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The optimal neoadjuvant regimen for nonsmall cell lung cancer

A meta-analysis

Yi Liu, MS[a], Chong Zhao, MS[b], Qiuliang Lu, MS[a], Yirong Hu, MS[c,*]

Abstract

Objective: To compare the efficacy and complications of different neoadjuvant to determine the optimal regimens for nonsmall cell lung cancer (NSCLC) patients.

Methods: A systematic search of the Web of Science, and PubMed databases was conducted through June 3, 2021, reporting a comparison of chemotherapy, chemoradiotherapy, and immunotherapy.

Results: Of 3462 studies, 25 were considered for evidence synthesis. 1035 patients who received chemotherapy or radiotherapy before surgery did not prolong the overall survival (OS) compared with 1038 patients who received surgery alone (hazard ratio [HR] 1.13, 95% CI 1·00–1·28, P = 0·05). 1192 patients received chemoradiotherapy and 864 patients received chemotherapy or radiotherapy; chemoradiotherapy prolonged the OS compared with chemotherapy (HR 0.52, 95% CI 0·29 to 0.95, P = .03). Compared with 110 patients who received other therapy, 93 patients who received immunotherapy had prolonged the OS (HR 1.56, 95% CI 1·08–2·25, P = .02). Chemoradiotherapy increased the pathological response rate (HR 1.68, 95% CI 1·33–2·12, P < .0001), and grade 3 and 4 adverse effects were not increased (HR 5.90, 95% CI 0.88 to 39.60, P = .007). Immunotherapy increased the pathological response (HR 2.79, 95% CI 1·71–4·54, P < .0001), with no significant effects on grades 3 and 4 adverse(HR 0.71, 95% CI 0·19–2·64, P = .61).

Conclusion: Our data showed that chemotherapy may prolong OS and PFS, but not statistically significant; however, the combination of chemotherapy and radiation did show an advantage, and immunotherapy may be also the choice for neoadjuvant therapy.

Abbreviations: CI = confidence interval, GVP = gemcitabine–vinorelbine–cisplatin, HR = hazard ratio, MIP = mitomycin–ifosfamide–cisplatin, NSCLC = non-small cell lung cancer, OR = odds ratio, OS = overall survival, PFS = progression-free survival

Keywords: complications, meta-analysis, neoadjuvant, non-small cell lung cancer, overall survival

1. Introduction

Almost one-quarter of all cancer deaths are due to lung cancer, and 5-year relative survival rates are merely 21% for all stages combined.[1] More than 80% of patients affected by nonsmall cell lung cancer (NSCLC), early-stage lung cancer can be treated by innovative imaging-guided resection, minimally invasive approach, or multiple approaches with very good short-term outcomes, enhanced recovery, and prolonged overall survival.[2] As symptoms present late in the disease, the majority of patients (approximately 70%) already suffer from the locally advanced or metastatic disease at diagnosis and have an extremely limited possibility of being cured.[3] Neoadjuvant therapy has acceptable treatment-related toxicity and adverse event profile, it increases the likelihood of achieving an R0 resection and a pathological complete response for cancer therapy, including gastric cancer, breast cancer, etc.[4,5] Innovative systemic treatments and perioperative medical care have changed the role of surgery in the treatment of lung cancer. Treatments such as radiotherapy, chemotherapy, molecular targeted therapies, immunotherapy, and a combination of chemotherapy and radiotherapy are optional and performed depending on the histological type, pathological

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Conflict of Interest Statement: All named authors have no conflicts of interest to declare.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval: All procedures performed in the included studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. This article does not contain any studies with human participants performed by any of the authors.

[a] *Department of Thoracic Surgery, The People's Hospital of Yichun City, Jiangxi, 336028, China,* [b] *Department of Respiratory, The People's Hospital of Yichun City, Jiangxi, 336028, China,* [c] *Department of Neurology, The People's Hospital of Yichun City, Jiangxi, 336028, China.*

**Correspondence: Yirong Hu, No 88, Zhongshan Western Road, Yichun, Jiangxi 336028, China (e-mail: 24282894@qq.com).*

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stage, presence of gene mutations, and overall condition of the patient.[3,6–8] Herbs or their derivatives were also found to exert antiproliferation and potential antineoplastic activity[9,10]; however, the genotoxicity, mutagenicity, and mechanisms on cancer cells needed more in-depth research.[11–13] These treatment strategies have been widely adopted for neoadjuvant therapies and can markedly improve the prognosis of patients with the various stage of lung cancer.[14–16] Neoadjuvant therapy aims to shrink the tumor size and increase the success rate of the surgery treatment.

However, the optimal neoadjuvant regimen for locally advanced resectable NSCLC remains controversial. Previous studies indicated preoperative chemotherapy significantly improves overall survival, time to distant recurrence, and recurrence-free survival in resectable NSCLC, but toxic effects could not be assessed,[17] neoadjuvant radiotherapy alone does not improve resectability or survival, radiotherapy and chemotherapy combined are used for patients, the meta-analysis showed that chemoradiotherapy significantly increased the pathological complete response in mediastinal lymph nodes,[18] study suggests that hyperfractionated accelerated radiotherapy in combination with chemotherapy is an effective strategy to treat patients with locally advanced lung cancer with the advantage of a smaller dose and shorter duration,[19] on the other hand, a study showed that combination may increase the adverse effect.[20] Recently, immune-oncology drugs have proven their efficacy in the treatment of NSCLC, numerous clinical trials are underway to investigate the efficacy of neoadjuvant immunotherapy in resectable NSCLC, and to compare these approaches with placebo or other treatments.[3,14,21] Here, we performed a meta-analysis to explore the optimal neoadjuvant regimen for NSCLC.

