Original Article

# Comparing the benefits of postoperative adjuvant chemotherapy *vs.* observation for stage IB non-small cell lung cancer: a meta-analysis

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**Background:** The aim of this meta-analysis was to compare the benefits of postoperative adjuvant chemotherapy vs. observation for stage IB non-small cell lung cancer (NSCLC).

**Methods:** A literature search was performed in PubMed, Embase, and Cochrane Library databases, and stage IB NSCLC patients were assigned to the postoperative adjuvant chemotherapy and observation groups. The 5-year overall survival (OS), 5-year disease-free survival (DFS), local recurrence, and distant metastasis were then assessed. In addition, statistical analysis was conducted using Review Manager 5.3 software.

**Results:** The meta-analysis involved nine articles and included 1,645 stage IB patients. There was no significance in the 5-year OS [relative risk (RR) =1.05; 95% confidence interval (CI): 0.98–1.13; P=0.14] and 5-year DFS (RR =1.29; 95% CI: 0.97–1.72; P=0.08) between the postoperative adjuvant chemotherapy and observation groups. However, there was a significant difference in local recurrence (RR =0.43; 95% CI: 0.23–0.80; P=0.007) and distant metastasis (RR =0.68; 95% CI: 0.48–0.97; P=0.03) between the two groups.

**Conclusions:** Adjuvant chemotherapy might not be recommended for stage IB NSCLC.

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

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## Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 80% of the lung carcinoma cases (1). Treatments for NSCLC patients include surgery, chemotherapy, radiotherapy, and targeted therapy. Fortunately, a randomized controlled trial (RCT) has shown that resected NSCLC patients benefit from adjuvant chemotherapy (2). However, the use of postoperative adjuvant chemotherapy for stage IB NSCLC in the setting of standard therapy remains controversial (3).

Some previous studies have reported that stage IB NSCLC patients should be treated with adjuvant chemotherapy (4,5). In contrast, other studies reported that there was no benefit of postoperative adjuvant chemotherapy (6). Using different guidelines, the European Society for Medical Oncology Clinical Practice Guidelines (7) suggested that adjuvant chemotherapy could be considered for patients with resected stage IB disease. However, according to the National Comprehensive Cancer Network (NCCN) guidelines (8), there is a lack of a standard to precisely assign chemotherapy to stage IB NSCLC patients. Typical high-risk factors in stage IB NSCLC patients include poorly differentiated tumors, vascular invasion, wedge resection, tumor sizes

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>4 cm, visceral pleural infiltration, and incomplete lymph node sampling. However, independent indication may not be used as an effective standard, but should be used only as a reference factor. Based on different guidelines, the use of postoperative adjuvant chemotherapy for stage IB NSCLC patients is still controversial. A meta-analysis was therefore performed to quantify the prognostic differences between stage IB NSCLC patients with postoperative adjuvant chemotherapy *vs.* observation, which should provide more reliable and updated evidence to treat resected stage IB NSCLC patients.

## Methods

### *Literature search*

A systematic literature search was conducted for the following terms: "lung cancer" (MeSH Terms) AND "adjuvant chemotherapy" (MeSH Terms) AND "surgery" (MeSH Terms), and was used to achieve the maximum sensitivity in the electronic PubMed, Embase, and Cochrane Library databases from the earliest publications to June 2018.

### *Selection criteria*

The criteria for inclusion were as follows: (I) resected NSCLC patients who received adjuvant chemotherapy or observation were eligible for inclusion; (II) an accurate p-stage IB (T2N0M0) NSCLC based on the 6th (same as 5th edition) and 7th edition of the Union for International Cancer Control Tumor Node Metastasis classification; and (III) all articles were published in English. The following studies were excluded: (I) NSCLC patients who received preoperative or any other postoperative antitumor treatments; (II) case reports, expert opinions, abstracts, conference presentations, guidelines, reviews, and low quality studies (Grade C); (III) data which could not be extracted from the literature; and (IV) if repeated results were chosen, the study with the smallest sample was excluded.

