Consolidation chwemotherapy after concurrent chemoradiotherapy vs. chemoradiotherapy alone for locally advanced unresectable stage III non-small-cell lung cancer: A meta-analysis

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Abstract. Concurrent chemoradiotherapy (CCRT) has been considered to be the standard of care for locally advanced unresectable stage III non-small-cell lung cancer (LA-NSCLC). Whether consolidation chemotherapy (CCT) following CCRT is able to further improve the clinical outcome remains unclear. We therefore undertook a meta-analysis to compare the two regimens for LA-NSCLC. A literature search was performed through PubMed, Embase, Cochrane Library and Chinese Biology Medicine, from their inception to November, 2015. Irrelevant studies were excluded using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards. Our primary endpoint was overall survival (OS), which was defined as the time from randomisation until death from any cause; the secondary endpoint was progression-free survival (PFS). All analyses were by intention-to-treat. Five phase III randomized controlled trials with 958 patients were included in the present meta-analysis. The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Compared with CCRT, CCT after CCRT was not associated with statistically significant differences in OS (OR=1.24; 95% CI: 0.89-1.72; P=0.21) or PFS (OR=1.16; 95% CI: 0.74-1.83; P=0.53), but increased the risk of toxicity, including infection (P=0.02), pneumonitis (P=0.003) and treatment-related death (P=0.04). There were no significant differences in terms of benefit according to particular patient characteristics, such as age, gender, performance status, tumor histology or clinical stage. Thus, the present study failed to support the use of CCT after CCRT over CCRT alone, as there was no significant OS and PFS benefit for LA-NSCLC patients, but the use of CCT after CCRT resulted in increased toxicity.

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Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with ~1.5 million new cases diagnosed annually (1). Approximately 87% of lung cancer patients have non-small cell lung cancer (NSCLC), and approximately one-third of NSCLC patients have locally advanced stage III disease (LA-NSCLC) at the time of diagnosis (2,3). For the treatment of LA-NSCLC, clinical trials have demonstrated that radiation therapy alone is associated with a 5-year survival rate of only ~5% (4,5). Concurrent chemoradiotherapy (CCRT) was found to result in survival improvement compared with radiation alone (6-8) and sequential CRT (9-15) and is currently the standard treatment for LA-NSCLC. A NSCLC Collaborative Group meta-analysis also demonstrated that CCRT, as compared with sequential CRT, improved the survival of patients with LA-NSCLC (16).

However, for LA-NSCLC patients, the prognosis following CCRT is still poor, with a median survival time of 15-18 months (17). Recently, close attention has been paid to the addition of consolidation chemotherapy (CCT) after CCRT for LA-NSCLC. Previous phase II studies of CCRT followed by CCT have reported promising response rates and survival results (18-20). In addition, 5 randomized phase III studies were recently reported to evaluate the survival benefit of CCT after CCRT compared with that of CCRT alone (21-25). However, the efficacy of CCT after CCRT in improving survival in LA-NSCLC patients remains controversial. We therefore conducted a meta-analysis of published phase III randomized controlled trials (RCTs) to quantitatively evaluate the survival benefit of patients who received the two regimens.

Materials and methods

Eligibility criteria. CCRT was defined as chemotherapy administered during radiotherapy. Radiation should be similar in both arms of the trial. CCRT followed by CCT was defined as chemotherapy administered after CCRT. RCTs comparing

CCT after CCRT with CCRT alone were conducted, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards (26) as the basis for reporting the materials and methods of this study. The following eligibility criteria for this meta-analysis were set prior to collecting the articles: i) Phase III RCTs; ii) studies involving patients with stage III locally advanced NSCLC based upon international staging criteria (27); iii) hazard ratios (HRs) and confidence intervals (CIs) of the patients who received CCRT and CCRT followed by CCT should be calculated at specific time intervals after therapy from the survival rates in the article; iv) the median follow-up time of the study should be ≥3 years.

