Systematic Review and Meta-Analysis

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S-1 plus cisplatin with concurrent radiotherapy for stage III non-small cell lung cancer

A meta-analysis (PRISMA) of randomized control trials

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Abstract

Introduction: The present study aims to assess the efficacy and safety of S-1 plus cisplatin as concurrent chemoradiation (experimental group [EG]) compared with standard concurrent chemoradiation regimens (control group[CG]) in patients with local advanced non-small cell lung cancer.

Methods: The Cochrane library, pubmed, and Ovid (elsevier) were retrieved. The included randomized controlled trials (RCT) were evaluated, and the statistical analysis was performed using RevMan 5.3 software. Cochrane handbook was applied to evaluate the methodological quality. Statistical significance was considered as $P < .05$.

Results: There were 5 randomized control trials identified eligible for the meta-analysis. Meta-analysis of the pooled date suggested that overall survival (OS) (HR, 0.81; 95% CI, 0.58–1.13; $P = .21$, heterogeneity $P = 1.00$, $I^2 = 0\%$), progressives free survival (PFS) (HR, 0.82; 95% CI, 0.62–1.09; $P = .18$, heterogeneity $P = .83$, $I^2 = 0\%$) and 1,2,3-year OS (1-year OS: RR 1.03; 95% CI: 0.92–1.15, p = 0.59), (2-year OS: RR 1.14; 95% CI: 0.98–1.34, $P = .09$), (3 -year OS: RR 1.14; 95% CI: 0.90–1.44, $P = .29$) were not significantly different. The combination of S-1 and cisplatin had lower grade 3 or 4 leukocytopenia, neutropenia, (RR = 0.54, 95% CI: 0.38–0.75, $P = .0003$; RR = 0.23,95% CI: 0.14–0.36, $P < .00001$;, respectively). The rates of nausea, diarrhea, thrombocytopenia, pneumonitis, anorexia, anemia, febrile neutropenia were much the same in the 2 groups (RR = 1.35, 95% CI: 0.68–2.68, $P = .38$; RR = 1.85, 95% CI: 0.61–5.60, $P = .28$; RR = 1.67, 95% CI: 0.88–3.17, $P = .12$; RR = 1.19, 95% CI: 0.44–3.21, $P = .73$; RR = 1.35, 95% CI: 0.68–2.68, $P = .38$; RR = 0.86, 95% CI:0.55–1.34, $P = .50$; RR = 0.63, 95% CI:0.35–1.14, $P = .13$;, respectively).

Conclusions: This meta-analysis of 5 randomized control trails demonstrates that EG results similar OS, PFS, and 1,2,3-year OS, compared with CG, with lower risk of leukocytopenia, neutropenia.

Abbreviations: CG = control group, EG = experimental group, OS = overall survival, PFS = progressives free survival.

Keywords: concurrent chemoradiation, meta-analysis, non-small cell lung cancer, radiotherapy, S-1

1. Introduction

The incidence of lung cancer is the first among male tumors, and the prognosis is poor due to early diagnosis. According to statistics released in 2017, the number of newly diagnosed lung cancer in 2017 is 222,500 and the death toll from lung cancer is 155,870.[1] A large number of studies have shown that smoking is the leading cause of increased mortality in lung cancer. The WHO classification of anatomical sites can be divided into central and peripheral lung cancer. There are 2 main types based on biology and treatment: small cell lung cancer and non-small cell lung cancer.[2] In current, the treatment model of stage III non-small cell lung cancer is the most controversial. For patients with inoperable IIIA or IIIB, chemotherapy combined radiotherapy is better than radiotherapy alone.[3] Concurrent chemoradiation is superior to sequential therapy.[4,5] Cisplatin combined with etoposide, cisplatin combined with vincristine and carboplatin combined with paclitaxel are recommended by NCCN guidelines for the concurrent chemoradiation for all histological types of non-small cell lung cancer.[6–9] However, these synchronization schemes can result in grade 3 or 4 esophagitis and hematological toxicity. The choice of treatment modalities should not only be based on expectant treatment responses, but also on the tolerance level of patients receiving treatment. Weak patients may not tolerate concurrent chemoradiation. Therefore, there is still a lot of room to improve the concurrent chemoradiation regimen with locally advanced non-small cell lung cancer. Therefore, the aim of this study is to evaluate the therapeutic effect and toxicity of S-1 plus cisplatin with concurrent radiotherapy in the treatment local advanced non-small cell lung cancer.

Recent years, S-1 has been widely used in the concurrent chemoradiation of various malignant tumors. A phase II trial proved promising efficacy with acceptable toxicities of chemoradiation concurrent with S-1 combined cisplatin in patients with locally advanced squamous cell carcinoma of the head and

Editor: Yuzuru Niibe.

SQ and YL contributed equally to this work.

The authors report no conflicts of interest.

The authors declare that they have no competing interests.

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Medicine (2018) 97:50(e13441)

Received: 17 June 2018 / Accepted: 5 November 2018

http://dx.doi.org/10.1097/MD.0000000000013441

neck.[10] In this review, S-1 plus thoracic irradiation could improve the efficacy of patients with non-metastatic esophageal squamous cell carcinoma and prolong their survival time without significantly increasing the acute adverse reaction of simple radiotherapy.[11] The addition of S-1 concurrent chemoradiation in patients with local advanced pancreatic cancer has an acceptable toxic reaction and efficacy.[12] Kim assessed efficacy and toxicities of S-1-based concurrent chemoradiation patients with advanced biliary tract cancer. The results showed that S-1-based regimen was feasible and tolerable.[13] There are more and more studies on the use of s-1 in the concurrent chemoradiation for non-small cell lung cancer, especially with many high quality randomized controlled trials.

