

# 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% Cl, 0.58–1.13; P = .21, heterogeneity P = 1.00,  $I^2 = 0\%$ ), progressives free survival (PFS) (HR, 0.82; 95% Cl, 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% Cl: 0.92–1.15, p = 0.59), (2-year OS: RR 1.14; 95% Cl: 0.98–1.34, P = .09), (3 -year OS: RR 1.14; 95% Cl: 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% Cl: 0.38–0.75, P = .0003; RR = 0.23,95% Cl: 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% Cl: 0.68–2.68, P = .38; RR = 1.87, 95% Cl: 0.88–3.17, P = .12; RR = 1.19, 95% Cl: 0.44–3.21, P = .73; RR = 1.35, 95% Cl: 0.68–2.68, P = .38; RR = 0.86, 95% Cl: 0.55–1.34, P = .50; RR =0.63, 95% Cl: 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.<sup>[11]</sup> 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

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Received: 17 June 2018 / Accepted: 5 November 2018 http://dx.doi.org/10.1097/MD.000000000013441 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.<sup>[2]</sup> 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.<sup>[3]</sup> Concurrent chemoradiation is superior to sequential therapy.<sup>[4,5]</sup> 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.<sup>[6-9]</sup> 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 nonsmall 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

SQ and YL contributed equally to this work.

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neck.<sup>[10]</sup> 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.<sup>[11]</sup> The addition of S-1 concurrent chemoradiation in patients with local advanced pancreatic cancer has an acceptable toxic reaction and efficacy.<sup>[12]</sup> 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.<sup>[13]</sup> 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) or (Carcinomas, Non-Small-Cell Lung) or (Lung Carcinomas, Non-Small-Cell Lung) or (Lung Carcinomas, Non-Small-Cell) or (Non-Small-Cell) or (Non-Small-Cell Lung Carcinomas) or (Non-Small-Cell Lung Carcinoma) or (Non-Small Cell Lung Carcinoma) or (Non-Smal

#### 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<sup>2</sup> tests, and no heterogeneity was regard when P > .1 and I<sup>2</sup> <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<sup>[14,15]</sup> 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	<ul> <li>Arm A: S-1 (p.o.q.d.40 mg/m<sup>2</sup>, on days 1–14), cisplatin (60mg/m<sup>2</sup>, on day 1).</li> <li>Arm B: Vinorelbine (20 mg/m<sup>2</sup>, on days 1 and 8), cisplatin (80mg/m<sup>2</sup>, on day 1).</li> <li>The treatment cycles in both arms were repeated every 4 weeks for a maximum of four cycles concurrent with radiotherapy.</li> </ul>
Sugawara. 2013	Arm A 35 Arm B 31	Arm A 28/7 Arm B 26/5	0–1	<ul> <li>Arm A: Cisplatin (80 mg/m<sup>2</sup> on days 8 and 36), UFT (p.o. 400 mg/m<sup>2</sup>, on days 1–14 and 29–42).</li> <li>Arm B: Vinorelbine (20 mg/m<sup>2</sup>) on days 1, 8, 29, and 36 and cisplatin (80 mg/m<sup>2</sup>) on days 1 and 29.</li> <li>The schedule of concurrent thoracic radiotherapy was 60Gy in 30 fractions.</li> </ul>
Seto. 2015	Arm A 55 Arm B 55	Arm A NG Arm B NG	0–1	<ul> <li>Arm A: S-1 (40 mg/m<sup>2</sup>/dose per oral, b.i.d, on days 1–14) and cisplatin (60 mg/m<sup>2</sup> on day 1) repeated every 4 weeks).</li> <li>Arm B: vinorelbine (20mg/m<sup>2</sup> on days 1, 8) and cisplatin (80 mg/m<sup>2</sup>on day) repeated every 4 weeks. The schedule of concurrent thoracic radiotherapy was 60Gy in 30 fractions.</li> </ul>
Yao. 2015	Arm A 20 Arm B 20	Arm A 15/5 Arm A 14/6	0–1	<ul> <li>Arm A: Cisplatin (60 mg/m<sup>2</sup> on day1, every 4 weeks for 2 cycles), S-1 (p.o.b.i.d. 40 mg/m<sup>2</sup>, on days1-14).</li> <li>Arm B: Cisplatin (60 mg/m<sup>2</sup> on day1, every 4 weeks for 2 cycles).</li> <li>Both arms received radiotherapy concurrently</li> </ul>
Feng. 2016	Arm A 36 Arm B 36	Arm A 24/12 Arm A 21/15	0–1	<ul> <li>Arm A: Cisplatin (60 mg/m<sup>2</sup> on day1 followed by at 4-week intervals), S-1 (p.o.b.i.d. 40 mg/m<sup>2</sup>, on days1-14).</li> <li>Arm B: Cisplatin (60 mg/m<sup>2</sup> on day1 followed by at 4-week intervals).</li> <li>Both arms received radiotherapy concurrently</li> </ul>

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.<sup>[4,7,8]</sup>

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,<sup>[18]</sup> Sugawara<sup>[17]</sup> and Shukuya<sup>[16]</sup> 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<sup>[14]</sup> and Feng<sup>[15]</sup> 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. 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.<sup>[19]</sup> 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		
Variable	EG	CG	Р
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.<sup>[20]</sup> 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