### *Data extraction*

Data from eligible studies were independently extracted in a standardized manner by two inspectors (R Li and G Yang). The data extraction included the following: first author, research type, time of publication, numbers of patients with 5-year overall survival (OS), 5-year disease-free survival (DFS), local recurrence, and distant metastasis. Discrepancies in data extraction were resolved by consensus with a senior inspector (Y Tian), and the study design and critical review was provided by the senior investigator (D Tian).

### *Quality evaluation*

The Cochrane Collaboration's tool for assessing risk of bias was used in RCTs including seven areas of the project team. Each indicator was judged by using "low risk of bias" "high risk of bias", and "uncertain risk of bias". For each study, if the conditions of the study were consistent with the seven areas of the project team, the study was regarded as a high quality study (Grade A); if the conditions of the study were partially consistent with the project team, the study was regarded as a medium quality study (Grade B); and the study was regarded as a low quality study (Grade C) when there was little consistency with the seven areas of project team.

### *Statistical analysis*

All statistical analyses were conducted using Review Manager 5.3 software. The $I^2$ test was used to appraise the heterogeneity in the meta-analysis. If the heterogeneity was low ($I^2 \leq 50\%$), the fixed-effects model was used. Otherwise, the random-effects model was used ($I^2 > 50\%$). Sensitivity analyses and subgroup analyses were used to evaluate the sources of heterogeneity. The evaluation of publication bias was analyzed using the funnel plot, and differences were considered significant at a value of $P<0.05$.

## Results

A total of 3,885 potential articles were retrieved from electronic databases. Finally, a total of nine RCTs (9-17) (*Figure 1*, *Table 1*) were obtained. The meta-analysis involved 1,645 patients who were assigned to the adjuvant chemotherapy (n=820) and observation (n=825) groups. Included in the meta-analysis were nine studies describing the 5-year OS, five studies describing the 5-year DFS, and two studies describing local recurrence and distant metastasis.

### *The 5-year OS*

There was no significance in the 5-year OS [relative risk (RR) =1.05; 95% confidence interval (CI): 0.98–1.13; P=0.14] (*Figure 2*) between postoperative adjuvant chemotherapy versus observation. There was low heterogeneity, so the

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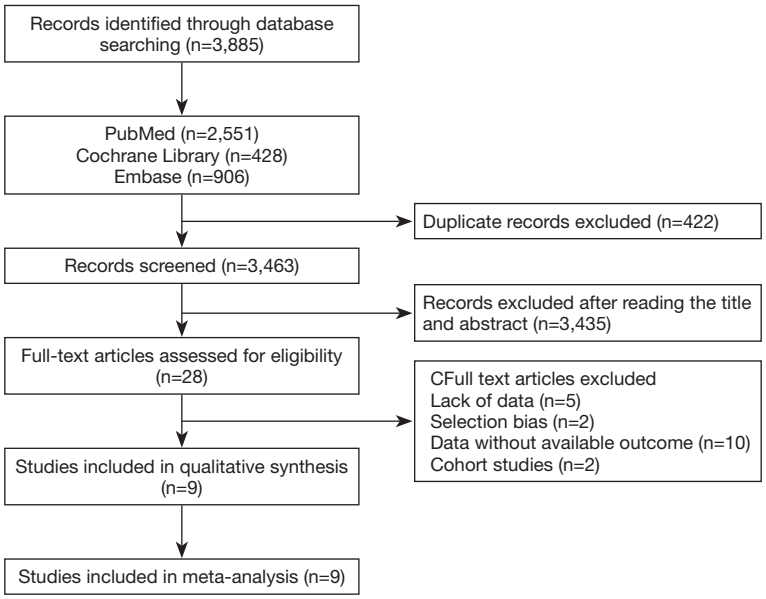