The results of some published clinical studies are controversial. Here, our study is to assess the therapeutic effect and the adverse event of S-1 plus cisplatin with concurrent radiotherapy for local advanced (stage III) non-small cell lung cancer by meta-analysis, relevant indices such as overall survival (OS), progressives free survival (PFS), 1,2,3-year OS, and toxicities to provide guidelines for clinical decisions and further researches.

2. Methods

All analyses were based on previously published studies, thus no ethical approval and patient consent are required.

2.1. Search strategy

We searched all published articles in the Embase and Pubmed databases between January, 1996 and February, 2018, and also searched the Cochrane Library databases with keywords: ((S-1 [Title/Abstract]) or TS-1[Title/Abstract]))AND ((Non-small Cell Lung Cancer[MeSH Terms]) or (Carcinoma, Non Small Cell Lung) or (Carcinomas, Non-Small-Cell Lung) or (Lung Carcinoma, Non-Small-Cell) or (Lung Carcinomas, Non-Small-Cell) or (Non-Small-Cell Lung Carcinomas) or (Nonsmall Cell Lung Cancer) or (Non-Small-Cell Lung Carcinoma) or (Non Small Cell Lung Carcinoma) or Carcinoma, Non-Small Cell Lung) or (Non-Small Cell Lung Cancer)).

2.2. Study selection

Only English-language literature were included. First, the selection was conducted by screening abstracts and titles, followed by perusing the full articles. Selecting all trails was conducted independently by 2 reviewers using the exclusion and inclusion criteria. A third reviewer was invited to determine when there were disagreements on whether an article should be included.

2.3. Inclusion and exclusion criteria

About patients: Inclusion criteria: all patients were histologically or pathologically confirmed locally advanced non-small cell lung cancer, including thorax computed tomography (CT) scan. Exclusion criteria: Except for patients with malignant pleural effusion, malignant peritoneal effusion, malignant pericardial effusion, and serious complications.

About study design and comparison: inclusion criteria: randomized controlled trial (RCT) of S-1-based or S-1 monotherapy concurrent chemoradiation regimens versus standard concurrent chemoradiation regimens. Exclusion criteria: cohort study, case report, reviews, letters, and low-quality clinical research were excluded. The study of unreported standard deviation, confidence interval, HR, 95% CI, and *P* value were excluded.

About outcome measurements: The included study reported PFS, OS, 1,2,3-year OS, and grade 3 or 4 toxicities. Our analysis complied with the guidelines reported as the PRISMA statement.

2.4. Quality assessment

The Cochrane handbook was used to evaluate the study quality. The literature quality evaluation includes method of randomization, allocation concealment, blingding, result data integrity, results of selective reporting and other sources of bias. (Figs. 1 and 2)

2.5. Data extraction

Two authors extracted the data from 4 eligible trails. A third reviewer made a final determination when not uniform. The following data of all eligible trials were extracted: name of the first author, trial phase, publication year, type of study, number of enrolled patients, sex ratio, average ages, patients' performance status, outcomes, and interventions.

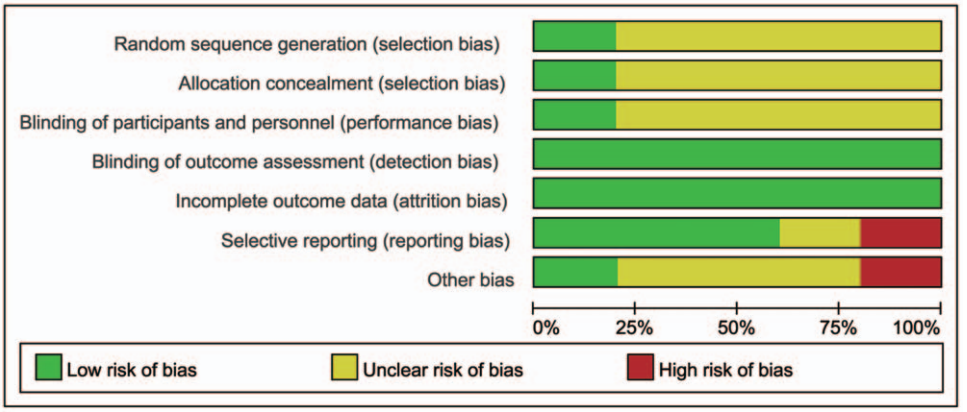

Figure 1. Risk of bias graph.