Data collection. Published and unpublished trials were sought by searching electronic databases (PubMed, Embase, Cochrane Library and Chinese Biology Medicine) without language restriction, using the Cochrane collaboration optimal search strategy for identifying RCTs. This was supplemented by manual searches. Two investigators independently searched eligible trials and discrepancies were resolved through discussion. Non-English publications were evaluated upon their English abstract and the translation of their main text. Using the keywords 'concurrent chemoradiotherapy + consolidation chemotherapy + non-small cell lung cancer', 365 citations were identified in total. Unrelated articles were excluded and, finally, only 5 studies (21-25) fulfilled all our eligibility criteria. Study characteristics were also recorded (period during which the study was conducted, chemoradiotherapy regimen and median follow-up) and patient characteristics [age, gender, cancer stage, performance status (PS), forced expiratory volume in 1 second (FEV1) and toxicity].

Validity assessment. Two reviewers independently evaluated the quality of the studies, with disagreements resolved by consensus. Using the Cochrane approach to allocation concealment, the trials were described as having adequate, unclear, or inadequate concealment (28). The reviewers assessed whether there was blinding of outcome assessment and adequate description of withdrawals (29). The adequacy of the method of randomization was assessed as described by Jadad *et al* (29). Finally, an assessment was made as to whether the trial results used intention-to-treat analysis (30,31). The authors of the included studies were asked to verify the assessments of study methodology where possible.

Statistical analysis. The primary endpoint was overall survival (OS), which was defined as the time from randomisation until death from any cause. The secondary endpoints were acute toxicity rates and progression-free survival (PFS), which was defined as the time from random assignment until first event (local or distant progression or death from any cause). Surviving patients were censored at the date of the last follow-up. The survival rates were derived from the published survival curves when not provided explicitly in the text or tables. Data extraction from the survival curves was independently performed by two researchers, and the mean measured values were used for the meta-analysis.

Statistical analyses for the meta-analysis were performed with Review Manager software for Windows, version 5.3 (Cochrane Collaboration, Oxford, UK, 2014) and a pooled relative risk was calculated with 95% CIs. Analyses were stratified by trials. The log-rank test was used to estimate the observed and expected number of events and associated variances were used to calculate individual trial and overall combined odds ratios (ORs) and their 95% CIs by the fixed-effects model. To undertake a random-effects meta-analysis, the standard errors of the study-specific estimates are adjusted to incorporate a measure of the extent of variation, or heterogeneity, among the treatment effects observed in different studies. Chi-quare (χ^2) heterogeneity tests were used to test for statistical heterogeneity among trials. The I^2 statistics were also used to assess the proportion of variability in the results attributable to heterogeneity across studies; I^2<25%, I^2 of ≥25% but <50%, and I^2 ≥50% were interpreted as indicating low-level, intermediate-level and high-level heterogeneity, respectively (28). Analyses by patient characteristics were performed to study the interaction between the treatment effect and the following characteristics: Gender, age, PS, FEV1, stage and toxicities. All P-values were two-sided. P<0.05 was considered to indicate statistically significant differences.

Results

Study characteristics. We identified 5 randomized phase III studies (21-25) including 958 patients, which investigated the survival of LA-NSCLC patients treated with CCRT followed by CCT (Fig. 1). All 5 studies reported mature data on survival benefit and toxicity, whereas 3 studies were reported as meeting abstracts (21,23,24). In 2 of these 3 trials (21,23), patients lacked specific OS and PFS; thus, their survival rates were not included in our meta-analysis, but the patient characteristics in those 2 trials are available. Our meta-analysis on OS and PFS was only based on 3 trials with 768 patients who were randomly assigned. The analyses of patient characteristics were based on all 5 trials and 958 patients.

Treatment regimens. Two trials (21,23) used the same chemotherapy regimen in both arms. In 1 trial (21), induction chemotherapy with paclitaxel 200 mg/cm^2 was used prior to CCRT followed by CCT. Paclitaxel (45 mg/m^2) and carboplatin (area under the curve = 2) were used as CCRT in another study (23). Another 3 trials (22,24,25) used cisplatin combined with one other drug (etoposide, docetaxel or vinorelbine). All the trials used a two-dimensional radiation technique as CCRT; the total dose was 66 Gy in 4 trials and 59.4 Gy in 1 trial (22). In the 3 trials (22,23,25), 3 cycles of CCT were scheduled, using the same chemotherapy regimen as CCRT. In another 2 trials (21,24) 7 and 2 cycles of CCT were delivered accordingly. The trial characteristics are summarized in Table I. There was no significant difference between the two treatments according to particular patient characteristics, such as age, gender, PS, histology, or clinical stage, in terms of benefit (Table II).