2. Materials and Methods

2.1. Search strategy

We performed this meta-analysis by searching Web of Science, PubMed, and EMBASE databases for studies published through June 3, 2021. Additional records were identified by screening the reference in the identified studies. The search term was "non-small cell lung cancer neoadjuvant."

2.2. Inclusion and exclusion criteria

Two investigators independently screened the data, and when different opinions occurred, an agreement was reached by discussion. The inclusion criteria were the followings:[17] comparing different neoadjuvant regimens; (2) nonsmall cell lung cancer was pathologically confirmed; (3) sufficient data that were reported or could be calculated. Major exclusion criteria were (1) incomplete data for analysis; (2) books and documents, meeting abstracts, comments, meta-analysis, reviews, and articles cannot extract sufficient data; (3) adjuvant but not neoadjuvant therapy; (4) small cell lung cancer; (5) gray literature; (6) papers written in other languages that cannot be translated into English; and (7) duplicate data.

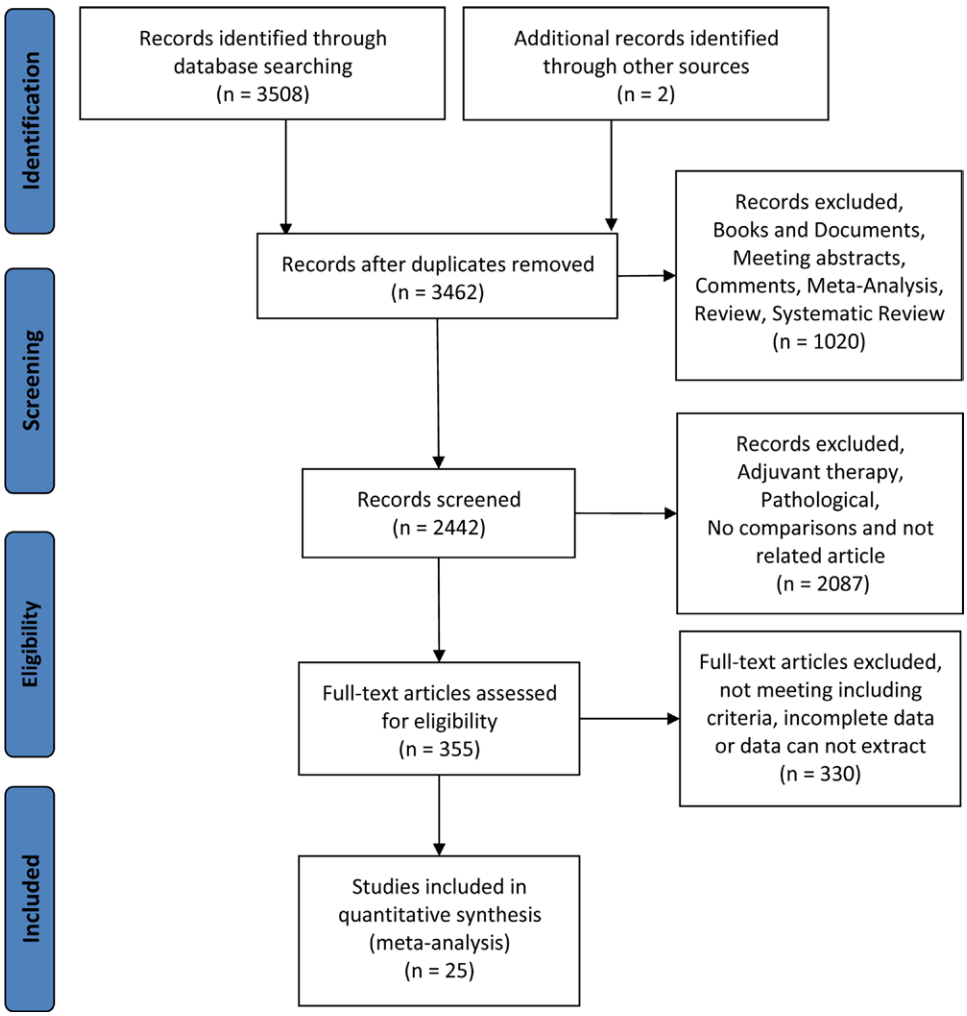

Figure 1. Flow diagram of the details of the study.

Table 1

Summary of included studies.

