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Updates on combination therapy for lung cancer

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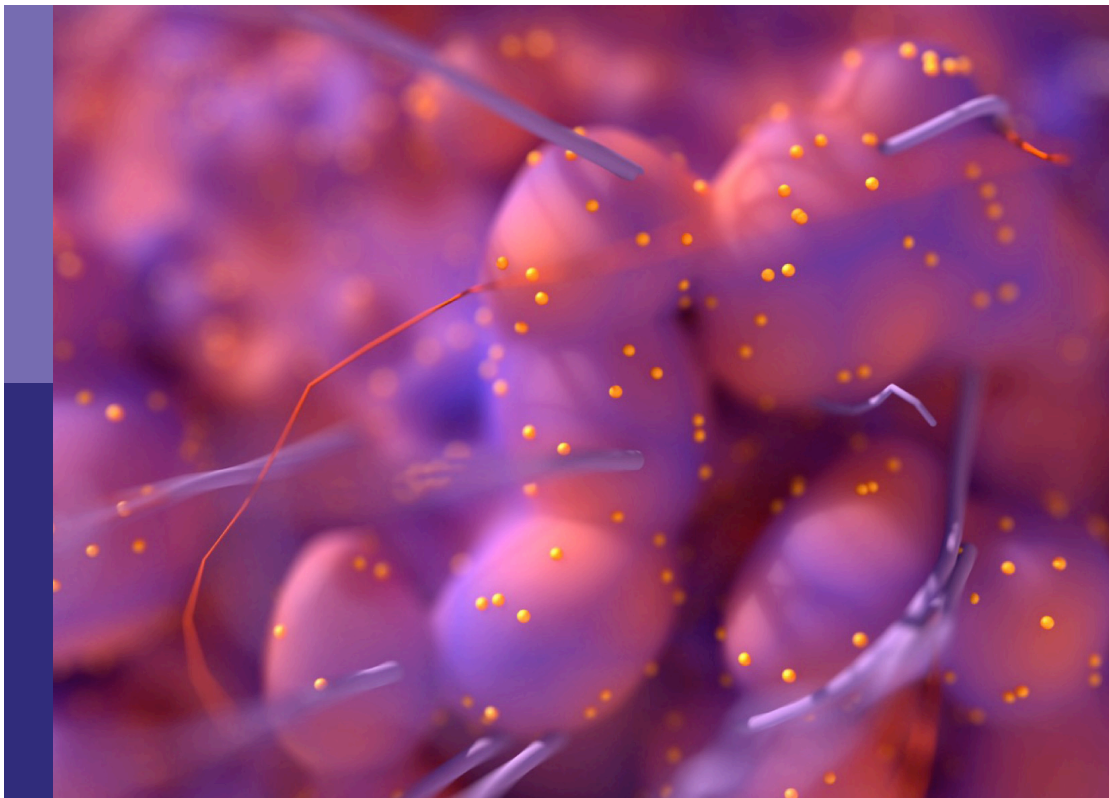

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Updates on combination therapy for lung cancer

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CASE REPORT
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Case Report: Durable Response to the Combination of Brigatinib and Cetuximab Plus Icotinib in a NSCLC Patient Harboring EGFR L858R-T790M-cis-G796S and L718Q Resistance Mutations Following Progression With Osimertinib

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The efficacy of osimertinib is severely limited by the emergence of EGFR C797S, which is detected in either the cis or trans position with T790M when osimertinib is used as a second-line treatment, and which is largely identified in combination with an EGFR 19 deletion. The EGFR T790M-cis-G796S mutation, which also occurs in exon 20 as C797S, participates in osimertinib resistance. To date, limited data for overcoming this resistance mutation have been reported. Here, we report data for an advanced NSCLC patient who developed EGFR L858R-T790M-cis-G796S and EGFR L718Q resistance co-mutations following progression with osimertinib. Such a case has rarely been reported, and under chemotherapy guidelines for this situation, no other effective treatment is recommended. The patient in our case experienced remarkable clinical improvement and good tolerance to the combination target therapy of brigatinib and cetuximab plus icotinib. At the time of our patient's last follow-up and prior to publication, our patient had reached more than 9 months of progression-free survival (PFS) and felt very well. Our finding provides clinical evidence that the combined target therapy of brigatinib and cetuximab may potentially be an effective treatment strategy for patients with an acquired EGFR T790M-cis-G796S resistance mutation following osimertinib treatment.