Study quality. The quality of the included trials is shown in Table III. All the included studies were found to have an unclear allocation concealment, but they were conducted with a method of adequate randomization and with intention-to-treat analysis. One trial clearly pointed out blinded assessment of

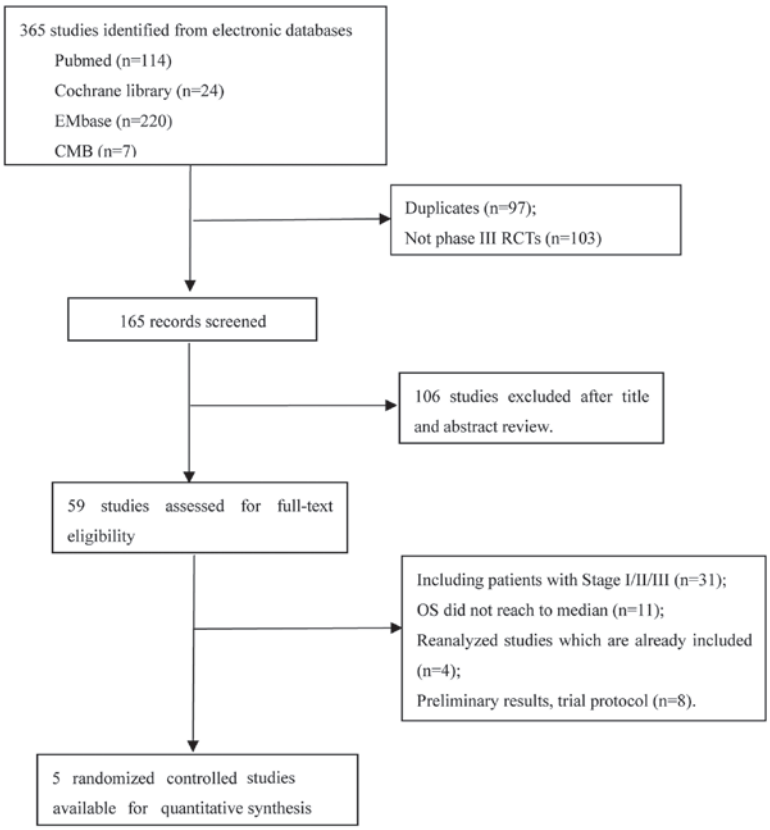

Figure 1. Flow diagram of studies included in systematic review and meta-analysis. RCTs, randomized controlled trials.

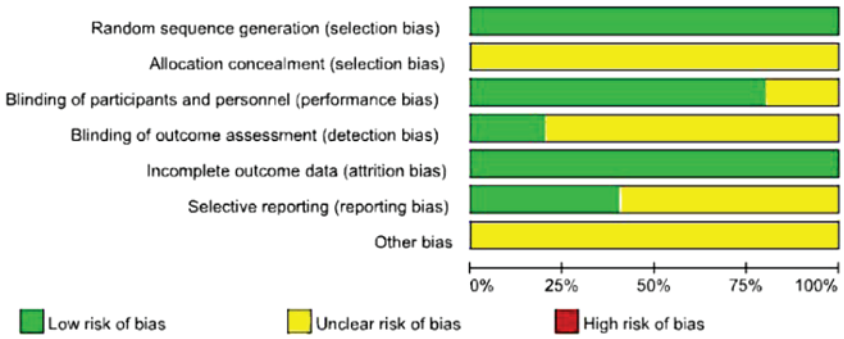

Figure 2. Risk of bias graph: Review of authors' assessment on each risk of bias item presented as percentages across all included studies.

outcome (22), whereas the remaining 4 trials did not describe the assessment method of outcome. According to the methodological quality of 3 trials, we reviewed the authors' judgement regarding each risk of bias item (Fig. 2).