			Treatment						Control						
Stydy	Year	Nation	Prescription	Case	Response	Grade 3-4 adverse events	PFS	OS	Prescription	Case	Response	Grade 3-4 adverse events	PFS	OS	Follow up (median)
Zhao, X	2016[42]	China	Antiangiogenic therapy and chemotherapy	16	50%	0%			Chemotherapy	10	40%	0%			
Ratto, G. B	2011[34]	European	Leukapheresis and chemotherapy	13	54%	0%			Chemotherapy	32	56%	0%			44.4
Girard, N	2010[20]	France	Chemoradiotherapy	32	87%				Chemotherapy	14	57%				
Hamouda, W	2007[28]	Egypt	Radiotherapy	32	22%				chemotherapy	34	41%				15
Pezzetta, E	2005[31]	Switzerland	Radiochemotherapy	46					chemotherapy	36					53
Kumar, R	2020[19]	India	Chemotherapy and hyper-fractionatedaccelerated radiation therapy	30	28%	16%		12	Chemotherapy and conventional chemo-radiotherapy	30	20%	8%		12	
Xiong, L	2020[3,40]	China	Erlotinib	15	67%				Cisplatin-based doublet chemotherapy	16	19%				
Altorki, N. K	2021[14	USA	Durvalumab plus radiotherapy	30	53.30%	20%			Durvalumab	30	6.70%	17%			
Zhong, W. Z	2019[43]	China	Erlotinib	31	10%	0%	21.5	45.8	Gemcitabine Plus Cisplatin	23	0%	29%	11.4	39.2	32.5
Berghmans, T	2012[22]	European	Gemcitabine–vinorelbine–cisplatin	71	65%			36.6	Mitomycine–ifosfamide–cisplatin	69	60%			47.2	60
Cascone, T	2021[23]	USA	Nivolumab plus ipilimumab	21	38%	10%			Nivolumab	23	22%	13%			22.2
Chen, W. Q	2018[24]	China	Erlotinib	43	67%	21%			Pemetrexed combined with cisplatin	43	44%	14%			
Scagliotti, G. V	2012[37]	European	Chemotherapy	129	35%	41%	48	93.6	Surgery alone	141		11%	34.8	57.6	39.6
Pisters, K. M	2010[32]	USA	Chemotherapy	169	41%				Surgery alone	168					64
Gilligan, D.	2007[27]	European	Chemotherapy	258	49%			54	Surgery alone	261				55	41
Pless, M	2015[33]	European	Chemoradiotherapy	117	71%			37.1	Chemotherapy	115	50%			26.2	52.4
Thomas, M	2008[38]	German	Chemoradiotherapy	264	50%	10%			Chemotherapy	260	46%	0.50%			70
Toyooka, S	2012[39]	Japan	Chemoradiotherapy	35	45.70%				Chemotherapy	15	13.30%				
Katakami, N	2012[29]	Japan	Chemoradiotherapy	28	25%	92.90%			Chemotherapy	28	25%	46.40%			
Yang, C. F	2015[41]	USA	Chemoradiotherapy	834	58%				Chemotherapy	528	46%				
Roth	1994[36]	USA	Chemotherapy	28				64	Surgery alone	32				11	37
Rosell	1994[35]	Spain	Chemotherapy	30			20	26	Surgery alone	30			5	8	
Depierre	2002[25]	France	Chemotherapy	179			26.7	37	Surgery alone	176			12.9	26	80
Nagai	2003[30]	Japan	Chemotherapy	31	28%			17	Surgery alone	31				16	
Felip	2010[26]	European	Chemotherapy	201	53.50%				Surgery alone	212					

OS = overall survival, PFS = progression-free survival.

2.3. Data extraction

Overall survival (OS), response rate, and complications were the main indices to evaluate the treatments. Authors' names, publication year, patient number, neoadjuvant regimen, and complications were collected from the included studies. Complications included leucopenia, anemia, thrombocytopenia, nausea/vomiting, diarrhea, alopecia, elevated aminotransferase, and elevated total bilirubin. Clavien–Dindo Grading System was used to classify the complications. We divided the complications into the minor and severe groups, the minor group included Clavien–Dindo grade I and II, and the severe group include grades III, IV, and V. There was no Clavien–Dindo grade V complication in all patients.

2.4. Statistical analysis

All data were entered into Review Manager Software (The Cochrane Collaboration, version 5.3). Odds ratio (OR) with 95 % confidence interval (CI) were analyzed. Statistical heterogeneity among studies was evaluated utilizing I^2 statistics and P values. When $I^2 < 50\%$ indicated homogeneity among studies, the fixed effects model method was applied. When $I^2 \geq 50\%$, the random-effects model was used. Publication bias was evaluated using a funnel figure. A sensitivity analysis was performed to assess the stability of the results. The statistical analysis was performed using Review Manager Software (The Cochrane Collaboration, version 5.3).

3. Results

3.1. Study selection and characteristics

A total of 3462 records were identified through datasets, 1020 records were excluded after initial analysis and further screening was performed. Finally, 25 research were included in this meta-analysis[14,22–43] (Fig. 1). Of these studies, 7 focus on immunotherapy,[14,23,24,34,40,43,43] 8 focus on chemoradiotherapy,[19,20,29,31,33,38,39,41] 5 focus on chemotherapy or radiotherapy.[22,27,28,32,37] Include patients varied from ten to hundreds, all the studies were recorded in the 21st century (Table 1). We compared the effectiveness of different treatments for neoadjuvant, overall survival, response rate, and complications were evaluated.