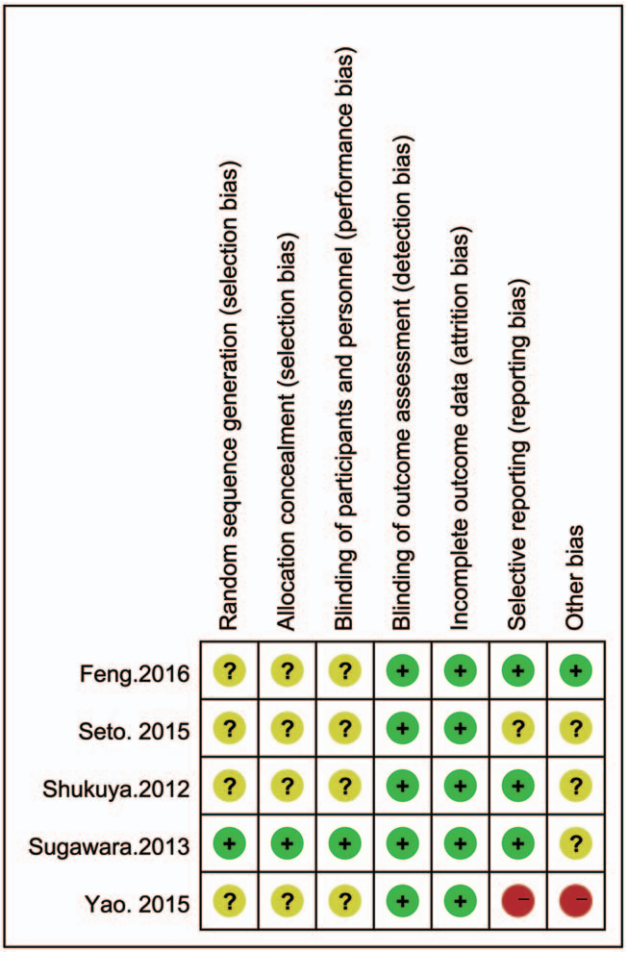

Figure 2. Risk of bias summary. +: low risk of bias; −: high risk of bias; ?: unclear risk of bias.

2.6. Outcome definition

Median OS, PFS, 1,2,3-year OS, and toxicities were the results of interest for our meta-analysis. Adverse reactions were assessed for all patients receiving any treatment. The criteria for assessing toxicity is the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0.

2.7. Statistical analysis

Heterogeneity was conducted using I^2 tests, and no heterogeneity was regard when $P > .1$ and $I^2 < 50\%$ with a fixed-effect statistical model, whereas a random-effect model was applied. The statistical significance was considered as $P < .05$. Our statistical analyses in this analysis were made by Revman 5.3.

3. Results

3.1. Selection of trails

Two hundred twelve studies were identified in all. Of the results, only 5 randomized control trials were included in this analysis by filtering title, abstracts and the full article (Fig. 3). All the patients in the group were divided into favorable prognosis group and unfavorable prognosis group, and the evaluation indexes were all PFS, OS, 1,2,3-year OS, and toxic effects.

3.2. General characteristics

The identified trails are shown in Table 1. All studies were conducted in Japan and China. The 5 trails were phase II or III randomized controlled trials that evaluated the therapeutic efficacy and toxicities of S-1-based or S-1 monotherapy concurrent regimens and standard concurrent chemoradiation regimens. A total of 377 patients were included in the present meta-analysis, with 185 patients undergoing S-1-based or S-1 monotherapy concurrent regimens and 192 patients undergoing standard concurrent chemoradiation regimens. The therapeutic efficacy outcomes included the OS, PFS, 1,2,3-year OS, and adverse events. The studies conducted by Yao and Feng[14,15] were phase II randomized comparisons of S-1 plus cisplatin with cisplatin monotherapy regimen with stage III NSCLC. Shukuya, Sugawara and Seto,[16–18] all randomized phase II studies, reported that comparisons of S-1 plus cisplatin with vinorelbine plus cisplatin regimen with local advanced NSCLC.

3.3. Results of meta-analysis

3.3.1. OS. In the fixed effects models, the analysis of OS showed no significant difference between experimental group (EG) and control group (CG). (HR, 0.81; 95% CI, 0.58–1.13; $P = .21$, heterogeneity $P = 1.00$, $I^2 = 0\%$). (Fig. 4A)

3.3.2. PFS. Pooling data from included studies revealed no significant difference in PFS between EG and CG (HR, 0.82; 95% CI, 0.62–1.09; $P = .18$, heterogeneity $P = .83$, $I^2 = 0\%$). (Fig. 4B)

3.3.3. 1,2,3-year OS. Meta-analysis for 1,2,3-year OS revealed no significant difference between the treatments(1-year OS: RR 1.03; 95% CI: 0.92–1.15, $P = .59$; Fig. 4C), (2-year OS: RR 1.14; 95% CI: 0.98–1.34, $P = .09$; Fig. 4D), (3-year OS: RR 1.14; 95% CI: 0.90–1.44, $P = .29$; Fig. 4E).

3.3.4. Grade 3 or 4 late toxicities. Grade 3 or 4 late toxicities are shown in Table 2. The meta-analysis demonstrated that there was no difference in the treatments in the incidence of grade 3 or 4 nausea, diarrhea, thrombocytopenia, pneumonitis, anorexia, anemia and febrile neutropenia. The RR was 1.35 (95% CI: 0.68–2.68, $P = .38$) for nausea, 1.85 (95% CI: 0.61–5.60, $P = .28$) for diarrhea, 1.67 (95% CI: 0.88–3.17, $P = .12$) for thrombocytopenia, 1.19 (95% CI: 0.44–3.21, $P = .73$) for pneumonitis and 1.35 (95% CI: 0.68–2.68, $P = .38$) for anorexia, 0.86 (95% CI: 0.55–1.34, $P = .50$) for anemia, 0.63 (95% CI: 0.35–1.14) for febrile neutropenia respectively. The results showed that the rates of grade 3 or 4 leukocytopenia, neutropenia, in EG were significantly lower than that with CG (RR = 0.54, 95% CI: 0.38–0.75, $P = .0003$; RR = 0.23,95% CI: 0.14–0.36, $P < .00001$; respectively).