Survival analysis. The survival analysis was based on 3 trials with 768 patients. CCRT followed by CCT failed to result in significant improvement in terms of 4-year OS (OR=1.24; 95% CI: 0.89-1.72; P=0.21) compared with CCRT alone (Fig. 3). There was no evidence of significant statistical heterogeneity with an I^2 value of 7% (χ^2 test for heterogeneity P=0.34). The PFS analysis was based on 2 trials including 567 patients. CCRT followed by CCT did not improve 3-year PFS (OR=1.16; 95% CI: 0.74-1.83; P=0.53) compared with CCRT alone (Fig. 4). There was no evidence of significant statistical heterogeneity, with an I^2 value of 0% (χ^2 test for heterogeneity P=0.52). Data were available for 491 patients (51%) for infection (P=0.02), peumonitis (P=0.003) and treatment-related death (P=0.04). Esophageal toxicity was analyzed by only 1 available trial (25) due to sparsity of data (P=0.09) (Table II).

Discussion

Despite the advances in the treatments for LA-NSCLC, the multidisciplinary approach for the management of LA-NSCLC remains controversial among clinicians. On the basis of large clinical trials (6-15), the treatment of choice for stage III unresectable NSCLC is CCRT. However, the main benefit of CCRT is likely to be due to decreased locoregional progression, rather than distant progression control and decreased acute toxicities (16). Recently, clinical trials on CCRT followed by

Table I. Characteristics of phase III randomized clinical trials of concurrent chemoradiotherapy (CCRT) with or without consolidation chemotherapy (CCT).

Study (Refs.)	Accrual years	Randomly assigned patients, n	Median follow-up, years	CCRT with CCT		CCRT without CCT
				CCRT	CCT	
Carter *et al* (21)	-	119	At least 36 months	Induction chemotherapy with PA 200 mg/m^2 + C AUC = 6 every 3 weeks for 2 cycles and then weekly PA 45 mg/m^2 + C AUC = 2 for 7 weeks, with concurrent daily XRT to 66.6 Gy	PA (70 mg/m^2 IV per week) for 7 weekly cycles	Induction chemotherapy with PA 200 mg/m^2 + C AUC = 6 every 3 weeks for 2 cycles, and then weekly PA 45 mg/m^2 + C AUC = 2 for 7 weeks, with concurrent daily XRT to 66.6 Gy
Hanna *et al* (22)	2002-2006	147	41.6 months	P 50 mg/m^2 IV D1, D8, D29 and D36 and E 50 mg/m^2 IV D1-5 and D29-33 concurrently with chest XRT to 59.40 Gy	D 75 mg/m^2 IV every 21 days for 3 cycles	The same as CCRT
Colin *et al* (23)	-	71	At least 36 months	PA (45 mg/m^2), C (AUC = 2), and XRT 60-66 Gy (5x2 Gy per week)	3 cycles of PA (175 mg/m^2) and C (AUC = 5) D1, D22 and D43	The same as CCRT
Huber *et al* (24)	2005-2009	201	At least 48 months	NVBo 50 mg/m^2 D1, D8, D15 + P20 mg/m^2 D1-D4 q4w/2 cycles + XRT (66 Gy/33 fractions)	NVBo 60-80 mg/m^2 D1 and D8 + P 80 mg/m^2 D1 q3w/2 cycles + BSC or BSC (non-CCT arm)	The same as CCRT
Ahn *et al* (25)	2005-2011	420	50.7 months	D 20 mg/m^2 IV and P 20 mg/m^2 IV D1, D8, D15, D22, D29 and D36 concurrently with chest XRT to 66.0 Gy	Three cycles of DP (35 mg/m^2 each on days 1 and 8, every 3 weeks)	The same as CCRT

XRT, radiation; IV, intravenously; P, cisplatin; E, etoposide; D, docetaxel; C, carboplatin; PA, paclitaxel; NVBo, oral vinorelbine; AUC, area under the curve; BSC, best supportive care.

Table II. Patient characteristics.

Characteristics	CCT after CCRT		CCRT		P-value
	No.	%	No.	%	
Median age, years	61		61		-
Range	31-86		33-86		-
Gender (female)	92	24.3	82	21.0	0.27
Performance status					
0	90	31.9	95	33.5	0.72
≥1.0	191	67.7	190	66.7	0.79
FEV1,1					
0.8 to <2.0	113	40.0	93	32.6	0.07
≥2.0	169	59.9	192	67.4	0.07
Stage					
IIIA	91	24.1	102	26.2	0.51
IIIB	286	75.7	287	73.6	0.51
Toxicity					
Infection	23	9.4	10	4.1	0.02
Pneumonitis	30	12.2	11	4.5	0.003
Treatment-related death	9	3.7	0	0.0	0.04
Esophagitis	61	35.3	46	26.9	0.09

Percentages were calculated on known values. CCT, consolidation chemotherapy; CCRT, concurrent chemoradiotherapy; FEV1, forced expiratory volume in 1 sec.

