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Innovative strategies and new insights for the treatment of stage III non-small cell lung cancer

Edited by
Aakash Desai, Andrea R. Filippi and Jessica Desiree Menis

Coordinated by
Francesco Cortiula

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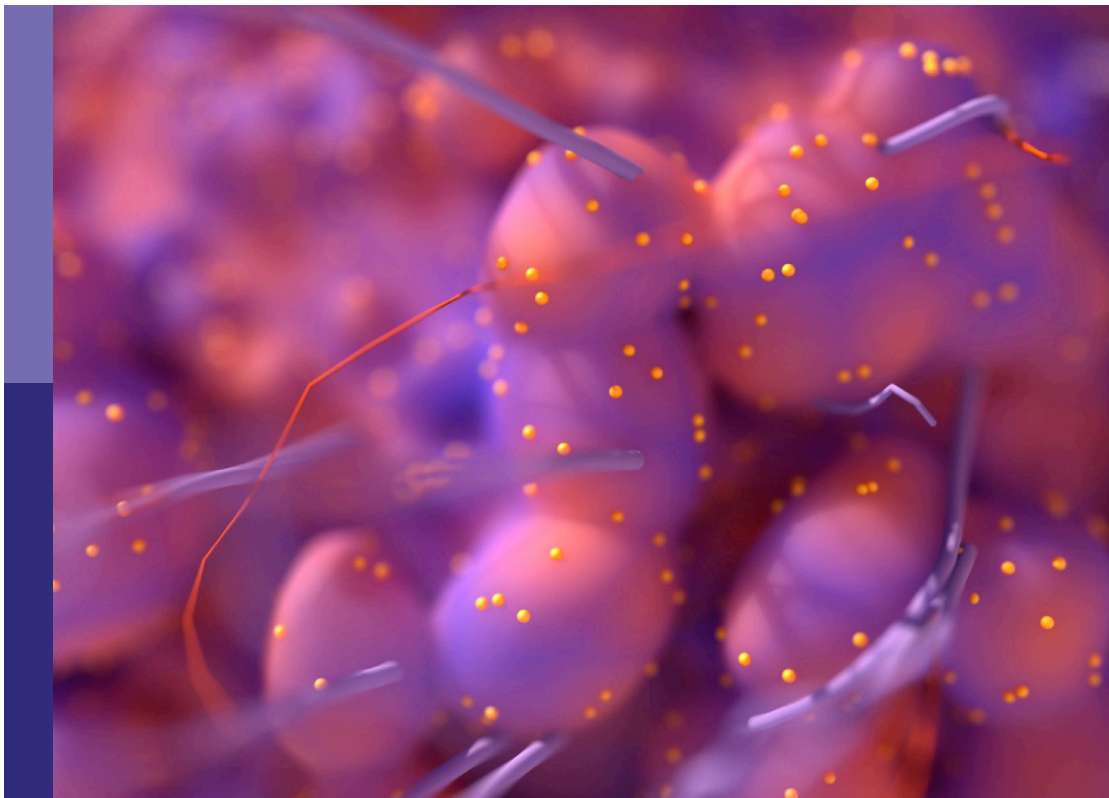

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Innovative strategies and new insights for the treatment of stage III non-small cell lung cancer

Topic editors

Aakash Desai — University of Alabama at Birmingham, United States

Andrea R. Filippi — Radiotherapy Unit, Istituto Nazionale Tumori, Italy

Jessica Desiree Menis — Oncology, Integrated University Hospital Verona, Italy

Topic coordinator

Francesco Cortiula — Maastricht University Medical Centre, Netherlands

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Sharon R. Pine,
University of Colorado Anschutz Medical Campus, United States

*CORRESPONDENCE
Francesco Cortiula
francesco.cortiula@maastro.nl

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Editorial: Innovative strategies and new insights for the treatment of stage III non-small cell lung cancer

Francesco Cortiula[1,2]*, Aakash Desai[3], Jessica Menis[4] and Andrea R. Filippi[5,6]

[1]Department of Oncology, University Hospital of Udine, Udine, Italy, [2]Department of Radiation Oncology (Maastro), Maastricht University Medical Centre (+), GROW School for Oncology and Reproduction, Maastricht, Netherlands, [3]Department of Medical Oncology, Mayo Clinic, Rochester, MN, United States, [4]Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona and University and Hospital Trust/Azienda Ospedaliero-Universitaria Integrata (AOUI), Verona, Italy, [5]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy, [6]Department of Radiotherapy, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

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stage III NSCLC, resectable NSCLC, radiation therapy, predictive model, biomarker

Editorial on the Research Topic
Innovative strategies and new insights for the treatment of stage III non-small cell lung cancer

About one third of patients with non-small cell lung cancer presents with stage III NSCLC at diagnosis (1). The standard of care for patients with unresectable stage III NSCLC is concurrent chemoradiation (CCRT) followed by adjuvant durvalumab (2). Adjuvant durvalumab led to a 5-year overall survival (OS) and progression free survival (PFS) rates of 42.9% and 33.1% respectively (3). For patients with resectable stage III NSCLC the standard of care is represented by surgery and (neo) adjuvant or perioperative immune checkpoint blockers (ICB), leading to a 2 years OS rate up to 80% and 2 years PFS rate up to 65% (4–7). For patients with stage III NSCLC harboring actionable driver alterations (AGA) radical treatment should be coupled with (neo)adjuvant target treatments, if available (8, 9). Despite the great survival improvements achieved in the recent years, most of the patients who are diagnosed with stage III NSCLC still face disease recurrence (PD). Moreover, many open questions and unmet clinical need are present in this setting (10, 11).

The manuscripts included in the present Research Topic try to address open questions and present new evidence about the treatment options for patients with stage III NSCLC.

Yu et al. performed a meta-analysis based on three randomized controlled trials (RCTs) investigating perioperative ICB for stage II-III NSCLC. Their findings showed that perioperative ICB combined with CT led to better OS, PFS and ORR compared to CT only. At the same time no statistically significant differences in terms of grade≥3 adverse events were noted. This meta-analysis confirmed that the use of ICB in the peri-operative

setting is the new gold-standard. Qiao et al. investigated the effectiveness and safety of Shenqi Fuzheng (SFI) injection combined with platinum-based chemotherapy for patients with NSCLC. SFI is an extraction of *Codonopsis pilosula and Astragalus membranaceus*, which reduces oxidative stress. Their findings are based on 44RCT involving 3475 patients. They showed that SFI significantly reduced CT adverse events (bone marrow depression; nausea; vomiting and diarrhea). This meta-analysis investigates the often neglected Research Topic of reducing side effects. This is paramount in stage III NSCLC since toxicity represents a main issue in radical treatments in this setting. Li et al. addressed the question whether ICB retreatment might be effective for patients with NSCLC. This retrospective study included 165 patients who were pretreated with ICB: 38.2% received ICB retreatment with atezolizumab while 12.7% and 49.1% received docetaxel and docetaxel+ramucirumab respectively. Patients treated with atezolizumab achieved a significantly better mOS compared to the other two groups [17.7 vs. 7.7 months for docetaxel (p=0.008) and vs 8.9 months for docetaxel +ramucirumab (p=0.047)]. These results are particularly interesting since patients with stage III NSCLC receive adjuvant ICB as standard of care but there are no robust data about a ICB retreatment at PD. In the retrospective study presented by Borghetti et al. (N=85), safety and effectiveness of adjuvant durvalumab in a real life scenario were investigated. Two-year OS was 69.4% in the durvalumab group and 47.9% in the non-durvalumab group (p = 0.015). Two-year PFS was 54.4% in the durvalumab group and 24.2% in the non-durvalumab group (p = 0.007). Of note, 79% had a PDL-1 positive NSCLC and in the remaining 21% PDL-1 status was unknown. A retrospective multicenter analysis (N=1874) described the pattern of treatments in the Asian population (Prabhash et al.). This study enrolled consecutive patients, from 57 centers, diagnosed with *de novo* locally advanced stage III NSCLC. CCRT was the most common treatment choice (34%) followed by curative surgery (23%), systemic treatments (21%) and sCRT (11%). The possible different approaches used in this wide cohort to treat stage III highlight that multidisciplinary discussion is paramount in this setting. Finally two studies presented in this Research Topic investigated new tools for personalizing the treatment of patients with stage III NSCLC. Yang et al. presented the data about 124 patients with stage III-N2 disease treated with surgery, adjuvant CT and post-operative RT (PORT). They showed that the presence of estrogen receptor was a significant negative prognostic factor, in terms of OS and PFS. These findings bring to light a possible new prognostic factor, possibly helping in tailoring the treatment of patients with stage III NSCLC. Jin et al. showed that machine learning models, trained with clinical data, could predict the survival of patients with resected stage III NSCLC better than the TNM staging only. These tools are particularly interesting considering the numerous new treatment option becoming available for patients with stage III NSCLC and the consequent need to find the best balance between reducing the risk of relapse, the risk of side effects and the financial toxicity.

Altogether, the manuscripts included in this Research Topic represent a resource to further deepen the knowledge of stage III NSCLC and they provide preliminary insights to develop future clinical trials. We believe that future studies in this setting should aim not only to test the efficacy of new drugs, but also to address open questions and unmet clinical needs, such as the need for predictive biomarkers and the development of adaptive treatment strategies to spare unnecessary toxicity or to escalate therapy when needed.

Author contributions

FC: Conceptualization, Writing – original draft. AD: Conceptualization, Project administration, Writing – review & editing. JM: Project administration, Writing – review & editing. AF: Project administration, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Amin MB, Edge S, Greene F, Byrd D. R., Brookland R. K., Washington M. K., et al. *AJCC Cancer Staging Manual. 8th Edition*. London (global) Berlin (corporate) New York City (sales): Springer International Publishing: American Joint Commission on Cancer (2017).

2. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. (2018) 379:2342–50. doi: 10.1056/NEJMoa1809697

3. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. (2022), JCO2101308. doi: 10.1200/JCO.21.01308

4. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee S-H, Gao S, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. *New Engl J Med*. (2023) 389:491–503. doi: 10.1056/NEJMoa2302983

5. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. (2022) 386:1973–85. doi: 10.1056/NEJMoa2202170

6. Felip E, Altorki N, Zhou C, Vallières E, Martínez-Martí A, Rittmeyer A, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Ann Oncol*. (2023) 34:907–19. doi: 10.1016/j.annonc.2023.07.001

7. Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, et al. Perioperative nivolumab in resectable lung cancer. *New Engl J Med*. (2024) 390:1756–69. doi: 10.1056/NEJMoa2311926

8. Remon J, Saw SPL, Cortiula F, Singh PK, Menis J, Mountzios G, et al. Perioperative treatment strategies in EGFR-mutant early-stage NSCLC: current evidence and future challenges. *J Thorac Oncol*. (2023) S1556-0864(23)02261-X. doi: 10.1016/j.jtho.2023.09.1451

9. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, et al. Alectinib in resected ALK-positive non–small-cell lung cancer. *New Engl J Med*. (2024) 390:1265–76. doi: 10.1056/NEJMoa2310532

10. Bortolot M, Cortiula F, Fasola G, De Ruysscher D, Naidoo J, Hendriks LEL. Treatment of unresectable stage III non-small cell lung cancer for patients who are under-represented in clinical trials. *Cancer Treat Rev*. (2024) 129:102797. doi: 10.1016/j.ctrv.2024.102797

11. Bartolomeo V, Cortiula F, Hendriks LEL, De Ruysscher D, Filippi AR. A glimpse into the future for unresectable stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. (2023), S0360–3016(23)08126-9. doi: 10.1016/j.ijrobp.2023.11.005

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EDITED BY
Lal Hussain,
University of Azad Jammu and Kashmir, Pakistan

REVIEWED BY
Peng-Chan Lin,
National Cheng Kung University, Taiwan
Adeel Ahmed Abbasi,
Central South University, China

*CORRESPONDENCE
Jia Ma
majia1110@sina.com

†These authors have contributed equally to this work

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Development and validation of machine learning models to predict survival of patients with resected stage-III NSCLC

Long Jin[1†], Qifan Zhao[2†], Shenbo Fu[3], Fei Cao[4], Bin Hou[5] and Jia Ma[6*]

[1]Department of Radiation Oncology, Shaanxi Provincial People's Hospital, Xi'an, China, [2]School of Material Science & Engineering, Huazhong University of Science and Technology, Wuhan, China, [3]Department of Radiation Oncology, Shaanxi Provincial Cancer Hospital, Xi'an, China, [4]Department of Oncology, Shaanxi Provincial People's Hospital, Xi'an, China, [5]Department of Thoracic Surgery, Shaanxi Provincial People's Hospital, Xi'an, China, [6]Shaanxi Provincial People's Hospital, Xi'an, China

Objective: To compare the performance of three machine learning algorithms with the tumor, node, and metastasis (TNM) staging system in survival prediction and validate the individual adjuvant treatment recommendations plan based on the optimal model.

Methods: In this study, we trained three machine learning madel and validated 3 machine learning survival models-deep learning neural network, random forest and cox proportional hazard model- using the data of patients with stage-al3 NSCLC patients who received resection surgery from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database from 2012 to 2017,the performance of survival predication from all machine learning models were assessed using a concordance index (c-index) and the averaged c-index is utilized for cross-validation. The optimal model was externally validated in an independent cohort from Shaanxi Provincial People's Hospital. Then we compare the performance of the optimal model and TNM staging system. Finally, we developed a Cloud-based recommendation system for adjuvant therapy to visualize survival curve of each treatment plan and deployed on the internet.

Results: A total of 4617 patients were included in this study. The deep learning network performed more stably and accurately in predicting stage-iii NSCLC resected patients survival than the random survival forest and Cox proportional hazard model on the internal test dataset (C-index=0.834 vs. 0.678 vs. 0.640) and better than TNM staging system (C-index=0.820 vs. 0.650) in the external validation. The individual patient who follow the reference from recommendation system had superior survival compared to those who did not. The predicted 5-year-survival curve for each adjuvant treatment plan could be accessed in the recommender system *via* the browser.

Conclusion: Deep learning model has several advantages over linear model and random forest model in prognostic predication and treatment recommendations. This novel analytical approach may provide accurate predication on individual survival and treatment recommendations for resected Stage-iii NSCLC patients.

KEYWORDS

non-small cell lung cancer (NSCLC), stage-III, machine learning, survival predication, treatment recommendation, adjuvant therapy

1 Introduction

Stage-iii non-small cell lung cancer (NSCLC) accounts for about 1/4 to 1/3 of total lung cancer and is a very heterogeneous disease with a discouraging clinical prognosis, the 5-year survival rate of NSCLC is only 15%-40% (1). For operable stage-iii lung cancer patients, surgery-based comprehensive treatment is recommended. However, even after radical tumor resection, there is still a high risk of recurrence and metastasis, so adjuvant therapy after surgery is required to improve long-term survival probability. Postoperative adjuvant therapy mainly includes adjuvant chemotherapy, radiotherapy and targeted therapy. Among them, adjuvant targeting is mainly aimed at the EGFR-amplified non-small cell lung cancer patients. Targeted therapy can improve its prognosis, but the proportion of this population is relatively low, only 9% of the total non-small cell lung cancer patients (2). For the vast majority of patients with EGFR-negative stage-iii lung cancer, studies have shown that postoperative chemotherapy (POCT) can improve the 5-year survival rate by 5% (3). Other researches confirm that the value of postoperative radiotherapy for high-risk subgroups (4–6), While the results of the meta-analysis in 1998 determines that postoperative adjuvant radiotherapy is not recommended for patients with stage I-IIIB (N0-N1) (7). In addition, the 2020 Lung ART study suggests that adjuvant radiotherapy is not recommended for patients with N2 after lung cancer surgery (8). Therefore, whether postoperative radiotherapy has a beneficial effect on overall survival (OS) is controversial. In the current clinical practice, the formulation and implementation of adjuvant chemotherapy and radiotherapy treatment plans are mainly based on the TNM staging system. Therefore, there are two drawbacks. The first defect is that only three clinical indicators of patients T, N, and M are considered to guide the clinical treatment of patients while ignoring other important characteristics of patients such as physiological characteristics (age, gender) and Other important clinical characteristics (surgical method, primary tumor location, tumor grade, number of positive lymph nodes (LNs), number of LNs examined, and adjuvant therapy methods). Secondly, the TNM staging system is used for risk stratification of the population, and cannot work as a tool to provide prognosis prediction for individual patients. Therefore, it cannot meet the need to improve patient prognosis. Today, with today's increasingly perfect electronic medical record system, deep learning has been widely used in the medical field to predict the survival rate of cancer patients, which performs better than the traditional cox regression method (9–17). In this experiment, we trained a deep learning model based on a large amount of clinical data and developed a patient-oriented assistant utilizing this model. A recommendation system for radiotherapy and chemotherapy can be accessed through the Internet to provide patients with reference opinions for postoperative radiotherapy and chemotherapy regimens Figure 1.

2 Method

2.1 Eligibility criteria and patient information

Regarding the training cohort, We selected 4517 medical cases from Database: Incidence - SEER Research Plus Data, 18 Registries, Nov 2019 Sub (2000–2017) - Linked To County Attributes - Total U.S., 1969-2018 Counties, National Cancer Institute,DCCPS, Surveillance Research Program, released April 2021, based on the November 2019 submission. We included Data records if they meet the criterion (1), patients pathologically diagnosed between January 2012 and December 2017 with primary stage-teriii non-small cell lung cancer (NSCLC) and (2) the existence of one malignant lesion. On the contrary, We excluded clinical cases according to the standard (1), patients whose regional lymph nodes performed during the initial work-up or first course of therapy are unknown or missing. Then we choose the features relevant to the OS (overall survival) of the NSCLC, including demographic information (Age and Sex) and NSCLC-cancer-related characteristics (TNM stage, histology type, primary site, tumor size, regional node number examined, regional node positive number and laterality of the tumor), and treatment details(surgery of primary site, radiation, and chemotherapy), The outcome is the patient survival time and death indicator. As for the cohort for external validation of the model, the inclusion criteria and exclusion criteria are consistent with the training group, So we randomly collected 100 stage-iii non-small cell lung cancer patients who underwent surgery (Lobectomy WITH mediastinal lymph node dissection and Pneumonectomy) from January 2012 to December 2017 in Shaanxi Provincial People's Hospital, China.

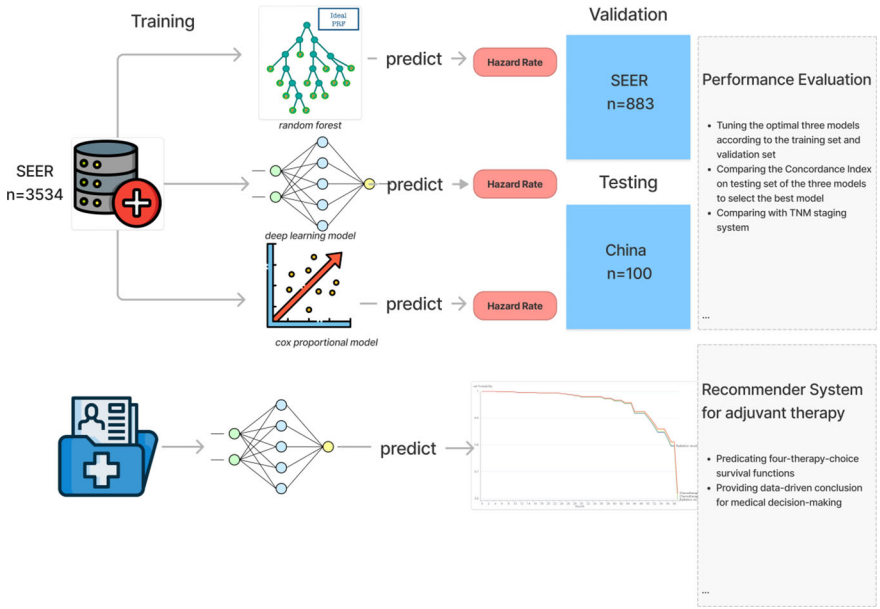

FIGURE 1
Diagram of the training and recommendation procedure.

2.2 Data preprocessing and feature engineering

The training data and the testing data are stored in CSV files. Both datasets contain two types of variables in the covariates, numerical variable and categorical variable. In the dataset, we have 3 numerical variable fields, including regional node positive number, regional node number examined and tumor size as well as other 10 categorical variable features. In order to avoid the evaluation problems *via* using label encoding conversion to categorical, we converse the 10 categorical features by utilizing one hot encoding to identify the different categorical values in the feature in a binary fashion. To illustrate, Regarding feature surgery on the primary site, before conversion, this field contains two values encoded for two surgery types (Lobectomy WITH mediastinal lymph node dissection, Pneumonectomy WITH mediastinal lymph node dissection). After transformation, the very field will be replaced by two surgery types, the value of the two features could only be 0 or 1 to identify the specific surgery type. In addition, as for feature tumor size, in the training set the unit is millimeter while in the testing dataset, the unit is centimeter. So we divide the value in the training set by 10 to make the unit the same. Finally, we perform normalization in order to accelerate the training process.

2.3 Machine learning survival model design

In this section, we created three machine learning models to perform the survival analysis to select the optimal one.

We developed a deep learning model based on DeepSurv to predict personal hazard rate according to the patient's current clinical condition. From the input to output, the patient's baseline data is the input to the neural network, followed by the fully-connected hidden layers of nodes as well as a drop layer after each hidden layer. The output of the network is the hazard rate. Regarding the activation function of each node, in order to overcome the problem of vanishing gradients, we select ReLU to add nonlinearity to the model which could help the model learn the complex relationship between covariates and the hazard rate. As for the loss function, we train the model to minimize the average negative log partial likelihood with regularization:

$$(\theta) = -\frac{1}{N_{E=1}} \sum_{i:Ei=1} \left(\hat{h}_\theta(x_i) - \log \sum_{j \in R(T_i)} e^{\hat{h}_\theta(x_j)} \right) + \lambda \cdot ||\theta||_2^2 \qquad (1)$$

where θ is the weight of every node in the network, $\frac{1}{N_{E=1}}$ is the number of dead patients and λ is the l_2 regularization parameter, $\hat{h}_\theta(x)$ is the predicated hazard rate. we use Adam for the gradient descent algorithm to update the parameter of the model for lots of epochs, because Adam is more efficient when working with problems involving high dimensional data and requiring less memory for optimization process compared with SGD method (18). We utilize random Search to optimize the hyper-parameters because compared to Grid Search, Random Search could try more cases for important hyper-parameters. In the experiment, we perform this on the log space of the learning rate in [0.00001, 0.1], the dropout rate in [0.2-0.5], the number of hidden layers in [1, 7] and the number of nodes in each hidden layer in [5,90].

We also trained a random forest model, this model is reliable because it forces each split to consider only a subset of the predictors. In this study, Random Search is still used to tune the number of the comprising trees in [100,300], the minimum number of samples required to split an internal node in [2,50] as well as the minimum number of samples required to be at a leaf node in [1,20].

Lastly, we trained the Penalized Cox Proportional hazard model with the same loss function as the deep learning model. we tuned the hyperparameter by using Random Search Method, specifically, the penalizer in [0.001,1] and the learning rate in [0.001,1].

2.4 Model training and evaluation

The concordance index(C-index) is used to measure the performance of the model. The C-index is the ratio of pairs of patients ordered correctly to all pairs. Thus the higher C-index, the better performance of the model. In the study, The 4517 SEER data records were divided into two groups, 3534(80%) records were used for training while 883(20%) records were treated as the validation set. The five-fold cross-validation was performed to tune the hyper-parameters of each model and select the best model for survival prediction. Additionally, external validation was performed on the selected optimal model and TNM staging system and compare the generalizability of the two models. Eventually, we performed the attribution analysis for the deep learning survival model by the integrated gradients (19) method based on the testing dataset to rank the clinical feature importance.

2.5 Cloud-based adjuvant therapy recommender system deployment

The deep learning algorithm could recommend treatment for patients according to their current clinical conditions (20). we could load the model and set the input according to the patient's demographic feature(age and gender), Surgery Type(lobectomy and pneumonectomy), Type(histology type and laterality) and the stage information of NSCLC(TNM, the number of the examined regional node, the number of the positive regional node and the tumor size). As for Adjuvant therapy, we predict the hazard rate under four adjuvant therapy treatments (with radiation and chemotherapy, with radiation and without chemotherapy, without radiation and with chemotherapy, and without radiation and chemotherapy). Then we could get the four cumulative hazard functions under each adjuvant therapy treatment and finally derive the four 5-year survival functions after negating and exponentiating the cumulative hazard function. In this application, we develop the backend code to calculate the four 5-year adjuvant therapy survival functions and implement the UI code to display the predicated survival functions in the line race chart.

2.6 Computation software

The three models are trained with Python v 3.9, PyTorch v 1.11.0 is used to train the deep learning algorithm and PySurvival v 0.1.2 is utilized to train the random survival forest and penalized cox proportional hazard model. The Front UI of the adjuvant therapy recommender system is developed with Vue.js javascript framework and a Material Design component framework called Vuetify. The backend code of the web application is implemented by the Django REST framework. The recommender system is deployed on Tencent Cloud, which could be accessed through a web browser.

3 Results

3.1 Patient baseline characteristics

Based on the inclusion criteria, we include 4617 stage-iii NSCLC patients who received Surgeries (Lobectomy and Pneumonectomy with mediastinal lymph node dissection) in this study. The 4517 patients out of 4617 are extracted from the SEER database and used as a training set while the other 100 patients are from China Database for model testing. The baseline medical characteristics of the two cohorts are shown in Table 1. From the AJCC TNM staging system's perspective, all patients in the training set and the testing set are stage-iii NSCLC patients. In the SEER cohort, most patients' histology type is Adenocarcinoma, which takes 44.28%. The next one is Squamous cell carcinoma, which takes 23.27%. Regarding the Received surgeries, 85.51% of patients received Lobectomy WITH mediastinal lymph node dissection while the rest (14.48%) accepted Pneumonectomy WITH mediastinal lymph node dissection for treatment. Concerning Adjuvant treatment, 74.12% of patients accepted chemotherapy and about 41.88% received beam radiation. On the contrary, in the test cohort, most patients received Lobectomy WITH mediastinal lymph node dissection, the two leading histology types are Squamous cell carcinoma and Adenocarcinoma, respectively 46% and 43% of the population. As for Adjuvant treatment, 1/3 received beam radiation and almost everyone received chemotherapy.

3.2 Training curve and model performance

After the process of random search, we finally settled down on the hyperparameter of the deep learning model, the model consists of 2 hidden layers, from input to output, including 60, 43 neurons in each layer with a dropping out unit between each layer. we improve neural network generalization by setting the learning rate to 0.001 and 0.5 as the dropout rate to avoid overfitting. Figure 2 shows the training loss curves of the survival network. At the beginning of the training process, the loss of the validation and training set decreases continually. After 331 epochs of parameter optimization, the loss of the validation set begins at 3.6936 and stops decreasing at 3.1753 while the training loss continues to decrease from 3.3844 started at 3.8446. Then we terminate the optimization to avoid overfitting and save the model for test.

In the random survival forest, We set the number of the estimating trees to 959, the minimum number of samples required to split an internal node to 10 and the minimum number of samples required to be at a leaf node to 15. In the Penalized Cox Proportional hazard model, we configure the penalizer to 0.005 and the learning rate to 0.01

Then we perform 5-fold cross-validation to select the optimal model for survival prediction. Figure 3 displays the exact value and

TABLE 1 Main Baseline Clinical Characteristics of Patients.

Characteristic	Data set, No. (%)	
Age		
85+ years	60 (1.35)	0
80-84 years	242 (5.47)	0
75-79 years	530 (11.99)	2 (2.00)
70-74 years	731 (16.54)	10 (10.00)
65-69 years	891 (20.17)	14 (14.00)
60-64 year	713 (16.14)	22 (22.00)
55-59 years	573 (12.97)	22 (22.00)
50-54 years	395 (8.94)	20 (20.00)
45-49 years	171 (3.87)	6 (6.00)
40-44 years	63 (1.42)	3 (3.00)
35-39 years	25 (0.56)	1 (1.00)
30-34 years	13 (0.31)	0
25-29 years	7 (0.57)	0
20-24 years	0 (0)	0
15-19 years	3 (0.07)	0
Histologic type		
Neoplasm, malignant	6 (0.13)	0
Carcinoma, NOS	11 (0.24	0
Large cell carcinoma, NOS	45 (1.01)	1 (1.00)
Large cell neuroendocrine carcinoma	40 (0.90)	0
Large cell carcinoma with rhabdoid phenotype	1 (0.02)	0
Pleomorphic carcinoma	20 (0.45)	0
Giant cell carcinoma	6 (0.13)	0
Spindle cell carcinoma, NOS	4 (0.09)	0
Pseudosarcomatous carcinoma	13 (0.29)	0
Combined small cell carcinoma	16 (0.36)	0
Non-small cell carcinoma	114 (2.58)	0
Papillary carcinoma, NOS	3 (0.06)	0
Papillary squamous cell carcinoma	2 (0.04)	0
Squamous cell carcinoma, NOS	1028 (23.27)	46 (46.00)
Squamous cell carcinoma, keratinizing, NOS	76 (1.72)	1 (1.00)
Squamous cell carcinoma, large cell, nonkeratinizing, NOS	26 (0.58)	0
Squamous cell carcinoma, spindle cell	2 (0.04)	0
Lymphoepithelial carcinoma	4 (0.09)	0
Basaloid squamous cell carcinoma	7 (0.15)	0
Squamous cell carcinoma, clear cell type	3 (0.07)	0
Basaloid carcinoma	4 (0.09)	0
Adenocarcinoma, NOS	1956 (44.28)	43 (43.00)
Adenoid cystic carcinoma	6 (0.13)	0
Solid carcinoma, NOS	20 (0.45)	0
Carcinoid tumor, NOS	66 (1.49)	0
Neuroendocrine carcinoma, NOS	31 (0.70)	0
Atypical carcinoid tumor	31 (0.70)	0
Bronchiolo-alveolar adenocarcinoma, NOS	57 (1.29)	0
Alveolar adenocarcinoma	1 (0.02)	0
Bronchiolo-alveolar carcinoma, non-mucinous	4 (0.09)	0
Adenocarcinoma with mixed subtypes	277 (6.27)	1 (1.00)
Papillary adenocarcinoma, NOS	78 (1.76)	1 (1.00)
Clear cell adenocarcinoma, NOS	11 (0.24)	0
Mixed cell adenocarcinoma	11 (0.24)	0
Papillary microcarcinoma	1 (0.02)	0
Mucoepidermoid carcinoma	2 (0.04)	0
Mucinous adenocarcinoma	97 (2.19)	2 (2.00)
Mucin-producing adenocarcinoma	19 (0.43)	0
Signet ring cell carcinoma	5 (0.11)	0
Ductal carcinoma, micropapillary	2 (0.04)	0
Acinar cell carcinoma	162 (3.66)	0
Adenosquamous carcinoma	129 (2.92)	4 (4.00)
Adenocarcinoma with neuroendocrine differentiation	4 (0.09)	1 (1.00
Carcinosarcoma, NOS	4 (0.09)	0
Bronchiolo-alveolar carcinoma, mucinous	7 (0.16)	0
Bronchiolo-alveolar carcinoma, mixed mucinous and non-mucinous	4 (0.09)	0
T stage		
T1	0	2 (2.00)
T1NOS	2 (0.05)	0
T1a	371 (8.40)	1 (1.00)
T1b	390 (8.83)	0
T2NOS	25 (0.56)	0

(Continued)

TABLE 1 Continued

Characteristic	Data set, No. (%)	
T2a	1162 (26.31)	35 (35.00)
T2b	353 (7.99)	15 (15.00)
T3	1285 (29.09)	27 (27.00)
T3	828 (18.74)	20 (20.00)
TX	1 (0.02)	0
N stage		
N0	404 (9.14)	5 (5.00)
N1	866 (19.61)	11 (11.00)
N2	3087 (69.88)	84 (84.00)
N3	60 (1.36)	0
M stage		
M0	4417 (100.00)	100 (100.00)
Sex		
Female	2141 (48.47)	24 (24.00)
Male	2276 (51.52)	76 (76.00)
Radiation		
Beam radiation	1850 (41.88)	34 (34.00
Combination of beam with implants or isotopes	2 (0.05)	0
None	2412 (54.60)	66 (66.00
Radiation, NOS method or source not specified	14 (0.31)	0
Recommended, unknown if administered	88 (1.99)	0
Refused	49 (1.11)	0
Radioactive implants (includes brachytherapy)	2 (0.05)	0
Chemotherapy		
Yes	3274 (74.12)	95 (95.00)
No/Unknown	1143 (25.87)	5 (5.00)
Surgery to primary site		
Lobectomy WITH mediastinal lymph node dissection	3777 (85.51)	81 (81.00)
Pneumonectomy WITH mediastinal lymph node dissection	640 (14.48)	19 (19.00)

(Continued)

TABLE 1 Continued

Characteristic	Data set, No. (%)	
Laterality		
Left - origin of primary	1923 (43.53)	43 (43.00)
Only one side - side unspecified	1 (0.02)	0
Paired site, but no information concerning laterality	1 (0.02)	0
Paired site, but no information concerning laterality	2492 (56.41)	57 (57.00)

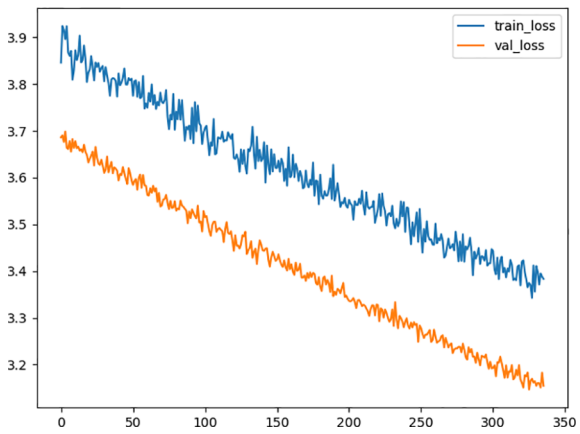

FIGURE 2
Diagram of the traing loss and the validation loss in the optimization procedure. The x-axis represents the number of epoch, and the y-axis represents value of loss function. The orange line is the validation loss function and the blue one represents the training loss function.

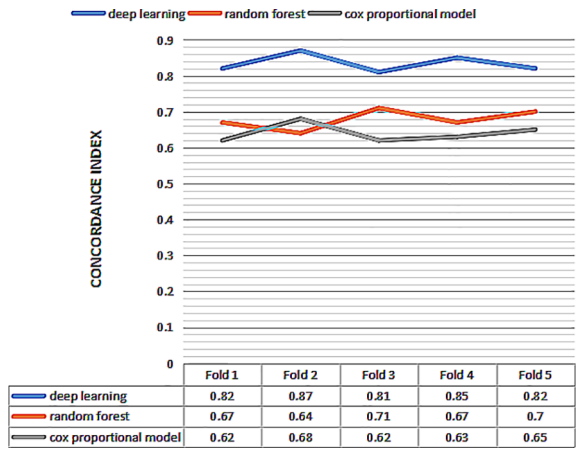

FIGURE 3
The concordance index of three models for 5 fold cross validation. The x-axis represents the number of fold, and the y-axis represents value of concordance index for each model.

the line chart of each model in every fold validation, the deep learning model shows a more stable and exceptional performance on the concordance index compared to the other two models. The mean of the concordance index of the deep learning algorithm is 0.843, which is much higher than the random forest (0.678) and cox proportional hazard model (0.678) (Table 2). Based on the result of cross-validation, deep learning is selected to compare the TNM staging system on external validation. The performance of the deep learning model is better (0.82 vs 0.65)

As for the feature importance for the network, from the Figure 4 we can observe four of the top important features: regional positive nodes (0.6634), regional examied nodes (-0.7648), tumor size (-0.5633) and Age(-0.4633). In terms of least important features, we observe that the surgery on the primary site (0.0632) is voted to be least significant based on attribution algorithm. The absolute value for attribution scores of other features is greater than 0.1 and less than 0.5.

Then we perform 5-fold cross-validation to select the optimal model for survival prediction. Figure 3 displays the exact value and the line chart of each model in every fold validation, the deep learning model shows a more stable and exceptional performance on the concordance index compared to the other two models. The mean of the concordance index of the deep learning algorithm is 0.843, which is much higher than the random forest (0.678) and cox proportional hazard model (0.678) (Table 2). Based on the result of cross-validation, deep learning is selected to compare the TNM staging system on external validation. The performance of the deep learning model is better (0.82 vs 0.65)

3.3 The adjuvant therapy recommender system

Since the deep learning model has better performance than the TNM staging system, we could not only predict the survival function of the current patient but also offer an adjuvant therapy reference to the oncology doctor based on prediction over different therapy treatment plans. Thus we deployed the recommender system to the Internet, which could be accessed with a browser in [http://1.15.80.136/nsclc/], input the current clinical status, including Demographic, surgery type, cancer type and stage information, of one patient, and click the submit button (Figure 5).

TABLE 2 Performance of the survival models to predict hazard rate of the stage-III NSCLC patient received resection surgery.

MODEL	Cross Validation	External Validation
	Concordance Index Mean	Concordance Index
Deep Learning	0.834	0.820
Random Forest	0.678	
Cox Proportional	0.640	
TNM Staging		0.650

Then the browser will redirect to the result page (Figure 6), and we could see four 5-year predicted survival curves for each treatment plan. Based on the plot, the predicted optimal treatment plan is only receiving beam radiation for adjuvant treatment, whose survival probability is highest in the next 60 months.

Thus, the specialist could get the reference for adjuvant treatment plan decision-making. Code related to this application can be found at https://github.com/snowflake-Zhao/nsclc.

4 Discussion

This study provides a model that is more accurate than the TNM staging system to predict the prognosis of the stage-iii received resection NSCLC cancer patients in 5 years. Additionally, the deep learning survival model is more precise and stable than the random survival forest and cox proportional model to predict the hazard rate of the stage-III resectable NSCLC cancer patients. This demonstrated our first goal that the deep learning approach is more reliable than TNM in predicting the hazard rate. Driven by the desire to resolve the controversy on devising adjuvant treatment plans for stage-iii received resection NSCLC cancer patients, we did solve this problem by developing a recommender system based on the externally validated deep learning model. To our best knowledge, this is the first recommender system to provide adjuvant treatment plans reference for stage-iii NSCLC cancer patients who received resection.

As reported, Adeoye J, et al. have trained DeepSurv and RSF (random survival forest) models for predicting the malignant transformation probability of oral leukoplakia and lichenoid lesions with (N=716) patients (21). Their exceptional results suggest a considerable improvement of accuracy for hazard prediction using the deep learning model when it is compared with the Cox proportional hazard model(C-index=0.95 vs 0.83), and RSF's performance is much better and more stable than that of Cox proportional hazard model(C-index=0.91 vs 0.83) in this task. Our outcome of the experiment is consistent with their conclusion. In another study, Huang C, et al. developed software to select adjuvant radiotherapy and chemotherapy treatment plan according to the corresponding output hazard rate. Our software has two major points different from their product (22). One is the output page for oncology specialists. Their output is just one hazard rate, which is difficult for specialists and patients to understand. On the contrary, we plot the four adjuvant treatments predicted survival curves in 60 months, which is more straightforward for patients and doctors because people could understand their probability of survival for each adjuvant treatment plan in the 5 years. The other point is our software could be accessed directly through the web browser either on mobile phones, iPad or personal computers instead of installed on the personal computer for seeking recommendation guidance, which is not convenient for doctors to use.

In our study, the random survival forest did not perform well as Lin J, et al's (C-index= 0.678 vs 0.723) (23), I think this is mainly because the two features in the dataset after one hot

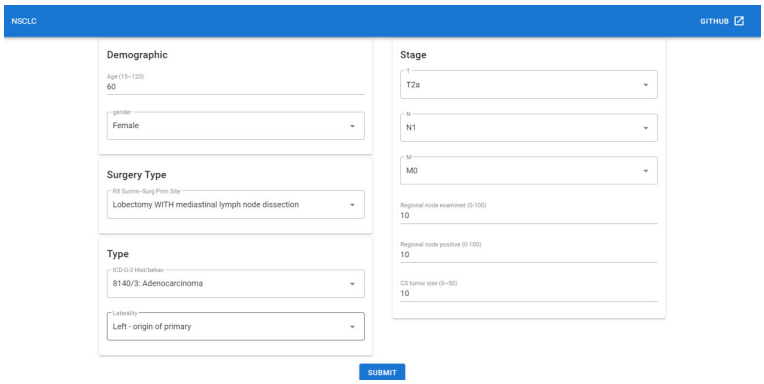

FIGURE 4
The attribution score of all input features in the deep learning model. The x-axis represents the name of the input features, and the y-axis represents value of attribution score for each feature.

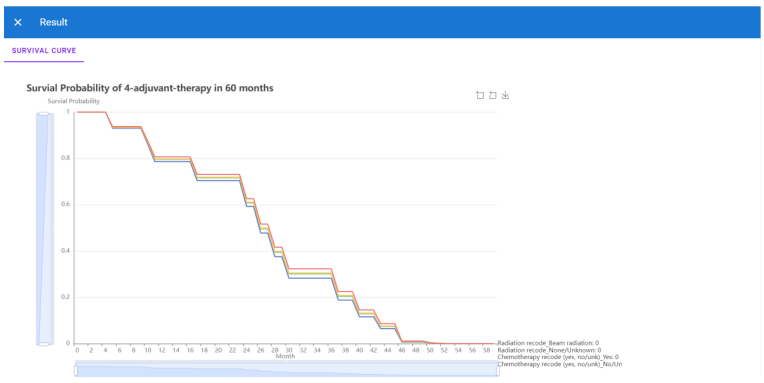

FIGURE 5
The input page of the recommender system.

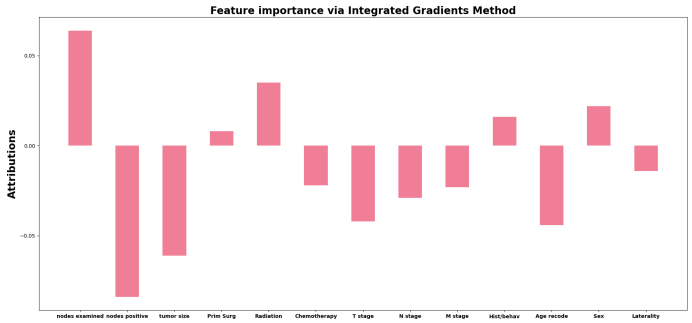

FIGURE 6
The output page of the recommender system.

encoding, the Histologic type and Radiation, generate lots of sparse variables, including Radioactive implants, Signet ring cell carcinoma and so on, which eventually cause harm to the formation of different estimator trees. The result that the deep learning model's C-index is higher than the Cox Proportional hazard model(C-index= 0.834 vs 0.640) meets our expectations, mainly because deep learning could formulate the complex relationships between clinical baseline characteristics and the

patient's hazard rate, which is more accurate than the linear relationship assumption of the Cox proportional hazard model. Additionally, the deep learning model has superior performance than the TNM staging system(C-index= 0.82 vs 0.65) is expected, because the neural network takes in more clinical features related to the prognosis of the patients, including Histologic type, age, sex, tumor size and many others, than the TNM staging system and the most important features of the network are regional postive nodes,regional examied nodes, tumor size and the Age, which is slightly different from the TNM stage system, even though the T stage value comes from the tumor size, N stage value comes form the regional nodes, we could tell the exact detailed number of the tumor size and the regional positive nodes could help the model to predict the prognoses more clearly than the general value. Besides the trained model could perform personal prognosis prediction while the TNM staging system could only predict the cohort prognosis. Thus, the deep learning model could possibly substitute the TNM staging system in the future if more medical records could be utilized for training.

In the current medical practice, there is a lack of consensus regarding the principles of adjuvant therapy for stage-iii NSCLC patients. For instance, According to the latest version of NCCN Guidelines for NSCLC(Version5.2022), one major controversy is inconsistent results among different randomized controlled trials of stage-III NSCLC (23–26). The one reason for the inconsistent results among different randomized controlled trials is the RCT lacks external validity (27), which means there might be neglected features that are effective for the prognosis. Because the externally validated deep learning model could include lots of features might related to the prognosis and be sensitive to the different inputs, the model could output the hazard risk of the different treatment plans, then the optimal plan could be obtained by comparing the output of different treatments. In our adjuvant recommendation system, we could obtain the reliable and accurate hazard rate for 4 adjuvant treatment plans from the developed externally validated model. To visualize the outcome, after mathematic transformation, the predicated survival curves for 4 treatment plans are displayed on the Web User Interface. Because of the significant prognostic benefit of following the treatment recommendation which clearly outweighs those who don't, the recommendation system is promising to serve as a dependable tool for decision-making on the adjuvant treatment plan for each stage-iii NSCLC patient.

From the results of our experiment, the deep learning model performs well in the survival analysis task. However, the model is lacking in explainability owing to the high complexity inside the neural network, which is not realistic to explain the process to humans. If we want to extensively apply the deep learning algorithm in the decision-making of the NSCLC, we definitely need to improve the explainability of the model (28–30). we could incorporate the causal inference ideas in designing inherently interpretable models by adding sample reweighting technique into the loss function to compare the performance with our deep learning result in the future (31–34). Even though the SEER database has numerous NSCLC patient's medical records, the database could record more detailed attributes in three aspects, including 1) resection information in detail, like resection status (R0/R1/R2) 2)detailed information related to beam radiation, for instance, total dose and dose per fraction 3) further information relevant to chemotherapy on drugs and dosage.

5 Conclusions

To our best knowledge, this study is the first to research the performance of a deep learning network and random forest in resected Stage-III NSCLC and obtain satisfactory results in survival prediction. In addition, the recommendation system for adjuvant therapy based on the deep learning model will be likely applied to offer recommendation reference to the specialist in the clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LJ and QZ designed the research. LJ collected the training and testing dataset. QZ trained the models and developed the web-application. LJ and QZ wrote the manuscript. JM, BH, SF and FC edited and critically revised the manuscript in regard to important intellectual content. All authors read and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1092478/full#supplementary-material

References

1. Putora PM, Leskow P, McDonald F, Batchelor T, Evison M. International guidelines on stage iii n2 nonsmall cell lung cancer: surgery or radiotherapy? *ERJ Open Res* (2020) 6. doi: 10.1183/23120541.00159-2019

2. Kato S, Okamura R, Mareboina M, Lee S, Goodman A, Patel SP, et al. Revisiting epidermal growth factor receptor (egfr) amplification as a target for anti-egfr therapy: analysis of cell-free circulating 290 tumor dna in patients with advanced malignancies. *JCO Precis Oncol* (2019) 3:1–14. doi: 10.1200/PO.18.00180

3. Felip E, Altorki N, Zhou C, Csoszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage ib–iiia non-small-cell lung cancer (impower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet* (2021) 398:1344–57. doi: 10.1016/S0140-6736(21)02098-5

4. Deng W, Xu T, Xu Y, Wang Y, Liu X, Zhao Y, et al. Survival patterns for patients with resected n2 non–small cell lung cancer and postoperative radiotherapy: a prognostic scoring model and heat map approach. *J Thorac Oncol* (2018) 13:1968–74. doi: 10.1016/j.jtho.2018.08.2021

5. Wei S, Xie M, Tian J, Song X, Wu B, Liu L. Propensity score-matching analysis of postoperative radiotherapy for stage iiia-n2 non-small cell lung cancer using the surveillance, epidemiology, and end results database. *Radiat Oncol* (2017) 12:1–11. doi: 10.1186/s13014-017-0836-6

6. Gao F, Li N, Xu Y, Yang G. Evaluation of postoperative radiotherapy effect on survival of resected stage iii-n2 non-small cell lung cancer patients. *Front Oncol* (2020) 10:1135. doi: 10.3389/fonc.2020.01135

7. Wang EH, Corso CD, Park HS, Chen AB, Wilson LD, Kim AW, et al. Association between radiation 303 dose and outcomes with postoperative radiotherapy for n0-n1 non–small cell lung cancer. *Am J Clin Oncol* (2018) 41:152–8. doi: 10.1097/COC.0000000000000245

8. Le Pechoux C, Pourel N, Barlesi F, Lerouge D, Antoni D, Lamezec B, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal n2 involvement (lung art): an open-label, randomised, phase 3 trial. *Lancet 3Oncology* (2022) 23:104–14. doi: 10.1016/S1470-2045(21)00606-9

9. Lee C, Light A, Alaa A, Thurtle D, van der Schaar M, Gnanapragasam VJ. Application of a novel machine learning framework for predicting non-metastatic prostate cancer-specific mortality in men 311 using the surveillance, epidemiology, and end results (seer) database. *Lancet Digital Health* (2021) 3 312:e158–65. doi: 10.1016/S2589-7500(20)30314-9

10. Jones O, Matin R, van der Schaar M, Bhayankaram KP, Ranmuthu C, Islam M, et al. Artificial intelligence and machine learning algorithms for early detection of skin cancer in community and primary care settings: a systematic review. *Lancet Digital Health* (2022) 4:e466–76. doi: 10.1016/S2589-7500(22)00023-1

11. Lee C, Light A, Saveliev ES, van der Schaar M, Gnanapragasam VJ. Developing machine learning algorithms for dynamic estimation of progression during active surveillance for prostate cancer. *NPJ digital Med* (2022) 5:1–7. doi: 10.1038/s41746-022-00659-w

12. Zhou H, Cheng C, Lipton ZC, Chen GH, Weiss JC. Predicting mortality risk in viral and unspecified pneumonia to assist clinicians with covid-19 ecmo planning. *arXiv preprint arXiv:2006.01898.* (2020). doi: 10.48550/arXiv.2006.01898

13. Hu S, Chen GH. Distributionally robust survival analysis: A novel fairness loss without demographics. *Mach Learn Health (PMLR)* (2022), 62–87. doi: 10.48550/arXiv.2211.10508

14. Chiappetta M, Tabacco D, Iaffaldano AG, Evangelista J, Congedo MT, Sassorossi C, et al. Clinical stage iii nsclc patients treated with neoadjuvant therapy and surgery: The prognostic role of nodal characteristics. *Life* (2022) 12:1753. doi: 10.3390/life12111753

15. Jagjampi A, Khadirnaikar S, Malik PS, Jain D, N MB, Shukla S. Deepmps: Development and validation of a deep learning model for whole slide image base prognostic prediction of low grade lung adenocarcinoma patients. *bioRxiv* (2022) 2022:12. doi: 10.1101/2022.12.27.522072

16. Lococo F, Chiappetta M, Evangelista J, Sperduti I, Nachira D, Porziella V, et al. Role of peripheral blood markers for detecting response and predicting prognosis in patients with non-small-cell lung cancer undergoing neoadjuvant therapy and surgery. *Lung* (2022) 200:393–400. doi: 10.1007/s00408-022-00541-2

17. Yang L, Fan X, Qin W, Xu Y, Zou B, Fan B, et al. A novel deep learning prognostic system improves survival predictions for stage iii non-small cell lung cancer. *Cancer Med* (2022) 11:4246–55. doi: 10.1002/cam4.4782

18. Kingma DP, Ba J. Adam: A method for stochastic optimization. *arXiv preprint arXiv* (2014) 1412:6980. doi: 10.48550/arXiv.1412.6980

19. Sundararajan M, Taly A, Yan Q. (2017). Axiomatic attribution for deep networks, in: *Proceedings of the 34th International Conference on Machine Learning*, 70 ICML'17:3319–28. doi: 10.5555/3305890.3306024

20. Katzman JL, Shaham U, Cloninger A, Bates J, Jiang T, Kluger Y. Deepsurv: personalized treatment recommender system using a cox proportional hazards deep neural network. *BMC Med Res Method* (2018) 18:1–12. doi: 10.1186/s12874-018-0482-1

21. Adeoye J, Koohi-Moghadam M, Lo AWI, Tsang RKY, Chow VLY, Zheng LW, et al. Deep learning predicts the malignant-transformation-free survival of oral potentially malignant disorders. *Cancers* (2021) 13:6054. doi: 10.3390/cancers13236054

22. Huang C, Dai Y, Chen Q, Chen H, Lin Y, Wu J, et al. Development and validation of a deep learning model to predict survival of patients with esophageal cancer. *Front Oncol* (2022) 12. doi: 10.3389/fonc.2022.971190

23. Lin J, Yin M, Liu L, Gao J, Yu C, Liu X, et al. The development of a prediction model based on random survival forest for the postoperative prognosis of pancreatic cancer: A seer-based study. *Cancers* (2022) 14:4667. doi: 10.3390/cancers14194667

24. Schaake-Koning C, Van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *New Engl J Med* (1992) 326:524–30. doi: 10.1056/NEJM199202203260805

25. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC, 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. doi: 10.1056/NEJM199010043231403

26. Dillman RO, Herndon J, Seagren SL, Eaton WLJr., Green MR. Improved survival in stage iii non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group b (calgb) 8433 trial. JNCI. *J Natl Cancer Institute* (1996) 88:1210–5. doi: 10.1093/jnci/88.17.1210

27. Mulder R, Singh AB, Hamilton A, Das P, Outhred T, Morris G, et al. The limitations of using randomised controlled trials as a basis for developing treatment guidelines. *Evidence-Based Ment Health* (2018) 21:4–6. doi: 10.1136/eb-2017-102701

28. Pearl J. Theoretical impediments to machine learning with seven sparks from the causal revolution. *arXiv preprint arXiv* (2018) 1801:04016. doi: 10.1145/3159652.3176182

29. Heinze-Deml C, Meinshausen N. Conditional variance penalties and domain shift robustness. *arXiv preprint arXiv* (2017) 1710:11469. doi: 10.48550/arXiv.1710.11469

30. Athey SC, Bryan KA, Gans JS. (2020). The allocation of decision authority to human and artificial intelligence, in: *AEA Papers and Proceedings*, American Economic Association 2014 Broadway, Suite 305, Nashville, TN 37203, Vol. 110. pp. 80–4. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3517287.

31. Cui P, Athey S. Stable learning establishes some common ground between causal inference and machine learning. *Nat Mach Intell* (2022) 4:110–5. doi: 10.1038/s42256-022-00445-z

32. Xu R, Cui P, Shen Z, Zhang X, Zhang T. Why stable learning works? a theory of covariate shift generalization. *arXiv preprint arXiv:2111.02355* (2021) 2. doi: 10.48550/arXiv.2111.02355

33. Kuang K, Cui P, Athey S, Xiong R, Li B. (2018). Stable prediction across unknown environments, in: *Proceedings of the 24th ACM SIGKDD international conference on knowledge discovery & data mining*, .pp. 1617–26. doi: 10.1145/3219819.3220082

34. Shen Z, Liu J, He Y, Zhang X, Xu R, Yu H, et al. Towards out-of-distribution generalization: A survey. *arXiv preprint arXiv:2108.13624* (2021). doi: 10.48550/arXiv.2108.13624

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EDITED BY
Nan Bi,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

REVIEWED BY
Hidehito Horinouchi,
National Cancer Center Hospital, Japan
Min Fan,
Fudan University, China

*CORRESPONDENCE
Byoung-Chul Cho
cbc1971@yuhs.ac

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Real-world clinical practice and outcomes in treating stage III non-small cell lung cancer: KINDLE-Asia subset

Kumar Prabhash[1], Daniel Shao Weng Tan[2], Ross A. Soo[3], Piyada Sitthideatphaiboon[4], Yuh Min Chen[5], Pei Jye Voon[6], Elisna Syahruddin[7], Sojung Chu[8], Reto Huggenberger[9] and Byoung-Chul Cho[10]*

[1]Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India, [2]Division of Medical Oncology, National Cancer Centre, Singapore, Singapore, [3]Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore, [4]Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand, [5]Taipei Veterans General Hospital, School of Medicine, National Yang-Ming Medical University, Taipei City, Taiwan, [6]Department of Radiotherapy and Oncology, Hospital Umum Sarawak, Kuching, Sarawak, Malaysia, [7]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan Hospital, Jakarta, Indonesia, [8]Medical Affairs, AstraZeneca, Seoul, Republic of Korea, [9]Medical Affairs, AstraZeneca, Baar, Switzerland, [10]Division of Medical Oncology, Yonsei Cancer Centre, Yonsei University College of Medicine, Seoul, Republic of Korea

Introduction: Stage III non-small cell lung cancer (NSCLC) is a heterogeneous disease requiring multimodal treatment approaches. KINDLE-Asia, as part of a real world global study, evaluated treatment patterns and associated survival outcomes in stage III NSCLC in Asia.

Methods: Retrospective data from 57 centers in patients with stage III NSCLC diagnosed between January 2013 and December 2017 were analyzed. Median progression free survival (mPFS) and median overall survival (mOS) estimates with two sided 95% confidence interval (CI) were determined by applying the Kaplan-Meier survival analysis.

Results: Of the total 1874 patients (median age: 63.0 years [24 to 92]) enrolled in the Asia subset, 74.8% were men, 54.7% had stage IIIA disease, 55.7% had adenocarcinoma, 34.3% had epidermal growth factor receptor mutations (EGFRm) and 50.3% had programmed death-ligand 1 (PD-L1) expression (i.e. PD-L1 $\geq$1%). Of the 31 treatment approaches as initial therapy, concurrent chemoradiotherapy (CRT) was the most frequent (29.3%), followed by chemotherapy (14.8%), sequential CRT (9.5%), and radiotherapy (8.5%). Targeted therapy alone was used in 81 patients of the overall population. For the Asia cohort, the mPFS and mOS were 12.8 months (95% CI, 12.2–13.7) and 42.3 months (95% CI, 38.1–46.8), respectively. Stage IIIA disease, Eastern Cooperative Oncology Group $\leq$1, age $\leq$65 years, adenocarcinoma histology and surgery/concurrent CRT as initial therapy correlated with better mOS ($p < 0.05$).

Conclusions: The results demonstrate diverse treatment patterns and survival outcomes in the Asian region. The high prevalence of EGFRm and PD-L1 expression in stage III NSCLC in Asia suggests the need for expanding access to molecular testing for guiding treatment strategies with tyrosine kinase inhibitors and immunotherapies in this region.

KEYWORDS

lung cancer, EGFR mutation, stage III NSCLC, adenocarcinoma, targeted therapy, concurrent chemoradiotherapy (CCRT)

1 Introduction

Lung cancer is amongst the most fatal cancers globally, accounting for 18% of all cancer deaths in 2020. About 59.6% of the world's new lung cancer cases and 61.9% of lung cancer-related deaths occurred in Asia, in 2020 (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases (2); about one-third (around 30%) of all NSCLC cases present with stage III (locally-advanced [LA]) disease (3, 4). The treatment choices for stage III NSCLC are primarily determined by tumor size, nodes and metastases staging, clinical presentation (patient's age, performance status) and tumor pathology at initial diagnosis. According to the American Joint Committee on Cancer (AJCC) staging system (7th edition), stage III includes two subtypes, stage IIIA and IIIB (5). In 2017, stage IIIC was added to include LA T3 and T4 tumors associated with N3 disease but without metastasis for better prognostication (AJCC, 8th edition) (6). The heterogeneous nature of stage III disease makes the management challenging and often warrants an integrative multidisciplinary decision for using a multimodal and personalized management approach (7). In the pre immuno-oncology (IO) era, curative surgery was the preferred treatment in a subset of stage IIIA disease, followed by chemotherapy (CT) (8). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) April 2022 recommend osimertinib for patients with completely resected stage III epidermal growth factor receptor (EGFR) mutation positive NSCLC who received previous adjuvant CT or are ineligible to receive platinum based CT (9). In patients with microscopic residual disease, sequential chemoradiotherapy (sCRT) or concurrent chemoradiotherapy (cCRT) and in patients with macroscopic residual disease cCRT is the preferred treatment option (9). For patients with unresectable stage III disease, definitive cCRT (platinum-based doublet regimens), followed by durvalumab consolidation is recommended as a treatment option in patients who have not progressed after definitive cCRT (9). The treatment practices within Asia vary from country to country such as induction CT followed by radiotherapy (RT) in India (stage III/IV), surgery or neoadjuvant therapy or definitive chemoradiotherapy (CRT) in Korea (stage III) and cCRT in Singapore (stage III) (10–12). With a high prevalence of epidermal growth factor receptor mutations (EGFRm) in China (46.5%, 309/665), CT was followed by tyrosine kinase inhibitors (TKIs) in most (66.3%, 205/309) patients with unresectable stage IIIB/IV (13). Regional adaptations to international guidelines have also been developed (2, 14).

The survival outcomes reported for stage III NSCLC in Asia are generally poor with 5-year survival ranging from 3.4% to 34.9% (15–17). Hence, there is a need to understand the factors responsible for treatment decisions in the Asian region to recognize the unmet need to translate the newer treatment modalities into clinical practice in this region, with the objective of improving survival in this patient population. Databases or resources from Asian countries having information on diagnosis, treatment patterns and clinical outcomes for patients with stage III NSCLC are scarce. The recently published real-world KINDLE study was conducted internationally to characterize the treatment patterns and survival outcomes in the pre IO/pre TKI era for patients with stage III NSCLC (18). We report on the treatment patterns and associated survival outcomes of the Asia subset of the KINDLE study.

2 Materials and methods

2.1 Study design

KINDLE-Asia subset included eight countries (India, Indonesia, Korea, Malaysia, Singapore, Taiwan, Thailand and Vietnam) with 57 centers and enrolled consecutive patients diagnosed with *de novo* LA stage III NSCLC (AJCC 7th edition) between January 2013 and December 2017 with at least 9 months of documented follow up. The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation, good clinical practices, good pharmacoepidemiology practices and the other applicable regulations for noninterventional studies. The study protocol (NCT03725475) was reviewed and approved by the Institutional Review Boards/Independent Ethics Committees from all the participating centers before the initiation of the study. The reporting in this manuscript has been done following the Strengthening the Reporting of Observational Studies in Epidemiology checklist (19). The study eligibility criteria and data collection methods have been reported by Jazieh et al. (18) The study data (demography, clinical characteristics, treatment patterns

and clinical outcomes) were collected retrospectively from patients' medical records after obtaining written informed consent from the patients or their next of kin (in the case of deceased patients), or the legal representatives. The study outcomes are defined in Supplementary Table S1.

