platinum-based combinations as neoadjuvant chemotherapeutic regimen are needed for further evaluation.

REFERENCES

1. Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: Results for the global burden of disease 2000. BMC Cancer 2002;2:37.

2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.

3. Siewert TY, Cohen EE. State-of-the art management of locally advanced head and neck cancer. Br J Cancer 2005;92:1341-8.

4. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. CA Cancer J Clin 1997;47:5-27.

5. Forastiere AA, Trotti A, Pfister DG, Grandis JR. Head and neck cancer: Recent advances and new standards of care. J Clin Oncol 2006;24:2603-5.

6. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous–cell carcinoma: Three meta-analyses of updated individual data. Lancet 2000;355:949-55.

7. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. N Engl J Med 1993;328:184-94.

8. Gleich LL, Ryzenman J, Gluckman JL, Wilson KM, Barrett WL, Redmond KP. Recurrent advanced (T3 or T4) head and neck squamous cell carcinoma: Is salvage possible? Arch Otolaryngol Head Neck Surg 2004;130:35-8.

9. Choong N, Vokes E. Expanding role of the medical oncologist in the management of head and neck cancer. CA Cancer J Clin 2008;58:32-53.

10. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: Preliminary result of a European Organization for Research and Treatment of Cancer phase? trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890-9.

11. Chandana SR, Conley BA. Neoadjuvant chemotherapy for locally advanced squamous cancers of the head and neck: Current status and future prospects. Curr Opin Oncol 2009;21:218-23.

12. Kohno N, Ikari T, Kawaida M, Tanaka K, Kawaura M, Kano S, et al. Survival results of neoadjuvant chemotherapy for advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol 2000;30:253-8.

13. Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: A study by the Gruppo di Studio sui

Tumori della Testa e del Collo. J Natl Cancer Inst 1994;86:265-72.

14. Richard JM, Sancho-Garnier H, Pessey JJ, Luboinski B, Lefebvre JL, Dehesdin D, et al. Randomized trial of induction chemotherapy in larynx carcinoma. Oral Oncol 1998;34:224-8.

15. Schuller DE, Metch B, Stein DW, Mattox D, McCracken JD. Preoperative chemotherapy in advanced resectable head and neck cancer: Final report of the Southwest Oncology Group. Laryngoscope 1988;98:1205-11.

16. Lewin F, Damber L, Jonsson H, Andersson T, Berthelsen A, Biörklund A, et al. Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the head and neck: A randomized phase III study. Radiother Oncol 1997;43:23-8.

17. Zorat PL, Paccagnella A, Cavaniglia G, Loreggian L, Gava A, Mione CA, et al. Randomized phase trial of neoadjuvant chemotherapy in head and neck cancer: 10-year follow-up. J Natl Cancer Inst 2004;96:1714-7.

18. Licitra L, Grandi C, Guzzo M, Mariani L, Lo Vullo S, Valvo F, et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: A randomized controlled trial. J Clin Oncol 2003;15:327-33.

19. Domenge C, Hill C, Lefebvre JL, De Raucourt D, Rhein B, Wibault P, et al. French Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC). Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC). Br J Cancer 2000;83:1594-8.

20. Tejedor M, Murias A, Soria P, Aguiar J, Salinas J, Hernandez MA, et al. Induction chemotherapy with carboplatin and ftorafur in advanced head and neck cancer. A randomized study. Am J Clin Oncol 1992;15:417-21.

21. Maipang T, Maipang M, Geater A, Panjapiyakul C, Watanaarepornchai S, Punperk S. Combination chemotherapy as induction therapy for advanced resectable head and neck cancer. J Surg Oncol 1995;59:80-5.

22. Martin M, Hazan A, Vergnes L, Peytral C, Mazeron JJ, Sénéchaut JP, et al. Randomized study of 5 fluorouracil and cisplatin as neoadjuvant therapy in head and neck cancer: A preliminary report. Int J Radiat Oncol Biol Phys 1990;19:973-5.

23. Ma J, Mai HQ, Hong MH, Min HQ, Mao ZD, Cui NJ, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients

with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2001;19:1350-7.

24. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1-12.

25. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses. Lancet 1998;352:609-13.

26. Kjaergard LL, Villumsen J, Gluud C. Quality of randomized clinical trials affects estimates of intervention efficacy (meeting abstract). Best Evid Health Care Cochrane Colloq 7th 1999 Univ S Tommaso Daquino 1999; 7; 57.

27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.

28. DerSimonian R, Laird A. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7:177-88.

29. Qadeer MA, Colabianchi N, Vaezi MF. Is GERD a risk factor for laryngeal cancer? Laryngoscope 2005;115:486-91.

30. Copas JB, Shi JQ. A sensitivity analysis for publication bias in systematic reviews. Stat Methods Med Res 2001;10:251-65.

31. Brock well SE, Gordon IR. A comparison of statistical methods for meta-analysis. Stat Med 2001;20:825-40.

32. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. Stat Med 1995;14:395-411.

33. Su YX, Zheng JW, Zheng GS, Liao GQ, Zhang ZY. Neoadjuvant chemotherapy of cisplatin and fluorouracil regimen in head and neck squamous cell carcinoma: A meta-analysis. Chin Med J(Engl) 2008;121:1939-44.

34. Piedbois P, Buyse M. Meta-analyses based on abstracted data: A step in the right direction, but only a first step. J Clin Oncol 2004;22:3839-41.

35. Zhuo XL, Wang Y, Zhuo WL, Zhang XY. Possible association of Helicobacter pylori infection with laryngeal cancer risk: An evidence-based meta-analysis. Arch Med Res 2008;39:625-8.

36. Clarke M, Oxman AD. Cochrane Reviewer's Handbook 4.1.Review Manager (RevMan) [Computer Program]. Version4.1. Oxford, England: The Cochrane Collaboration; 2000.

37. Winquist E, Oliver T, Gilbert R. Postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck: A systematic review with meta-analysis. Head Neck 2007;29:38-46.