**Figure 1** Flow chart depicting the study selection and screening processes.

**Table 1** Characteristics of the included studies for the meta-analysis

| The study of stage IB | Year | Accrual year | Country | Study design | Postoperative adjuvant chemotherapy | Size | Outcome | Journal |
|---|---|---|---|---|---|---|---|---|
| Butts *et al.* (9) | 2010 | 1994–2001 | Canada | RCT | Cisplatin (50 mg/m$^2$) d1, d8, 4 weeks; vinorelbine (25 mg/m$^2$), weekly 16 weeks | 219 | 5-year OS | *Journal of Clinical Oncology* |
| Strauss *et al.* (10) | 2008 | 1996–2003 | USA | RCT | Paclitaxel (200 mg/m$^2$), carboplatin (AUC =6); every 3 weeks | 344 | 5-year OS; 5-year DFS | *Journal of Clinical Oncology* |
| Douillard *et al.* (11) | 2006 | 1994–2000 | France | RCT | Vinorelbine (30 mg/m$^2$), cisplatin (100 mg/m$^2$); every 4 weeks | 301 | 5-year OS | *Lancet Oncology* |
| Roselli *et al.* (12) | 2006 | 1988–1994 | Italy | RCT | Cisplatin (100 mg/m$^2$) d1, etoposide (120 mg/m$^2$) d1, 2, 3; every 4 weeks | 140 | 5-year OS; 5-year DFS; local recurrence; distant metastasis | *International Journal of Cancer* |
| Park *et al.* (13) | 2005 | 1989–1998 | Korea | RCT | Mitomycin C (10 mg/m$^2$) d1, vinblastine (6 mg/m$^2$) d1, cisplatin (100 mg/m$^2$) d1–d5; every 3 weeks | 97 | 5-year OS; 5-year DFS | *European Journal of Cardio-thoracic Surgery* |
| Nakagawa *et al.* (14) | 2005 | 1992–1994 | Japan | RCT | Uracil and tegafur 400 mg/d | 111 | 5-year OS | *Annals of Oncology* |
| Kato *et al.* (15) | 2004 | 1994–1997 | Japan | RCT | Uracil and tegafur 250 mg twice a day | 263 | 5-year OS; 5-year DFS | *The New England journal of Medline* |
| Waller *et al.* (16) | 2004 | 1995–2001 | UK | RCT | Cisplatin (50 mg/m$^2$), mitomycin (6 mg/m$^2$), ifosfamide (3 g/m$^2$); vinblastine (6 mg/m$^2$); cisplatin (50 mg/m$^2$), vindesine (3 mg/m$^2$), vinorelbine (30 mg/m$^2$); 3 weeks | 103 | 5-year OS | *European Journal of Cardio-thoracic Surgery* |
| Mineo *et al.* (17) | 2001 | 1988–1994 | Italy | RCT | Cisplatin (CDDP) (100 mg/m$^2$) given on day 1 and etoposide (VP16) (120 mg/m$^2$) administered on days 1–3; every 4 weeks | 66 | 5-year OS; 5-year DFS; local recurrence; distant metastasis | *European Journal of Cardio-thoracic Surgery* |

RCT, randomized controlled trial.

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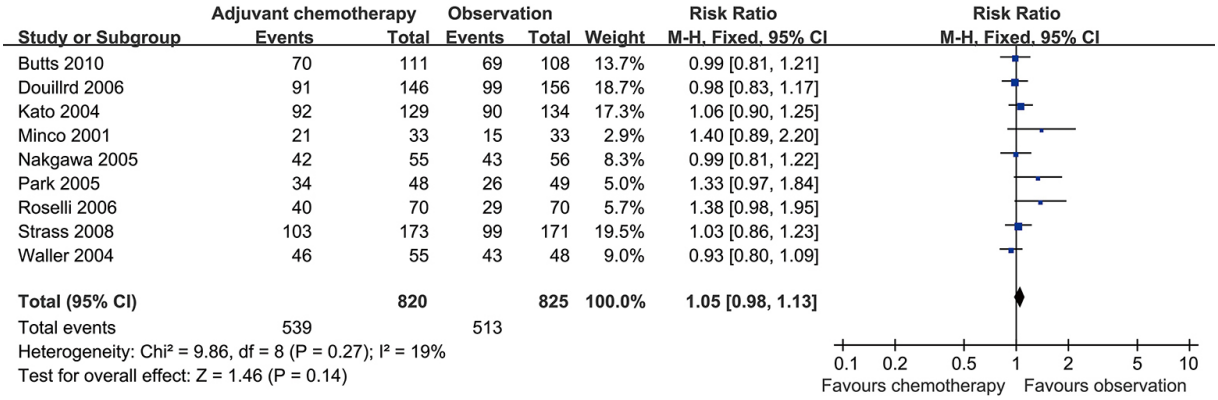


**Figure 2** Forest plot of the 5-year OS associated with adjuvant chemotherapy compared with observations of stage IB NSCLC patients. OS, overall survival; NSCLC, non-small cell lung cancer.