Study or Subaroup Events Total Events Total Weight M-H. Exed, 95% CI       M-H. Exed, 95% CI         2.11.1 Cisplatin monotherapy       Feng.2016       5       38       6       32       0.29%       1.33 [0.34, 5.21]         Yao. 2015       4       20       3       20       2.9%       1.33 [0.34, 5.21]         Subtotal (95% CI)       56       56       5.7%       1.00 [0.43, 2.33]         Total events       9       9         Heterogeneity: Chi <sup>2</sup> = 0.00 (P = 1.00)       2.11.2 vinorelbine plus cisplatin         Study of Subtotal (95% CI)       128       55       40.6%       0.43 [0.29, 0.64]         Study of Subtotal (95% CI)       129       136       91.3%       0.38 [0.28, 0.51]         Yours for overail effect: Z = 6.30 (P < 0.00001)       129       136       91.3%       0.38 [0.33, 0.57]         Total (95% CI)       185       192       100.0%       0.43 [0.33, 0.57]       0.01       0.01       0.1       10         Fetorogeneity: Chi <sup>2</sup> = 0.50, df = 2 (P = 0.75); P = 0%       Test for overail effect: Z = 5.84 (P < 0.00001)       Test for overail effect: Z = 5.84 (P < 0.00001)       Favours [control]       Favours [control]         Study of Subbroup       Experimental       Control       Risk Ratio       Risk Ratio       Risk Ratio <th></th> <th colspan="2">Experimental</th> <th colspan="2">Control</th> <th></th> <th>Risk Ratio</th> <th colspan="2">Risk Ratio</th> <th></th>		Experimental		Control			Risk Ratio	Risk Ratio		
2.11.1 Cisplatin monotherapy Feng.2016 5 5 86 6 36 5.8% 0.83 [0.28, 2.49] Yao.2015 4 20 3 20 2.9% 1.33 [0.34, 5.21] Subtotal (95% CI) 56 56 8.7% 1.00 [0.43, 2.33] Total events 9 9 Heterogeneity: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60); P = 0%, Test for overall effect: Z = 0.00 (P = 1.00) 2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0%, Test for overall effect: Z = 6.30 (P < 0.0001) Total (95% CI) 129 136 91.3% 0.34 [0.17, 0.71] Subtotal (95% CI) 129 136 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 0%, Test for overall effect: Z = 6.46. df = 1 (P = 0.03), P = 77.6% Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% CI 2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.25 (0.39, 3.99] Subtotal (95% CI) 5 20 4 20 6.3% 1.25 (0.39, 3.99] Subtotal (95% CI) 74 = 0.01, df = 1 (P = 0.03); P = 0% Test for overall effect: Z = 5.80 (f = 0.00001) Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.93); P = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukvya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.35); P = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukvya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Total events 20 57 Heterogeneity: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.25); P = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukvya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Total events 20 57 Heterogeneity: Ch <sup>2</sup> = 0.04, df = 1 (P = 0.25); P = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukvya.2012 12 9 30 38 70 0.25 (0.566] Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.04, df = 1 (P = 0.25); P = 0% Test for overall effect: Z = 4.59	Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% Cl	M-H. Fixe	ed. 95% Cl	
Feng.2016 5 3 6 6 36 5.8% 0.83 (0.28, 2.49) Yao. 2015 4 20 3 20 2.9% 1.33 (0.34, 5.21) Subtotal (95% CI) 56 56 8.7% 1.00 [0.43, 2.33] Total events 9 9 9 Heterogeneity: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60); P = 0% Test for overall effect: $Z = 0.00$ (P = 1.00) 2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Total events 33 5 98 Heterogeneity: Ch <sup>2</sup> = 0.53, 0 f = 2 (P = 0.75); P = 0% Test for overall effect: $Z = 6.30$ (P < 0.00001) Total (95% CI) 185 192 100.0% 0.43 [0.33, 0.57] Test for overall effect: $Z = 5.34$ (P < 0.00001) Total (95% CI) 185 192 100.0% 0.43 [0.33, 0.57] Test for overall effect: $Z = 5.34$ (P < 0.00001) Total (95% CI) 185 192 100.0% 0.43 [0.33, 0.57] Test for overall effect: $Z = 5.34$ (P < 0.00001) Total (95% CI) 185 192 100.0% 0.43 [0.33, 0.57] Test for overall effect: $Z = 5.34$ (P < 0.00001) Total (95% CI) 185 192 100.0% 0.43 [0.33, 0.57] Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.33 [0.53, 3.46] Yao. 2015 5 20 4 20 6.3% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.33); P = 0% Test for overall effect: $Z = 0.70$ (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shuktyac 2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugavara.2013 8 35 19 31 31.86% 0.37 [0.19, 0.73] Subtotal (95% CI) 74 4 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Ch <sup>2</sup> = 0.04, df = 1 (P = 0.85); P = 0% Test for overall effect: $Z = 0.70$ (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shuktyac 2015 1 2 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shuktyac 2015 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shuktyac 2015 (P = 0.48); P = 00% Test for overall effect: $Z = 0.70$ (P = 0.65); P = 0% Test for overall effect: $Z = 4.59$ (P < 0.00001) Total (95% CI) 130 137 100.0% 0.54 [0.38, 0.75] Heterogeneity: Ch <sup>2</sup> = 2.92 (P = 0.26); P = 62%	2.11.1 Cisplatin mo	notherapy								
