



Benefit of adjuvant chemotherapy for patients with stage IB non-small cell lung cancer: a systematic review and meta-analysis

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Background: Adjuvant chemotherapy (ACT) is routinely the recommended treatment for patients with advanced non-small cell lung cancer (NSCLC) but remains a controversial option in stage IB patients. We therefore pooled the current evidence to determine the prognostic impact of ACT in stage IB NSCLC patients in the context of the eighth tumor, node, metastasis (TNM) staging system.

Methods: Five electronic databases were searched for eligible studies up to December 2020 without language restrictions. The primary and secondary outcomes were overall survival (OS) and disease-free survival (DFS). Search results were filtered by a set of eligibility criteria and analyzed in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The risk of bias was assessed independently using a modified set. Stata 16.0 was used for general data analysis and meta-analysis, and subgroup analyses were performed to investigate the source of interstudy heterogeneity.

Results: In all, 12 eligible studies were identified and 15,678 patients included. Our results demonstrated that ACT was associated with improved OS [n=11; hazard ratio (HR) =0.65; 95% confidence interval (CI): 0.60–0.70; P<0.001; I²=33.4%, P=0.131] and DFS (n=9; HR =0.73; 95% CI: 0.63–0.83; P<0.001; I²=66.7%, P=0.002) in stage IB NSCLC patients. Subgroup analysis by histology indicated that administration of ACT conferred more favorable survival to both stage IB squamous cell carcinoma (n=1; HR =0.56; 95% CI: 0.28–0.84; P<0.001) and adenocarcinoma (n=6; HR =0.59; 95% CI: 0.47–0.71; P<0.001; I²=31.0%, P=0.203). Meanwhile, both platinum-based ACT (n=7; HR =0.62; 95% CI: 0.51–0.74; P<0.001; I²=44.8%, P=0.093) and other regimens (n=2; HR =0.66; 95% CI: 0.61–0.72; P<0.001; I²=0.7%, P=0.316) could benefit patients with stage IB disease.

Discussion: ACT might provide survival benefits to patients with stage IB NSCLC irrespective of histology or regimens. Patient selection and time trend biases were inevitable due to the limitation of retrospective studies. More prospective studies should be initiated to investigate the optimal ACT regimens in different histologic types in stage IB NSCLC patients.

Keywords: Non-small cell lung cancer (NSCLC); stage IB; adjuvant chemotherapy; meta-analysis

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Introduction

Non-small cell lung cancer (NSCLC) has been the major cause of global lung cancer–related morbidity and mortality for decades (1). Due to the widespread adoption of thin-slice computed tomography (CT) for screening pulmonary nodules, a large portion of early-stage NSCLC cases are detected, among which lung adenocarcinoma (ADC) accounts for the overwhelming majority (2,3). However, the 5-year survival of patients with early-stage NSCLCs still vary considerably, from 90% in stage IA1 to 73% in stage IB (4). Surgical resection was previously considered to be adequate treatment for NSCLC patients without lymph node involvement (5). However, the postoperative survival of patients with stage IB disease has been unsatisfactory and marred by a high susceptibility to recurrence (6). In recent years, a number of retrospective studies (7-9) proposed that adjuvant chemotherapy (ACT) could improve the probability of freedom from recurrence and lower the death rate in both stage IB lung ADC and squamous cell carcinoma (SCC). However, these studies lacked up-to-date and synthesized evidence concerning whether ACT should be administered to patients with stage IB NSCLC. Therefore, there is an urgent need for physicians to investigate the role of ACT in improving survival in patients with stage IB NSCLC.

The current National Comprehensive Cancer Network (NCCN) guidelines recommend postoperative chemotherapy for NSCLC patients with a tumor size ≥ 4 cm, based on the analysis of the CALGB 9633 trial subgroup analysis (10). In the eighth tumor, node, metastasis (TNM) staging system (11), T2 was subdivided into T2a (>3 – 4 cm) and T2b (>4 – 5 cm) with T2bN0M0 elevated to IIA, which had an unprecedented effect on the population eligible to receive ACT. However, it has not been specified whether patients with stage IB NSCLC (<4 cm) can benefit from ACT in the context of the eighth TNM staging system.

To address this issue, we conducted a systematic review meta-analysis that included a homogenous subset of stage IB NSCLC patients according to the eighth edition of the TNM classification for lung cancer, followed by a subgroup analysis comparing different chemotherapy regimens and between different pathological subtypes. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-4001>).

Methods

Search Strategy

This meta-analysis was performed in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (12). We conducted searches of the PubMed, Web of Science, MEDLINE, Embase, and Cochrane Library databases to identify eligible studies published until December 2020. The main search terms were “adenocarcinoma of lung”, “postoperative period”, and “Drug Therapy”. The full search strategy is summarized in Table S1.

Study selection and inclusion criteria

Three reviewers (Wang X., Chen D., and Wen J.) independently identified potentially eligible studies. Initially, the titles and abstracts were screened to evaluate study eligibility, which was followed by review of the full text. If any disagreement regarding study selection could not be resolved through discussion, another reviewer (Mao Y.) would be invited to reach a consensus. Studies that met the following criteria were included: (I) patients with stage IB NSCLCs according to the eighth TNM staging system and treated with cancer-directed surgery; (II) studies with hazard ratio (HR) and 95% confidence interval (CI) for overall survival (OS) or disease-free survival (DFS), or indirect information such as Kaplan-Meier curve; (III) in cases where the same population or database were included in 2 or more studies, the study with the largest sample size or the most recent information would be included. The exclusion criteria have been described in our previous study (13).

Data extraction

Data extraction was conducted by 2 reviewers (Wang X. and Chen D.) independently. The following demographic and clinicopathological characteristics were recorded: author’s name, year of publication, country or region, study design, inclusion period, number of patients, age of patients, histology, ACT regimen, follow-up period, study end points, analysis of HR, and adjustment of variables. In addition, 2 reviewers (Wen J. and Mao Y.) also extracted individual HR estimates and corresponding 95% CIs for OS or DFS. If some studies included stage I–III patients, only the data of patients with stage IB (tumor size ≤ 4 cm) disease

were extracted for analyses. Studies were excluded if the individual data of stage IB patients were unavailable.

Definitions of study end points

The primary end point was OS, defined as the interval between the initial surgery and death from any cause. The secondary end point was DFS, defined as the time from the initial surgery to the first recorded recurrence.

Quality assessment

In the present study, we compared surgery plus ACT with surgery alone by estimating HRs for OS and DFS. The risk of bias was assessed by 2 reviewers (Wang X. and Chen D.) independently using a modified set of predefined criteria (14) described previously (13). A score of 7 or higher was considered as a high-quality score, whereas a score of less than 7 was a low-quality one. Disagreements, if any, were resolved through discussion.