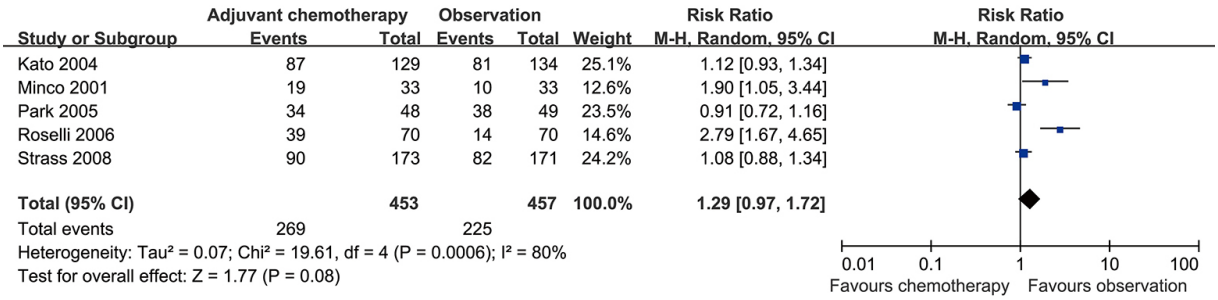


**Figure 3** Forest plot of the 5-year DFS associated with adjuvant chemotherapy compared with observation of stage IB NSCLC patients. DFS, disease-free survival; NSCLC, non-small cell lung cancer.

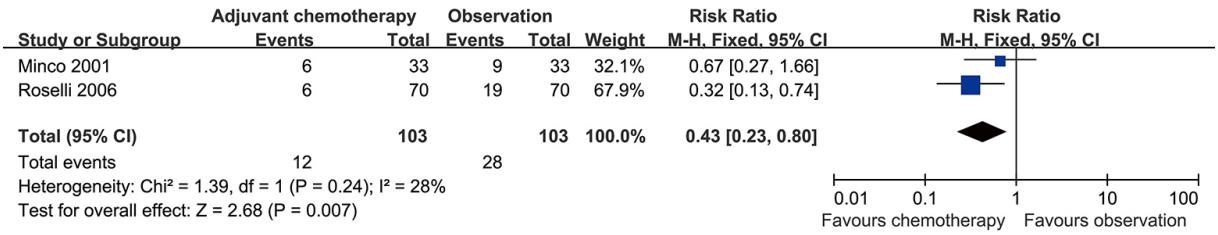


**Figure 4** Forest plot of local recurrence associated with adjuvant chemotherapy compared with observation in stage IB NSCLC patients. NSCLC, non-small cell lung cancer.

fixed-effects model was used.

### *Five-year DFS*

There was no significant difference in the 5-year DFS (RR =1.29; 95% CI: 0.97–1.72; $I^2$ =80%; P=0.08) (*Figure 3*) between postoperative adjuvant chemotherapy versus observation, and there was substantial heterogeneity, so the random-effects model was used.

### *Local recurrence*

There was a significant difference in the local recurrence (RR =0.43; 95% CI: 0.23–0.80; $I^2$ =28%; P=0.007) (*Figure 4*) between the postoperative adjuvant chemotherapy and observation groups, and there was low heterogeneity, so the

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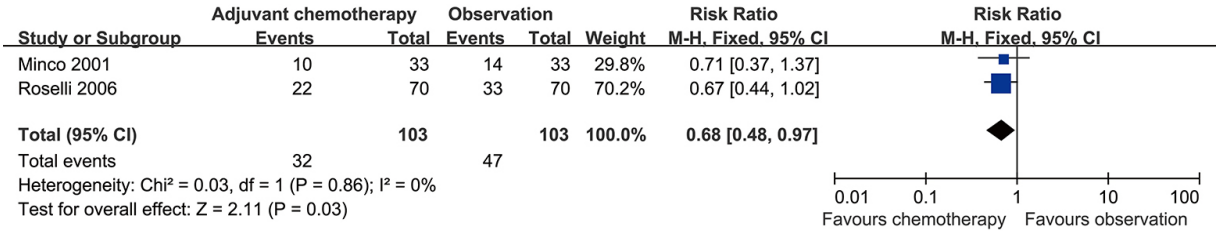


**Figure 5** Forest plot of distant metastasis associated with adjuvant chemotherapy compared with observation in stage IB NSCLC patients. NSCLC, non-small cell lung cancer.