Keywords: brigatinib, cetuximab, T790M-cis-G796S, NSCLC, osimertinib resistance

INTRODUCTION

The third-generation, irreversible epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) osimertinib targets both the EGFR-sensitive mutation and the EGFR T790M resistance mutation following the progression of first- or second-generation EGFR-TKIs. Yet, most patients that have progressed on osimertinib have been found to have activation bypass pathways or newly acquired EGFR-resistant mutations (1). Recently, greater numbers of EGFR mutations have been determined for patients. However, the roles of these EGFR mutations in osimertinib resistance remain unknown. The

EGFR L718Q and EGFR G796S mutations have been reported to participate in osimertinib resistance, although limited data related to overcoming these resistance mutations have been reported (2, 3). Since there is currently no effective treatment strategy, with the exception of chemotherapy, understanding triple EGFR mutations in cis is now an unmet need. The combination of brigatinib and cetuximab has been reported to be an effective treatment for patients who acquire EGFR T790M-cis-C797S-mediated resistance to osimertinib (4). As such, brigatinib and cetuximab may be a promising treatment strategy for triple EGFR-resistant mutations.

Here, we report the first successful case for the combined use of brigatinib, cetuximab, and icotinib as a treatment for overcoming the resistance co-mutations of L858R-T790M-cis-G796S and EGFR L718Q following progression with osimertinib.

CASE PRESENTATION

In April 2018, a 61 year-old Chinese man, who was a former smoker, was diagnosed with Stage IV (T1N2M1) lung adenocarcinoma at Daping Hospital, located in Chongqing, China. Owing to the detection of an EGFR L858R mutation in tumor biopsy sample using the amplification-refractory mutation system (ARMS), the patient received gefitinib 250 mg/qd as a first-line treatment. The best objective response (OR) was a partial response (PR), with the carcinoma embryonic antigen (CEA) level decreasing from 109.38 to 14.65 ng/ml (**Figure 1**). The patient experienced an increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels during treatment with gefitinib. In December 2018, 8.1 months from the time of diagnosis, the patient developed progressive disease in the lung. Liquid biopsy from plasma using next-generation sequencing (NGS) identified T790M (mutant allele frequency (MAF): 2.60%) and L858R (MAF: 5.17%) mutations. Given this outcome, osimertinib 80 mg/qd was initiated, and the best OR was PR. Unfortunately, in September 2020, the patient once again experienced disease progression following 21.7 months of osimertinib treatment, with the CEA level increasing to 48.39 ng/ml. Chest CT scans revealed an enlargement of the primary lung tumor. Liquid biopsy NGS testing from plasma indicated that the EGFR L858R (MAF: 2.52%) and T790M (MAF: 0.22%) mutations remained. A new EGFR L718Q (MAF: 1.91%) mutation additionally emerged.

L718Q has been reported to be a resistance mechanism for osimertinib, although, according to previous reports (5, 6), it may be sensitive to first- or second-generation EGFR-TKIs. Given the hepatotoxicity of gefitinib and the fact that our patient's T790M mutation still existed, osimertinib 80 mg/qd plus icotinib 125 mg/tid was administrated beginning in October 2020. The best OR was stable disease (SD), with the CEA level decreasing to 17.09 ng/ml. Approximately 2.2 months later, the patient developed a cough and dyspnea, with the CEA level increasing to 96.00 ng/ml. Chest CT scans indicated that lymphangitic carcinomatosis had appeared. A plasma-based NGS assay was again performed and yielded a new EGFR G796S (MAF: 0.84%) mutation and a PIK3CA (MAF: 0.13%) mutation, in addition to the previously determined EGFR L858R (MAF: 2.30%), T790M (MAF: 0.78%), and L718Q (MAF: 1.41%) mutations.

For our patient, the EGFR G796S mutation, which also occurred in exon 20, existed in cis for T790M. T790M-cis-G796S has been reported to be a resistance mechanism for osimertinib and the lack of recommendations for subsequent treatment (2). Based on our previous studies, we understood that combined targeted therapy, consisting of brigatinib and cetuximab, may be an effective treatment strategy for patients with EGFR T790M-cis-C797S occurring in exon 20 and having a resistance to osimertinib (4). Therefore, since, at this point, no other targeted therapy options for EGFR T790M-cis-G796S and L718Q mutations existed given previous treatment interventions, beginning in February 2021, we decided to treat our patient with brigatinib (taken orally once daily at an initial dose of 90 mg for 7 days and increased to 180 mg from day 8) and cetuximab (500

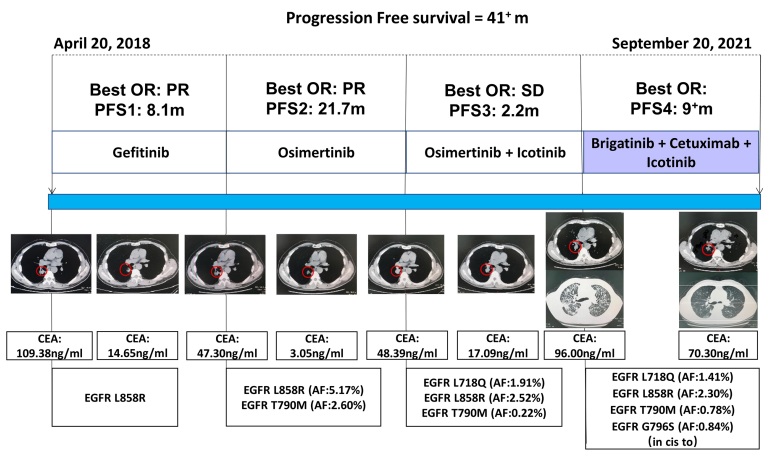

FIGURE 1 | The therapeutic regimens received, the associated best objective response (OR), progression-free survival (PFS), the CEA for each line of therapy, and the major mutations detected. PR indicates a partial response. SD indicates stable disease.

mg/m^2, administered intravenously on days 1 and 8 for a 21-day cycle) in combination with icotinib.