Statistical analyses

To minimize interference caused by the number of studies, differences between studies were estimated using I^2 test, rather than Cochran's Q test (15), as results of Cochran's Q test were strongly correlated with the number of included studies. The heterogeneity was graded as low ($I^2 < 25\%$), moderate ($I^2 = 25\text{--}75\%$), or high ($I^2 > 75\%$). When heterogeneity was significant ($I^2 > 50\%$ or $P < 0.1$), a random effects model would be employed to calculate the pooled effect; otherwise, a fixed effects model would be applied.

For general data analysis and meta-analysis, Stata 16.0 (StataCorp, College Station, TX, USA) was used. Subgroup analyses were performed to investigate the source of interstudy heterogeneity. Sensitivity analyses were also carried out by omitting single a study to assess the stability of the results. A simple funnel plot-based method would be applied if publication bias was confirmed with recalculated pooled estimates (16). All statistical tests were 2-sided, and statistical significance was defined as a P value less than 0.05.

Results

Selection of eligible studies

Figure S1 displays the general flowchart for identifying eligible studies. In brief, 799 studies were available from

online databases according to our search strategy, and 8 duplicate records were initially excluded from these studies. We further excluded 779 studies by screening titles and abstracts, as well as reviewing the full text. Eventually, 12 studies were confirmed as eligible for our present meta-analysis.

Study characteristics

A total of 15,678 patients were included in the present meta-analysis and had a median follow-up period of 53 months. Table 1 and Table S2 provide the baseline and main characteristics of the eligible studies. In summary, 10 of the 12 studies had a retrospective design and were published between 2016 and 2020; the other 2 studies were randomized clinical trials (RCTs) published before 2010. Lung ADC and SCC were the 2 main histologic types in these studies; 11 of the 12 studies reporting OS and 9 studies reporting DFS used multivariate analysis to adjust covariates. As shown in Table S3, all the included studies were identified as high quality.

Adjuvant chemotherapy and clinical outcomes: OS and DFS

In the analysis of ACT benefit to OS, 11 studies comprising 14,702 patients were included. The data (Figure 1A) indicated that administration of ACT could bring improved OS to stage IB NSCLC patients (HR = 0.65; 95% CI: 0.60–0.70; $P < 0.001$) with moderate heterogeneity in the included studies ($I^2 = 33.4\%$, $P = 0.131$). The stability of the OS subsets was assessed in a sensitivity analysis by omitting each single study, which did not affect the pooled HR (Figure 1B).

A total of 4,590 patients from 9 studies were involved in the analysis of ACT and DFS. The pooled data (Figure 1C) indicated that administration of ACT confers an advantage in freedom from recurrence to stage IB patients (HR = 0.73; 95% CI: 0.63–0.83; $P < 0.001$) with moderate heterogeneity ($I^2 = 66.7\%$; $P = 0.002$). Similar to the analysis of OS, a stable pooled HR was shown in our sensitivity analysis of the DFS subsets (Figure 1D).

We also performed subgroup analyses to investigate potential sources of heterogeneity (Tables 2,3). There were no remarkable changes in the pooled HRs for most subgroups, except for the ones by number of included individuals. Surprisingly, subgroup analysis indicated that ACT negatively affected OS ($n = 4$; HR = 1.115; 95% CI:

Table 1 Baseline characteristics of the associations between adjuvant chemotherapy and clinical outcomes in stage IB NSCLCs (n=12).

No.	Study	Country or region (inclusion period)	Study design	Gender (female/male) (%)	Median age (years)	Tumor type	Histology	Median follow-up period (months)	Study end points	Chemotherapy regimens	Surgical alone/surgery plus ACT	Quality score
1	Morgensztern [2016]	United States [2004–2011]	Retrospective	44.2/55.8	NR	NSCLC	43.6% SCC; 43.9% ADC; 12.5% other	60	OS	NR	1,608/8,979 (15.19%/84.81%)	7
2	Xu [2018]	China [2008–2014]	Retrospective	5.6/94.4	NR	Lung SCC	–	45.9	OS/DFS	4 cycles of platinum-based or single-agent chemotherapy	201/159 (55.83%/44.17%)	8
3	Strauss [2008]	United States [1996–2003]	RCT	36.0/64.0	61	NSCLC	34.3% SCC; 51.5% ADC; 14.2% other	74	OS/DFS	4 cycles of paclitaxel 200 mg/mL + carboplatin 6 mg/mL	63/71 (47.01%/52.99%)	8
4	Qian [2017]	China [2008–2015]	Retrospective	61.6/38.4	60	Lung ADC	66.2% SMPN; 23.8% SMPM; 10.0% SMPP	46.8	DFS	4 cycles of platinum-based chemotherapy	488/488 (50.00%/50.00%)	7
5	Butts [2010]	United States [2004–2011]	RCT	34.0/65.1	60.9	NSCLC	37.1% SCC; 53.1% ADC; 9.8% other	111.6	OS	4 cycles of vinorelbine/cisplatin or observation	45/54 (45.45%/54.55%)	8
6	Wang [2018]	China [2003–2014]	Retrospective	35.9/64.1	60	NSCLC	33.0% SCC; 60.0% ADC; 7.0% other	56.04	OS	4–6 cycles of cisplatin with gemcitabine or paclitaxel	265/137 (65.92%/34.08%)	7
7	Wang [2019]	China [2007–2013]	Retrospective	54.7/45.3	59	Lung ADC	1.9% LEP; 53.3% ACN; 32.1% PAP; 9.4% SOL; 1.4% MIP; 1.9% other	46.7	OS/DFS	platinum-based	106/106 (50.00%/50.00%)	8
8	Chen [2020]	China [2009–2016]	Retrospective	44.6/55.4	65	Lung ADC	27.9% LEP; 30.0% ACN; 17.9% PAP; 16.6% SOL; 7.7% MIP	90.8	OS/DFS	platinum-based	468/859 (35.27%/64.73%)	8
9	Jang [2017]	Korea [2000–2009]	Retrospective	50.9/49.1	63.1	Lung ADC	–	49.3	OS/DFS	platinum-based	110/218 (33.54%/66.46%)	7
10	Ito [2020]	Japan [2008–2015]	Retrospective	46.1/53.9	64.9	Lung ADC	35.2% LEP; 24.2% ACN; 18.4% PAP; 15.4% SOL; 1.0% MIP; 5.8% other	66.0	OS/DFS	UFT for at least 6 months	70/70 (50.00%/50.00%)	8
11	Cao [2018]	China [2006–2015]	Retrospective	35.6/64.4	60	Lung ADC	NR	41	OS/DFS	platinum-based	193/116 (62.46%/37.54%)	8
12	Chen [2018]	China [2010–2015]	Retrospective	58.6/41.4	NR	Lung ADC	NR	34.27	OS/DFS	4 cycles of platinum-based chemotherapy	402/402 (50.00%/50.00%)	8

NSCLC, non-small cell lung cancer; OS, overall survival; DFS, disease-free survival; SCC, squamous cell carcinoma; ADC, adenocarcinoma; NR, not reported; Lob, lobectomy; SR, sublobar resection; Pneumo, pneumonectomy; RCT, randomized clinical trials; SMPN, solid/micropapillary-negative; SMPM, solid/micropapillary-minor; SMPP, solid/micropapillary-predominant adenocarcinoma; LEP, lepidic-predominant adenocarcinoma; ACN, acinar-predominant adenocarcinoma; PAP, papillary-predominant adenocarcinoma; SOL, solid-predominant adenocarcinoma; MIP, micropapillary-predominant adenocarcinoma; UFT, uracil and fluorouracil.