3.4. Subgroup analysis

We also did subgroup analysis due to the heterogeneity of neutropenia (heterogeneity: $P = .02$; $I^2 = 66\%$) and leukocytopenia (heterogeneity: $P = .05$; $I^2 = 62\%$). In the subgroup of compared with cisplatin monotherapy, there was no significant difference in both neutropenia (Fig. 5A) (RR = 1.00, 95% CI: 0.43–2.33, $P = 1.00$) and leukocytopenia (Fig. 5B) (RR = 1.30, 95% CI: 0.62–2.71, $P = .48$). While compared with the subgroup of vinorelbine plus cisplatin, the incidence of neutropenia (RR = 0.38, 95% CI: 0.28–0.51, $P < .00001$) and leukocytopenia (RR = 0.39, 95% CI: 0.26–0.59, $P < .00001$) was significantly lower in

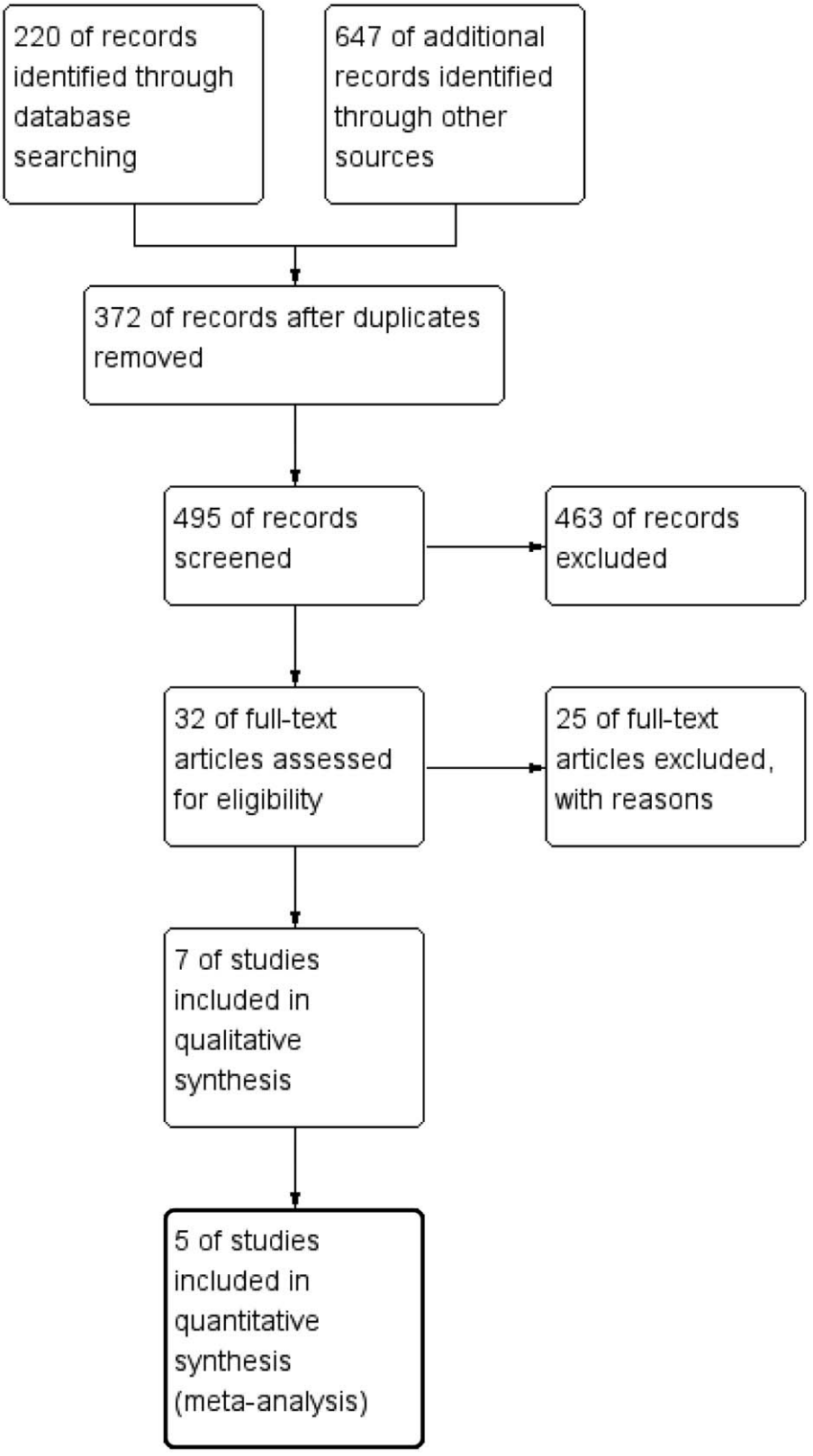

Figure 3. Flowchart of the study selection.

S-1-based concurrent chemoradiation group. We also found that in the both subgroups, the heterogeneity analysis provided an I^2 value that was equal to 0%, which demonstrated no statistical heterogeneity.

3.5. Publication bias

In this study, the funnel plot (Fig. 6), based on OS, was drawn with the LogHR as the vertical axis and HR value as the x-coordinate. When the funnel map is not symmetric, it indicates

Table 1

The characteristics of the studies included.