3.2. Chemotherapy or radiotherapy

Nine studies assessed the results of overall survival,[22,25–27,30,32,35–37] 1035 patients who received chemotherapy or radiotherapy before surgery did not prolong the OS compared with 1038 patients who received surgery alone (hazard ratio [HR] 1.13, 95% CI 1.00–1·28, $P = 0.05$, Fig. 2A). However, chemotherapy did contribute to progression-free survival (PFS, HR 1.13, 95% CI 1.04–1.36, $P = 0.01$, Fig. 2B). The pathological response was about 22–65%, Hamouda, W, etc[28] compared the radiotherapy and chemotherapy, no significant difference was found between the 2 groups (HR 0.40, 95% CI 0.14–1·18, $P = 0.10$), Berghmans, T, etc[22] compared to 2 neoadjuvant chemotherapy (gemcitabine–vinorelbine–cisplatin, GVP VS mitomycin–ifosfamide–cisplatin, MIP), objective response rates to induction CT were 65%(GVP) and 60% (MIP)($P = .55$), while GVP was associated with more hematological toxicity, mainly thrombopenia ($P = .03$). Scagliotti, G. V, etc[37] also found chemotherapy increased the grade 3 or 4 adverse (HR 5.59, 95% CI 2.94 to 10·63, $P < 0.0001$).

3.3. Chemoradiotherapy

As shown in Figure 3, 1192 patients received chemoradiotherapy and 864 patients received chemotherapy or radiotherapy, chemoradiotherapy prolonged the OS compared with chemotherapy (HR 0.52, 95% CI 0.29 to 0.95, $P = .03$, Fig. 3A), PFS was also found a significant difference between chemoradiotherapy and chemotherapy (HR 0.58, 95% CI 0.37 to 0.92, $P = .02$, Fig. 3B). Chemoradiotherapy increased the response rate by 68% (HR 1.68, 95% CI 1.33–2·12, $P < .0001$, Fig. 3C), and grade 3 and 4 adverse effects were no difference between the 2 groups (HR 5.90, 95% CI 0.88 to 39.60, $P = .007$, Fig. 3D).

3.4. Immunotherapy

Compared with other therapy, 93 patients who received immunotherapy did prolong the OS (HR 1.56, 95% CI 1.08–2·25, $P = .02$, Fig. 4A), 1 study indicated immunotherapy was a benefit for PFS (HR 0.39, 95% CI 0.24–0.64, $P = .0002$, Fig. 4B). Immunotherapy increased the pathological response by 2.79 folds(HR 2.79, 95% CI 1.71–4·54, $P < .0001$, Fig. 4C), with no significant effects on grade 3 and 4 adverse (HR 0.71, 95% CI 0.19–2·64, $P = .61$, Fig. 4D).

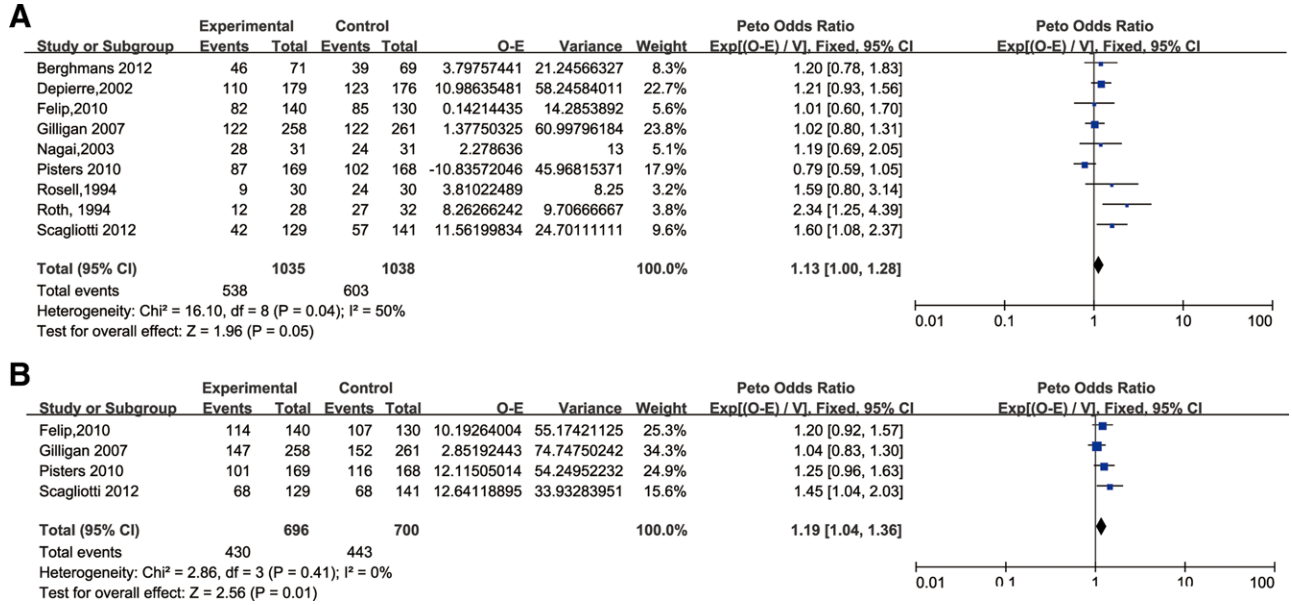

Figure 2. Forest plot for overall survival (A) and progression-free survival (B) for chemotherapy neoadjuvant comparing surgery alone.