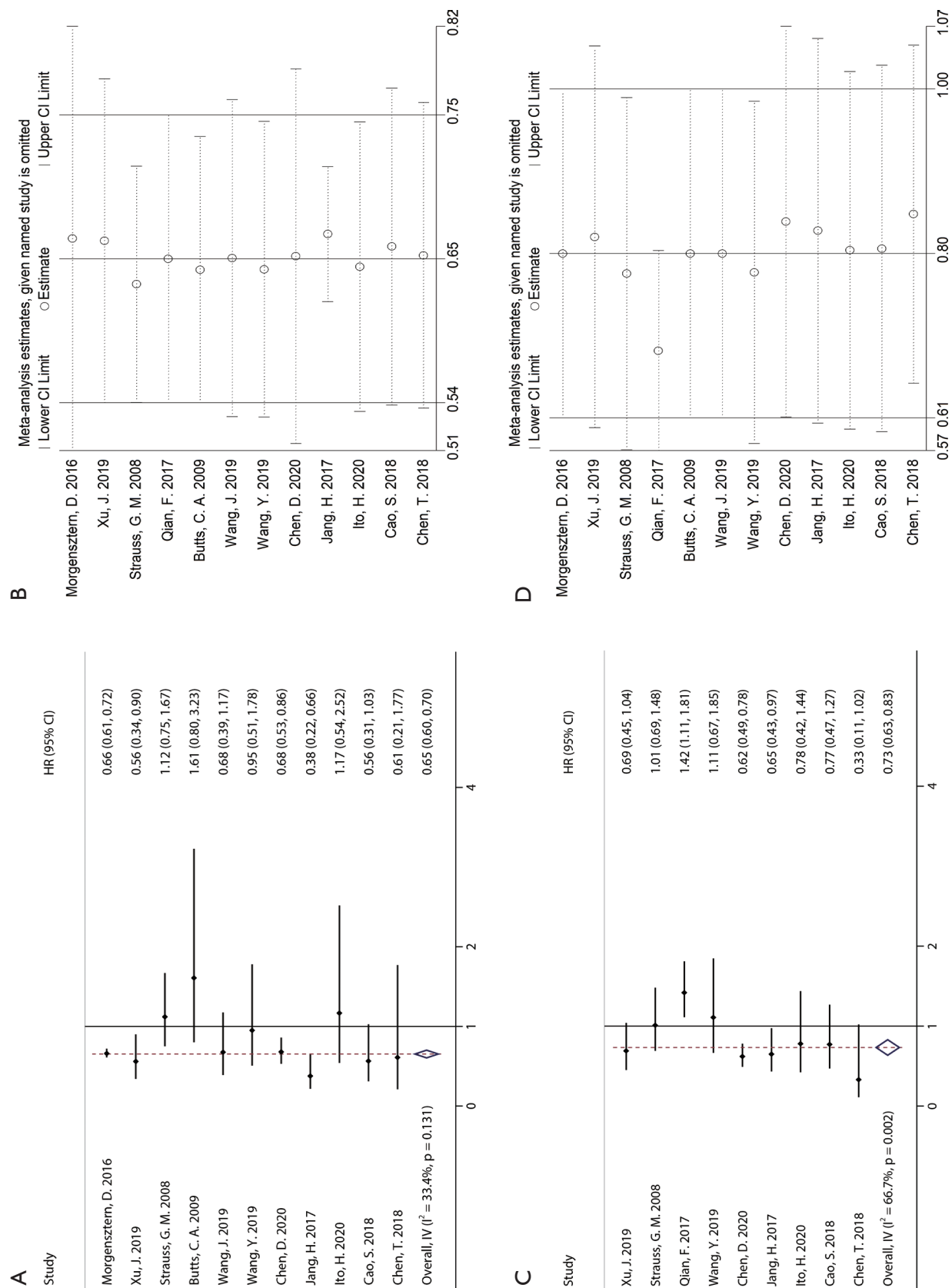


Figure 1 Meta-analysis of the associations between adjuvant chemotherapy (ACT) and overall survival (OS) and disease-free survival (DFS). (A) Pooled evidence for the relationship between ACT and OS; (B) sensitivity analysis for the pooled effect of the relationship between ACT and OS; (C) pooled evidence for the relationship between ACT and DFS; (D) sensitivity analysis for the pooled effect of the relationship between ACT and DFS.

Table 2 Subgroup analyses of the associations between adjuvant chemotherapy and OS

Variable	Studies	Test of association			Test of heterogeneity	
		HR	95% CI	P value	I ² (%)	P value
Publication year						
<2017	3	0.668	0.614–0.723	0.000	67.2	0.048
≥2017	8	0.595	0.489–0.701	0.000	6.3	0.381
Research region						
China	6	0.652	0.531–0.773	0.000	0.0	0.899
United States	3	0.668	0.614–0.723	0.000	67.2	0.048
Other	2	0.415	0.199–0.631	0.000	57.2	0.126
Number of included individuals						
<300	4	1.115	0.780–1.451	0.000	0.0	0.825
≥300	7	0.643	0.594–0.692	0.000	9.8	0.354
Histology type						
NSCLC	4	0.669	0.614–0.723	0.000	50.8	0.107
ADC	6	0.594	0.474–0.714	0.000	31.0	0.203
SCC	1	0.560	0.280–0.840	0.000	-	-
Chemotherapy plan						
Platinum-based	7	0.624	0.513–0.736	0.000	44.8	0.093
Others	2	0.662	0.607–0.716	0.000	0.7	0.316
Follow-up period						
<53 months	5	0.501	0.352–0.650	0.000	0.0	0.480
≥53 months	6	0.671	0.610–0.722	0.000	0.0	0.636
Quality score						
<8	3	0.644	0.591–0.697	0.000	66.3	0.052
≥8	8	0.700	0.578–0.821	0.000	16.8	0.298

OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

0.780–1.451; $P < 0.001$) but benefited DFS ($n=3$; HR =0.963; 95% CI: 0.688–1.239; $P < 0.001$) in small-scale studies with extremely low heterogeneity (OS: $I^2=0.0\%$, $P=0.825$; DFS: $I^2=0.0\%$, $P=0.673$; *Tables 2,3*). Interestingly, subgroup analysis by different follow-up periods revealed that administration of ACT stably improved OS irrespective of the length of follow-up (*Figure S2*).