Yeo. 2015 4 20 3 20 2.9% 1.33 [0.34, 5.21] Subtotal (95% CI) 56 56 8.7% 1.00 [0.43, 2.33] Total events 9 9 Heterogeneity: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60); P = 0% Test for overall effect: Z = 0.00 (P = 1.00) 2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Shukuya 2012 10 39 38 50 32.2% 0.34 [0.19, 0.59] Subtotal (95% CI) 129 136 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0% Test for overall effect: Z = 6.30 (P < 0.0001) Total (95% CI) 185 192 100.0% 0.43 [0.33, 0.57] Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 22% Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 22% Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.03), P = 77.6% Experimental Subtotal (95% CI) 55 20 4 20 6.3% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.25 [0.39, 3.99] Subtotal (95% CI) 56 56 15.8% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.33); P = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 thoreblate plus cisplatin Shukuya2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugavara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% CI) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 Total ev	Feng.2016	5	36	6	36	5.8%	0.83 [0.28, 2.49]			
Subtotal (95% CI) 56 56 8.7% 1.00 [0.43, 2.33] Total events 9 9 Heterogeneity: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60); P = 0% Test for overall effect: $Z = 0.00$ (P = 1.00) 2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Shukuya 2012 10 39 38 50 32.2% 0.34 [0.17, 0.71] Subtotal (95% CI) 129 136 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0% Test for overall effect: Z = 6.30 (P < 0.0001) Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 22% Test for overall effect: Z = 6.30 (P < 0.0001) Test for overall effect: Z = 6.44, df = 1 (P = 0.03), P = 77.6% Experimental Control Risk Ratio Risk Ratio Study or Subgroup Events Total Events Total Weight M-H-Fixed, 95% CI M-H	Yao. 2015	4	20	3	20	2.9%	1.33 [0.34, 5.21]			
Total events 9 9 Heterogeneity: Ch <sup>2</sup> = 0.28, df = 1 (P = 0.60); P = 0% Test for overall effect: Z = 0.00 (P = 1.00) 2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Shukuya.2012 10 39 38 50 32.2% 0.34 [0.17, 0.71] Subtotal (95% Cl) 129 136 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0% Test for overall effect: Z = 6.30 (P < 0.00001) Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0% Test for overall effect: Z = 5.84 (P < 0.00001) Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 0.48, df = 1 (P = 0.03); P = 77.6% Experimental Control Risk Ratio Studtor or Subgroup Events Total Events Total Weight M-H. Fixed. 95% Cl 2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.25 [0.39, 3.99] Subtotal (95% Cl) 15 6 56 156 15.5% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.03); P = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% Cl) 130 137 100.0% 0.54 [0.38, 0.75] Total events 20 57 Heterogeneity: Ch <sup>2</sup> = 0.04, df = 1 (P = 0.08); P = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.02, df = 3 (P = 0.08); P = 0% Test for overal effect: Z = 4.59 (P < 0.00001) Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.07 (D = 0.48); P = 0.08; P = 0% Test for overal effect: Z = 4.59 (P < 0.00001) Total (95% Cl) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.07 (D = 0.85); P = 0% Test for overal effect: Z = 4.59 (P < 0.00001)	Subtotal (95% CI)		56		56	8.7%	1.00 [0.43, 2.33]			
Heterogeneity: Ch <sup>2</sup> = 0.28, df = 1 ( $P = 0.60$ ); $P = 0.%$ Test for overall effect: Z = 0.00 ( $P = 1.00$ ) 2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Shukuya.2012 10 39 38 50 32.2% 0.34 [0.19, 0.59] Sugawara.2013 7 35 18 31 18.5% 0.34 [0.17, 0.71] Subtotat [85% Cl) 122 138 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 ( $P = 0.75$ ); $P = 0\%$ Test for overall effect: Z = 6.30 ( $P < 0.0001$ ) Total (95% Cl) 185 192 100.0% 0.43 [0.33, 0.57] Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 ( $P = 0.27$ ); $P = 22\%$ Test for overall effect: Z = 5.8 ( $P < 0.00001$ ) Test for subcroup differences: Ch <sup>2</sup> = 4.46, df = 1 ( $P = 0.03$ ), $P = 77.6\%$ Experimental Control Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl M-H.	Total events	9		9						
Test for overall effect: $Z = 0.00$ (P = 1.00) 2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Shukuya.2012 10 39 38 50 32.2% 0.34 [0.19, 0.59] Shukuya.2013 7 35 18 31 18.5% 0.34 [0.17, 0.71] Subtotal (95% Cl) 129 136 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0% Test for overall effect: $Z = 5.46$ (P < 0.00001) Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 22% Test for overall effect: $Z = 5.46$ (P < 0.00001) Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 22% Test for overall effect: $Z = 5.46$ (P < 0.00001) Test for subcroup Events Total Events Total Weight M-H. Fixed. 95% Cl 2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.07 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% Cl) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Ch <sup>2</sup> = 0.04 df = 1 (P = 0.93); P = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total events 20 57 Heterogeneity: Ch <sup>2</sup> = 0.02, df = 1 (P = 0.93); P = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.02, df = 3 (P = 0.07); P = 0.68; P = 0.05% Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.02, df = 3 (P = 0.07); P = 0.68; P = 0.05%	Heterogeneity: Chi <sup>2</sup> =	= 0.28, df = 1	(P = 0.	60); l <sup>2</sup> = 0	0%					