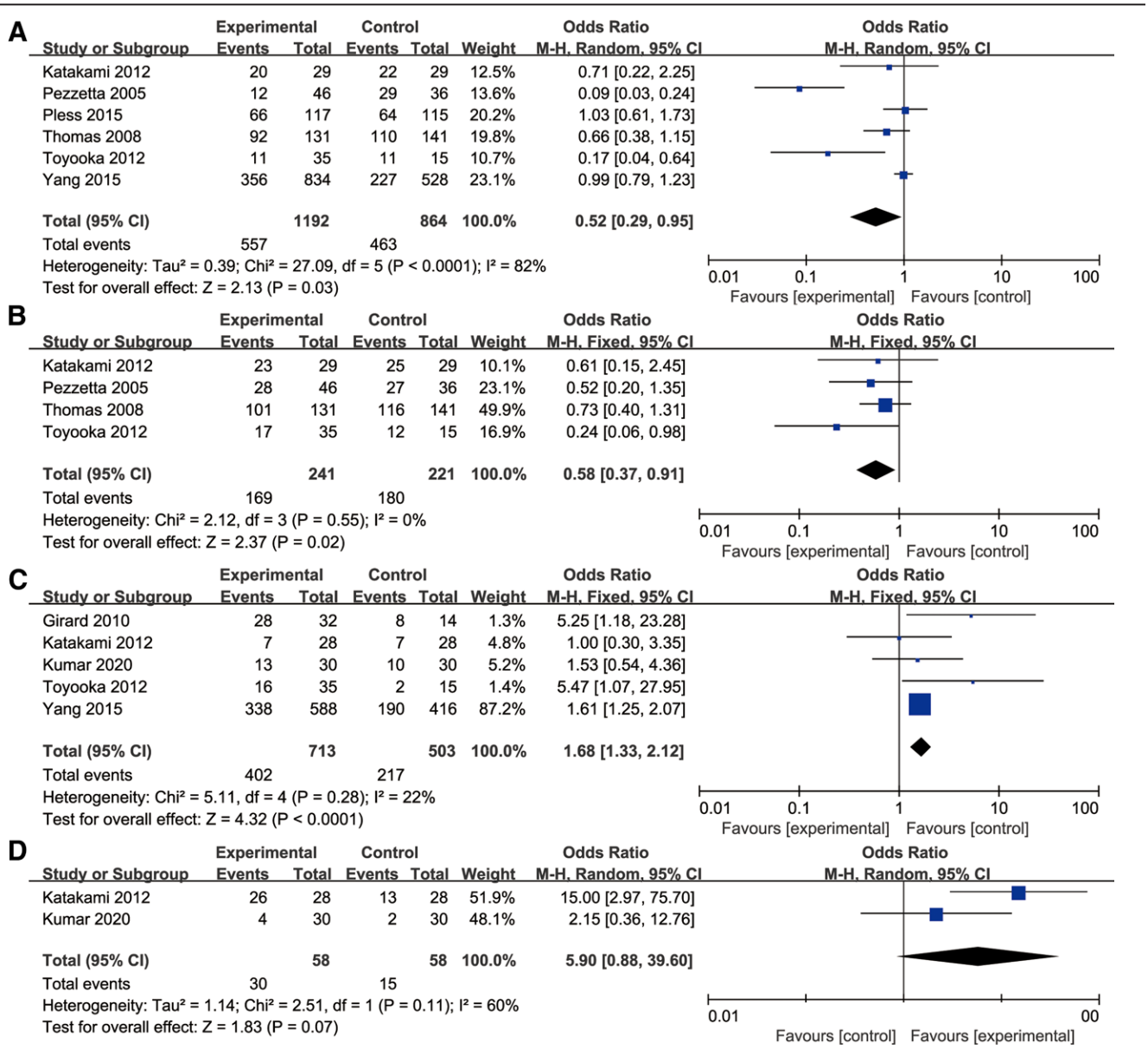

Figure 3. Forest plot for overall survival (A), progression-free survival (B), pathological response rate (C), and grade 3–4 adverse (D) for neoadjuvant chemoradiotherapy comparing chemotherapy or radiation.

3.5. Publication bias

Funnel figures were used to evaluate the publication bias for OS, no obvious bias was found as the figure was fundamental symmetry in the chemotherapy or radiotherapy group (Fig. 5A), chemoradiotherapy group (Fig. 5B), and immunotherapy group (Fig. 5C).

4. Discussion

Our meta-analysis summarizes the efficacy and safety outcomes of the currently published trials. A comprehensive search and systematic analysis of adjuvant therapy for nonsmall cell lung cancer were conducted in this paper. Results indicated that the neoadjuvant no matter chemotherapy, radiotherapy, chemoradiotherapy, or immunotherapy did not alter the OS, PFS was benefited from neoadjuvant in the immunotherapy group, but it was noted only 1 study investigated the PFS in this group, the sample size was small,[43] data showed chemoradiotherapy and immunotherapy were contributing to the pathological response (Figs. 3C and 4C), which may reduce tumor stage and increase the chance of complete resection, on the other hand, we found the sever complications were associated with chemoradiotherapy (Fig. 3D). The choice of treatment requires a trade-off between survival benefits and the risk of complications.