Adjuvant chemotherapy and OS: histology and regimens

As shown in *Figure 2A*, a pooled analysis of 1 study (9)

demonstrated the role of ACT in stage IB lung SCC. By pooling the available evidence, we found that ACT administration was associated with significantly better OS in stage IB SCC (HR =0.56; 95% CI: 0.28–0.84; $P < 0.001$). Meanwhile, a pooled analysis of 6 studies (17–22) compared the OS of stage IB lung ADC patients treated with surgery plus ACT with that of patients treated with surgery alone. Similarly, the pooled HR showed that ACT was associated with improved OS in stage IB ADC (HR =0.59; 95% CI: 0.47–0.71; $P < 0.001$), and a moderate statistical heterogeneity was suggested regarding this result ($I^2=31.0\%$,

Table 3 Subgroup analyses of the associations between adjuvant chemotherapy and DFS

Variable	Studies	Test of association			Test of heterogeneity	
		HR	95% CI	P value	I ² (%)	P value
Publication year						
<2017	1	1.010	0.615–1.405	0.000	–	–
≥2017	8	0.714	0.614–0.815	0.000	68.20	0.003
Research region						
China	6	0.722	0.611–0.833	0.000	77.00	0.001
United States	1	1.010	0.615–1.405	0.000	–	–
Other	2	0.678	0.439–0.917	0.000	0.00	0.658
No. of included individuals						
<300	3	0.963	0.688–1.239	0.000	0.00	0.673
≥300	6	0.699	0.595–0.803	0.000	75.20	0.001
Histology type						
NSCLC	1	1.010	0.615–1.405	0.000	–	–
ADC	7	0.717	0.610–0.824	0.000	72.70	0.001
SCC	1	0.690	0.395–0.985	0.000	–	–
Chemotherapy plan						
Platinum-based	7	0.736	0.630–0.841	0.000	74.90	0.001
Others	1	0.779	0.271–1.287	0.003	–	–
Follow-up period						
<53 months	6	0.804	0.658–0.949	0.000	73.50	0.002
≥53 months	3	0.674	0.542–0.805	0.000	42.50	0.176
Quality score						
<8	2	0.938	0.724–1.152	0.000	91.40	0.001
≥8	7	0.678	0.569–0.788	0.000	24.80	0.240

DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

P=0.203).

We also performed a pooled analysis of 7 studies (10,17-19,21-23) to assess the impact of platinum-based regimens in stage IB NSCLC patients receiving ACT (Figure 2B). The pooled analysis indicated that platinum-based ACT was associated with favorable OS in stage IB patients (HR =0.62; 95% CI: 0.51–0.74; P<0.001) with moderate heterogeneity (I²=44.8%, P=0.093). Meanwhile, a pooled analysis of 2 studies (20,24) investigated other regimens in stage IB NSCLC patients receiving ACT (Figure 2B). The pooled data revealed that administration of

other regimens could also be beneficial to stage IB patients (HR =0.66; 95% CI: 0.61–0.72; P<0.001). Additionally, there was evidence of extremely low heterogeneity for this result (I²=0.7%, P=0.316).

Publication bias

As shown in Table S4, Begg's and Egger's tests confirmed that there was no significant publication bias in terms of HRs for OS (Begg's test, P=0.436; Egger's test, P=0.379) or DFS (Begg's test, P=1.000; Egger's test, P=0.481).