Table III. Methodological quality of included trials.

Study (Refs.)	Allocation concealment	Method of randomization	Blinded assessment of outcome	Description of withdrawals	Intention to treat analysis
Carter *et al* (21)	Unclear	Adequate	None described	Yes	Yes
Hanna *et al* (22)	Unclear	Adequate	Yes	Yes	Yes
Colin *t al* (23)	Unclear	Adequate	None described	Yes	Yes
Huber *et al* (24)	Unclear	Adequate	None described	Yes	Yes
Ahn *et al* (25)	Unclear	Adequate	None described	Yes	Yes

CCT (18-25) or induction treatment followed by CCRT (32-34) have became progressively more popular in an attempt to improve distant disease control. However, there is no clear evidence in terms of conferring survival benefits compared with the current standard CCRT for LA-NSCLC patients. Against this background, we conducted a meta-analysis to evaluate the efficacy and toxicity of CCRT followed by CCT vs. CCRT alone in the treatment of LA-NSCLC.

To the best of our knowledge, ours is the first meta-analysis of CCRT followed by CCT compared with CCRT alone, including 5 complete phase III RCTs. Although a pooled analysis performed by Tsujino *et al* (35) demonstrated the inefficiency of CCT after CCRT for LA-NSCLC, their subsequent letters to the editor (36) pointed out several limitations that may have affected their study results. First, the authors failed to assess the heterogeneity at the individual patient level, indicating that they did not analyze the specific characteristics of the patients. In addition, the diversity of the CCT regimens among trials is another important factor that may affect their study results. Two patterns were included: Continuous CCT, which continues the same chemotherapy as CCRT, and switch CCT, which changes to different agents in the consolidation phase. However, in our meta-analysis, we overcame these limitations by selecting complete phase III RCTs with specific patient characteristics. In addition, the trials included only investigated continuous CCT, suggesting that our study significantly decreased publication bias.

Our meta-analysis revealed no significant survival benefit in terms of OS (OR=1.24; 95% CI: 0.89-1.72; P=0.21) and PFS (OR=1.16; 95% CI: 0.74-1.83; P=0.53) for CCRT followed by CCT compared with CCRT alone. In accordance with the results from the 5 included phase III RCTs, the difference in OS and PFS was not significant between patients receiving CCRT followed by CCT and those receiving CCRT alone. In

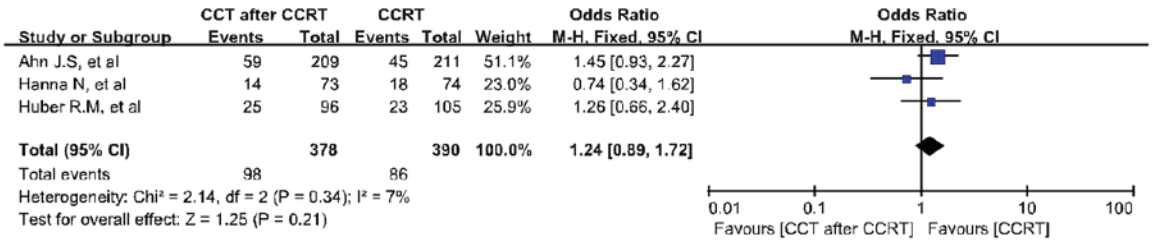

Figure 3. 4-year overall survival. CCT, consolidation chemotherapy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; df, degree of freedom.