2.2 Statistical analyses

Patient demographics, clinical characteristics and treatment patterns were described using frequencies and percentages for categorical variables, mean/median and standard deviation with a 95% confidence interval (CI) as applicable for continuous variables. Median survival estimates (progression-free survival [PFS] and overall survival [OS]) were determined descriptively by applying the Kaplan-Meier survival analysis and log-rank test. A multivariate Cox proportional hazards model and hazards ratio (HR) along with 95% CI were used to identify the effects of clinical and demographic factors on OS and PFS by controlling relevant covariates affecting OS and PFS. A p value of less than 0.05 was considered statistically significant.

3 Results

3.1 Demographic and clinical characteristics

A total of 1874 patients were enrolled in the Asia subset with India (26%) and Korea (25%) combined contributing to around half of the study population. Detailed demographic and clinical characteristics are presented previously, as part of global data (18). The median age of the subset was 63.0 years (range: 24 to 92); 74.8% were men and 28.0% never smoked. At diagnosis, 54.7% of the patients had stage IIIA disease (AJCC, 7th edition) and 55.7% had adenocarcinoma. Of the patients with available data on Eastern Cooperative Oncology Group (ECOG) performance status, 88.9% had a performance status of ≤1. Surgical resection was performed in 23.3% (437/1874) (IIIA: 379; IIIB: 46) of the patients and 40.4% (758/1874) (IIIA: 320; IIIB: 417) had an unresectable disease. There were significant differences between resectable and unresectable patients in all clinical characteristics (all p<0.001) except for PD-L1 expression (Supplementary Table S2).

About one-third (600/1874, 32.0%) of the cases were discussed in the multidisciplinary team (MDT) meetings. Similar percentages of patients with stages IIIA and IIIB (34.8% and 30.2%) and those with resectable and unresectable diseases (33.4% and 31.7%) were discussed in MDT meetings (Table 1).

3.2 Molecular testing

A total 865 (46.2%) patients underwent EGFRm testing at primary diagnosis, of whom 297 (34.3%) patients were found to have EGFRm in the Asia subset (Supplementary Table S2).

In stage IIIA disease, the percentage of patients undergoing a test for EGFRm was higher in resectable compared with unresectable patients (64.1% vs 40.3%) whereas, in stage IIIB, it was almost similar (52.2% vs 54.2%). The percentage of patients with of EGFRm was higher in resectable than in unresectable patients in stage IIIA disease (46.1% vs 30.2%); however, it was almost similar irrespective of resectability status in stage IIIB (25.0% vs 28.8%) (Supplementary Table S3).

The percentages of EGFRm were similar irrespective of gender (51.5% in females vs 48.5% in males) and resectability (52.9% in resectable vs unresectable in 47.1%) and were higher in never smokers than in current smokers (58.9% vs 11.4%) (Supplementary Table S4).

At primary diagnosis, testing for programmed death-ligand 1 (PD-L1) expression was performed for 292 (15.6%) patients of whom 147 (50.3%) tested positive for PD L1 (i.e. PD-L1 ≥1%) (Supplementary Table S2). The percentage of testing for PD-L1 expression was similar in both resectable and unresectable patients (21.6% vs 18.7%). In stage IIIA, a higher percentage of resectable than unresectable patients tested positive for PD L1 (52.9% vs 45.5%), whereas, in stage IIIB, higher percentage of patients with unresectable than the resectable disease (66.7% vs 57.1%) were positive for PD-L1 expression (Supplementary Table S3).

3.3 Treatment patterns

Overall, 94.5% (1771/1874) of the patients received an initial therapy (stage IIIA: 95.4% [931/976], stage IIIB: 94.8% [766/803]). cCRT-based therapies (34.3%) were used more frequently than curative surgery-based therapies (23.2%), systemic treatment (20.5%), RT-based (11.6%) and sCRT-based therapies (10.4%) (Supplementary Table S5). These categories included 31 different treatment approaches. The frequent approach used as the initial line was cCRT (29.3%), followed by CT (14.8%), sCRT (9.5%), RT (8.5%) and other surgeries such as surgery combined with neoadjuvant and/or adjuvant cCRT/CT/RT/sCRT/targeted

TABLE 1 Outcome discussed at the multidisciplinary team meeting in KINDLE-Asia.

Was the patient case discussed at an MDT meeting?	Asia (N = 1874)	Stage IIIA (N = 976)	Stage IIIB (N = 808)	Resectable (N = 437)	Unresectable (N = 758)
Yes, n (%)	600 (32.1)	339 (34.8)	244 (30.2)	146 (33.4)	240 (31.7)
No, n (%)	859 (46.0)	451 (46.3)	367 (45.5)	222 (50.8)	443 (58.4)
Unknown, n (%)	409 (21.9)	184 (18.9)	196 (24.3)	69 (15.8)	75 (9.9)

MDT, Multidisciplinary team; N, Number of patients; n, Number of patients in the subcategories.

therapy/IO drugs (6.5%). Post relapse, 746/1874 (39.8%) patients received second-line therapy and 282 (15.1%) of them received third-line therapy. In second- and third-line settings, CT was the predominant treatment (37.8% [282/746] and 36.9% [104/282]) followed by RT (18.9% [141/746] and 20.9% [59/282]) and targeted therapy alone (13.4% [100/746] and 11.0% [31/282]) in overall stage III population (Supplementary Table S5 and Figure S1).

In stage IIIA, curative surgery-based treatment was the most common approach (37.5%) as initial treatment followed by cCRT-based therapies (30.2%), systemic treatment (13.6%), sCRT-based (9.3%) and RT-based therapies (9.3%). Whereas in stage IIIB, cCRT-based therapy was the most common approach (39.4%) as initial treatment followed by systemic treatment (29.0), RT based (13.2%), sCRT-based (11.5%) and curative surgery-based therapies (6.9%) (Supplementary Table S5).

Treatment pattern analyses as per resection status revealed that other surgery (22.2%), surgery+CT (20.0%) and surgery+sCRT (16.0%) were the top three treatments used in resectable patients (n=437) as initial-line treatment. The use of cCRT predominated (44.7%) in unresectable patients (n=758); the other frequent treatments were CT alone (15.2%), RT (11.8%), sCRT (8.9%) and targeted therapy alone (5.5%) (Supplementary Figure S2 and Table S6).

In this unresectable category, when compared with patients receiving initial therapy with cCRT, a significantly higher percentage of patients receiving targeted therapy were females (50% vs 21.7%, p=0.0001), had stage IIIB disease (79.5% vs 51.9%, p=0.008), had adenocarcinoma histology (95%, vs 50.2%, p=0.002) and never smoked (67.5% vs 24.5%, p<0.001) (Supplementary Table S7).

3.4 Survival outcomes

In stage III NSCLC, the median progression-free survival (mPFS) and the median overall survival (mOS) for the Asia subset were 12.8 months (95% CI, 12.2 to 13.7) and 42.3 months (95% CI, 38.1 to 46.8), respectively. The mPFS and mOS were better for stage IIIA (15.1 months, 95% CI, 14.0 to 16.6 and 51.4 months, 95% CI, 43.8 to 64.1) than stage IIIB (10.3 months, 95% CI, 9.3 to 11.3 and 32.8 months, 95% CI, 27.7 to 40.6) (Figures 1A, B).

The mPFS (19.8 months vs 11.0 months) and mOS (65.4 months vs 31.8 months) were comparatively higher in patients with resectable than the unresectable disease (Figures 1C, D).

3.4.1 Survival outcomes by initial treatment

The survival outcomes are presented as per the resection status and initial treatment. Amongst the top five treatments in the resectable category, surgery-based initial treatment followed by adjuvant treatment strategies in sequence showed better mPFS (29.9 months) than surgery alone (15.4 months) or CT alone (15.1 months), while mOS was better with CT alone (65.4 months) and surgery+CT (57.9 months) than surgery alone (32.1 months) (Table 2 and Supplementary Table S8).

We found mPFS to be almost similar for all top five treatments used in unresectable category, except for CT alone; whereas mOS was better with cCRT (n=323, 39.2 months, 95% CI, 32.4 to 50.8) compared to sCRT (n=64, 26.6 months, 95% CI, 18.7 to 36.7, p=0.04), CT alone (n=110, 25.1 months, 95% CI, 17.3 to 42.6, p=0.02), targeted therapy alone (n=40, 24.0 months, 95% CI, 14.6 to 30.5, p=0.0006) or RT alone (n=85, 16.8 months, 95% CI, 12.2 to 27.2, p<0.0001) used until 1st progressive disease (Table 2 and Supplementary Tables S8, S9).

Survival outcomes as per initial treatment according to AJCC staging (7th Edition) are described in Table 2 and Supplementary Table S10.

In stage IIIA disease, amongst the top five treatments as initial treatments, other surgery showed better mPFS (n=93, 26.7 months) compared with cCRT (n=247,14.4 months), sCRT (n=82, 13.4 months) or CT alone (n=100, 9.6 months). While the mOS was better with surgery+CT (n=87, 57.9 months) than cCRT (n=247, 50.8 months), CT (n=100, 40.7 months) or sCRT (n=82, 29.0 months). In stage IIIB disease, the mPFS was almost similar for all top treatments, whereas mOS was better with cCRT (n=254, 36.0 months) compared with targeted therapy alone (n=58, 27.7 months), sCRT (n=78, 25.7 months) or CT alone (n=149, 24.2 months) (Table 2 and Supplementary Table S10).

3.4.2 Survival outcomes by EGFR mutation status

The mPFS and mOS for patients with EGFRm were 14.1 months (95% CI, 12.6 to 16.4) and 51.5 months (95% CI, 45.4 to 67.7), respectively, which were longer than patients not having EGFRm (Figures 2A, B). In patients with EGFRm having resectable disease, the mPFS and mOS were longer (19.1 months, 59.5 months) compared to patients with the unresectable disease (13.2 months, 48.2 months) (Supplementary Table S11).

The use of targeted therapy was more frequent as initial therapy in patients with EGFRm (61/297, 20.5%); the mPFS and mOS for these patients were 11.2 months (n=61, 95% CI, 7.16 to14.3) and 25.4 months (n=61, 95% CI, 21.6 to 34.9). The other preferred treatment options in EGFR mutated patients were cCRT (43/297, 14.5%); the mPFS and mOS for these patients were 11.5 months (95% CI, 6.05 to 16.16) and 50.8 months (95% CI, 47.21 to not calculable [NC]), respectively (Supplementary Figure S3 and Table 3).

3.5 Prognostic factors of mPFS and mOS

Clinical and demographic prognostic factors for mPFS and mOS for the overall population (Table 4) were assessed using univariate and multivariate analyses.

In the overall stage III population, univariate analyses showed significantly longer mPFS and mOS in patients with stage IIIA disease, aged ≤65 years, with ECOG ≤1, with resected disease and having undergone surgery or received triple therapy as initial treatment ($p < 0.05$ for all). Additionally, EGFRm, female gender, no smoking history, adenocarcinoma and having received cCRT as part of initial treatment predicted longer mOS ($p < 0.05$ for all).

In multivariate analyses, stage IIIA disease, ECOG ≤1, and surgery or cCRT as part of initial therapy were independently associated with better mPFS and mOS in the overall stage III population (p<0.05 for

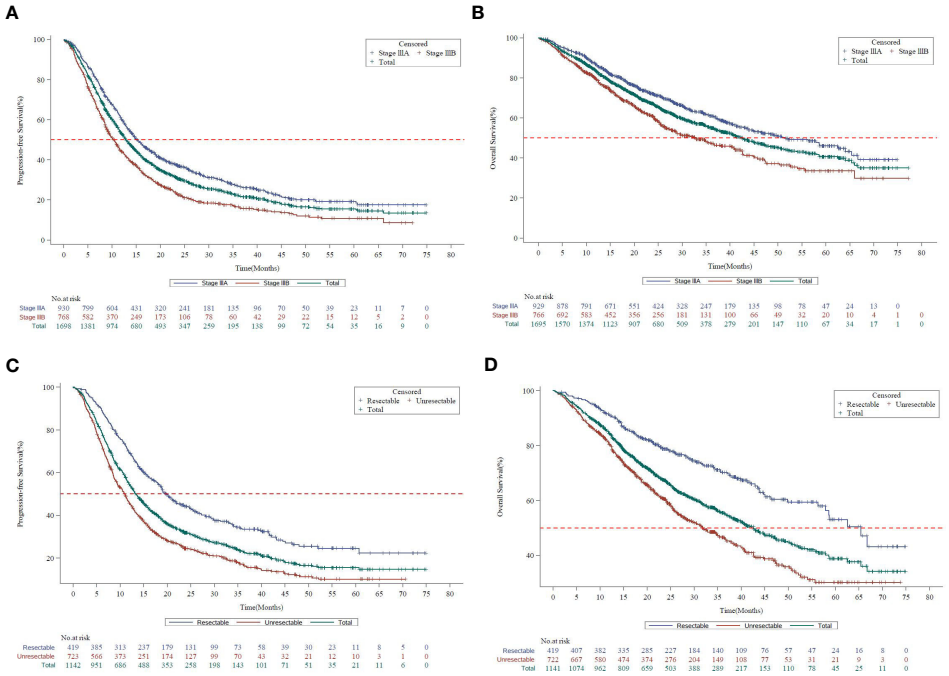

FIGURE 1
Survival curves by disease stage in KINDLE-Asia. **(A)** Kaplan-Meier survival curves for progression-free survival by disease stage (AJCC 7th Edition). AJCC=American Joint Committee on Cancer; CI=Confidence interval; mPFS=Median progression-free survival; NSCLC=Non-small cell lung cancer. Kaplan-Meier Survival curves for progression-free survival for all stage III NSCLC patients are shown in green, whereas stage IIIA and stage IIIB patients are shown in blue or red, respectively. mPFS for the entire cohort, 12.8 months (95% CI, 12.19 to 13.70). mPFS for stage IIIA, 15.1 months (95% CI, 14.03 to 16.56). mPFS for stage IIIB, 10.3 months (95% CI, 9.26 to 11.27). **(B)** Kaplan-Meier survival curves for overall survival by disease stage (AJCC 7th Edition). AJCC=American Joint Committee on Cancer; CI=Confidence interval; mOS=Median overall survival; NSCLC=Non-small cell lung cancer. Kaplan-Meier survival curves for overall survival for all stage III NSCLC patients are shown in green, whereas stage IIIA and stage IIIB patients are shown in blue or red, respectively. mOS for the entire cohort, 42.3 months (95% CI, 38.08 to 46.75). mOS for stage IIIA, 51.4 months (95% CI, 43.83 to 64.07). mOS for stage IIIB, 32.8 months (95% CI, 27.66 to 40.61). **(C)** Kaplan-Meier survival curves for progression-free survival by resection status. CI=Confidence interval; mPFS=Median progression-free survival; NSCLC=Non-small cell lung cancer. Kaplan-Meier survival curves for progression-free survival for all stage III NSCLC patients are shown in green, whereas resectable and unresectable patients are shown in blue or red, respectively. mPFS for the entire cohort, 12.8 months (95% CI, 12.19 to 13.70). mPFS for resectable patients, 19.8 months (95% CI, 18.00 to 22.67). mPFS for unresectable patients, 11.0 months (95% CI, 9.66 to 11.86) **(D)** Kaplan-Meier survival curves for overall survival by resection status. CI=Confidence interval; mOS=Median overall survival; NSCLC=Non-small cell lung cancer. Kaplan-Meier survival curves for overall survival for all stage III NSCLC patients are shown in green, whereas resectable and unresectable patients are shown in blue or red, respectively. mOS for the entire cohort, 42.3 months (95% CI, 38.08 to 46.75). mOS for resectable patients, 65.4 months (95% CI, 57.86 to Not Calculable). mOS for unresectable patients, 31.8 months (95% CI, 27.40 to 36.70).

all). Age ≤65 years and adenocarcinoma were additional independent predictors of better mOS (p<0.05 each). Whereas no smoking history was independently associated with better mPFS (p<0.05).

Further, the predictors associated with stage IIIA and IIIB disease are shown in Supplementary Tables S12, S13 present.

4 Discussion

We present the multinational retrospective data from Asia on treatment practices and survival outcomes for stage III NSCLC patients, as a subset of the KINDLE study. Asian patients were predominantly older (>60 years) males. We found a higher percentage of patients in Asia who never smoked (28%) compared to other regions of the KINDLE study (Latin America, 14.8% and the Middle East and Africa, 16%) (18). The treatment diversity, with the use of about 31 approaches, indicates challenges posed by the heterogeneity of stage III disease and optimization of the treatment decision-making process in Asia.

As initial therapy, the most frequent treatment approach for the entire Asia subset (overall, stages IIIA and IIIB) was cCRT (29.3%, 26.5% and 33.2%) followed by CT alone (14.8%, 10.7% and 19.6%). These findings are in line with KINDLE-Global results (18). Because the majority of the patients had unresectable NSCLC, the choice of cCRT as the predominant initial therapy was appropriate as per the contemporary guidelines (20). In the second and third lines, CT alone was the most preferred treatment option. Unlike our findings, the predominant treatment patterns observed in other Asian real-word studies were curative intent surgery in Korea (49.6%) (10), platinum-based CT in Japan (56.0%) (21) and cCRT in Singapore (31.2%) (11). Our study provides more recent insights on treatment patterns in stage III NSCLC from the Asian countries compared with these studies. With changing treatment paradigm, more empirical studies are required from this region to explore patient, social and economic factors affecting the selection of

TABLE 2 Survival outcomes with top initial treatment patterns according to resection status and disease stage (AJCC 7th Edition) in KINDLE-Asia.

2A. Per resection status										
S. No.	Treatment	Resectable months (95% CI)				Treatment	Unresectable months (95% CI)			
		N	mPFS	N	mOS		N	mPFS	N	mOS
1	Other surgery	93	29.9 (21.13-43.20)	93	NC (NC-NC)	cCRT	323	11.3 (9.40-13.04)	323	39.2 (32.36-50.79)
2	Surgery+CT	84	17.8 (12.06-25.03)	84	57.9 (42.94-NC)	CT	110	6.7 (5.91-8.71)	110	25.1 (17.31-42.61)
3	Surgery+sCRT	67	29.3 (18.00-NC)	67	NC (43.83-NC)	RT	85	10.4 (7.39-12.19)	85	16.8 (12.19-27.24)
4	CT	37	15.1 (6.74-23.72)	37	65.4 (43.83-NC)	sCRT	64	12.5 (9.43-14.95)	64	26.6 (18.56-36.70)
5	Surgery	33	15.4 (11.24-24.41)	33	32.1 (23.26-66.73)	Targeted therapy	40	13.8 (6.44-16.56)	40	24.0 (14.62-30.52)
2B. Per disease stage										
S. No	Treatment	Stage IIIA months (95% CI)				Treatment	Stage IIIB months (95% CI)			
		N	mPFS	N	mOS		N	mPFS	N	mOS
1	cCRT	247	14.4 (12.45-18.04)	247	50.8 (37.09-NC)	cCRT	254	9.3 (8.21-11.20)	254	36.0 (28.62-47.38)
2	CT	100	9.6 (6.64-12.48)	100	40.7 (29.24-65.38)	CT	150	7.4 (6.51-9.30)	149	24.2 (19.98-38.08)
3	Other surgery	93	26.7 (20.17-39.95)	93	NC (45.01-NC)	sCRT	78	9.4 (8.51-12.42)	78	25.7 (17.18-NC)
4	Surgery+CT	87	15.6 (11.66-21.91)	87	57.9 (37.82-NC)	RT	63	8.0 (4.60 -10.84)	63	13.0 (9.13-28.71)
5	sCRT	82	13.4 (10.74-14.95)	82	29.0 (26.05-NC)	Target therapy	58	10.5 (6.05-15.31)	58	27.7 (24.18-50.33)

AJCC, American Joint Committee on Cancer; cCRT, Concurrent chemoradiotherapy; CI, Confidence interval; CT, Chemotherapy; mOS, Median overall survival; mPFS, Median progression-free survival; N, Number of patients; NC, Not calculable; RT, Radiotherapy; sCRT, Sequential chemoradiotherapy.
The treatment pattern definitions based on the available patterns from the full analysis set for first line used until 1st progressive disease.
IO: Immuno-oncology, Surgery+CT: surgery and chemotherapy were used in sequence, surgery+sCRT: surgery and sCRT were used in sequence, CT: only chemotherapy was used, Surgery: only surgery was used, Other Surgery: other therapies used in combination with surgery, cCRT: only cCRT was used, RT: only radiotherapy was used, Targeted therapy: only targeted therapy was used.

treatment approaches including insurance coverage, accessibility and availability of newer targeted drugs.

The mPFS observed in the Asian population with stage III disease was 12.8 months, which is similar to the KINDLE-Global results (18) whereas, the mOS of 42.3 months is higher than the global cohort (34.9 months) (18). The mOS according to resectability and staging observed in our Asia subset were longer (in unresectable: 31.8 months; stage IIIB: 32.8 months) than other large-scale real-world studies from the United States in unresected stage III NSCLC (mOS: 20 months) (22), and Portugal (mOS: 11.4 months in stage IIIB disease) (23). We found an independent association between longer mOS and stage IIIA disease, ECOG ≤1, age ≤65 years, adenocarcinoma histology, and surgery or cCRT as initial therapy. Similarly, other real world studies have reported an association between decent ECOG performance status, younger age, early-stage disease, cCRT or surgery as a part of initial treatment and a lesser risk of death in patients with NSCLC (22, 24). In our cohort, we also noted an association between EGFRm and better mOS (HR: 0.723, 95% CI, 0.568 to 0.920, p=0.0082). The role of higher prevalence of EGFRm in deciding subsequent treatment choices and better survival in Asian population needs further exploration.

In a Korean study in stage III NSCLC, the mOS was highest for curative-intent surgery (52.5 months, 95% CI, 43.1 to 61.9), and 49.2 months (95% CI, 42.0 to 56.5) in those who received neoadjuvant therapy (10). We report similar OS benefits in stage IIIA patients receiving surgery based treatments such as surgery +CT (57.9 months, 95% CI, 37.8 to NC) or surgery+RT (58.6 months, 95% CI, 14.5 to NC). In unresectable patients, cCRT significantly improved OS compared with sCRT, CT alone or RT alone. These findings resonate with significantly improved survival outcomes reported with cCRT than sCRT (HR: 0.84; p=0.004) (25), CT alone and RT alone in a systematic review and meta analyses and in a few other single-center studies (26–28).

The role of a MDT in treatment decision-making is well established and augments patient outcomes (29–32). The MDT was involved in treatment decisions for only one third of the cases (32.0%) in this study. Considering the upcoming molecular and immunology testing-based novel modalities, active involvement of MDT needs to be encouraged in Asia for patient-centric management of stage III NSCLC.

The advent of immunotherapy and TKIs have changed the treatment paradigm of NSCLC over the past few years. Studies have shown that multimodal regimens using molecular targeting and/or immunotherapy provide survival benefits (33–36), leading to change in NCCN® Guidelines (9) incorporating durvalumab as consolidation post CRT and adjuvant osimertinib post-surgery with or without platinum-based CT in the management of resectable stage III NSCLC. In Asian patients with NSCLC, the prevalence of EGFRm is high compared to the Western population (50% vs 15%) (37). Yang et al. reported an overall EGFRm rate of 51.4% in NSCLC stage IIIB/IV adenocarcinoma in the Asia region (range: 22.2% to 64.2%) (38). The KINDLE-Asia subset showed a higher EGFRm rate (34.3%) in stage III NSCLC, than other KINDLE regions (Middle East and Africa, 20.0% and Latin America, 28.4%) (39). EGFRm were more frequently found in females (51.5%), never smokers (58.9%), stage IIIA (62.2%), those with adenocarcinoma histology (92.3%) and resectable disease (52.9%).

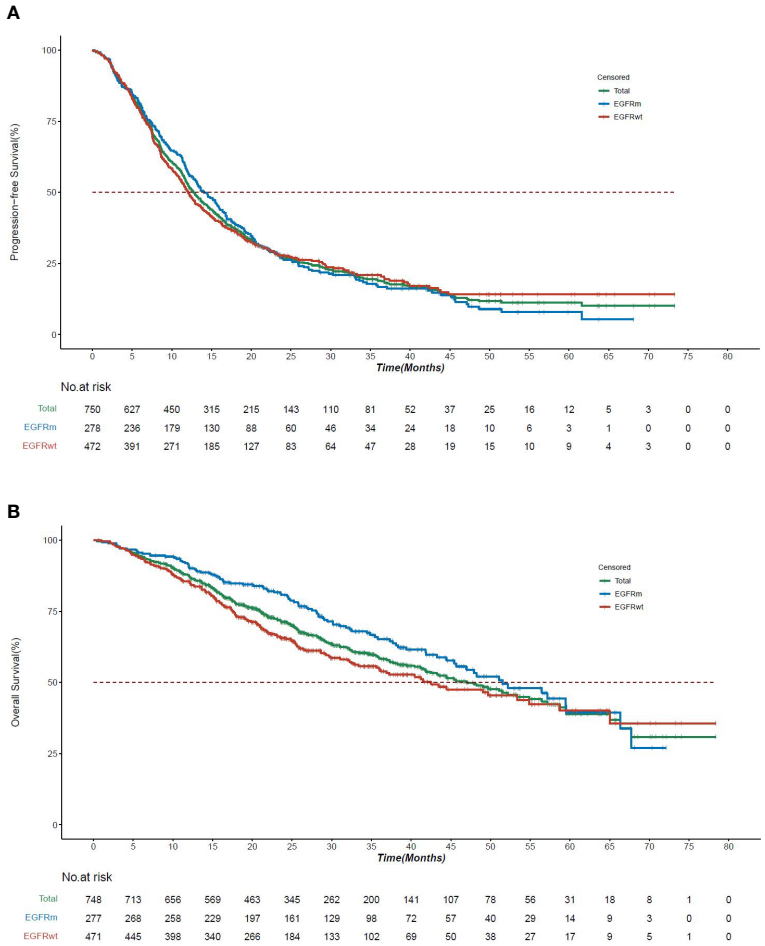

FIGURE 2
Survival curves by EGFR mutation status in KINDLE-Asia. **(A)** Kaplan-Meier survival curves for progression-free survival by EGFR mutation status. CI=Confidence interval; EGFR=Epidermal growth factor receptor; EGFRm=Epidermal growth factor receptor mutation; EGFRwt=Epidermal growth factor receptor wild type mutation; mPFS=Median progression-free survival; NSCLC=Non-small cell lung cancer. Kaplan-Meier survival curves for progression-free survival for all stage III NSCLC patients are shown in green, whereas EGFRm and EGFRwt patients are shown in blue or red, respectively. mPFS for the entire cohort, 12.8 months (95% CI, 12.19 to 13.70). mPFS for EGFRm patients, 14.1 months (95% CI, 12.6 to 16.4). mPFS for EGFRwt patients, 12.0 months (95% CI, 11.1 to 13.6). **(B)** Kaplan-Meier survival curves for overall survival by EGFR mutation status. CI=Confidence interval; EGFR=Epidermal growth factor receptor; EGFRm=Epidermal growth factor receptor mutation; *EGFR*wt=Epidermal growth factor receptor wild type mutation; mOS=Median overall survival; NSCLC=Non-small cell lung cancer. Kaplan-Meier survival curves for overall survival for all stage III NSCLC patients are shown in green, whereas EGFRm and EGFRwt patients are shown in blue or red, respectively. mOS for the entire cohort, 42.3 months (95% CI, 38.08 to 46.75). mOS for EGFRm patients, 51.5 months (95% CI, 45.4 to 67.7). mOS for EGFRwt patients, 42.5 months (95% CI, 35.7 to 58.7).

TABLE 3 Survival outcomes with top initial treatment patterns according to *EGFR* mutation status in KINDLE-Asia.

			EGFRm					EGFRwt		
S. No.	Treatment	N	mPFS months (95% CI)	N	mOS months (95% CI)	Treatment	N	mPFS months (95% CI)	N	mOS months (95% CI)
1	Target therapy	61	11.2 (7.16-14.29)	61	25.4 (21.62 34.92)	cCRT	139	9.5 (8.41-12.29)	139	40.6 (25.59-64.07)
2	cCRT	43	11.5 (6.05-16.16)	43	50.8 (47.21-NC)	CT	96	7.4 (5.91-10.32)	95	29.2 (20.44-NC)
3	Other surgery	31	25.6 (16.66-41.59)	31	NC (31.31-NC)	Other surgery	37	28.1 (16.07-NC)	37	NC (35.61- NC)
4	Surgery+CT	23	13.0 (8.87- 28.19)	23	58.6 (37.82- NC)	Surgery+CT	36	15.6 (12.06-20.67)	36	29.4 (21.13-57.86)
5	CT	23	15.4 (6.67-19.02)	23	NC (65.38-NC)	sCRT	32	12.6 (8.48-16.99)	32	36.7 (17.31 to NC)

cCRT, Concurrent chemoradiotherapy; CI, Confidence interval; CT, Chemotherapy; EGFRm, Epidermal growth factor receptor mutation; EGFRwt, Epidermal growth factor receptor wild type mutation; mOS, Median overall survival; mPFS, Median progression-free survival; N, Number of patients; NC, Not calculable; RT, Radiotherapy; sCRT, Sequential chemoradiotherapy.
The treatment pattern definitions based on the available patterns from the full analysis set for first line used until 1st progressive disease
IO: Immuno-oncology, Surgery+CT: surgery and chemotherapy were used in sequence, surgery+sCRT: surgery and sCRT were used in sequence, CT: only chemotherapy was used, Surgery: only surgery was used, Other Surgery: other therapies used in combination with surgery, cCRT: only cCRT was used, RT: only radiotherapy was used, Targeted therapy: only targeted therapy was used.

TABLE 4 Univariate and multivariate analyses for survival outcomes in KINDLE-Asia.

Characteristics	Univariate analyses					
	PFS			OS		
	N	HR (95% CI)	p-value	N	HR (95% CI)	p-value
Stage IIIA vs IIIB	930 vs 768	0.671 (0.600-0.750)	**<0.0001**	929 vs 766	0.659 (0.566-0.768)	**<0.0001**
Age >65 vs ≤65	717 vs 1055	1.156 (1.035-1.291)	**0.0103**	717 vs 1051	1.345 (1.157-1.563)	**0.0001**
ECOG 0/1 vs 2/3/4	989 vs 124	0.688 (0.559-0.849)	**0.0005**	985 vs 124	0.533 (0.409-0.696)	**<0.0001**
EGFRm vs EGFRwt	281 vs 488	1.008 (0.855-1.188)	0.9221	280 vs 487	0.723 (0.568-0.920)	**0.0082**
Male vs female	1320 vs 452	1.026 (0.906-1.162)	0.6847	1316 vs 452	1.542 (1.284-1.853)	**<0.0001**
Smoking history yes vs no	1096 vs 504	1.109 (0.980-1.255)	0.1022	1094 vs 502	1.534 (1.288-1.826)	**<0.0001**
Resectable yes vs no	419 vs 723	0.553 (0.478-0.640)	**<0.0001**	419 vs 722	0.477 (0.388-0.585)	**<0.0001**
Adenocarcinoma vs others	983 vs 786	0.967 (0.866-1.080)	0.5531	980 vs 785	0.635 (0.546-0.737)	**<0.0001**
Surgery in initial treatment yes vs no	410 vs 1362	0.510 (0.443-0.586)	**<0.0001**	410 vs 1358	0.513 (0.422-0.624)	**<0.0001**
cCRT as initial treatment yes vs no	519 vs 1253	1.005 (0.891-1.134)	0.9349	519 vs 1249	0.940 (0.796-1.109)	0.4617
cCRT as initial treatment vs sCRT as initial treatment	519 vs 169	0.868 (0.711-1.058)	0.1616	519 vs 168	0.705 (0.541-0.920)	**0.0100**
Trimodality as initial treatment yes vs no	142 vs 1630	0.541 (0.432-0.677)	**<0.0001**	142 vs 1626	0.511 (0.367-0.712)	**<0.0001**
Characteristics	Multivariate analyses					
	PFS			OS		
	N	HR (95% CI)	p-value	N	HR (95% CI)	p-value
Stage IIIA vs IIIB	538 vs 458	0.779 (0.668-0.908)	**0.0014**	537 vs 456	0.709 (0.577-0.870)	**0.0010**
Age >65 vs ≤65	413 vs 583	1.085 (0.936-1.258)	0.2805	413 vs 580	1.304 (1.073-1.585)	**0.0076**
ECOG 0/1 vs 2/3/4	897 vs 99	0.752 (0.598-0.945)	**0.0147**	894 vs 99	0.584 (0.441-0.775)	**0.0002**
Male vs female	745 vs 251	0.962 (0.757-1.222)	0.7494	742 vs 251	1.140 (0.823-1.580)	0.4300
Smoking history yes vs no	685 vs 311	1.288 (1.027-1.615)	**0.0283**	684 vs 309	1.253 (0.926-1.696)	0.1438
Adenocarcinoma vs others	554 vs 442	1.140 (0.975-1.333)	0.1010	551 vs 442	0.809 (0.658-0.995)	**0.0451**
Surgery in initial treatment yes vs no	217 vs 779	0.504 (0.392-0.649)	**<0.0001**	217 vs 776	0.642 (0.463-0.891)	**0.0080**
cCRT as initial treatment yes vs no	335 vs 661	0.745 (0.632-0.878)	**0.0004**	335 vs 658	0.694 (0.558-0.864)	**0.0011**
Trimodality as initial treatment yes vs no	85 vs 911	0.902 (0.629-1.293)	0.5755	85 vs 908	0.807 (0.487-1.339)	0.4070

AJCC, American Joint Committee on Cancer; cCRT, Concurrent chemoradiotherapy; CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFRm, Epidermal growth factor receptor mutation; EGFRwt, Epidermal growth factor receptor wild type mutation; HR, Hazard ratio; N, Number of patients; OS, overall survival; PFS, Progression-free survival; sCRT, Sequential chemoradiotherapy.
Stage of tumor is per AJCC 7th edition.
Values in bold indicate significant difference (p<0.05).

At primary diagnosis, a higher percentage of EGFR-mutated patients in our study had resectable tumors compared with patients without EGFRm (52.9% vs 37.3%). Results of the ADAURA phase III study demonstrated a clinically meaningful and significant improvement in disease-free survival with osimertinib in patients with NSCLC stage II-IIIA with EGFRm compared to placebo (HR: 0.17; 99.06% CI, 0.11 to 0.26, p<0.001) (33). Osimertinib reduced the risk of disease recurrence or death by 83%. In the overall study population of patients with stage IB-IIIA disease and EGFRm, the risk of disease recurrence or death was reduced by 80% (HR: 0.20, 99.12% CI, 0.14 to 0.30; p<0.001) (33). The updated 2022 NCCN guidelines recommend molecular testing for EGFRm to assess whether adjuvant TKI therapy could be an option for resectable stage IB IIIA NSCLC (9). The guidelines further recommend osimertinib for patients with completely resected stage IB-IIIA EGFRm-positive (exon 19 deletion, L858R) NSCLC, who received previous adjuvant CT or are ineligible to receive platinum-based CT (9). Furthermore, the ongoing LAURA phase III trial (NCT03521154) which is evaluating the role of osimertinib as maintenance therapy in patients with unresectable stage III NSCLC with EGFRm following cCRT will provide important evidence if EGFR-targeted therapy is beneficial for survival gain in unresectable stage III NSCLC with EGFR-mutated patients (40). In the background of this evolving evidence, treating oncologists should encourage genomic profiling in stage III NSCLC; in cases of resected patients, biopsied or resected samples are routinely sent for biomarker testing to plan further course of treatment; however, in unresectable patients, genomic profiling is delayed until

progression to stage IV, when a liquid biopsy is a recommended option for planning targeted therapy (41).

In our study, in unresectable disease, cCRT was used in about one-third of the study population (in line with NSCLC management guidelines) and provided better mPFS (11.3 months) and mOS (39.2 months) than CT or RT alone; however, the remaining patients received CT alone, sCRT and RT alone with poor survival. Now, with durvalumab being approved, this group of unresectable stage III NSCLC patients would most likely benefit from durvalumab consolidation post cCRT (42), if early PD-L1 testing is encouraged. The 5-year OS data from the PACIFIC study demonstrated robust and sustained OS plus durable PFS benefit with the PACIFIC regimen with 42.9% of patients being alive and approximately 33% of the patients remained alive and free of disease progression (43). A retrospective study found that in clinical practice, approximately 70% of patients with unresectable stage III NSCLC not progressing on cCRT would be eligible to receive consolidation therapy with durvalumab (44).

The current findings from this Asia subset provide a benchmark to understand the existing treatment landscape, which will be important for implementing newer therapies and evaluating their effectiveness in this population. Though the study provides insights into treatment practices for stage III NSCLC in the Asian region, the retrospective design may limit the representativeness of the findings before immunotherapy approval. Being a real-word study, the data collection was limited to clinicians' reports from the existing medical records and the data captured included data pertaining to the protocol-defined outcomes only. The details of histopathology (including pathologic confirmation of N2 lymph nodes) and other diagnostic work-up were not captured; which might have resulted in missing information about diagnostic practices. Some patients might have been lost to routine clinical follow-up, thus resulting in missing data. Additionally, retrospective data collection may have favored patients with longer survival, resulting in a potential bias in the study outcomes.

5 Conclusions

The results from this large, real-world study demonstrate diverse treatment patterns and survival outcomes in the Asian region, providing baseline data for evaluating novel therapies for stage III NSCLC in the near future. Nearly 31 treatment approaches were used with around 32% of the cases being discussed in MDT meetings. In unresectable disease, cCRT as initial therapy showed longer survival benefits than sCRT, RT alone, CT and targeted therapy. Surgery followed by adjuvant CT in resectable disease showed longer survival benefit than surgery alone. However, our findings also demonstrate limited adherence to the treatment guidelines applicable before immunotherapy approval including treatment decisions based on MDT discussions. The EGFRm testing rate of 46.2% in the overall stage III population and EGFRm positivity reported as 44.2% and 29.3% in resectable and unresectable categories, respectively, suggests the need for expanding access to molecular testing for guiding treatment strategies with TKIs and immunotherapies in the Asian region.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The study protocol (NCT03725475) was reviewed and approved by the Institutional Review Boards/Independent Ethics Committees from all the participating centers before the initiation of the study: The Institutional Ethics Committees (IECs) Tata Memorial Centre (TMC), Mumbai; The SingHealth Centralised Institutional Review Board (CIRB), Singapore; The Domain Specific Review Board (DSRB), Singapore; The Institutional Review Board of the Faculty of Medicine at Chulalongkorn University, Thailand; Institutional Review Board of Taipei Veterans General Hospital, Taiwan; Medical Research and Ethics Committee (MREC), National Institute of Health, Malaysia; Persahabatan Hospital Ethic Committee, Indonesia; Yonsei University Health System, Severance hospital, Institutional review board, Republic of Korea. Written informed consent was obtained from the patients or their next of kin/legal representatives (in the case where patients were deceased) before retrospective data were collected.

Author contributions

KP: Conceptualization, Methodology, Investigation, Writing, Review, Editing, Visualization, Validation. DT: Conceptualization, Investigation, Methodology, Review, Editing. RS: Conceptualization, Investigation, Methodology, Review, Editing. PS: Conceptualization, Investigation, Methodology, Review, Editing. YC: Conceptualization, Investigation, Methodology, Review, Editing. PV: Conceptualization, Investigation, Methodology, Review, Editing. ES: Conceptualization, Investigation, Methodology, Review, Editing. SC: Conceptualization, Investigation, Methodology, Review, Editing. RH: Conceptualization, Investigation, Methodology, Review, Editing. B-CC: Conceptualization, Methodology, Investigation, Writing, Review, Editing, Visualization, Validation. The work reported in the paper has been performed by the authors, unless clearly specified in the text. All authors contributed to the article and approved the submitted version.

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KINDLE Global data poster presented at ASCO: Abdul Rahman Jazieh, et al. Contemporary management and associated outcomes of 3,151 patients with stage III non-small cell lung cancer (NSCLC) in a real-world setting: Results of KINDLE, a multicountry observational study. Journal of Clinical Oncology 2020 38:15_suppl, 9043-9043.

KINDLE Global data manuscript published: Jazieh AR et al. Real-world treatment patterns and clinical outcomes in patients with stage III NSCLC: Results of KINDLE, a Multicountry observational study. Journal of Thoracic Oncology. 2021;16 (10):1733-1744. doi: 10.1016/j.jtho.2021.05.003.

KINDLE Singapore Subset Data presented at ESMO Asia Congress 2020 Virtual November 22, 2020. Soo RA, Cho BC, Prabhash K, et al. Treatment patterns and outcomes in stage III non-small cell lung cancer (NSCLC): Real-world experience in Singapore from the KINDLE study).

KINDLE India subset data presented at ESMO Asia Congress 2020 Virtual November 22, 2020. Prabhash K, Jazieh AR, Onal HC, et al. Real-world insights into treatment patterns and outcomes in stage III non-small cell lung cancer (NSCLC): KINDLE study India analysis.

KINDLE Korean subset data was published online as an abstract (J. P04. 03) on March 01 2021 in J Thorac Oncol. Cho BC, Kim S, Lee SS, et al. Patient characteristics and clinical outcomes of stage III NSCLC in a Real-world setting: KINDLE Korean subset data.

KINDLE Vietnam subset data manuscript published: Van Dao T, Diep TB, Le Phuong T, Huggenberger R, Kumar A. Real-world treatment patterns and clinical outcomes in patients with stage III non-small-cell lung cancer: Results of KINDLE-Vietnam cohort. Frontiers in Oncology. 2022;12:842296. doi: 10.3389/fonc.2022.842296.

Conflict of interest

The authors declare that the KINDLE study, manuscript writing support, and article processing fees for the journal have been funded by AstraZeneca. The funder had the following involvement with the study: study design, analysis, interpretation of data, and the writing of this article.

DT – Received research grants: Novartis, Bayer, Astra Zeneca; Advisory role and consultant: Novartis, Bayer, Boehringer Ingelheim, Astra Zeneca, Eli Lilly, Loxo, Merrimack, Takeda, Pfizer; Travel and honorarium: Merck, Novartis, Boehringer Ingelheim, Roche. RS – Advisory board member: Amgen, Astra-Zeneca, Bayer, BMS, Boehringer Ingelheim, Lilly, Merck, Novartis, Pfizer, Puma, Roche, Taiho, Takeda, Yuhan; Received research grant: Astra-Zeneca, Boehringer Ingelheim

SC – Employment full time: AstraZeneca. RH – Employment full time: AstraZeneca Plc; stock ownership: AstraZeneca. B-CC – Received research grants from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, MSD, Abbvie, Medpacto, GIInnovation, Eli Lilly, Blueprint medicines, Interpark Bio Convergence Corp; Consultant role: Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD, Janssen, Medpacto, Blueprint medicines; Stock ownership: TheraCanVac Inc, Gencurix Inc, Bridgebio therapeutics, KANAPH Therapeutic Inc, Cyrus therapeutics, Interpark Bio Convergence Corp; Advisory board member: KANAPH Therapeutic Inc, Brigebio therapeutics, Cyrus therapeutics, Guardant Health, Joseah BIO; Board of director for Gencurix Inc, Interpark Bio Convergence Corp; Founder for DAAN Biotherapeutics; Royalty: Champions Oncology.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1117348/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Frequent treatment patterns used in various lines of therapy for stage III NSCLC in KINDLE-Asia. cCRT, Concurrent chemoradiotherapy; CT, Chemotherapy; NSCLC, Non-small cell lung cancer; RT, Radiotherapy; sCRT, Sequential chemoradiotherapy. The treatment pattern definitions are based on the available patterns from the full analysis set for first line used until 1st progressive disease. Other Surgery: other therapies used in combination with surgery, cCRT: only cCRT was used, sCRT: only sCRT was used, CT: only chemotherapy was used, IO: only immunotherapy was used, RT: only radiotherapy was used, Targeted therapy: only targeted therapy was used.

SUPPLEMENTARY FIGURE S2
Frequent initial treatment patterns according to disease stage (AJCC 7th Edition) and resection status in KINDLE-Asia. AJCC, American Joint Committee on Cancer; cCRT, Concurrent chemoradiotherapy; CT, Chemotherapy; IO, immune-oncology; RT, Radiotherapy; sCRT, Sequential chemoradiotherapy. The treatment pattern definitions are based on the available patterns from the full analysis set for first line used until 1st progressive disease. Surgery alone: only surgery was used, Surgery+sCRT: surgery and sCRT were used in sequence, Surgery+CT: surgery and chemotherapy were used in sequence, Other Surgery: other therapies used in combination with surgery, cCRT: only cCRT was used, sCRT: only sCRT was used, CT: only chemotherapy was used, RT: only radiotherapy was used, Targeted therapy: only targeted therapy was used

SUPPLEMENTARY FIGURE S3
Frequent initial treatment patterns according to *EGFR* mutation status. cCRT, Concurrent chemoradiotherapy; CT, Chemotherapy; *EGFR*, Epidermal growth factor receptor; IO, Immuno-oncology; RT, Radiotherapy; sCRT, Sequential chemoradiotherapy. The treatment pattern definitions are based on the available patterns from the full analysis set for first line used until 1st progressive disease. Surgery+sCRT: surgery and sCRT were used in sequence, Surgery+CT alone: surgery and chemotherapy were used in sequence, cCRT: only cCRT was used, CT alone: only chemotherapy was used, Targeted therapy alone: only targeted therapy was used.

References

1. *The global cancer observatory 2020: Factsheets, lung cancer* . Available at: https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf (Accessed July 13, 2021).

2. Chinese Guidelines for diagnosis and treatment of primary lung cancer 2018 (English version). *Chin J Cancer Res* (2019) 31:1–28. doi: 10.21147/j.issn.1000-9604.2019.01.01

3. Huber RM, De Ruysscher D, Hoffmann H, Reu S, Tufman A. Interdisciplinary multimodality management of stage III nonsmall cell lung cancer. *Eur Respir Rev Off J Eur Respir Soc* (2019) 28. doi: 10.1183/16000617.0024-2019

4. Mohan A, Garg A, Gupta A, Sahu S, Choudhari C, Vashistha V, et al. Clinical profile of lung cancer in north India: A 10-year analysis of 1862 patients from a tertiary care center. *Lung India* (2020) 37:190. doi: 10.4103/lungindia.lungindia_333_19

5. Edge SB, Compton CC. The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* (2010) 17:1471–4. doi: 10.1245/s10434-010-0985-4

6. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg* (2018) 8:709–18. doi: 10.21037/qims.2018.08.02

7. Vansteenkiste J, Ruysscher DD, Eberhardt WEE, Lim E, Senan S, Felip E, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* (2013) 24: vi89–98. doi: 10.1093/annonc/mdt241

8. Zarogoulidis K, Zarogoulidis P, Darwiche K, Boutsikou E, Machairiotis N, Tsakiridis K, et al. Treatment of non-small cell lung cancer (NSCLC). *J Thorac Dis* (2013) 5:S389–96. doi: 10.3978/j.issn.2072-1439.2013.07.10

9. Non-small cell lung cancer V.3.2022. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)National Comprehensive Cancer Network, Inc. 2022. All rights reservedTo view the most recent and complete version of the guideline, go online to NCCN.org.guidelines. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

10. Jung Ha, Sun Jm, Lee Sh, Ahn Js, Ahn Mj, Park K. Ten-year patient journey of stage III non-small cell lung cancer patients: A single-center, observational, retrospective study in Korea (Realtime autOmatically updated data warehOuse in healTh care; UNIVERSE-ROOT study). *Lung Cancer Amst Neth* (2020) 146:112–9. doi: 10.1016/j.lungcan.2020.05.033

11. Soo RA, Cho BC, Prabhash K, Jazieh A-R, Onal C, Kumar A, et al. Treatment patterns and outcomes in stage III non-small cell lung cancer (NSCLC): Real-world experience in Singapore from the KINDLE study. *Ann Oncol* (2020) 31:S1384. doi: 10.1016/j.annonc.2020.10.365

12. Tiwana MS, Lee HN, Saini S, Verma SK, Gupta M, Gupta M, et al. Outcomes of patients with unresected stage III and stage IV non-small cell lung cancer: A single institution experience. *Lung India Off Organ Indian Chest Soc* (2013) 30:187–92. doi: 10.4103/0970-2113.116250

13. Zhou Q, Song Y, Zhang X, Chen G-Y, Zhong D-S, Yu Z, et al. A multicenter survey of first-line treatment patterns and gene aberration test status of patients with unresectable stage IIIB/IV nonsquamous non-small cell lung cancer in China (CTONG 1506). *BMC Cancer* (2017) 17:462. doi: 10.1186/s12885-017-3451-x

14. Tan WL, Chua KLM, Lin C-C, Lee VHF, Tho LM, Chan AW, et al. Asian Thoracic oncology research group expert consensus statement on optimal management of stage III NSCLC. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer* (2020) 15:324–43. doi: 10.1016/j.jtho.2019.10.022

15. Ou S-HI, Ziogas A, Zell JA. Asian Ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. *J Thorac Oncol* (2009) 4:1083–93. doi: 10.1097/JTO.0b013e3181b27b15

16. Liang W, Shao W, Jiang G, Wang Q, Liu L, Liu D, et al. Chinese Multi-institutional registry (CMIR) for resected non-small cell lung cancer: survival analysis of 5,853 cases. *J Thorac Dis* (2013) 5:746. doi: 10.3978/j.issn.2072-1439.2013.12.32

17. Asamura H, Goya T, Koshiishi Y, Sohara Y, Eguchi K, Mori M, et al. A Japanese lung cancer registry study: Prognosis of 13,010 resected lung cancers. *J Thorac Oncol* (2008) 3:46–52. doi: 10.1097/JTO.0b013e31815e8577

18. Jazieh AR, Onal HC, Tan DSW, Soo RA, Prabhash K, Kumar A, et al. Real-world treatment patterns and clinical outcomes in patients with stage III NSCLC: Results of KINDLE, a multicountry observational study. *J Thorac Oncol* (2021) 16:1733–44. doi: 10.1016/j.jtho.2021.05.003

19. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. STROBE initiative. strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PloS Med* (2007) 4:e297. doi: 10.1371/journal.pmed.0040297

20. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2017) 28:iv1–iv21. doi: 10.1093/annonc/mdx222

21. Wang F, Mishina S, Takai S, Le TK, Ochi K, Funato K, et al. Systemic treatment patterns with advanced or recurrent non–small cell lung cancer in Japan: A retrospective hospital administrative database study. *Clin Ther* (2017) 39:1146–60. doi: 10.1016/j.clinthera.2017.04.010

22. Ryan KJ, Skinner KE, Fernandes AW, Punekar RS, Pavilack M, Walker MS, et al. Real-world outcomes in patients with unresected stage III non-small cell lung cancer. *Med Oncol* (2019) 36:24. doi: 10.1007/s12032-019-1249-1

23. Soares M, Antunes L, Redondo P, Borges M, Hermans R, Patel D, et al. Real-world treatment patterns and survival outcomes for advanced non-small cell lung cancer in the pre-immunotherapy era in Portugal: a retrospective analysis from the I-O optimise initiative. *BMC Pulm Med* (2020) 20:240. doi: 10.1186/s12890-020-01270-z

24. Moore S, Leung B, Wu J, Ho C. Real-world treatment of stage III NSCLC: The role of trimodality treatment in the era of immunotherapy. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer* (2019) 14:1430–9. doi: 10.1016/j.jtho.2019.04.005

25. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol Off J Am Soc Clin Oncol* (2010) 28:2181–90. doi: 10.1200/JCO.2009.26.2543

26. Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* (2011) 103:1452–60. doi: 10.1093/jnci/djr325

27. Agulnik J, Kasymjanova G, Pepe C, Hurry M, Walton RN, Sakr L, et al. Understanding clinical practice and survival outcomes in patients with unresectable stage III non-small-cell lung cancer in a single centre in Quebec. *Curr Oncol* (2020) 27: e459–66. doi: 10.3747/co.27.6241

28. Sakin A, Sahin S, Atci MM, Sakin A, Yasar N, Geredeli C, et al. The effect of different treatment modalities on survival in elderly patients with locally advanced non-small cell lung cancer. *Pulmonology* (2019) 27:26–34. doi: 10.1016/j.pulmoe.2019.11.007

29. Pan C-C, Kung P-T, Wang Y-H, Chang Y-C, Wang S-T, Tsai W-C. Effects of multidisciplinary team care on the survival of patients with different stages of non-small cell lung cancer: a national cohort study. *PloS One* (2015) 10:e0126547. doi: 10.1371/journal.pone.0126547

30. Bilfinger TV, Albano D, Perwaiz M, Keresztes R, Nemesure B. Survival outcomes among lung cancer patients treated using a multidisciplinary team approach. *Clin Lung Cancer* (2018) 19:346–51. doi: 10.1016/j.cllc.2018.01.006

31. Stone E, Rankin N, Kerr S, Fong K, Currow DC, Phillips J, et al. Does presentation at multidisciplinary team meetings improve lung cancer survival? findings from a consecutive cohort study. *Lung Cancer Amst Neth* (2018) 124:199–204. doi: 10.1016/j.lungcan.2018.07.032

32. Ung KA, Campbell BA, Duplan D, Ball D, David S. Impact of the lung oncology multidisciplinary team meetings on the management of patients with cancer. *Asia Pac J Clin Oncol* (2016) 12:e298–304. doi: 10.1111/ajco.12192

33. Wu Y-L, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non–Small-Cell lung cancer. *N Engl J Med* (2020) 383:1711–23. doi: 10.1056/NEJMoa2027071

34. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–Small-Cell lung cancer. *N Engl J Med* (2017) 377:1919–29. doi: 10.1056/NEJMoa1709937

35. Fu Z, Yang X, Wang W, Deng L, Zhang T, Bi N, et al. Radiotherapy combined with gefitinib for patients with locally advanced non-small cell lung cancer who are unfit for surgery or concurrent chemoradiotherapy: a phase II clinical trial. *Radiat Oncol* (2020) 15:155. doi: 10.1186/s13014-020-01596-2

36. Yang Z, Tam KY. Combination strategies using EGFR-TKi in NSCLC therapy: Learning from the gap between pre-clinical results and clinical outcomes. *Int J Biol Sci* (2018) 14:204–16. doi: 10.7150/ijbs.22955

37. Nguyen K-SH, Neal JW, Wakelee H. Review of the current targeted therapies for non-small-cell lung cancer. *World J Clin Oncol* (2014) 5:576–87. doi: 10.5306/wjco.v5.i4.576

38. Yang P-C, Shi Y, Au JS, Srinivasan S, Cornelio GH, Tsai C-M, et al. Molecular epidemiological prospective study of EGFR mutations from Asian patients (pts) with advanced lung adenocarcinoma (PIONEER). *J Clin Oncol* (2012) 30:1534–4. doi: 10.1200/jco.2012.30.15_suppl.1534

39. Jazieh A, Onal H, Tan D, Soo R, Prabhash K, Kumar A, et al. OA05.03 real-world global data on targeting epidermal growth factor receptor in stage III non-small cell lung cancer: The results of the KINDLE study. *J Thorac Oncol* (2021) 16:S110–1. doi: 10.1177/17588359221122720

40. Lu S, Casarini I, Kato T, Cobo M, Özgüroğlu M, Hodge R, et al. Osimertinib maintenance after definitive chemoradiation in patients with unresectable EGFR mutation positive stage III non-small-cell lung cancer: LAURA trial in progress. *Clin Lung Cancer* (2021) 22:371–5. doi: 10.1016/j.cllc.2020.11.004

41. Rolfo C, Mack P, Scagliotti GV, Aggarwal C, Arcila ME, Barlesi F, et al. Liquid biopsy for advanced NSCLC: A consensus statement from the international association for the study of lung cancer. *J Thorac Oncol* (2021) 16:1647–62. doi: 10.1016/j.jtho.2021.06.017

42. Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer* (2021) 16:860–7. doi: 10.1016/j.jtho.2020.12.015

43. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares LG, et al. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. *J Clin Oncol* (2021) 39:8511. doi: 10.1200/JCO.2021.39.15_suppl.8511

44. Sakaguchi T, Ito K, Furuhashi K, Nakamura Y, Suzuki Y, Nishii Y, et al. Patients with unresectable stage III non-small cell lung cancer eligible to receive consolidation therapy with durvalumab in clinical practice based on PACIFIC study criteria. *Respir Investig* (2019) 57:466–71. doi: 10.1016/j.resinv.2019.03.011

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EDITED BY
Aakash Desai,
Mayo Clinic, United States

REVIEWED BY
Wencheng Zhang,
Tianjin Medical University Cancer Institute and Hospital, China
Zhe Ji,
Peking University Third Hospital, China

*CORRESPONDENCE
Ning An
annning0921@qdu.edu.cn

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ER predicts poor prognosis in male lung squamous cell cancer of stage IIIA-N2 disease after sequential adjuvant chemoradiotherapy

Xue Yang[1], Lili Wang[2], Xiangfeng Jin[3], Rongjian Xu[3], Zhuang Yu[1], Hongmei Li[1], Haijun Lu[4] and Ning An[4]*

[1]Department of Medical Oncology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China, [2]Department of Pathology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China, [3]Department of Thoracic Surgery, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China, [4]Department of Radiation Oncology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

Introduction: The efficacy of postoperative radiotherapy (PORT) is still unclear in non-small cell lung cancer (NSCLC) patients with pIIIA-N2 disease. Estrogen receptor (ER) was proven significantly associated with poor clinical outcome of male lung squamous cell cancer (LUSC) after R0 resection in our previous study.

Methods: A total of 124 male pIIIA-N2 LUSC patients who completed four cycles of adjuvant chemotherapy and PORT after complete resection were eligible for enrollment in this study from October 2016 to December 2021. ER expression was evaluated using immunohistochemistry assay.

Results: The median follow-up was 29.7 months. Among 124 patients, 46 (37.1%) were ER positive (stained tumor cells≥1%), and the rest 78 (62.9%) were ER negative. Eleven clinical factors considered in this study were well balanced between ER+ and ER- groups. ER expression significantly predicted a poor prognosis in disease-free survival (DFS, HR=2.507; 95% CI: 1.629-3.857; log-rank p=1.60×10^{-5}). The 3-year DFS rates were 37.8% with ER- *vs.* 5.7% with ER+, with median DFS 25.9 *vs.* 12.6 months, respectively. The significant prognostic advantage in ER- patients was also observed in overall survival (OS), local recurrence free survival (LRFS), and distant metastasis free survival (DMFS). The 3-year OS rates were 59.7% with ER- *vs.* 48.2% with ER+ (HR, 1.859; 95% CI: 1.132-3.053; log-rank p=0.013), the 3-year LRFS rates were 44.1% *vs.* 15.3% (HR=2.616; 95% CI: 1.685-4.061; log-rank p=8.80×10^{-6}), and the 3-year DMFS rates were 45.3% *vs.* 31.8% (HR=1.628; 95% CI: 1.019-2.601; log-rank p=0.039). Cox regression analyses indicated that ER status was the only significant factor for DFS (p=2.940×10^{-5}), OS (p=0.014), LRFS (p=1.825×10^{-5}) and DMFS (p=0.041) among other 11 clinical factors.

Conclusions: PORT might be more beneficial for ER negative LUSCs in male, and the examination of ER status might be helpful in identifying patients suitable for PORT.

KEYWORDS

postoperative radiotherapy, lung squamous cell cancer, stage IIIA-N2, survival, estrogen

Introduction

Radical surgery and dissection of mediastinal lymph node is the standard therapy for non-small cell lung cancer (NSCLC) patients with resectable lymph node(s) if the operation is endurable. Multiple randomized clinical trials (RCTs) confirmed a definitive survival benefit brought by adjuvant chemotherapy in selected patients (1–3). Nevertheless, disease-free survival (DFS) is still suboptimal, with considerable local failures leading to high risk in disease recurrence and worse overall survival (OS), especially in stage III N2 patients, even after adjuvant chemotherapy (4).

However, the evidences for postoperative radiation therapy (PORT) of R0 resected NSCLC are quite controversial. PORT has been found to be detrimental for pathologic N0/1 disease based on OS in meta-analyses (majorly population-based analysis of data from SEER database of small RCTs) (5, 6). Some meta-analyses showed a prognostic advantage of PORT in patients with pathologic N2 disease (6–8). However, the evidences from these meta-analyses were highly flawed. Most of these enrolled researches were from 1960s, when no definite staging system had ever been established. Moreover, the majority of patients received outdated radiotherapy technologies, for instance, 2-dimension conventional radiotherapy and Cobalt-60 equipment, leading to enormous unevenness in dose distribution and great heterogeneity in dose prescriptions, target volumes, and fractionations. Additionally, clinical information, including margin status, performance status, use of adjuvant chemotherapy and subsequent clinical implementations, was not available in these public databases, which was certainly not discussed in these meta-analyses. Besides, these analyses only took OS into consideration to evaluate the survival benefit brought by PORT, giving us no information about the DFS, local recurrence free survival (LRFS), and distant metastasis free survival (DMFS), which are also important to evaluate the therapeutic advantage of PORT after R0 resection.

Despite of some approval from meta-analyses, the therapeutic benefit of PORT in pIIIA-N2 patients was still unclear based on RCTs, especially in patients after R0 radical surgery and adjuvant chemotherapy. The ANITA retrospective RCT found that PORT increased OS in patients with pathologic N2 disease after adjuvant chemotherapy (9), whereas both LungART (10) and PORT-C (11) studies, the so-far only two completed prospective RCTs, failed in validating this survival advantage of PORT in stage IIIA-N2 patients. Therefore, the grim prospect of PORT in this subgroup of patients implies that a molecular predictor is urgently needed to identify the particular section of patients who can actually benefit from PORT.