Previous studies showed that the use of neoadjuvant chemotherapy before surgery could give additional benefits for NSCLC patients with mediastinal involvement compared to surgery alone, however, the survival benefit after long-term follow-up was not observed, some other studies supported chemotherapy offered a significant 5-year overall survival advantage,[22,27,28,32,37,44] we noted that there are a variety of chemotherapy options, gemcitabine-cisplatin, paclitaxel-carboplatin, gemcitabine-vinorelbine-cisplatin, mitomycin-ifosfamide-cisplatin, etc were optional, these regimens were mainly platinum-based chemotherapy. Both gemcitabine-vinorelbine-cisplatin (GVP) and mitomycin-ifosfamide-cisplatin (MIP) neoadjuvant chemotherapy regimens shared similar efficacy in patients with NSCLC, costs were significantly higher for GVP regimens.[22] The advantages of neoadjuvant chemotherapy may be limited due to the progress of anesthesia and surgery, 2 of

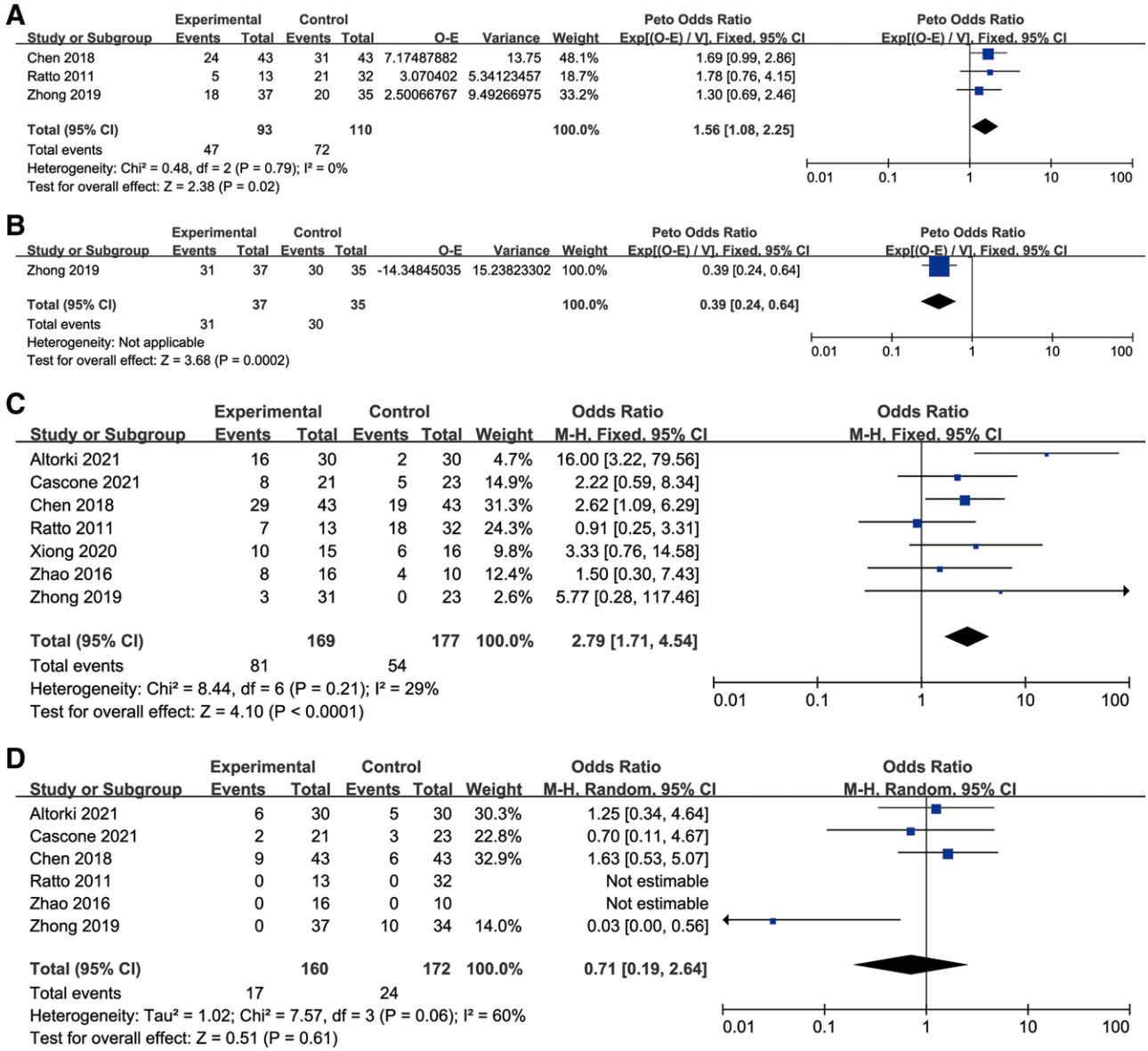

Figure 4. Forest plot for overall survival (A), progression-free survival (B), pathological response rate (C), and grade 3-4 adverse (D) for neoadjuvant immunotherapy comparing chemotherapy or radiation.

included studies indicated neoadjuvant chemotherapy favored better OS, and 1 suggested perioperative chemotherapy consisted of cyclophosphamide (500 mg per square meter of the body-surface area given intravenously on day 1), etoposide (100 mg per square meter of the body-surface area given intravenously on days 1, 2, and 3), and cisplatin (100 mg per square meter of the body-surface area given intravenously on day 1), the other suggested 3 cycles of gemcitabine 1250 mg per square meter of the body-surface area on days 1 and 8 every 3 weeks plus cisplatin 75 mg per square meter of the body-surface area on day 1 every 3 weeks.[36,37] Radiotherapy alone was rarely applied for neoadjuvant therapy; the OS benefit was limited.[28]