2.11.2 vinorelbine plus cisplatin Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Shukuya.2012 10 39 38 50 32.2% 0.34 [0.19, 0.59] Sugawara.2013 7 35 18 31 18.5% 0.34 [0.17, 0.71] Subtotal (95% Cl) 129 136 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Chi <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0% Test for overall effect: Z = 6.30 (P < 0.00001) Total events 44 107 Heterogeneity: Chi <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 22% Test for overall effect: Z = 5.84 (P < 0.00001) Test for subarouo differences: Chi <sup>2</sup> = 4.46. df = 1 (P = 0.03), P = 77.6% Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl 2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6 3% 1.33 [0.51, 3.46] Yao. 2015 5 5 20 4 2.20 6.3% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Chi <sup>2</sup> = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Total events 20 57 Heterogeneity: Chi <sup>2</sup> = 0.40; df = 1 (P = 0.85); P = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total (95% Cl) 130 137 100.0% 0.54 [0.38, 0.75] Fotal events 33 67 Heterogeneity: Chi <sup>2</sup> = 0.20; H = 3 (P = 0.06); P = 2%	Test for overall effect	t: Z = 0.00 (P	9 = 1.00)							
Seto. 2015 18 55 42 55 40.6% 0.43 [0.29, 0.64] Shukuya.2012 10 39 38 50 32.2% 0.34 [0.17, 0.71] Subtotal (95% Cl) 129 136 91.3% 0.38 [0.28, 0.51] Total events 35 98 Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0% Test for overall effect: Z = 6.30 (P < 0.00001) Total (95% Cl) 185 192 100.0% 0.43 [0.33, 0.57] Total events 44 107 Heterogeneity: Ch <sup>2</sup> = 5.54 (P < 0.00001) Test for subaroup differences: Ch <sup>2</sup> = 4.46. df = 1 (P = 0.03), P = 77.6% Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl 2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.25 [0.39, 3.99] Subtotal (95% Cl) 56 56 15.8% 1.30 [0.52, 2.71] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.07, df = 1 (P = 0.33); P = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% Cl) 74 81 84.2% 0.39 [0.26, 0.59] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.04, df = 1 (P = 0.85); P = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.05, df = 3 (P = 0.05); P = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 0.05, df = 3 (P = 0.05); P = 2%	2.11.2 vinorelbine p	lus cisplatir	1							
Shukuya.2012       10       39       38       50       32.2% $0.34$ [0.19, 0.59]         Sugawara.2013       7       35       18       31       18.5% $0.34$ [0.17, 0.71]         Subtotal (95% CI)       129       136       91.3% $0.38$ [0.28, 0.51]         Total events       35       98         Heterogeneity: Ch <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0%         Test for overall effect: Z = 6.30 (P < 0.0001)         Total events       44       107         Heterogeneity: Ch <sup>2</sup> = 5.15, df = 4 (P = 0.27); P = 22%       0.01       0.1       10         Test for overall effect: Z = 5.48 (P < 0.00001)       185       192       100.0%       0.43 [0.33, 0.57]         Test for subcroup differences: Ch <sup>2</sup> = 4.46, df = 1 (P = 0.03); P = 77.6%       0.01       0.1       10         Favours [control]       Experimental       Control       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Events       Total Events       Total       Weight       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         2.10.1 Cisplatin monotherapy       Feng.2016       8       36       6       36       9.5%       1.33 [0.51, 3.46]       Favours [control]         Statukya.2012       13       13	Seto. 2015	18	55	42	55	40.6%	0.43 [0.29, 0.64]			
Sugawara.2013       7       35       18       31       18.5% $0.34$ [0.17, 0.71]         Subtotal (95% CI)       129       136       91.3% $0.38$ [0.28, 0.51]         Total events       35       98         Heterogeneity: Chi <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0%       Test for overall effect: Z = 6.30 (P < 0.00001)         Total events       44       107         Heterogeneity: Chi <sup>2</sup> = 5.54 (P < 0.0201)       185       192       100.0%       0.43 [0.33, 0.57]         Test for overall effect: Z = 5.84 (P < 0.00001)       185       192       100.0%       0.43 [0.33, 0.57]         Test for subcroup differences: Chi <sup>2</sup> = 4.46. df = 1 (P = 0.03), I <sup>2</sup> = 77.6%       Experimental       Control       Risk Ratio         Study or Subgroup       Events       Total Events       Total Weight       M-H. Fixed, 95% CI       M-H. Fixed, 95% CI         C101       0.1       1       10       Favours [control]       Risk Ratio         Study or Subgroup       Events       Total Events       Total Weight       M-H. Fixed, 95% CI       M-H. Fixed, 95% CI         C101       5       5       20       4       20       6.3%       1.25 [0.39, 3.99]       Subtotal (95% CI)       56       56       57       63       50       52.5% <td>Shukuva.2012</td> <td>10</td> <td>39</td> <td>38</td> <td>50</td> <td>32.2%</td> <td>0.34 [0.19, 0.59]</td> <td></td> <td></td> <td></td>	Shukuva.2012	10	39	38	50	32.2%	0.34 [0.19, 0.59]			