Estrogen has been extensively reported to have an important function in NSCLC (12, 13). Some studies attempted to establish the correlation between estrogen receptor (ER) expression and NSCLC using immunohistochemistry (IHC) stain. Nevertheless, the reported results are contradictory and hard to interpret (14–17). Notably, the majority of these studies were only focusing upon female patients (18–20), probably caused by the stereotypical thinking that only women are subjected to the biofunction of estrogen. Moreover, the majority of ER-related studies in NSCLC were focusing on adenocarcinoma, while lung squamous cell cancer (LUSC) was seldom paid attention to let alone male LUSC patients. The treatment modality for lung adenocarcinoma has been ushered into a new era during the past decades. The tyrosine kinase inhibitors (TKIs) of EGFR and ALK have been proven remarkably beneficial in bringing a better clinical outcome in patients with lung adenocarcinoma in both adjuvant or salvage settings (21, 22), whose impact upon the observation of PORT efficacy was not considered by these RCTs. Thus, it is greatly necessary to analyze the efficacy of PORT in lung adenocarcinoma and LUSC separately, in order to eliminate the bias caused by targeted therapy.

LUSC patients are mainly male, and ER expression was reported as a significant unfavorable predictor of the clinical outcome in male LUSCs after radical resection in our previous study (23). In this study, we specifically focused on male stage IIIA-N2 LUSC who received sequential adjuvant chemotherapy and PORT, in attempt to establish the correlation between ER status and the prognosis of these patients. Despite the fact that the therapeutic effects of these inhibitors have been seldom discussed in LUSC patients (24), the EGFR mutation rate was reported around 5% in LUSCs, indicating these LUSCs might benefit from EGFR TKIs (25, 26). Therefore, in order to avoid the masking effect upon PORT by targeted therapy, molecular testing of EGFR mutation and ALK fusions was conducted in all the enrolled patients to exclude those with sensitive mutations of EGFR or ALK.

Materials and methods

Ethical approval

This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Ethical standards of national and institutional research committee were strictly followed in all the procedures involving human participants. Written informed consent was provided by all the enrolled participants.

Patient enrollment

Enrollment criteria in this study were as follows: male LUSC patients with the age 18 to 70 years old, weight loss < 10% before surgery, and Eastern Cooperative Oncology Group performance (ECOG) score < 2. Patients were excluded if they had any kind of neo-adjuvant treatments, a history of other cancer(s), EGFR sensitive mutation (including 19 exon deletion and 21 exon L858R mutation), ALK fusions, pneumonectomy, moderate/severe interstitial pulmonary disease, or uncontrolled infections. All the patients underwent thorough staging evaluations at most 60 days before surgery, including enhanced CT scan of the chest and abdomen; enhanced MRI of the brain; ultrasound test of supraclavicular lymph nodes and bone scan. Enrolled patients must be confirmed as pathologic stage IIIA-N2 (pT1-3N2) LUSC based on the seventh edition of American Joint Committee on Cancer staging system after R0 radical resection. Only those who

completed the whole process of platinum-based adjuvant chemotherapy and PORT were enrolled.

Surgery

After the diagnosis of LUSC through biopsy, patients were evaluated by a multiple disciplinary team (MDT), including at least a radiologist, a thoracic surgeon, a pathologist, a radiation oncologist, and a medical oncologist, to achieve consensus as follows: (a) technically resectable tumor. (b) N2 disease to the extent that adjuvant sequential chemoradiotherapy should be applied according to the knowledge at that time. All of the enrolled patients received lobectomy/bilobectomy of R0 resection, and complete dissection and exploration of the mediastinal lymph nodes, at least including the levels 4 (if accessible), 5, 6, 7, and 10 for left LUSC, and levels 4, 7, and 10 for right LUSC. All the resected lymph nodes were separately labeled with their corresponding locations for pathological examination. R0 resection was all confirmed by thoracic surgeons and two independent experienced pathologists.

Sequential adjuvant chemoradiotherapy

Four cycles of platinum-based doublet regimen were administrated in adjuvant chemotherapy, i.e., GP [gemcitabine (1,000 mg/m2 intravenously on days 1 and 8) and cisplatin (40 mg/m2 intravenously on days 1-2) for every 21 days] or TP [paclitaxel (135 mg/m2 intravenously on days 1) and cisplatin (40 mg/m2 intravenously on days 1-2) for every 21 days]. Only intensity-modulated radiotherapy (IMRT) was adopted as the technique for PORT, with the clinical target volume (CTV) including the stump of the central lesions, the ipsilateral hilum, subcarinal region, and the region of bilateral mediastinum. The planning target volume (PTV) was formed by extending 0.5-0.8 cm margins from CTV (adjusted based on the irradiation and the condition of the residual lung). The total dose of radiation was up to 50 Gy at 2 Gy per fraction, 5 days per week, with 6 MV X-rays. Dose constraints for normal tissues were required as follows: the maximum dose should be ≤45 Gy for spinal cord; the mean dose should be ≤12Gy for lung, and ≤ 5% of the residual normal lung received 20Gy (V20 <25%); and the mean dose should be ≤30Gy for heart, with V30 < 40% and V40 <30%. PORT should proceed within six weeks from the fourth cycle of chemotherapy. The total interruption of PORT for any reason should be no more than 10 days.

IHC assay to identify ER expression

The primary tumors embedded with formalin-fixed paraffin were collected. Slides of the tumors were stained with anti-ERα antibody (Zhongshan Bio-chemistry, China), and then incubated with anti-mouse secondary antibody (Zhongshan Bio-chemistry, China). The positivity of staining was evaluated based on PV-6000 detecting system, and each slide was then counterstained with hematoxylin. The microscope system of Olympus BX37 was adopted to obtain digital images. Each slide was examined by two blinded, experienced, and independent pathologists. The tumor was regarded as ER positive if IHC showed more than 1% of the cells were stained.

Statistical analysis

DFS was defined as the duration from the date of operation to the date of any disease recurrence, death due to any cause or the last follow-up. OS was defined as the time span from the date of surgery to the date of death due to any cause or the last follow-up. LRFS was defined as the duration from the date of surgery to the date of loco-regional disease recurrence, death due to any cause or the last follow-up. DMFS was defined as the duration from the date of surgery to the date of distant metastasis of this disease, death due to any cause or the last follow-up. Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) was adopted to grade the radiation toxicity related to PORT. R programming system (Version 4.0.3) was used in all the data analyses of this study. Log-rank test and Kaplan–Meier analysis were conducted to demonstrate the survival difference (significant if $p<0.05$). As for Cox analysis, variables of interest were first tested in univariate analysis, and those indicated as significant (if $p<0.05$) were further included in multivariate analysis to test their independence (significant if $p<0.05$). If only one variable was significant in univariate cox analysis, no further multivariate analysis was needed.

Results

Patient characteristics

In this study, 124 male LUSC patients who received complete resection in Department of Thoracic Surgery in the Affiliated Hospital of Qingdao University from October 2016 to December 2021 were enrolled based on aforementioned criteria. Clinical target volume (CTV) and planning target volume (PTV) were shown in Figure 1. The median follow-up time was 29.7 months, with the range from 3.4 to 65.3 months. Among these patients, 46 (37.1%) were ER positive, and the other 78 (62.9%) were ER negative according to IHC assay (Table 1 and Figure 2). Eleven clinical factors were considered in baseline characteristic analysis, including age (<60 *vs.* ≥60 years old), ECOG score (0 *vs.* 1), grade (G1-2 *vs.* G3), pathological tumor size (pT, T1-2 *vs.* T3), visceral pleura invasion (positive *vs.* negative), vascular invasion (positive *vs.* negative), location (left *vs.* right), chemotherapy regimen (GP *vs.* TP), detected lymph nodes (DLNs, <20 *vs.* ≥20), positive N2 lymph nodes (PLNs, <3 *vs.* ≥3), and stations of N2 lymph nodes (<2 *vs.* ≥2). Table 1 showed that all the clinico-pathological factors were well balanced between ER+ and ER- groups.

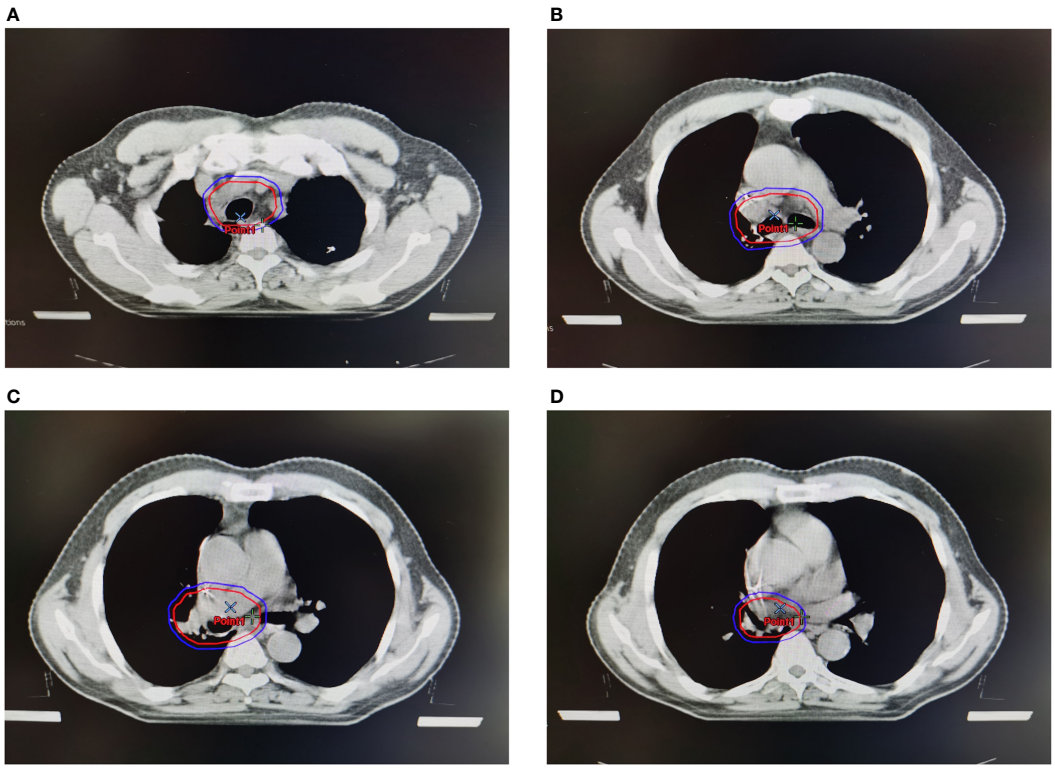

FIGURE 1
Clinical target volume (CTV) and planning target volume (PTV) of PORT. Red lines represented CTV, and blue lines represented PTV. **(A)**. CTV and PTV at the level of sternoclavicular joint. **(B)** CTV and PTV at the level of trachea carina. **(C)** CTV and PTV at the stump of the bronchia. **(D)** CTV and PTV at the level of ipsilateral hilum.

PORT toxicities

Acute toxicities related to PORT was defined as the adverse events happening within the duration between the beginning of PORT and the 3 months after PORT (Table 2). Twenty-two patients (17.7%) suffered from grade 1 (n=16) or grade 2 (n=6) acute pneumonitis. Additionally, 58 patients (46.8%) experienced grade 1 (n=48) or grade 2 acute esophagitis (n=10). No patients with grade 3 or higher acute pneumonitis or/and esophagitis were observed. There were 3 patients with grade 3 neutropenia and 5 patients with grade 3 thrombocytopenia. No patient with grade 4 or higher acute toxicities was observed (Table 2). There was no difference between two arms in respect to acute toxicities. As for late toxicity, only 4 patients (3.2%, 1 patient with ER+ and 3 with ER-) experienced pulmonary fibrosis. No treatment-related deaths have been observed for all the enrolled patients.

ER expression predicted a poor prognosis

In this study, 86 DFS events (44 in ER- arm and 42 in ER+ arm) were observed at the time of the last follow-up of this study. The median DFS for ER- patients was 23.8 [95% confidence interval (CI), 14.6-NA] months, while the median DFS for ER+ arm was only 11.2 (95% CI, 10.2-13.9) months. The 3-year DFS for ER- and ER+ patients was 37.8% and 5.7%, respectively, showing a significant difference [hazard ratio (HR) = 2.507; 95% confidence interval (CI): 1.629-3.857; log-rank p=1.60×10^{-5}; Figure 3A and Table 3].

Sixty-three deaths (31 in ER- arm and 32 in ER+ arm) were observed at the time of last follow-up. The median OS was 48.1 (95% CI: 34.1-NA) months for ER- patients, and 35.5 (95% CI, 28.9-45.1) months for ER+ patients. The 3-year OS rates were 59.7% and 48.2% for each arm, respectively, indicating a significant OS difference between patients with different ER status (HR, 1.859; 95% CI: 1.132-3.053; log-rank p=0.013; Figure 3B and Table 3).

Eighty-one patients (40 in ER- arm and 41 in ER+ arm) suffered from loco-regional recurrence. The median LRFS was 25.9 (95% CI: 21.5-NA) months in ER- patients, and the median LRFS was 12.6 (95% CI: 10.6-15.8) months for ER+ patients. The 3-year LRFS rates were 44.1% and 15.3% for ER- and ER+ arms, respectively, indicating a significant difference (HR=2.616; 95% CI: 1.685-4.061; log-rank p=8.80×10^{-6}; Figure 3C and Table 4).

Seventy-one patients (38 in ER- arm and 33 in ER+ arm) suffered from distant metastasis. The median DMFS was 29.7 (95% CI: 23.5-NA) months in ER- patients, while the median DMFS was 20.9 (95% CI: 15.9-47.3) months in ER+ patients. The 3-year DMFS rates were 45.3% and 31.8% for ER- and ER+ arms, respectively, and a significant difference was observed between the two arms (HR=1.628; 95% CI: 1.019-2.601 log-rank p=0.039; Figure 3D and Table 4).

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TABLE 1 Patient baseline characteristics.

Characteristics	ER+	ER-	X^2	*p*
Age (years)				
<60	12	25	0.248	0.619
≥60	34	53		
ECOG				
0	24	46	0.303	0.582
1	22	32		
Grade				
G1-2	22	34	0.074	0.786
G3	24	44		
pT				
T1-2	34	60	0.026	0.872
T3	12	18		
Visceral pleura				
Positive	12	25	0.248	0.619
Negative	34	53		
Vascular invasion				
Positive	27	37	1.053	0.305
Negative	19	41		
Location				
Left	24	35	0.360	0.548
Right	22	43		
Chemotherapy				
GP	24	30	1.691	0.194
TP	22	48		
DLNs				
<20	20	26	0.878	0.349
≥20	26	52		
PLNs				
<3	25	56	3.156	0.076
≥3	21	22		
Station				
<2	27	48	0.015	0.902
≥2	19	30		

DLNs, detected lymph nodes; PLNs, positive N2 lymph nodes.

Cox regression analyses of DFS, OS, LRFS, and DMFS (Tables 3, 4) were conducted among ER status and the other 11 clinico-pathological factors in these 124 patients, respectively. The result indicated that ER status was the only significant prognostic factor for DFS (p=2.940×10^{-5}), OS (p=0.014), LRFS (p=1.825×10^{-5}), and DMFS (p=0.041).

Discussion

No concrete evidence has ever been established to support the prognostic advantage of PORT in pIIIA-N2 NSCLCs using modern radiotherapy techniques after R0 radical surgery and adjuvant chemotherapy, let alone for the subgroup of male LUSC patients. The landmark meta-analyses and RCTs were only concentrating on the clinical factors associated with the outcomes of PORT. However, the conflicting results of these studies demonstrated that only clinical factors were not sufficient to fulfill the mission, and molecular biomarkers should certainly be taken into consideration.

LUSC and lung adenocarcinoma, the two major components of NSCLC, were proven with great distinction on the basis of both pathology and treatment modality. Two milestone prospective RCTs, including ADAURA and EVIDENCE studies, demonstrated that EGFR TKIs could significantly improve clinical outcome and have a better tolerability profile in patients with EGFR-mutant NSCLCs after radical surgery (27, 28). Since almost all the EGFR-mutant NSCLCs were lung adenocarcinoma (more than 95% in ADAURA trial), EGFR TKI, instead of sequential chemoradiotherapy, was currently the standard of treatment for stage IIIA-N2 EGFR-mutant lung adenocarcinoma after complete resection. Therefore, LUSC and lung adenocarcinoma should be discussed separately in terms of adjuvant clinical implementations, and patients with driver gene mutations, including EGFR sensitive mutations or ALK fusions, were excluded from the present study in order to eliminate the systematic bias.

Although the optimal sequence of sequential adjuvant chemoradiotherapy is not established, PORT is generally administered after postoperative chemotherapy (29–31). Sequential adjuvant chemoradiotherapy in this study was strictly conducted according to PORT-C trial. Only those who completed all the four cycles of GP or TP chemotherapy and subsequent PORT of 2Gy×25 fractions were enrolled in attempt to decrease the potential bias causing by different clinical managements. Notably, only IMRT was adopted as the radiation technique to reduce the potential bias brought by other techniques, for instance, 3-dimensional conformal radiotherapy (3D-CRT) used by LungART and PORT-C studies. Modern radiation technology brings a very low toxicity, which hopefully might be translated into prognostic advantage of PORT. For instance, no grade 4 or higher adverse event related to PORT using IMRT has been observed in our study. The CTV in our radiation center includes the contralateral mediastinum but not supraclavicular region (Figure 1), of which the target volume is between PORT-C (ipsilateral mediastinum and subcarinal region) and LungART study (bilateral mediastinum and supraclavicular region). Superior 5-year OS advantage has been reported in N2 NSCLC patients who received PORT with the total dose between 45 to 54 Gy (32), while the prognostic advantage was not observed if the total dose > 54Gy because of an increased cardiac toxicity (33). Thus, all the enrolled patients received PORT with the dosage of 50Gy, in an attempt to balance between efficacy and toxicity. Both LungART and PORT-C studies failed in observing prognostic

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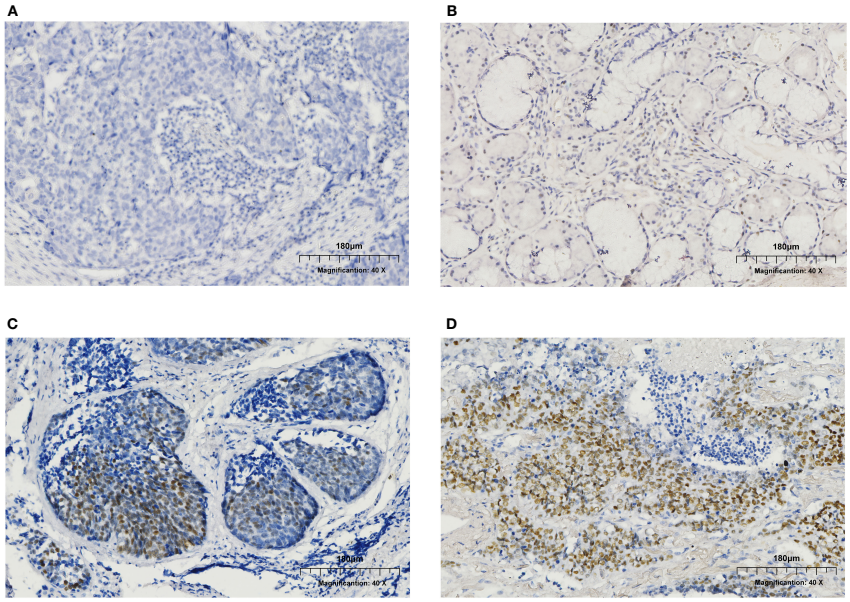

FIGURE 2
Immunohistochemistry (IHC) results of ER expression in male patients. **(A)** ER negative. **(B)** ER expression at the level of 5-10%. **(C)** ER expression at the level of 30-40%. **(D)** ER expression at the level of 70-80%.

advantage of PORT in respect to DFS and OS, while both studies demonstrated the prognostic advantage of PORT in reducing local failure. It is possible since pIII-N2 NSCLC is highly heterogeneous, and thus only a part of patients could benefit from PORT.

The relationship between ER and NSCLC's clinical outcome varies tremendously, and the most of these studies only focused on female adenocarcinoma. The remarkable controversy is probably due to many reasons, for instance, the patient population selected for research, the heterogeneous definitions of positivity, the differences in detecting methodology, and so on (14, 15, 34). Our previous finding indicated that the expression of ER predicted a poor clinical outcome in male LUSCs after receiving radical operation, which was also demonstrated by IHC assay (23). In present study, ER was significantly associated with DFS, OS, LRFS, and DMFS in male LUSCs after adjuvant sequential chemoradiotherapy. Currently, no effective biomarker has been confirmed to predict the therapeutic efficacy of PORT, and ER might be a promising biomarker to fulfill the mission. The result indicated that PORT might be more beneficial for ER negative LUSCs in male, and the examination of ER status might be helpful to identify male LUSCs suitable for PORT. As for ER positive male LUSCs with much worse prognosis, it is very intriguing that ER antagonist might be beneficial for treating these patients in adjuvant clinical setting.

The primary limitation of this study is the limited patient number (n=124), since we set a very strict enrollment criterion to

TABLE 2 Overall acute toxicities related to PORT.

Toxicity	ER positive (n=46)				ER negative (n=78)			
	Grade				Grade			
	1	2	3	4	1	2	3	4
Pneumonitis	6	2	0	0	10	4	0	0
Esophagitis	20	4	0	0	28	6	0	0
Neutropenia	6	5	1	0	10	9	2	0
Anemia	3	0	0	0	5	1	0	0
Leukopenia	5	2	0	0	9	4	0	0
Thrombocytopenia	5	3	2	0	8	5	3	0
Nausea and/or emesis	2	1	0	0	4	2	0	0
Cardiac	2	1	0	0	3	2	0	0
Fatigue	4	2	0	0	7	3	0	0

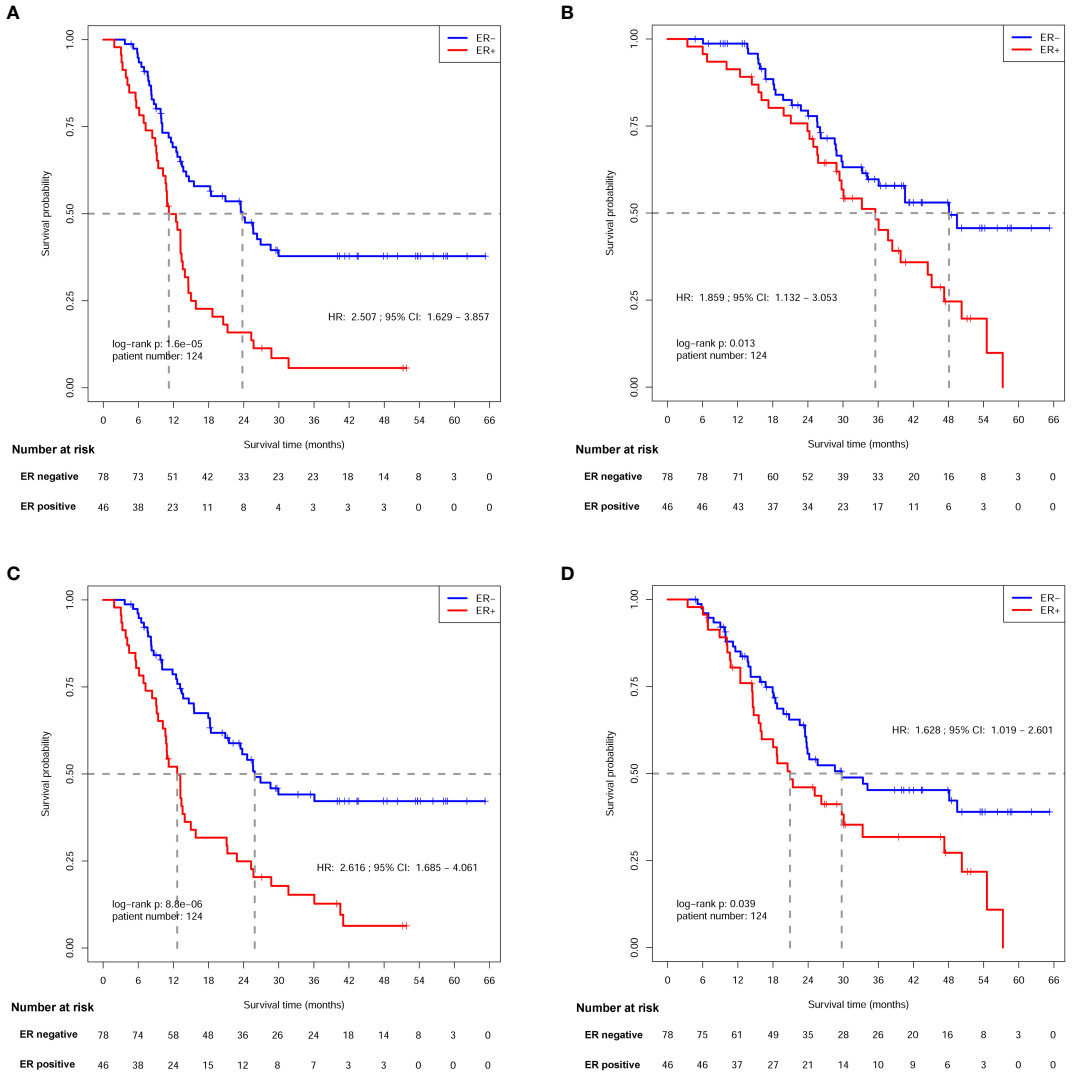

FIGURE 3
Survival analysis of patients between ER- and ER+ arms. **(A)** Disease free survival (DFS) analysis. **(B)** Overall survival (OS) analysis. **(C)** local recurrence free survival (LRFS) analysis. **(D)** Distant metastasis free survival (DMFS) analysis.

TABLE 3 Cox regression analyses of DFS and OS.

Factors	DFS		OS	
	HR (95% *CI*)	*p*	HR (95% *CI*)	*p*
Age (years)				
<60	Reference	–	Reference	–
≥60	0.937 (0.603~1.456)	0.773	0.895(0.533~1.504)	0.676
ECOG				
0	Reference	–	Reference	–
1	1.086 (0.709~1.661)	0.705	1.122(0.680~1.853)	0.651
Grade				
G1-2	Reference	–	Reference	–

(Continued)

TABLE 3 Continued

Factors	DFS		OS	
	HR (95% *CI*)	*p*	HR (95% *CI*)	*p*
G3	1.085 (0.707~1.663)	0.709	1.153 (0.695~1.911)	0.582
pT				
T1-2	Reference	–	Reference	–
T3	0.972 (0.616~1.534)	0.903	1.067 (0.622~1.831)	0.814
Visceral pleura				
Negative	Reference	–	Reference	–
Positive	0.941 (0.591~1.499)	0.797	1.127 (0.666~1.907)	0.656
Vascular invasion				
Negative	Reference	–	Reference	–
Positive	1.219 (0.796~1.865)	0.362	1.406 (0.856~2.311)	0.179
Location				
Left	Reference	–	Reference	–
Right	0.946 (0.620~1.445)	0.798	0.751 (0.454~1.242)	0.264
Chemotherapy				
GP	Reference	–	Reference	–
TP	0.845 (0.553~1.291)	0.435	1.089 (0.661~1.793)	0.739
DLNs				
<20	Reference	–	Reference	–
≥20	1.099 (0.714~1.693)	0.667	0.907 (0.548~1.501)	0.704
PLNs				
<3	Reference	–	Reference	–
≥3	1.314 (0.850~2.030)	0.219	1.111 (0.666~1.854)	0.686
Station				
<2	Reference	–	Reference	–
≥2	0.965 (0.597~1.560)	0.245	0.877 (0.492~1.563)	0.295
ER				
Negative	Reference	–	Reference	–
Positive	2.507 (1.629~3.857)	**2.940×10^{-5}**	1.859 (1.132~3.053)	**0.014**

Significant p values were in bold ($p<0.05$). HR, hazard ratio; CI, confidence interval.

TABLE 4 Cox regression analyses of LRFS and DMFS.

Factors	LRFS		DMFS	
	HR (95% *CI*)	*p*	HR (95% *CI*)	*p*
Age (years)				
<60	Reference	–	Reference	–
≥60	1.031 (0.652~1.632)	0.896	0.915 (0.561~1.494)	0.722

(Continued)

TABLE 4 Continued

Factors	LRFS		DMFS	
	HR (95% *CI*)	*p*	HR (95% *CI*)	*p*
ECOG				
0	Reference	–	Reference	–
1	1.154 (0.745~1.785)	0.521	1.157 (0.722~1.853)	0.545
Grade				
G1-2	Reference	–	Reference	–
G3	1.096 (0.705~1.705)	0.684	1.217 (0.755~1.959)	0.420
pT				
T1-2	Reference	–	Reference	–
T3	0.950 (0.592~1.523)	0.830	0.920 (0.551~1.535)	0.750
Visceral pleura				
Negative	Reference	–	Reference	–
Positive	0.935 (0.577~1.517)	0.787	0.926 (0.559~1.533)	0.764
Vascular invasion				
Negative	Reference	–	Reference	–
Positive	1.331 (0.858~2.064)	0.201	1.225 (0.767~1.956)	0.395
Location				
Left	Reference	–	Reference	–
Right	0.863 (0.558~1.335)	0.507	0.818 (0.511~1.309)	0.401
Chemotherapy				
GP	Reference	–	Reference	–
TP	0.753 (0.486~1.165)	0.203	1.474 (0.914~2.376)	0.112
DLNs				
<20	Reference	–	Reference	–
≥20	1.024 (0.657~1.597)	0.916	1.079 (0.670~1.736)	0.754
PLNs				
<3	Reference	–	Reference	–
≥3	1.304 (0.833~2.042)	0.246	1.262 (0.783~2.034)	0.339
Station				
<2	Reference	–	Reference	–
≥2	0.956 (0.584~1.565)	0.251	1.120 (0.645~1.944)	0.281
ER				
Negative	Reference	–	Reference	–
Positive	2.616 (1.685~4.061)	**1.825×10^{-5}**	1.628 (1.019~2.601)	**0.041**

Significant p values were in bold ($p<0.05$). HR, hazard ratio; CI, confidence interval.

reduce the potential bias. We only focused on male stage IIIA-N2 LUSCs with definitive molecular information of their EGFR and ALK status, and only patients strictly completed the sequential adjuvant chemoradiotherapy were enrolled, trying to validate the hypothesis inspired by our previous study (23). Additionally, this study is a single-center retrospective study. As we know, single-center studies have certain limitations in providing robustness and generalizability (35), but they might also reduce the bias brought by the inconsistency among different centers. However, external validations with more patients are certainly needed to further

demonstrate the association between ER expression and PORT. PORT might be more beneficial for ER negative LUSCs in male, and the examination of ER status might be helpful in identifying patients with stage-IIIA N2 LUSC who are suitable for PORT.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of the Affiliated Hospital of Qingdao University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Data curation: LW, XJ, RX, HML, HJL, and ZY; formal analysis: NA and LW; funding acquisition: NA and XY; investigation: NA and XY; methodology: NA, XY, and LW; project administration: NA, XY, LW, XJ, and RX; resources: LW, XJ, RX, NA, and HJL; software: NA and LW; supervision: ZY; validation: XY; visualization: LW, XJ, and RX; writing-original draft: NA and XY; writing review and editing: all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* (2005) 352:2589–97. doi: 10.1056/NEJMoa043623

2. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE collaborative group. *J Clin Oncol* (2008) 26:3552–9. doi: 10.1200/JCO.2007.13.9030

3. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* (2004) 350:351–60. doi: 10.1056/NEJMoa031644

4. Higgins KA, Chino JP, Berry M, Ready N, Boyd J, Yoo DS, et al. Local failure in resected N1 lung cancer: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* (2012) 83:727–33. doi: 10.1016/j.ijrobp.2011.07.018

5. PORT meta-analysis trialists group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT meta-analysis trialists group. *Lancet* (1998) 352:257–63. doi: 10.1016/S0140-6736(98)06341-7

6. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* (2006) 24:2998–3006. doi: 10.1200/JCO.2005.04.6110

7. Robinson CG, Patel AP, Bradley JD, DeWees T, Waqar SN, Morgensztern D, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the national cancer data base. *J Clin Oncol* (2015) 33:870–6. doi: 10.1200/JCO.2014.58.5380

8. Patel SH, Ma Y, Wernicke AG, Nori D, Chao KS, Parashar B. Evidence supporting contemporary post-operative radiation therapy (PORT) using linear accelerators in N2 lung cancer. *Lung Cancer* (2014) 84:156–60. doi: 10.1016/j.lungcan.2014.02.016

9. Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant navelbine international trialist association (ANITA) randomized trial. *Int J Radiat Oncol Biol Phys* (2008) 72:695–701. doi: 10.1016/j.ijrobp.2008.01.044

10. Le Pechoux C, Pourel N, Barlesi F, Lerouge D, Antoni D, Lamezec B, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial. *Lancet Oncol* (2022) 23:104–14. doi: 10.1016/S1470-2045(21)00606-9

11. Hui Z, Men Y, Hu C, Kang J, Sun X, Bi N, et al. Effect of postoperative radiotherapy for patients with pIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: the phase 3 PORT-c randomized clinical trial. *JAMA Oncol* (2021) 7:1178–85. doi: 10.1001/jamaoncol.2021.1910

12. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst* (1996) 88:183–92. doi: 10.1093/jnci/88.3-4.183

13. Siegfried JM. Women and lung cancer: does oestrogen play a role? *Lancet Oncol* (2001) 2:506–13. doi: 10.1016/S1470-2045(01)00457-0

14. Baik CS, Eaton KD. Estrogen signaling in lung cancer: an opportunity for novel therapy. *Cancers (Basel)* (2012) 4:969–88. doi: 10.3390/cancers4040969

15. Kawai H. Estrogen receptors as the novel therapeutic biomarker in non-small cell lung cancer. *World J Clin Oncol* (2014) 5:1020–7. doi: 10.5306/wjco.v5.i5.1020

16. Kawai H, Ishii A, Washiya K, Konno T, Kon H, Yamaya C, et al. Estrogen receptor alpha and beta are prognostic factors in non-small cell lung cancer. *Clin Cancer Res* (2005) 11:5084–9. doi: 10.1158/1078-0432.CCR-05-0200

17. Schwartz AG, Prysak GM, Murphy V, Lonardo F, Pass H, Schwartz J, et al. Nuclear estrogen receptor beta in lung cancer: expression and survival differences by sex. *Clin Cancer Res* (2005) 11:7280–7. doi: 10.1158/1078-0432.CCR-05-0498

18. Honma N, Hosoi T, Arai T, Takubo K. Estrogen and cancers of the colorectum, breast, and lung in postmenopausal women. *Pathol Int* (2015) 65:451–9. doi: 10.1111/pin.12326

19. Ganti AK, Sahmoun AE, Panwalkar AW, Tendulkar KK, Potti A. Hormone replacement therapy is associated with decreased survival in women with lung cancer. *J Clin Oncol* (2006) 24:59–63. doi: 10.1200/JCO.2005.02.9827

20. Chlebowski RT, Schwartz AG, Wakelee H, Anderson GL, Stefanick ML, Manson JE, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's health initiative trial): a *post-hoc* analysis of a randomised controlled trial. *Lancet* (2009) 374:1243–51. doi: 10.1016/S0140-6736(09)61526-9

21. Pasche B, Grant SC. Non-small cell lung cancer and precision medicine: a model for the incorporation of genomic features into clinical trial design. *JAMA* (2014) 311:1975–6. doi: 10.1001/jama.2014.3742

22. Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Shen Y, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. *Lancet Oncol* (2018) 19:139–48. doi: 10.1016/S1470-2045(17)30729-5

23. Yang X, Jin X, Xu R, Yu Z, An N. ER expression associates with poor prognosis in male lung squamous carcinoma after radical resection. *BMC Cancer* (2021) 21:1043. doi: 10.1186/s12885-021-08777-6

24. Perez-Moreno P, Brambilla E, Thomas R, Soria JC. Squamous cell carcinoma of the lung: molecular subtypes and therapeutic opportunities. *Clin Cancer Res* (2012) 18:2443–51. doi: 10.1158/1078-0432.CCR-11-2370

25. Cheung AH, Tong JH, Chung LY, Chau SL, Ng CS, Wan IYP, et al. EGFR mutation exists in squamous cell lung carcinoma. *Pathology* (2020) 52:323–8. doi: 10.1016/j.pathol.2019.12.003

26. Taniguchi Y, Matsumoto Y, Furukawa R, Ohara S, Usui K. The clinical features of squamous cell lung carcinoma with sensitive EGFR mutations. *Int J Clin Oncol* (2018) 23:452–7. doi: 10.1007/s10147-017-1233-8

27. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non-Small-Cell lung cancer. *N Engl J Med* (2020) 383:1711–23. doi: 10.1056/NEJMoa2027071

28. He J, Su C, Liang W, Xu S, Wu L, Fu X, et al. Icotinib versus chemotherapy as adjuvant treatment for stage II-IIIA EGFR-mutant non-small-cell lung cancer (EVIDENCE): a randomised, open-label, phase 3 trial. *Lancet Respir Med* (2021) 9:1021–9. doi: 10.1016/S2213-2600(21)00134-X

29. Burdett S, Stewart LPORT Meta-analysis Group. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. *Lung Cancer* (2005) 47:81–3. doi: 10.1016/j.lungcan.2004.09.010

30. Keller SM, Adak S, Wagner H, Herskovic A, Komaki R, Brooks BJ, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern cooperative oncology group. *N Engl J Med* (2000) 343:1217–22. doi: 10.1056/NEJM200010263431703

31. Bradley JD, Paulus R, Graham MV, Ettinger DS, Johnstone DW, Pilepich MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the radiation therapy oncology group–RTOG 9705. *J Clin Oncol* (2005) 23:3480–7. doi: 10.1200/JCO.2005.12.120

32. Corso CD, Rutter CE, Wilson LD, Kim AW, Decker RH, Husain ZA. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the national cancer database. *J Thorac Oncol* (2015) 10:148–55. doi: 10.1097/JTO.0000000000000406

33. Karakoyun-Celik O, Yalman D, Bolukbasi Y, Cakan A, Cok G, Ozkok S. Postoperative radiotherapy in the management of resected non-small-cell lung carcinoma: 10 years' experience in a single institute. *Int J Radiat Oncol Biol Phys* (2010) 76:433–9. doi: 10.1016/j.ijrobp.2009.02.010

34. Siegfried JM, Stabile LP. Estrongenic steroid hormones in lung cancer. *Semin Oncol* (2014) 41:5–16. doi: 10.1053/j.seminoncol.2013.12.009

35. Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single-center trials. *Crit Care Med* (2009) 37:3114–9. doi: 10.1097/CCM.0b013e3181bc7bd5

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EDITED BY
Aakash Desai,
Mayo Clinic, United States

REVIEWED BY
Antonin Levy,
Gustave Roussy Cancer Campus, France
Francesco Cortiula,
Maastricht University Medical Centre, Netherlands
Valerio Nardone,
University of Campania Luigi Vanvitelli, Italy

*CORRESPONDENCE
Eneida Mataj
e.mataj@unibs.it

†PRESENT ADDRESSES
Giulia Volpi,
Radiation Oncology Department, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
Jessica Imbrescia,
Radiotherapy Unit, Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy

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Unresectable stage III non-small cell lung cancer: could durvalumab be safe and effective in real-life clinical scenarios? Results of a single-center experience

Paolo Borghetti[1], Giulia Volpi[1†], Giorgio Facheris[1], Gianluca Cossali[1], Eneida Mataj[1*], Salvatore La Mattina[1], Navdeep Singh[1], Jessica Imbrescia[1†], Marco Lorenzo Bonù[1], Davide Tomasini[1], Paola Vitali[1], Diana Greco[1], Michela Bezzi[2], Flavia Melotti[3], Mauro Benvenuti[4], Andrea Borghesi[5], Salvatore Grisanti[6] and Michela Buglione di Monale e Bastia[1] for ASST Spedali Civili of Brescia Lung Unit

[1]Radiation Oncology Department, Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili and University of Brescia, Brescia, Italy, [2]Division of Pneumology, University Hospital Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili, Brescia, Italy, [3]Institute of Pathology, Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili, Brescia, Italy, [4]Thoracic Surgery, Department of Cardio-Thoracic Surgery, Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili, Brescia, Italy, [5]Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili and University of Brescia, Brescia, Italy, [6]Medical Oncology Department, Azienda Socio Sanitaria Territoriale (ASST) Spedali Civili and University of Brescia, Brescia, Italy

Introduction: The standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC) is chemoradiotherapy (CRT) followed by consolidation durvalumab as shown in the PACIFIC trial. The purpose of this study is to evaluate clinical outcomes and toxicities regarding the use of durvalumab in a real clinical scenario.

Methods: A single-center retrospective study was conducted on patients with a diagnosis of unresectable stage III NSCLC who underwent radical CRT followed or not by durvalumab. Tumor response after CRT, pattern of relapse, overall survival (OS) and progression-free survival (PFS), and toxicity profile were investigated.

Results: Eighty-five patients met the inclusion criteria. The median age was 67 years (range 45–82 years). Fifty-two patients (61.2%) started sequential therapy with durvalumab. The main reason for excluding patients from the durvalumab treatment was the expression of PD-L1 < 1%. Only two patients presented a grade 4 or 5 pneumonitis. A median follow-up (FU) of 20 months has been reached. Forty-five patients (52.9%) had disease progression, and 21 (24.7%) had a distant progression. The addition of maintenance immunotherapy confirmed a clinical benefit in terms of OS and PFS. Two-year OS and PFS were respectively 69.4%

and 54.4% in the durvalumab group and 47.9% and 24.2% in the no-durvalumab group (p = 0.015, p = 0.007).

Conclusion: In this real-world study, patients treated with CRT plus durvalumab showed clinical outcomes and toxicities similar to the PACIFIC results. Maintenance immunotherapy after CRT has been shown to be safe and has increased the survival of patients in clinical practice.

KEYWORDS

non-small cell lung cancer (NSCLC), stage III, durvalumab, chemo-radiotherapy (CRT), real-world data (RWD)

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all types of lung cancer (1). Approximately one-third of patients have locally advanced (LA) disease at diagnosis and are not eligible for surgical resection (2, 3). Concurrent chemoradiotherapy (cCRT) has been the standard of care (SoC) for patients with unresectable stage III NSCLC over the years (3), but the introduction of durvalumab (Imfinzi©, AstraZeneca Inc.) as consolidation immunotherapy after definitive cCRT have drastically improved overall survival (OS) and progression-free survival (PFS), as reported by the results of the PACIFIC trial (4). The PACIFIC regimen is now adopted in clinical practice, and it is considered the SoC for patients with unresectable stage III NSCLC suitable for chemoradiotherapy with radical intent (4–6).

Based on data from the PACIFIC study, regardless of levels of PD-L1 expression, on 16 February 2018, the Food and Drug Administration approved durvalumab as consolidation therapy following effective cCRT for patients with unresectable stage III NSCLC (7). The European Medical Agency (EMA) and the Italian Agency for Drugs (Agenzia Italiana del Farmaco (AIFA)) approved durvalumab after cCRT and sequential chemoradiotherapy (sCRT) in the same group of patients but exclusively in the case of PD-L1 expression of at least 1% (8).

The safety profile and results of pivotal randomized clinical trials (RCTs) often diverge from those achieved in real-world practice because they are designed for highly selected patient populations due to strict eligibility criteria and always do not represent the range of patients seen in real-world practice (9).

This is a single-center retrospective series of patients with unresectable stage III NSCLC treated with cCRT or sCRT followed or not by durvalumab while the PACIFIC regimen arose as SoC in Italy (October 2018). The objectives of this real-life analysis are twofold: the first one is to explore and describe the reasons for accessing or rejecting durvalumab as maintenance in daily practice. The second one is to analyze the clinical features, tumor response to cCRT, the pattern of relapse, toxicity profiles, and the survival outcomes of patients treated with CRT in comparison with the PACIFIC study.

Material and methods

This is a single-center, retrospective, and observational study including all patients with unresectable stage III NSCLC treated with cCRT or sCRT followed or not by durvalumab at Radiation Oncology Department of Spedali Civili and the University of Brescia between October 2018 and July 2022.

The inclusion criteria were histological diagnosis of NSCLC, stage III disease according to TNM American Joint Committee on Cancer (AJCC) 8th edition (10) and unresectable disease as defined after multidisciplinary discussion in the lung unit with thoracic surgeons, radiologists, medical oncologists, and pneumologists.

Eligible patients received curative CRT. The prescribed dose was 60 Gy in 30 fractions (2 Gy/fr) delivered with intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), or helical IMRT (H-IMRT). Patients underwent free-breathing four-dimensional computed tomography (CT) simulation for treatment planning on which the gross tumor volume (GTV) was contoured as reported by ESTRO ACROP guidelines (11). All patients had a diagnostic positron emission tomography scan (PET-CT) later co-registered with the simulation CT to guide target volume delineation. An internal target volume (ITV) was created by the deformation of the clinical target volume (CTV) contour from one breathing phase to the others using the treatment planning system (TPS) Velocity©. All patients received daily image-guided radiotherapy (IGRT) with cone-beam CT (CBCT) or megavoltage CT (MVCT).

All patients were treated with platinum-based doublet chemotherapy with cCRT (at least two cycles during radiotherapy and no more than one cycle before radiotherapy) or sCRT (radiotherapy started after at least three cycles of chemotherapy).

Maintenance immunotherapy (durvalumab) after cCRT or sCRT was prescribed for patients with PD-L1 expression ≥1%, free from disease progression after completion of CRT, without clinical history of primary/secondary immunodeficiency, active infection, and pulmonary toxicity after CRT higher or equal to grade 3 (G3; according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0) (12).

During follow-up, total body CT scans were commonly performed: every 3 months in the first 2 years and every 6 months in the following years, or more frequently when clinically indicated.

Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Locoregional progression included all sites of relapse within the involved pulmonary lobe(s) and the hilar and mediastinal nodal stations. Distant metastasis included the other sites of progression, as well as pulmonary lesions absent at the onset. OS was defined as the time between the end of radiotherapy and death or last assessment of vital status, while PFS was defined as the time from the end of radiotherapy to disease progression (any site) or death or last follow-up. Follow-up was defined as the time from the end of radiotherapy to the last assessment of clinical status.

All reported adverse events (AEs) were recorded according to CTCAE version 5.0 (11). All lung toxicities have been reported. In particular, pneumonia was recorded if the pulmonary infection was confirmed by blood, sputum, or bronchoalveolar lavage culture. The other non-infectious lung toxicities, such as acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis, were all included in the group of pneumonitis/radiation pneumonitis. The latter grouping was necessary due to the unfeasibility to distinguish the etiology of this pneumonitis in patients treated with either CRT or durvalumab.

Statistical analysis of the collected data provided a description of the numerical frequency and the percentage of the variables. The chi-square test and t-test were applied for correlations between categorical and continuous variables, respectively. Survival curves were calculated using the Kaplan–Meier method. Survival estimates were calculated at 1 and 2 years. Log-rank test was used for comparison between groups. All statistical analyses were conducted using Software IBM-SPSS® ver. 26.0.1 (IBM SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

The Ethics Committee reviewed and approved the study protocol (Protocol No. 4762, approved on 16 June 2021).

Results

Eighty-five patients were retrospectively included in this analysis.

Patient, pathological, and treatment features

The median age was 67 years (range 45–82 years), and 60 patients were male (70.6%). All patients had Eastern Cooperative Oncology Group—Performance Status (ECOG PS) of 0 or 1, and Charlson Comorbidity Index ranged between 3 and 9. Only six patients had never smoked; the median pack-year resulted in 45. Forty-five patients (52.9%) reported chronic obstructive pulmonary disease (COPD) as respiratory comorbidity (grade 3 for eight patients).

Adenocarcinoma and squamous cell carcinoma were the histological types in 55.3% and 37.6% of cases, respectively. A PD-L1 expression was observed in 67 cases (78.8%), and mutation status was known in 45 patients. Within this group, 10 patients presented an oncogenic driver mutation; EGFR was mutated in 2.3% of patients.

All of the patients received PET-CT, only three patients had brain MRI, and 55 patients (64.7%) underwent endobronchial ultrasound (EBUS) as mediastinal staging.

Thirty-six (41.4%), 42 (49.4%), and seven patients (8.2%) were staged as IIIA, IIIB, and IIIC, respectively. The median volume of planning target volume (PTV) was 439 cc, ranging between 169 and 1171 cc. Most of the patients were treated with the VMAT technique.

All patients received 60 Gy, and the median overall treatment time was 42 days.

Forty-four patients (51.8%) received chemotherapy with a 3-weekly schedule, and the most-used drug combination was carboplatin and paclitaxel doublet. Seventy-four patients (87.1%) had a cCRT, and 11 patients received sCRT. No statistical differences in terms of clinical, pathological, and treatments were detectable between the groups of patients treated with or without durvalumab, except for PD-L1 expression (Table 1).

CRT response and sequential immunotherapy

A total body CT scan was performed for all patients to evaluate tumor response after CRT. A complete response (CR) was achieved in 2 cases, while partial response (PR) and stable disease (SD) were reported in 41 and 31 cases, respectively. Eight patients showed progression of disease (PD) at the CT scan. Three patients were not evaluated for the decline of clinical conditions (Table S1 in the Supplementary Material).

Fifty-two patients (61.2%) started maintenance immunotherapy with durvalumab. Two patients received durvalumab within the expanded access program (EAP). The main reasons for exclusion from durvalumab treatment were the negative expression of PD-L1 in 13 patients (15.3%) and disease progression in eight patients (9.4%). Only two patients did not receive durvalumab because of G3 pulmonary toxicity after CRT (Table 2).

The median time elapsed between the end of CRT and the start of durvalumab amounted to 47 days (ranging between 2 and 105 days). Seven patients underwent a new biopsy after CRT, and only in two cases did this lead to a positive expression of PD-L1.

Ten patients (19.2%) and 22 patients (42.3%) had respectively a temporary and definitive interruption in the group treated with durvalumab. Of the latter, the interruption was related to PD in 15 patients and severe toxicity in six patients, and one patient died of COVID-19. The median time of treatment with durvalumab was 46

TABLE 1 Patient, histological and treatment features.

		All		CRT		CRT+durvalumab		p-Value
		Median	Min–max	Median	Min–max	Median	Min–max	
Age (years)		68	45–82	68	45–81	69	50–82	-
Charlson Comorbidity Index		5	3–9	5	3–9	6	3–9	–
Pack years		45	0–150	45	0–120	50	0–150	-
PTV (cc)		439	168.9–1,170.7	481	168.9–1,170.7	432	174–1,150	–
		N	%	N	%	N	%	
Sex	Male	60	70.6	21	63.6	39	75.0	0.262
	Female	25	29.4	12	36.4	13	25.0	
Age (years)	<65 years	32	37.6	12	36.4	20	38.5	0.789
	65–75 years	38	44.7	14	42.4	24	46.2	
	>75 years	15	17.6	7	21.2	8	15.4	
ECOG	0	47	55.3	20	60.6	27	51.9	0.432
	1	38	44.7	13	39.4	25	48.1	
Educational status	Primary school	28	32.9	10	30.3	18	34.6	0.946
	Secondary school	32	37.6	13	39.4	19	36.5	
	High school	21	24.7	8	24.2	13	25.0	
	Graduation	4	4.7	2	6.1	2	3.8	
Smoking status	Current	43	50.6	21	63.6	22	42.3	0.154
	Former	36	42.4	10	30.3	26	50.0	
	Never	6	7.1	2	6.1	4	7.7	
COPD	No	40	47.1	18	54.5	22	42.3	0.390
	Grade 1	19	22.4	7	21.2	12	23.1	
	Grade 2	18	21.2	7	21.2	11	21.2	
	Grade 3	8	9.4	1	3.0	7	13.5	
Histology	Adenocarcinoma	47	55.3	18	54.5	29	55.8	0.328
	Squamous cell carcinoma	32	37.6	11	33.3	21	40.4	
	Other	6	7.1	4	12.1	2	3.8	
Mutations detected	Mutational status known	48	56.5	21	24.7	27	31.8	0.238
	EGFR	2	2.3	0	0.0	2	2.4	
	KRAS	7	8.2	3	3.5	4	4.7	
	ALK	0	0	0	0.0	0	0.0	
	ROS1	2	2.3	0	0.0	2	2.4	
	MET	1	1.2	0	0.0	1	1.2	
PD-L1 expression	Not evaluated or 0	18	21.2	17	51.5	1	1.9	<0.00001
	1%–50%	35	41.2	5	15.2	30	57.7	
	>50%	32	37.6	11	33.3	21	40.4	
Stage (sec. WHO VIII ed.)	IIIA	36	41.4	12	36.4	24	46.2	0.672
	IIIB	42	49.4	18	54.5	24	46.2	
	IIIC	7	8.2	3	9.1	4	7.7	

(Continued)

TABLE 1 Continued

		All		CRT		CRT+durvalumab		p-Value
		Median	Min–max	Median	Min–max	Median	Min–max	
Treatment	Concurrent	74	87.1	27	81.8	47	90.4	0.664
	Sequential	11	12.9	6	18.2	5	9.6	
Chemo schedule	Weekly	41	48.2	14	42.4	27	51.9	0.393
	3-weekly	44	51.8	19	57.6	25	48.1	
Chemo type	Carboplatin–paclitaxel	70	82.3	26	78.8	44	84.6	0.686
	Cisplatin–etoposide	3	3.5	1	3.0	2	3.8	
	Other	12	14.2	6	18.2	6	11.5	
RT technique	VMAT	80	94.1	33	100.0	47	90.4	0.079
	TOMO	5	5.9	0	0.0	5	9.6	

CRT, chemoradiotherapy; PTV, planning target volume; ECOG, Eastern Cooperative Oncology Group; COPD, chronic obstructive pulmonary disease; RT, radiation therapy; VMAT, volumetric modulated arc therapy; TOMO, tomotherapy.

TABLE 2 Reasons for exclusion from durvalumab.

	N	(%)
PD-L1 < 1%	13	15.3
Progression disease	8	9.4
Death	3	3.5
CRT pulmonary toxicity	2	2.4
History of autoimmune pathology	1	1.2
Other	6	7.1
All	33	38.8

CRT, chemoradiotherapy.

weeks (ranging between 5 and 74 weeks).

Pattern of recurrence and survivals

After a median follow-up of 20 months, 45 patients (52.9%) showed PD. Within this group, the pattern of recurrence was distant metastasis in 21 cases (46.6%), locoregional failure in seven cases (15.6%), and both distant and locoregional in 17 cases (37.8%). Twelve patients (14.1%) had bone metastasis, 11 patients (12.9%) presented brain metastasis, and seven patients (8.2%) had a local recurrence in the ipsilateral lung.

Locoregional recurrences, distant metastasis, and total progression events resulted higher in the group that did not receive durvalumab, but these differences were not statistically significant ($p = 0.797$, $p = 0.506$, and $p = 0.509$, respectively). The cumulative death rate at the end of follow-up was 36.5% for patients who received durvalumab (median follow-up 21 months) and 51.5% for patients not treated with immunotherapy (median follow-up 11 months), $p = 0.031$.

The addition of immunotherapy maintenance confirmed a clinical benefit in terms of either OS or PFS. Median OS, 1-year OS, and 2-year OS in the group treated with durvalumab were 52 months, 82.5%, and 69.4%, respectively; in the group without durvalumab, they were 21 months, 56.2%, and 47.9%, respectively ($p = 0.015$). Median PFS, 1-year PFS, and 2-year PFS in the durvalumab group were 26 months, 66.8%, and 54.4%, respectively; in the other group, they were 7 months, 42.4%, and 24.2%, respectively ($p = 0.007$) (Figures 1, 2).

In the group without durvalumab, excluding patients who progressed or died after CRT, the median OS and PFS were 39 and 16 months, respectively. One- and 2-year OS rates were 62.8% and 62.8%, respectively; 1- and 2-year PFS rates were 57.8% and 38.5%, respectively. These findings did not reach statistical significance when compared with the group of patients who received durvalumab.

Adverse events

During CRT, 39 patients (45.9%) had G1-2 esophagitis. No esophagitis of G3-4 events were reported.

After CRT, 27 patients experienced lung toxicity (pneumonitis or pneumonia), and it was the most frequent AE reported. Two

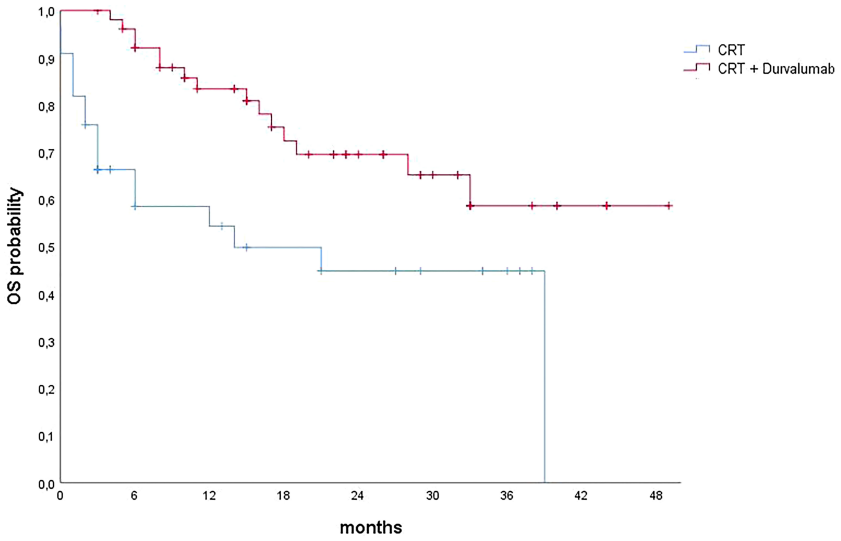

FIGURE 1
Overall survival curves calculated using the Kaplan–Meier method. CRT, chemoradiotherapy; OS, overall survival.

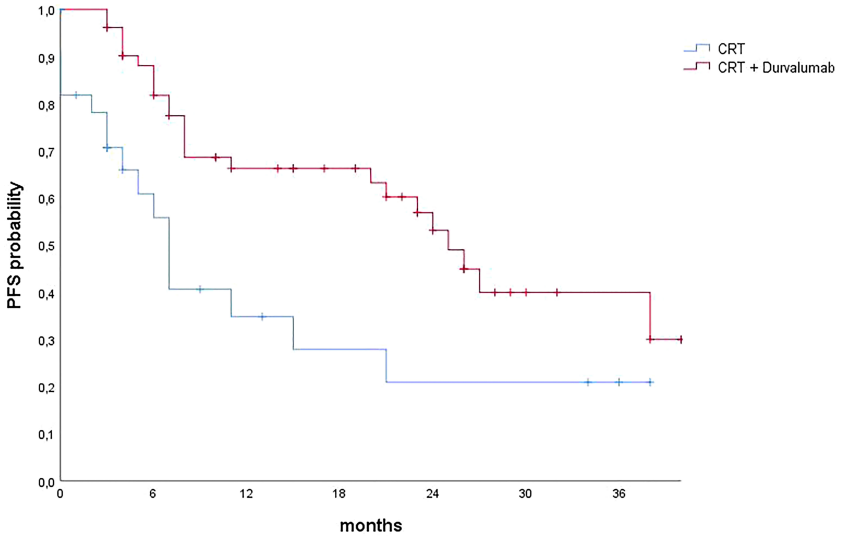

FIGURE 2
Progression-free survival curves calculated using the Kaplan–Meier method. CRT, chemoradiotherapy; PFS, progression-free survival.

patients presented a G3-4 AE pneumonitis/radiation pneumonitis. The second most frequent AE reported was endocrinological alterations (five patients, 9.6%) (Table 3).

Discussion

Although RCTs remain the gold standard to generate evidence to change the SoC, they often do not represent real-world clinical practice due to the highly selective inclusion criteria and the applicability after regulatory body approval.

This has led to the necessity to consider the use of real-world data (RWD) and real-world studies (RWS) to confirm the benefits or risks of a new medical product (13). After the PACIFIC trial publication, several data have confirmed that durvalumab has changed the clinical scenario of unresectable NSCLC stage III (6, 9, 14–16).

This retrospective, single-center study on 85 patients, with 52 treated with durvalumab, represents a fairly large experience compared to other single-center reports present in the literature (range 21–83 patients) (17–23).

Compared to the PACIFIC trial, this analysis showed some differences in the selected population. Patients' median age was

higher than in PACIFIC trial one (68 *vs.* 64 years), and the majority of patients were current smokers (50.6% *vs.* 16.4%). Stage IIIC was more represented (8.2% *vs.* 2.4%), and eight patients were treated for post-surgical locoregional relapse (data collected and analyzed in a multicentric series) (24). Finally, only a minority group received sCRT, which was not allowed in the PACIFIC trial, but PACIFIC-6 and GEMSTONE-301 are recently published trials that show the benefit of maintenance immunotherapy even after sCRT (25, 26). Durvalumab consolidation started, when indicated, after a longer median time (47 *vs.* <42 days). These differences could be mainly due to management issues (such as waiting lists) and clinical reasons (like slow toxicity resolution).

Despite these differences denoting a negatively selected population, similar results to the PACIFIC study were obtained for tumor response after CRT. On the contrary, PD after CRT was 9.4% in this series and 2.6% in the PACIFIC trial. Moreover, in patients treated with durvalumab, 1-year OS was 82.5% (83.1% in the PACIFIC trial), and 2-year OS was 69.4% (63.3% in the PACIFIC trial). One-year OS for patients who did not receive durvalumab was lower than in the placebo arm in the PACIFIC trial (56.2% *vs.* 74.6%). In the same group, the 1-year PFS was 42.4% *vs.* 35.3% of the PACIFIC (6).