Trail	Patients enrolled	Gender M/F	PS	Interventions
Shukuya. 2012	Arm A 39 Arm B 50	Arm A 34/5 Arm B 37/13	0–1	Arm A: S-1 (p.o.q.d.40 mg/m^2, on days 1–14), cisplatin (60mg/m^2, on day 1). Arm B: Vinorelbine (20 mg/m^2, on days 1 and 8), cisplatin (80mg/m^2, on day 1). The treatment cycles in both arms were repeated every 4 weeks for a maximum of four cycles concurrent with radiotherapy.
Sugawara. 2013	Arm A 35 Arm B 31	Arm A 28/7 Arm B 26/5	0–1	Arm A: Cisplatin (80 mg/m^2 on days 8 and 36), UFT (p.o. 400 mg/m^2, on days 1–14 and 29–42). Arm B: Vinorelbine (20 mg/m^2) on days 1, 8, 29, and 36 and cisplatin (80 mg/m^2) on days 1 and 29. The schedule of concurrent thoracic radiotherapy was 60Gy in 30 fractions.
Seto. 2015	Arm A 55 Arm B 55	Arm A NG Arm B NG	0–1	Arm A: S-1 (40 mg/m^2/dose per oral, b.i.d, on days 1–14) and cisplatin (60 mg/m^2 on day 1) repeated every 4 weeks). Arm B: vinorelbine (20mg/m^2 on days 1, 8) and cisplatin (80 mg/m^{2}on day) repeated every 4 weeks. The schedule of concurrent thoracic radiotherapy was 60Gy in 30 fractions.
Yao. 2015	Arm A 20 Arm B 20	Arm A 15/5 Arm A 14/6	0–1	Arm A: Cisplatin (60 mg/m^2 on day1, every 4 weeks for 2 cycles), S-1 (p.o.b.i.d. 40 mg/m^2, on days1–14). Arm B: Cisplatin (60 mg/m^2 on day1, every 4 weeks for 2 cycles). Both arms received radiotherapy concurrently
Feng. 2016	Arm A 36 Arm B 36	Arm A 24/12 Arm A 21/15	0–1	Arm A: Cisplatin (60 mg/m^2 on day1 followed by at 4-week intervals), S-1 (p.o.b.i.d. 40 mg/m^2, on days1–14). Arm B: Cisplatin (60 mg/m^2 on day1 followed by at 4-week intervals). Both arms received radiotherapy concurrently

that there is a bias. In this study, the distribution of scattered points in the literature was distributed on both sides of the line, and the overall distribution was relatively uniform, indicating that the publication bias of the study was relatively small.

4. Discussion

NSCLC accounts for 85% of all lung cancers, about a quarter of which are locally advanced. Concurrent chemoradiation is standard treatment. Compared with sequential chemoradiation, concurrent chemoradiation can significantly reduce the risk of death and prolong the total survival of patients. However, there has been no international agreement on the best chemotherapy regimen for radiotherapy. Two of the most commonly used regimens for concurrent chemoradiation are EP and PC. The former regimen is more commonly in Europe, and it can be full dose combined with radiotherapy, which is relatively convenient and economical. The latter is widely used in the United States, and it is one of the standard protocols for the patients with chemotherapy alone. The synchronous chemotherapy regimens for all histologies recommend by NCCN guidelines were cisplatin/etoposide, cisplatin/vinblastine, and carboplatin/paclitaxel. However, the rates of grade 3 or 4 esophagitis and bone marrow suppression are much higher in concurrent chemoradiation group than that in sequential chemoradiation group.[4,7,8]

In recent years, a number of clinical randomized controlled trials on S-1 based synchronous chemotherapy, as a new option, have been published. Because some of the results are controversial, clinical question of the efficiency and safety of local advanced NSCLC patients based on S-1 based synchronous chemotherapy was unclear. Many high-quality clinical trials evaluated the therapeutic effect and toxicity of S-1 concurrent chemoradiation. Seto,[18] Sugawara[17] and Shukuya[16] all compared the efficacy and safety of S-1 plus cisplatin to vinorelbine plus cisplatin with synchronous chemoradiation for inoperable locally advanced non-small cell lung cancer. Yao[14] and Feng[15] compared the therapeutic efficacy of S-1 plus cisplatin to cisplatin monotherapy. These trails were all included in the present meta-analysis.

To the best of our knowledge, the present study is the most updated meta-analysis to evaluate the therapeutic effect of S-1 based synchronous chemotherapy on RCTs in patients with local advanced of non-small cell lung cancer. The present meta-analysis included 5 randomized control trails assessing S-1 plus cisplatin as concurrent chemoradiation. The result of this meta-analysis demonstrated that S-1 plus cisplatin as concurrent chemoradiation had no significant advantage on OS, PFS, 1,2 and 3-year OS. Notably, OS and PFS were statistically significant in the trails conducted by Yao and Feng. Yao showed that OS and PFS in S-1 plus cisplatin with concurrent thoracic radiation group were 33 months ($P=.048$) and 31 months ($P=.037$), respectively. Feng compared S-1 plus cisplatin with cisplatin monotherapy in terms of OS and PFS, and OS was 35.1 months and 24.6 months for the S-1 plus cisplatin with concurrent thoracic radiation group and cisplatin monotherapy groups, respectively ($P=.016$). The median PFS for the S-1 plus cisplatin with concurrent thoracic radiation group and cisplatin monotherapy groups was 31.4 months and 22.3 months, respectively ($P=.023$). However, there was no significant difference in OS between the S-1 plus cisplatin as concurrent chemoradiation and standard concurrent chemoradiation regimen (HR, 0.81; 95% CI, 0.58–1.13; $P=.21$). Similarly, there was no significant difference in PFS (HR, 0.82; 95% CI, 0.62–1.09; $P=.18$). We speculate that this phenomenon is due to different stages of included patients. The stage IIIA patients accounted for 80% and 75% in trails conducted by Yao and Feng, respectively. We know that the prognosis of stage IIIA patients is significantly better than that in stage IIIB patients.