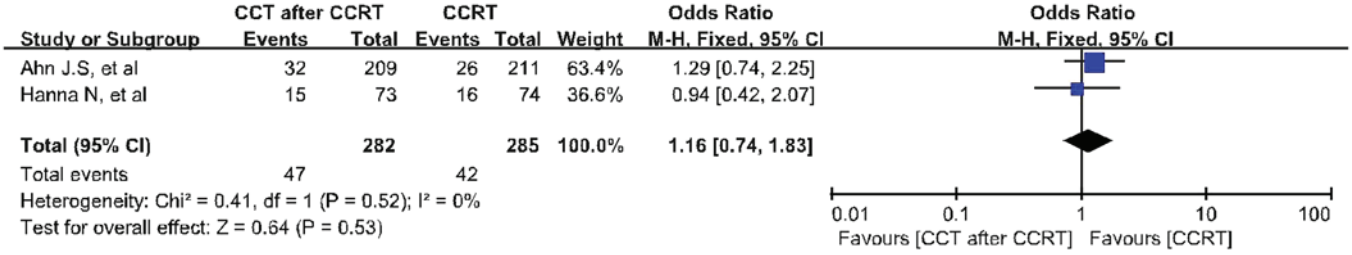

Figure 4. Three-year progression-free survival. CCT, consolidation chemotherapy; CCRT, concurrent chemoradiotherapy; CI, confidence interval; df, degree of freedom.

addition, the OS and PFS synthesis included 3 trials (22,24,25), which were based on cisplatin combined with one other drug as chemotherapeutic agents, and used almost the same radiation technique and doses for treatment. This way, treatment heterogeneity may be lowered to the minimum degree. Collectively, our meta-analysis provided clinicians with highly persuasive evidence that the survival benefit of CCT after CCRT is moderate. Moreover, Kelly *et al* (37) conducted a progressive phase III trial of maintenance gefitinib or placebo after CCRT and docetaxel cosolidation in inoperable stage III NSCLC. Although treatment with epidermal growth factor receptor-tyrosine kinase inhibitors as maintenance after CCT was delivered to the patients, gefitinib still failed to improve distant progression and survival, suggesting that the concept of CCT requires further investigation. However, a number of oncologists still treat LA-NSCLC patients with CCT after CCRT. It appears that clinicians reached a plateau in survival benefit using the current treatment (CCRT followed by CCT as well as CCRT alone) against stage III NSCLC.

With regards to our meta-analysis, we noted significant differences in toxicities, such as infection (P=0.02), pneumonitis (P=0.003) and treatment-related death (P=0.04). By contrast, the pooled analysis (35) indicated that no difference was observed in toxicity between the two groups, mainly as several included studies were phase I/II clinical trials without sufficient available toxicity data. Our meta-analysis included all phase III RCTs with specific data, so that we were able to analyze the differences in toxicity between patients who received CCT after CCRT and those who received CCRT alone. Schild *et al* (38) reported that older patients experienced higher rates of grade 4 toxicity (81 vs. 62%, P=0.007), hematological toxicity (78 vs. 56%, P=0.003) and pneumonitis (6 vs. 1%, P=0.02). Additionally, based on the HOG LUN 01-24 phase III trial (22), Jalal *et al* (39) published undated survival and outcome data that also support grade 3 and 4 toxicity noted during the induction and consolidation phases of the trial, particularly for patients aged ≥70 years vs. younger patients (87 vs. 73%, respectively; P=0.02). However, KCSG-LU05-04 (25) reported a significant benefit with CCT after CCRT in patients aged >60 years, suggesting that a more gradual strategy may be more appropriate for the elderly population. This results were consistent with a population-based study from the National Cancer Institute's Surveillance, Epidemiology and End Results database (40). There are two possible reasons for this discrepancy: First, for CCT after CCRT, several patients were unable to complete all the CCT cycles; thus, we could not exclude the possibility that the patients who did complete CCT after CCRT were aged ≥60 years. Furthermore, although the radiation was delivered under the same conditions, cisplatin combined with weekly docetaxel as second-line chemotherapy may be superior to the first-line chemotherapy due to the acceptable toxicity profile. In addition, several phase III trials and a meta-analysis demonstrated a significant benefit in grade 3-4 neutropenia compared with docetaxel every 3 weeks (41-44).

There were two limitations in this meta-analysis. First, since we included published trials, our analysis may include heterogeneous studies. For example, eligible patients were not selected based on rigid inclusion criteria. A number of patients who were unable to complete all the cycles of CCT after CCRT were included in the analysis. Second, 3 abstract meetings were included in our analysis, for which not all survival data were available; our meta-analysis may be updated following publication of their specific data.

On the basis of our meta-analysis, CCT after CCRT, as compared with CCRT alone, failed to improve the OS and PFS rates; in addition, CCT after CCRT was associated with increased toxicity. Thus, further clinical trials are warranted to seek novel breakthrough treatment options to improve the prognosis of patients with LA-NSCLC.

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