These results could be partly explained by the fact that in the PACIFIC trial, patients were randomized to durvalumab or placebo exclusively after demonstration of not progressed disease after CRT. Therefore, patients with PD after CRT were excluded from the trial. In the present analysis, patients who progressed after CRT have been also included in the survival analysis. This aspect could be considered a sort of methodological deviation within the study. However, this work did not expect to faithfully replicate the PACIFIC trial but wanted to carry out a global evaluation of patients treated with radical intent for unresectable stage III NSCLC. Nevertheless, after excluding from the analysis patients who died or progressed after CRT, PFS and OS still improved in the durvalumab group despite no statistical significance. This result could be explained by the limited number of censored events and the surprising performance of patients treated without durvalumab.

In this series, 33 patients (38.8%) did not start durvalumab. Among these, 13 patients had negative levels of PD-L1 expression. In the PACIFIC trial, the benefit in terms of OS and PFS was detected in all the subgroups of PD-L1 expression in the durvalumab arm, except for OS in patients with PD-L1 expression less than 1%. These specific data, extracted from a *post hoc* analysis, led the European Medicines Agency (EMA) to approve the maintenance with durvalumab only for cases with PD-L1 expression higher than 1%. Furthermore, in clinical practice for patients with basal PD-L1 expression of less than 1%, a re-biopsy after CRT in order to re-test PD-L1 expression could be considered as an option. In fact, it is assumed that CRT can induce changes in the tumor microenvironment and, consequently, in the expression of PD-L1 (27). In this regard, two patients presented a PD-L1 expression higher than 1% after re-biopsy following CRT, so they were started on durvalumab.

In this study, patients presented good compliance to immunotherapy and developed toxicities in line with the results of the RCT and RWD. Pulmonary toxicity (all grades) was observed in 31.8% of patients, and grade 3 was minimal (3.8%), just like in PACIFIC (33.9%—G3 3.4%) and other RWDs (35%—G3 6%) (4, 9). This good compliance allowed patients to continue immunotherapy; in fact, in our study, only 11.5% of patients discontinued the maintenance program due to toxicity. In the PACIFIC trial, these data were reported in 15.4% of patients.

Though 87% of patients underwent a concurrent regimen of CRT, grade 2 acute esophageal toxicity occurred in 25.9% of the population and none of grade 3 or higher. Furthermore, patients included in this analysis had worse clinical features (such as age, COPD, and smoke status) and higher stages of disease than patients included in RCTs.

These data could probably suggest that, with accurate clinical support (prevention and management of toxicities or pulmonary rehabilitation) and the use of modern radiotherapy techniques, even fragile patients could aspire to treatment with curative intent (28–31).

The largest real-world study is surely PACIFIC-R, which enrolled 1,399 patients in 11 countries. This is an international, retrospective study of patients who started durvalumab within an early access program between September 2017 and December 2018 (16).

Notably, the OS and PFS reported in PACIFIC-R are similar to those in the current series. Instead, the all-grade pneumonitis rate is lower.

A comparison of clinical and toxicities outcomes among the PACIFIC trial, PACIFIC-R study, and the current series is summarized in Table 4. It should be noted that these three studies have some inherent differences, such as overall maintenance immunotherapy time (PACIFIC-R allowed durvalumab even beyond 1 year) and start date for calculating survival and FU (randomization date for PACIFIC, initiation of durvalumab for PACIFIC-R, and end of radiotherapy for ongoing series).

This work describes a monocentric, large, and homogeneous experience of patients treated with radical treatment for unresectable stage III NSCLC. As foreseeable, the selection of patients and the treatment conditions were slightly less favorable than the registration study. However, globally, patients were properly identified, and the clinical results were in line with the reference study and other similar experiences.

Unfortunately, due to the shorter follow-up, this experience is unable to evaluate the 5-year OS, which represents one of the major strengths of the PACIFIC trial. This RWS, like others, is useful to consolidate the data obtained from the PACIFIC trial and can be used to investigate still open issues, as the role of durvalumab in patients with oncogene-addicted NSCLC and in patients with controlled autoimmune diseases and the choice of treatment after progression to durvalumab, including local ablative therapies if oligometastases are evident.

Currently, real-world data on the use of durvalumab for unresectable NSCLC III stage confirm the safety and efficacy of this treatment in an evolving scenario. Indeed, recent new drugs, such as monalizumab, oleclumab, and sugemalimab are appearing as a potential alternative for maintenance after CRT (26, 32).

The introduction of durvalumab after CRT in stage III NSCLC has changed the standard of care. The data reported in this clinical

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TABLE 3 Adverse events (AEs) reported according to CTCAE v. 5.0.

	RCT N	RCT+durvalumab N	Total N (%)
Lung toxicity			
Pneumonitis or radiation pneumonitis*	6	16	22 (25.9)
Pneumonia	2	1	3 (3.5)
Other	0	2	2 (2.4)
Lung toxicity grade			
G1	1	7	8 (9.4)
G2	3	9	12 (14.1)
G3	2	3	5 (5.9)
G4	1	0	1 (1.2)
G5	1	0	1 (1.2)
Endocrinological alterations			
G2	0	4	4 (7.7)
G3	0	1	1 (1.9)
Gastrointestinal			
G3	0	2	2 (3.8)
Hematological			
G3	0	1	1 (1.9)
Cutaneous			
G1	0	2	2 (3.8)
G2	0	2	2 (3.8)
G3	0	1	1 (1.9)
Osteoarticular			
G2	0	3	3 (5.8)

RCT, randomized clinical trial; CTCAE, Common Terminology Criteria for Adverse Events.
*Pneumonitis includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, and pulmonary fibrosis.

TABLE 4 Comparison among current series (excluding patients who progressed or died after CRT) and PACIFIC trial and PACIFIC-R.

		Current series		PACIFIC trial		PACIFIC-R
		CRT	CRT+durvalumab	Placebo	Durvalumab	Durvalumab
Time between end of RCT and start of durvalumab (days)		–	47	–	–	56.0
Median FU (months)		20.0		34.2		23.5
OS	1 year (%)	62.8	82.5	74.6	83.1	–
	2 years (%)	62.8	69.4	55.3	66.3	71.2
	Median (months)	39	52	29.1	47.5	NR
PFS	1 year (%)	57.8	66.8	34.5	55.7	62.2
	2 years (%)	38.5	54.4	25.1	45	48.2
	Median (months)	16	26	5.6	16.9	21.7
Pneumonitis any grade		18.8	30.7	24.8	33.9	17.9

CRT, chemoradiotherapy; RCT, randomized clinical trial; FU, follow-up; OS, overall survival; PFS, progression-free survival.

scenario show that durvalumab as maintenance has an acceptable toxicity and a favorable efficacy, supporting the use of this therapeutic strategy with curative intent by recommending an accurate selection of the patient and his/her management within a multidisciplinary team.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of Brescia. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

All the authors have equally contributed in conceptualization, analysis, evaluation, investigation, data curation and in writing this research paper. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1208204/full#supplementary-material

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Erratum to "Cancer statistics, 2021". *CA Cancer J Clin* (2021) 71(4). doi: 10.3322/caac.21669

2. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, et al. Non-small-cell lung cancer. *Nat Rev Dis Primers.* (2015) 1(1):15009. doi: 10.1038/nrdp.2015.9

3. Govindan R, Bogart J, Vokes EE. Locally advanced non-small cell lung cancer: the past, present, and future. *J Thorac Oncol* (2008) 3(8):917–28. doi: 10.1097/JTO.0b013e318180270b

4. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–Small-Cell lung cancer. *New Engl J Med* (2017) 377(20):1919–29. doi: 10.1056/NEJMoa1709937

5. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *New Engl J Med* (2018) 379(24):2342–50. doi: 10.1056/NEJMoa1809697

6. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-Small-Cell lung cancer. *J Clin Oncol* (2022) 40 (12). doi: 10.1200/JCO.21.01308

7. FDA. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-after-chemoradiation-unresectable-stage-iii-nsclc.

8. *Determina AIFA 142833/2018*. Italy: AIFA (Agenzia Italiana del Farmaco) (2018).

9. Wang Y, Zhang T, Huang Y, Li W, Zhao J, Yang Y, et al. Real-world safety and efficacy of consolidation durvalumab after chemoradiation therapy for stage III non-small cell lung cancer: a systematic review and meta-analysis. *Int J Radiat OncologyBiologyPhysics.* (2022) 112(5):1154–64. doi: 10.1016/j.ijrobp.2021.12.150

10. UICC. TNM classification of malignant tumours 2017. In: *Oncoline*. The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK: John Wiley & Sons, Ltd. (2017).

11. Nestle U, De Ruysscher D, Ricardi U, Geets X, Belderbos J, Pöttgen C, et al. ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. *Radiotherapy Oncol* (2018) 127(1):1–5. doi: 10.1016/j.radonc.2018.02.023

12. National Cancer Institute (U.S.). *Common terminology criteria for adverse events (CTCAE) national cancer institute - NCI - U.S. department of health and human services; version 5.0*, Bethesda, Md.: U.S. Department of Health and Human Services (2017).

13. Makady A, de Boer A, Hillege H, Klungel O, Goettsch W. What is real-world data? a review of definitions based on literature and stakeholder interviews. *Value Health* (2017) 20(7):858–65. doi: 10.1016/j.jval.2017.03.008

14. Ferro A, Sepulcri M, Schiavon M, Scagliori E, Mancin E, Lunardi F, et al. The multidisciplinary approach in stage III non-small cell lung cancer over ten years: from radiation therapy optimisation to innovative systemic treatments. *Cancers (Basel)* (2022) 14(22). doi: 10.3390/cancers14225700

15. Bruni A, Scotti V, Borghetti P, Vagge S, Cozzi S, D'Angelo E, et al. A real-world, multicenter, observational retrospective study of durvalumab after concomitant or sequential chemoradiation for unresectable stage III non-small cell lung cancer. *Front Oncol* (2021) 11. doi: 10.3322/caac.21669

16. Girard N, Bar J, Garrido P, Garassino MC, McDonald F, Mornex F, et al. Treatment characteristics and real-world progression-free survival in patients with unresectable stage III NSCLC who received durvalumab after chemoradiotherapy: findings from the PACIFIC-r study. *J Thorac Oncol* (2023) 18(2):181–93. doi: 10.1016/j.jtho.2022.10.003

17. Miura Y, Mouri A, Kaira K, Yamaguchi O, Shiono A, Hashimoto K, et al. Chemoradiotherapy followed by durvalumab in patients with unresectable advanced non-small cell lung cancer: management of adverse events. *Thorac Cancer.* (2020) 11 (5):1280–7. doi: 10.1111/1759-7714.13394

18. LeClair JN, Merl MY, Cohenuram M, Luon D. Real-world incidence of pneumonitis in patients receiving durvalumab. *Clin Lung Cancer.* (2022) 23(1):34–42. doi: 10.1016/j.cllc.2021.08.006

19. Chu C, Chiu T, Wang C, Chang W, Huang AC, Liu C, et al. Consolidation treatment of durvalumab after chemoradiation in real-world patients with stage III unresectable non-small cell lung cancer. *Thorac Cancer.* (2020) 11(6):1541–9. doi: 10.1111/1759-7714.13426

20. Jung HA, Noh JM, Sun JM, Lee SH, Ahn JS, Ahn MJ, et al. Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer. *Lung Cancer.* (2020) 146:23–9. doi: 10.1016/j.lungcan.2020.05.035

21. Shaverdian N, Thor M, Shepherd AF, Offin MD, Jackson A, Wu AJ, et al. Radiation pneumonitis in lung cancer patients treated with chemoradiation plus durvalumab. *Cancer Med* (2020) 9(13):4622–31. doi: 10.1002/cam4.3113

22. Taugner J, Käsmann L, Eze C, Rühle A, Tufman A, Reinmuth N, et al. Real-world prospective analysis of treatment patterns in durvalumab maintenance after chemoradiotherapy in unresectable, locally advanced NSCLC patients. *Invest New Drugs* (2021) 39(4):1189–96. doi: 10.1007/s10637-021-01091-9

23. Offin M, Shaverdian N, Rimner A, Lobaugh S, Shepherd AF, Simone CB, et al. Clinical outcomes, local–regional control and the role for metastasis-directed therapies in stage III non-small cell lung cancers treated with chemoradiation and durvalumab. *Radiotherapy Oncol* (2020) 149:205–11. doi: 10.1016/j.radonc.2020.04.047

24. Borghetti P, Imbrescia J, Volpi G, Scotti V, Aquilano M, Bruni A, et al. Chemo-radiotherapy plus durvalumab for loco-regional relapse of resected NSCLC. *Radiat Oncol* (2022) 17(1). doi: 10.1186/s13014-022-02084-5

25. Wang Y, Kim TH, Fouladdel S, Zhang Z, Soni P, Qin A, et al. PD-L1 expression in circulating tumor cells increases during radio(chemo)therapy and indicates poor prognosis in non-small cell lung cancer. *Sci Rep* (2019) 9(1):566. doi: 10.1038/s41598-018-36096-7

26. Garassino MC, Mazieres J, Reck M, Chouaid C, Bischoff H, Reinmuth N, et al. Durvalumab after sequential chemoradiotherapy in stage III, unresectable NSCLC: the phase 2 PACIFIC-6 trial. *J Thorac Oncol* (2022) 17(12). doi: 10.1016/j.jtho.2022.07.1148

27. Zhou Q, Chen M, Jiang O, Pan Y, Hu D, Lin Q, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* (2022) 23(2):209–19. doi: 10.1016/S1470-2045(21)00630-6

28. Borghetti P, Imbrescia J, Volpi G, Costantino G, Cossali G, Greco D, et al. Prevention and management of acute esophageal toxicity during concomitant chemoradiotherapy for locally advanced lung cancer. *Tumori* (2022) 108(5). doi: 10.1177/03008916211025609

29. Borghetti P, Branz J, Volpi G, Pancera S, Buraschi R, Bianchi LNC, et al. Home-based pulmonary rehabilitation in patients undergoing (chemo)radiation therapy for unresectable lung cancer: a prospective explorative study. *Radiol Med* (2022) 127 (12):1322–32. doi: 10.1007/s11547-022-01562-w

30. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non–Small-Cell lung cancer. *J Clin Oncol* (2010) 28(13):2181–90. doi: 10.1200/JCO.2009.26.2543

31. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* (2015) 16(2):187–99. doi: 10.1016/S1470-2045(14)71207-0

32. Herbst RS, Majem M, Barlesi F, Carcereny E, Chu Q, Monnet I, et al. COAST: an open-label, phase II, multidrug platform study of durvalumab alone or in combination with oleclumab or monalizumab in patients with unresectable, stage III non-Small-Cell lung cancer. *J Clin Oncol* (2022). doi: 10.1200/JCO.22.00227

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EDITED BY
Sharon R. Pine,
University of Colorado Anschutz Medical Campus, United States

REVIEWED BY
Deena Snoke,
University of Vermont, United States
Wanying Wu,
Chinese Academy of Sciences (CAS), China

*CORRESPONDENCE
Wei Hou
houwei1964@163.com

†These authors have contributed equally to this work and share first authorship

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Effectiveness and safety of Shenqi Fuzheng injection combined with platinum-based chemotherapy for treatment of advanced non-small cell lung cancer: a systematic review and meta-analysis

Chenxi Qiao[1†], Shuaihang Hu[1†], Dandan Wang[1†], Kangdi Cao[1,2], Zhuo Wang[1,2], Xinyan Wang[1,2], Xiumei Ma[1], Zheng Li[1] and Wei Hou[1*]

[1]Department of Oncology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Graduate School of Beijing University of Chinese Medicine, Beijing, China

Objective: To evaluate the efficacy and safety of Shenqi Fuzheng Injection (SFI) combined with platinum-based chemotherapy (PBC) for the treatment of advanced non-small cell lung cancer (NSCLC).

Methods: Seven electronic databases, including CNKI and Wanfang, were comprehensively searched to screen randomized controlled trials (RCTs) until May 1, 2022. The quality of each trial was evaluated according to the Cochrane Handbook for Systematic Reviews of Interventions, and systematic reviews were conducted according to the PRISMA guidelines. Statistical analysis was performed using Review Manager 5.3, and the results were expressed as relative risk (RR) and 95% confidence interval (95% CI). The primary outcome measures were objective response rate (ORR) and disease control rate (DCR). The secondary outcome measures were quality of life and toxicity. Subgroup analysis was performed according to the number of days of SFI single-cycle treatment and combined PBC regimen.

Results: A total of 44 RCTs involving 3475 patients were included in the study. The meta-analysis results showed that, compared with PBC alone, SFI combined with PBC significantly improved the ORR (RR = 1.27, 95% CI = 1.18–1.37, P < 0.00001), DCR (RR = 1.12, 95% CI = 1.08–1.15, P < 0.00001), and quality of life (RR = 1.41, 95% CI = 1.31–1.52, P < 0.00001). It also reduced chemotherapy-induced hemoglobin reduction (RR = 0.57, 95% CI = 0.48–0.67, P < 0.00001), leukopenia (RR = 0.61, 95% CI = 0.53–0.71, P < 0.00001), thrombocytopenia (RR = 0.62, 95% CI = 0.55–0.70, P < 0.00001), and simple bone marrow suppression (RR = 0.55, 95% CI = 0.41–0.73, P < 0.0001). Nausea and vomiting (RR = 0.63, 95% CI = 0.52–0.77, P < 0.00001), diarrhea (RR = 0.48, 95% CI = 0.37–0.64, P < 0.00001), and simple digestive tract reactions (RR = 0.63, 95% CI = 0.49–0.80, P = 0.0002) also decreased with the treatment of SFI.

Conclusion: SFI combined with PBC for the treatment of advanced NSCLC improved the ORR, DCR, and quality of life, and reduced the incidence of myelosuppression and gastrointestinal adverse reactions. However, considering the limitations of existing evidence, further verification using high-quality RCTs is required.

Systematic review registration: https://inplasy.com/inplasy-2022-7-0026, identifier INPLASY202270026.

KEYWORDS

non-small cell lung cancer, platinum-based chemotherapy, Shenqi Fuzheng injection, efficacy and safety, randomized controlled trial, systematic review, meta-analysis 2.2 retrieval strategy

1 Introduction

GLOBOCAN 2020 data shows that lung cancer incidence and mortality are increasing annually worldwide (1). It is the most common type of malignant tumor and accounted for about 1.8 million deaths in 2020 (2). According to projections by the World Health Organization (WHO), by 2025 there may be 1 million people dying of lung cancer in China every year (3). The current incidence and mortality of lung cancer in China accounts for 37.0 and 39.8% of the world, respectively (1). Clinically, lung cancer is mainly divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for approximately 85% of all lung cancers (4). The incidence of lung cancer in China is highest in the age group of 80–84-years (5). As the cancer onset is subtle, patients are often diagnosed in the middle and late stages, reducing the opportunity for surgical treatment and resulting in poor prognosis (6). For advanced patients with NSCLC without positive gene drive, platinum-based doublet chemotherapy is the first-line standard treatment (7), such as cisplatin or carboplatin with vinorelbine, paclitaxel, gemcitabine, or pemetrexed. However, the efficacy of chemotherapy is limited, and there are some disadvantages such as toxicity, side effects, reduced immunity, and high costs. In particular, the adverse bone marrow suppression and digestive system reactions affect the quality of life of patients, making it difficult for patients to complete the standard chemotherapy cycle. Therefore, reducing the side effects of chemotherapy, improving the immune function and quality of life of patients, and enhancing the effects of chemotherapy are urgent problems that need to be solved to prolong the survival of patients, making them current research hotspots.

In recent years, traditional Chinese medicine adjuvant chemotherapy has played an important role in the comprehensive treatment of lung cancer. Modern studies have shown that traditional Chinese medicine and its preparations use the broad-spectrum pharmacological effects of various components to affect multiple targets (8), regulate signaling pathways that mediate cancer cell invasion and metastasis, promote apoptosis, improve tumor microenvironment, and stimulate immune response to play an anti-NSCLC role (9, 10). A multicenter prospective cohort study by Zhang et al. (11) showed that traditional Chinese medicine can significantly prolong the disease-free survival of patients with NSCLC and reduce the non-hematologic toxicity of chemotherapy, especially nausea, loss of appetite, diarrhea, pain, and fatigue. Traditional Chinese medicine has the advantages of lower costs, toxicity, and side effects, individualized treatment based on syndrome differentiation, and good clinical tolerance. It can also alleviate some of the disadvantages of chemotherapy and has shown advantages as an adjuvant therapy.

Shenqi Fuzheng injection (SFI) (Limin Pharmaceutical Factory of Lizhu Group, Guangdong, China, Z19990065, China Food and Drug Administration (CFDA)) is a traditional Chinese medicine injection extracted using modern scientific techniques from the raw materials *Codonopsis pilosula* and *Astragalus membranaceus*. The effect of SFI is to strengthen the body and replenish qi. Studies have shown that SFI efficiently extended the overall survival by alleviating the oxidative stress injury in the animal model of amyotrophic lateral sclerosis, meanwhile the astragaloside IV, an active component of Radix Astragali significantly enhanced cell viability and suppressed apoptosis by increasing the expressions of Nrf2 and HO-1 (12), which might support the idea that SFI 'strengthens the body'. It is widely used in the adjuvant treatment of colorectal, gastric, and breast cancers, as well as other advanced malignant tumors in China, and shows beneficial results (13–15). A number of clinical studies have reported that the combination of SFI and chemotherapy can improve the symptoms of lung and spleen qi deficiency and Karnofsky performance status (KPS) score in lung cancer, as well as reduce drug toxicity, alleviate adverse reactions of chemotherapy, improve the immune function and chemotherapy sensitivity of patients, delay tumor recurrence and metastasis, and have obvious advantages for short-term effectiveness (16).

At present, there are many clinical reports on SFI combined with platinum-based chemotherapy (PBC) in the treatment of NSCLC. However, most studies are low quality clinical trials, which failure to implement blinding, unscientific randomization methods, multiple confounding factors and risk of bias; the

chemotherapy regimens are inconsistent, the short-term objective effective rate, toxicity, and side effects are different, and there are contradictory results.According to the Cochrane 'RCT bias risk assessment tool', each randomized controlled trial was evaluated for a separate risk of bias. The GRADE score was used to evaluate the level of evidence of all studies. The results showed that some studies had lower levels of evidence and higher risks. The results between the studies were quite different or even opposite. Therefore the quality of research is uneven. The efficacy of using SFI with PBC lacks support from large sample and multicenter clinical trials, limiting the value of the conclusions drawn. Leung et al. (17) reported that the combination of herbs or traditional Chinese medicine preparations with drugs may lead to various degrees of herb-drug interactions, which may be life-threatening. A real-world study by Wang et al. (18) showed that approximately 82.76% of SFI treatments in China were combined with chemical drugs, most of which inhibited gastric acid production and showed anti-tumor effects. It was also reported that the incidence of adverse drug reactions such as palpitation, chest tightness, chills, abdominal pain, dyspnea, and elevated blood pressure after injection of SFI was 0.17% (19). As the clinical efficacy of SFI has not yet reached an international consensus, this study used meta-analysis to conduct methodological analysis and quality evaluation by searching relevant national and international randomized controlled trials (RCTs) to provide medical evidence for the effectiveness and safety of SFI combined with PBC for the treatment of NSCLC, to guide clinical practice and further research.

2 Methods

2.1 Study design

This systematic review and meta-analysis strictly followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (20). The registration number in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) is INPLASY202270026.

2.2 Retrieval strategy

Literature was sourced by searching PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang Database, China Biomedical Database, and Chongqing VIP Chinese Science and Technology Periodical Full-text Database from inception to May 1, 2022. All relevant literature was searched to screen RCTs that included SFI combined with prescribed chemotherapy regimens. All literature was independently reviewed by two researchers (Suaihang Hu and Chenxi Qiao) to determine whether they met the inclusion criteria. Any disagreement arising in this process was resolved by consultation with a third researcher (Wei Hou).

The retrieval strategy of RCTs strictly followed the requirements of the Cochrane system evaluation manual, used the combination of subject words and free words for searching, and was adjusted according to the specific database. Multiple pre-searches were performed to determine the final retrieval strategy. Chinese search terms included: traditional Chinese medicine injection, Shenqi Fuzheng injection, Shenqi Fuzheng, lung cancer, and non-small cell lung cancer. English search terms included: lung cancer, non-small cell lung cancer, NSCLC, Chinese herbal injection, Chinese medicine injection, injection of TCM (traditional Chinese medicine), microemulsion injection, and Ginseng-Qi Fuzheng.

2.3 Inclusion and exclusion criteria

2.3.1 Inclusion criteria

2.3.1.1 Research type

RCTs of SFI combined with platinum-containing double-agent chemotherapy for the treatment of advanced NSCLC were published nationally and internationally, with or without blinding or allocation concealment. The language was limited to Chinese and English.

2.3.1.2 Research object

Inclusion criteria was determined as follows: (1) Age was ≥ 18 years old and expected survival ≥ 3 months, with measurable clinical or observational indicators; (2) All cases were diagnosed as stage III–IV (according to WHO TNM staging) NSCLC by pathology or cytology, or were referred to as "advanced"; (3) Access was unrestricted to sex, race, nationality, economy, and education; (4) There were no contraindications related to chemotherapy or traditional Chinese medicine injection, no serious liver and kidney function, blood routine, and electrocardiogram abnormalities or other serious medical diseases, no obvious complications; (5) No patients received any concomitant radiotherapy, non-platinum chemotherapy, or other Chinese herbal medicine or Chinese patent medicine treatment, and there was non-postoperative or postoperative recurrence; (6) The baseline data of the two groups were similar and comparable.

2.3.1.3 Intervention measures

The control group only received PBC treatment. The PBC regimen was defined as vinorelbine + cisplatin (NP), vinorelbine + carboplatin (NC), paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin (TP), paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin (TC), gemcitabine + cisplatin (GP), gemcitabine + carboplatin (GC), docetaxel + cisplatin (DP), docetaxel + carboplatin (DC), pemetrexed + cisplatin (AP), or pemetrexed + carboplatin (AC). The experimental group was treated with PBC combined with intravenous SFI. The dose and duration of the drugs used were not limited. According to the drug instructions of SFI, the standard dose of SFI is 250ml 1/day, and the dose range of SFI in this study is 200-260ml. In terms of the dose of chemotherapeutic drugs, gemcitabine was 1000-1500mg/m^2, and the medication time was the 1st and 8th days of chemotherapy; vinorelbine was 25-40mg/m^2, and the medication time was the 1st

and 8th day of chemotherapy. Paclitaxel was 135-210mg/m^2, and the medication time was the 1st day of chemotherapy. Pemetrexed was 510 mg/m^2, and the medication time was the 1st day of chemotherapy. Cisplatin was 25-75mg/m^2, and the medication time was the 1st to 3d days of chemotherapy, or 75-100mg/m^2 was injected within one day; carboplatin was injected 300-500mg/m^2 within one day.In each trial, the chemotherapy regimen was administered by intravenous drip.

2.3.1.4 Outcome index

The outcome indexes were based on the WHO evaluation criteria for solid tumor efficacy (21) or Response evaluation criteria in solid tumors (RECIST) for solid tumor efficacy. These two methods have good consistency in the evaluation of tumor chemotherapy efficacy (22). WHO solid tumor efficacy evaluation criteria included: complete response (CR), complete disappearance of the tumor mass and duration of more than 1 month; partial response (PR), reduction of the product of tumor maximum diameter and maximum vertical diameter by 50% and maintained for more than 1 month; stable disease (SD), reduction in the product of the two diameters of the lesion by < 50% or increase by < 25% for more than 1 month; progressive disease (PD), increase in the product of the two diameters of the lesion by > 25% or appearance of new lesions. RECIST solid tumor efficacy evaluation criteria included: complete response (CR), tumor mass disappearance; partial response (PR), decrease in the tumor volume by more than 50% and normal auxiliary examination; stable disease (SD), decrease in the tumor volume by 50% or less and no improvement in auxiliary examination; progressive disease (PD), increase in the solid tumors by 25% or more and deterioration of the condition. The primary outcomes were objective response rate (ORR) and disease control rate (DCR). CR and PR were considered effective outcomes. Calculations were performed as follows: ORR = (CR + PR)/total number of cases; DCR = (CR + PR + SD)/total number of cases. The included studies contained the main outcome indicators.

Secondary outcome measures were quality of life improvement rate and incidence of adverse reactions (bone marrow suppression and gastrointestinal reactions). After the completion of the total course of treatment, the quality of life of patients was evaluated according to the KPS score: “improved score” was when the KPS score was improved >10 points, “stable score” when the KPS increased or decreased ≤10 points, and “decreased score” when KPS score decreased >10 points (23). Calculation of KPS improvement rate = (improved cases + stable cases)/total number of cases. Safety indicators were then assessed according to the WHO “acute and subacute toxicity criteria for chemotherapy drugs (24).” Bone marrow suppression was evaluated according to the occurrence of leukopenia, thrombocytopenia, and hemoglobin reduction. Gastrointestinal reactions were evaluated according to the occurrence of nausea, vomiting, and diarrhea. The incidence of adverse drug reactions is equal to the number of adverse reactions divided by the total number of cases. The included studies may or may not consist secondary outcome indicators or be evaluated with reference to other evaluation criteria.

2.3.2 Exclusion criteria

The exclusion criteria included: (1) Non-RCTs or self-controlled studies, non-clinical trials such as case reports, experience summaries, cross-sectional studies or reviews, or those that did not implement real randomization or incorrectly established controls; (2) Patients with other primary tumors; (3) Intervention measures combined with radiotherapy, targeted surgery, other western medicine treatments, Chinese medicine compound, Chinese patent medicine, acupuncture, acupoint application, other Chinese medicine treatment, or SFI without chemotherapy; (4) SFI was administered non-intravenously; (5) Patients with severe complications such as serious hepatic and renal dysfunction, heart disease,diabetes, malnutrition, malignant anemia. (6) Lack of research on main outcome indicators; (7) The research data was incomplete or the data was wrong (such as obvious inconsistency in the number of cases before and after); (8) For repeatedly published literature, only publications of the highest quality, most recent year of publication, and with comprehensive information were selected following the quality evaluation of the literature; (9) Dissertations, abstracts, and other literature.

2.4 Data extraction

The retrieved studies were imported into NoteExpress software. Two researchers (Kangdi Cao and Zhuo Wang) browsed the topics, abstracts, and full texts according to the established inclusion and exclusion criteria, independently completed the screening and data extraction of the studies, and produced the flow chart. The relevant data from the final included studies were entered into an Excel table. The specific extraction contents included: (1) The first author, publication year, sampling and randomization methods, blind application, and other basic research information; (2) Sample size, age range, pathological type, disease stage and drug dose, and duration of the treatment group and the control group; (3) Outcome indicators, data, and evaluation scale; (4) The key factors of bias risk assessment of the study. When the relevant data was incomplete, the clinical trial leader was contacted by e-mail to supplement it. During literature screening and data extraction, the same standards and methods were adopted to reduce deviation. The results of the extracted data were compared and any disagreement was resolved by the third researcher (Wei Hou).

2.5 Methodological quality assessment

Two researchers (Shuaihang Hu and Chenxi Qiao) used the Cochrane Handbook for Systemic Review of Investments (version 5.1.0) RCT bias risk assessment tool to conduct a separate bias risk assessment for each RCT (25). The evaluation was carried out through the following seven contents: (1) whether the random sequence generation method was correct; (2) whether the allocation scheme hiding was described; (3) whether the researchers and subjects were blinded; (4) blind evaluation of research outcome;

(5) integrity of outcome data; (6) whether to selectively report the research results; (7) other bias. The risk of bias in each field was evaluated as three levels: low risk, high risk, and unclear. Low risk level indicated that the test met all the criteria, whereas high risk indicated that any of the above items existed and the level of evidence was reduced. Unclear risk level indicated that it was neither high nor low risk, or the relevant content was not mentioned. The reasons for the evaluation level were recorded for high risk or unclear publications. The level of evidence for all studies was assessed by using GRADE (provided by the Cochrane Collaboration) (26). Any differences arising in this process were resolved through consultation with the third researcher (Wei Hou).

2.6 Statistical analysis

The Review Manager 5.3 software provided by the Cochrane Collaboration was used to generate forest maps using the included studies for meta-analysis. The data included were two categorical variables, and the effect value was expressed as relative risk (RR) and 95% confidence interval (95% CI). Differences were considered statistically significant when $P < 0.05$. The heterogeneity of included studies was analyzed using Cochran's Q test and I^2 test in Review Manager 5.3. When $P > 0.1$ and $I^2 < 50\%$, there was no significant heterogeneity in the included studies, and the fixed effect model (FEM) was used for combined analysis. When $P < 0.1$ and $I^2 > 50\%$, it was considered that there was significant heterogeneity in the included studies, and the source of heterogeneity was analyzed. Random effect model(REM) analysis was used when there was no clinical heterogeneity among the studies. Descriptive analysis was performed when there was significant clinical heterogeneity that disabled data combining.

2.7 Subgroup analysis

Subgroup analysis was performed according to the number of days of single-cycle SFI or the specific type of chemotherapy to reveal clinical heterogeneity and its effect on efficacy and safety. Studies using multiple chemotherapy regimens were not included in subgroup comparisons stratified by chemotherapy type.

2.8 Sensitivity analysis

Sensitivity analysis was carried out by limiting the literature to studies that met the "low deviation risk/high quality" criteria, such as excluding relevant studies with earlier publication years, smaller sample size, lower research quality, and insufficient or unclear allocation schemes. The impact on the overall effect size was observed to verify the robustness of the results; smaller influence was correlated with a more stable result. In other situations, the source of sensitivity was discussed. This paper excludes high-risk studies and studies published before 2010 to verify the stability of Meta-analysis results.

2.9 Publication bias

To ensure the reliability of the funnel plot assessment, we refer to Wang Shuo's study (23). If at least ten included studies were available for meta-analysis, a funnel plot was drawn to assess potential publication bias by analyzing the distribution of the collected clinical data.

3 Literature screening results

3.1 Search process

According to the defined search strategy, a total of 1598 articles were retrieved from the databases, including 340 articles from China National Knowledge Infrastructure (CNKI), 282 articles from VIP database, 415 articles from Wanfang database, 332 articles from China Biomedical Literature Service System (CBM), 33 articles from PubMed database, 148 articles from Cochrane Library database, and 48 articles from Embase database. After removing 572 duplicate articles, the titles and abstracts of the remaining 1026 articles were browsed. A total of 639 articles were removed that did not meet the inclusion criteria or were irrelevant. The full text was read of the remaining 387 articles, and a further 343 articles were excluded because they did not meet the criteria for advanced NSCLC, they used non-PBC regimens, no major outcome indicators were reported, data were incomplete, or they were non-RCT. The remaining 44 articles met the inclusion criteria (27–69). The literature screening process is detailed in Figure 1.

3.2 Characteristics of included studies

The RCTs included in this study were published between 2004–2021 and all were conducted in mainland China. In terms of the test population, a total of 3475 patients with advanced NSCLC were recruited, including 1745 in the experimental group and 1730 in the control group. Among them, one study (35) had incomplete outcome data. A total of 3460 patients had actual outcome data, including 1738 in the experimental group and 1722 in the control group. The number of males was 2216 and that of females was 1136, but the sum of the number of men and women in one study (48) was inconsistent with the total number of patients, and the number of biological sexin one study (40) was not recorded in detail. We contacted the author by email, but did not get a reply.The number of participants in each RCT ranged from 36–143. The age range was 25–83 years old.13 studies (27, 40, 48, 51, 53, 57, 60, 61, 64, 65, 67, 68, 70) only described the median age, and articles described the average age had a total of 2476 patients, with an average age of 62.21 years. 27 studies (27, 30, 33, 34, 36, 37, 39, 40, 43–45, 48, 50–53, 55, 56, 59, 61–68) included patients with KPS no less than 60 points, and 38 studies (27, 29–34, 36–39, 41–46, 48–53, 55–68, 70) included patients with expected survival of no less than 3 months. Five studies (27, 36, 45, 56, 62) carried out syndrome differentiation and only included people with qi deficiency. In terms of intervention

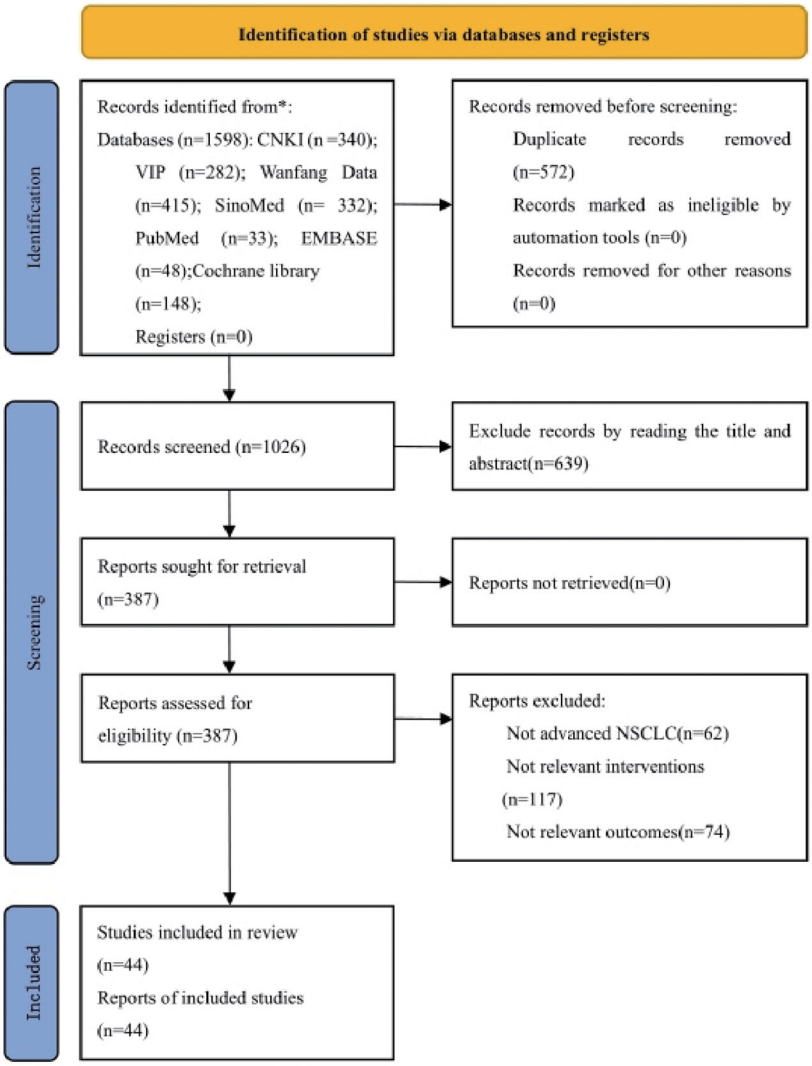

FIGURE 1
Flow chart of literature screening.

measures, both the experimental group and the control group adopted the same PBC regimens: 13 studies (33–38, 40–46) adopted GP, 10 NP (49, 50, 52–59), 9 TP (61–69), 4 DP (30–33), 2 NC (48, 51), 1 AP (29), 1 GC (40), and 1 TC regimen (60). Three studies used a mixture of regimens: one used GP or TP (27), one used GP or AC (28), and one used TP, TC, or NP regimens (70). The experimental group was treated with intravenous infusion of SFI and the reported chemotherapy regimen. In terms of the evaluation indicators, all included studies reported ORR of short-term efficacy and DCR was reported or calculated, except for two studies (39, 63). Thirty-two studies (27, 29–31, 35, 36, 38, 39, 41–43, 45, 47–49, 51–61, 63, 64, 67–70) used WHO solid tumor efficacy criteria, eight studies (28, 32, 33, 37, 50, 62, 65, 66) used RECIST criteria, and four studies (34, 40, 44, 46) did not describe the efficacy criteria. A total of 25 studies (27, 30, 32, 33, 35–37, 39, 40, 47, 48, 50, 51, 53, 54, 56, 57, 60–62, 64, 66–69) evaluated the improvement in the quality of life by KPS score. Except for four studies (33, 44, 56, 58), all the included literature described the secondary outcome indicators with binary variables. For reporting adverse reactions, 26 studies (27, 29, 31, 32, 35–37, 40, 43, 47, 48, 50–52, 54, 55, 57, 60–68) adopted the performance and grading standards of acute and subacute adverse reactions of WHO, 2 studies (28, 59) adopted the grading standards of acute and subacute toxicity of anticancer drugs, and 16 studies (30, 33, 34, 38, 39, 41, 42, 44–46, 49, 53, 56, 58, 69, 70) did not explain the evaluation criteria. The number of incidence of bone marrow suppression was counted in 34 studies, of which 17 (27, 31, 35–37, 45, 47, 48, 50, 52, 57, 59, 64–68) reported hemoglobin reduction, 30 (27, 29, 31, 32, 34–37, 39, 41, 42, 45–47, 49–55, 57, 59, 61, 64–69) reported leukopenia, 27 (27, 31, 32, 34–37, 39, 41, 42, 45, 47–52, 54, 55, 57, 59, 61, 64–68) reported thrombocytopenia, and 3 (28, 30, 62) described only bone marrow suppression. The incidence of gastrointestinal reactions

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was described in 29 studies, of which 18 (29, 30, 35, 37, 46, 49–53, 55, 59–61, 64, 65, 68, 69) counted nausea and vomiting, 5 (29, 30, 35, 46, 51) counted diarrhea, and 11 (31, 32, 34, 39, 41, 42, 48, 57, 66, 67, 70) only described simple gastrointestinal reactions. The basic data of the included studies are shown in Table 1.

3.3 Methodological quality evaluation of included studies

The Cochrane risk bias assessment tool was used to evaluate the methodological quality of the included studies. The 44 studies that

TABLE 1 Basic characteristics of the Included Studies.

Study ID	N(T/C)	Sex(M/F)	Age	TNM stages	Intervention group	Control group	Interested outcomes
Ding CJ 2012 (27)	35/35	42/28	38-70	IIIb-IV	250mL/day,10days/course;4 courses	GP/TP,4 courses	①②③④⑤⑥
Qi SG 2019 (28)	70/70	72/68	45-75	advanced	200mL/day;3 courses	GP/AC,3 courses	①②⑦
Ren JS 2015 (29)	42/42	49/35	53-73	IIIb-IV	250mL/day,10days/course;2 courses	AP,2 courses	①②⑤⑧⑨
Wang WM 2011 (30)	24/28	37/15	32-75	IV	250mL/day,10+ days;2 courses	DP,2 courses	①②③⑦⑧⑨
Yu F 2007 (31)	30/30	44/16	50-78	IIIb-IV	250mL/day,10days/course;2-3 courses	DP,2-3 courses	①②④⑤⑥⑩
Ma CG 2013 (32)	28/28	35/21	65-83	IIIa-IV	250mL/day,7days/course;3 courses	DP,3 courses	①②③⑤⑥⑩
Shan HG 2014 (33)	40/40	44/36	41-76	IIIb-IV	250mL/day,14days/course;2 courses	DP,2 courses	①②③
Bao Z 2019 (34)	47/47	61/33	65-71	advanced	250mL/day,21days/course;3 courses	GP,3 courses	①②⑤⑥⑩
Gui YX 2016 (35)	45/48	64/29	36-75	advanced	260mL/day,10days/course;4 courses	GP,4 courses	①②③④⑤⑥⑧⑨
Yao DJ 2013 (36)	50/50	84/16	30-70	III-IV	250mL/day,28days/course	GP,2 courses	①②③④⑤⑥
Zhao ZY 2014 (37)	50/52	80/22	49-67	IIIb-IV	250mL/day,10-14days/course	GP,2-6 courses	①②③④⑤⑥⑧
Zhang LM 2017 (38)	52/52	59/45	41-82	IIIb-IV	250mL/day,10days/course;2 courses	GP,2 courses	①②
Huang AX 2014 (39)	38/38	51/25	45-75	IIIb-IV	250mL/day,7days/course;2 courses	GP,2 courses	①②③⑤⑥⑩
Song Y 2007 (40)	59/58	UN	60-79	III-IV	250mL/day,10days/course;2 courses	GC,2 courses	①③
He WX 2021 (41)	48/48	58/38	56-78	III-IV	250mL/day,21days/course;4 courses	GP,4 courses	①②⑤⑥⑩
Jia J 2020 (42)	40/40	58/22	58-78	III-IV	UN	GP,4 courses	①②⑤⑥⑩
Li HT 2019 (43)	40/40	53/27	47-77	IIIb-IV	250mL/day,21days/course;2 courses	GP,2 courses	①②
Liu YF 2021 (44)	34/34	52/16	53-77	III-IV	250mL/day,10days/course;2 courses	GP,2 courses	①②
Luo BP 2018 (45)	48/48	61/35	33-64	IV	21days/course;2 courses	GP,2 courses	①②④⑤⑥
Wang HL 2021 (46)	53/53	58/48	47-73	IIIb-IV	250mL/day,21days/course;2 courses	GP,2 courses	①②⑤⑧⑨
Wu ZY 2019 (47)	28/28	29/27	38-71	advanced	250mL/day,21days/course;2 courses	GP,2 courses	①②③④⑤⑥

(Continued)

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TABLE 1 Continued

Study ID	N(T/C)	Sex(M/F)	Age	TNM stages	Intervention group	Control group	Interested outcomes
Wang YZ 2007 (48)	28/27	37/12	46-75	IIIb-IV	250mL/day,21days/course;3 courses	NC,3 courses	①②③④⑥⑩
Ding PQ 2016 (49)	60/60	78/42	62-80	III-IV	250mL/day,14days/course;2 courses	NP,2 courses	①②⑤⑥⑧
Wang TX 2014 (50)	41/41	60/22	43-80	III-IV	250mL/day,14days/course;2 courses	NP,2 courses	①②③④⑤⑥⑧
Jia YL 2012 (51)	72/71	98/45	60-77	IIIa-IV	250mL/day,14days/course;2 courses	NC,2 courses	①②③⑤⑥⑧⑨
Zhao ZY 2007 (52)	35/34	51/18	61-82	IIIa-IV	250mL/day,10days/course;2-3 courses	NP,2-3 courses	①②④⑤⑥⑧
Yu QZ 2007 (53)	30/32	65/19	35-76	III-IV	250mL/day,8-10days/course;4 courses	NP,4 courses	①②③⑤⑧
Wang K 2007 (54)	18/18	26/10	34-75	IIIb-IV	250mL/day,8days/course;3 courses	NP,3 courses	①②③⑤⑥
Li Y 2007 (55)	44/43	65/22	42-81	advanced	250mL/day,16days/course;4 courses	NP,4 courses	①②⑤⑥⑧
Geng L 2004 (56)	25/15	25/15	25-68	III-IV	250mL/day,21days/course;2 courses	NP,2 courses	①②③
Lv J 2008 (57)	40/40	65/15	51-78	advanced	250mL/day,21days/course;2 courses	NP,2 courses	①②③④⑤⑥⑩
Chen YF 2018 (58)	40/40	45/35	42-77	III-IV	250mL/day,14days/course;2 courses	NP,2 courses	①②
Zheng JH 2009 (59)	42/42	52/32	43-79	advanced	250mL/day,8days/course;3 courses	NP,3 courses	①②④⑤⑥⑧
Zou Y 2005 (60)	24/24	33/15	32-72	IIIa-IV	250mL/day,21days/course;2 courses	TC,2 courses	①②③⑧
Luo SZ 2006 (61)	25/25	33/17	33-75	IIIb-IV	250mL/day,21days/course;2 courses	TP,2 courses	①②③⑤⑥⑧
Cheng ZJ 2017 (62)	31/30	31/30	40-80	IIIb-IV	250mL/day,21days/course;2 courses	TP,2 courses	①②③⑦
Li HT 2012 (63)	30/30	44/16	49-82	IIIb-IV	250mL/day,10days/course;2 courses	TP,2 courses	①②
Luo SW 2007 (64)	30/30	39/21	33-75	IIIa-IV	250mL/day,14days/course;2 courses	TP,2 courses	①③④⑤⑥⑧
Liu R 2011 (65)	27/27	36/18	46-78	IIIa-IV	250mL/day,15days/course;2 courses	TP,2 courses	①②④⑤⑥⑧
Li DH 2014 (66)	50/40	57/33	38-74	IIIb-IV	250mL/day,14days/course;2 courses	TP,2 courses	①②③④⑤⑥⑩
Wang LY 2009 (67)	40/40	59/21	32-67	IIIa-IV	250mL/day,10-14days/course;2+ courses	TP,2+ courses	①②③④⑤⑥⑩
Zhang FL 2008 (68)	30/30	43/17	36-73	IIIa-IV	250mL/day,10-14days/course;2 courses	TP,2 courses	①②③④⑤⑥⑧
Zhao Q 2019 (69)	52/52	59/45	57-71	advanced	250mL/day,21days/course;2 courses	TP,2 courses	①②③⑤⑧
Wu L 2004 (70)	30/30	46/14	32-80	IIIb-IV	250mL/day,21days/course;2-3 courses	TP/TC/NP,2-3 courses	①②⑩

N, number of people; T/C, experimental group/control group; M/F, male/female; GP,gemcitabine + cisplatin; TP, paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin; AC,pemetrexed + carboplatin; AP, pemetrexed + cisplatin; DP, docetaxel + cisplatin; GC,gemcitabine + carboplatin; NC, vinorelbine + carboplatin; NP, vinorelbine + cisplatin; TC, paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin. ①Objective remission rate ORR=(CR+PR)/total cases×100%; ②Disease control rate DCR=(CR+PR+SD)/total cases×100%; ③KPS improvement rate=(number of improved cases + number of stable cases)/total cases; ④incidence of hemoglobin reduction = number of adverse reactions/total number of cases × 100%, calculated in the same way as below; ⑤incidence of leukopenia; ⑥incidence of thrombocytopenia; ⑦simple bone marrow suppression; ⑧incidence of nausea and vomiting; ⑨incidence of diarrhea; ⑩simple gastrointestinal reactions; UN, Unclear.

met the inclusion criteria all described the baseline conditions, with no statistical difference. In terms of random sequence generation, all included studies mentioned random grouping, and 18 studies were evaluated as "low risk," using either the random number table method (17 studies (27, 31, 34–37, 41, 44, 46, 47, 49, 50, 57, 58, 62, 63, 70)) or the envelope method (1 study (64)). Four studies (29, 60, 61, 65) were evaluated as "high risk" because the random method used the order of admission. Rest 22 studies (28, 30, 32, 33, 38–40, 42, 43, 45, 48, 51–56, 59, 66–69) did not describe the specific random method used, and there may be selective bias. In terms of allocation concealment and blindness, none of the included studies described concealment, no placebo was used, and no intention-to-treat analysis was performed; therefore, there may be selective and implementation bias. In blinding of researchers and subjects, blinding of outcome evaluators. All 44 studies had ORR primary objective indicators. In terms of subjective indicators, 19 studies (28, 29, 31, 34, 38, 41–46, 49, 52, 55, 58, 59, 63, 65, 70) did not have subjective indicators of KPS improvement rate and were evaluated as "low risk". Although one study (64) analyzed the KPS improvement rate, it was still evaluated as "low risk" because the random method used was the envelope method and it was not subjectively affected. The results of 24 studies (27, 30, 32, 33, 35–37, 39, 40, 47, 48, 50, 51, 53, 54, 56, 57, 60–62, 66–69) included subjective indicators such as quality of life. It was difficult to estimate the impact on the results of the study, so the evaluation was "unclear" and there may be measurement bias. In terms of the integrity of the outcome data, some patients withdrew without a reported reason or ITT analysis in one study (35), resulting in a possibility of bias; the rest had no cases of withdrawal or loss of follow-up. The outcome indicators of all studies were fully reported without selective reporting bias. In terms of other sources of bias, the number of biological sex or pathological types in three studies (43, 48, 55) did not match the total number, which was evaluated as "high risk," and there was no sufficient information to determine whether there were other sources of bias. The results of methodological quality evaluation are shown in Figure 2. The GRADE score is shown in Table 2, of which 6 are low-level evidence and 4 are very low-level evidence. The reasons for the downgrading are shown in the figure, indicating that the overall quality of the included literature was low and there were defects with respect to different aspects.

4 Meta-analysis results

4.1 SFI combined with PBC increases the objective response rate

All included studies reported ORR and had detailed data. Heterogeneity test analysis showed that there was no heterogeneity among the 44 studies (P = 0.98, I^2 = 0%), so the FEM was used to combine the analysis. The results of meta-analysis showed that the ORR of the experimental group increased by approximately 27% compared with the control group (RR = 1.27, 95% CI = 1.18–1.37; combined effect test, Z = 6.42, P < 0.00001). This suggested that the ORR of the SFI + PBC group was significantly better than that of the PBC group.

In the subgroup analysis of single-cycle SFI medication days, a total of 3460 patients were included, with 1738 in the experimental group and 1722 in the control group. There was no significant improvement in ORR when the single-cycle SFI medication was administered for 0–7 d (RR = 1.11, 95% CI = 0.76–1.62, P = 0.60, I^2 = 0%) (Figure 3). However, significant improvements were observed in the 8–14 d group (RR = 1.24, 95% CI = 1.12–1.38, P < 0.0001, I^2 = 0%) and 15–28 d group (RR = 1.33, 95% CI = 1.18–1.51, P < 0.00001, I^2 = 0%). The results suggested that SFI + PBC had a significant advantage over PBC alone in improving ORR. While the longer single-cycle SFI medication days had the most

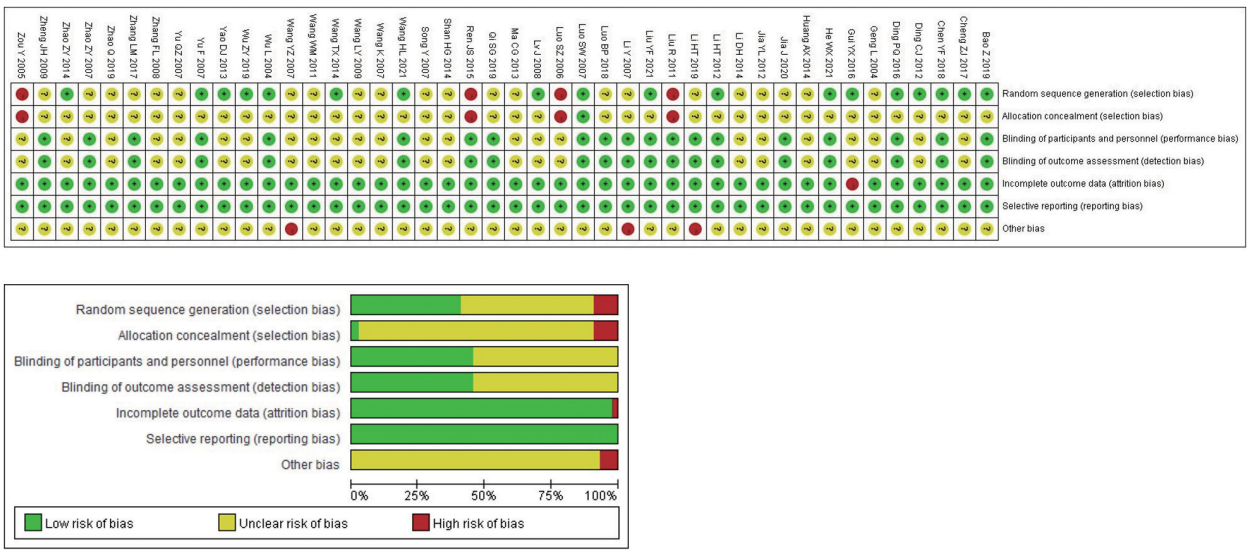

FIGURE 2
Methodological quality evaluation.

TABLE 2 GRADE score.

Quality assessment	No of RCTs	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	RR (95% CI)	Quality
ORR	44	fixed trials	serious[1]	no serious	no serious	no serious	Strongly suspected[4]	1.27 (1.18–1.37)	⊕⊕x̂x̂ LOW
DCR	42	randomised trials	serious[1]	no serious	no serious	no serious	Strongly suspected[4]	1.12 (1.08–1.15)	⊕⊕x̂x̂ LOW
KPS improvement	25	randomised trials	Very serious[1]	serious[2]	no serious	no serious	Strongly suspected[4]	1.41 (1.31–1.52)	⊕x̂x̂x̂ VERY LOW
Hemoglobinia	17	fixed trials	serious[1]	no serious	no serious	no serious	Strongly suspected[4]	0.57 (0.48–0.67)	⊕⊕x̂x̂ LOW
Leukopenia	30	randomised trials	serious[1]	serious[2]	no serious	no serious	Strongly suspected[4]	0.61 (0.53–0.71)	⊕x̂x̂x̂ VERY LOW
Thrombocytopenia	27	fixed trials	serious[1]	no serious	no serious	no serious	Strongly suspected[4]	0.62 (0.55–0.70)	⊕⊕x̂x̂ LOW
Myelosuppression	3	fixed trials	serious[1]	no serious	no serious	Serious[3]	undetected	0.55 (0.41–0.73)	⊕⊕x̂x̂ LOW
Nausea and Vomiting	18	randomised trials	serious[1]	serious[2]	no serious	no serious	Strongly suspected[4]	0.63 (0.52–0.77)	⊕x̂x̂x̂ VERY LOW
Diarrhea	5	fixed trials	serious[1]	no serious	no serious	Serious[3]	undetected	0.48 (0.37–0.64)	⊕⊕x̂x̂ LOW
Gastrointestinal Reaction	11	randomised trials	serious[1]	serious	no serious	Serious[3]	Strongly suspected[4]	0.63 (0.49–0.80)	⊕x̂x̂x̂ VERY LOW

[1] Unclear description of the hidden methods of random sequence and random allocation. [2] Point estimates vary widely from study to study. [3] The number of studies was too small and the confidence interval was too wide to be accurate.[4] The funnel plots were asymmetrical, which indicated that publication bias might influence the results of the analysis.Objective remission rate ORR=(CR+PR)/total cases×100%; Disease control rate DCR=(CR+PR+SD)/total cases×100%; KPS improvement rate=(number of improved cases + number of stable cases)/total cases.

obvious overall ORR improvement, this difference was not statistically significant (P = 0.73, I^2 = 0%). Three studies (28, 30, 42) did not clearly explain the number of days of single-cycle SFI medication and the observation period. Meta-analysis showed that the ORR of the experimental group was better than that of the control group, and the effective rate was statistically significant (RR = 1.28, 95% CI = 1.03–1.59, Z = 2.27, P = 0.02), which was consistent with the original research results.

In the stratified subgroup analysis of the combined specific chemotherapy type, 3190 patients were included after removing the three studies (27, 28, 70) using multiple chemotherapy regimens, with 1603 in the experimental group and 1587 in the control group. The ORR of SFI + GP (RR = 1.31, 95% CI = 1.16–1.49, P < 0.0001, I^2 = 6%), SFI + NP (RR = 1.20, 95% CI = 1.03–1.41, P = 0.02, I^2 = 0%), SFI + TP (RR = 1.34, 95% CI = 1.12–1.60, P = 0.001, I^2 = 0%), and SFI + GC (RR = 1.60, 95% CI = 1.03–2.49, P = 0.04) for the treatment of NSCLC was significantly better than that of the PBC alone (Figure 4). However, no ORR improvement with SFI treatment compared with PBC alone was observed in SFI + DP (RR = 1.12, 95% CI = 0.80–1.55, P = 0.51, I^2 = 0%), SFI + NC (RR = 1.08, 95% CI = 0.78–1.49, P = 0.64, I^2 = 0%), SFI + AP (RR = 1.22, 95% CI = 0.78–1.92, P = 0.39), or SFI + TC (RR = 1.22, 95% CI = 0.62–2.40, P = 0.56) groups.