Compared with the standard treatment group, anemia and febrile neutropenia were not significantly increased in the S-1 plus cisplatin group. On the other hand, in the S-1 treatment group, the frequency of nausea, diarrhea, pneumonitis, anorexia, and thrombocytopenia was similar to that in the standard treatment group. However, the rates of leukocytopeni, neutropenia are significantly lower in S-1 plus cisplatin group than that in standard treatment group. In addition, we also performed subgroup analysis on neutropenia and leukocytopenia due to the heterogeneity stratified by whether cisplatin was used alone. S-1 plus cisplatin as concurrent chemoradiation group showed a

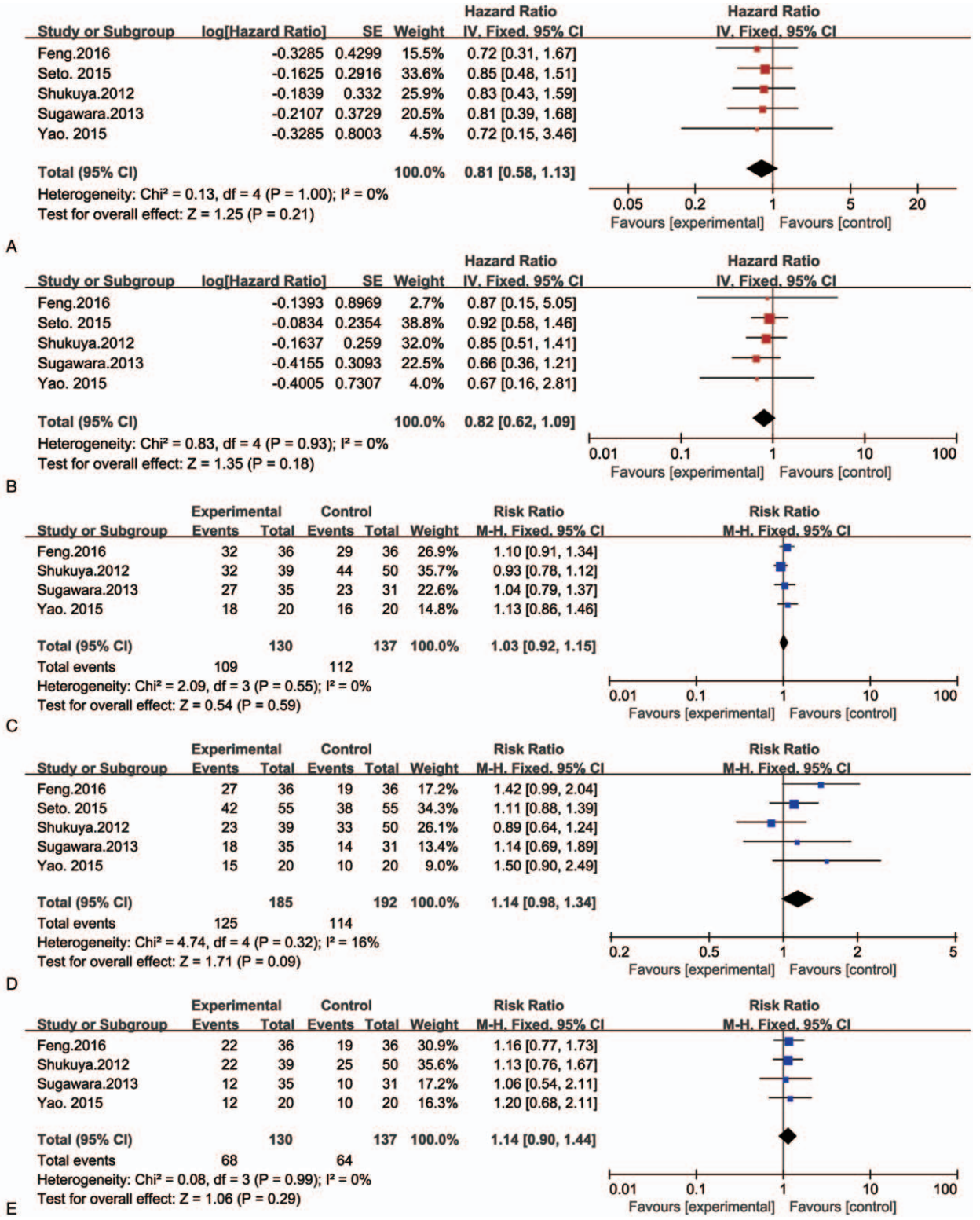

Figure 4. A, Forest plot of OS associated with S-1 plus cisplatin versus control. There was no significant difference among 2 groups. B, Forest plot of PFS associated with S-1 plus cisplatin versus control. There was no significant difference among 2 groups. C, Forest plot of 1-year OS associated with S-1 plus cisplatin versus control. There was no significant difference among 2 groups. D, Forest plot of 2-year OS associated with S-1 plus cisplatin versus control. There was no significant difference among 2 groups. E, Forest plot of 3-year OS associated with S-1 plus cisplatin versus control. There was no significant difference among 2 groups. OS = overall survival, PFS = progressives free survival.

favorable result than vinorelbine plus cisplatin group. The incidence of neutropenia and leukocytopenia was similar with cisplatin monotherapy. Therefore, S-1 plus cisplatin as concurrent chemoradiation was recommended for the future research.

Our outcomes of OS and PFS were not in agreement with the meta-analysis by Sun published in 2017.[19] Only 2 trails were included in that meta-analysis. Because these 2 original literatures did not report HP value and confidence interval, the authors

Table 2

Toxicity outcomes.

	Grade 3 or 4 late toxicities		
Variable	**EG**	**CG**	***P***
Nausea	11	13	.89
Anemia	15	35	.008
Neutropenia	44	107	.00001
Febrile neutropenia	11	25	.03
Diarrhea	7	3	.28
Thrombocytopenia	21	13	.12
Leukocytopenia	33	57	.0003
Pneumonitis	7	6	.73
Anorexia	17	13	.38

CG = control group, EG = experimental group.

chose relative risk (RR) as an effect to evaluate OS and PFS. This method has some inherent defects, mainly because of the HP takes into consideration the time experienced by the end of event, but the RR does not take into account the time factor, thus lost some important information, the effects of the RR is adopted as the survival data is as a regular choice.