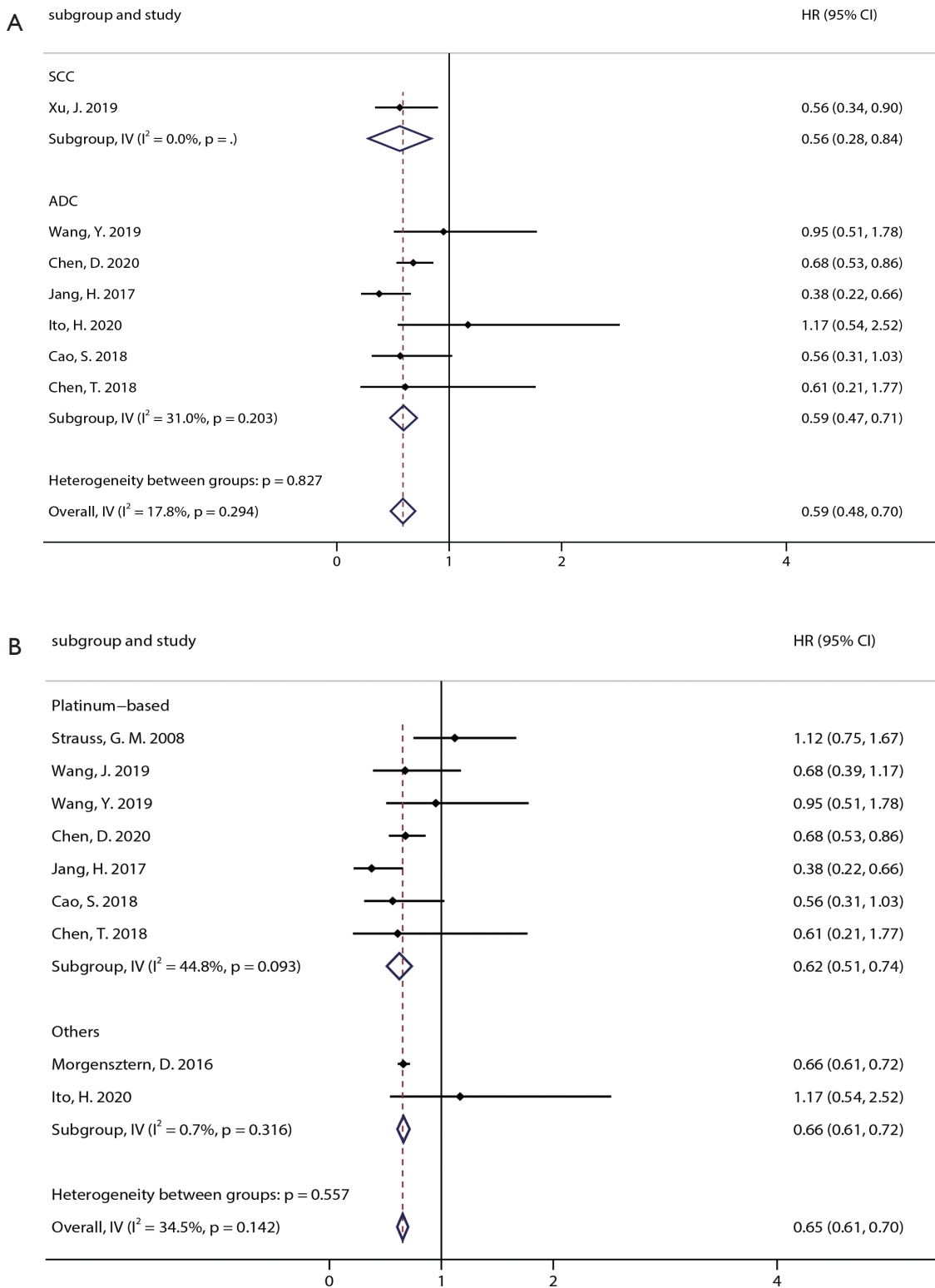


Figure 2 Subgroup analyses of (A) the associations between lung adenocarcinoma (ADC) and squamous cell carcinoma (SCC) and (B) the associations between platinum-based chemotherapy and other chemotherapy.

Discussion

This systematic review and meta-analysis show that administration of ACT might bring benefits in OS and DFS to stage IB patients within the context of the eighth edition of TNM staging system. Furthermore, ACT exhibited its value not only in patients with SCC but also in those with ADC. Moreover, subset analyses indicated that both platinum-based regimens and others could effectively prolong the OS of stage IB patients. Interestingly, subset analysis by follow-up period also suggested that administration of ACT could improve both short- and long-term OS. To the best of our knowledge, this study is the largest and most recent meta-analysis of its kind to demonstrate the prognostic impact of ACT on stage IB NSCLCs since the widespread application of the eighth edition TNM classification.

In this study, we identified 12 relevant studies to determine the prognostic impact of ACT on stage IB NSCLC patients. Notably, 7 of the 12 eligible studies (9,18,19,21-24) showed the prescription of ACT to be associated with better OS in patients with stage IB NSCLC. However, the other 5 studies (8,10,17,20,25) did not support routine use of ACT for patients with stage IB NSCLC. Consequently, the pooled evidence not only highlighted a clear survival benefit of ACT in both the OS (n=11; HR =0.65; 95% CI: 0.60–0.70; P<0.001) and DFS (n=9; HR =0.73; 95% CI: 0.63–0.83; P<0.001) of stage IB patients, but also addressed the debate of whether ACT should be administered even for malignancies <4 cm. The recent increase in early-stage ADC presenting as pulmonary nodules detected by CT examination has led to a surge in surgical patients, and prescribing ACT for postoperative patients with pathologically identified stage IB ADC has also become a matter of debate. Among the 6 included studies investigating ACT and DFS in ADC patients, only 3 (18,19,22) reported a positive influence of ACT on stage IB ADC patients. Meanwhile, only 2 studies (18,19) identified survival benefits from ACT for OS in stage IB ADC patients. Interestingly, our pooled data confirmed the value of ACT for stage IB ADC (OS: n=6; HR =0.594; 95% CI: 0.475–0.741; P<0.001; DFS: n=7; HR =0.717; 95% CI: 0.610–0.824; P<0.001). In other words, the current study provides robust evidence for the administration of ACT in stage IB ADC patients, especially in those with high-grade tumor components.

Notably, the majority of included participants in the CALGB 9633 study were diagnosed with lung ADC (10).

Previous evidence suggests that patients with early-stage lung SCC might be more susceptible to recurrence of malignancies compared to those with lung ADC (26-28). In addition, there is a close link between lung SCC and smoking, one of the independent predictors of recurrence. In another study (29), stage I lung SCC patients exhibited higher expression levels of Ki67 and Bcl-2 proteins, which are associated with proliferation and metastasis, compared with ADC patients. These results suggest that timely clinical interventions should be implemented to prevent recurrence in early-stage SCC patients. Our subset analysis also indicated that patients with stage IB SCC might benefit from administration of ACT (HR =0.56; 95% CI: 0.28–0.84; P<0.001). Therefore, more attention should be paid to prescribing prompt ACT for stage IB SCC patients.

In terms of biomarkers for predicting efficacy of ACT, Buhl *et al.* (30) found that molecular profiles derived from NSCLC tissues were prognostic and predictive for selection of patients benefiting from platinum-based ACT. Additionally, Lin *et al.* (31) showed that TP53 mutation was significantly correlated with tumor progression, which may provide a rationale for the selective use of ACT in stage IB patients with TP53 mutations. However, Ma *et al.* (32) claimed the opposite, as they declared that TP53 mutations were not significant predictors of outcome in ACT, but may be associated with a tendency towards worse outcomes upon treatment. In addition to tissue-based genetic testing, Kuang *et al.* (33) proposed that circulating tumor DNA analyses based on peripheral blood samples might define a subgroup that remained at high risk of relapse despite standard ACT, and could help to inform intensified therapeutic strategies, which was supported by other researchers (34).

Recently, several studies (35,36) recommended that postoperative PD-L1 testing be performed in surgical patients and with those TPS $\geq 1\%$ could be tried with adjuvant immunotherapy or adjuvant chemotherapy combined with or without concomitant immunotherapy. However, the robust evidence supporting administration of immune checkpoint inhibitors combined with chemotherapy as adjuvant treatment in stage IB disease has not been available in clinical practices, which awaits further investigation.

Several limitations of this study should be acknowledged. As this meta-analysis was performed mainly on retrospective studies, patient selection and time trend biases were inevitable. Second, given the limited available information, it was impossible to perform subset analyses by radiological

features and histologic subtypes of ADCs. Notably, ADCs presenting as pure ground-glass opacity or harboring a lepidic-predominant pattern might not benefit from ACT. Third, there was inherent heterogeneity in the administration of ACT, including the administration of different cycles of ACT and prescribed regimens, which might have been affected by physicians' preferences. More multi-institutional, prospective, randomized clinical trials should be performed to validate the survival benefits conferred by ACT in stage IB NSCLC patients.