4.2 SFI combined with PBC increases the disease control rate

Only two articles (40, 64) did not report DCR, and statistical analysis of DCR could be performed for all other studies. In the subgroup analysis of single-cycle SFI medication days, a total of 3283 patients were included in the study, with 1649 in the experimental group and 1634 in the control group. Heterogeneity test analysis showed that there was heterogeneity in the 0–7 d subgroup (P = 0.10, I^2 = 64%). However, because there were only two studies in this subgroup, further heterogeneity testing could not be performed. M-H method and REM were used for combined analysis. The results of meta-analysis showed that the use of SFI had little effect on the DCR

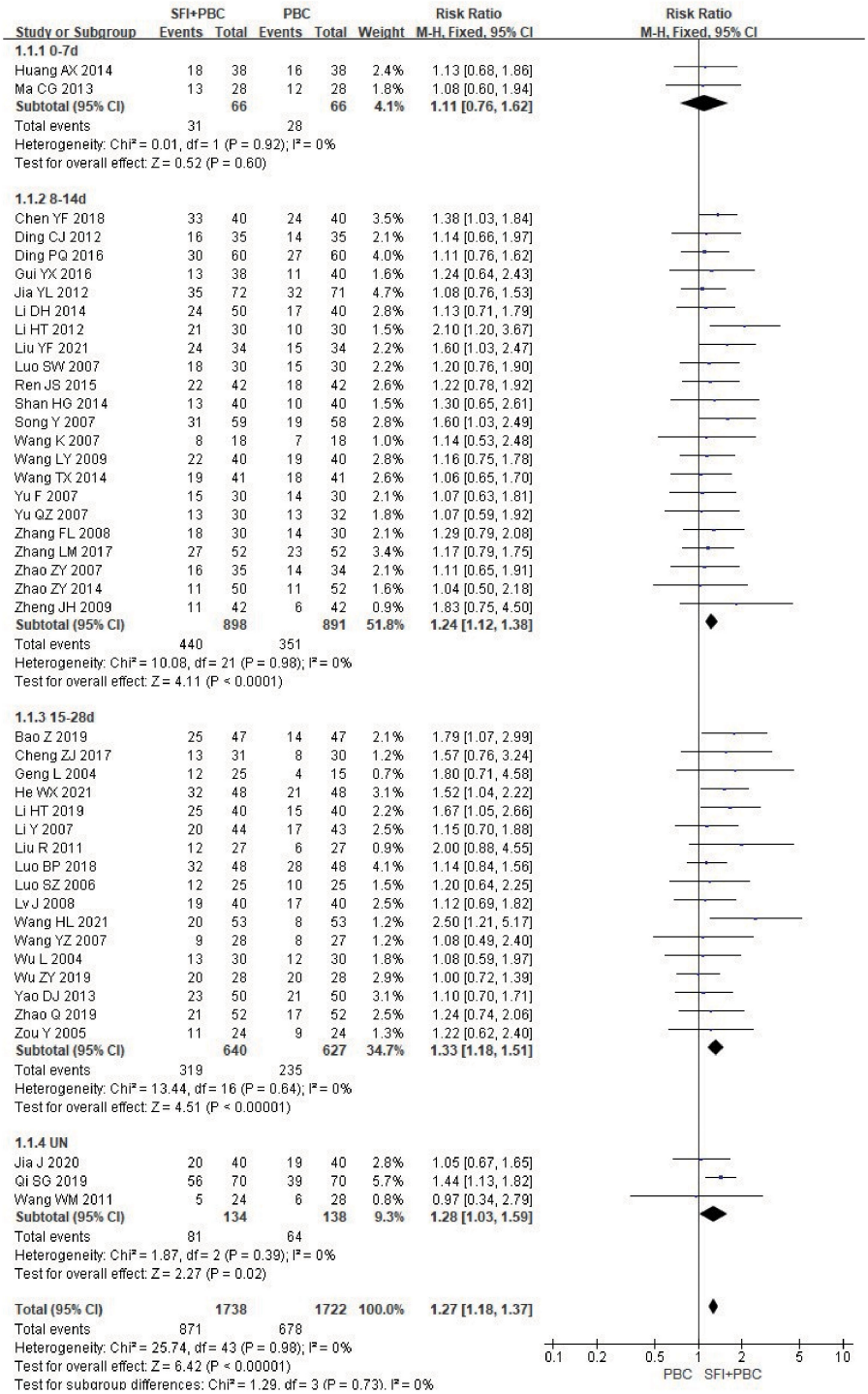

FIGURE 3
ORR forest plot stratified by days of single-cycle SFI dosing. Objective remission rate ORR=(CR+PR)/total cases×100%; UN, Unclear.

when the number of days of single-cycle SFI was 0–7 d (RR = 1.18, 95% CI = 0.84–1.66, P = 0.35, I^2 = 64%) (Figure 5). The DCR of the SFI + PBC group was significantly better than that of PBC alone group in 8–14 d (RR = 1.13, 95% CI = 1.07–1.18, P < 0.00001, I^2 = 0%) and 15–28 d SFI treatment subgroups (RR = 1.11, 95% CI = 1.05–1.18, P = 0.0002, I^2 = 26%). Overall combined analysis indicated that the DCR of SFI + PBC group was significantly better than that of PBC alone (RR = 1.12, 95% CI = 1.08–1.15, Z = 6.60, P < 0.00001). Three studies (28, 30, 42) did not clearly explain the number of days of single-cycle SFI medication and the observation period. Meta-analysis showed that the DCR of the experimental group was better than that of the control group, however, it was not statistically significant (RR = 1.08, 95% CI = 0.95–1.23, P = 0.25, I^2 = 44%). There was no heterogeneity between the subgroups (P = 0.93,

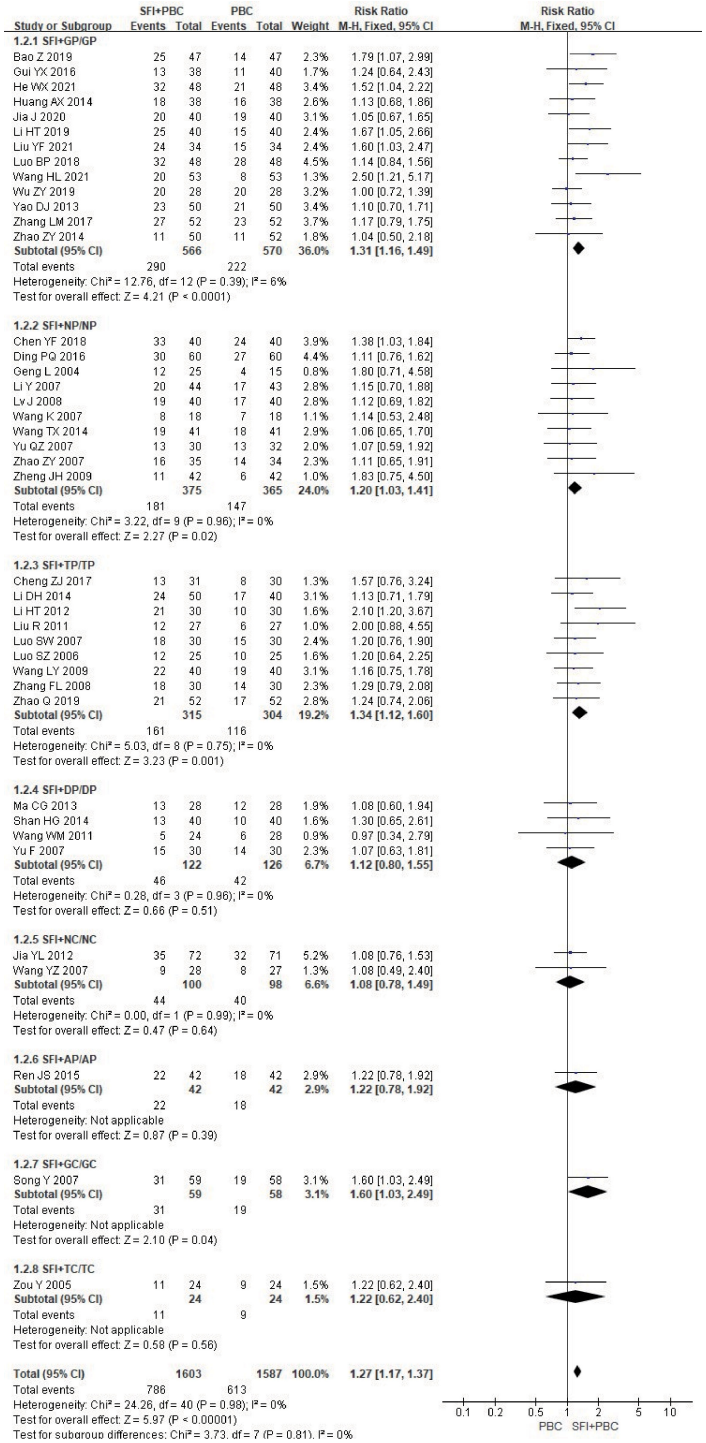

FIGURE 4
ORR forest plot stratified by chemotherapy regimen. Objective remission rate ORR=(CR+PR)/total cases×100%; GP, gemcitabine + cisplatin; NP, vinorelbine + cisplatin; TP, paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin; DP, docetaxel + cisplatin; NC, vinorelbine + carboplatin; AP, pemetrexed + cisplatin; GC, gemcitabine + carboplatin; TC, paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin.

I^2 = 0%), and the relationship between the number of days of single-cycle SFI medication and the DCR was not obvious.

In the subgroup analysis stratified by the specific type of chemotherapy combined, after removing 3 studies (27, 28, 70) using multiple regimens, a total of 3013 patients were included, with 1514 in the experimental group and 1499 in the control group. Heterogeneity test analysis showed that there was no heterogeneity in each group (P = 0.98, I^2 = 0%), so M-H method and FEM were used for analysis. The subgroup results of SFI + GP (RR = 1.15, 95% CI = 1.08–1.23, P < 0.0001, I^2 = 32%), SFI + NP (RR = 1.08, 95% CI = 1.02–1.15, P = 0.01, I^2 = 0%), and SFI + TP (RR = 1.26, 95% CI = 1.15–1.39, P < 0.00001, I^2 = 0%) suggested that SFI

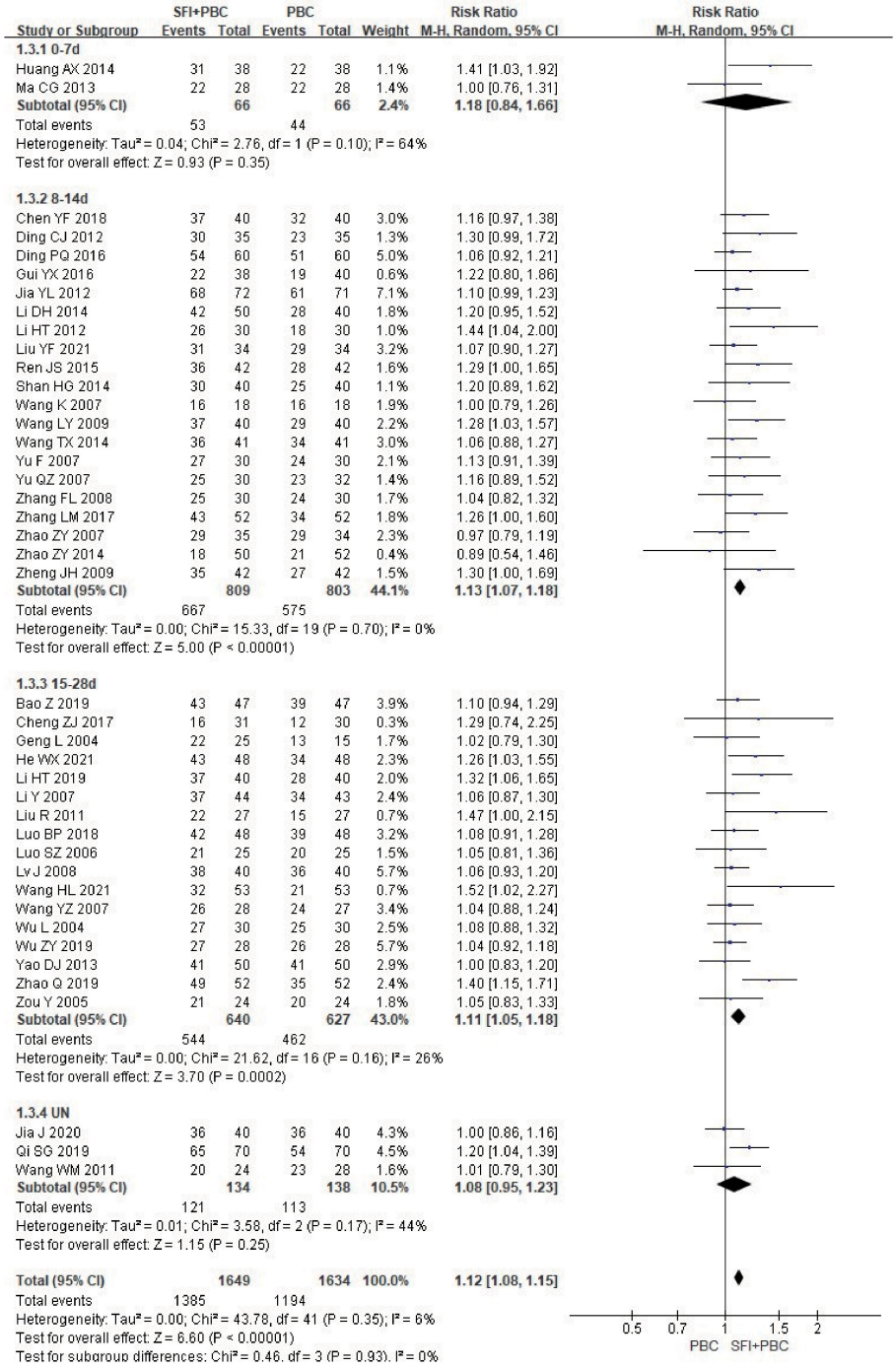

FIGURE 5
DCR forest plot stratified by days of single-cycle SFI dosing. Disease control rate DCR=(CR+PR+SD)/total cases×100%; UN, Unclear.

assisted GP, NP, TP chemotherapy could significantly improve the DCR, especially in the TP regimen (Figure 6). In contrast, SFI + DP (RR = 1.09, 95% CI = 0.96–1.24, P = 0.20, I^2 = 0%), SFI + NC (RR = 1.08, 95% CI = 0.99–1.19, P = 0.09, I^2 = %), SFI + AP (RR = 1.29, 95% CI = 1.00–1.65, P = 0.05), and SFI + TC (RR = 1.05, 95% CI = 0.83–1.33, P = 0.68) did not show any improvement; SFI assisted DP, NC, AP, and TC regimens had no improvement in DCR. However, only one study was included in the subgroups using AP and TC regimens, which may limit the accuracy of the conclusions. Overall, combined analysis showed that the DCR of the SFI + PBC group was significantly better than that of PBC alone (RR = 1.14, 95% CI = 1.10–1.19; combined effect size test Z = 7.19, P < 0.00001).

4.3 Quality of life

The KPS score was used to evaluate the quality of life. A total of 25 items (27, 30, 32, 33, 35–37, 39, 40, 47, 48, 50, 51, 53, 54, 56, 57,

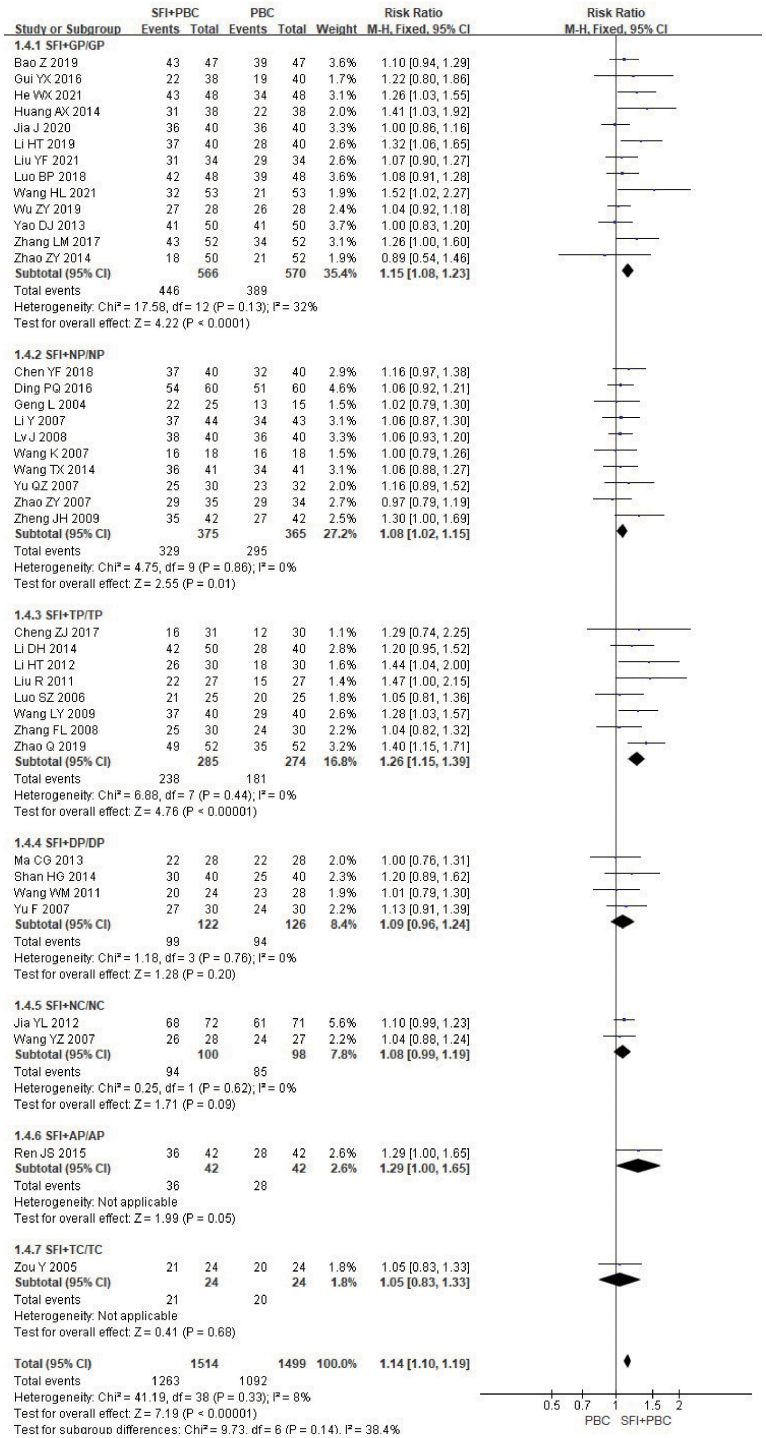

FIGURE 6
DCR forest plot stratified by chemotherapy regimen. Disease control rate DCR=(CR+PR+SD)/total cases×100%; GP, gemcitabine + cisplatin; NP, vinorelbine + cisplatin; TP, paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin; DP, docetaxel + cisplatin; NC, vinorelbine + carboplatin; AP, pemetrexed + cisplatin; TC, paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin.

60–62, 64, 66–69) were analyzed by two categorical variables. There was heterogeneity among the studies, so the REM was used to analyze the data. The results of meta-analysis showed that the improvement rate of KPS in the experimental group was approximately 41% higher than in the control group (RR = 1.41, 95% CI = 1.31–1.52; combined effect test Z = 8.93, P < 0.00001). This suggested that the improvement rate of KPS in the SFI + PBC group was significantly better than that in the PBC group.

In the subgroup analysis of single-cycle SFI medication days, a total of 1838 patients were included, with 926 in the experimental

group and 912 in the control group. Treatment with SFI in a single-cycle for 0–7 d (RR = 1.42, 95% CI = 0.88–2.30, Z = 1.45, P = 0.15) had no significant effect on KPS score improvement (Figure 7). The results of 8–14 d (RR = 1.47, 95% CI = 1.33–1.62, P < 0.00001, I^2 = 21%) and 15–28 d (RR = 1.40, 95% CI = 1.28–1.54, P < 0.00001, I^2 = 0%) subgroups showed that SFI treatment could effectively improve the quality of life. One study (30) did not specify the number of days of single-cycle SFI medication and the observation period. The results of meta-analysis showed that the KPS improvement rate of the experimental group was lower than that of the control group (RR = 0.97, 95% CI = 0.77–1.23, P = 0.81), which was inconsistent with the results of the original study. This discrepancy may be related to the fact that the included patients were all in the stage IV, and the quality of life was generally low and difficult to improve. There was heterogeneity between the groups (P = 0.02, I^2 = 70.4%), suggesting that prolonging the duration of a single-cycle of SFI dosing had a significant improvement in the quality of life of the patients.

In the subgroup analysis of the specific types of chemotherapy combined, one study (27) using multiple chemotherapy regimens was excluded. A total of 1768 patients were included, with 891 in the experimental group and 877 in the control group. The results showed that SFI combined with GP (RR = 1.31, 95% CI = 1.18–1.46, P < 0.00001, I^2 = 0%), NP (RR = 1.35, 95% CI = 1.17–1.55, P < 0.0001, I^2 = 0%), TP (RR = 1.56, 95% CI = 1.38–1.76, P < 0.00001, I^2 = 4%), NC (RR = 1.22, 95% CI = 1.04–1.43, P = 0.02, I^2 = 0%), GC (RR = 1.59, 95% CI = 1.19–2.12, P = 0.002), and TC regimens (RR = 1.80, 95% CI = 1.06–3.05, P = 0.03) significantly improved quality of life (Figure 8); SFI effectively improved the quality of life of patients with advanced NSCLC undergoing chemotherapy. In contrast, the results of SFI + DP (RR = 1.43, 95% CI = 0.86–2.36, P = 0.17, I^2 = 85%) suggested that SFI had little significance in improving the quality of life of patients with DP chemotherapy, however, the heterogeneity of this group was high. Overall combined analysis showed SFI significantly improved the quality of life of chemotherapy patients

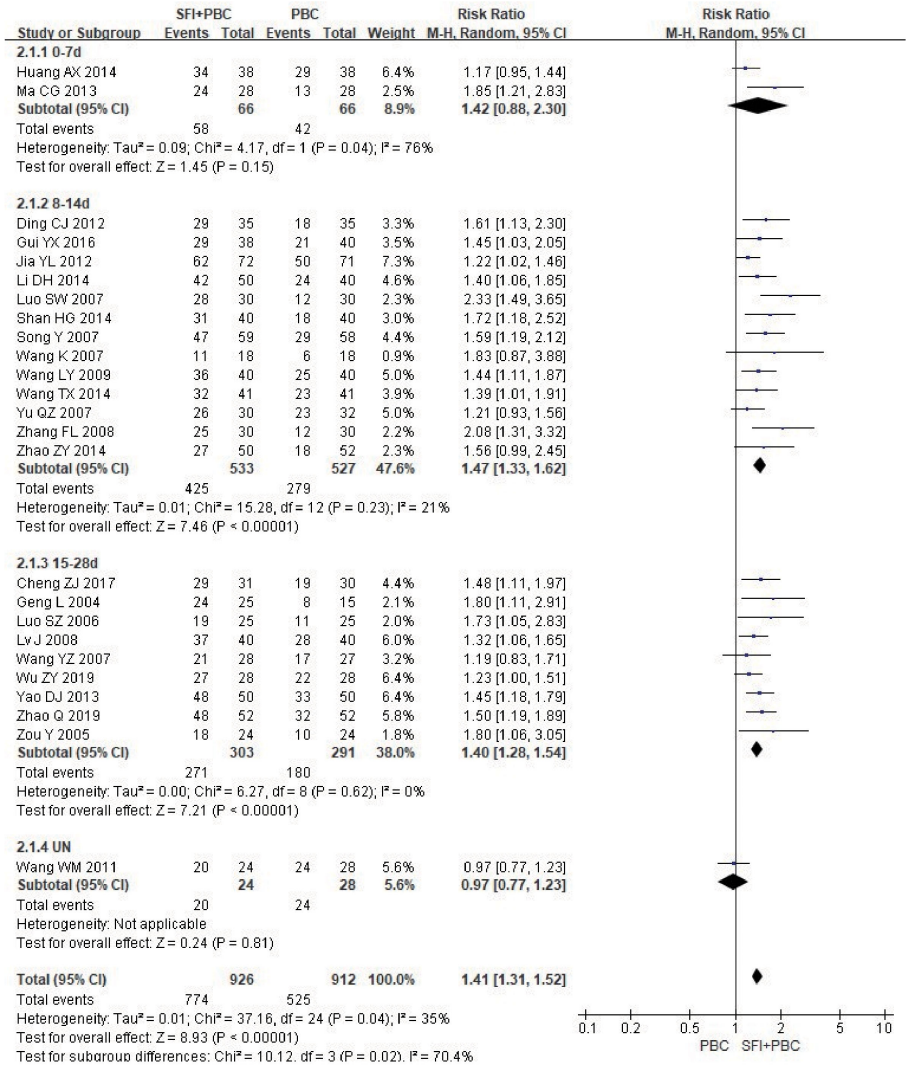

FIGURE 7
Forest plot of KPS improvement rate stratified by days of single-cycle SFI dosing. KPS improvement rate=(number of improved cases + number of stable cases)/total cases; UN, Unclear.

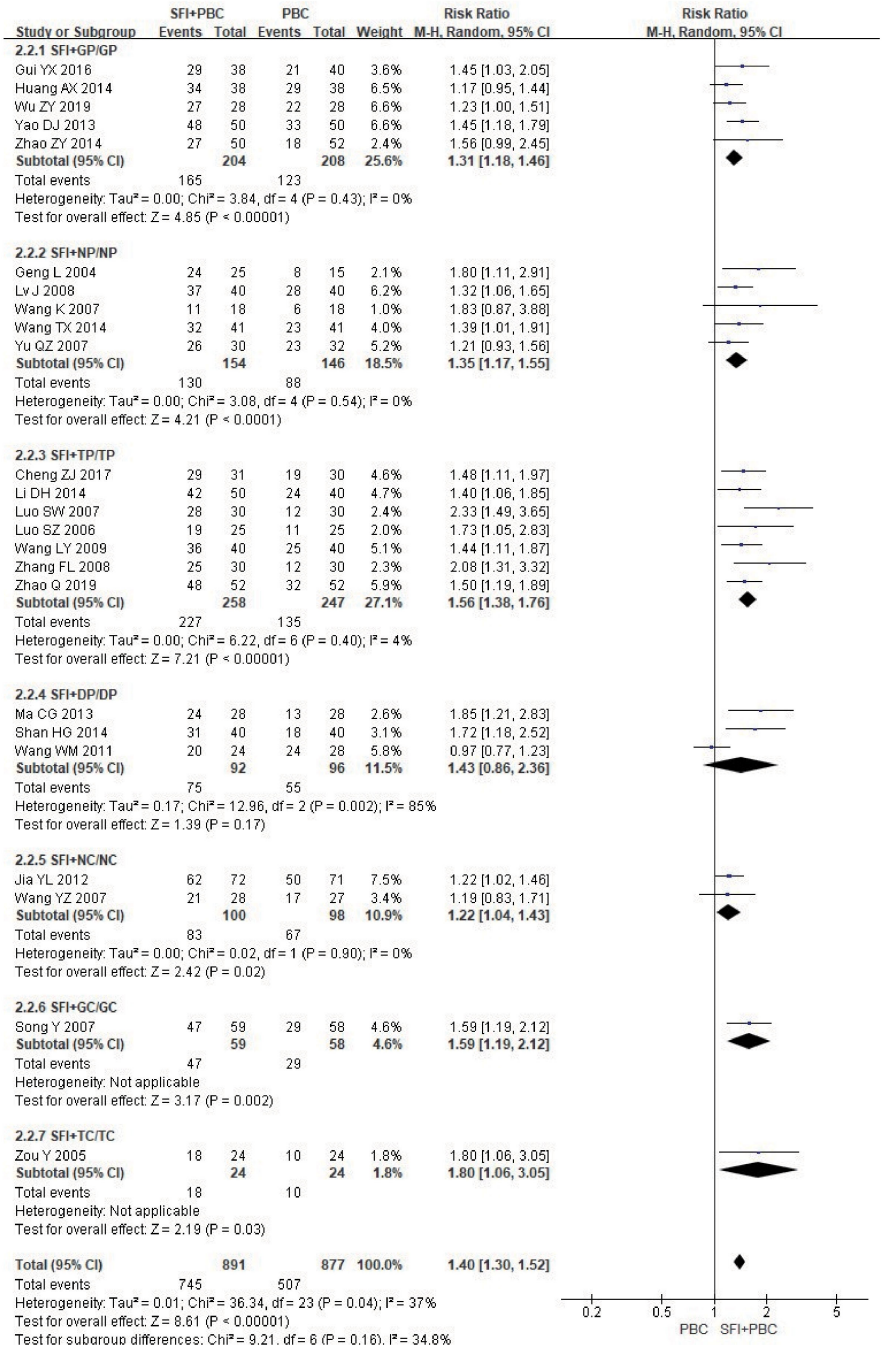

FIGURE 8
Forest plot of KPS improvement rate stratified by chemotherapy regimen. KPS improvement rate=(number of improved cases + number of stable cases)/total cases; GP, gemcitabine + cisplatin; NP, vinorelbine + cisplatin; TP, paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin; DP, docetaxel + cisplatin; NC, vinorelbine + carboplatin; GC, gemcitabine + carboplatin;TC, paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin.

(RR = 1.40, 95% CI = 1.30–1.52, P < 0.00001, I^2 = 37%), and there was no significant difference between subgroups (P = 0.16, I^2 = 34.8%).

Among the chemotherapy regimens, the SFI + DP subgroup did not pass the heterogeneity test, and the balance between the groups was poor. When the REM was selected, the combined RR was 1.43 (95% CI = 0.86–2.36). When the FEM was selected, the combined RR was 1.44 (95% CI = 1.18–1.76); changing the effect model had no obvious effect on the combined results. When the study by Wang et al. (30) (RR = 0.97, 95% CI = 0.77–1.23) was removed, I^2 decreased to 0%, indicating that this study was the main source of heterogeneity. This may be related to the lack of included participants. The patients included were all in stage IV, with poor quality of life. After removal, there was a significant difference between the experimental group and the control group in this subgroup (RR = 1.78, 95% CI = 1.34–2.36, P < 0.0001), which was consistent with the original conclusion.

4.4 Bone marrow suppression

4.4.1 Hemoglobin reduction

Seventeen studies (27, 31, 35–37, 45, 47, 48, 50, 52, 57, 59, 64–68) observed hemoglobin reduction events in 1276 patients, including 642 in the experimental group and 634 in the control group. Heterogeneity test analysis showed that there was no heterogeneity among the 17 studies (P = 0.78, I^2 = 0%), so the FEM was used for analysis. The results showed that the red blood cell reduction rate in the experimental group was approximately 43% lower than in the control group (RR = 0.57, 95% CI = 0.48–0.67; combined effect size test Z = 6.63 and P < 0.00001). The incidence of hemoglobin reduction in the SFI + PBC group was significantly lower than in the PBC group.

Subgroup analysis based on the number of days of single-cycle SFI medication showed that when the single-cycle SFI medication was 8–14 d, the probability of hemoglobin reduction in SFI combined with PBC for NSCLC was 44% lower than with PBC alone (RR = 0.56, 95% CI = 0.46–0.69, P < 0.00001, I^2 = 0%) (Table 3). Similar results were observed when the medication was

TABLE 3 Analysis of toxicities and side effects stratified by days of single-cycle SFI dosing.

Subgroups	Number of studies	SFI+PBC n/N	PBC n/N	Heterogeneity	PooledRRs(95%CI)	Z	P
Hemoglobinia							
8-14d	11	94/421	163/414	P=0.76, I^2 = 0%	0.56(0.46–0.69)	5.52	<0.00001
15-28d	6	51/221	88/220	P=0.43, I^2 = 0%	0.58(0.43–0.77)	3.70	0.0002
Total	17	145/642	251/634	P=0.78, I^2 = 0%	0.57(0.48–0.67)	6.63	<0.00001
Leukopenia							
0-7d	2	33/66	50/66	P=0.32, I^2 = 0%	0.69(0.54–0.89)	2.91	0.004
8-14d	16	267/643	419/637	P<0.00001, I^2 = 85%	0.62(0.49–0.78)	4.13	<0.0001
15-28d	11	160/462	275/461	P=0.15, I^2 = 31%	0.59(0.50–0.71)	5.82	<0.00001
UN	1	15/40	25/40	Not applicable	0.60(0.38–0.96)	2.15	0.03
Total	30	475/1211	769/1204	P<0.00001, I^2 = 77%	0.61(0.53–0.71)	6.49	<0.00001
Thrombocytopenia							
0-7d	2	13/66	30/66	P=0.56, I^2 = 0%	0.43(0.25–0.75)	3.01	0.003
8-14d	14	170/571	250/563	P=0.23, I^2 = 21%	0.67(0.58–0.78)	5.27	<0.00001
15-28d	10	101/385	167/383	P=0.13, I^2 = 34%	0.60(0.49–0.74)	4.89	<0.00001
UN	1	11/40	22/40	Not applicable	0.50(0.28–0.89)	2.36	0.02
Total	27	295/1062	469/1052	P=0.12, I^2 = 25%	0.62(0.55–0.70)	8.05	<0.00001
Myelosuppression							
Total	3	35/125	67/128	P=0.53, I^2 = 0%	0.55(0.41–0.73)	4.01	<0.0001
Nausea and vomiting							
8-14d	12	195/494	307/502	P<0.0001, I^2 = 71%	0.65(0.51–0.84)	3.28	0.001
15-28d	6	64/225	113/224	P=0.34, I^2 = 11%	0.59(0.46–0.76)	4.01	<0.0001
Total	18	259/719	420/726	P=0.0002, I^2 = 63%	0.63(0.52–0.77)	4.63	<0.00001
Diarrhea							
Total	5	46/229	96/234	P=0.11, I^2 = 47%	0.48(0.37–0.64)	5.09	<0.00001
Gastrointestinal Reaction							
0-7d	2	40/66	52/66	P=0.02, I^2 = 82%	0.71(0.36–1.43)	0.95	0.34
8-14d	3	38/120	65/110	P=0.12, I^2 = 53%	0.56(0.36–0.88)	2.55	0.01
15-28d	5	82/193	129/192	P<0.0001, I^2 = 85%	0.63(0.40–0.99)	2.02	0.04
UN	1	14/40	25/40	Not applicable	0.56(0.34–0.91)	2.34	0.02
Total	11	174/419	271/408	P<0.00001, I^2 = 78%	0.63(0.49–0.80)	3.67	0.0002

n,number of cases with adverse reactions; N,total number of cases included in this study; UN,Unclear.

administered for 15–28 d (RR = 0.58, 95% CI = 0.43–0.77, P = 0.0002, I^2 = 0%). There was no heterogeneity among subgroups (P = 0.87, I^2 = 0%).

Subgroup analysis stratified by the specific type of chemotherapy combined was then performed. After removing one study (27) using multiple chemotherapy regimens, 1206 patients were included, with 607 in the experimental group and 599 in the control group. Compared with chemotherapy alone, SFI + GP (RR = 0.56, 95% CI = 0.42–0.76, P = 0.0002, I^2 = 9%), SFI + NP (RR = 0.53, 95% CI = 0.37–0.74, P = 0.0003, I^2 = 0%), SFI + TP (RR = 0.58, 95% CI = 0.40–0.83, P = 0.003, I^2 = 12%), and SFI + DP groups (RR = 0.65, 95% CI = 0.43–0.98, P = 0.04) significantly reduced the incidence of hemoglobin reduction (Table 4). No advantage of SFI treatment was observed in the SFI + NC group

TABLE 4 Toxic side effect analysis stratified by the specific type of chemotherapy combined.

Subgroups	Number of studies	SFI+PBC n/N	PBC n/N	Heterogeneity	Pooled RRs(95% CI)	Z	P
Hemoglobinia							
SFI+GP/GP	5	46/214	83/218	P=0.35, I^2 = 9%	0.56(0.42–0.76)	3.77	0.0002
SFI+NP/NP	4	35/158	66/157	P=0.84, I^2 = 0%	0.53(0.37–0.74)	3.65	0.0003
SFI+TP/TP	5	35/177	55/167	P=0.34, I^2 = 12%	0.58(0.40–0.83)	2.96	0.003
SFI+DP/DP	1	15/30	23/30	Not applicable	0.65(0.43–0.98)	2.05	0.04
SFI+NC/NC	1	6/28	7/27	Not applicable	0.83(0.32–2.15)	0.39	0.70
Total	16	137/607	234/599	P=0.75, I^2 = 0%	0.57(0.48–0.68)	6.29	<0.00001
Leukopenia							
SFI+GP/GP	10	158/440	255/444	P=0.17, I^2 = 30%	0.64(0.54–0.76)	5.05	<0.00001
SFI+NP/NP	8	141/310	215/310	P<0.00001, I^2 = 91%	0.66(0.47–0.95)	2.27	0.02
SFI+TP/TP	7	87/254	162/244	P=0.11, I^2 = 42%	0.52(0.40–0.68)	4.90	<0.00001
SFI+DP/DP	2	26/58	41/58	P=0.41, I^2 = 0%	0.66(0.48–0.90)	2.64	0.008
SFI+NC/NC	1	40/72	52/71	Not applicable	0.76(0.59–0.97)	2.17	0.03
SFI+AP/AP	1	9/42	17/42	Not applicable	0.53(0.27–1.05)	1.82	0.07
Total	29	461/1176	742/1169	P<0.00001, I^2 = 77%	0.61(0.53–0.71)	6.29	<0.00001
Thrombocytopenia							
SFI+GP/GP	9	109/387	169/391	P=0.02, I^2 = 58%	0.63(0.46–0.87)	2.81	0.005
SFI+NP/NP	7	81/280	126/278	P=0.59, I^2 = 0%	0.67(0.54–0.82)	3.79	0.0001
SFI+TP/TP	6	40/202	84/192	P=0.88, I^2 = 0%	0.45(0.33–0.62)	4.97	<0.00001
SFI+DP/DP	2	18/58	27/58	P=0.22, I^2 = 33%	0.67(0.37–1.20)	1.34	0.18
SFI+NC/NC	2	32/100	47/98	P=0.80, I^2 = 0%	0.67(0.48–0.93)	2.39	0.02
Total	26	280/1027	453/1017	P=0.14, I^2 = 23%	0.62(0.54–0.72)	6.65	<0.00001
Myelosuppression							
Total	3	35/125	67/128	P=0.53, I^2 = 0%	0.55(0.41–0.73)	4.01	<0.0001
Nausea and vomiting							
SFI+GP/GP	3	40/141	70/145	P=0.02, I^2 = 73%	0.53(0.24–1.19)	1.54	0.12
SFI+NP/NP	6	102/252	138/252	P=0.01, I^2 = 65%	0.75(0.54–1.04)	1.74	0.08
SFI+TP/TP	5	46/164	111/164	P=0.002, I^2 = 77%	0.40(0.22–0.72)	3.02	0.003
SFI+DP/DP	1	13/24	15/28	Not applicable	1.01(0.61–1.67)	0.04	0.97
SFI+NC/NC	1	35/72	49/71	Not applicable	0.70(0.53–0.94)	2.42	0.02
SFI+AP/AP	1	18/42	30/42	Not applicable	0.60(0.40–0.89)	0.01	0.01
SFI+TC/TC	1	5/24	7/24	Not applicable	0.71(0.26–1.94)	0.66	0.51

(Continued)

TABLE 4 Continued

Subgroups	Number of studies	SFI+PBC n/N	PBC n/N	Heterogeneity	Pooled RRs(95% CI)	Z	P
Total	18	259/719	420/726	P=0.0002, I^2 = 63%	0.63(0.52–0.77)	4.63	<0.00001
Diarrhea							
Total	5	46/229	96/234	P=0.11, I^2 = 47%	0.48(0.37–0.64)	5.09	<0.00001
Gastrointestinal Reaction							
SFI+GP/GP	4	78/173	120/173	P=0.004, I^2 = 78%	0.64(0.43–0.96)	2.17	0.03
SFI+NP/NP	1	13/40	22/40	Not applicable	0.59(0.35–1.00)	1.96	0.05
SFI+TP/TP	2	23/90	47/80	P=0.81, I^2 = 0%	0.45(0.30–0.66)	4.04	<0.0001
SFI+DP/DP	2	25/58	38/58	P=0.16, I^2 = 49%	0.66(0.40–1.09)	1.62	0.10
SFI+NC/NC	1	25/28	25/27	Not applicable	0.96(0.82–1.14)	0.43	0.67
Total	10	164/389	252/378	P<0.00001, I^2 = 79%	0.64(0.49–0.82)	3.40	0.0007

NP, vinorelbine + cisplatin; NC, vinorelbine + carboplatin; TP, paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin; TC ,paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin; GP, gemcitabine + cisplatin; GC, gemcitabine + carboplatin; DP, docetaxel + cisplatin; DC, docetaxel + carboplatin; AP, pemetrexed + cisplatin; AC, pemetrexed + carboplatin.

(RR = 0.83, 95% CI = 0.32–2.15, P = 0.70), however, the number of included studies was small, and these results require further verification. There was no significant difference between the subgroups (P = 0.88, I^2 = 0%).

4.4.2 Leukopenia

Thirty studies (27, 29, 31, 32, 34–37, 39, 41, 42, 45–47, 49–55, 57, 59, 61, 64–69) used dichotomous variables to report the reduction of white blood cells, with detailed data for a total of 2415 patients, including 1211 in the experimental group and 1204 in the control group. Heterogeneity test analysis showed that there was significant heterogeneity among the included studies (P < 0.00001, I^2 = 77%), so the REM was used. The results of pooled analysis showed that the rate of leukopenia in the experimental group was approximately 39% lower than in the control group (RR = 0.61, 95% CI = 0.53–0.71; combined effect size test Z = 6.49, P < 0.00001), suggesting that the use of SFI with PBC helped to reduce the occurrence of leukopenia.

In the subgroup analysis stratified by the number of days of single-cycle SFI medication, treatment for 0–7 d (RR = 0.69, 95% CI = 0.54–0.89, P = 0.004, I^2 = 0%), 8–14 d (RR = 0.62, 95% CI = 0.49–0.78, P < 0.0001, I^2 = 85%), and 15–28 d (RR = 0.59, 95% CI = 0.50–0.71, P < 0.00001, I^2 = 31%) significantly reduced the incidence of leukopenia. While there was a correlation between increasing the number of days of single-cycle SFI medication and RR of leukopenia improvement, the difference between the groups was not statistically significant (P = 0.81, I^2 = 0%). One study (42) did not describe the medication time. The results of meta-analysis showed that the incidence of leukopenia in the SFI + PBC group was lower than in the PBC group (RR = 0.60, 95% CI = 0.38–0.96, P = 0.03). The difference between the two groups was statistically significant, which was consistent with the original conclusion.

In the subgroup analysis of the specific types of chemotherapy combined, after removing one study (27) using multiple chemotherapy regimens, 2345 patients were included, with 1176 in the experimental group and 1169 in the control group. The results showed SFI + GP (RR = 0.64, 95% CI = 0.54–0.76, P < 0.00001, I^2 = 30%), SFI + NP (RR = 0.66, 95% CI = 0.47–0.95, P = 0.02, I^2 = 91%), SFI + TP (RR = 0.52, 95% CI = 0.40–0.68, P < 0.00001, I^2 = 42%), SFI + DP (RR = 0.66, 95% CI = 0.48–0.90, P = 0.008, I^2 = 0%), and SFI + NC (RR = 0.76, 95% CI = 0.59–0.97, P = 0.03) could significantly reduce white blood cells compared with PBC alone. The greatest improvement was observed in the SFI + TP group, however, the difference between the groups was not significant (P = 0.47, I^2 = 0%). SFI + AP (RR = 0.53, 95% CI = 0.27–1.05, P = 0.07) did not significantly improve leukopenia, but only 1 study was included in this subgroup, so further research is required to draw accurate conclusions.

Heterogeneity test analysis showed that there was significant heterogeneity in the subgroup of 8–14 d of SFI single-cycle (P < 0.00001, I^2 = 85%), subgroup of chemotherapy with the NP regimen (P < 0.00001, I^2 = 91%), and overall combined analysis (P < 0.00001, I^2 = 77%). After excluding individual studies one by one, it was found that after removing Wang (54), the I^2 of the subgroup with 8–14 d of SFI single-cycle was reduced to 48%, the subgroup with NP regimen was reduced to 57%, and the overall combined I^2 was reduced to 37%. After removing the studies of Wang (54) and Zheng (59) individually and at the same time, I^2 decreased to 30%, 31% and 31%, respectively, indicating that these two studies were the main sources of heterogeneity. This may be because the sample size used by Wang (54) was small, with 18 patients in the experimental and control group having leukopenia, and the cisplatin dosage by Zheng (59) small (25 mg/m^2) compared to other studies and bone marrow suppression was weak. The results after eliminating these studies were consistent with the original analysis (RR = 0.63, 95% CI = 0.58–0.70, P < 0.00001, I^2 = 31%).

4.4.3 Thrombocytopenia

A total of 27 studies (27, 31, 32, 34–37, 39, 41, 42, 45, 47–52, 54, 55, 57, 59, 61, 64–68) observed thrombocytopenia events with detailed data for 2114 patients, including 1062 in the experimental group and 1052 in the control group. Heterogeneity test analysis showed that there was no significant difference between the 27 studies (P = 0.12, I^2 = 25%), hence, the FEM was used.

The overall analysis results showed that the incidence of thrombocytopenia in the experimental group was approximately 38% lower than in the control group (RR = 0.62, 95% CI = 0.55–0.70; combined effect size test Z = 8.05, P < 0.00001); the SFI + PBC group reduced the incidence of thrombocytopenia during the treatment of advanced NSCLC compared with the PBC group.

Subgroup analysis based on the number of days of single-cycle SFI medication showed that treatment for 0–7 d (RR = 0.43, 95% CI = 0.25–0.75, P = 0.003, I^2 = 0%), 8–14 d (RR = 0.67, 95% CI = 0.58–0.78, P < 0.00001, I^2 = 21%), and 15–28 d (RR = 0.60, 95% CI = 0.49–0.74, P < 0.00001, I^2 = 34%) could significantly improve the occurrence of thrombocytopenia. However, there was no significant correlation between the degree of improvement and the duration of single-cycle SFI (P = 0.36, I^2 = 6.6%). One study (42) did not report the number of days of medication. The incidence of thrombocytopenia in the experimental group was significantly lower than that in the control group (RR = 0.50, 95% CI = 0.28–0.89, P = 0.02), which was consistent with the original conclusion.

In the subgroup analysis of the specific types of chemotherapy combined, one study (27) using multiple chemotherapy regimens was excluded. A total of 2044 patients were included, with 1027 in the experimental group and 1017 in the control group. Due to the large heterogeneity within the SFI + GP group (P = 0.02, I^2 = 58%), a REM was used. Results of SFI + GP (RR = 0.63, 95% CI = 0.46–0.87, P = 0.005, I^2 = 58%), SFI + NP (RR = 0.67, 95% CI = 0.54–0.82, P = 0.0001, I^2 = 0%), SFI + TP (RR = 0.45, 95% CI = 0.33–0.62, P < 0.00001, I^2 = 0%), and SFI + NC (RR = 0.67, 95% CI = 0.48–0.93, P = 0.02) suggested that SFI combined with PBC significantly improved thrombocytopenia. There was no significant difference between the groups (P = 0.33, I^2 = 13%). There was also no significant alleviation of thrombocytopenia in patients with the SFI + DP regimen (RR = 0.67, 95% CI = 0.37–1.20, P = 0.18, I^2 = 33%).

The SFI + GP subgroup did not pass the heterogeneity test (P = 0.02, I^2 = 58%). After excluding three studies (34, 37, 45), I^2 decreased to 0%, indicating that these three articles were the main source of heterogeneity. In the Bao study (34), heterogeneity may have been introduced because the patients included were too old (over 65 years old), and the hematopoietic function of bone marrow was easily restricted, resulting in slow platelet production, or may have been related to taking anti-platelet and blood-activating drugs at the same time. In the Zhao study (37), the dosage of cisplatin was high (80–100 mg/m^2), and many cycles were used to evaluate the efficiency; most other studies observed 2 cycles to evaluate the efficacy, whereas they study observed 2–6 cycles and patients may have stopped treatment because they could not tolerate the continued treatment. In the Luo study (45), patients included were in stage IV, most of the basic hematopoietic levels were poor, and the SFI dosage was not specified. The results after exclusion of these studies were consistent with the original conclusion.

4.4.4 Simple bone marrow suppression

Three studies (28, 30, 62) only described simple bone marrow suppression and did not specify the specific type of bone marrow suppression. These studies included a total of 253 patients, with 125 cases in the experimental group and 128 cases in the control group. Heterogeneity test analysis showed that there was no heterogeneity among the three studies (P = 0.53, I^2 = 0%), so the FEM was used for combined analysis. The results showed that the incidence of simple bone marrow suppression in the experimental group was approximately 45% lower than that in the control group (RR = 0.55, 95% CI = 0.41–0.73; combined effect size test Z = 4.01, P < 0.0001), indicating that SFI combined with PBC could significantly improve the incidence of simple bone marrow suppression.

4.5 Digestive tract reaction

4.5.1 Nausea and vomiting

Eighteen studies (29, 30, 35, 37, 49–53, 55, 59–61, 64, 65, 68, 69) observed the occurrence of nausea and vomiting with detailed data, including a total of 1445 patients, with 719 in the experimental group and 726 in the control group. Heterogeneity test analysis showed that there was significant heterogeneity among the 18 studies (P = 0.0002, I^2 = 63%), so the REM was used for analysis. The overall analysis results showed that the incidence of nausea and vomiting in the experimental group was approximately 37% lower than that in the control group (RR = 0.63, 95% CI = 0.52–0.77; combined effect size test Z = 4.63, P < 0.00001). Therefore, the incidence of nausea and vomiting in the SFI + PBC group was significantly lower than that in the PBC group.

In the subgroup analysis of single-cycle SFI medication days, treatment for 8–14 d (RR = 0.65, 95% CI = 0.51–0.84, P = 0.001, I^2 = 71%) and 15–28 d (RR = 0.59, 95% CI = 0.46–0.76, P < 0.0001, I^2 = 11%) could reduce the incidence of nausea and vomiting, and there was no significant difference between the groups (P = 0.58, I^2 = 0%).

In the subgroup analysis stratified by the specific type of chemotherapy, SFI + TP (RR = 0.40, 95% CI = 0.22–0.72, P = 0.003, I^2 = 77%), SFI + NC (RR = 0.70, 95% CI = 0.53–0.94, P = 0.02), and SFI + AP (RR = 0.60, 95% CI = 0.40–0.89, P = 0.01) subgroups had a significant effect on reducing nausea and vomiting in patients compared with TP, NC, and AP chemotherapy alone. The subgroup results of SFI + GP (RR = 0.53, 95% CI = 0.24–1.19, P = 0.12, I^2 = 73%), SFI + NP (RR = 0.75, 95% CI = 0.54–1.04, P = 0.08, I^2 = 65%), SFI + DP (RR = 1.01, 95% CI = 0.61–1.67, P = 0.97), and SFI + TC (RR = 0.71, 95% CI = 0.26–1.94, P = 0.51) showed that SFI had no advantage in reducing the incidence of nausea and vomiting compared with GP, NP, DP, and TC chemotherapy regimens.

Four subgroups did not pass the heterogeneity test (overall combined P = 0.0002, I^2 = 63%): the 8–14 d SFI single-cycle subgroup (P < 0.0001, I^2 = 71%) and GP (P = 0.02, I^2 = 73%), NP (P = 0.01, I^2 = 65%), and TP (P = 0.002, I^2 = 77%) chemotherapy subgroups. After removing four studies (46, 59, 64, 68), the overall combined I^2 decreased to 0%, indicating that these four studies were the main source of heterogeneity. In the study performed by Wang (46), the heterogeneity may have been because the range of KPS scores of the enrolled patients was not described. In the Zheng (59) study, the cisplatin dosage was smaller than other studies (25 mg/m^2) and the occurrence of nausea and vomiting treatment group/control group was 15/4, indicating there may have been a data entry

error. Finally, Luo (64) and Zhang (68) were the only two studies to use the TP chemotherapy regimen. The heterogeneity in this subgroup may have been derived from the different pathological types of the included patients. After excluding these two studies, the conclusion was consistent with the original analysis (RR = 0.70, 95% CI = 0.62–0.78, P < 0.00001, I^2 = 0%).

4.5.2 Diarrhea

Five studies (29, 30, 35, 46, 51) reported the incidence of diarrhea with detailed data on a total of 463 patients, including 229 in the experimental group and 234 in the control group. Heterogeneity test analysis showed that there was no significant heterogeneity among the five studies (P = 0.11, I^2 = 47%), hence, the FEM was used for combined analysis. The results of meta-analysis showed that the incidence of diarrhea in the experimental group was approximately 52% lower than in the control group (RR = 0.48, 95% CI = 0.37–0.64; combined effect size test Z = 5.09, P < 0.00001). Therefore, the incidence of diarrhea in SFI + PBC treatment of advanced NSCLC was lower than that of PBC alone.

4.5.3 Simple gastrointestinal reaction

Eleven studies (31, 32, 34, 39, 41, 42, 48, 57, 66, 67, 70) observed the occurrence of simple gastrointestinal reactions and had detailed data for a total of 827 patients, including 419 in the experimental group and 408 in the control group. Heterogeneity test analysis showed that there was significant heterogeneity among the 11 studies (P < 0.00001, I^2 = 78%), so the REM was used for combined analysis. The overall results showed that the incidence of simple gastrointestinal reactions in the experimental group was approximately 37% lower than in the control group (RR = 0.63, 95% CI = 0.49–0.80; combined effect size test Z = 3.67, P = 0.0002), indicating that the incidence of simple gastrointestinal reactions in SFI + PBC was significantly lower than that in PBC alone. However, the heterogeneity within the subgroup was large, with few studies included in the analysis, limiting the credibility of the conclusion.

In the subgroup analysis stratified by the number of days of single-cycle SFI medication, no significant improvement of simple gastrointestinal reactions was observed in the 0–7 d group (RR = 0.71, 95% CI = 0.36–1.43, P = 0.34, I^2 = 82%). Whereas, a significant improvement was observed in the 8–14 d (RR = 0.56, 95% CI = 0.36–0.88, P = 0.01, I^2 = 53%) and 15–28 d (RR = 0.63, 95% CI = 0.40–0.99, P = 0.04, I^2 = 85%) subgroups. This suggested that prolonging the days of medication significantly improved the simple gastrointestinal reaction.

In the subgroup analysis of the specific chemotherapy types combined, one study (70) with multiple chemotherapy regimens was excluded. A total of 767 patients were included, with 389 in the experimental group and 378 in the control group. SFI + GP (RR = 0.64, 95% CI = 0.43–0.96, P = 0.03, I^2 = 78%) and SFI + TP (RR = 0.45, 95% CI = 0.30–0.66, P < 0.0001, I^2 = 0%) showed significant differences between the experimental group and the control group. However, no significant difference was observed with SFI + NP (RR = 0.59, 95% CI = 0.35–1.00, P = 0.05), SFI + DP (RR = 0.66, 95% CI = 0.40–1.09, P = 0.10, I^2 = 49%), and SFI + NC (RR = 0.96, 95% CI = 0.82–1.14, P = 0.67), suggesting that SFI had little effect on the simple digestive tract reaction of NP, DP, and NC chemotherapy. Only one study was included that used either SFI + NP or SFI + NC, which may have affected the accuracy of the conclusion.

Due to the heterogeneity among the 11 studies, individual studies were excluded one by one for re-analysis. Three studies were identified as the main sources of heterogeneity: removing Yu (31) decreased the I^2 of the 8–14 d SFI single-cycle medication subgroup from 57% to 0%; removing Wang (48) decreased the I^2 of the 15–18 d subgroup from 85% to 0%; removing Huang (39) decreased the I^2 of the SFI + GP subgroup from 78% to 0%; and removing both Huang and Wang decreased the overall I^2 from 78% to 0%. The heterogeneity introduced by Yu (31) may have been because patients were included with KPS scores less than 60, which was lower than other groups and easier to impact digestive tract reaction. Compared with other studies, Huang (39) used a shorter SFI single-cycle (7 d), the effect of Yiqi Fuzheng Jianpi was not obvious, and the dose of cisplatin was high (100 mg/m^2). The study by Wang (48), the only study using the NC protocol, was classified as high-risk as the biological sex and number of pathological types did not match the total number, indicating that there may be counting errors. The conclusion after excluding these studies was consistent with the original conclusion (RR = 0.52, 95% CI = 0.44–0.62, P < 0.00001, I^2 = 0%).

4.6 Publication bias analysis

More than 10 studies were included that documented the ORR, DCR, and KPS improvement rate, incidence of hemoglobin reduction, leukopenia, thrombocytopenia, nausea, and vomiting, and simple gastrointestinal reaction of SFI combined with PBC in the treatment of advanced NSCLC. A funnel plot was plotted based on the data of these studies, with the RR value as the abscissa and the logarithmic standard error SE (logRR) of RR value as the ordinate (Figure 9). The funnel plot showed asymmetry and skewed distribution, suggesting that there may be potential publication bias or low methodological quality, which may be related to the difficulty of publishing negative results, small sample size of some studies, different chemotherapy regimens of the control group, different intervention doses, and different courses of treatment.

4.7 Sensitivity analysis

Eight high-risk studies (29, 35, 43, 48, 55, 60, 61, 65) were excluded from sensitivity analysis, and the ORR results did not change significantly. The difference in the effective rate of SFI combined with PBC for the treatment of advanced NSCLC was statistically significant (RR = 1.26, 95% CI = 1.17–1.37, P < 0.00001). After the exclusion of 16 studies (31, 40, 48, 52–57, 59–61, 64, 67, 68, 70) published before 2010, the ORR results did not significantly change (RR = 1.29, 95% CI = 1.18–1.41, P < 0.00001), indicating that the meta-analysis results were stable and the conclusions were reliable.

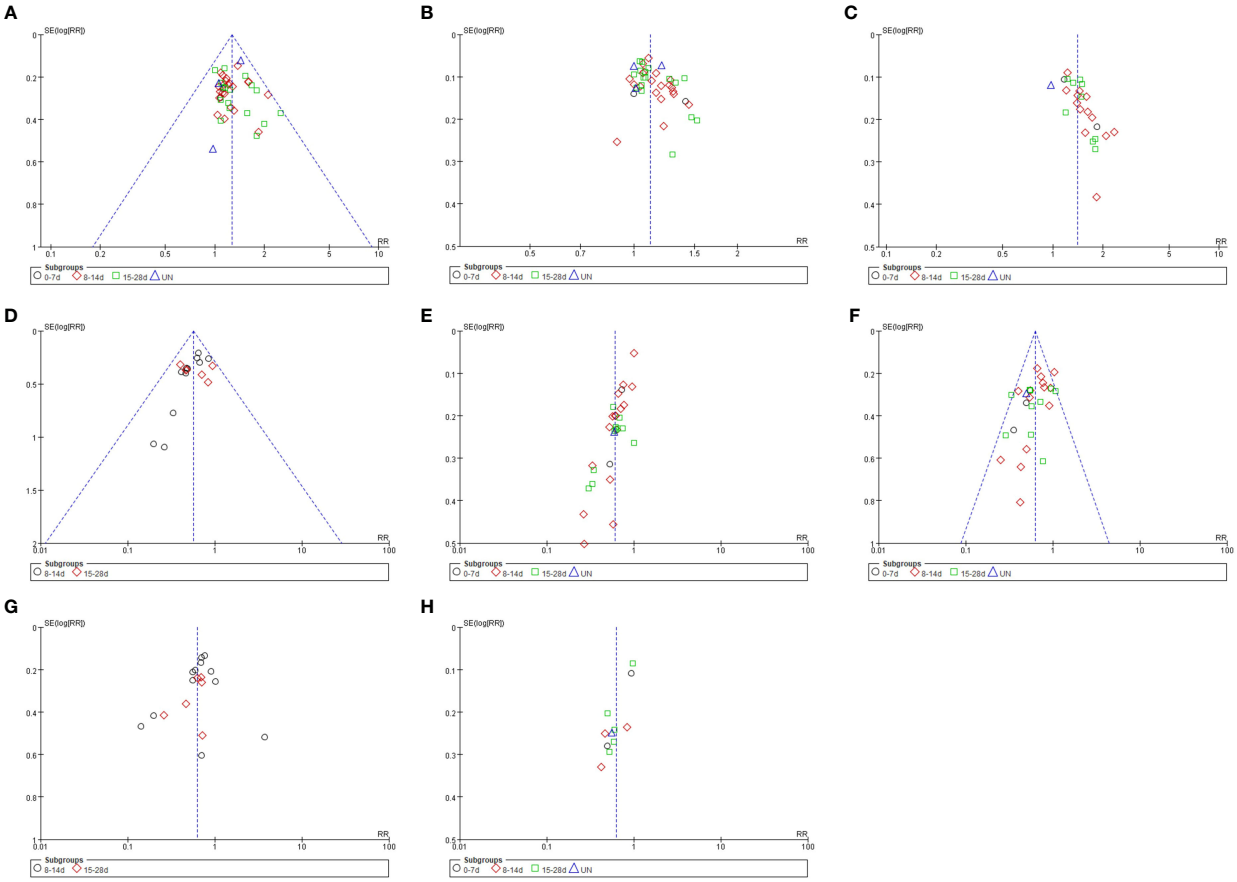

FIGURE 9
Funnel plot of analysis results. **(A)** ORR; **(B)** DCR; **(C)** KPS; **(D)** Hemoglobinia; **(E)** Leukopenia; **(F)** Thrombocytopenia; **(G)** Nausea and Vomiting; **(H)** Gastrointestinal Reaction.

5 Discussion

5.1 Efficacy analysis

5.1.1 Overall analysis

This paper systematically evaluated the efficacy and safety of SFI combined with PBC for the treatment of advanced NSCLC. The results showed that SFI combined with PBC had advantages in improving ORR, DCR, and quality of life and could improve clinical symptoms. At the same time, SFI adjuvant chemotherapy could reduce bone marrow suppression such as hemoglobin reduction, leukopenia, and thrombocytopenia, as well as gastrointestinal adverse reactions such as nausea, vomiting, and diarrhea, which helps to improve patient compliance and treatment confidence. In general, SFI synergistic chemotherapy reduced toxicity and increased efficiency, which was consistent with previous studies. Sensitivity analysis suggested that the results of the meta-analysis were stable. Modern pharmacological studies have shown that the Astragalus polysaccharide in *A. membranaceus* has immune regulation effects and can activate non-specific immunity. It may affect the tumor inflammatory microenvironment through the TLR4/MyD88/NF-κB signaling pathway and regulation of extracellular matrix (71), affecting tumor cell apoptosis and tissue metabolism. Ginsenosides in *C. pilosula* have been shown to improve macrophage function, reduce fatigue, inhibit tumor angiogenesis, and regulate nerves. By inhibiting the expression of the Keap1-Nrf2/ARE signaling pathway, STAT3/c-myc pathway, and key enzymes of glycolysis, ginsenosides can significantly inhibit the proliferation of NSCLC cells, promote apoptosis (72, 73), effectively reduce the level of VEGF in serum, and reverse drug resistance (74). The combination of *A. membranaceus* and *C. pilosula* plays a role in reducing toxicity and increasing efficiency and comprehensive regulation in tumor treatment, which embodies the idea of "strengthening the body resistance and eliminating pathogenic factors" in traditional Chinese medicine. SFI has been shown to reduce the expression of VEGF and SIL-2R, promote the expression of IL-2 and IFN-γ, improve the cellular immune function of patients (increase of NK, $CD3^+$, and $CD4^+$ cells), reduce the levels of CEA, CA125 and CA19-9, and exert anti-tumor effects, prolonging survival (75, 76). Studies have shown that Astragalus membranaceus can enhance musclar hypertrophy by increasing PI3K/Akt/mTOR signaling phosphorylation, increase the diameter and thickness of myotubes by 1.16 times,and maintain muscle structure and force production (77). Therefore, SFI can be used for clinical adjuvant chemotherapy for the treatment of NSCLC, especially for patients with lung and spleen qi deficiency.