Another meta-analysis was reported on Future Medicine by Abdel-Rahman in 2016.[20] Abdel-Rahman compared the efficacy and safety of S-1 plus cisplatin as concurrent chemoradiation with standard regimens for patients with locally advanced non-small cell lung cancer. That meta-analysis has reached the same conclusion that S-1 plus cisplatin as concurrent chemoradiation failed to improve OS (HR, 0.84; 95% CI, 0.55–1.29; $P = .43$) and PFS (HR, 0.89; 95% CI, 0.63–1.25; $P = .49$). As for the side effects, this study was only

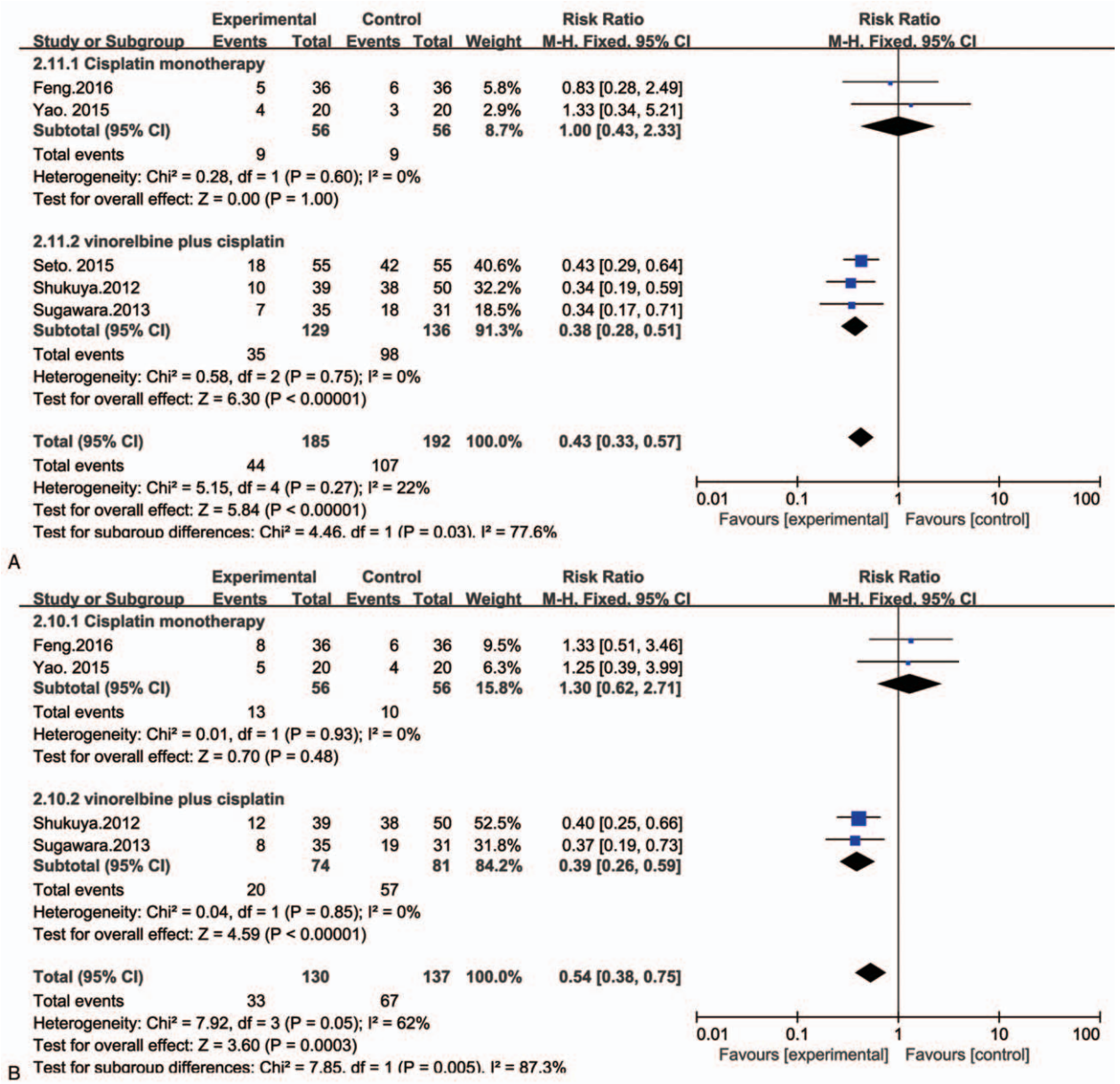

Figure 5. A, Forest plot of neutropenia in the meta-analysis and subgroup analysis. There was a significant difference among 2 groups. B, Forest plot of leukocytopenia in the meta-analysis and subgroup analysis. There was a significant difference among 2 groups.

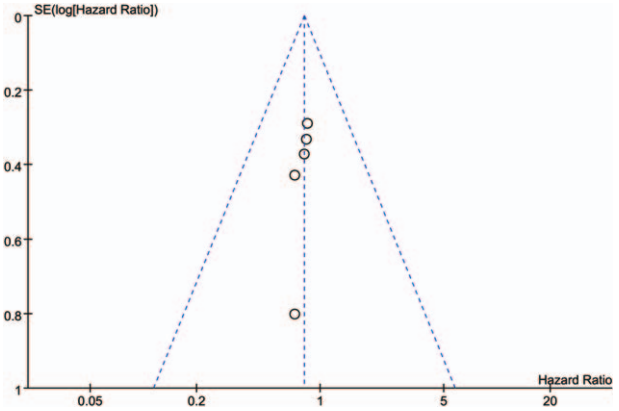

Figure 6. Funnel plot for publication bias.

reported on hematological toxicity and non-hematological toxicity. There is no further detailed analysis. However, we included more randomized controlled trials (5 trails), and we reported more detailed and complete side reactions in the present meta-analysis.