Studies have focused on the combined application of radiotherapy and chemotherapy,[19,20,29,31,33,38,39,41] however, the pooled results were not satisfactory (Fig. 3A, B). The advent of novel irradiation techniques, such as 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated RT (IMRT), and volumetric-modulated arc therapy (VMAT), may improve clinical outcomes in some situations,[45] our meta-analysis indicated clinical response was better in chemoradiotherapy, meanwhile, adverse effects were more common (Figs. 3C and 3D). Docetaxel plus cisplatin with concurrent radiation at a dose of 40 to 46 Gy used for induction chemoradiotherapy was verified by Toyooka, S, et al that it could prolong patients' overall survival and disease-free survival than the chemotherapy group (OS, $P = .0020$; PFS, $P = .015$).[39]

Our data indicated immunotherapy favored better OS and PFS than chemotherapy (Figs. 4A and 4B), the response rate was also higher in the immunotherapy group (Fig. 4C), and the adverse effect was not increased (Fig. 4D). Over the last decade, there has been an acceleration in the emergence of new inhibitors approved in NSCLC immunotherapy, since the first epidermal growth factor receptor inhibitor developed in 1990, dozens of new drugs have been developed.[46] Nowadays, ipilimumab, nivolumab, and erlotinib were commonly applied in the clinic, data showed immunotherapy alone may be sufficient for neoadjuvant.[24,34,43] Carcinogenesis is initiated when an irreversible and heritable mutation occurs in one of the key proteins that control many vital cell functions, various genes such as MET, NTRK, ROS1, ALK, etc. were potential oncogenes, and drugs aimed to inhibit the activity of these genes were developed,[46] individual immunotherapy will be possible soon.

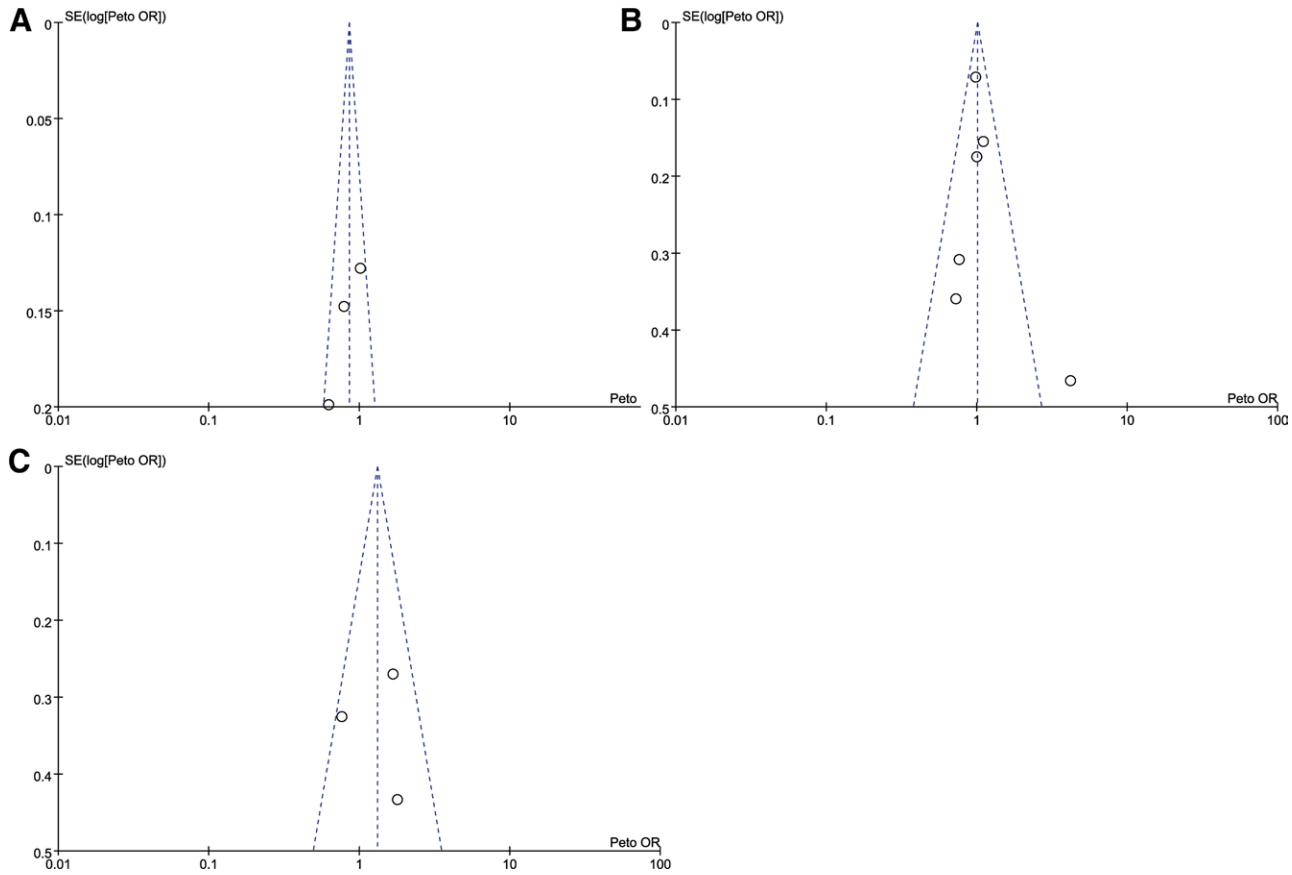

Figure 5. Funnel plots evaluating possible publication bias.