5.1.2 Subgroup analysis

This study conducted a stratified analysis based on the number of days of single-cycle SFI medication, especially in improving the quality of life of patients with significant time correlation. According to the number of days of single-cycle SFI medication, we divided treatments into three subgroups: 0–7, 8–14, and 15–28 d. The results showed that 0–7 d subgroup had no significant improvement in ORR, DCR, KPS, and simple gastrointestinal reaction, but the improvement of thrombocytopenia was better than that of single-cycle long-term medication. Treatment for 8–14 d was advantageous in improving KPS, hemoglobin reduction incidences, and gastrointestinal adverse reactions. Treatment for 15–28 d had the most significant improvement in ORR, leukopenia incidences, and nausea and vomiting incidences. Therefore, prolonging the single-cycle SFI medication time could improve multiple outcome indicators. Based on these findings, we recommend that the single-cycle SFI medication time should be 15–28 d, which was the most beneficial length for tumor adjuvant therapy. The second recommendation is 8–14 d, which was most beneficial for improving the quality of life of patients and reducing adverse reactions. SFI combined with PBC could significantly reduce the incidence of bone marrow suppression (including the incidence of hemoglobin reduction, leukopenia, and thrombocytopenia), regardless of the length of single-cycle medication. This may be due to the direct protection of hematopoietic stem cells by astragalus polysaccharides and the promotion of hematopoietic stem cell development by regulating FOS gene expression (78). Animal experiments have shown that ginsenosides promote hematopoietic cell proliferation and differentiation by regulating GATA transcription factors in mouse bone marrow cells (79), which is consistent with the conclusions of this and previous studies (80). The results suggest that SFI has good clinical application value in adjuvant PBC for improving bone marrow suppression (Table 5).

According to the subgroup analysis of the specific chemotherapy type, SFI combined with GP, NP, TP, and GC significantly improved the curative effect and the quality of life of patients. SFI combined with GP, NP, TP, DP, and NC regimens could significantly reduce bone marrow suppression. For ORR, SFI combined with GP, GC, and TP groups had the most obvious advantages. For DCR, the effect was greatest in the SFI + TP group, while the combination with NC, DP, and TC was not recommended. In terms of improving the quality of life, SFI combined with TP, GC, and TC showed obvious advantages. However, GC and TC regimens were reported in only one study each, therefore further studies are required to confirm the beneficial effects. In terms of reducing myelosuppression, the SFI + TP regimen had a clear advantage, while SFI combined with NP, DP, and NC regimens were not recommended. In general, SFI was the most effective for patients treated with the TP regimen, with obvious significance for reducing bone marrow suppression and improving gastrointestinal reactions. However, the outcome indicators of the literature included in this study are quite different, and some have no relevant data, so it is impossible to make a comprehensive comparative analysis.

In summary, combining results for ORR, DCR, improvement of quality of life, and adverse reactions, we recommend a single-cycle of SFI medication for 15–28 d combined with the TP regimen to achieve the most beneficial outcomes (Figure 10).

The heterogeneity test analysis showed that, except for the two studies (54, 59) in the leukocyte group, heterogeneity was not obvious in the short-term efficacy, quality of life evaluation, and bone marrow suppression. However, the heterogeneity of digestive tract reaction was obvious. This may be because the dosage of chemotherapy was quite different, digestive tract reactions have individual differences, and it is susceptible to non-chemotherapy factors. However, SFI adjuvant chemotherapy still had a clear remission effect on gastrointestinal adverse reactions.

5.2 Limitations of this study

There are a number of limitations to the meta-analysis based on the chemotherapy regimen. (1) The vast majority of source reports use more male patients than women, and the ratio of male to female will affect the results. However, most of the current experimental designs do not take into account biological sex differences, so this article may have certain limitations on biological sex factors. In the subsequent design of RCTs, male and female outcome indicators should be described separately to further explore the biological sex differences in SFI efficacy. (2) Along with stage and metastases, weight loss is closely tied to mortality in patients with NSCLC. But the studies did not report post-treatment weight, and most of the studies only had baseline data on weight. Therefore the meta-analysis could not summarize the weight change before and after treatment.The inability to report whether SFI combined with chemotherapy has any effect on the prevention of weight loss is one of the limitations of this paper.(3)The literature included in the study was limited to single-center studies, and no reference was made to the basis of sample size estimation. The minimum sample size was 36, and the median sample size was 80. Often, the number of studies included in the subgroup analysis was small and there was a certain degree of heterogeneity among the studies. This possibly resulted in bias in the study results and reduced test efficacy. (4) Random allocation was mentioned in the included literature, but 23 studies did not describe the specific random sequence generation method. Except for one study using the envelope method, there was no mention of whether allocation concealment was implemented. Therefore, there were some limitations in methodology, which meant the existence of selective bias could not be ruled out and may have affected the accuracy of the results. (5) Implementing blind methodology with randomization in clinical trials of chemotherapy and traditional Chinese medicine injection is difficult, and this method was not mentioned in the literature. This means the results may be subjectively affected by patients, implementers, and outcome measurers, causing implementation and measurement bias. (6) Literature bias analysis showed the inverted funnel plots of KPS, leukopenia incidence, and

TABLE 5 Result summary table.

Group	ORR	DCR	KPS	Hemoglobinia	Leukopenia	Thrombo-cytopenia	Myelosup-pression	Nausea and vomiting	Diarrhea	Gastrointestinal Reaction
Subgroups divided according to the duration of single-cycle SFI										
0-7d	N	N	N	U	Y	Y	Unclassified	U	Unclassified	N
8-14d	Y	Y	Y	Y	Y	Y		Y		Y
15-28d	Y	Y	Y	Y	Y	Y		Y		Y
UN	Y	N	U	U	Y	U		U		U
Total	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Heterogeneity	P=0.98 I^2=0%	P=0.35 I^2=6%	P=0.04 I^2=35%	P=0.78 I^2=0%	P<0.00001 I^2=77%	P=0.12 I^2=25%	P=0.53 I^2=0%	P=0.0002 I^2=63%	P=0.11 I^2=47%	P<0.00001 I^2=78%
Test for subgroup differences	P=0.73 I^2=0%	P=0.93 I^2=0%	P=0.02 I^2=70.4%	P=0.87 I^2=0%	P=0.81 I^2=0%	P=0.36 I^2=6.6%	U	P=0.58 I^2=0%	U	P=0.93 I^2=0%
Subgroups divided according to the chemotherapy plan										
SFI+GP/GP	Y	Y	Y	Y	Y	Y	Unclassified	N	Unclassified	Y
SFI+NP/NP	Y	Y	Y	Y	Y	Y		N		N
SFI+TP/TP	Y	Y	Y	Y	Y	Y		Y		Y
SFI+DP/DP	N	N	N	Y	Y	Y		N		N
SFI+NC/NC	N	N	Y	N	Y	Y		Y		N
SFI+GC/GC	Y	U	Y	U	U	U		U		U
SFI+AP/AP	N	N	U	U	N	N		Y		U
SFI+TC/TC	N	N	Y	U	U	U		N		U
Total	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Test for subgroup differences	P=0.81 I^2=0%	P=0.14 I^2=38.4%	P=0.16 I^2=34.8%	P=0.88 I^2=0%	P=0.47 I^2=0%	P=0.33 I^2=13.0%	U	P=0.36 I^2=9.5%	U	P=0.003 I^2=75.4%

Y, statistically significant difference between the test group and the control group; N, no statistically significant difference between the test group and the control group; U, no relevant data in the included literature, or only 1 piece of literature, which could not be analyzed. GP, gemcitabine + cisplatin; NP, vinorelbine + cisplatin; TP, paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin; DP, docetaxel + cisplatin; NC, vinorelbine + carboplatin; GC, gemcitabine + carboplatin; AP, pemetrexed + cisplatin; TC, paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin. Objective remission rate ORR=(CR+PR)/total cases×100%; Disease control rate DCR=(CR+PR+SD)/total cases×100%; KPS improvement rate=(number of improved cases + number of stable cases)/total cases.

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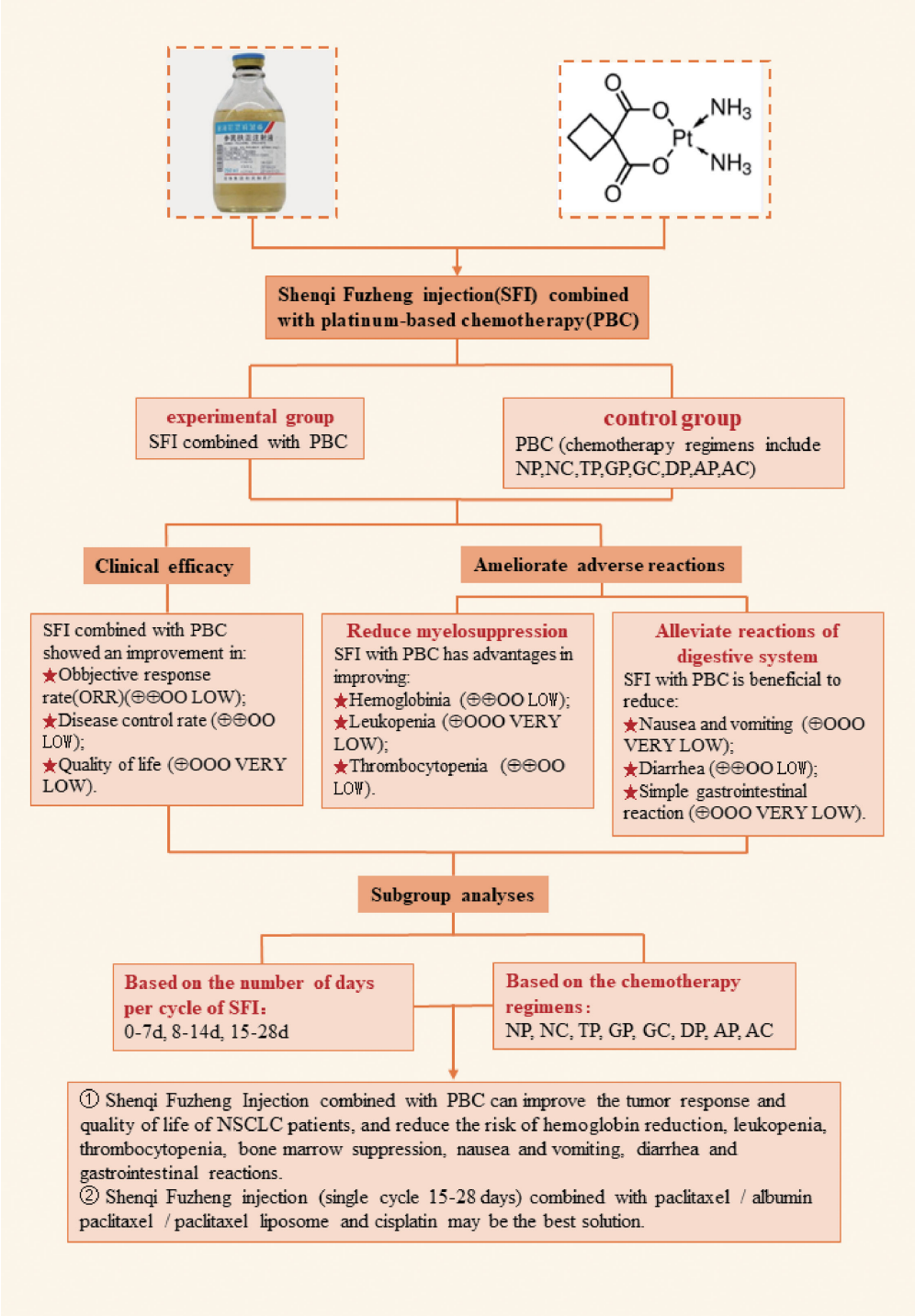

FIGURE 10
SFI combined with PBC for non-small cell lung cancer. NP, vinorelbine + cisplatin; NC, vinorelbine + carboplatin; TP, paclitaxel/albumin paclitaxel/paclitaxel liposome + cisplatin; TC, paclitaxel/albumin paclitaxel/paclitaxel liposome + carboplatin; GP, gemcitabine + cisplatin; GC, gemcitabine + carboplatin; DP, docetaxel + cisplatin; DC, docetaxel + carboplatin; AP, pemetrexed + cisplatin; AC, pemetrexed + carboplatin.

thrombocytopenia incidence were asymmetrically distributed, suggesting that there may be publication bias; the efficacy of SFI combined chemotherapy needs further study and verification. (7) No adverse reactions caused by SFI were noted in the included literature; observations of SFI safety in clinical application needs to be improved. In summary, the methodology and research quality of the literature included in this study were generally low. The above limitations may reduce the stability and reliability of the results, and affect the recommendation level and evidential support of the system evaluation.

5.3 Future research possibilities

There are a number of areas that would benefit from further research. (1) In subsequent studies we can design high-quality RCTs, using weight change and/or cachexia in patients with NSCLC as observational indicators to explore the preventive and curative effects of SFI and to observe whether patients with weight loss respond differently to treatment than controls. (2) Currently there are more RCTs of SFI combined with platinum-based chemotherapy in China, while there are fewer RCTs of combined radiotherapy. At the same time, in China, the treatment of NSCLC with SFI is mostly combined in the chemotherapy stage, while the radiotherapy stage is mostly treated with compound matrine injection. Therefore, the systematic evaluation of SFI combined with radiotherapy for NSCLC has certain research value. (3) To conclusively verify the results of the existing clinical RCTs, studies need to further expand the sample size, improve the quality of clinical trials, conduct a standardized and comprehensive design, or carry out high-quality multicenter randomized double-blind trials. (4) Strict randomization and allocation concealment methods should be used in clinical research, and RCTs should incorporate explicit reporting of randomization implementation methods when conducting systematic evaluations. When the double-blindness of subjects and researchers cannot be achieved, blinding of evaluators can be implemented to further improve the objectivity of the results. (5) The dosage, frequency, and cycle of SFI and chemotherapy drugs should be standardized to reduce heterogeneity. This will facilitate accurate comparisons to understand the role of SFI. (6) Adverse reactions should be fully reported and the clinical safety of traditional Chinese medicine injections requires greater attention to provide evidence for rational drug use. (7) RCT reports should be carried out according to the Consort standard as far as possible (81), and the outcome indicators should be reported truthfully to obtain more reliable research results. (8) Long-term follow-up studies should be carried out following clinical trials to report comprehensive and meaningful outcome and endpoint indicators. Further research should be carried out on whether combined treatment can improve the long-term survival rate, efficacy, and the quality of life of patients, for scientifically guided clinical decision-making. (9) The results of this study showed that, compared with other chemotherapy regimens, the efficacy of SFI combined with TP regimen was more obvious in all aspects. Investigations into whether there is a specific mechanism that increases the synergy of SFI with TP would be valuable.

5.4 Conclusion

In summary, the incidence and mortality of lung cancer are high in the world. Platinum-based doublet chemotherapy is the first-line standard treatment, but the efficacy of chemotherapy is limited and the side effects are large, which affects the quality of life of patients.The treatment of advanced NSCLC was improved with by using SFI combined with PBC compared with PBC alone. SFI combined with PBC could significantly improve the clinical efficiency and quality of life, while reducing adverse reactions and improving thee safety. Use of SFI with PBC has high research value and wide application prospects. A total of 44 RCTs were included in this study, with a total of 3460 patients. Compared with the existing research, the latest research is supplemented, and more comprehensive search and inclusion studies are included.So the results were more objective. In this paper, subgroup analysis was carried out according to the number of days of single-cycle SFI medication and the combined chemotherapy regimen, and the optimal number of days of single-cycle SFI medication and the optimal chemotherapy regimen combined with SFI were obtained. This is not perfect in previous studies, but also the most significant improvement in this paper.However, this study has limitations such as low quality of the included literature, small sample size, and insufficient standardization and rigorous experimental design. In order to further verify SFI efficacy and adverse reactions, multicenter, large sample, scientific, and standardized RCTs and basic research are needed to provide higher quality medical evidence.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

Conception and design: WH, ZL. Provision of study material or patients: All authors. Collection and assembly of data: All authors. Data analysis and interpretation: CQ, SH, DW, KC, ZW, XW, XM. Manuscript writing: CQ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1198768/full#supplementary-material

References

1. Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. *Ann Glob Health* (2019) 85:8–53. doi: 10.5334/aogh.2419

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca-Cancer J Clin* (2021) 71:209–49. doi: 10.3322/CAAC.21660

3. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends–An update. *Cancer Epidemiol Biomarkers Prev* (2016) 25:16–27. doi: 10.1158/1055-9965.EPI-15-0578

4. Narjust D, Rafael SD, Julian RM. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. *Mayo Clin Proc* (2019) 94:1623–40. doi: 10.1016/j.mayocp.2019.01.013

5. Hao J, Li N, Chen WQ, Wu N, Shen HB, Jiang Y, et al. China guideline for the screening and early detection of lung cancer(2021,Beijing). *China Cancer[Chinese Journal]* (2021) 30:81–111. doi: 10.11735/j.issn.1004-0242.2021.02.A001

6. National Cancer Institute. *SEER stat fact sheets: lung and bronchus cancer* . Available at: http://seer.cancer.gov/statfacts/html/lungb.html (Accessed December 22,2016).

7. de Castro J, Tagliaferri P, de Lima VCC, Ng S, Thomas M, Arunachalam A, et al. Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer(NSCLC): PIvOTAL study. *Eur J Cancer Care* (2017) 26:e12734. doi: 10.1111/ecc.12734

8. Mukherjee PK, Shiv B, Ranjit KH, Sayan B, Subhadip B. Paradigm shift in natural product research: traditional medicine inspired approaches. *Phytochem Rev* (2017) 16:803–26. doi: 10.1007/s11101-016-9489-6

9. Wang SM, Long SQ, Wu WY. Application of traditional chinese medicines as personalized therapy in human cancers. *Am J Chin Med* (2018) 46:953–70. doi: 10.1142/S0192415X18500507

10. Jian TW, Li YH. Anti-vascular endothelial growth factor (VEGF) herbal medicine associated with non-small cell lung cancer. *MEDS Clin Med* (2022) 3:64–73. doi: 10.23977/MEDSC.2022.030212

11. Zhang X, Guo QJ, Li CH, Liu R, Xu T, Jin ZC, et al. Immortal time bias-corrected effectiveness of traditional` chinese medicine in non-small cell lung cancer (C-EVID): A prospective cohort study. *Front Oncol* (2022) 12:845613. doi: 10.3389/FONC.2022.845613

12. Sugimoto K, Liu J, Li M, Song Y, Zhang C, Zhai Z, et al. Neuroprotective effects of shenqi fuzheng injection in a transgenic SOD1-G93A mouse model of amyotrophic lateral sclerosis. *Front Pharmacol* (2021) 12:701886. doi: 10.3389/fphar.2021.701886

13. Qiao C, Hu S, Wang D, Cao K, Wang Z, Wang X, et al. Systematic review of shenqi fuzheng injection combined with chemotherapy for treatment of breast cancer. *China J Chin Mater Med[Chinese Journal]* (2019) 44:589–96. doi: 10.19540/j.cnki.cjcmm.20180925.003

14. Xu R, Lin L, Li Y, Li Y. ShenQi FuZheng Injection combined with chemotherapy in the treatment of colorectal cancer: A meta-analysis. *PloS One* (2017) 12:e0185254. doi: 10.1371/journal.pone.0185254

15. Zhang H, Chen T, Shan L. ShenQi Fu Zheng injection as an adjunctive treatment to chemotherapy in breast cancer patients: a meta-analysis. *Pharm Biol* (2019) 57:612–24. doi: 10.1080/13880209.2019.1660383

16. Li X, Cui YY, Dong Q, Jia M. Clinical study on shenqi fuzheng injection in the treatment of cancer-related fatigue. *World J Integr Tradit Chin West Med[Chinese Journal]* (2020) 15:1967–71. doi: 10.13935/j.cnki.sjzx.201102

17. Leung EL, Wu QB. Concurrent use of herbal products with prescription drugs is a double-Edged sword and evidence-Based medicine contributes to reshaping the practice. *Pharmacol Res* (2019) 141:609–10. doi: 10.1016/j.phrs.2019.01.033

18. Wang LX, Xie YM, Ai QH, Feng Q. Registration of 30026 cases of Shenqi Fuzheng injection combined with other drugs in real world. *China J Chin Mater Med [Chinese Journal]* (2016) 41:4500–9. doi: 10.4268/cjcmm20162405

19. Wang LX, Xie YM, Ai QH, Xu WF. Clinical safety studies based on 30 026 post-marketing cases of Shenqi Fuzheng injection by intensive hospital monitoring nested NCCS. *China J Chin Mater Med[Chinese Journal]* (2015) 40:4739–47. doi: 10.4268/cjcmm20152404

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement:An updated guideline for reporting systematic reviews. *Syst Rev-London* (2021) 372:n71. doi: 10.1186/S13643-021-01626-4

21. James K, Eisenhauer E, Christian M, Terenziani M, Vena D, Muldal A, et al. Measuring response in solid tumors: unidimensional versus bidimensional measurement. *J Natl Cancer I* (1999) 91:523–8. doi: 10.1093/jnci/91.6.523

22. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline(Version 1.1). *Eur J Cancer* (2008) 45:228–47. doi: 10.1016/j.ejca.2008.10.026

23. Wang S, Wang XQ, Zhou T, Hu SH, Tian PY, Li Z, et al. Effectiveness and safety of chinese herbal injections combined with fluoropyrimidine and oxaliplatin-based chemotherapy for advanced colorectal cancer:A systematic review and meta-analysis of 63 randomized controlled trials. *J Cancer* (2021) 12:7237–54. doi: 10.7150/JCA.60895

24. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer-Am Cancer Soc* (1981) 47:207–14. doi: 10.1002/1097-0142(19810101)47:1<207::AID-CNCR2820470134>3.0.CO;2-6

25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical Res ed.)* (2011) 343:d5928. doi: 10.1136/bmj.d5928

26. Atkins D, Best D, Briss PA, Eccles M, Falck- YY, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* (2004) 328:1490. doi: 10.1136/bmj.328.7454.1490

27. Ding CJ, Yang L. Shenqi Fuzheng injection combined with chemotherapy in treatment of 35 cases of advanced non-small cell lung cancer. *Shaanxi J Tradit Chin Med[Chinese Journal]* (2012) 33:30–2. doi: 10.3969/j.issn.1000-7369.2012.01.016

28. Qi SG, Qiao JL. Clinical analysis of Shenqi Fuzheng injection in the treatment of bone marrow suppression after chemotherapy for advanced non-small cell lung cancer. *Orient Med Diet[Chinese Journal]* (2019) 20:27–8.

29. Ren JS. Preventive effect of Shenqi Fuzheng injection on adverse reactions of chemotherapy in the treatment of advanced non small cell lung cancer. *Mod J Integr Tradit Chin West Med[Chinese Journal]* (2015) 24:1286–9. doi: 10.3969/j.issn.1008-8849.2015.12.011

30. Wang WM, Kong FL, Li CF, Yao RJ, Cheng YX, Zhang LJ. The treatment of Shenqifuzheng injection combined with docetaxel and cisplatin for advanced lung cancer. *Anhui Med Pharm J[Chinese Journal]* (2011) 32:939–41. doi: 10.3969/j.issn.1000-0399.2011.07.025

31. Yu F, Li K. Clinical observation of Shenqi Fuzheng injection assisted chemotherapy in treatment of non-small cell lung cancer. *Chin J Integr Med[Chinese Journal]* (2007) 27:166–7. doi: 10.3321/j.issn:1003-5370.2007.02.020

32. Ma CG, Gan BN, Zhang XF, Zhang XH, Pu Y. Curative effect of Shenqi Fuzheng injection combined with chemotherapy on senile advanced non-small cell lung cancer. *Chin J Sch Doct[Chinese Journal]* (2013) 27:368–9. doi: 10.3969/j.issn.1004-5775.2013.06.008

33. Shan HG, Pan JQ, Zhou XF. Effect evaluation on DP regimen combined with Shenqifuzheng injection in treating 40 cases of non-Small cell lung cancer. *China Pharm[Chinese Journal]* (2014) 23:25–6. doi: CNKI:SUN:YYGZ.0.2014-24-014

34. Bao Z, He YY. Effects of Shenqi Fuzheng injection combined with chemotherapy on peripheral blood T lymphocyte subsets and tumor markers in elderly patients with

advanced non-Small cell lung cancer. *Chin J Gerontol[Chinese Journal]* (2019) 39:2359–61. doi: 10.3969/j.issn.1005-9202.2019.10.019

35. Gui YX, Tian GF. A prospective randomized controlled clinical study of Shenqi Fuzheng injection combined with gemcitabine and cisplatin in the treatment of advanced NSCLC. *J Chin Prescr Drug[Chinese Journal]* (2016) 14:53–4. doi: 10.3969/j.issn.1671-945X.2016.07.035

36. Yao DJ, Cai Y, Chen Y. Clinical observation of Shenqi Fuzheng injection combined with GP scheme in treatment of advanced non-Small cell lung cancer. *Chin J Clin Res[Chinese Journal]* (2013) 26:1378–9.

37. Zhao ZY, Ma YL. Effect of Shenqi Fuzheng injection on the adverse reactions of chemotherapy in patients with advanced non-Small cell lung cancer. *Med J Wuhan Univ[Chinese Journal]* (2014) 35:744–6. doi: 10.14188/j.1671-8852.2014.05.062

38. Zhang LM, Chen JH, Wang W, Wen XP, Zhou WW, Yi HH. Clinical effect of Shenqi Fuzheng injection on advanced non-small cell lung cancer. *World Clin Med [Chinese Journal]* (2017) 11:113–4.

39. Huang AX, Yao GX, Chen Y, Qian W, Pu LM, Lu LW. Efficacy of Shenqifuzheng injection combined PG therapy in treatment of non-small cell lung cancer. *Chin J Biochem Pharm[Chinese Journal]* (2014) 34:88–9+92. doi: CNKI:SUN:SHYW.0.2014-01-032

40. Song Y, Jia SW, Sun WZ. Injection Shengqifuzheng plus combined with gemcitabine plus carboplatin cure intermediate and advanced NSCLC in the aged. *Proc Chin Geriatric Oncol Congress second CGOS Annu Conf* (2007), 376–80.

41. He WX. Effect of Shenqi Fuzheng injection assisted GP regimen on advanced non-small cell lung cancer. *J Pract Clin Integr Tradit Chin West Med[Chinese Journal]* (2021) 21:44–5. doi: 10.13638/j.issn.1671-4040.2021.11.022

42. Jia J, Zhang LY, Xu YX, Gao XQ, Liu S, Liu ZJ. Efficacy of Shenqi Fuzheng Injection in the treatment of advanced lung cancer and its impact on immune function and quality of life. *World J Integr Tradit Chin West Med[Chinese Journal]* (2020) 15:1133–5+9. doi: 10.13935/j.cnki.sjzx.200637

43. Li HT, Li R. Short-term curative effect observation of Shenqi Fuzheng Injection combined with conventional western medicine in the treatment of non-small cell lung cancer. *Jilin J Tradit Chin Med[Chinese Journal]* (2019) 39:331–3. doi: 10.13463/j.cnki.jlzyy.2019.03.015

44. Liu YF, Ding XM, Liu M. Guanqi Fuzheng injection combined with GP chemotherapy to treat non-Small cell lung cancer. *Shenzhen J Integr Tradit Chin West Med[Chinese Journal]* (2021) 31:48–50. doi: 10.16458/j.cnki.1007-0893.2021.19.019

45. Luo BP, Zhou Y, Cao T, Zuo P, Jiang MH. Clinical Trial of Shenqi Fuzheng injection on quality of life in patients with non-Small cell lung cancer after chemotherapy. *Chin J Clin Pharmacol[Chinese Journal]* (2018) 34:2137–9. doi: 10.13699/j.cnki.1001-6821.2018.18.003

46. Wang HL. Effect evaluation of Shenqi Fuzheng injection assisted GP chemotherapy in the treatment of stage IIIB-IV Non-small cell lung cancer. *Clin Med[Chinese Journal]* (2021) 41:123–5. doi: 10.19528/j.issn.1003-3548.2021.011.047

47. Wu ZY. Adjuvant effect of Shenqi Fuzheng injection on advanced NSCLC chemotherapy patients. *Smart Healthcare[Chinese Journal]* (2019) 5:103–4. doi: 10.19335/j.cnki.2096-1219.2019.12.051

48. Wang YZ, Yang ZX, Liao SH, Shen X. Clinical observation of Shenqi Fuzheng injection combined with vinorelbine and carboplatin in the treatment of advanced non-small cell lung cancer. *J Clin Intern Med[Chinese Journal]* (2007) 03:206–7. doi: 10.3969/j.issn.1001-9057.2007.03.023

49. Ding PQ, Huang HW, Lin KS. Observation on efficacy of Shenqifuzheng injection combined with chemotherapy in treatment of elderly patients with non small cell lung cancer. *Eval. Anal Drug-use Hosp Chin[Chinese Journal]* (2016) 16:461–3. doi: 10.14009/j.issn.1672-2124.2016.04.012

50. Wang TX, Dou CF. Clinical observation on Shenqi Fuzheng Injection combined with chemotherapy for 41 cases of non-Small cell lung cancer. *J Tradit Chin Med [Chinese Journal]* (2014) 55:775–7. doi: 10.13288/j.11-2166/r.2014.09.015

51. Jia YL, Huang YN. Efficacy of Shenqi Fuzheng injection in advanced non-Small cell lung chemotherapy in elderly patients. *Clin J Chin Med[Chinese Journal]* (2012) 4:13–5. doi: 10.3969/j.issn.1674-7860.2012.07.005

52. Zhao ZY, Wu DL, Chen M, Jiang H, Yan GJ. The short-Term observation of Shenqi Fuzheng injection combined with NP chemotherapy in treating elderly patients with advanced non-Small cell lung cancer. *Mod Oncol[Chinese Journal]* (2007) 01:42–3. doi: 10.3969/j.issn.1672-4992.2007.01.017

53. Yu QZ. Shenqi Fuzheng injection combined with chemotherapy in treatment of advanced non-small cell lung cancer. *Chin J Integr Med[Chinese Journal]* (2007) 27:473–4. doi: 10.3321/j.issn:1003-5370.2007.05.026

54. Wang K, Qin JX, Nong Y. Clinical observation of Shenqi Fuzheng injection combined with NP chemotherapy in treatment of advanced non-Small cell lung cancer. *Mod J Integr Tradit Chin West Med[Chinese Journal]* (2007) 26:3797–8. doi: 10.3969/j.issn.1008-8849.2007.26.012

55. Li Y, Chen XS, Huang RW. Clinical observation of Shenqi Fuzheng injection combined with NP chemotherapy iin treatment of advanced non-Small cell lung cancer. *Mod Med J Chin[Chinese Journal]* (2007) 09:40–1. doi: 10.3969/j.issn.1672-9463.2007.03.014

56. Geng L. Clinical research of injection Shengifuzheng combined with chemotherapy to treat NSCL. *J Med Forum[Chinese Journal]* (2004) 25:29–31. doi: 10.3969/j.issn.1672-3422.2004.17.015

57. Lv J. Clinical observation of Shenqi Fuzheng injection assisted chemotherapy in treatment of advanced non-small cell lung cancer. *China Med Her[Chinese Journal]* (2008) 5:73–4. doi: 10.3969/j.issn.1673-7210.2008.36.045

58. Chen YF, Sun YN, Ou WH, Qin A. Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in the treatment of non-Small cell lung cancer. *Chin J Clin Ration Drug Use[Chinese Journal]* (2018) 11:86–7. doi: 10.15887/j.cnki.13-1389/r.2018.19.046

59. Zheng JH, Chen YF. Shenqi Fuzheng injection combined with NP in treatment of 42 cases of advanced non-Small cell lung cancer. *Jiangxi J Tradit Chin Med[Chinese Journal]* (2009) 40:58–9. doi: 10.3969/j.issn.0411-9584.2009.06.040

60. Zou Y, Bai YJ, Ruan PG. Clinical observation of Shenqi Fuzheng injection combined with paclitaxel and carboplatin in treatment of advanced non-small cell lung cancer. *J Pract Oncol[Chinese Journal]* (2005) 20:260–2. doi: 10.3969/j.issn.1001-1692.2005.03.029

61. Luo SZ, Long JH, Yu XY. The clinical observation of advanced non small cell lung cancer treated with Shenqifuzheng injections combined with PTX and DDP. *J Cancer Res Clin Oncol[Chinese Journal]* (2006) 18:181–3. doi: 10.3760/cma.j.issn.1006-9801.2006.03.014

62. Cheng ZJ, Xi FR. Randomized parallel study of Shenqi Fuzheng injection combined with chemotherapy in the treatment of moderate and advanced non-small cell lung cancer (Qi deficiency). *J Pract Tradit Chin Intern Med[Chinese Journal]* (2017) 31:43–5. doi: 10.13729/j.issn.1671-7813.2017.12.15

63. Li HT, Huang JH, Lei YQ. Effect of Shenqi Fuzheng injection on the efficacy and adverse reactions of TP chemotherapy in the treatment of non-Small cell lung cancer. *Chin J Clin Ration Drug Use[Chinese Journal]* (2012) 5:77–8. doi: 10.3969/j.issn.1674-3296.2012.09.061

64. Luo SW, Huang YP, Shan HL, Yang YW, Mo C, Wu XE. Clinical observation of Shenqi Fuzheng Injection Combined With Paclitaxel Plus Cisplatin in Treatment of Advanced Non-Small Cell Lung Cancer. *Chin J Clin Oncol[Chinese Journal]* (2007) 12:381–2. doi: 10.3969/j.issn.1009-0460.2007.05.019

65. Liu R. Clinical Observation of TCM Combined With Chemotherapy in Treatment of Advanced Non-Small Cell Lung Cancer. *J Med Theory Pract[Chinese Journal]* (2011) 24:1291–2. doi: 10.3969/j.issn.1001-7585.2011.11.026

66. Li DH, Yang HL. Clinical Observation of Shenqi Fuzheng liquid combined with TP in treatment of advanced non-Small cell lung cancer. *Med Forum[Chinese Journal]* (2014) 18:1291–2. doi: CNKI:SUN:YXLT.0.2014-10-048

67. Wang LY, Tu QS, Li JH, Wu HJ. Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in treatment of advanced non-Small cell lung cancer. *J Chin Physician[Chinese Journal]* (2009) 11:1417–8. doi: 10.3760/cma.j.issn.1008-1372.2009.10.048

68. Zhang FL. The clinical observation of advanced non small cell lung cancer treated with Shenqi-Fuzheng injection combined with PTX and DDP. *Mod Oncol [Chinese Journal]* (2008) 16:1165–6. doi: 10.3969/j.issn.1672-4992.2008.07.034

69. Zhao Q. Clinical observation of Shenqi Fuzheng injection in treatment of advanced non-small cell carcinoma. *Guide Chin Med[Chinese Journal]* (2019) 17:194. doi: 10.15912/j.cnki.gocm.2019.15.146

70. Wu L, Jiang B, Yang J. Shenqi Fuzheng injection combined with chemotherapy in treatment of 30 cases of advanced non-small cell lung cancer. *Chin J Integr Med [Chinese Journal]* (2004) 24:567–8. doi: 10.3321/j.issn:1003-5370.2004.06.031

71. Hu KD, Yang KG, Soumia C, Wu MY, Yan C, Li XY, et al. Proteomics analysis of APS on TLR4-activated lung cancer cell-derived exosome. *China J Chin Mater Med[Chinese Journal]* (2022) 47:5908–15. doi: 10.19540/j.cnki.cjcmm.20220613.707

72. Zhang YC, Shen JC, Qu YJ, Xu PP. Effect and mechanism of ginsenosides on proliferation and apoptosis of lung cancer cell. *Clin J Med Offic[Chinese Journal]* (2022) 50:23–6. doi: 10.16680/j.1671-3826.2022.01.07

73. Sun XD, Wang TM, Li H, Zhao PY, Liu Y, Cheng Y. Mechanism of ginsenoside rh2 on inhibiting proliferation of human non-small cell lung cancer cells. *ChinTradit Herb Drugs[Chinese Journal]* (2022) 53:441–8. doi: 10.7501/j.issn.0253-2670.2022.02.014

74. Peng Z, Wu WW, Yi P. The efficacy of ginsenoside rg3 combined with first-line chemotherapy in the treatment of advanced non-Small cell lung cancer in China: A systematic review and meta-Analysis of randomized clinical trials. *Front Pharmacol* (2021) 11:1–13. doi: 10.3389/fphar.2020.630825

75. Jia J, Zhang LY, Xu YX, Gao XQ, Liu S, Liu ZJ. Effect of Shenqi fuzheng iniection on patients with non-small cell lung cancer and related cytokines. *Mod Oncol[Chinese Journal]* (2020) 28:2250–4. doi: 10.3969/j.issn.1672-4992.2020.13.015

76. Chen R, Li M, Ji BY, Qi SJ. Clinical observation of Shenqi Fuzheng injection combined with chemotherapy in treatment of non small cell lung cancer and the regulation of th17/treg cells in patients. *Chin Arch Tradit Chin Med[Chinese Journal]* (2018) 36:1994–7. doi: 10.13193/j.issn.1673-7717.2018.08.054

77. Yeh TS, Lei TH, Liu JF, Hsu MC. Astragalus membranaceus Enhances Myotube Hypertrophy through PI3K-Mediated Akt/mTOR Signaling Phosphorylation. *Nutrients* (2022) 14:1670. doi: 10.3390/nu14081670

78. Bao WR, Zhang QW, Zheng HM, Li LF, Liu M, Cheng HY, et al. Radix astragali polysaccharide RAP directly protects hematopoietic stem cells from chemotherapy-Induced myelosuppression by increasing fos expression. *Int J Biol Macromol* (2021) 183:1715–22. doi: 10.1016/j.ijbiomac.2021.05.120

79. Dai TY, Lan JJ, Gao RL, Zhao YN, Yu XL, Liang SX, et al. Panaxdiol saponins component promotes hematopoiesis by regulating gata transcription factors of intracellular signaling pathway in mouse bone marrow. *Ann Transl Med* (2022) 10:38. doi: 10.21037/ATM-21-4800

80. Yu H, Fei YC, Chen PF. Meta-analysis of Shenqi Fuzheng injection in the treatment of bone marrow suppression after chemotherapy for advanced non-small cell lung cancer. *Zhejiang J Integr Tradit Chin West Med[Chinese Journal]* (2019) 29:240–4. doi: 10.3969/j.issn.1005-4561.2019.03.026

81. Moher D, Kenneth FS, Douglas A. The CONSORT statement: revised recommendations for improving the qualityof reports of parallel-group randomized trials. *JAMA* (2001) 285:1987–91. doi: 10.1001/pubs.JAMA-ISSN-0098-7484-285-15-jsc00437

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EDITED BY
Aakash Desai,
Mayo Clinic, United States

REVIEWED BY
Francesco Pepe,
University of Naples Federico II, Italy
Guobin Fu,
Shandong Provincial Hospital, China

*CORRESPONDENCE
Yang Li
ly66457809@163.com

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Osimertinib inhibits brain metastases and improves long-term survival in a patient with advanced squamous cell lung cancer: a case report and literatures review

Zhiqin Zhang[1,2], Jiamao Lin[3], Linke Yang[4] and Yang Li[5]*

[1]Department of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong First Medical University, Jinan, China, [2]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University, Academy of Medical Sciences, Jinan, China, [3]Department of Traditional Chinese and Western Medicine, Shandong Cancer Hospital and Institute, Shandong First Medical University, Academy of Medical Sciences, Jinan, China, [4]Department of Pathology, Shandong Cancer Hospital and Institute, Shandong First Medical University, Academy of Medical Sciences, Jinan, China, [5]Shandong Provincial Key Laboratory of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University, Academy of Medical Sciences, Jinan, China

Background: Squamous cell carcinoma (SCC) is one of the most common subtypes of non-small cell lung cancer, but its treatment options remain limited. Epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitors (TKIs) have limited efficacy in the treatment of lung SCC. Here, we report an SCC patient who developed EGFR-T790M mutation and showed gefitinib resistance achieved an extremely long survival by taking Osimertinib alternatively.

Case summary: A patient, 66-year-old non-smoking and drinking male with advanced SCC who was deemed inoperable at the time of diagnosis. The first genetic testing showed deletion mutation of exon 19 of EGFR. The patient was then treated with gefitinib with no significant efficacy. EGFR-T790M mutation was found in the second genetic test. The treatment regimen was changed to radiotherapy with Osimertinib, and the patient's primary lesion and the brain metastases were well controlled.

Conclusion: This typical case highlights the important role of Osimertinib in patients with SCC carrying EGFR mutations.

KEYWORDS

non-small cell lung carcinoma, squamous cell carcinoma, EGFR mutation, targeted therapy, cancer

Introduction

Lung cancer is the second most common cancer and the most common cause of cancer death worldwide. In 2020, 2.2 million new cases of lung cancer, accounting for 11.4% of the total 18 million cancer cases, were reported and 1.8 million new cancer deaths were related to lung cancer, accounting for 18% of all cancer deaths (1). The treatment of squamous non-small cell lung cancer, which constitutes 25%–30% of NSCLC, is challenging because of its specific clinicopathologic characteristics and rare incidence of targetable mutations (2). NSCLC has a poor prognosis, especially in stage IIIB/IV patients, with a 5-year overall survival (OS) rate of less than 5% (3).

The median survival time of patients with squamous cell carcinoma (SCC) was approximately 30% shorter than that of patients with other NSCLC subtypes (2). Here, we report a case of stage Ⅳ SCC patient who had lost the opportunity for surgery at the initial diagnosis. He was treated with first- and third-generation epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitors (TKIs), and he is still alive over 5 years after treatment.

Case description

On 29 December 2016, a 66-year-old Chinese male patient with no history of smoking and drinking presented to the Department of Oncology, Shandong Cancer Hospital and Institute (Jinan, China) with a cough and chest tightness for 1 month. Space occupying lesions in the lower lobe of the right lung were found during CT examination, and then he was admitted to our hospital for further treatment. At this time, the ECOG score was 1, and the patient had no previous history of related drugs and surgery. CT showed an irregular soft tissue mass in the lower lobe of the right lung with a cross section of about 4.8 cm × 4.6 cm, multiple lung masses, right hilar and mediastinal lymph node, and abdominal lymph node involvement, with metastases of right pleural, rib, and the brain. The clinical stage was T4N3M1, IV, and the pathological biopsy showed non-small cell lung cancer combined with immunohistochemical tendency of SCC. A deletion mutation of exon 19 of EGFR was found in genetic testing. The patient received 14 cycles of targeted therapy with gefitinib (250 mg/d, qd) from January 2017 to March 2018. The best response was stable disease (SD) (Figure 1). In March 2018, the CT reexamination showed the progress of the disease, and EGFR T790M mutation was found after genetic testing of specimen acquired by pathological puncture (Figure 2). Then the patient was admitted to the hospital for radiotherapy of the lower lobe of the right lung and metastatic lymph nodes, DT = 6000 cGy (200 cGy dose per time). In the same month, patient received targeted therapy with Osimertinib (80 mg/d, qd) until now. The effect was evaluated as SD. At this time, the patient's clinical stage was T4N3M1, IV. After taking Osimertinib for more than 4 years, the primary lesion in the right lung was well controlled (Figure 3) and the brain metastases almost disappeared (Figure 4).

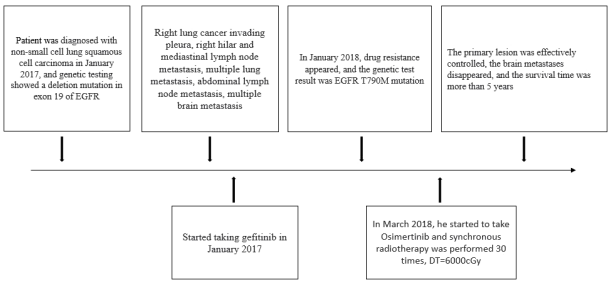

FIGURE 1
Timeline of our case's treatment for advanced squamous cell carcinoma.

Discussion

Here, we described a patient with stage IV advanced SCC. At initial diagnosis, the mutation of EGFR exon 19del was found. After taking gefitinib for more than 1 year, the patient developed drug resistance. The result of second genetic test showed EGFR-T790M mutation, which is an acquired drug resistance mutation. When treatment was switched to Osimertinib with the combination of primary and metastatic lymph node radiotherapy resulted in a long progression-free survival (PFS).

The first-generation EGFR-TKIs Gefitinib (ZD1839) was approved as first-line therapy for the treatment of patients with NSCLC harboring EGFR sensitive mutation, specifically. EGFR exon 19 deletions (ex19del) and/or EGFR L858R mutation in exon 21. These mutations occur in 10%–40% of patients with NSCLC. However, the patient's condition deteriorated after 10–14 months of treatment with gefitinib. Studies have indicated that approximately 50% of the progression of NSCLC was due to the additional EGFR T790M resistance mutation (4–7). The patient was consistent with clinical cohort data during gefitinib use. During this process, the patient developed drug resistance.

In patients with non-adenocarcinoma (ADC) non-small cell lung cancer carrying EFGR mutations, clinical studies have shown that the median OS of patients treated with EGFR-TKIs is significantly higher than patients not treated with EGFR-TKIs, and there is no significant difference in clinical characteristics between patients who respond to EGFR-TKIs and those who do not (8). Based on the literature review, the efficacy of EGFR-TKIs in lung SCC with EGFR mutant is lower than that in adenocarcinoma. According to a clinical study, 33 (13.3%) of 249 patients with SCC included in the study had EGFR mutations. Twenty of these patients received EGFR-TKI (erlotinib or gefitinib) with a response rate of 25% (95% confidence interval, 8.7%–49.1%). PFS was 1.4 months, and OS was 14.6 months. Approximately one-third of patients with EGFR-mutated lung SCC have PFS of more than 6 months (9). EGFR-T790M is a common drug resistance mutation, resulting in about 60% of NSCLC patients with EFGR mutation who are resistant to EGFR-TKIs (10). There are two types of T790M mutations: primary mutation and acquired mutation. The acquired T790M mutation is usually the resistance gene generated after the

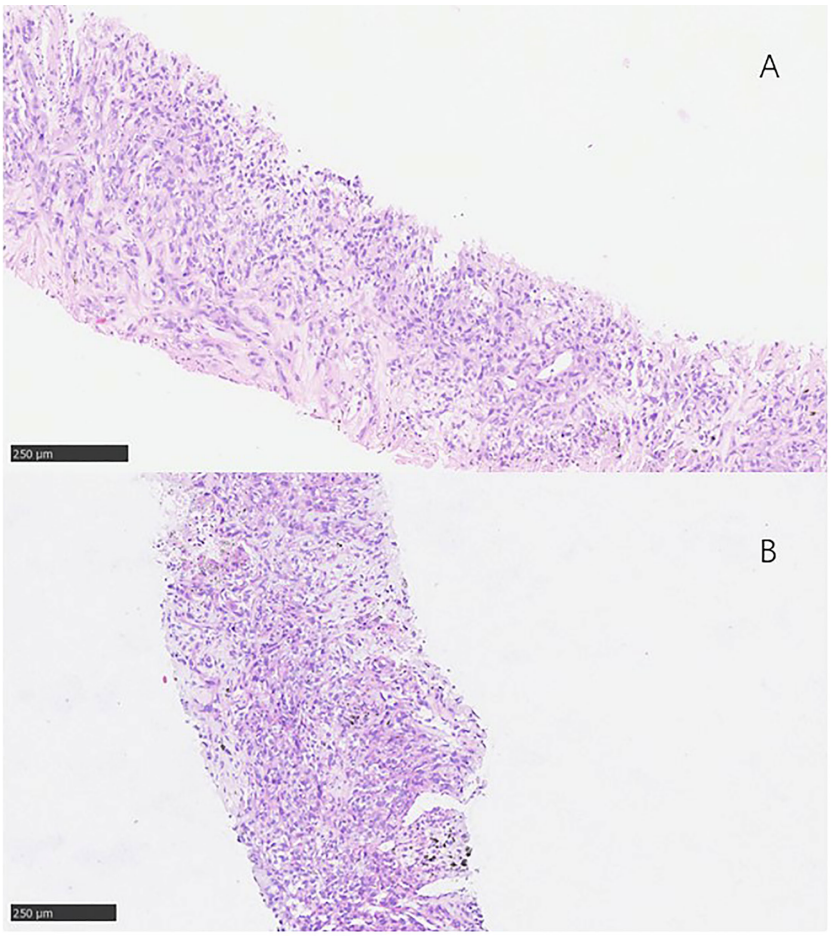

FIGURE 2
Pathological findings. **(A)** 3 January 2017, the pathological result was squamous cell carcinoma of non-small cell lung cance. **(B)** 17 January 2018, the pathological result was still lung squamous cell carcinoma.

first- or second-generation EGFR-TKI treatment. Both the primary and the acquired mutations showed good response to the third generation EFGR-TKI Osimertinib (11, 12). In NSCLC patients with acquired (Chiang, Huang et al., 2020) resistance to first- or second-generation EGFR-TKIs, Osimertinib is an alternative choice of treatment. Osimertinib was superior to platinum doublet chemotherapy with a higher rate (71% vs. 31%), a longer PFS (10.1 *vs.* 4.4 months) and median OS (26.8 *vs.* 22.5 months) (13, 14). Compared with traditional chemotherapy, EGFR-TKI–targeted therapy enable patients of NSCLC with EGFR mutations to achieve longer progression free survival and OS (15). In the patient who acquired the EGFR-T790M resistance mutation after taking gefitinib, we selected Osimertinib for the treatment that was successful.

Among the metastatic sites of advanced lung cancer, the central nervous system (CNS) is the most common site, and 20%–65% of patients will develop brain metastases during the course of the disease (16). In advanced lung cancer, 20%–65% of patients will develop brain metastases. Up to 50% of Asian patients with NSCLC carry EGFR-gene mutations. The cumulative incidence of brain metastases was significantly high in patients with EGFR mutations, with 46%, 64%, and 71% at 1, 3, and 5 years, respectively (17). Preclinical studies of Osimertinib demonstrated a more homogeneous distribution in the brain than other TKIs (18, 19). Osimertinib can delay the development of symptomatic CNS metastases. After taking Osimertinib for more than 3 years, the brain metastases even disappeared, which indicates that Osimertinib has a good therapeutic effect on metastasis.

At present, there are few studies on the efficacy of EGFR-TKIs for lung SCC. SCC only accounts for less than 1% in FLURA and AURA trials to explore the efficacy of Osimertinib in lung cancer. No clinical studies of patients with lung SCC carrying EGFR mutations have been performed yet.

In the case of newly diagnosed advanced lung cancer with brain metastases and bone metastases, the patient received gefitinib or Osimertinib combined with radiotherapy extended a survival time to more than 60 months. The disease was stabilized, the primary lesion was well controlled, the brain metastases disappeared, and no tertiary or quaternary adverse reactions occurred after Osimertinib treatment. The results suggest that Osimertinib might be the choice of treatment for patients of lung SCC with EGFR mutations.

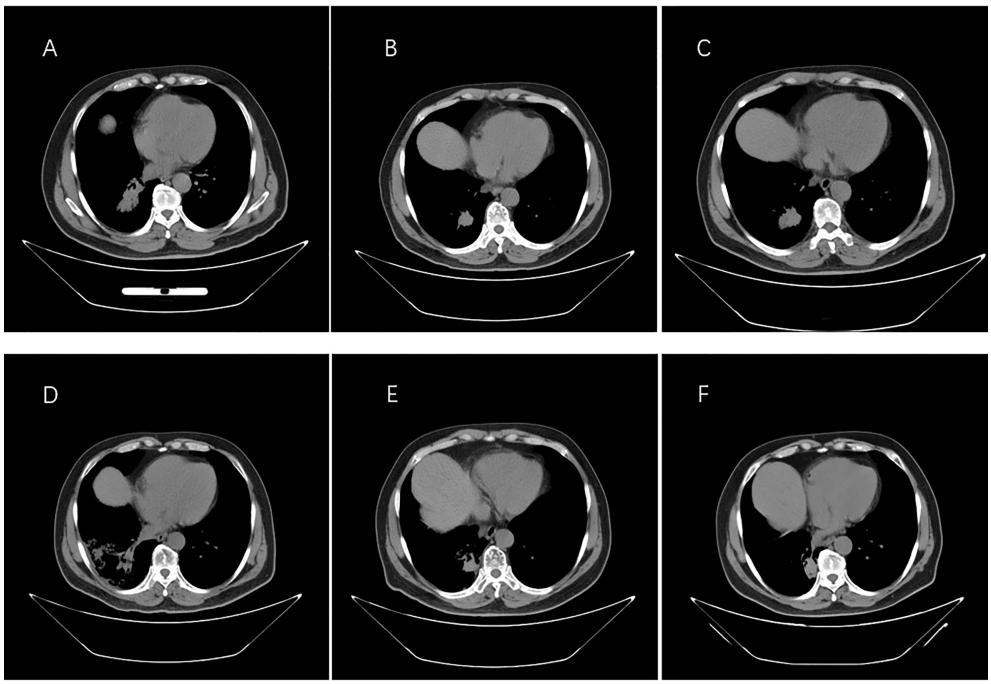

FIGURE 3
Images from computed tomography showing the tumor in the right lung in response to therapy. **(A)** Before therapy, imaging was performed on 30 December 2016. **(B)** Six months after taking gefitinib on 18 August 2017. **(C)** Resistance progresses on 20 January 2018. **(D)** After the radiotherapy on 5 June 2018. **(E)** One year after taking Osimertinib on 18 February 2019. **(F)** Last check on 20 May 2022.

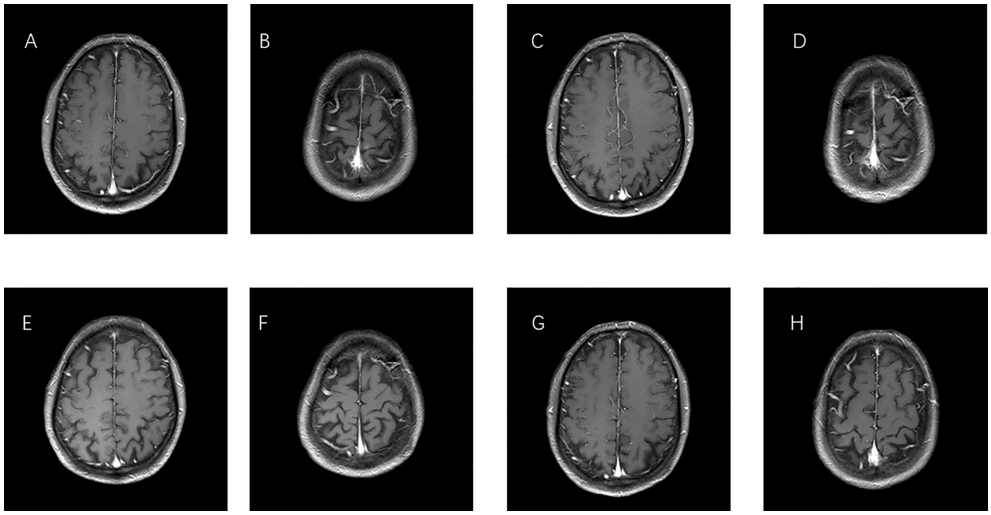

FIGURE 4
MRI images of brain metastases. **(A, B)** Before therapy, imaging performed on 30 December 2016. **(C, D)** One year after taking gefitinib on 19 March 2018. **(E, F)** One year after taking Osimertinib on 18 February 2019. **(G, H)** Last check on 20 May 2022.

Conclusion

We present here a case with Osimertinib and radiotherapy treated advanced SCC. Throughout the course of treatment, patients showed significant responses to both Osimertinib and radiotherapy, with prolonged PFS and OS. The results suggest that Osimertinib might be a good choice for the treatment of patients with lung SCC accompanied by EGFR mutations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Shandong Cancer Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZZ is responsible for thesis writing and picture editing. JL was responsible for case data collection. LY is responsible for the production and scanning of pathological sections. YL is responsible for reviewing articles and revising formats. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Socinski MA, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn PA Jr, et al. Current and emergent therapy options for advanced squamous cell lung cancer. *J Thorac Oncol* (2018) 13:165–83. doi: 10.1016/j.jtho.2017.11.111

3. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature* (2018) 553:446–54. doi: 10.1038/nature25183

4. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer* (2007) 7:169–81. doi: 10.1038/nrc2088

5. Park K, Tan E-H, O'Byrne K, Zhang L, Boyer M, Mok T, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol* (2016) 17:577–89. doi: 10.1016/S1470-2045(16)30033-X

6. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* (2013) 19:2240–7. doi: 10.1158/1078-0432.CCR-12-2246

7. Tanaka K, Nosaki K, Otsubo K, Azuma K, Sakata S, Ouchi H, et al. Acquisition of the T790M resistance mutation during afatinib treatment in EGFR tyrosine kinase inhibitor-naïve patients with non-small cell lung cancer harboring EGFR mutations. *Oncotarget* (2017) 8:68123–30. doi: 10.18632/oncotarget.19243

8. Kobayashi K, Soejima K, Fukunaga K, Shintani Y, Sekine I, Shukuya T, et al. Key prognostic factors for EGFR-mutated non-adenocarcinoma lung cancer patients in the Japanese Joint Committee of Lung Cancer Registry Database. *Lung Cancer* (2020) 146:236–43. doi: 10.1016/j.lungcan.2020.06.015

9. Hata A, Katakami N, Yoshioka H, Kunimasa K, Fujita S, Kaji R, et al. How sensitive are epidermal growth factor receptor-tyrosine kinase inhibitors for squamous cell carcinoma of the lung harboring EGFR gene-sensitive mutations? *J Thorac Oncol* (2013) 8:89–95. doi: 10.1097/JTO.0b013e31827690b5

10. Li X, Lian Z, Wang S, Xing L, Yu J. Interactions between EGFR and PD-1/PD-L1 pathway: Implications for treatment of NSCLC. *Cancer Lett* (2018) 418:1–9. doi: 10.1016/j.canlet.2018.01.005

11. Wang S, Yan B, Zhang Y, Xu J, Qiao R, Dong Y, et al. Different characteristics and survival in non-small cell lung cancer patients with primary and acquired EGFR T790M mutation. *Int J Cancer* (2019) 144:2880–6. doi: 10.1002/ijc.32015

12. Chiang CL, Huang HC, Shen CI, Luo YH, Chen YM, Chiu CH. Post-progression survival in secondary EGFR T790M-mutated non-small-cell lung cancer patients with and without Osimertinib after failure of a previous EGFR TKI. *Target Oncol* (2020) 15:503–12. doi: 10.1007/s11523-020-00737-7

13. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* (2017) 376:629–40. doi: 10.1056/NEJMoa1612674

14. Papadimitrakopoulou VA, Mok TS, Han JY, Ahn MJ, Delmonte A, Ramalingam SS, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. *Ann Oncol* (2020) 31:1536–44. doi: 10.1016/j.annonc.2020.08.2100

15. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* (2010) 362:2380–8. doi: 10.1056/NEJMoa0909530

16. Page S, Milner-Watts C, Perna M, Janzic U, Vidal N, Kaudeer N, et al. Systemic treatment of brain metastases in non-small cell lung cancer. *Eur J Cancer* (2020) 132:187–98. doi: 10.1016/j.ejca.2020.03.006

17. Han G, Bi J, Tan W, Wei X, Wang X, Ying X, et al. A retrospective analysis in patients with EGFR-mutant lung adenocarcinoma: is EGFR mutation associated with a higher incidence of brain metastasis? *Oncotarget* (2016) 7:56998–7010. doi: 10.18632/oncotarget.10933

18. Soria JC, Ohe Y, Vansteenkiste J, John T, Grohe C, Majem M, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* (2018) 378:113–25. doi: 10.1056/NEJMoa1713137

19. Colclough N, Chen K, Johnstrom P, Strittmatter N, Yan Y, Wrigley GL, et al. Preclinical comparison of the blood-brain barrier permeability of osimertinib with other EGFR TKIs. *Clin Cancer Res* (2021) 27:189–201. doi: 10.1158/1078-0432.CCR-19-1871

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EDITED BY
Aakash Desai,
University of Alabama at Birmingham, United States

REVIEWED BY
Xiaofei Wang,
Tennessee State University, United States
Magdalena Knetki-Wróblewska,
Maria Sklodowska-Curie National Research Institute of Oncology, Poland

*CORRESPONDENCE
Yanyan Lou
lou.yanyan@mayo.edu

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Clinical outcomes of atezolizumab versus standard-of-care docetaxel with and without ramucirumab in patients with advanced non-small-cell lung cancer who received prior immunotherapy

Shenduo Li[1], Rami Manochakian[1], Ruqin Chen[1], Jaydeepbhai Patel[1], Jyothik Varun Inampudi[2], Koshiya R. Hiren[3], Yujie Zhao[1] and Yanyan Lou[1]*

[1]Division of Hematology and Oncology, Department of Medicine, Mayo Clinic, Jacksonville, FL, United States, [2]Department of Internal Medicine, Detroit Medical Center/Wayne State University, Detroit, MI, United States, [3]Department of Medicine, Desert Valley Hospital, Victorville, CA, United States

Background: Atezolizumab is superior to docetaxel for patients with advanced non-small-cell lung cancer (NSCLC) who are pretreated with platinum-based chemotherapy based on the POPLAR and OAK trials. However, patients who received prior immunotherapy were excluded from these trials. The standard of care second-line therapy for these patients remains to be docetaxel with or without ramucirumab. The efficacy and safety of atezolizumab as a subsequent therapy in immunotherapy-pretreated patients are unknown.

Methods: We conducted a retrospective study of all patients with locally advanced or metastatic NSCLC who were pretreated with immunotherapy at Mayo Clinic Jacksonville and Rochester from 2016 to 2022. Patients who received subsequent therapy of atezolizumab alone (Atezo), docetaxel (Doce), or docetaxel + ramucirumab (Doce+Ram) were included.