However, some limitations in the present meta-analysis should not be ignored. First, the total number of patient included is small and large-scale, high-quality randomized controlled trials need to be conducted to confirm the results of the present study in the future. Second, in the study conducted by Sugawara,[17] radiotherapy techniques include 2D and 3D technology, where 2D technology is outdated and the role of radiotherapy in this literature may be underestimated. Third, of the 5 documents included, all the patients were Chinese and Japanese, so the results of this study were limited to Asians. And literature retrieval is limited to English, which may lead to potential language bias. Finally, about the group of patients with no subsequent treatment were reported, no targeted therapy of gene mutation status and follow-up information, therefore, it is difficult to judge the use of targeted therapy in the long-term survival of patients.

5. Conclusions

No significant difference existed in OS, 1,2,3-year OS, and PFS. Compared with standard regimens, S-1plus cisplatin as concurrent chemoradiation is well tolerated with much lower grade 3 or 4 late toxicities in terms of leukocytopenia, and neutropenia.

Author contributions

Data curation: Shuai Qie.
Formal analysis: Shuai Qie.
Investigation: Hongyun Shi.
Methodology: Shuai Qie, Hongyun Shi, Lanhui Yuan.
Project administration: Lanhui Yuan.
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Software: Shuai Qie, Yanhong Li, Xi Zhang.
Supervision: Yanhong Li, Xi Zhang.
Visualization: Xi Zhang.
Writing – original draft: Shuai Qie, Yanhong Li.
Writing – review & editing: Hongyun Shi.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[2] Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10:1243–60.
[3] Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. New Engl J Med 1990;323:940–5.
[4] Curran WJJr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Nat Cancer Inst 2011;103:1452–60.
[5] Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181–90.
[6] Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: a modified phase I/II trial. Cancer 2001;92:1213–23.
[7] Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase iii trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2016;34:953–62.
[8] Santana-Davila R, Devisetty K, Szabo A, et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. J Clin Oncol 2015;33:567–74.
[9] Ezer N, Smith CB, Galsky MD, et al. Cisplatin vs. carboplatin-based chemoradiotherapy in patients >65 years of age with stage III non-small cell lung cancer. Radiother Oncol 2014;112:272–8.
[10] Tahara M, Kiyota N, Mizusawa J, et al. Phase II trial of chemo-radiotherapy with S-1 plus cisplatin for unresectable locally advanced head and neck cancer (JCOG0706). Cancer Sci 2015;106:726–33.
[11] Song GM, Tian X, Liu XL, et al. Concurrent chemo-radiotherapy with S-1 as an alternative therapy for elderly Chinese patients with non-metastatic esophageal squamous cancer: evidence based on a systematic review and meta-analysis. Oncotarget 2017;8:37963–73.
[12] Goji T, Kimura T, Miyamoto H, et al. A phase I/II study of fixed-dose-rate gemcitabine and S-1 with concurrent radiotherapy for locally advanced pancreatic cancer. Cancer Chemother Pharmacol 2015;76:615–20.
[13] Kim HM, Lee KJ, Cha J, et al. A pilot study of S-1-based concurrent chemoradiotherapy in patients with biliary tract cancer. Cancer Chemother Pharmacol 2014;74:861–5.
[14] Yao L, Xu S, Xu J, et al. S-1 plus cisplatin with concurrent radiotherapy versus cisplatin alone with concurrent radiotherapy for stage III non-small cell lung cancer: a pilot randomized controlled trial. Radiat Oncol (Lond, Engl) 2015;10:10.
[15] Feng J, Xu J, Wang X, et al. S-1 plus cisplatin with concurrent radiotherapy versus cisplatin alone with concurrent radiotherapy in Chinese patients with nonsmall-cell lung cancer: A multicentre randomized controlled trial. Medicine 2016;95:e4557.
[16] Shukuya T, Takahashi T, Harada H, et al. Comparison of vinorelbine plus cisplatin and S-1 plus cisplatin in concurrent chemoradiotherapeutic regimens for unresectable stage III non-small cell lung cancer. Anticancer Res 2012;32:675–80.
[17] Sugawara S, Maemondo M, Tachihara M, et al. Randomized phase II trial of uracil/tegafur and cisplatin versus vinorelbine and cisplatin with concurrent thoracic radiotherapy for locally advanced unresectable stage III non-small-cell lung cancer: NJLCG 0601. Lung Cancer (Amsterdam, Netherlands) 2013;81:91–6.
[18] Sasaki T, Seto T, Yamanaka T, et al. A randomised phase II trial of S-1 plus cisplatin versus vinorelbine plus cisplatin with concurrent thoracic radiotherapy for unresectable, locally advanced non-small cell lung cancer: WJOG5008L. Br J Cancer 2018;119:675–82.
[19] Sun X, Sun L, Zhang SL, et al. Meta-analysis exploring the effectiveness of S-1-based chemotherapy for advanced non-small cell lung cancer. Tohoku J Exp Med 2017;241:1–1.
[20] Abdel-Rahman O, ElHalawani H. S-1-based regimens for locally advanced/metastatic non-small-cell lung cancer: a meta-analysis. Future Oncol (Lond, Engl) 2016;12:701–13.