**Table 2** The risk of bias analysis of the included RCTs

| Study | A | B | C | D | E | F | G | Grade |
|---|---|---|---|---|---|---|---|---|
| Butts *et al.* (9) | + | + | + | ? | + | + | ? | B |
| Strauss *et al.* (10) | + | + | + | ? | + | + | – | B |
| Douillard *et al.* (11) | + | + | + | + | + | + | + | A |
| Roselli *et al.* (12) | + | + | + | + | + | + | ? | A |
| Park *et al.* (13) | + | + | + | + | – | + | ? | B |
| Nakagawa *et al.* (14) | + | + | + | ? | + | + | ? | B |
| Kato *et al.* (15) | + | + | + | + | – | + | ? | B |
| Waller *et al.* (16) | + | + | + | + | + | ? | ? | B |
| Mineo *et al.* (17) | + | + | + | + | ? | ? | ? | B |

A, random sequence generation; B, allocation concealment; C, blinding of participants and personnel; D, blinding of outcome assessment; E, incomplete outcome data; F, selective reporting; G, other bias; +, low risk of bias; –, high risk of bias; ?, uncertain risk of bias. RCT, randomized controlled trial.

fixed-effects model was used.

### *Distant metastasis*

Distant metastasis (RR =0.68; 95% CI: 0.48–0.97; $I^2$ =0%; P=0.03) (*Figure 5*) was significantly different in the postoperative adjuvant chemotherapy *vs.* observation groups, and as there was low heterogeneity, so the fixed-effects model was used.

### *The analysis of methodological quality*

The Cochrane Collaboration's tool was used for RCTs (*Table 2*).

### *The analysis of sensitivity analysis and publication bias*

The sensitivity test was conducted by successively excluding individual studies and recalculating the consequences. However, the source of heterogeneity was not confirmed by using sensitivity analysis in the analysis of the 5-year DFS. The evaluation of publication bias was analyzed by the funnel plot, which was an asymmetrical funnel diagram when the data were biased. The analysis showed that multiple points were evenly distributed on both sides of the longitudinal axis, so there was no obvious publication bias (*Figure 6*).

## Discussion

According to NCCN guidelines, the value of adjuvant chemotherapy has been proven by multiple large randomized trials for resected stage II and IIIA NSCLC patients, but the role of adjuvant chemotherapy is controversial for stage IB patients. The objective of this meta-analysis was therefore to assess the therapeutic effect of adjuvant chemotherapy *vs.* observation on resected stage IB NSCLC patients. The data included the 5-year OS, 5-year DFS, local recurrence, and distant metastasis.

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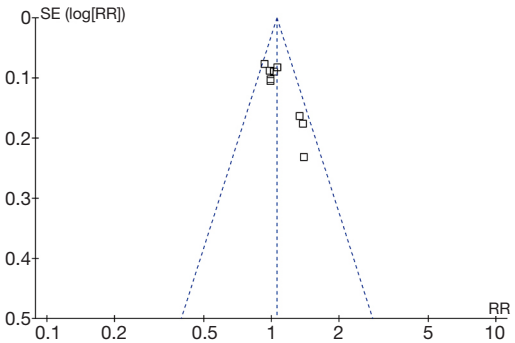


**Figure 6** Funnel plot for nine RCTs associated with adjuvant chemotherapy compared with observation in stage IB NSCLC patients. RCT, randomized controlled trial; NSCLC, non-small cell lung cancer.