Subtotal (95% CI)       129       136       91.3%       0.38 [0.28, 0.51]         Total events       35       98         Heterogeneity: Chi <sup>2</sup> = 0.58, df = 2 (P = 0.75); P = 0%         Test for overall effect: Z = 6.30 (P < 0.00001)	Sugawara.2013	7	35	18	31	18.5%	0.34 [0.17, 0.71]			
Total events 35 98 Heterogeneity: $Chi^2 = 0.58$ , $df = 2 (P = 0.75)$ ; $P = 0\%$ Test for overall effect: $Z = 6.30 (P < 0.00001)$ Total events 44 107 Heterogeneity: $Chi^2 = 5.15$ , $df = 4 (P = 0.27)$ ; $P = 22\%$ Test for overall effect: $Z = 5.84 (P < 0.00001)$ Test for subcroup differences: $Ch^2 = 4.46$ . $df = 1 (P = 0.03)$ ; $P = 77.6\%$ Experimental Control Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl 2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.25 [0.39, 3.99] Subtotal (95% Cl) 55 20 4 20 6.3% 1.26 [0.39, 3.99] Subtotal (95% Cl) 56 56 15.8% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: $Chi^2 = 0.01$ , $df = 1 (P = 0.93)$ ; $P = 0\%$ Test for overall effect: $Z = 0.70 (P = 0.48)$ 2.10.2 vinorelbine plus cisplatin Shukya2.012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% Cl) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: $Chi^2 = 0.04$ , $df = 1 (P = 0.85)$ ; $P = 0\%$ Test for overall effect: $Z = 4.59 (P < 0.00001)$ Total (95% Cl) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 67 Heterogeneity: $Chi^2 = 0.04$ , $df = 1 (P = 0.85)$ ; $P = 0\%$ Test for overall effect: $Z = 4.59 (P < 0.00001)$	Subtotal (95% CI)		129	20	136	91.3%	0.38 [0.28, 0.51]	+		
Heterogeneity: Chi <sup>2</sup> = 0.58, df = 2 (P = 0.75); l <sup>2</sup> = 0% Test for overall effect: Z = 6.30 (P < 0.00001) Total (95% CI) 185 192 100.0% 0.43 [0.33, 0.57] Total events 44 107 Heterogeneity: Chi <sup>2</sup> = 5.15, df = 4 (P = 0.27); l <sup>2</sup> = 22% Test for overall effect: Z = 5.84 (P < 0.00001) Test for suboroud differences: Chi <sup>2</sup> = 4.46. df = 1 (P = 0.03). l <sup>2</sup> = 77.6% Experimental Control Risk Ratio Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% CI 2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.25 [0.39, 3.99] Subtotal (95% CI) 56 56 15.8% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% CI) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total (95% CI) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 6 67 Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.95); l <sup>2</sup> = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total (95% CI) 130 137 100.0% 0.54 [0.38, 0.75]	Total events	35		98						
Test for overall effect: $Z = 6.30$ ( $P < 0.00001$ )         Total (95% CI)       185       192       100.0%       0.43 [0.33, 0.57]         Total events       44       107         Heterogeneity: Chi <sup>2</sup> = 5.15, df = 4 ( $P = 0.27$ ); $P = 22\%$ 0.01       0.1       1         Test for overall effect: $Z = 5.84$ ( $P < 0.02001$ )       Favours [experimental]       Favours [control]         Test for subaroup differences: Chi <sup>2</sup> = 4.46. df = 1 ( $P = 0.03$ ). $P = 77.6\%$ Favours [experimental]       Favours [control]         Study or Subgroup       Events       Total Events       Total Weight       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         2.10.1 Cisplatin monotherapy       Feng.2016       8       36       6       36       9.5%       1.33 [0.51, 3.46]         Yao. 2015       5       20       4       20       6.3%       1.25 [0.39, 3.99]         Subtotal (95% CI)       56       56       1.30 [0.62, 2.71]       Total events       13       10         Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 ( $P = 0.93$ ); $P = 0\%$ Test for overall effect: $Z = 0.70$ ( $P = 0.48$ )       2.10.2 (inorelbine plus cisplatin       Shukuya.2012       12       39       38       50       52.5%       0.40 [0.25, 0.66]       Total events       20       57         Heterogeneity: Chi <sup>2</sup> =	Heterogeneity: Chi <sup>2</sup> =	= 0.58. df = 2	(P = 0.7)	75): $ ^2 = 0$	0%					