Results: In this cohort of 165 patients, 12.7% (n=21), 49.1% (n=81), and 38.2% (n=63) patients received subsequent Atezo, Doce, and Doce+Ram, respectively. 1-year landmark progression-free survival (PFS) were 23.8%, 6.2%, and 3.2% (p=0.006), and 2-year landmark PFS were 14.3%, 0%, and 0% (p<0.0001), in the Atezo, Doce, and Doce+Ram groups, respectively. About 20% patients with positive PD-L1 had durable response to atezolizumab. The Atezo group showed significantly greater overall survival (OS) improvement over Doce group (median OS 17.7 vs. 7.7 months, HR 0.47, 95% CI 0.29 – 0.76, p=0.008), and over Doce +Ram group (median OS 17.7 vs. 8.9 months, HR 0.55, 95% CI 0.32 – 0.95, p=0.047). 4 of 21 (19%) patients in the Atezo group developed immune-related adverse events (irAE).

Conclusion: We observed statistically significant and clinically meaningful overall survival benefits of atezolizumab monotherapy compared with docetaxel +/- ramucirumab in patients with advanced NSCLC who were pretreated with immunotherapy. The survival benefit seems to be mainly from PD-L1 positive patients. Subsequent immunotherapy with Atezolizumab did not increase irAE rate.

KEYWORDS

NSCLC, immunotherapy, atezolizumab, docetaxel, ramucirumab, PD-1/L1

Introduction

Immune checkpoint inhibitors (ICIs), most commonly programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) inhibitors, have revolutionized the treatment and significantly improved the survival of patients with advanced non-small-cell lung cancer (NSCLC). However, for most patients, their tumor cells inevitably become refractory to treatment over time, resulting in disease progression or recurrence. Subsequent systemic therapy options for patients whose disease progressed on ICI are limited, mostly single agent chemotherapies. Docetaxel is widely used as the preferred subsequent systemic therapy if no actionable driver mutations exist but often has limited survival benefit with reported OS of 6.0-9.1 months (1–4). Ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) receptors, was tested in combination with docetaxel in the phase 3 REVEL clinical trial (3). It was shown to have a 1.4-month improvement in overall survival over docetaxel alone in patients with NSCLC who were pre-treated with platinum-based therapy. Tolerability was a concern as more than 70% of patients experienced grade 3 or higher adverse events (3). In the era of immunotherapy, the efficacy of ramucirumab plus docetaxel was evaluated in a retrospective study where 288 patients who had received previous chemo-immunotherapy were subsequently treated with ramucirumab plus docetaxel. The median PFS and median OS were 4.1 months and 11.6 months, respectively (5).

Atezolizumab is a monoclonal antibody inhibiting PD-L1. It showed improved overall survival (median OS 12.6-13.3 months) compared to docetaxel alone in NSCLC patients who received platinum-based chemotherapy, as demonstrated in the POPLAR and OAK trials (6, 7). Of note, patients who received prior PD-1/PD-L1 inhibitors were excluded from both trials. Sequential use of PD-1/PD-L1 inhibitors has not been adequately assessed in clinical trials, and its efficacy and safety in lung cancer are largely unknown. Few studies consisting of small-size cohorts and case series have been published (8–11). All of them were single-arm studies and did not include control groups of docetaxel with or without ramucirumab for comparison.

Here we conducted a retrospective cohort study including patients with locally advanced or metastatic NSCLC who were pretreated with immunotherapy and received subsequent atezolizumab, docetaxel, or docetaxel plus ramucirumab. We compared the survival outcomes between these three regimens and evaluated the safety and adverse events of ICI rechallenge with atezolizumab in NSCLC patients who received prior PD-1/PD-L1 inhibitors.

Methods

Study design and patients

This is a single-institution retrospective study conducted at Mayo Clinic Cancer Center. Patients who were diagnosed with advanced NSCLC and received care at Mayo Clinic Jacksonville and Rochester campuses from 1/1/2016 to 12/31/2022 were screened. Patients were included if they met the following criteria: 1) diagnosed with stage III or stage IV NSCLC, not amendable by localized therapy and had received immunotherapy with a PD-1 or PD-L1 inhibitor; 2) discontinued immunotherapy due to disease progression or adverse events; 3) received subsequent therapy of atezolizumab alone (Atezo), docetaxel (Doce), or docetaxel plus ramucirumab (Doce+Ram). Patients were excluded if they had received maintenance durvalumab after concurrent chemoradiotherapy without subsequent PD-1/PD-L1 inhibitors, or if they lost follow up before the first follow-up visit at our institution.

Data collection

Data were manually abstracted from the medical chart of each patient, including demographics, pathological diagnosis and staging, treatments, radiographic assessments, biomarkers, and survival status. Categorical variables were summarized as frequency (percentage) and continuous variables were reported as median (range). Patients were grouped based on subsequent therapy (Atezo, Doce, or Doce+Ram). All patients were stratified according to PD-L1 status.

Outcomes

PFS was defined as the duration from the first dose of subsequent therapy to the date of first radiographic evidence of disease progression, or death of any reason (if occurred before disease progression), or the last follow-up date (if lost follow up before disease progression), or the date cutoff date (if no disease progression). OS was defined as the duration from the first dose of subsequent therapy to death of any reason, or the date that last known to be alive (if lost follow up), or the data cutoff date (if still alive). The data cutoff date was 8/1/2023. Previous immunotherapy best response was defined as the best response from the start of treatment until disease progression based on radiographic assessment, and was categorized into complete response, partial response, stable disease, or disease progression. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

Differences in baseline characteristics among groups were compared by χ^2 test, Fisher's exact test, or one-way ANOVA test. Survival analysis was performed by Kaplan-Meier method. The differences between groups were compared using the log-rank test. The correlation of previous ICI response to PFS of atezolizumab was done by Cox proportional hazards regression. All comparisons were two-tailed, with $p<0.05$ considered significant. The analysis was performed using GraphPad Prism 9.5.0 software and SAS software.

Results

We screened 646 patients who were previously treated with ICI at Mayo Clinic Jacksonville and Rochester from 2016 to 2022. After applying above inclusion/exclusion criteria, 165 patients were included in this study, and divided into three groups based on subsequent therapies: atezolizumab alone (Atezo, n=21), docetaxel (Doce, n=81), or docetaxel plus ramucirumab (Doce+Ram, n=63). Patients' demographic characteristics were shown in Table 1.

In this cohort of 165 patients, 52% were female. The median age was 66 (35 – 92). Most patients (58%) had Eastern Cooperative Oncology Group (ECOG) performance status 1. The histology was predominantly adenocarcinoma (78%). The median number of prior therapies was 2 (1 – 8). Pembrolizumab was the most used prior ICI (87%), followed by nivolumab (8%). 14% patients received prior targeted therapy. 90% patients had PD-L1 status available. Across the three groups, most baseline characteristics were similar. Compared with the other two groups, the Atezo group contained higher percentage of PD-L1 high expression, and more patients who received prior immunotherapy as monotherapy rather than in combination with chemotherapy. The Atezo group tended to have more elderly patients and higher ECOG scale, but not statistically different from the other two groups. These differences could possibly be attributed to treating clinician's choice of treatment based on the evidence that elderly and fragile patients with high PD-L1 expression may have better efficacy and tolerability of immunotherapy than chemotherapy (12). At the data cutoff date, the median follow-up time is 27.7 months, 127 patients had died, 18 patients had lost follow up, and 20 patients were alive.

PFS analysis is shown in Figure 1. We observed no statistically different median PFS across three groups (3.4 vs. 3.8 vs. 4.9 months in Atezo, Doce, and Doce+Ram groups, respectively, p=0.07). However, a prominent percentage of patients in the Atezo group appear to have long-term PFS benefits, demonstrated by 1-year landmark PFS of 23.8%, 6.2%, and 3.2% (p=0.006), and 2-year landmark PFS of 14.3%, 0%, and 0% (p<0.0001) in the Atezo, Doce, and Doce+Ram groups, respectively. In subgroup analysis stratified by PD-L1 level, no significant difference in median PFS was observed across treatments in each PD-L1 subgroup. However, about 20% patients with positive PD-L1 appeared to have durable response to atezolizumab (Figures 1C, D).

Figure 2 showed the results of OS analysis. We observed statistical difference in median OS across three treatments (17.7 vs. 7.7 vs. 8.9 months in Atezo, Doce, and Doce+Ram groups respectively, p=0.027). Atezolizumab showed significantly prolonged OS compared to docetaxel (median OS 17.7 vs. 7.7 months, HR 0.47, 95% CI 0.29 – 0.76, p=0.008) and docetaxel plus ramucirumab (median OS 17.7 vs. 8.9 months, HR 0.55, 95% CI 0.32 – 0.95, p=0.047). 1- and 2-year landmark OS were also much higher in Atezo group (1-year OS rates of 57.1%, 28.4%, and 29.5% [p=0.035], and 2-year PFS rates of 28.6%, 7.4%, and 7.4% [p=0.007] in the Atezo, Doce, and Doce+Ram groups, respectively). In terms of PD-L1 levels, Atezolizumab demonstrated significantly prolonged OS compared with docetaxel in PD-L1-positive subgroup (median PFS 14.3 vs. 6.6 months, HR 0.43, 95% CI 0.24 – 0.78, p=0.014) and in PD-L1-high subgroup (median PFS 30.0 vs. 7.3 months, HR 0.39, 95% CI 0.16 – 0.97, p=0.033). When compared with docetaxel plus ramucirumab, atezolizumab showed numerically longer median OS in all PD-L1 subgroups. The OS benefit appears greater in PD-L1 high population.

We further compared PFS and best treatment response of atezolizumab to those of prior immunotherapy for each patient in the Atezo group (Figure 3A). During previous ICI treatment, one patient had complete response, 10 patients had partial response, 8 patients had stable disease, and 2 patients had disease progression. 17 patients discontinued previous ICI due to eventual disease progression, and 4 patients discontinued due to adverse events but all had disease progression subsequently. During atezolizumab treatment, the median of PFS to atezo is 3.4 months, 8 patients remained as stable disease, 3 patients had partial response and 10 patients had cancer progression. Best treatment response to prior immunotherapy does not correlate with PFS of subsequent atezolizumab, though the patient number is small to derive statistical difference (Figure 3B).

4 of 21 (19%) patients in the Atezo group developed immune-related adverse events (irAE) (Table 2). Two patients were grade 3. One patient had possible grade 4 pneumonitis. No grade 5 event. Additionally, one patient stopped atezolizumab due to grade 2 anemia, which was later considered to be caused by concurrent chemotherapy. One patient stopped atezolizumab after grade 3 colitis likely of infectious etiology rather than immune related.

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TABLE 1 Baseline characteristics of ICI-pretreated NSCLC patients who received atezolizumab, docetaxel, or docetaxel + ramucirumab.

Characteristic	Atezolizumab N=21	Docetaxel N=81	Doce + Ram N=63	p value
Sex				0.51
Male	(43%)	43 (53%)	28 (44%)	
Female	12 (57%)	38 (47%)	35 (56%)	
Age-year				0.11
Median	73	65	69	
Range	45-89	35-92	38-81	
ECOG PS				0.07
0	3 (14%)	(17%)	15 (24%)	
1	10(48%)	47 758%)	38 (60%)	
2 and above	7 (33%)	18 (22%)	(8%)	
Histology				0.07
Adenocarcinoma	13 (62%)	64 (79%)	51 (79%)	
Squamous	6 (39%)	17 (21%)	10 (16%)	
Others	2 (10%)	0 (0%)	2 (3%)	
Prior ICI regimen				0.24
Pembrolizumab	17 (81%)	73 (90%)	56 (89%)	
Nivolumab	4 (19%)	4 (5%)	5 (8%)	
Others	0 (0%)	4(5%)	2 (3%)	
With/without chemo				<0.001***
ICI + chemo	7(33%)	58 (72%)	49 (78%)	
ICI alone	14 (67%)	23 (28%)	14 (22%)	
Lines of prior therapies				0.46
Median	2	2	2	
Range	1-8	1-5	1-5	
Prior targeted therapies				0.76
Yes	2 (10%)	11 (14%)	10 (16%)	
No	19(90%)	70 (86%)	53 (84%)	
PD-L1 status				0.02*
0	6(29%)	27 (33%)	19 (30%)	
1-49%	(14%)	33 (41%)	16 (25%)	
>50%	11(52%)	14 (17%)	19 (30%)	
Not available	1 (5%)	7 (9%)	9 (14%)	

ECOG, Eastern Cooperative Oncology Group; PS, performance status; ICI, immune checkpoint inhibitor; PD-L1, programmed cell death-ligand 1; Doce, docetaxel; Ram, ramucirumab; * denotes $p \leq 0.05$; *** denotes $p \leq 0.001$.

Discussion

There is an unmet need for an effective subsequent therapy for patients with NSCLC without targetable mutation and disease progressed on chemoimmunotherapy. In 2014, ramucirumab was approved by the U.S. Food and Drug Administration (FDA) to be used in combination with docetaxel as a subsequent therapy before the immunotherapy era. Recently, as the immunotherapy is widely used in first-line setting, several retrospective studies re-evaluated the efficacy of adding ramucirumab to docetaxel, and the additional survival benefit appears only modest (5, 13). In our single-institution retrospective study, we observed statistically significant and clinically meaningful OS advantage of atezolizumab monotherapy over standard-of-care docetaxel with or without

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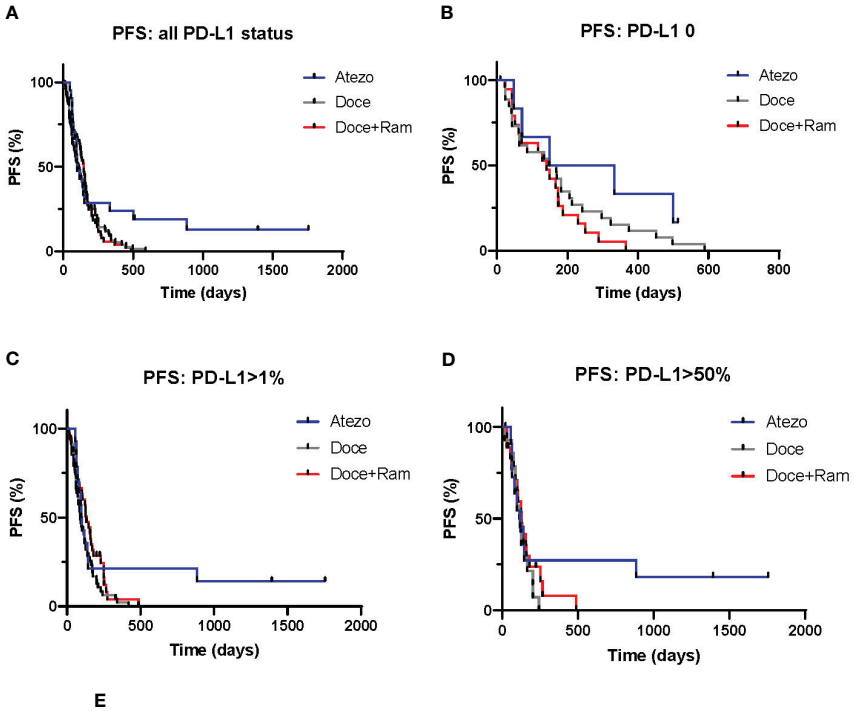

E

Median PFS (months)	Atezolizumab N=21	Docetaxel N=81	Doce + Ram N=63	p value
All PD-L1	3.4	3.8	4.9	0.07
PD-L1 0	8.0	5.3	4.7	0.14
PD-L1>1%	3.9	3.2	4.4	0.12
PD-L1>50%	3.9	3.9	4.2	0.42
1-year PFS rate	23.8%	6.2%	3.2%	0.006**
2-year PFS rate	14.3%	0.0%	0.0%	p<0.0001****

FIGURE 1
Progression-free survival (PFS) comparison by Kaplan-Meier curves for all patients **(A)**, and stratified by PD-L1 negative **(B)**, PD-L1 positive **(C)**, and PD-L1 high **(D)**. Summary of median PFS and 1- and 2-year landmark PFS across three groups **(E)**. Atezo, atezolizumab; Doce, docetaxel; Ram, ramucirumab; PD-L1, programmed cell death-ligand 1; HR, hazard ratio; CI, confidence interval. ** denotes $p \leq 0.01$; **** denotes $p \leq 0.0001$.

ramucirumab. Although median PFS was not increased in Atezo group (3.4 months) compared with Doce (3.8 months) or Doce +Ram (4.9 months), the 1-year and 2-year landmark PFS are significantly prolonged in the Atezo group in compared to other two groups. This is consistent with many other clinical studies that landmark PFS is likely better reflecting the clinical benefits of immune checkpoints due to durable response in selective patients. In addition, we also observed significantly improved OS (17.7 vs. 7.7 vs. 8.9 months) in the Atezo group in compared to other two groups despite small sample size. This discordance between PFS and OS is consistent with previous studies that showed atezolizumab and other ICIs may have delayed anti-tumor effect that lasts beyond treatment period (6, 14, 15). Median PFS correlates poorly with median OS and may underestimate the clinical benefits of immunotherapy (16, 17). This phenomenon can possibly be explained by the initial tumor volume increase due to immune infiltration and delayed antitumor immune activation (6). Nevertheless, overall survival is still considered the best criterion and gold standard for evaluating treatment efficacy in lung cancer (18).

PD-L1 expression is a pivotal although imperfect biomarker to predict ICI efficacy in NSCLC. In our study, we observed greater OS advantage in PD-L1 high (>50%) patients with a median OS of 30 months. The survival curve separated and plateaued much earlier apart from the Doce+/-Ram groups when compared with PD-L1 low or negative subgroups. Our observation is consistent with findings in several large prospective studies including IMpower110, Impower150, and OAK trials that PD-L1 high expression is associated with greater survival benefit in response to atezolizumab (6, 19, 20). In our cohort, there were more PD-L1 high patients in the Atezo group, which may potentially correlate with the prolonged survival outcomes compared with the other two treatment groups. Other biomarkers, such as tumor mutation burden (TMB) and microsatellite instability (MSI), were

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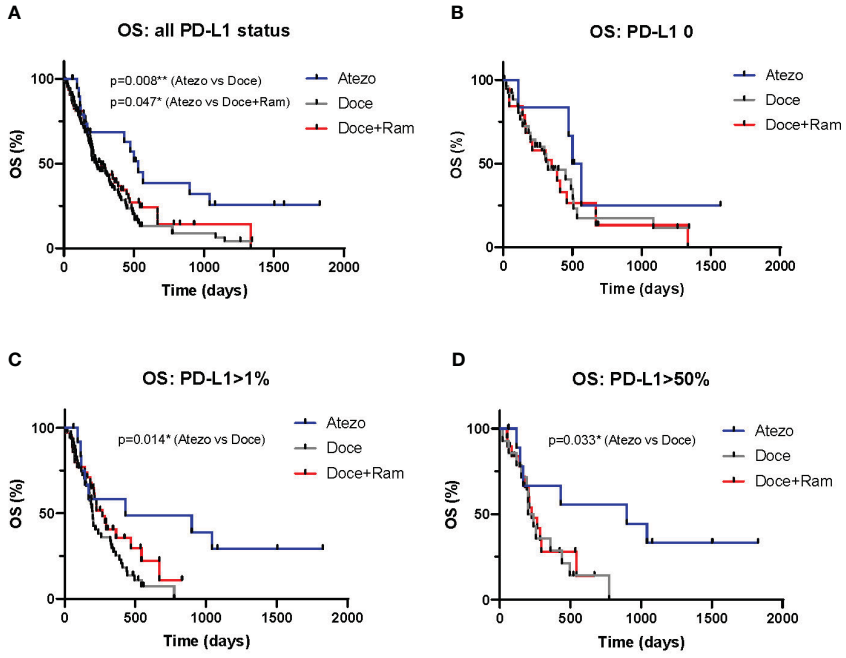

E

Median OS (months)	Atezolizumab N=21	Docetaxel N=81	Doce + Ram N=63	p value
All PD-L1	17.7	7.7	8.9	0.027*
PD-L1 0	17.7	10.8	11.7	0.41
PD-L1>1%	14.3	6.6	8.9	0.022*
PD-L1>50%	30.0	7.3	7.5	0.07
1-year OS rate	57.1%	28.4%	29.5%	0.035*
2-year OS rate	28.6%	7.4%	6.4%	0.007**

FIGURE 2
Overall survival (OS) comparison by Kaplan-Meier curves for all patients **(A)**, and stratified by PD-L1 negative **(B)**, PD-L1 positive **(C)**, and PD-L1 high **(D)**. Summary of median OS and 1- and 2-year landmark OS across three groups **(E)**. Atezo, atezolizumab; Doce, docetaxel; Ram, ramucirumab; PD-L1, programmed cell death-ligand 1; HR, hazard ratio; CI, confidence interval. * denotes $p \leq 0.05$; ** denotes $p \leq 0.01$.

reportedly to correlate with ICI efficacy (21, 22). However, only limited number of patients in our cohort had TMB or MSI information available, insufficient for meaningful analysis.

Sequential use or rechallenge of PD-1/PD-L1 inhibitors remains controversial in lung cancer treatment. Current NCCN guideline does not recommend subsequent use of another PD-1/PD-L1 inhibitor after disease progression on first-line PD-1/PD-L1 inhibitor (23). Low efficacy is a major concern. As all PD-1/PD-L1 inhibitors target similar pathway, resistance to one ICI may lead to class resistance and treatment response to a second ICI is likely low (8, 9, 24). Another concern is increased toxicity. One study showed subsequent treatment of PD-1 and PD-L1 inhibitors can lead to fulminant cardiotoxicity (25). To challenge this notion, a recent phase II randomized study demonstrated OS benefit of pembrolizumab in combination with ramucirumab over standard of care (mainly docetaxel and ramucirumab) in patients whose disease progressed on chemoimmunotherapy (median OS 14.5 vs. 11.6 months, HR 0.69, 80% CI 0.51 to 0.92, p=0.05). irAE incidence was not higher than what's expected for ICIs (26). To our knowledge, so far, no prospective studies have evaluated PD-1/PD-L1 inhibitor monotherapy after prior immunotherapy in advanced NSCLC. Our study suggested that subsequent use of atezolizumab alone may confer prominent clinical benefits and overcome immunotherapy resistance in those patients. Toxicity appears to be acceptable (irAE rate 19%, 4/21 patients).

PD-1 inhibitor and PD-L1 inhibitor work on the same PD-1/L1 axis but slightly different. PD-1 inhibitor blocks both PD-L1 and PD-L2, whereas PD-L1 inhibitor also blocks the binding to CD80 which releases CTLA-4-mediated anti-tumor immunity (27, 28). In our atezolizumab group, all patients had experienced disease progression on a PD-1 inhibitor either pembrolizumab or nivolumab. It is unclear whether PD-L1 inhibitor such as atezolizumab may overcome the immunotherapy resistance through alternative pathways. Further, it is unknown whether the survival benefit observed in our study is limited to the specific PD-1-then-PD-L1 blockade sequential treatment strategy.

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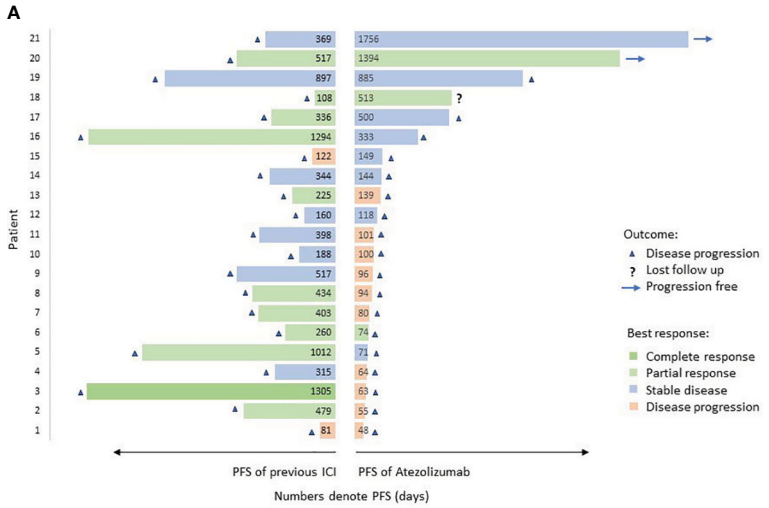

B

	Hazard ratio (95% CI)	p value
Previous ICI best response:		
Complete and partial response	1 (ref)	
Stable disease	0.90 (0.32 – 2.45)	0.84
Disease progression	1.64 (0.25 – 6.60)	0.54

FIGURE 3
Comparison of PFS (in length) and best response (in color) between atezolizumab and previous immunotherapy for each patient. Numbers represent PFS in days **(A)**. Correlation of previous ICI response to PFS of atezolizumab by Cox proportional hazards regression analysis **(B)**. PFS, progression-free survival; Atezo, atezolizumab; ICI, immune checkpoint inhibitor.

Previous study showed that immunotherapy rechallenge after prior nivolumab treatment resulted in better survival in patients with a longer duration of initial nivolumab treatment (29). Therefore, we examined whether treatment response to previous ICI can predict PFS of subsequent atezolizumab monotherapy and found no correlation. In our study, we did not identify a reliable factor or biomarker that correlates or predicts the efficacy of subsequent atezolizumab therapy. Finding effective predictive biomarkers to select patients likely to benefit from immunotherapy still remains a prevalent challenge worldwide.

TABLE 2 Adverse events occurred in patients receiving atezolizumab.

Patient	irAE	Grade
#1	mucositis	2
#2	elevated LFT	3
#3	adrenal insuff.	3
#4	pneumonitis	4
#5	anemia*	2
#6	colitis*	3

Grade is based on Common Terminology Criteria for Adverse Events (CTCAE) 5.0. irAE, immune-related adverse event; LFT, liver function test.
*likely non-immune related.

Our study has several limitations. It was a single-institution experience with a relatively small cohort. Atezolizumab alone after prior use of immunotherapy is not widely used nationwide which makes the expansion of cohort difficult. For example, we did not find an eligible patient to be included in Mayo Clinic Arizona campus. The small number of patients in the atezolizumab group, limited the power of statistical analysis, especially subgroup analysis. The study was retrospective, which means the treatment strategy was not randomized into all three groups. In addition, the imbalanced clinical features among the groups were also noticed in our study, partially due to overall small sample size. For example, squamous cell carcinoma represented 39% of patients in the Atezolizumab arm versus 21% in Docetaxel arm, although the difference was not statistically significant. Similarly, much more patients received prior chemotherapy in combination with immunotherapy in the docetaxel with or without ramucirumab arm in comparison to Atezolizumab arm, highlighting that potential factors, such as age, ECOG status, PD-L1 expression, histology and response to previous ICI, may have influenced clinician's treatment choice. Recently, a pooled analysis of KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies showed pembrolizumab monotherapy is superior to chemotherapy in elderly patients with positive PD-L1 (12). Our study showed that similar population of patients may also benefit from subsequent atezolizumab monotherapy. However, we do not

know why a subset of ICI-pretreated patients achieved long term response and survival advantage on atezolizumab. Further studies are needed to identify better predictive factors or establish an algorithmic model to select patients who will benefit from sequential immunotherapy.

In conclusion, we observed statistically significant and clinically meaningful survival benefits of atezolizumab monotherapy compared with docetaxel +/- ramucirumab in patients with advanced NSCLC who were pretreated with ICI. The OS benefits of atezolizumab over docetaxel was greater in PDL1>1% and PD-L1>50% subgroups. Our study challenged the current treatment guideline by showing subsequent use of immunotherapy alone may be beneficial to ICI-pretreated NSCLC patients, particularly PD-L1 >1% and PD-L1>50% patients. Further multi-institutional retrospective study is needed to verify these results. Prospective clinical trials are in demand to evaluate the clinical efficacy of immunotherapy rechallenge as a new strategy for ICI-pretreated NSCLC patients. Additionally, whether immune checkpoint inhibitors other than atezolizumab can be subsequently used in this setting. Finally, other immune-based therapeutic strategies, such as chimeric antigen receptor-T-cell therapy, bispecific T cell engagers, cancer vaccines, should be explored for the goal of benefiting NSCLC patients who suffer from disease progression after first-line chemoimmunotherapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Mayo Clinic institutional review board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Based on the nature of retrospective study.

Author contributions

SL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. RM: Conceptualization, Investigation, Supervision, Writing – review & editing. RC: Formal Analysis, Investigation, Methodology, Writing – review & editing. JP: Data curation, Writing – review & editing. JI: Data curation, Writing – review & editing. KH: Data curation, Writing – review & editing. YZ: Writing – review & editing. YL: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

RM: Advisory Board: AstraZeneca, Takeda, Guardant health, Janssen, Novocure, Turning Point, OncoHost. RC: Stocks: Eli Lilly and company, Gilead Sciences. YZ: Research Funding Support: PDS Biotechnology, Zai Lab, Incyte, Mirati, alpine, Pfizer, Merck, Elucida Oncology. YL: Advisory board: AstraZeneca Pharmaceuticals, Janssen Pharmaceutical, Lilly Oncology, Turning Point Therapeutics, Cardinal Health, Clinical Education Alliance, Oncohost, Mirati Therapeutics Honorarium to Mayo Clinic; Research Funding Support: Merck, Tolero Pharmaceuticals, AstraZeneca, Blueprint Medicines, Sun Pharma, Mirati Therapeutics, Genmab, EMD Serono, Jacobio pharma, TOPALLIAN, Daiichi Sankyo.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* (2000) 18(10):2095–103. doi: 10.1200/JCO.2000.18.10.2095

2. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* (2016) 387(10027):1540–50. doi: 10.1016/S0140-6736(15)01281-7

3. Garon EB, Ciuleanu T-E, Arrieta O, Prabhash K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* (2014) 384(9944):665–73. doi: 10.1016/S0140-6736(14)60845-X

4. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *New Engl J Med* (2015) 373(2):123–35. doi: 10.1056/NEJMoa1504627

5. Nakamura A, Yamaguchi O, Mori K, Miura K, Tamiya M, Oba T, et al. Multicentre real-world data of ramucirumab plus docetaxel after combined platinum-based chemotherapy with programmed death-1 blockade in advanced non-small cell lung cancer: NEJ051 (REACTIVE study). *Eur J Cancer* (2023) 184:62–72. doi: 10.1016/j.ejca.2023.01.025

6. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* (2017) 389(10066):255–65. doi: 10.1016/S0140-6736(16)32517-X

7. Mazieres J, Rittmeyer A, Gadgeel S, Hida T, Gandara DR, Cortinovis DL, et al. Atezolizumab versus docetaxel in pretreated patients with NSCLC: final results from the randomized phase 2 POPLAR and phase 3 OAK clinical trials. *J Thorac Oncol* (2021) 16(1):140–50. doi: 10.1016/j.jtho.2020.09.022

8. Watanabe H, Kubo T, Ninomiya K, Kudo K, Minami D, Murakami E, et al. The effect and safety of immune checkpoint inhibitor rechallenge in non-small cell lung cancer. *Jpn J Clin Oncol* (2019) 49(8):762–5. doi: 10.1093/jjco/hyz066

9. Niki M, Nakaya A, Kurata T, Yoshioka H, Kaneda T, Kibata K, et al. Immune checkpoint inhibitor re-challenge in patients with advanced non-small cell lung cancer. *Oncotarget* (2018) 9(64):32298–304. doi: 10.18632/oncotarget.25949

10. Kitagawa S, Hakozaki T, Kitadai R, Hosomi Y. Switching administration of anti-PD-1 and anti-PD-L1 antibodies as immune checkpoint inhibitor rechallenge in individuals with advanced non-small cell lung cancer: Case series and literature review. *Thorac Cancer* (2020) 11(7):1927–33. doi: 10.1111/1759-7714.13483

11. Fujita K, Uchida N, Kanai O, Okamura M, Nakatani K, Mio T. Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases. *Cancer Chemother Pharmacol* (2018) 81 (6):1105–9. doi: 10.1007/s00280-018-3585-9

12. Nosaki K, Saka H, Hosomi Y, Baas P, de Castro G, Reck M, et al. Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1–positive advanced non–small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies. *Lung Cancer* (2019) 135:188–95. doi: 10.1016/j.lungcan.2019.07.004

13. Ishida M, Morimoto K, Yamada T, Shiotsu S, Chihara Y, Yamada T, et al. Impact of docetaxel plus ramucirumab in a second-line setting after chemoimmunotherapy in patients with non-small-cell lung cancer: A retrospective study. *Thorac Cancer* (2022) 13(2):173–81. doi: 10.1111/1759-7714.14236

14. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50. *J Clin Oncol* (2021) 39(21):2339–49. doi: 10.1200/JCO.21.00174

15. Sun L, Bleiberg B, Hwang W-T, Marmarelis ME, Langer CJ, Singh A, et al. Association between duration of immunotherapy and overall survival in advanced non–small cell lung cancer. *JAMA Oncol* (2023) 9(8):1075–82. doi: 10.1001/jamaoncol.2023.1891

16. Shukuya T, Mori K, Amann JM, Bertino EM, Otterson GA, Shields PG, et al. Relationship between overall survival and response or progression-free survival in advanced non-small cell lung cancer patients treated with anti-PD-1/PD-L1 antibodies. *J Thorac Oncol* (2016) 11(11):1927–39. doi: 10.1016/j.jtho.2016.07.017

17. Mushti SL, Mulkey F, Sridhara R. Evaluation of overall response rate and progression-free survival as potential surrogate endpoints for overall survival in immunotherapy trials. *Clin Cancer Res* (2018) 24(10):2268–75. doi: 10.1158/1078-0432.CCR-17-1902

18. Berghmans T, Pasleau F, Paesmans M, Bonduelle Y, Cadranel J, Cs Toth I, et al. Surrogate markers predicting overall survival for lung cancer: ELCWP recommendations. *Eur Respir J* (2012) 39(1):9–28. doi: 10.1183/09031936.00190310

19. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *New Engl J Med* (2018) 378(24):2288–301. doi: 10.1056/NEJMoa1716948

20. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. *New Engl J Med* (2020) 383(14):1328–39. doi: 10.1056/NEJMoa1917346

21. Zhao P, Li L, Jiang X, Li Q. Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. *J Hematol Oncol* (2019) 12(1):54. doi: 10.1186/s13045-019-0738-1

22. Mok TSK, Lopes G, Cho BC, Kowalski DM, Kasahara K, Wu YL, et al. Associations of tissue tumor mutational burden and mutational status with clinical outcomes in KEYNOTE-042: pembrolizumab versus chemotherapy for advanced PD-L1-positive NSCLC. *Ann Oncol* (2023) 34(4):377–88. doi: 10.1016/j.annonc.2023.01.011

23. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. Non–small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Network* (2022) 20(5):497–530. doi: 10.6004/jnccn.2022.0025

24. Martini DJ, Lalani A-KA, Bossé D, Steinharter JA, Harshman LC, Hodi FS, et al. Response to single agent PD-1 inhibitor after progression on previous PD-1/PD-L1 inhibitors: a case series. *J ImmunoTher Cancer* (2017) 5(1):66. doi: 10.1186/s40425-017-0273-y

25. Liu S-Y, Huang W-C, Yeh H-I, Ko C-C, Shieh H-R, Hung C-L, et al. Sequential blockade of PD-1 and PD-L1 causes fulminant cardiotoxicity—From case report to mouse model validation. *Cancers* (2019) 11(4):580. doi: 10.3390/cancers11040580

26. Reckamp KL, Redman MW, Dragnev KH, Minichiello K, Villaruz LC, Faller B, et al. Phase II randomized study of ramucirumab and pembrolizumab versus standard of care in advanced non–small-cell lung cancer previously treated with immunotherapy—Lung-MAP S1800A. *J Clin Oncol* (2022) 40(21):2295–307. doi: 10.1200/JCO.22.00912

27. Zhao Y, Lee CK, Lin C-H, Gassen RB, Xu X, Huang Z, et al. PD-L1:CD80 cis-heterodimer triggers the co-stimulatory receptor CD28 while repressing the inhibitory PD-1 and CTLA-4 pathways. *Immunity* (2019) 51(6):1059–73.e9. doi: 10.1016/j.immuni.2019.11.003

28. Zhang Y, Song Q, Cassady K, Lee M, Tang H, Zheng M, et al. Blockade of trans PD-L1 interaction with CD80 augments antitumor immunity. *Proc Natl Acad Sci* (2023) 120(16):e2205085120. doi: 10.1073/pnas.2205085120

29. Giaj Levra M, Cotté F-E, Corre R, Calvet C, Gaudin A-F, Penrod JR, et al. Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: A national data base analysis. *Lung Cancer* (2020) 140:99–106. doi: 10.1016/j.lungcan.2019.12.017

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EDITED BY
Aakash Desai,
University of Alabama at Birmingham, United States

REVIEWED BY
Pietro Bertoglio,
IRCCS Azienda Ospedaliero Universitaria di Bologna, Italy
Mitchell Von Itzstein,
University of Texas, United States

*CORRESPONDENCE
Meijian Yu
Ymj_yy_happy@163.com

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Perioperative immunotherapy for stage II-III non-small cell lung cancer: a meta-analysis base on randomized controlled trials

Anping Yu[1,2], Feng Fu[3], Xiongying Li[1,2], Mengxin Wu[3], Meijian Yu[3]* and Wenxiong Zhang[4]

[1]Department of Oncology, Fengcheng People's Hospital, Yichun, China, [2]Department of Oncology, The Affiliated Fengcheng Hospital of Yichun University, Yichun, China, [3]Department of Oncology, Shangrao People's Hospital, Shangrao, China, [4]Department of Thoracic Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang, China

Background: In recent years, we have observed the pivotal role of immunotherapy in improving survival for patients with non-small cell lung cancer (NSCLC). However, the effectiveness of immunotherapy in the perioperative (neoadjuvant + adjuvant) treatment of resectable NSCLC remains uncertain. We conducted a comprehensive analysis of its antitumor efficacy and adverse effects (AEs) by pooling data from the KEYNOTE-671, NADIM II, and AEGEAN clinical trials.

Methods: For eligible studies, we searched seven databases. The randomized controlled trials (RCTs) pertaining to the comparative analysis of combination neoadjuvant platinum-based chemotherapy plus perioperative immunotherapy (PIO) versus perioperative placebo (PP) were included. Primary endpoints were overall survival (OS) and event-free survival (EFS). Secondary endpoints encompassed drug responses, AEs, and surgical outcomes.

Results: Three RCTs (KEYNOTE-671, NADIM II, and AEGEAN) were included in the final analysis. PIO group (neoadjuvant platinum-based chemotherapy plus perioperative immunotherapy) exhibited superior efficacy in OS (hazard ratio [HR]: 0.63 [0.49-0.81]), EFS (HR: 0.61 [0.52, 0.72]), objective response rate (risk ratio [RR]: 2.21 [1.91, 2.54]), pathological complete response (RR: 4.36 [3.04, 6.25]), major pathological response (RR: 2.79 [2.25, 3.46]), R0 resection rate (RR: 1.13 [1.00, 1.26]) and rate of adjuvant treatment (RR: 1.08 [1.01, 1.15]) compared with PP group (neoadjuvant platinum-based chemotherapy plus perioperative placebo). In the subgroup analysis, EFS tended to favor the PIO group in almost all subgroups. BMI (>25), T stage (IV), N stage (N1-N2) and pathological response (with pathological complete response) were favorable factors in the PIO group. In the safety assessment, the PIO group exhibited higher rates of serious AEs (28.96% vs. 23.51%) and AEs leading to treatment discontinuation (12.84% vs. 5.81%). Meanwhile, although total adverse events, grade 3-5 adverse events, and fatal adverse events tended to favor the PP group, the differences were not statistically significant.

Conclusion: PIO appears to be superior to PP for resectable stage II-III NSCLC, demonstrating enhanced survival and pathological responses. However, its elevated adverse event (AE) rate warrants careful consideration.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/#recordDetails, identifier CRD42023487475.

KEYWORDS

immunotherapy, neoadjuvant, adjuvant, surgery, non-small cell lung cancer, meta-analysis

Introduction

For decades, lung cancer (LC) has been the leading global cause of cancer-related deaths, with over 80% attributed to non-small cell lung cancer (NSCLC) (1, 2). Comprehensive treatment based on surgery is the standard of care for selected resectable stages II-III NSCLC (3). In previous approaches to neoadjuvant and adjuvant treatment for stage II-III NSCLC, chemotherapy played a vital role, but its solitary use yielded unsatisfactory results (4). In recent years, immunotherapy has gained widespread acceptance in solid tumor treatment, demonstrating superior efficacy in both neoadjuvant and adjuvant treatment for resectable NSCLC (5–7). Nevertheless, controversy persists in clinical settings regarding whether perioperative immunotherapy (neoadjuvant +adjuvant) can yield superior results (8).

The use of immunotherapy in the perioperative period of resectable lung cancer has been a hot topic in recent years. In neoadjuvant therapy, the CheckMate 816 study demonstrated that the addition of nivolumab to platinum-based chemotherapy (PBC) could significantly increase event-free survival (EFS) and drug responses (9). Similar results were also validated in the TD-FOREKNOW study (Camrelizumab) (10). In adjuvant therapy, the KEYNOTE-091 study showed that the addition of pembrolizumab to PBC could significantly increase disease-free survival (DFS) (11). The IMpower010 study also confirmed that adding atezolizumab to PBC could improve DFS and overall survival (OS), especially in patients with programmed cell death 1 ligand 1 (PD-L1)-positive NSCLC (12). Regarding the use of immunotherapy in combination of neoadjuvant and adjuvant therapy, both the KEYNOTE-671 study (pembrolizumab) and the AEGEAN study (durvalumab) found that perioperative immunotherapy could significantly improve OS and EFS, and similar results were also validated in the NADIM II study (nivolumab) (13–15).

This study conducted a meta-analysis based on randomized controlled trials (RCTs) to evaluate the impact of perioperative immunotherapy with neoadjuvant PBC on survival, pathological responses, and adverse reactions.

Abbreviations: AEs, Adverse effects; ALK, Anaplastic lymphoma kinase; ALTD, AEs leading to treatment discontinuation; BMI, Body mass index; DFS, Disease-free survival; Durva, Durvalumab; ECOG, Eastern Cooperative Oncology Group; EFS, Event-free survival; EFSR, Event-free survival rate; EGFR, Epidermal growth factor receptor; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HR, Hazard ratio; LC, Lung cancer; M/F, male/female; MPR, Major pathological response; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse; Nivo, Nivolumab; NSCLC, Non-small cell lung cancer; ORR, Objective response rate; OS, Overall survival; OSR, Overall survival rate; P, Probability; PCR, Pathological complete response; PD-L1, Programmed cell death 1 ligand 1; Pembro, Pembrolizumab; PICOS, Participants, Intervention, Control, Outcome and Study design; PIO, Perioperative immunotherapy; PP, Perioperative placebo; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; RR, Risk ratio; TPS, Tumor cell Proportion Score.

Materials and methods

This study was conducted in accordance with PRISMA guidelines and registered in PROSPERO (ID: CRD42023487475) (Supplementary Table S1).

Search strategy

The search strategy involved the use of keywords: "lung cancer," "randomized," and immune checkpoint inhibitors (nivolumab, pembrolizumab, treprinumab, cedilimumab, camrelizumab, tislelizumab, penpulimab, zimberelimab, serplulimab, durvalumab, atezolizumab, envolizumab, sugemalimab, adebrelimab, ipilimumab, and tremelimumab). Seven databases (PubMed, ScienceDirect, Ovid MEDLINE, the Cochrane Library, Scopus, EMBASE and Web of Science) were thoroughly searched for eligible RCTs from the inception of the databases to November 15, 2023 (Supplementary Table S2). Additionally, we reviewed the reference lists of the included RCTs to identify any further eligible studies.

Selection criteria

The studies published in English were selected following PICOS criteria:

(1) Participants (P): patients with stage II-III NSCLC, evaluated per the American Joint Committee on Cancer staging system, 8th edition (16).

(2) Intervention (I): neoadjuvant (PBC+immunotherapy) + adjuvant (immunotherapy), defined as the perioperative immunotherapy (PIO) group.

(3) Control (C): neoadjuvant (PBC+placebo) + adjuvant (placebo), defined as the perioperative placebo (PP) group.

(4) Outcomes (O): survival (OS, EFS), pathological responses, and adverse events (AEs).

(5) Study design (S): RCTs.

Articles lacking initial data, as well as meta-analyses, conference articles, and case reports, were not considered for inclusion. Distinct articles covering the same trial with diverse outcomes were included, but for identical outcomes, only the most recent data were utilized in the analysis.

Data extraction

Two investigators independently extracted data, including study characteristics (publication date, first author, etc.), participant details (sex, age, etc.), cancer specifics (histopathology, stage, etc.), antitumor effectiveness (OS, EFS, pathological responses, etc.), and counts of adverse events (total AEs, serious AEs, etc.). Disagreements were resolved through a process of re-evaluation and discussion.

Outcome assessments

The primary endpoints analyzed were OS and EFS. Simultaneously, the overall survival rate (OSR) and event-free survival rate (EFSR) at 6, 12, 18, 24, 30, 36, 42, and 48 months were compared between the two groups. Additionally, we examined EFS within specific subgroups, including patient characteristics (sex, age, etc.), histologic features, pathological stage, T stage, N stage, PD-L1 tumor cell proportion score (TPS), epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) translocation, pathological response (major pathological response [MPR]), and pathological response (pathological complete response [PCR]).

Quality assessment

We assessed the quality of RCTs using the Jadad scale, a 5-point system reflecting randomization, blinding, and patient inclusion. A score of ≥3 points was considered indicative of high quality (17). Additionally, the Cochrane Risk Assessment Tool was employed, which evaluates bias related to selection, performance, detection, attrition, and reporting and categorizes risk as low, unclear, or high (18). The results are presented in a bias graph.

We assessed the quality of the results using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method, which primarily encompasses bias, indirectness, inaccuracy, and publication bias. The outcomes are classified into four levels: very low, low, medium, and high (19).

Statistical analysis

The pooled data were assessed using Review Manager 5.3. Hazard ratios (HR) were employed for the analysis of survival data, favoring the PIO group when HR < 1. For dichotomous variables, we used the risk ratio (RR), with results favoring the PP group when RR > 1, particularly in the AE analysis. Conversely, support for the PIO group emerged in the analysis of OSR, EFSR, and drug responses. Heterogeneity was assessed using the I^2 statistic and $\chi 2$ test. In cases where I^2 was less than 50% or p was greater than 0.1, indicating the absence of significant heterogeneity, we employed a fixed-effects model; otherwise, a random-effects model was utilized. Statistical significance was defined by P values less than 0.05, and we assessed publication bias by visually inspecting funnel plots.

Results

Search results

Three high-quality RCTs (KEYNOTE-671, NADIM II, and AEGEAN) were included in the analysis. The PIO group included 820 patients, and the PP group included 803 patients (Figure 1, Supplementary Figure S1, Supplementary Table S3) (13–15). These comprised two global multicenter studies (KEYNOTE-671 and AEGEAN) and one study conducted in Spain (NADIM II) (13–15). As per the GRADE method, the quality of all results was categorized within the medium-high range (Supplementary Table S4). Table 1 provided a summary of the baseline information for the included studies.

Antitumor efficacy

The OS in the PIO group surpassed that in the PP group (HR: 0.63 [0.49-0.81], p = 0.0003; Figure 2). At 24-48 months, OSR favored the PIO group (OSR-24 m, RR: 1.07 [1.00, 1.15]; OSR-30 m, RR: 1.16 [1.07, 1.26]; OSR-36 m, RR: 1.23 [1.12, 1.35]; OSR-42 m, RR: 1.23 [1.12, 1.36]; OSR-48 m, RR: 1.49 [1.32, 1.68]) (Supplementary Figure S2). As survival extended, PIO demonstrated an increasing OS advantage compared to PP (Figures 3A, C).

The EFS in the PIO group surpassed that in the PP group (HR: 0.61 [0.52, 0.72], p < 0.00001; Figure 2). At 6-48 months, EFSR favored the PIO group (EFSR-6 m, RR: 1.11 [1.06, 1.16]; EFSR-12 m, RR: 1.22 [1.14, 1.31]; EFSR-18 m, RR: 1.28 [1.18, 1.40]; EFSR-24 m, RR: 1.36 [1.24, 1.49]; EFSR-30 m, RR: 1.49 [1.35, 1.65]; EFSR-36

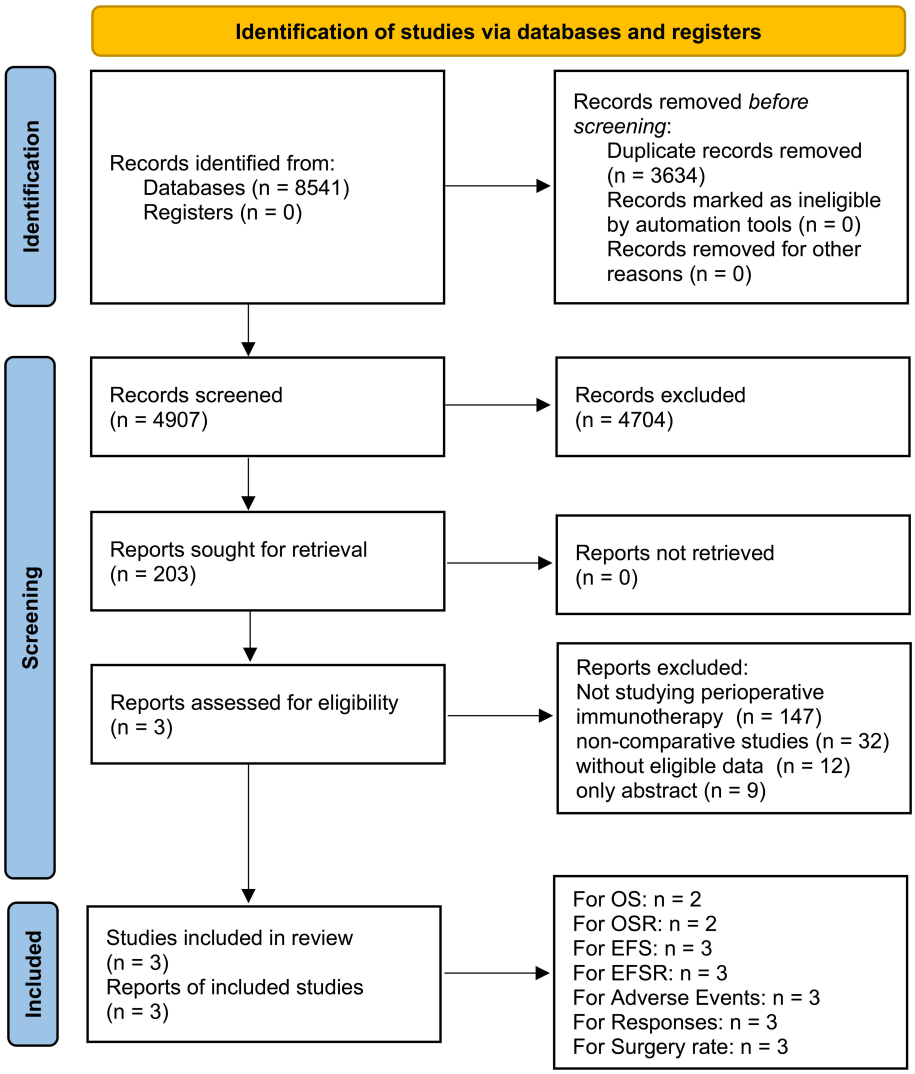

FIGURE 1
Study selection flow.

m, RR: 1.51 [1.36, 1.69]; EFSR-42 m, RR: 1.52 [1.36, 1.70]; EFSR-48 m, RR: 1.84 [1.52, 2.23]; Supplementary Figure S3). Regarding extended survival, PIO demonstrated an increasing advantage in EFS compared to PP (Figures 3B, D).

In subgroup analysis, EFS tended to favor the PIO group across most subgroups. High BMI (>25), advanced T stage (IV), involved N stage (N1-N2), and favorable pathological response (with PCR) might benefit PIO treatment. Simultaneously, the EFS advantage of PIO increased with higher PD-L1 expression (PD-L1 TPS, < 1%, RR: 0.77 [0. 59-1.00]; 1-49%, RR: 0.56 [0. 42-0.73]; > 50%, RR: 0.48 [0. 35-0.67]) (Figure 4).

The objective response rate (ORR, RR: 2.21 [1.91, 2.54]), PCR (RR: 4.36 [3.04, 6.25]), and MPR (RR: 2.79 [2.25, 3.46]) surpassed those in the PIO group (Figure 5). The surgery rates were similar between the two groups, and the R0 resection rate (RR: 1.08 [1.01, 1.16]) was higher in the PIO group (Supplementary Figure S4). The started rate (RR: 1.08 [1.01, 1.15]) and completed rate (RR: 1.13 [0.98, 1.30]) of adjuvant therapy tended to favor the PIO group (Supplementary Figure S5).

Toxicity

To summarize, PIO treatment resulted in a greater incidence of serious AEs (28.96% vs. 23.51%, RR: 1.24 [1.05, 1.46]) and AEs leading to treatment discontinuation (ALTD, 12.84% vs. 5.81%, RR: 2.21 [1.58, 3.10]). Total AEs, grade 3-5 AEs and fatal AEs tended to favor the PP group without significant differences (Table 2, Supplementary Figure S6).

In the neoadjuvant treatment phase, total AEs, grade 3-5 AEs, serious AEs, and fatal AEs tended to favor the PP group without a significant difference (Table 2, Supplementary Figure S7). More cases of rash, pruritus, increased alanine aminotransferase, hypothyroidism, and pneumonitis were found in the PIO group

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TABLE 1 Characteristics of the three randomized controlled trials (KEYNOTE-671, NADIM II and AEGEAN).

Study	KEYNOTE-671		NADIM II		AEGEAN	
Register number	NCT03425643		NCT03838159		NCT03800134	
Design	RCT		RCT		RCT	
Clinical trial stage	Phase III		Phase II		Phase III	
Included articles	Wakelee 2023 (13)		Provencio 2023 (14)		Heymach 2023 (15)	
Country	Global multicenter		Spain		Global multicenter	
Period	2018.04-2021.12		2019.06-2021.02		2019.01-2022.04	
Treatment arm	PIO	PP	PIO	PP	PIO	PP
Neoadjuvant therapy	PBC+Pembro 4 cycles	PBC+Placebo 4 cycles	PBC+Nivo 3 cycles	PBC+Placebo 3 cycles	PBC+Durva 4 cycles	PBC+Placebo 4 cycles
Adjuvant therapy	Pembro up to 13 cycles	Placebo up to 13 cycles	Nivo up to 6 cycles	Placebo up to 6 cycles	Durva up to 12 cycles	Placebo up to 12 cycles
Patients (n)	397	400	57	29	366	374
Sex (M/F)	279/118	284/116	36/21	16/13	252/114	278/96
Median age (year)	63	64	65	63	65	65
Race category						
White	250	239	57	29	206	191
Asian	124	125	0	0	143	164
Others	23	36	0	0	17	19
ECOG status						
0	253	246	31	16	251	255
1	144	154	26	13	115	119
Smoking status						
Current	96	103	30	21	95	95
Former	247	250	22	8	220	223
Never	54	47	5	0	51	56
Histologic classification						
Squamous	226	173	21	14	169	193
Nonsquamous	171	227	36	15	197	181
TNM stage						
II	118	121	0	0	104	110
IIIA	217	225	44	24	174	165
IIIB	62	54	13	5	88	98
PD-L1 expression						
<1%	138	151	20	9	122	125
1-49%	127	115	21	11	135	142
>50%	132	134	16	9	109	107
Cut off time (months)	25.2		26.1		34	
Tumor response assessment	RECIST, version 1.1		RECIST, version 1.1		RECIST, version 1.1	

(Continued)

TABLE 1 Continued

Study	KEYNOTE-671	NADIM II	AEGEAN
PD-L1 expression			
Adverse events assessment	NCI-CTCAE, version 4.03	NCI-CTCAE, version 5.0	NCI-CTCAE, version 5.0
Funding	Merck Sharp and Dohme	Bristol Myers Squibb	AstraZeneca

Durva, Durvalumab; ECOG, Eastern Cooperative Oncology Group; M/F, male/female; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse; Nivo, Nivolumab; PD-L1, Programmed cell death 1 ligand 1; Pembro, Pembrolizumab; PIO, Perioperative immunotherapy; PP, Perioperative placebo; RCT, Randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors.

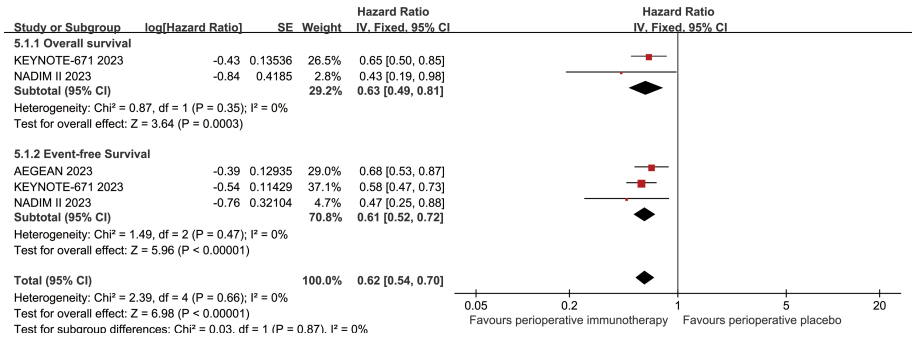

FIGURE 2
Forest plots of overall survival and event-free survival associated with perioperative immunotherapy versus perioperative placebo.

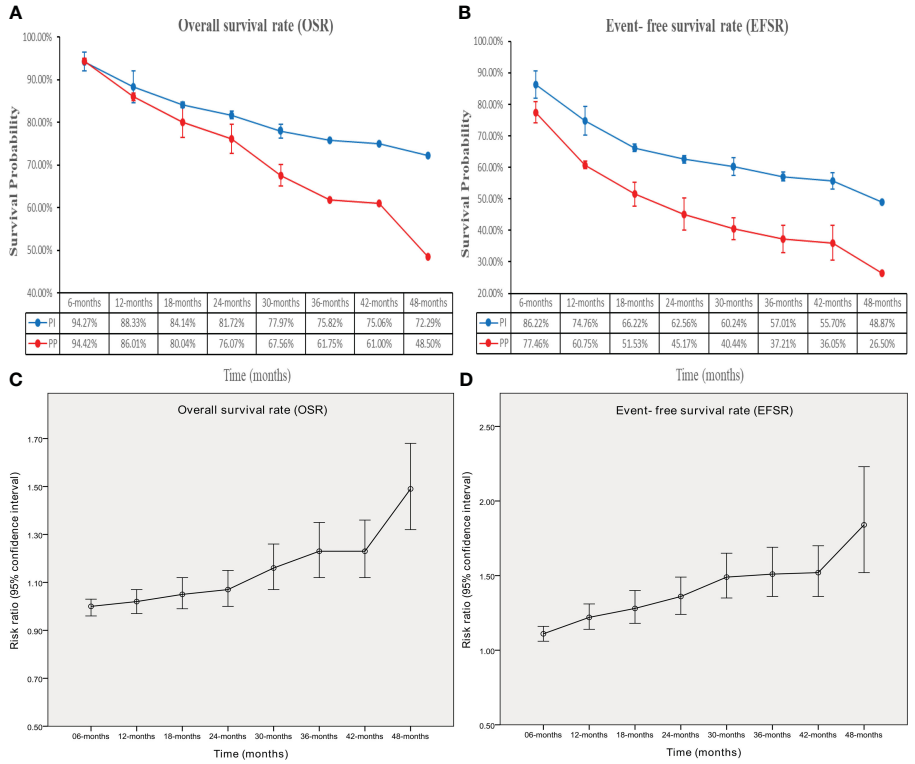

FIGURE 3
Comparisons of overall survival rate (6-48 months, **A**: trend of overall survival rate; **C**: trend of risk ratios) and event-free survival rate (6-48 months, **B**: trend of event-free survival rate; **D**: trend of risk ratios) associated with perioperative immunotherapy versus perioperative placebo according to survival time.

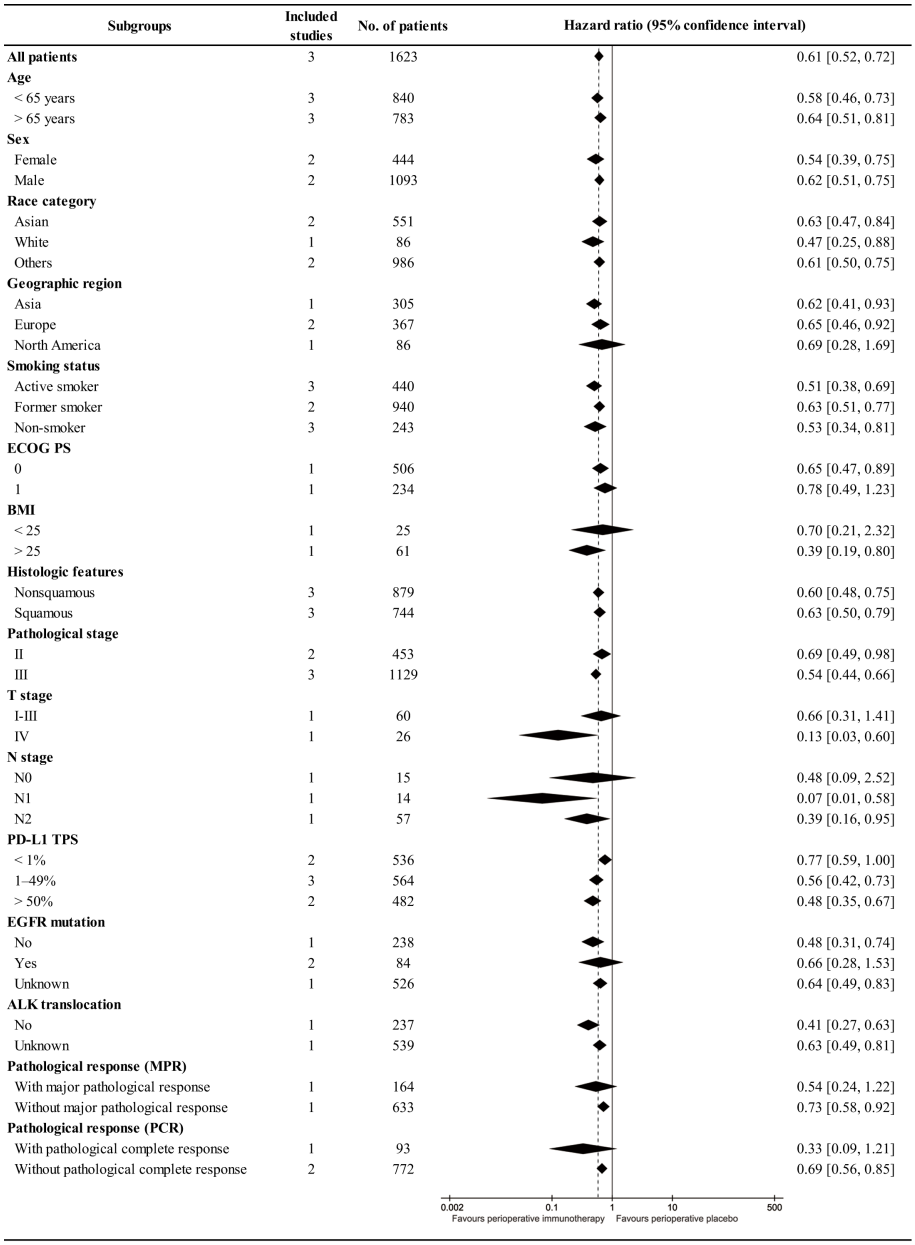

FIGURE 4
Subgroup analysis of event-free survival.