Conclusions

The present study indicated that ACT is associated with improved survival in stage IB NSCLC patients irrespective of histology. Different ACT regimens were found to benefit patients with stage IB NSCLC. Prospective studies should be initiated to investigate the optimal ACT regimens in different histologic types in stage IB NSCLC patients.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://dx.doi.org/10.21037/atm-21-4001>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/atm-21-4001>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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Table S1 Search Strategies

Sources searched : PubMed, MEDLINE, Embase, Web of Science, and Cochrane Library. Search strategy: search date was from the inception to December 2020

1.1 PubMed search strategy

1. "Adenocarcinoma of Lung" (Mesh)
2. Adenocarcinoma of Lung (Title/Abstract)
3. Lung Adenocarcinoma (Title/Abstract)
4. Lung Adenocarcinomas (Title/Abstract)
5. Adenocarcinoma, Lung (Title/Abstract)
6. Adenocarcinomas, Lung (Title/Abstract)
7. Pulmonary Adenocarcinoma (Title/Abstract)
8. Pulmonary Adenocarcinomas (Title/Abstract)
9. Adenocarcinoma, Pulmonary (Title/Abstract)
10. Adenocarcinomas, Pulmonary (Title/Abstract)
11. "Carcinoma, Non-Small-Cell Lung" (Mesh)
12. Carcinoma, Non Small Cell Lung (Title/Abstract)
13. Carcinoma*, Non-Small-Cell Lung (Title/Abstract)
14. Lung Carcinoma*, Non-Small-Cell (Title/Abstract)
15. Non-Small Cell Lung Carcinoma (Title/Abstract)
16. Non-Small-Cell Lung Carcinomas (Title/Abstract)
17. Nonsmall Cell Lung Cancer (Title/Abstract)
18. Non-Small-Cell Lung Carcinoma (Title/Abstract)
19. Non Small Cell Lung Carcinoma (Title/Abstract)
20. Carcinoma, Non-Small Cell Lung(Title/Abstract)
21. Non-Small Cell Lung Cancer (Title/Abstract)
22. Non-Small Cell Lung Neoplasm (Title/Abstract)
23. Non-Small Cell Lung Tumor(Title/Abstract)
24. NSCLC (Title/Abstract)
25. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26. "Postoperative Period" (Mesh)
27. Period, Postoperative (Title/Abstract)
28. Periods, Postoperative (Title/Abstract)
29. Postoperative Periods (Title/Abstract)
30. 26 OR 27 OR 28 OR 29
31. "Drug Therapy" (Mesh)
32. Therapy, Drug (Title/Abstract)
33. Drug therapies (Title/Abstract)
34. Pharmacotherapy (Title/Abstract)
35. Pharmacotherapies (Title/Abstract)
36. Chemotherapy (Title/Abstract)
37. 31 OR 32 OR 33 OR 34 OR 35 OR 36
38. 25 AND 30 AND 37

1.2 MEDLINE search strategy

1. Adenocarcinoma of Lung/
2. (Lung Adenocarcinoma).ti,ab,kf
3. (Lung Adenocarcinomas).ti,ab,kf
4. (Adenocarcinoma, Lung).ti,ab,kf
5. (Adenocarcinomas, Lung).ti,ab,kf
6. (Pulmonary Adenocarcinoma).ti,ab,kf
7. (Pulmonary Adenocarcinomas).ti,ab,kf
8. (Adenocarcinoma, Pulmonary).ti,ab,kf
9. (Adenocarcinomas, Pulmonary).ti,ab,kf
10. non small cell lung cancer/
11. (non small cell lung cancer).ti,ab,kf
12. (non-small cell lung cancer).ti,ab,kf
13. (carcinoma, non small cell lung).ti,ab,kf
14. (carcinoma*, non-small-cell lung).ti,ab,kf
15. (lung carcinoma*, non-small-cell).ti,ab,kf
16. (non-small cell lung carcinoma).ti,ab,kf
17. (non-small-cell lung carcinomas*.ti,ab,kf
18. (nonsmall cell lung cancer).ti,ab,kf
19. (non-small-cell lung carcinoma).ti,ab,kf
20. (non small cell lung carcinoma). ti,ab,kf
21. (carcinoma, non-small cell lung).ti,ab,kf
22. (non-small cell lung neoplasm).ti,ab,kf
23. (non-small cell lung tumor).ti,ab,kf
24. (NSCLC).ti,ab,kf
25. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26. Postoperative Period/
27. (Period, Postoperative).ti,ab,kf
28. (Periods, Postoperative).ti,ab,kf
29. (Postoperative Periods).ti,ab,kf
30. 26 OR 27 OR 28 OR 29
31. Drug Therapy/
32. (Therapy, Drug).ti,ab,kf
33. (Drug therapies).ti,ab,kf
34. (Pharmacotherapy).ti,ab,kf
35. (Pharmacotherapies).ti,ab,kf
36. (chemotherapy).ti,ab,kf
37. 31 OR 32 OR 33 OR 34 OR 35 OR 36
38. 25 AND 30 AND 37

ti, title; ab, abstract; kf, key field.

1.3 Embase search strategy

1. 'Lung Adenocarcinoma'/exp
2. 'Lung Adenocarcinoma':ti,ab,kw
3. 'Lung Adenocarcinomas':ti,ab,kw
4. 'Adenocarcinoma, Lung':ti,ab,kw
5. 'Adenocarcinomas, Lung':ti,ab,kw
6. 'Pulmonary Adenocarcinoma':ti,ab,kw
7. 'Pulmonary Adenocarcinomas':ti,ab,kw
8. 'Adenocarcinoma, Pulmonary':ti,ab,kw
9. 'Adenocarcinomas, Pulmonary':ti,ab,kw
10. 'Non Small Cell Lung Cancer'/exp
11. 'Non Small Cell Lung Cancer':ti,ab,kw
12. 'Non-Small Cell Lung Cancer':ti,ab,kw
13. 'Carcinoma, Non Small Cell Lung':ti,ab,kw
14. 'Carcinoma*, Non-Small-Cell Lung':ti,ab,kw
15. 'Lung Carcinoma*, Non-Small-Cell':ti,ab,kw
16. 'Non-Small Cell Lung Carcinoma':ti,ab,kw
17. 'Non-Small-Cell Lung Carcinomas':ti,ab,kw
18. 'Nonsmall Cell Lung Cancer':ti,ab,kw
19. 'Non-Small-Cell Lung Carcinoma':ti,ab,kw
20. 'Non Small Cell Lung Carcinoma':ti,ab,kw
21. 'Carcinoma, Non-Small Cell Lung':ti,ab,kw
22. 'Non-Small Cell Lung Neoplasm':ti,ab,kw
23. 'Non-Small Cell Lung Tumor':ti,ab,kw
24. 'NSCLC':ti,ab,kw
25. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26. 'Postoperative Period'/exp
27. 'Period, Postoperative':ti,ab,kw
28. 'Periods, Postoperative':ti,ab,kw
29. 'Postoperative Periods':ti,ab,kw
30. 26 OR 27 OR 28 OR 29
31. 'Drug Therapy'/exp
32. 'Therapy, Drug':ti,ab,kw
33. 'Drug therapies':ti,ab,kw
34. 'Pharmacotherapy':ti,ab,kw
35. 'Pharmacotherapies':ti,ab,kw
36. 'Chemotherapy':ti,ab,kw
37. 31 OR 32 OR 33 OR 34 OR 35 OR 36
38. 25 AND 30 AND 37

ti, title; ab, abstract; kw, keywords.