We found two positive retrospective studies (18,19), which were designed specifically for stage IB NSCLC patients; both recommended adjuvant chemotherapy for these patients. However, the use of non-randomized studies was of minimal value and the results of these studies were more relevant to high risk stage IB NSCLC patients. Although impressive, the small sample size and the large effect size prompted questions about the reproducibility of these findings. Because they might cause selection bias and reduce the scientific strength of the meta-analysis, we excluded these two retrospective studies. Nine RCTs, including the 5-year OS and seven RCTs, including the 5-year DFS were finally included. Three studies in the 5-year OS and two studies in the 5-year DFS supported efficacy for adjuvant chemotherapy in stage IB NSCLC patients, but these originated from small RCTs. Conversely, other RCTs did not indicate a clear benefit of adjuvant chemotherapy. The meta-analysis found updated results showing no significance in the 5-year OS, including 1,645 patients and a 5-year DFS, by comparing 910 patients involved in postoperative adjuvant chemotherapy and observation. Obviously, adjuvant chemotherapy is not recommended as a standard of therapy in stage IB NSCLC patients. The outcome was consistent with NCCN guidelines, which indicated a lack of an effective standard to precisely assign chemotherapy to stage IB NSCLC patients.

Remarkably, based on the results of previous meta-analyses, Burdett *et al.* (20) reported that platinum-based adjuvant chemotherapy in patients with stage IB tumors was similar to estimates for patients with stage II and III tumors. However, it was found that the relative effect of adjuvant chemotherapy did not differ significantly by stage in their meta-analysis. Although application of the overall hazard ratio to survival in the control group by stage suggested absolute improvements in 5-year survival of 5% of the patients with stage IB (from 55% to 60%), there were no significance between postoperative adjuvant chemotherapy and observation in stage IB NSCLC patients. These results differed from our conclusion, which might be explained by the eligibility criteria for inclusion involved in the p-stage I to IV disease in the previous meta-analysis. However, the criteria for inclusion in our meta-analysis was p-stage IB (T2N0M0) NSCLC, so it was a more targeted analysis.

Two RCTs described data of local recurrence and distant metastasis. The results showed that stage IB NSCLC patients might receive a benefit from adjuvant chemotherapy to reduce risks of local recurrence and distant metastasis after surgery. It might be interpreted that the value of postoperative adjuvant chemotherapy could reduce risks of recessive micrometastases (tumor cell deposition in the lymph tissue of 1/6 of the patients deposited at 0.2–2 mm), which might generate recurrence or metastasis after tumor resection (21). However, more attention should be directed to the fact that only 206 patients were included in local recurrence and distant metastasis in the meta-analysis, and the number of positive events was small. These results might be influenced by sample number in the meta-analysis. Although we concluded a positive result, there was not enough evidence to recommend adjuvant chemotherapy for stage IB patients, so we expect that additional RCTs will contribute more reliable results to assess whether adjuvant chemotherapy clearly reduces the risks of local recurrence and distant metastasis.

In addition, Strauss recommend considering patients with stage IB disease and larger tumors (≥4 cm) for cisplatin-based adjuvant chemotherapy on an individualized basis. In previous studies, there has been controversy about the effect of adjuvant chemotherapy for stage IB NSCLC patients with 4 cm tumor sizes (22,23). However, there is currently insufficient data concerning stage IB and tumor size, and the size of tumors is outside of the objectives of our meta-analysis, so we will evaluate the effect of adjuvant chemotherapy for stage IB tumor size in the future.

Our meta-analysis had several limitations. There was a limitation of sample size in the study. In addition, the patients' individual data included sex, age, smoking, type of pathology, differentiation, tumor size, type of chemotherapy, tumor marker, and drug toxicity. If the data were available, we might perform a more comprehensive guideline study for stage IB NSCLC patients in the future

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and could find the sources of heterogeneity.

## Conclusions

The 5-year OS and 5-year DFS of stage IB NSCLC patients were not improved by adjuvant chemotherapy. In addition, there was not enough evidence to show that adjuvant chemotherapy reduced the risks of local recurrence and distant metastasis after surgery, because these results might be influenced by sample size in the meta-analysis. In conclusion, adjuvant chemotherapy might not be recommended for stage IB NSCLC patients.

## Acknowledgments

We would like to thank Dali Tian, at The Fourth Affiliated Hospital of China Medical, for study design and critical review.

## Footnote

*Conflicts of Interest:* 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. All data in this study were obtained from databases, so ethical approval and informed consent are not required.

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