Total (95% Cl)       185       192       100.0%       0.43 [0.33, 0.57]         Total events       44       107         Heterogeneity: Chi <sup>2</sup> = 5.15, df = 4 (P = 0.27); l <sup>2</sup> = 22%       0.01       0.1       1       10         Test for overall effect: Z = 5.84 (P < 0.0001)       Experimental       Control       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Events       Total Events       Total Weight       M-H. Fixed. 95% Cl       M-H. Fixed. 95% Cl         2.10.1 Clisplatin monotherapy       Ferg.2016       8       36       6       36       9.5%       1.33 [0.51, 3.46]         Yao. 2015       5       20       4       20       6.3%       1.25 [0.39, 3.99]       M-H. Fixed. 95% Cl         Subtotal (95% Cl)       56       56       15.8%       1.30 [0.62, 2.71]       M-H. Fixed. 95% Cl         Column and the events       13       10       Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0%       Test for overall effect: Z = 0.70 (P = 0.48)       2.10.2       38       50       52.5%       0.40 [0.25, 0.66]         Subtotal (95% Cl)       74       81       84.2%       0.39 [0.26, 0.59]       40       40         Total events       20       57       Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P =	Test for overall effect	t: Z = 6.30 (P	< 0.000	001)						
Total events       44       107         Heterogeneity: $Chi^2 = 5.15$ , $df = 4$ (P = 0.27); $l^2 = 22\%$ 0.01       0.1       10         Test for overall effect: Z = 5.44 (P < 0.00001)	Total (95% CI)		185		192	100.0%	0.43 [0.33, 0.57]	•		
Heterogeneity: $Chi^2 = 5.15$ , $df = 4$ (P = 0.27); $l^2 = 22\%$ 0.01       0.1       1       10         Test for overall effect: Z = 5.84 (P < 0.00001)	Total events	44		107						
Test for overall effect: $Z = 5.84$ ( $P < 0.0001$ )       0.01       0.1       1       10         Fest for overall effect: $Z = 5.84$ ( $P < 0.0001$ )       Favours [experimental]       Favours [experimental]       Favours [control]         Test for overall effect: $Z = 5.84$ ( $P < 0.0001$ )         Test for overall effect: $Z = 5.84$ ( $P < 0.0001$ )         Test for overall effect: $Z = 5.84$ ( $P < 0.0001$ )         Test for overall effect: $Z = 5.84$ ( $P < 0.0001$ )         Total Events Total Weight M-H. Fixed, 95% CI         2.10.1 Cisplatin monotherapy         Feng.2016       8       36       6       36       9.5%       1.33 [0.51, 3.46]         Yao. 2015       5       20       4       20       6.3%       1.25 [0.39, 3.99]         Subtotal (95% CI)       56       56       15.8%       1.30 [0.62, 2.71]         Total events       13       10         Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 ( $P = 0.93$ ); $I^2 = 0\%$ Test for overall effect: Z = 0.70 ( $P = 0.48$ )         2.10.2 vinorelbine plus cisplatin       Shukuya.2012       12       39       38       50       52.5%       0.40 [0.25, 0.66]       Image: Figure Figur	Heterogeneity: Chi2 =	= 5.15 df $= 4$	(P = 0)	$(27):  ^2 = 2$	2%			L	<u> </u>	
Test for subarous differences: Chi <sup>2</sup> = 4.46. df = 1 (P = 0.03). I <sup>2</sup> = 77.6%         Favours [experimental]         Subarous differences: Chi <sup>2</sup> = 4.46. df = 1 (P = 0.03). I <sup>2</sup> = 77.6%         Favours [experimental]         Subarous differences: Chi <sup>2</sup> = 4.46. df = 1 (P = 0.03). I <sup>2</sup> = 77.6%         Experimental       Control       Risk Ratio         Subdroup Events Total Events Total Weight M-H. Fixed, 95% Cl         2.10.1 Cisplatin monotherapy       Feg.2016       8 36       6 36       9.5%       1.33 [0.51, 3.46]         Yao, 2015       5 20       4 20       6.3%       1.25 [0.39, 3.99]       9.99         Subtotal (95% Cl)       56       56       15.8%       1.30 [0.62, 2.71]         Total events       13       10         Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); I <sup>2</sup> = 0%       74       81       84.2%       0.39 [0.26, 0.59]         2.10.2 vinorelbine plus cisplatin       Shukuya.2012       12       39       38       50       52.5%       0.40 [0.25, 0.66]       10         Sugawara.2013       8       35       19       31       31.8%       0.37 [0.19, 0.73]       10         Total events       20       57       57       57       57	Test for overall effect	T = 5.84 (P	< 0.000	001)				0.01 0.1	1 10	100
Experimental         Control         Risk Ratio         Risk Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H. Fixed. 95% Cl         M-H. Fixed. 95% Cl           2.10.1 Cisplatin monotherapy         Feng.2016         8         36         6         36         9.5%         1.33 [0.51, 3.46]           Yao. 2015         5         20         4         20         6.3%         1.25 [0.39, 3.99]           Subtotal (95% Cl)         56         56         15.8%         1.30 [0.62, 2.71]           Total events         13         10           Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0%         Test for overall effect: Z = 0.70 (P = 0.48)           2.10.2 vinorelbine plus cisplatin         Shukuya.2012         12         39         38         50         52.5%         0.40 [0.25, 0.66]           Sugawara.2013         8         35         19         31         31.8%         0.37 [0.19, 0.73]         Image: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%           Test for overall effect: Z = 4.59 (P < 0.00001)	Test for subaroup dif	ferences: Ch	j <sup>2</sup> = 4.46	6. df = 1 (	P = 0.0	3) $l^2 = 77$	6%	Favours [experimental]	Favours [control]	