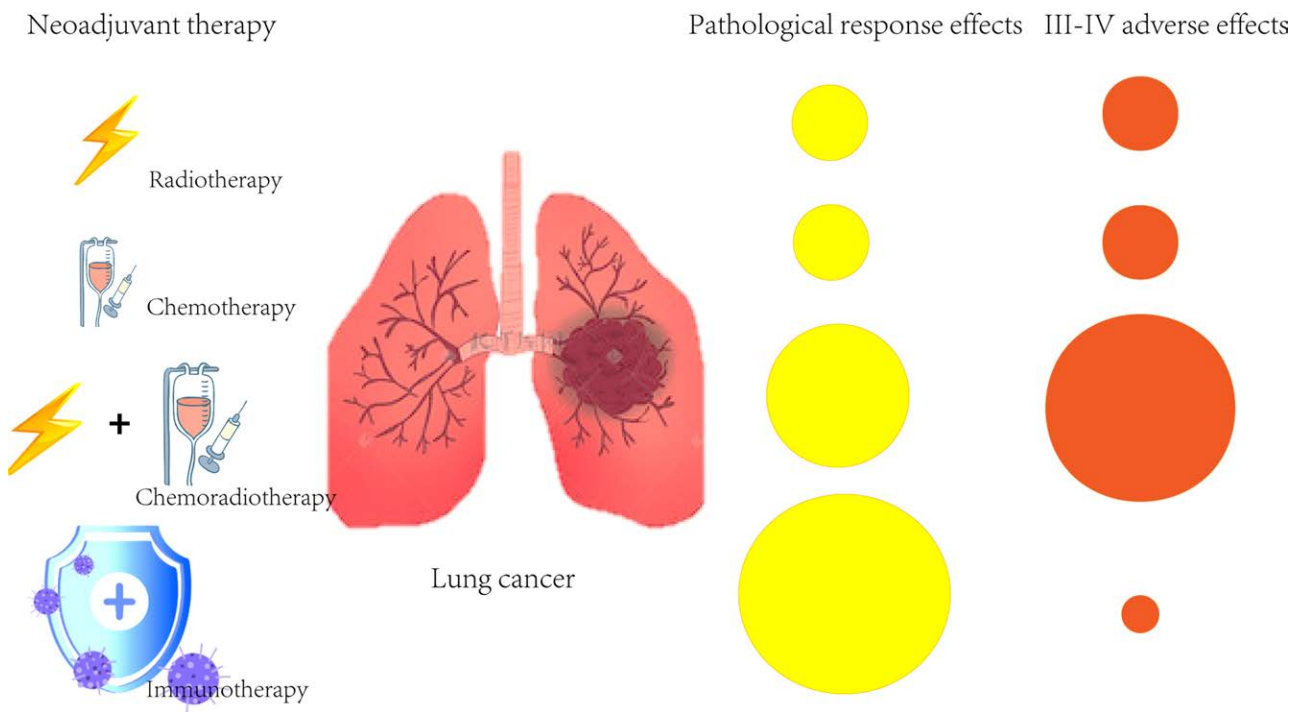

Figure 6. The pathological responses and adverse effects were indicated, the pathological response was about 22–65% for the radiotherapy or chemotherapy, chemoradiotherapy increased the response rate by 1.68 folds, and immunotherapy increased the pathological response by 2.79 folds. III–IV adverse effects occurred in 15/58 in the radiotherapy or chemotherapy group, 30/58 in the chemoradiotherapy group, and 17/160 in the immunotherapy group.

Several limitations should be noted in this meta-analysis. First, subgroup analysis was not performed, neoadjuvant may exert different effect in distinct stage NSCLC, the role of neoadjuvant may be more vital for stage III NSCLC than stage I NSCLC; Second, studies from different country may achieved various results, racial and regional differences may lead to different efficacy of neoadjuvant; Third, differences in surgical techniques may lead to differences in patient survival, and advances in surgical techniques may vary in the selection of surgical patients; Forth, NSCLC consist of squamous cell carcinoma, adenocarcinoma, and large cell lung cancer, this study did not focus on the response of different pathological types of lung cancer to neoadjuvant therapy; Fifth, adjuvant was applied for some patients, this study did not investigate the effect of adjuvant therapy on outcome; Sixth, the effect of neoadjuvant therapy on surgery-related data and complications was not analyzed; Seventh, the sample size of some studies is too small, the reliability of pooled results may be affected. Despite these shortcomings, this study is the most systematic meta-analysis to date, and we look forward to the results of more high-level clinical trials for further analysis.

5. Conclusion

In conclusion, our data showed the combination of chemotherapy and radiation show an advantage for prolonging OS and PFS, immunotherapy may be the best choice for neoadjuvant (Fig. 6).

Author contributions

Project development: Yirong Hu; data collection or management: Yirong Hu and Yi Liu; data analysis and interpretation: Yi Liu and Chong Zhao; manuscript writing: Yi Liu and Chong Zhao; manuscript editing: Qiuliang Lu; and study supervision: Yirong Hu.

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