(Supplementary Table S5). There was no significant difference in the incidence of all grade 3-5 adverse events between the two groups in the neoadjuvant treatment phase (Supplementary Table S6).

In the surgical treatment phase, total AEs, grade 3-5 AEs, serious AEs, and fatal AEs tended to favor the PP group without a significant difference. PIO treatment was associated with more ALTD (4.79% vs. 1.75%, RR: 2.73 [1.16, 6.43]) (Table 2, Supplementary Figure S8). More diarrhea of any grade was found in the PIO group (Supplementary Table S7). There was no significant difference in the incidence of all grade 3-5 adverse events between the two groups in the surgical treatment phase (Supplementary Table S8).

In the adjuvant treatment phase, PIO treatment resulted in a greater incidence of total AEs (40.09% vs. 20.51%, RR: 1.97 [1.58, 2.46]) and grade 3-5 AEs (7.30% vs. 3.75%, RR: 1.95 [1.06, 3.58]). Serious AEs and fatal AEs tended to favor the PP group, but the difference was not significant (Table 2, Supplementary Figure S9). More grade pruritus, rash, and hypothyroidism were found in the PIO group (Supplementary Table S9). There was no significant difference in the incidence of all grade 3-5 adverse events between the two groups in the adjuvant treatment phase (Supplementary Table S10).

Sensitivity analysis

Analysis of ORR, surgery rate, and R0 resection rate revealed significant heterogeneity. Excluding any study did not affect the

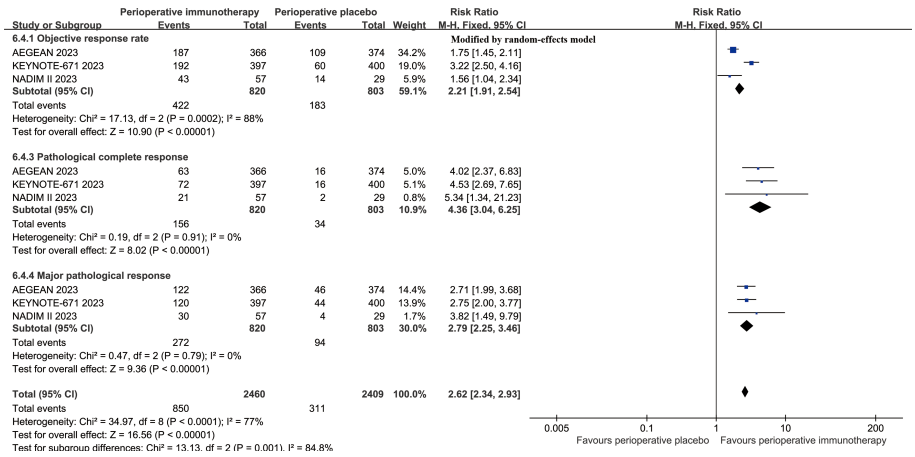

FIGURE 5
Forest plots of pathological responses (objective response rate, pathological complete response, and major pathological response) associated with perioperative immunotherapy versus perioperative placebo according to survival time.

TABLE 2 Summary of adverse events.

Adverse events	Studies involved	PIO		PP		Risk ratio [95% CI]	P
		Event/total	%	Event/total	%		
During all phases							
Total adverse events	3	806/820	98.29%	781/803	97.26%	1.01 [0.99, 1.03]	0.19
Grade 3-5 adverse events	3	360/820	43.90%	324/803	40.35%	1.11 [0.99, 1.25]	0.07
Serious adverse events	2	221/763	28.96%	182/774	23.51%	1.24 [1.05, 1.46]	0.01
Fatal adverse events	2	27/763	3.54%	18/774	2.33%	1.53 [0.85, 2.74]	0.15
Adverse event leading to treatment discontinuation	2	98/763	12.84%	45/774	5.81%	2.21 [1.58, 3.10]	<0.00001
During the Neoadjuvant Treatment Phase							
Total adverse events	2	436/454	96.04%	403/429	93.94%	1.02 [0.99, 1.05]	0.23
Grade 3-5 adverse events	2	173/454	38.11%	149/429	34.73%	1.14 [0.95, 1.35]	0.15
Serious adverse events	1	56/397	14.11%	52/400	13.00%	1.09 [0.76, 1.54]	0.65
Fatal adverse events	1	3/397	0.76%	3/400	0.75%	1.01 [0.20, 4.96]	0.99
During the Surgical Treatment Phase							
Total adverse events	1	231/397	58.19%	226/400	56.50%	1.03 [0.91, 1.16]	0.63
Grade 3-5 adverse events	1	84/397	21.16%	68/400	17.00%	1.24 [0.93, 1.66]	0.14
Serious adverse events	1	59/397	14.86%	54/400	13.50%	1.10 [0.78, 1.55]	0.58
Fatal adverse events	1	9/397	2.27%	5/400	1.25%	1.81 [0.61, 5.36]	0.28
Adverse event leading to treatment discontinuation	1	19/397	4.79%	7/400	1.75%	2.73 [1.16, 6.43]	0.02
During the Adjuvant Treatment Phase							
Total adverse events	2	182/454	40.09%	88/429	20.51%	1.97 [1.58, 2.46]	<0.00001
Grade 3-5 adverse events	1	29/397	7.30%	15/400	3.75%	1.95 [1.06, 3.58]	0.03
Serious adverse events	1	16/397	4.03%	7/400	1.75%	2.30 [0.96, 5.54]	0.06
Fatal adverse events	1	1/397	0.25%	0/400	0.00%	3.02 [0.12, 73.97]	0.50

CI, confidence interval; P, Probability; PIO, Perioperative immunotherapy; PP, Perioperative placebo.

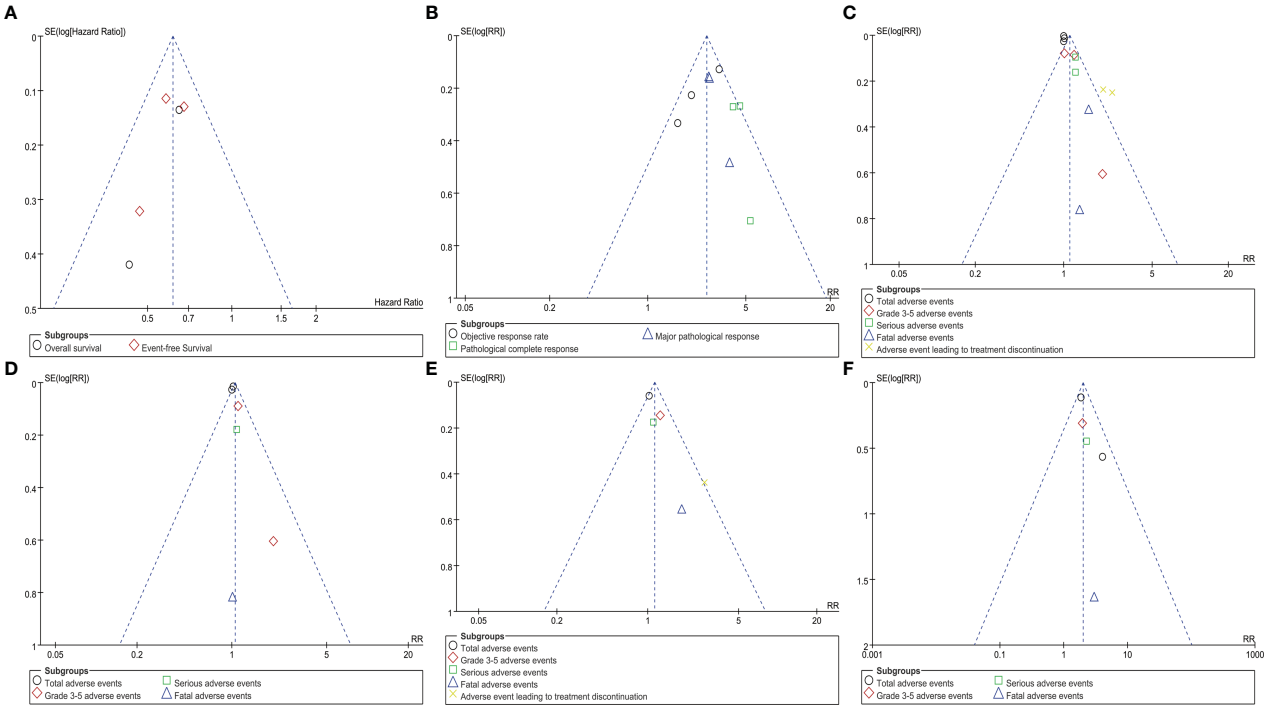

FIGURE 6
Funnel plots of survival summary **(A)**, pathological responses **(B)**, adverse events' summary during all treatment phase **(C)**, adverse events' summary during the neoadjuvant treatment phase **(D)**, adverse events' summary during the surgical treatment phase **(E)**, adverse events' summary during the adjuvant treatment phase **(F)** associated with perioperative immunotherapy versus perioperative placebo according to survival time.

stability or reliability of the results, as indicated by the sensitivity analysis (Supplementary Figure S10).

Publication bias

Symmetrical funnel plots were observed for survival summary (Figure 6A), pathological responses (Figure 6B), and AEs (Figures 6C-F), indicating acceptable publication bias.

Discussion

Resectable stage II-III NSCLC cases can have improved outcomes if neoadjuvant and/or adjuvant treatment is given in addition to surgery (20–22). However, although traditional PBC can improve patient survival, it is very limited (23, 24). In recent years, the introduction of immunotherapy in neoadjuvant therapy and adjuvant therapy for resectable NSCLC has brought new hope to the long-term survival of these patients (9–15). This study represents the first meta-analysis analyzing the perioperative use (neoadjuvant +adjuvant) of immunotherapy for stage II-III NSCLC based on RCTs. The results suggested that PIO exhibited superior efficacy in OS, EFS, ORR, PCR, MPR, R0 resection rate, and rate of adjuvant treatment compared with PP. In safety assessment, more serious AEs and ALTD were found in the PIO group.

The primary advantage of PIO treatment lies in improved survival, particularly in terms of OS. In this study, the HR for survival was 0.63 [0.49-0.81] for OS and 0.61 [0.52, 0.72] for EFS. EFS is currently the primary endpoint in most RCTs on the perioperative treatment of NSCLC. In neoadjuvant therapy, the HR of EFS was 0.63 [0.43-0.91] in the CheckMate 816 study (9). In adjuvant therapy, the HR of EFS was 0.66 [0.50-0.88] in the Impower 010 study and 0.76 [0.63-0.91] in the KEYNOTE-091 study (11, 12). In addition, the Neotorch study (toripalimab) has reported interim research results with EFS (HR, 0.40 [0. 277-0. 565]) in ASCO 2023 (25). Thus, many scholars believed that the combined use of immunotherapy during the perioperative period might bring more survival benefits to patients than using neoadjuvant therapy and adjuvant therapy alone (8, 26). Meanwhile, this study also confirmed that PIO demonstrated an increasing advantage in survival (OS, EFS) compared to PP, which was consistent with the tail effect of immunotherapy (27). In the subgroup analysis, EFS tended to favor the PIO group in almost all subgroups. BMI (>25), T stage (IV), N stage (N1-N2) and pathological response (with PCR) were favorable factors in the PIO group, as substantiated in several studies (28, 29). Additionally, the EFS advantage of the PIO group increased with increasing PD-L1 expression (PD-L1 TPS, < 1%, RR: 0.77 [0.59-1.00]; 1-49%, RR: 0.56 [0.42-0.73]; > 50%, RR: 0.48 [0.35-0.67]).

Neoadjuvant immunotherapy may have improved survival benefits, although a direct comparative randomized trial would need to be conducted to determine this (30, 31). Therefore, the pathological response and its impact on surgical treatment are crucial indicators for evaluating drug efficacy. In summary, the ORR, PCR and MPR were 51.46%, 19.02% and 32.44% in the PIO

group, which was similar to the results of NADIM study and SAKK 16/14 study (32, 33). In this study, patients in the PIO group achieved better ORR (RR: 2.21 [1.91, 2.54]), PCR (RR: 4.36 [3.04, 6.25]) and MPR (RR: 2.79 [2.25, 3.46]) compared to patients in the PP group. Similar results were also confirmed by the CheckMate 816 study and the Neotorch study (9, 25). Better pathological response was also associated with increased surgery rate (82.07% vs. 79.58%) and R0 resection rate (75.24% vs. 67.87%), playing a crucial role in the long-term survival of patients. Furthermore, we confirmed that the EFS advantage in the PIO group was particularly notable in the PCR subgroup. Therefore, it can be indirectly confirmed that a better pathological response could lead to a better prognosis in perioperative immunotherapy.

Safety is another concern in the perioperative and long-term use of immunotherapy after surgery. The IMpower010 trial reported that Atezolizumab-related adverse events leading to hospitalization occurred in 7% of the surgery groups (34). In clinical practice, although the incidence of AEs in immunotherapy is often much lower than that in chemotherapy, immune related AEs (such as pneumonitis, myocarditis, etc.) are often challenging to manage and can substantially impact the quality of life (35). At different periods of this study, it was observed that the incidence of total AEs, grade 3-5 AEs, serious AEs, and fatal AEs was higher in the PIO group than in the PP group in varying degrees, especially during the neoadjuvant treatment phase. In this phase, the top 5 AEs in the PIO group were nausea (41.15%), anemia (36.17%), neutrophil count decreased (30.28%), constipation (26.87%), and fatigue (23.17%), similar to those in the PP group. These common AEs are often associated with chemotherapy (13). The incidences of rash, pruritus, alanine aminotransferase increased, hypothyroidism, and pneumonitis were significant higher in the PIO group. These significantly increased AEs are often associated with immunotherapy (36). Therefore, although PIO can substantially improve survival, the monitoring and treatment of AEs at different phases still requires close attention.

This meta-analysis has limitations. Firstly, the inclusion of only English articles may introduce language bias. Secondly, including only 3 RCTs may reduce the overall clinical value. Thirdly, all the data analyzed were extracted from previously published articles, leading to increased data heterogeneity. Fourthly, the absence of individual patient data prevented a meta-analysis at the patient level, potentially decreasing the clinical value. Fifthly, variations in median follow-up times across studies might contribute to increased data heterogeneity.

Conclusion

PIO appears superior to PP for resectable stage II-III NSCLC, exhibiting better survival (OS and EFS) and improved pathological responses. Survival tended to favor the PIO group across almost all subgroups. Additionally, PIO demonstrated an increased advantage in survival compared to PP with longer follow up and increased PD-L1 expression. However, the higher rate of AEs in the PIO group warrants serious consideration.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

AY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FF: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. XL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. MW: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. MY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. WZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1351359/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Cochrane Risk Assessment.

SUPPLEMENTARY FIGURE 2
Comparisons of overall survival rate (6-48 months) associated with perioperative immunotherapy versus perioperative placebo according to survival time.

SUPPLEMENTARY FIGURE 3
Comparisons of event-free survival rate (6-48 months) associated with perioperative immunotherapy versus perioperative placebo according to survival time.

SUPPLEMENTARY FIGURE 4
Forest plots of surgery rate and R0 resection rate associated with perioperative immunotherapy versus perioperative placebo according to survival time.

SUPPLEMENTARY FIGURE 5
Treatment summary of adjuvant phase.

SUPPLEMENTARY FIGURE 6
Forest plots of adverse events' summary during all treatment phase associated with perioperative immunotherapy versus perioperative placebo.

SUPPLEMENTARY FIGURE 7
Forest plots of adverse events' summary during the neoadjuvant treatment phase associated with perioperative immunotherapy versus perioperative placebo.

SUPPLEMENTARY FIGURE 8
Forest plots of adverse events' summary during the surgical treatment phase associated with perioperative immunotherapy versus perioperative placebo.

SUPPLEMENTARY FIGURE 9
Forest plots of adverse events' summary during the adjuvant treatment phase associated with perioperative immunotherapy versus perioperative placebo.

SUPPLEMENTARY FIGURE 10
Sensitivity analysis of objective response rate **(A)**, surgery rate **(B)**, and R0 resection rate **(C)**.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. (2023) 73:17–48. doi: 10.3322/caac.21763.

2. Wolf AMD, Oeffinger KC, Shih TY, Walter LC, Church TR, Fontham ETH, et al. Screening for lung cancer: 2023 guideline update from the American Cancer Society. *CA Cancer J Clin*. (2023). doi: 10.3322/caac.21811

3. Expert Consensus Panel, Kidane B, Bott M, Spicer J, Backhus L, Chaft J, et al. The American Association for Thoracic Surgery (AATS) 2023 Expert Consensus Document: Staging and multidisciplinary management of patients with early-stage non-small cell lung cancer. *J Thorac Cardiovasc Surg*. (2023) 166:637–54. doi: 10.1016/j.jtcvs.2023.04.039.

4. Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, et al. Management of stage III non-small-cell lung cancer: ASCO guideline. *J Clin Oncol*. (2022) 40:1356–84. doi: 10.1200/JCO.21.02528.

5. Fillon M. Adding immunotherapy to chemotherapy improves survival for endometrial cancer patients. *CA Cancer J Clin*. (2023) 73:445–7. doi: 10.3322/caac.21809.

6. Yu S, Zhai S, Gong Q, Xiang C, Gong J, Wu L, et al. Neoadjuvant immunotherapy and non-small cell lung cancer: A systematic review and meta-analysis of randomized controlled trials. *Am J Clin Oncol*. (2023) 46:517–28. doi: 10.1097/COC.0000000000001046.

7. Li Z, Zhang X, Wang Y, Yu Z, Yang C, Zhou Y, et al. Adjuvant therapy in completely resected, EGFR-mutant non-small cell lung cancer: a comparative analysis of treatment efficacy between EGFR-TKI and anti-PD-1/PD-L1 immunotherapy. *J Immunother Cancer*. (2023) 11:e007327. doi: 10.1136/jitc-2023-007327.

8. Lovly CM. Perioperative immunotherapy-A KEY toward improved outcomes for early-stage lung cancer? *N Engl J Med*. (2023) 389:560–1. doi: 10.1056/NEJMe2305762.

9. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. (2022) 386:1973–85. doi: 10.1056/NEJMoa2202170.

10. Lei J, Zhao J, Gong L, Ni Y, Zhou Y, Tian F, et al. Neoadjuvant camrelizumab plus platinum-based chemotherapy vs chemotherapy alone for chinese patients with resectable stage IIIA or IIIB (T3N2) non-small cell lung cancer: the TD-FOREKNOW randomized clinical trial. *JAMA Oncol*. (2023) 9:1348–55. doi: 10.1001/jamaoncol.2023.2751.

11. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. (2022) 23:1274–86. doi: 10.1016/S1470-2045(22)00518-6

12. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. (2021) 398:1344–57. doi: 10.1016/S0140-6736(21)02098-5.

13. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med*. (2023) 389:491–503. doi: 10.1056/NEJMoa2302983.

14. Provencio M, Nadal E, González-Larriba JL, Martínez-Martí A, Bernabé R, Bosch-Barrera J, et al. Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. (2023) 389:504–13. doi: 10.1056/NEJMoa2215530.

15. Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med*. (2023) 389:1672–84. doi: 10.1056/NEJMoa2304875.

16. Edwards JG, Chansky K, Van Schil P, Nicholson AG, Boubia S, Brambilla E, et al. The IASLC lung cancer staging project: analysis of resection margin status and proposals for residual tumor descriptors for non-small cell lung cancer. *J Thorac Oncol*. (2020) 15:344–59. doi: 10.1016/j.jtho.2019.10.019

17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. (1996) 17:1–12. doi: 10.1016/0197-2456(95)00134-4.

18. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. (2011) 343:d5928. doi: 10.1136/bmj.d5928.

19. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*. (2011) 64:380–2. doi: 10.1016/j.jclinepi.2010.09.011.

20. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN guidelines® Insights: non-small cell lung cancer, version 2.2023. *J Natl Compr Canc Netw*. (2023) 21:340–50. doi: 10.6004/jnccn.2023.0020

21. Wang C, Chen KN, Chen Q, Wu L, Wang Q, Li X, et al. Neoadjuvant nivolumab plus chemotherapy versus chemotherapy for resectable NSCLC: subpopulation analysis of Chinese patients in CheckMate 816. *ESMO Open*. (2023) 8:102040. doi: 10.1016/j.esmoop.2023.102040.

22. Felip E, Altorki N, Zhou C, Vallières E, Martínez-Martí A, Rittmeyer A, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Ann Oncol*. (2023) 34:907–19. doi: 10.1016/j.annonc.2023.07.001.

23. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet*. (2014) 383:1561–71. doi: 10.1016/S0140-6736(13)62159-5.

24. Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev*. (2015) 2015:CD011430. doi: 10.1002/14651858.CD011430.

25. Lu S, Wu L, Zhang W, Zhang P, Wang WX, Fang WT, et al. Perioperative toripalimab+platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): interim event-free survival (EFS) analysis of the phase III Neotorch study. *J Clin Oncol*. (2023) 41:Suppl:425126. doi: 10.1200/JCO.2023.41.36_suppl.425126

26. Ni Y, Lei J, Huang W, Wang J, Guo H, Lv F, et al. Systematic review of the perioperative immunotherapy in patients with non-small cell lung cancer: evidence mapping and synthesis. *Front Oncol*. (2023) 13:1092663. doi: 10.3389/fonc.2023.1092663.

27. Sim JK, Choi J, Lee SY. Perioperative immunotherapy in stage IB-III non-small cell lung cancer: a critical review of its rationale and considerations. *Korean J Intern Med*. (2023) 38:787–96. doi: 10.3904/kjim.2023.345.

28. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med*. (2019) 25:141–51. doi: 10.1038/s41591-018-0221-5.

29. Zhao J, Hao S, Li Y, Liu X, Liu Z, Zheng C, et al. Comparative efficacy and safety of neoadjuvant immunotherapy with chemotherapy versus chemotherapy alone in non-small cell lung cancer: A propensity score and inverse probability treatment weighting analysis. *Immunotargets Ther*. (2023) 12:113–33. doi: 10.2147/ITT.S437911.

30. Gaudreau PO, Negrao MV, Mitchell KG, Reuben A, Corsini EM, Li J, et al. Neoadjuvant chemotherapy increases cytotoxic T cell, tissue resident memory T cell, and B cell infiltration in resectable NSCLC. *J Thorac Oncol*. (2021) 16:127–39. doi: 10.1016/j.jtho.2020.09.027.

31. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science*. (2020) 367:eaax0182. doi: 10.1126/science.aax0182.

32. Provencio M, Serna-Blasco R, Nadal E, Insa A, García-Campelo MR, Casal Rubio J, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). *J Clin Oncol*. (2022) 40:2924–33. doi: 10.1200/JCO.21.02660.

33. Rothschild SI, Zippelius A, Eboulet EI, Savic Prince S, Betticher D, Bettini A, et al. SAKK 16/14: durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small-cell lung cancer-A multicenter single-arm phase II trial. *J Clin Oncol*. (2021) 39:2872–80. doi: 10.1200/JCO.21.00276.

34. Lee JM, Vallières E, Ding B, Johnson A, Bhagwakar J, Rashidi S, et al. Safety of adjuvant atezolizumab after pneumonectomy/bilobectomy in stage II-IIIA non-small cell lung cancer in the randomized phase III IMpower010 trial. *J Thorac Cardiovasc Surg*. (2023) 166:655–666.e7. doi: 10.1016/j.jtcvs.2023.01.012.

35. Xu Y, Lyu X, Qin Y, Ma D, Wang M, Shi J, et al. Multi-organs perioperative immune-related adverse events and postoperative bronchial anastomotic fistula in a patient receiving neoadjuvant immunotherapy with NSCLC. *Thorac Cancer*. (2022) 13:2340–5. doi: 10.1111/1759-7714.14567.

36. Anpalakhan S, Huddar P, Behrouzi R, Signori A, Cave J, Comins C, et al. Immunotherapy-related adverse events in real-world patients with advanced non-small cell lung cancer on chemoimmunotherapy: a Spinnaker study sub-analysis. *Front Oncol*. (2023) 13:1163768. doi: 10.3389/fonc.2023.1163768.

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EDITED BY
Aakash Desai,
University of Alabama at Birmingham, United States

REVIEWED BY
Magdalena Knetki-Wróblewska,
Maria Sklodowska-Curie National Research Institute of Oncology, Poland
Xiaofei Wang,
Tennessee State University, United States

*CORRESPONDENCE
Nir Peled
nirp@szmc.org.il

†These authors have contributed equally to this work and share first authorship

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Case report: The effect of induction targeted therapies in stage III driver mutants non-small cell lung cancer

Waleed Kian[1,2,3†], Belal Krayim[1†], Betsy Giles[3], Nasim A. Elkiaan[3], Amjad Idris[4], Daniel Fink[4], Nir Peled[1*] and Laila C. Roisman[1]

[1]Helmsley Cancer Center, Shaare Zedek Medical Center, Jerusalem, Israel, [2]Institute of Oncology, Samson Assuta Ashdod University Hospital, Ashdod, Israel, [3]Ben-Gurion University of the Negev, Be'er Sheva, Israel, [4]Thoracic Surgery Department, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Over the past decade, progress in the diagnosis and treatment of Non-Small Cell Lung Cancer (NSCLC) has led to the identification of many targeted mutations. This has enhanced PFS and OS in both advanced and early-stage NSCLC. The current standard of care for stage III NSCLC varies, and it may combine chemotherapy with either immunotherapy or radiotherapy. This study evaluated the role of induction targeted therapies in patients with driver mutations and inoperable NSCLC.

Methods: This is a single-center, retrospective study assessing the efficacy of targeted therapy in resectable stage III NSCLC patients who are *EGFR* or *ALK*-positive, using patient records, PET-CT, brain MRI staging, and mediastinal lymph node evaluation.

Results: Between January 2020 and February 2024, we identified four patients with either *EML4-ALK* fusions (2/4) or *EGFR* mutations (2/4) who underwent treatment with brigatinib or osimertinib before surgery. All patients experienced clinical benefits. Of the two patients with *ALK* fusion, one responded almost completely, while the other exhibited a notable partial response. Among the patients with *EGFR* mutations, one had a complete response and the other displayed a significant partial response. All four patients subsequently underwent lobectomy surgical resection.

Conclusions: This case series highlights the potential of targeted therapies for resectable NSCLC in the neoadjuvant setting. Further research is required to confirm their benefits, assess their safety and efficacy, and determine optimal timing and sequencing.

KEYWORDS

brigatinib, osimertinib, neoadjuvant, *ALK*, *EGFR*, lung cancer

Introduction

Lung cancer, the most common form of cancer globally, has the highest mortality rate among all cancers. Smoking is the primary risk factor. Lung cancer is broadly classified into two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC, which makes up around 85% of cases, includes subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (1). Technological advancements and immunohistochemical techniques have enabled personalized treatments based on specific driver mutations in individual tumors, providing new hope for lung cancer patients (2).

Patients who undergo surgical resection are still at a high risk of relapse. To address this concern, adjuvant and neoadjuvant chemotherapy have been studied extensively and have shown promising results in improving disease-free survival (DFS) and overall survival (OS) (3–5). In addition to chemotherapy, recent trials have explored the potential benefits of adjuvant immunotherapy and targeted therapy in patients with early-stage disease. One notable study is a phase III trial that compared adjuvant atezolizumab to the standard of care (SOC) in patients with resected stage II or III disease and PD-L1 expression of 1% or greater. The results of this trial demonstrated a significant improvement in DFS for patients with PD-L1 >1% and OS, particularly for those with high PD-L1 expression (>50%) (6, 7). Another important trial investigated the use of adjuvant pembrolizumab versus placebo in patients with stage IB-III, regardless of tumor proportion score PD-L1 expression. This study also revealed a notable enhancement in DFS (8).

Finally, the ADAURA trial, a phase III trial comparing adjuvant osimertinib to SOC, demonstrated an improvement in DFS and OS for patients with *EGFR* mutant NSCLC (9, 10). Furthermore, the Phase III ALINA trial also showed an improvement in DFS with the addition of adjuvant alectinib (11). These results, along with those from other ongoing trials, highlight the integration of immunotherapy and targeted therapies in the treatment approach for patients with surgically resected NSCLC. As a result, the FDA and EMA have granted approvals for specific populations.

In the neoadjuvant setting, a phase III trial comparing chemotherapy and nivolumab with chemotherapy alone demonstrated an improvement in the rate of pathological complete response and event-free survival in patients with stage IB-IIIA disease (12). Neoadjuvant trials have explored new endpoints, such as major and complete pathological response, which could potentially serve as surrogate endpoints in future trials. We recently published a Phase II trial focusing on neoadjuvant Osimertinib in Stage III *EGFR*-positive NSCLC, followed by definitive radiation and/or surgery. The trial showed a high response rate of 95.2% with excellent safety, as well as a nearly 50% reduction in the radiation field (13). In light of this, we present four patients who received neoadjuvant targeted therapies for potentially resectable stage III NSCLC with oncogenic driver mutations (*EGFR* or *ALK*), with the goal of determining their efficacy in this setting.

Methods

This document pertains to a single-center, retrospective, observational study aimed at assessing the efficacy of neoadjuvant targeted therapy in patients with potentially resectable NSCLC harboring *EGFR* or *ALK*-positive mutations. Data were extracted from patient records, including PET-CT scans, brain MRI for baseline tumor staging (according to the AJCC 8th edition), and pathological evaluation of mediastinal lymph nodes. Eligible patients demonstrated normal organ function, adequate pulmonary function, and an Eastern Cooperative Oncology Group performance status score of zero. Driver mutations were confirmed through next-generation sequencing.

Among the cohort, two patients had *ALK* fusions and two had *EGFR* mutations, all of whom received targeted tyrosine kinase inhibitor (TKI) therapies. Patients with *ALK* fusion genes were treated with brigatinib at a daily dosage of 180mg, while those with *EGFR* mutations received osimertinib at a daily dosage of 80mg. It is important to note that the off-label use of treatment in these cases was conducted as part of a local scientific project.

PET-CT scans and brain MRIs were utilized to evaluate treatment efficacy. Following induction of targeted therapy, all responsive patients underwent surgery, after which pathological response was assessed.

Case presentation

Case 1

In August 2021, a 51-year-old non-smoking female underwent a routine imaging exam which revealed the presence of a 5 cm mass in the left lower lobe. This mass was diagnosed as adenocarcinoma of lung origin through a CT-guided biopsy. Further testing using PET-CT showed significant fluorodeoxyglucose (FDG) uptake in the left lower lobe and moderate uptake in the mediastinal lymph nodes on the same side, indicating the absence of distant metastasis (Figure 1). Brain MRI results were negative for intracranial metastasis.

According to the American Joint Committee on Cancer (AJCC) 8th Edition, the patient's condition was classified as T3N2M0. To address the patient's condition, the multidisciplinary team decided to initiate neoadjuvant treatment with brigatinib, followed by surgery. After six weeks of treatment, a chest CT showed a partial response with significant tumor shrinkage. Subsequently, the patient underwent left lower lobectomy and mediastinal lymph node dissection. The pathology report indicated a pathological response of pT1cN2 and negative Spread through air spaces (STAS). Currently, the patient is 27 months post-surgery and is undergoing adjuvant treatment with a daily dose of 90mg of brigatinib. Recent PET-CT scan and brain MRI results showed no evidence of disease, as summarized in Table 1.

Case 2

A 46-year-old nonsmoking female presented with a suspicious mass on a chest x-ray while hospitalized with SARS-CoV-2 in February 2021. A chest CT scan revealed a 5.5 cm mass involving the costophrenic angle in the right lower lobe. A subsequent PET-CT scan revealed high FDG uptake in the right lower lobe and

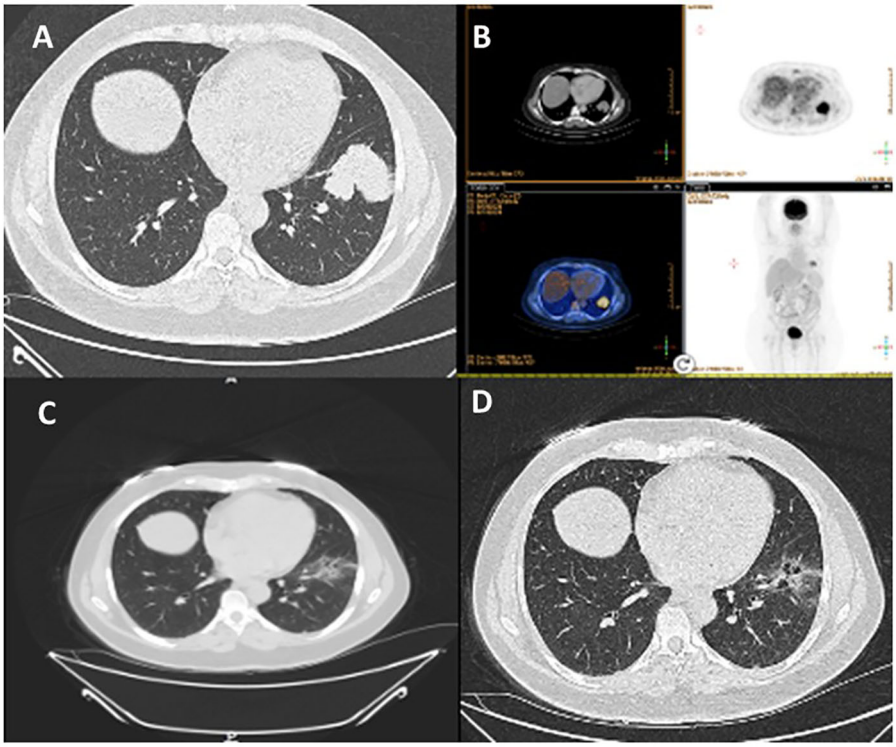

FIGURE 1
Case 1: A 51-year-old female with NSCLC-adenocarcinoma and *EML4–ALK* fusion. **(A)** Chest CT shows a 5cm mass in the left lower lobe, classified as T3N2M0. **(B)** PET-CT scan indicates no metastasis. **(C, D)** Follow-up CT chest after 6 weeks of treatment with brigatinib 180mg daily.

moderate FDG uptake in the ipsilateral mediastinal lymph nodes but no distant metastasis (Figure 2). An MRI of the brain revealed no evidence of intracranial metastasis. Adenocarcinoma of the lung was confirmed by CT-guided biopsy and tissue next-generation sequencing revealed an *EML4-ALK* fusion rearrangement. The patient was classified as T3N2M0. The patient began neoadjuvant brigatinib, but experienced side effects such as fever and weakness, resulting in a 50% reduction in dosage from 180mg to 90mg, which was maintained for 7 weeks. Based on a follow-up chest CT, the patient showed a partial response to treatment, with 60% remarkable tumor shrinkage. The patient had a right lower lobectomy and mediastinal lymph node dissection (pT1cN1 pathological response, STAS negative). Following surgery, the patient received adjuvant brigatinib 90 mg once daily for 32

TABLE 1 Summary of patient characteristics and treatments.

	P1	P2	P3	P4
Age	51	46	74	59
Histology	ADC	ADC	ADC	ADC
Symptoms	No	Cuogh	Cough/dyspnea Weight loss	No
Smoker status	Never	Never	Never	Never
Stage at diagnosis	T3N2M0	T3N2M0	T2bN2M0	T2aN2M0
Brain mets	NO	NO	NO	NO
Driver mutation	ALK-EML4 fusion	ALK-EML4 fusion	EGFR L858R&L861Q	EGFR exon 19 deletion
PDL-1 status	PDL-1 <1%	PDL-1 <1%	PDL-1 1-49%	PD-L1 > 50%.
Targeted therapy	Brigatinib 180 mg	Brigatinib 180 mg	Osimertinib 80 mg	Osimertinib 80 mg
Duration of neoadjuvant treatment	6 weeks	7 weeks	12 weeks	12 weeks

(Continued)

TABLE 1 Continued

	P1	P2	P3	P4
Best response %	PR	PR	PR	CR
Surgical procedure	VATS LLL lobectomy	VATS RLL lobectomy	VATS RUL lobectomy	VATS LUL lobectomy
Pathlogical respnse	T1cN2	T1cN1	pT1aN0	pCR
Adjuvant treatment	Brigatinib 90 mg	Brigatinib 90 mg	No	osimertinib 80mg
DFS	27 month	32 month	42 month	24 months
Recurrence disease	No	No	No	NO

ADC, Adenocarcinoma; PD-L1, Programmed death ligand; RUL, Right upper lobe; LLL, Left lower lobe; LUL, Left upper lobe; RLL, Right lower lobe; VAST, Video,assisted thoracoscopic surgery; pCR, pathological complete response; PR, partial response, CR, complete response; DFS, disease free survival.

months, with no evidence of disease detected on PET-CT. An MRI also revealed no brain metastases, as summarized in Table 1.

Case 3

In January 2020, a 74-year-old female non-smoker was diagnosed with a 3.5 cm mass in the right upper lobe during a routine imaging examination. A PET-CT scan revealed high FDG uptake in the right upper lobe and moderate FDG uptake in the ipsilateral mediastinal lymph nodes, without distant metastasis (Figure 3). Brain MRI showed no intracranial metastasis. A CT-guided biopsy revealed lung adenocarcinoma. Tissue next-generation sequencing showed an EGFR L858R and L861Q mutations. According to the AJCC 8th Edition guidelines, the patient was staged as T2bN2M0. The patient was treated with osimertinib for 12 weeks, demonstrating a partial response to treatment of 80% on chest CT. In August 2020, the patient underwent right upper lobectomy and mediastinal lymph node dissection (pT1aN0 pathological response, STAS negative). Following recovery from surgery, no adjuvant therapy was taken. After 42 months of follow-up, there was no evidence of disease on PET-CT or brain MRI, as summarized in Table 1.

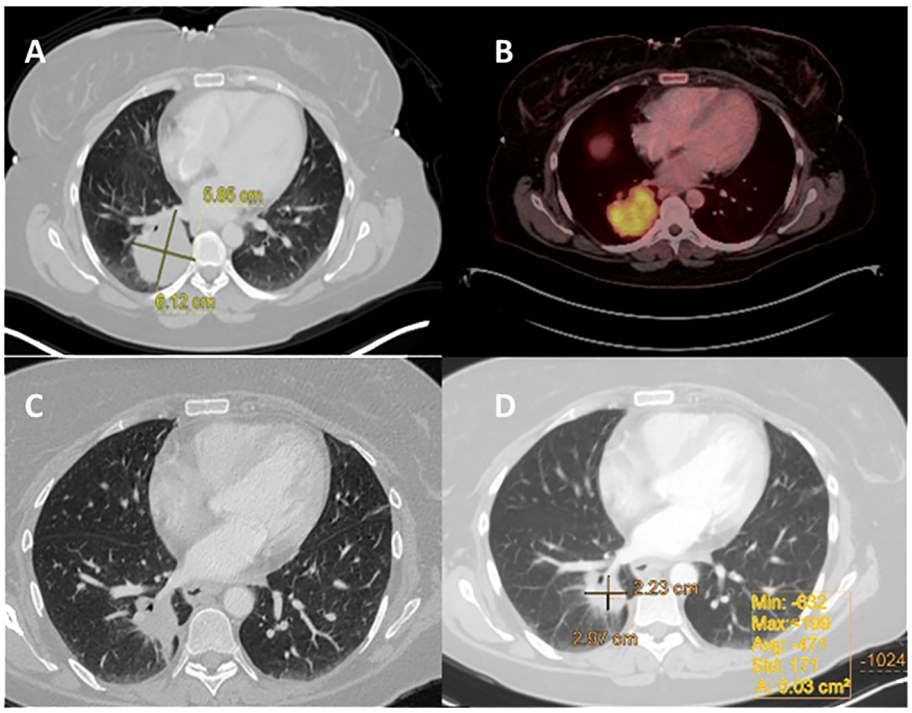

FIGURE 2
Case 2: A 46-year-old female with NSCLC-adenocarcinoma and *EML4-ALK* Fusion. **(A)** Chest CT shows a right lower lobe (RLL) mass measuring 5.5 cm, with a staging of T3N0M0. **(B)** PET CT shows FDG uptake in the RLL mass measuring 5.5 cm, without metastasis. **(C, D)** After 6 weeks of treatment with brigatinib 180 mg daily, CT chest was performed.

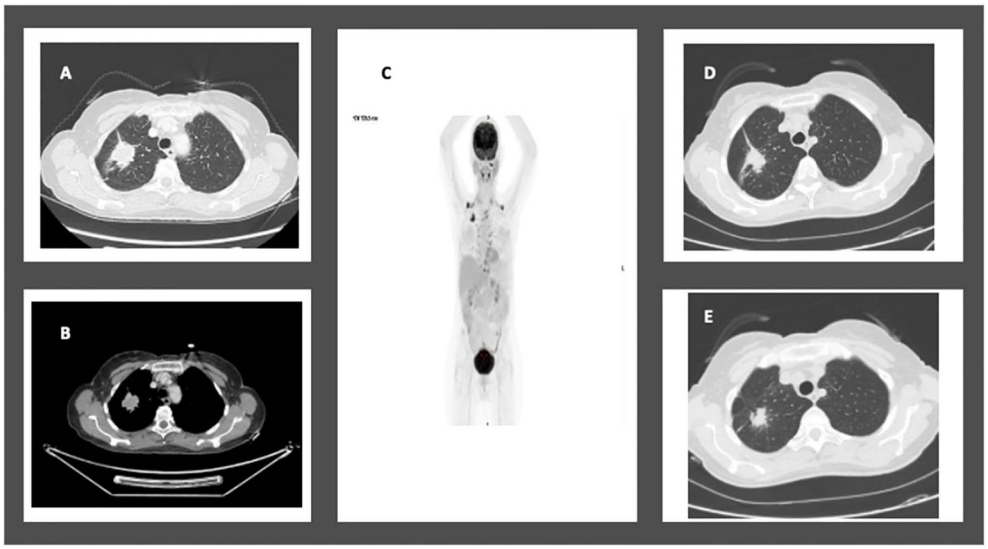

FIGURE 3
Case 4: A 74-year-old female with NSCLC-adenocarcinoma and *EGFR* exon 21 L858R mutation. **(A, B)** Chest CT showing a 3.5cm mass in the right upper lobe. **(C)** RUL mass and moderate FDG uptake in the ipsilateral mediastinal lymph nodes. **(D, E)** CT chest after 12 weeks of treatment with Osimertinib 80mg daily showing partial response.

Case 4

A 59-year-old former smoker was diagnosed with a 3.7 cm mass in her left lower lung lobe during a routine imaging exam in September 2021. A PET-CT scan revealed high FDG uptake in the left upper lobe and moderate FDG uptake in both the ipsilateral and contralateral mediastinal lymph nodes, with no distant metastasis (Figure 4). No intracranial metastasis was detected on a brain MRI.

A CT-guided biopsy confirmed the mass to be an adenocarcinoma of lung origin. Tissue next generation sequencing revealed an *EGFR* exon 19 deletion. The patient was classified as T2aN2M0.

The patient started treatment with Osimertinib, taking an 80 mg dose daily for 12 weeks. This resulted in a radiological complete response on the PET-CT. In February 2022, she underwent a resection of the left upper lobe, achieving a pathological complete response. She continued with adjuvant Osimertinib treatment. After

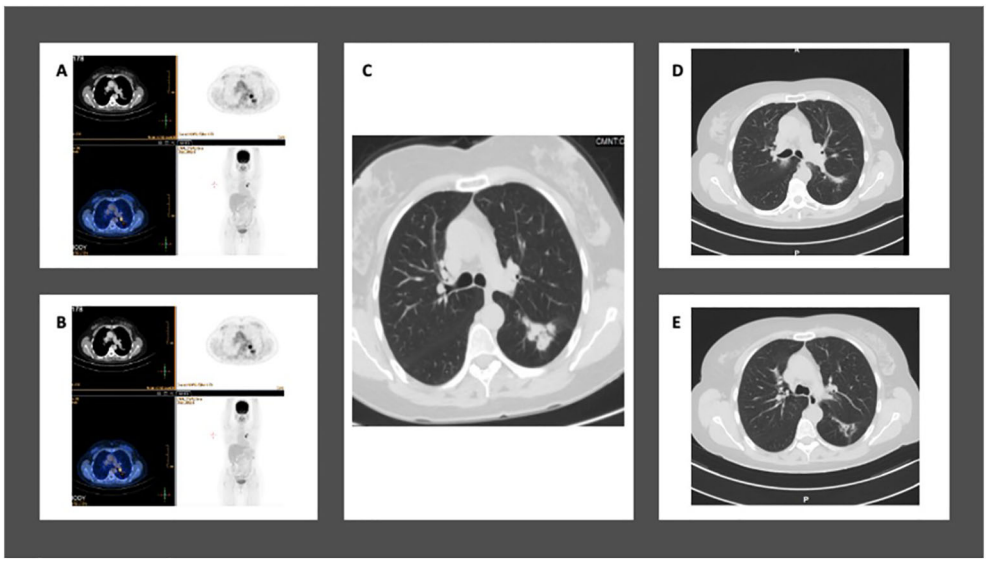

FIGURE 4
Case 5: A 59-year-old female with NSCLC-adenocarcinoma and *EGFR* exon 19 deletion. **(A, B)** PET-CT shows a 3.5 cm mass in the left lower lobe with mediastinal lymph nodes, but without distant metastasis. The staging is T2aN2M0. **(C)** Chest CT shows a mass in the left lower lobe measuring 3.5 cm. **(D, E)** After 12 weeks of treatment with Osimertinib at a daily dose of 80 mg, CT chest shows complete response.

24 months of follow-up, there is no sign of metastasis on her PET-CT and brain MRI, as summarized in Table 1.

Results

Between January 2020 and February 2024, four enrolled participants received targeted therapy. All patients had been diagnosed with adenocarcinoma, with two Stage IIIA patients and two Stage IIIB patients. The participants characteristics shown in Tables 1, 2. Representative radiologic and pathological responses after 6 to 12 weeks of brigatinib or osimertinib are shown in Table 3.

Among the two patients who had an *ALK* fusion, one showed a radiological response of 90%, while the other showed a partial response of 60%. The first *EGFR* patient had a partial radiological response rate of about 80%, while the second patient had a complete radiological response. During neoadjuvant therapy, only one patient experienced grade 3 side effects (fever and weakness) that necessitated a dose reduction, as summarized in Table 4.

All the patients underwent lobectomy resection. After surgery, one patient had a major pathological response (MPR), another patient had a complete pathological response, and the other two had a partial pathological response. The patients underwent postoperative follow-up using PET-CT and brain MRI every four months. All patients showed no evidence of disease. The treatment regimen was tolerable, and no new adverse events related to the targeted therapies osimertinib and brigatinib were reported, shown in Table 4.

TABLE 2 Demographics.

Patient Characteristics (n = 4)	
Age, years	
Median (range)	59 (46-74)
Gender, n (%)	
Male	0 (0)
Female	4 (100)
Smoking history n (%)	
Never smoker	4 (100)
Former smoker	0 (0)
Performance status, n (%)	
0	4 (100)
1	0
Tumor histology, n (%)	
Adenocarcinoma	4 (100)
Driver -mutation Type, n (%)	
Exon 19 deletion	1 (25)
Exon 21 L858R & L861Q	1 (25)
ALK-EML4 fusion	2 (50)
Stage, n (%)	
IIIA	2 (50)
IIIB	2 (50)

EGFR, epidermal growth factor receptor.

TABLE 3 Radiological and pathological outcomes of induction targeted therapy.

Outcome	Osimeratinib/ Brigatinib (N=4)
Radiologic outcome; ORR (95% CI)	100% (4)
Complete response	25% (1)
Partial response	75% (3)
Stable disease	0%
Progression of disease	0%
Range of neoadjuvant DoT, months (95% CI)	6-12 weeks
Pathological outcome	
Complete pathological response	25% (1)
Major partial response	25% (1)
Partial response	50% (2)
Median DFS, months	18 months
Disease relapse	0/4

ORR, objective response rate; DoT, duration of treatment; DFS, disease free survival.

Discussion

The efficacy of the respective targeted therapies has been confirmed for patients with metastatic NSCLC (14, 15). These confirmatory trials suggest that these treatments prolong the progression free survival and overall survival compared to chemotherapy alone or the combination of chemo-immunotherapy (16, 17). The emergence of next-generation TKIs has ignited significant interest among researchers, with encouraging signs of sustained enhancements in disease-free survival rates observed across various intervals, as demonstrated in trials such as ADAURA with osimertinib. Furthermore, these advancements have led to

TABLE 4 Adverse event related to the targeted therapies osimertinib and brigatinib.

	Any grade	Grade1	Grade2	Grade3	Grade4
N=4 (%)					
Rash or acne	1 (25)	0	1 (25)	0	0
Diarrehea	3 (75)	2 (50)	1 (25)	0	0
Nausea	1 (25)	1 (25)	0	0	0
Fatigue	4 (100)	2 (50)	1 (25)	1 (25)	0
Anemia	2 (50)	0	2 (50)	0	0
Pyrexia	1(25)	0	0	1(25)	0

improved overall survival outcomes in the adjuvant treatment of EGFR-positive NSCLC (9, 10). Notably, the recent ALINA trial revealed that adjuvant alectinib, a second-generation ALK-TKI, significantly enhanced disease-free survival compared to platinum-based chemotherapy among patients with resected ALK-positive NSCLC of stage IB, II, or IIIA (18). The use of neoadjuvant targeted therapy in NSCLC remains an important topic for study as there are many advantages of administering molecular treatment with targeting molecules before planned definitive surgery to patients with non-metastatic disease (3, 12).

The exploration of neoadjuvant targeted therapy in NSCLC represents a pivotal area of investigation, offering several advantages, especially for patients with non-metastatic disease. Early-stage NSCLC management has seen notable progress, with studies indicating that neoadjuvant chemotherapy presents a viable alternative to adjuvant chemotherapy, leading to a substantial reduction in the relative risk of death, along with significant improvements in overall survival and time-to-distant recurrence (19, 20). Specifically, for stage IIIA (N2) NSCLC, several randomized-controlled trials and meta-analyses have shown a significant survival advantage with neoadjuvant chemotherapy. Preoperative chemoradiotherapy increases the proportion of complete resections (75% vs 60%), while also increasing the rate of mediastinal downstaging (46% vs. 29%, P=0.02) and pathological responses (60% vs. 20%, P=0.0001) (21). However, both treatment strategies appear to be effective.

Recent studies have reported encouraging outcomes of neoadjuvant chemo-immunotherapy in early-stage NSCLC, surpassing previous benchmarks set by neoadjuvant chemotherapy or chemoradiation alone (22). However, the role of immunotherapy in patients with oncogenic drivers remains under scrutiny, particularly due to observed low response rates in advanced disease (23, 24).

Approximately 15% of NSCLC cases present with locoregional N2 disease (stage IIIA). The optimal treatment strategies for patients with N2 disease, as well as the criteria for defining resectability, remain subjects of ongoing debate in thoracic oncology (25). While there is still controversy surrounding the definition of resectability, the management of patients with 'unresectable' N2 disease is more clear-cut. The current standard of care involves concurrent chemo-radiotherapy followed by maintenance therapy with durvalumab if there is no evidence of disease progression post-induction treatment, as demonstrated in the PACIFIC trial (21, 26). For patients with potentially resectable stage IIIA (N2) disease, various trimodal approaches, including surgery, perioperative chemotherapy, and radiotherapy, are being explored by multidisciplinary thoracic teams, particularly in cases where a microscopically margin-negative resection is anticipated. Significantly, several recently published phase III trials have assessed the efficacy of perioperative chemo-immunotherapy, encompassing resectable N2 diseases, demonstrating promising improvements in event-free survival and pathological complete response (27–29). Notably, the KEYNOTE 671 trial exhibited enhancements in overall survival (27). However, it is crucial to acknowledge that these trials included a limited number of patients with EGFR or ALK fusion mutations, rendering it challenging to draw definitive conclusions based on these findings.

The principal advantage of targeted therapy lies in its ability to commence treatment promptly, facilitating the reduction of micro-metastatic disease burden and potentially rendering tumors more amenable to surgery, particularly in cases of lymph node involvement or unresectable disease (30). Our case series underscores the effectiveness and reliability of targeted therapy as a perioperative treatment option for stage III NSCLC patients harboring EGFR mutations or ALK fusion. Promisingly, our findings revealed a median objective response rate of 100%, with no disease progression observed during the presurgical interval and no significant adverse events reported. Larger-scale studies are warranted to validate these findings across a broader patient population.

Conclusion

This case series provides insights into the potential benefits of targeted therapies for locally advanced non-small cell lung cancer (NSCLC) in the neoadjuvant setting. The findings suggest that the use of targeted therapies in this context could be a promising approach to improve treatment outcomes for NSCLC patients.

However, while these results are certainly encouraging, more research is necessary to fully establish the role of targeted therapies in the neoadjuvant setting for NSCLC. For example, further studies are needed to verify the effectiveness and safety of these treatments, and to develop a better understanding of the optimal timing and sequencing of such therapies.

Overall, the findings of this case series underscore the importance of ongoing research into new and innovative therapeutic approaches for NSCLC and suggest that targeted therapies may have a key role to play in improving outcomes for patients with this challenging disease.

Limitations

This case study has some limitations that should be taken into consideration. Firstly, the number of patients included in the study is relatively small, which may limit the generalizability of the results. Secondly, the follow-up period for these patients is relatively short. Thirdly, it is important to acknowledge that in actual clinical settings, postoperative patients who receive adjuvant treatments cannot be controlled compulsorily.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

WK: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. BK: Formal analysis, Data collection, Conceptualization, Writing – original draft. BG: Data analysis, Data collection, Conceptualization, Visualization, Writing – original draft. NE: Formal analysis, Conceptualization, Writing – original draft. AI: Formal analysis, Data collection, Conceptualization, Writing – original draft. DF: Formal analysis, Data Conceptualization, Visualization, Writing – review & editing. NP: Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing. LR: Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Kian W, Zemel M, Levitas D, Alguayn W, Remilah AA, Rahman NA, et al. Lung cancer screening: a critical appraisal. *Curr Opin Oncol.* (2022) 34:36–43. doi: 10.1097/CCO.0000000000000801

2. Guan X, Qin T, Qi T. Precision medicine in lung cancer theranostics: paving the way from traditional technology to advance era. *Cancer Control.* (2022) 29. doi: 10.1177/10732748221077351

3. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE collaborative group. *J Clin Oncol.* (2008) 26:3552–9. doi: 10.1200/JCO.2007.13.9030

4. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* (2012) 13:239–46. doi: 10.1016/S1470-2045(11)70393-X

5. Subramanian MP, Puri V. Neoadjuvant vs. adjuvant chemotherapy in locally advanced non-small cell lung cancer—is timing everything? *J Thorac Dis.* (2019) 11:5674. doi: 10.21037/JTD.2019.12.40

6. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet.* (2021) 398:1344–57. doi: 10.1016/S0140-6736(21)02098-5

7. Felip E, Altorki N, Zhou C, Vallières E, Martínez-Martí A, Rittmeyer A, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Ann Oncol.* (2023) 0. doi: 10.1016/j.annonc.2023.07.001

8. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol.* (2022) 23:1274–86. doi: 10.1016/S1470-2045(22)00518-6

9. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected EGFR -mutated non–small-cell lung cancer. *N Engl J Med.* (2020) 383:1711–23. doi: 10.1056/NEJMOA2027071

10. Herbst RS, Tsuboi M, John T, Kato T, Majem M, Grohé C, et al. Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC). *J Clin Oncol.* (2023) 41(17_suppl):LBA3–3. doi: 10.1200/JCO.2023.41.17_SUPPL.LBA3

11. ALINA study of alectinib meets primary DFS end point in ALK+ NSCLC. Available online at: https://www.targetedonc.com/view/alina-study-of-alectinib-meets-primary-dfs-end-point-in-alk-nsclc (Accessed February 10, 2024).

12. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med.* (2022) 386:1973–85. doi: 10.1056/NEJMOA2202170

13. Peled N, Roisman LC, Levison E, Dudnik J, Chernomordikov E, Heching N, et al. Neoadjuvant osimertinib followed by sequential definitive radiation therapy and/or surgery in stage III epidermal growth factor receptor-mutant non-small cell lung cancer: an open-label, single-arm, phase 2 study. *Int J Radiat Oncol Biol Phys.* (2023) 117. doi: 10.1016/J.IJROBP.2023.03.042

14. Shaw AT, Kim D-W, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK -positive lung cancer. *N Engl J Med.* (2013) 368:2385–94. doi: 10.1056/NEJMOA1214886

15. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med.* (2010) 362:2380–8. doi: 10.1056/NEJMOA0909530

16. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BCG, Jhanelle EO, Yuichiro Z, et al. Overall survival with osimertinib in untreated, *EGFR* -mutated advanced NSCLC. *N Engl J Med.* (2020) 382:41–50. doi: 10.1056/NEJMoa1913662

17. Camidge DR, Kim HR, Ahn M-J, Yang JC, Han JY, Lee JS, et al. Brigatinib versus crizotinib in ALK -positive non–small-cell lung cancer. *N Engl J Med.* (2018) 379:2027–39. doi: 10.1056/NEJMOA1810171

18. Wu Y-L, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, et al. Alectinib in resected *ALK* -positive non–small-cell lung cancer. *N Engl J Med.* (2024) 390:1265–76. doi: 10.1056/NEJMOA2310532

19. Shukla N, Hanna N. Neoadjuvant and adjuvant immunotherapy in early-stage non-small cell lung cancer. *Lung Cancer Targets Ther.* (2021) 12:51. doi: 10.2147/LCTT.S277717

20. Reyes R, Reguart N. Neoadjuvant treatment of stage IIIA-N2 in EGFR-Mutant/ALK-rearranged non-small cell lung cancer. *Transl Lung Cancer Res.* (2021) 10:607. doi: 10.21037/TLCR-20-780

21. Sher DJ. Neoadjuvant chemoradiotherapy for stage III non-small cell lung cancer. *Front Oncol.* (2017) 7:281. doi: 10.3389/FONC.2017.00281

22. Shao L, Lou G. Neoadjuvant immunotherapy in non-small cell lung cancer: a narrative review on mechanisms, efficacy and safety. *J Thorac Dis.* (2022) 14:3565–74. doi: 10.21037/JTD-22-1192/COIF

23. Upfront atezolizumab plus bevacizumab and chemo shows no significant PFS benefit in NSCLC. Available online at: https://www.targetedonc.com/view/upfront-

atezolizumab-plus-bevacizumab-and-chemo-shows-no-significant-pfs-benefit-in-nsclc (Accessed September 25, 2023).

24. Pembro plus chemo fails to show efficacy benefit in TKI-resistant, EGFR-mutated, metastatic nonsquamous NSCLC. Available online at: https://dailynews.ascopubs.org/do/pembro-plus-chemo-fails-show-efficacy-benefit-tki-resistant-egfr–mutated-metastatic (Accessed September 25, 2023).

25. Provencio-Pulla M, Nadal E, Larriba JLG, Martinez-Marti A, Bernabé R, Bosch-Barrera J, et al. Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: Primary endpoint results of pathological complete response (pCR) from phase II NADIM II trial. *J Clin Oncol*. (2022) 40 (16_suppl):8501–1. doi: 10.1200/JCO.2022.40.16_SUPPL.8501

26. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. (2022), JCO2101308. doi: 10.1200/JCO.21.01308

27. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. *N Engl J Med*. (2023) 389:491–503. doi: 10.1056/NEJMOA2302983

28. Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, et al. Perioperative durvalumab for resectable non–small-cell lung cancer. *N Engl J Med*. (2023) 389:1672–84. doi: 10.1056/NEJMOA2304875

29. Perioperative nivolumab plus chemotherapy improves event-free survival in resectable non–small cell lung cancer - the ASCO post. Available online at: https://ascopost.com/issues/december-10-2023-supplement-esmo-highlights/perioperative-nivolumab-plus-chemotherapy-improves-event-free-survival-in-resectable-non-small-cell-lung-cancer/ (Accessed May 14, 2024).

30. Peled N, Roisman LC, Levison E, Dudnik J, Chernomordikov E, Heching N, et al. Neoadjuvant osimertinib followed by sequential definitive radiotherapy and/or surgery in stage III EGFR-mutant NSCLC: An open-label, single-arm, phase II study. *Int J Radiat Oncol Biol Phys*. (2023). doi: 10.1016/J.IJROBP.2023.03.042

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