Experimental         Control         Risk Ratio         Risk Ratio           Study or Subgroup         Events         Total         Events         Total         Weight         M-H. Fixed. 95% CI         M-H. Fixed. 95% CI           2.10.1 Cisplatin monotherapy         Feng.2016         8         36         6         36         9.5%         1.33 [0.51, 3.46]           Yao. 2015         5         20         4         20         6.3%         1.25 [0.39, 3.99]           Subtotal (95% CI)         56         56         15.8%         1.30 [0.62, 2.71]           Total events         13         10           Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0%           Test for overall effect: Z = 0.70 (P = 0.48)           2.10.2 vinorelbine plus cisplatin           Shukuya.2012         12         39         38         50         52.5%         0.40 [0.25, 0.66]           Sugawara.2013         8         35         19         31         31.8%         0.37 [0.19, 0.73]         Image: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%           Test for overall effect: Z = 4.59 (P < 0.00001)			1 2. 1. 1.				1.194			
Study or Subgroup         Events         Total         Events         Total         Weight         M-H. Fixed. 95% CI           2.10.1 Cisplatin monotherapy         Feng.2016         8         36         6         36         9.5%         1.33 [0.51, 3.46]           Yao. 2015         5         20         4         20         6.3%         1.25 [0.39, 3.99]           Subtotal (95% CI)         56         56         15.8%         1.30 [0.62, 2.71]           Total events         13         10           Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0%           Test for overall effect: Z = 0.70 (P = 0.48)           2.10.2 vinorelbine plus cisplatin           Shukuya.2012         12         39         38         50         52.5%         0.40 [0.25, 0.66]           Sugawara.2013         8         35         19         31         31.8%         0.39 [0.26, 0.59]         Image: colored bit of the state stat	9	Experimental		Control		Risk Ratio		Risk Ratio		
2.10.1 Cisplatin monotherapy Feng.2016 8 36 6 36 9.5% 1.33 [0.51, 3.46] Yao. 2015 5 20 4 20 6.3% 1.25 [0.39, 3.99] Subtotal (95% CI) 56 56 15.8% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0% Test for overall effect: $Z = 0.70$ (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% CI) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: $Z = 4.59$ (P < 0.00001) Total (95% CI) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 67 Heterogeneity: Chi <sup>2</sup> = 7 92 df = 3 (P = 0.05); l <sup>2</sup> = 62%	Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% Cl	M-H. Fixe	ed, 95% Cl	
Feng.2016       8       36       6       36       9.5%       1.33 [0.51, 3.46]         Yao. 2015       5       20       4       20       6.3%       1.25 [0.39, 3.99]         Subtotal (95% CI)       56       56       15.8%       1.30 [0.62, 2.71]         Total events       13       10         Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0%         Test for overall effect: Z = 0.70 (P = 0.48)         2.10.2 vinorelbine plus cisplatin         Shukuya.2012       12       39       38       50       52.5%       0.40 [0.25, 0.66]         Sugawara.2013       8       35       19       31       31.8%       0.37 [0.19, 0.73]         Subtotal (95% CI)       74       81       84.2%       0.39 [0.26, 0.59]       •         Total events       20       57       57       57       57         Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%       78       0.54 [0.38, 0.75]       •         Total events       33       67         Heterogeneity: Chi <sup>2</sup> = 7.92 (df = 3 (P = 0.05); l <sup>2</sup> = 62%       •       •	2.10.1 Cisplatin mo	notherapy								
Yao. 2015 5 20 4 20 6.3% 1.25 [0.39, 3.99] Subtotal (95% CI) 56 56 15.8% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Ch <sup>2</sup> = 0.01, df = 1 (P = 0.93); $ ^2 = 0\%$ Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% CI) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Ch <sup>2</sup> = 0.04, df = 1 (P = 0.85);   <sup>2</sup> = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total (95% CI) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 67 Heterogeneity: Ch <sup>2</sup> = 7.92 df = 3 (P = 0.05);   <sup>2</sup> = 62%	Fena.2016	8	36	6	36	9.5%	1.33 [0.51, 3.46]		-	
Subtotal (95% CI) 56 56 15.8% 1.30 [0.62, 2.71] Total events 13 10 Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% CI) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total (95% CI) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 67 Heterogeneity: Chi <sup>2</sup> = 7.92 df = 3 (P = 0.05); l <sup>2</sup> = 62%	Yao, 2015	5	20	4	20	6.3%	1.25 [0.39, 3.99]		-	