1.4 Web of Science search strategy

1. Lung Adenocarcinoma Subject search
2. Lung Adenocarcinomas Subject search
3. Adenocarcinoma, Lung Subject search
4. Adenocarcinomas, Lung Subject search
5. Pulmonary Adenocarcinoma Subject search
6. Pulmonary Adenocarcinomas Subject search
7. Adenocarcinoma, Pulmonary Subject search
8. Adenocarcinomas, Pulmonary Subject search
9. Carcinoma, Non Small Cell Lung Subject search
10. Carcinoma*, Non-Small-Cell Lung Subject search
11. Lung Carcinoma*, Non-Small-Cell Subject search
12. Non-Small Cell Lung Carcinoma Subject search
13. Non-Small-Cell Lung Carcinomas Subject search
14. Nonsmall Cell Lung Cancer Subject search
15. Non-Small-Cell Lung Carcinoma Subject search
16. Non Small Cell Lung Carcinoma Subject search
17. Carcinoma, Non-Small Cell Lung Subject search
18. Non-Small Cell Lung Cancer Subject search
19. Non-Small Cell Lung Neoplasm Subject search
20. Non-Small Cell Lung Tumor Subject search
21. NSCLC Subject search
22. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. Postoperative Period Subject search
24. Period, Postoperative Subject search
25. Periods, Postoperative Subject search
26. Postoperative Periods Subject search
27. 23 OR 24 OR 25 OR 26
28. Drug Therapy Subject search
29. Therapy, Drug Subject search
30. Drug therapies Subject search
31. Pharmacotherapy Subject search
32. Pharmacotherapies Subject search
33. Chemotherapy Subject search
34. 28 OR 29 OR 30 OR 31 OR 32 OR 33
35. 22 AND 27 AND 34

1.5 Cochrane Library search strategy

1. Lung Adenocarcinoma: Title,Abstract,Keywords
2. Lung Adenocarcinomas: Title,Abstract,Keywords
3. Adenocarcinoma, Lung: Title,Abstract,Keywords
4. Adenocarcinomas, Lung: Title,Abstract,Keywords
5. Pulmonary Adenocarcinoma
6. Pulmonary Adenocarcinomas
7. Adenocarcinoma, Pulmonary
8. Adenocarcinomas, Pulmonary
9. 'Carcinoma, Non-Small-Cell Lung':Mesh
10. Carcinoma, Non Small Cell Lung: Title,Abstract,Keywords
11. Carcinoma*, Non-Small-Cell Lung: Title,Abstract,Keywords
12. Lung Carcinoma*, Non-Small-Cell: Title,Abstract,Keywords
13. Non-Small Cell Lung Carcinoma: Title,Abstract,Keywords
14. Non-Small-Cell Lung Carcinomas: Title,Abstract,Keywords
15. Nonsmall Cell Lung Cancer: Title,Abstract,Keywords
16. Non-Small-Cell Lung Carcinoma: Title,Abstract,Keywords
17. Non Small Cell Lung Carcinoma: Title,Abstract,Keywords
18. Carcinoma, Non-Small Cell Lung: Title,Abstract,Keywords
19. Non-Small Cell Lung Cancer: Title,Abstract,Keywords
20. Non-Small Cell Lung Neoplasm: Title,Abstract,Keywords
21. Non-Small Cell Lung Tumor: Title,Abstract,Keywords
22. NSCLC: Title,Abstract,Keywords
23. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. 'Postoperative Period' :Mesh
25. Period, Postoperative: Title,Abstract,Keywords
26. Periods, Postoperative: Title,Abstract,Keywords
27. Postoperative Periods: Title,Abstract,Keywords
28. 24 OR 25 OR 26 OR 27
29. 'Carcinoma, Non-Small-Cell Lung' :Mesh
30. Therapy, Drug: Title,Abstract,Keywords
31. Drug therapies: Title,Abstract,Keywords
32. Pharmacotherapy: Title,Abstract,Keywords
33. Pharmacotherapies: Title,Abstract,Keywords
34. chemotherapy: Title,Abstract,Keywords
35. 29 OR 30 OR 31 OR 32 OR 33 OR 34
36. 23 AND 28 AND 35

Table S2 Main characteristics of the included studies (n=12)

Characteristics	Number of studies (%)	Patients (%)
Total	12 (100.00)	15,678 (100.00)
Year of publication		
2008	1 (8.33)	134 (0.85)
2010	1 (8.33)	99 (0.63)
2016	1 (8.33)	10,587 (67.53)
2017	2 (16.67)	1,304 (8.32)
2018	4 (33.33)	1,875 (11.96)
2019	1 (8.33)	212 (1.35)
2020	2 (16.67)	1,467 (9.36)
Number of cases		
<300	4 (33.33)	585 (3.73)
≥300	8 (66.67)	15,093 (96.27)
Research region		
China	7 (58.33)	4,390 (28.00)
United States	3 (25.00)	10,820 (69.01)
Other	2 (16.67)	468 (2.99)
Histology type		
NSCLC	4 (33.33)	11,222 (71.58)
ADC	7 (58.33)	4,096 (26.13)
SCC	1 (8.33)	360 (2.30)
Follow-up period (month)		
<53	6 (50.00)	12,689 (80.94)
≥53	6 (50.00)	2,989 (19.06)
Study end points		
OS	11 (91.67)	14,702 (80.54)
DFS	9 (75.00)	3,552 (19.46)
Quality score		
<8	4 (33.33)	12,293 (78.41)
≥8	8 (66.67)	3,385 (21.59)

NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; OS, overall survival; DFS, disease-free survival.

Table S3 Quality assessment of the included studies (n=12)

No.	Author	Representativeness of population	Nonexposed cohort	Ascertainment of exposure	Outcome not present at start of study	Appropriate confounding measurement and account	Sufficient measurement of outcomes	Completeness of follow-up	Quality score
1	Morgensztern [2016]	0	1	1	1	2	1	1	7
2	Xu [2018]	0	1	1	1	2	1	2	8
3	Strauss [2008]	0	1	1	1	2	1	2	8
4	Qian [2017]	0	1	1	1	2	1	1	7
5	Butts [2010]	0	1	1	1	2	1	2	8
6	Wang [2018]	0	1	1	1	2	1	1	7
7	Wang [2019]	0	1	1	1	2	1	2	8
8	Chen [2020]	0	1	1	1	2	1	2	8
9	Jang [2017]	0	1	1	1	2	1	1	7
10	Ito [2020]	0	1	1	1	2	1	2	8
11	Cao [2018]	0	1	1	1	2	1	2	8
12	Chen [2018]	0	1	1	1	2	1	2	8

Table S4 The publication bias assessment with different tests for OS and DFS

Publication bias	Begg's P value	Egger's P value
OS	0.436	0.379
DFS	1.000	0.481

DFS, disease-free survival; OS, overall survival.