Total events       13       10         Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0%         Test for overall effect: Z = 0.70 (P = 0.48)         2.10.2 vinorelbine plus cisplatin         Shukuya.2012       12       39       38       50       52.5%       0.40 [0.25, 0.66]         Sugawara.2013       8       35       19       31       31.8%       0.37 [0.19, 0.73]         Subtotal (95% Cl)       74       81       84.2%       0.39 [0.26, 0.59]         Total events       20       57         Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 4.59 (P < 0.00001)         Total (95% Cl)       130       137       100.0%       0.54 [0.38, 0.75]         Total events       33       67         Heterogeneity: Chi <sup>2</sup> = 7.92 df = 3 (P = 0.05); l <sup>2</sup> = 62%	Subtotal (95% CI)		56	11	56	15.8%	1.30 [0.62, 2.71]			
Heterogeneity: Chi <sup>2</sup> = 0.01, df = 1 (P = 0.93); l <sup>2</sup> = 0% Test for overall effect: Z = 0.70 (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% Cl) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total (95% Cl) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 67 Heterogeneity: Chi <sup>2</sup> = 7.92 df = 3 (P = 0.05); l <sup>2</sup> = 62%	Total events	13		10						
Test for overall effect: $Z = 0.70$ (P = 0.48) 2.10.2 vinorelbine plus cisplatin Shukuya.2012 12 39 38 50 52.5% 0.40 [0.25, 0.66] Sugawara.2013 8 35 19 31 31.8% 0.37 [0.19, 0.73] Subtotal (95% CI) 74 81 84.2% 0.39 [0.26, 0.59] Total events 20 57 Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0% Test for overall effect: Z = 4.59 (P < 0.00001) Total (95% CI) 130 137 100.0% 0.54 [0.38, 0.75] Total events 33 67 Heterogeneity: Chi <sup>2</sup> = 7.92 df = 3 (P = 0.05); l <sup>2</sup> = 62%	Heterogeneity: Chi <sup>2</sup> :	= 0.01 df = 1	(P = 0)	93)· 12 = 0	1%					
2.10.2 vinorelbine plus cisplatin         Shukuya.2012       12       39       38       50       52.5%       0.40 [0.25, 0.66]         Sugawara.2013       8       35       19       31       31.8%       0.37 [0.19, 0.73]         Subtotal (95% CI)       74       81       84.2%       0.39 [0.26, 0.59]         Total events       20       57         Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); l² = 0%         Test for overall effect: Z = 4.59 (P < 0.00001)	Test for overall effect	t: Z = 0.70 (P	= 0.48)	)	//0					
Shukuya.2012       12       39       38       50       52.5%       0.40 [0.25, 0.66]         Sugawara.2013       8       35       19       31       31.8%       0.37 [0.19, 0.73]         Subtotal (95% CI)       74       81       84.2%       0.39 [0.26, 0.59]         Total events       20       57         Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 4.59 (P < 0.00001)         Total (95% CI)       130       137       100.0%       0.54 [0.38, 0.75]         Total events       33       67         Heterogeneity: Chi <sup>2</sup> = 7.92 df = 3 (P = 0.05); l <sup>2</sup> = 62% $l = 62\%$	2.10.2 vinorelbine n	lus cisplati	1							
Sugawara.2013       8       35       19       31       31.8% $0.37 [0.19, 0.73]$ Subtotal (95% CI)       74       81       84.2% $0.39 [0.26, 0.59]$ Total events       20       57         Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 4.59 (P < 0.00001)	Shukuya 2012	12	30	38	50	52 5%	0 40 10 25 0 661			
Subtotal (95% Cl)       74       81       84.2% $0.39 [0.26, 0.59]$ Total events       20       57         Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 4.59 (P < 0.00001)	Sugawara 2012	9	35	10	31	31 8%	0.37 [0.20, 0.00]			
Total events       20       57         Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Total (95% Cl)       130       137       100.0%       0.54 [0.38, 0.75]         Total events       33       67         Heterogeneity: Chi <sup>2</sup> = 7.92, df = 3 (P = 0.05); l <sup>2</sup> = 62%       4	Subtotal (95% CI)	0	74	19	81	84 2%	0.39 [0.16, 0.73]	•		
Heterogeneity: Chi <sup>2</sup> = 0.04, df = 1 (P = 0.85); l <sup>2</sup> = 0%         Test for overall effect: Z = 4.59 (P < 0.00001)	Total ovente	20	14	F7	01	04.2 /0	0.00 [0.20, 0.00]	200		
Test for overall effect: Z = 4.59 (P < 0.00001)	Hotorogonoity: Chi2	-0.04 df - 1	(D - 0)	05): 12 - 0	0/					
Test for overall effect: 2 = 4.59 (P < 0.00001)	Test for everall offer	-0.04, 01 = 1	(== 0.0	(0,0); F = 0	70					
Total (95% Cl)         130         137         100.0%         0.54 [0.38, 0.75]           Total events         33         67           Heterogeneity:         Chi² = 7.92         df = 3 (P = 0.05): l² = 62%	rest for overall effect	L Z = 4.59 (P	< 0.000	(100						
Total events 33 67	Total (95% CI)		130		137	100.0%	0.54 [0.38, 0.75]	+		
Heterogeneity: Chi <sup>2</sup> = 7 92 df = 3 (P = 0.05): l <sup>2</sup> = 62%	Total events	33		67				2 45	1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.	
	Heterogeneity: Chi2 =	= 7.92, df = 3	(P = 0.	05); l <sup>2</sup> = 6	52%			0.01 0.1	1 10	404
Test for overall effect: Z = 3.60 (P = 0.0003)	Test for overall effect	Test for overall effect: Z = 3.60 (P = 0.0003)							Fourier Coontroll	100

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.



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,<sup>[17]</sup> 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**

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