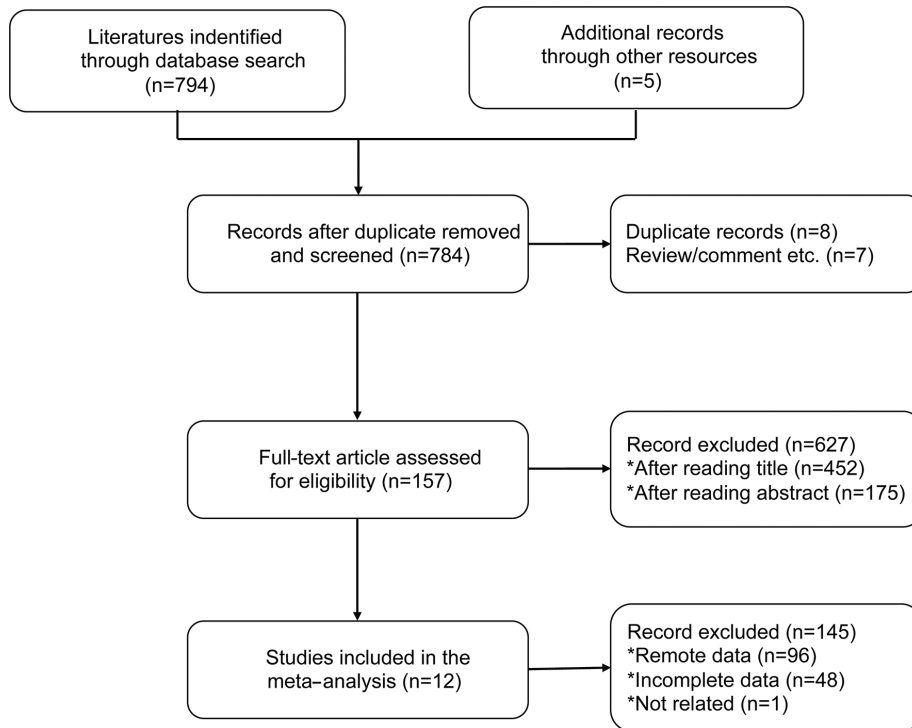


Figure S1 Literature Search of Eligible Studies.

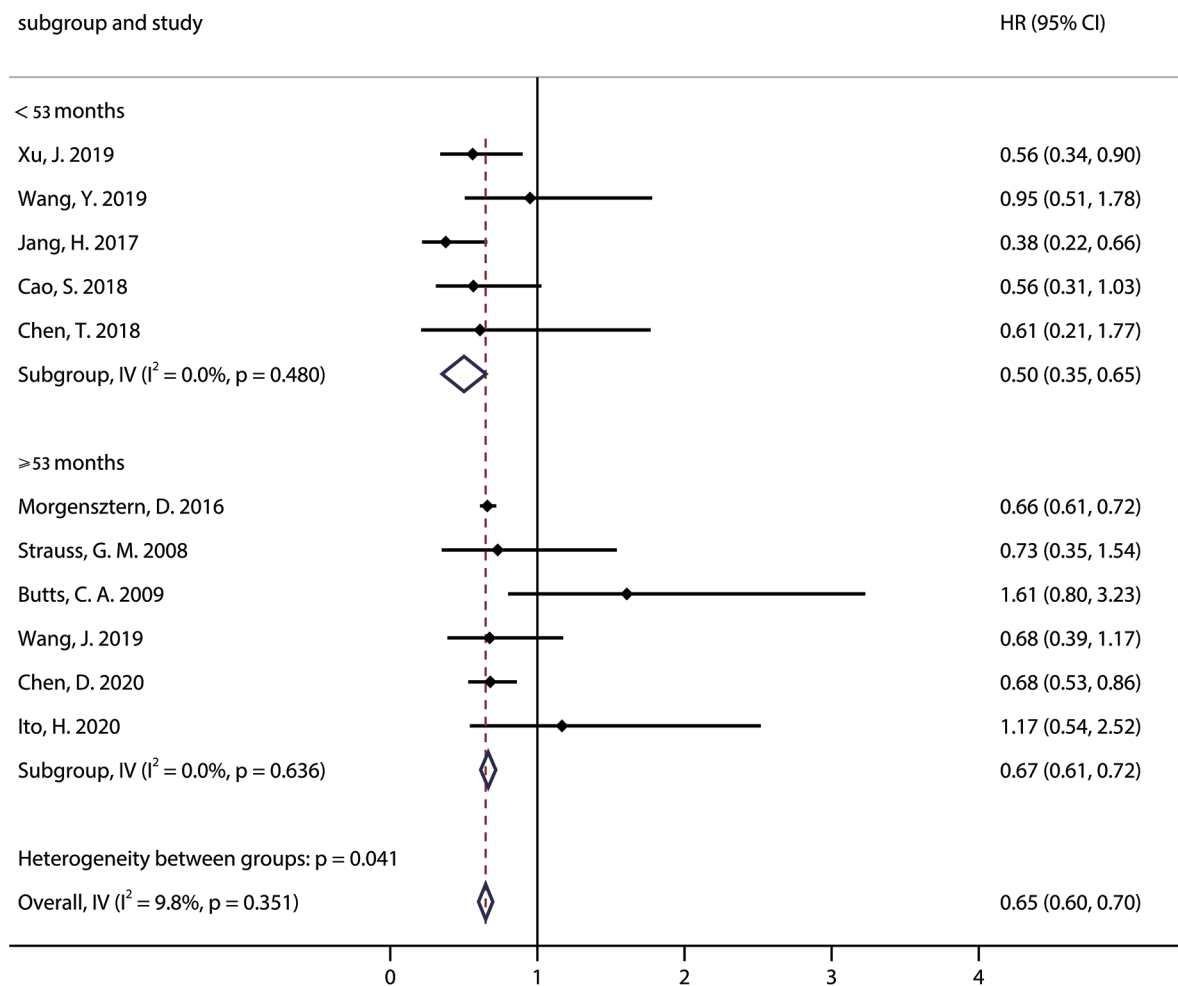


Figure S2 Subgroup Analyses of the Associations between Follow-Up Periods and Overall Survival (OS).