Given this new treatment plan, our patient's cough and dyspnea were significantly and quickly relieved. A follow-up CT scan demonstrated that the lung primary lesion had obviously shrank and that the best OR was PR. Until the time of the last follow-up and at the time of publication, our patient was still responding to the brigatinib and cetuximab plus icotinib treatment, with a PFS of more than 9 months. To date, the only reported treatment side effects have been a grade II rash and grade I fatigue.

DISCUSSION

Resistance mechanisms for osimertinib have been investigated for a long period of time. However, some resistance mechanisms remain largely unknown. The efficacy of osimertinib as a second-line treatment is severely limited by the emergence of EGFR C797S, detected in either the cis or trans position with T790M, and mostly identified in combination with an EGFR 19 deletion. Like EGFR C797S, EGFR T790M-cis-G796S mutation also occurs in exon 20 and participates in osimertinib resistance as well. However, limited data for overcoming this resistance mutation have been reported (3). EGFR G796S in cis with T790M indicates that a combination of different generations of EGFR-TKIs are unlikely to be successful (3).

A previous case report described a patient with an EGFR L858R-T790M-cis-G796S mutation following osimertinib treatment that was enrolled in a clinical trial of pembrolizumab in combination with the oral IDO-1 inhibitor epacadostat; the patient reached PR for at least 5 months (2). A recently updated case report for the same patient indicated that the patient responded to the treatment of amivantamab (JNJ-61186372) for more than 100 days following progression with pembrolizumab (7). Although the above treatments may be effective, the accessibility of these drugs prevents clinical application. The guideline for treatment following the progression of late-line osimertinib is limited, with only local therapies and systemic therapies such as chemotherapy being recommended.

For our case, in addition to an EGFR T790M-cis-G796S resistance mutation, EGFR L718Q also still existed, which increased treatment difficulty. Due to the lack of recommendations for subsequent treatment, with the exception of chemotherapy, we employed brigatinib and cetuximab, based on our previous experience (4), in order to overcome the EGFR L858R-T790M-cis-G796S-resistant mutation. Icotinib was continued as treatment for the EGFR L718Q mutation that still existed. Our patient provided written informed consent to receive this combination therapy. Fortunately, this combination targeted therapy was successful. After receiving four lines of targeted therapy, the PFS for our patient reached more than 9 months and he was, at the time of publication, still receiving this combination treatment.

Despite the fact that the three targeted drugs are currently being taken together, tolerant toxicity has been maintained. To our knowledge, this is the first case report that provides clinical evidence that brigatinib combined with cetuximab is a promising strategy for resolving EGFR L858R-T790M-cis-G796S-resistant mutation following osimertinib progression. Although, here, we are just providing a case report, we hope our experience can still shed some light for overcoming this EGFR tertiary-resistant mutation.

CONCLUSION

In this case report, we presented the first successful case of the combined use of brigatinib, cetuximab, and icotinib for overcoming the resistance co-mutations of EGFR L858R-T790M-cis-G796S and L718Q following progression with osimertinib. Our findings provide clinical evidence that the combined targeted therapy of brigatinib and cetuximab may be an effective treatment strategy for patients with an acquired EGFR T790M-cis-G796S resistance mutation following osimertinib progression.

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) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YW: writing—original draft preparation. RH: data curation, software. MZ: figure preparation. TH: original data collection. YH: writing—reviewing and editing. 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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CASE REPORT
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Multiple Primary Lung Cancers With ALK Rearrangement: A Case Report and Literature Review

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Multiple primary lung cancers (MPLCs) are that patients with lung cancer may present with two primary tumors at the same time (synchronous multiple primary lung cancer, SMPLC) or may develop a second, metachronous primary lung cancer after treatment of the initial lesion. Currently, there are no definitive guidelines for the diagnosis and treatment of multiple primary lung cancers. Herein, we report a case of double primary lung cancers with ALK rearrangement. The patient was treated with chemotherapy, targeted therapy, and radiotherapy. After these treatments, the patient was free of locally recurrent or distant disease at 2 years.

Keywords: multiple primary malignant neoplasms, small cell lung cancer, non-small cell lung cancer, combined small cell lung cancer, anaplastic lymphoma kinase

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INTRODUCTION

We report a case of double primary lung cancers (DPLCs) with ALK rearrangement and review the literature. The patient has provided her written informed consent for the publication of this manuscript and any identifying images or data. DPLC is one type of MPLC. MPLC is divided into synchronous MPLC (sMPLC) and metachronous MPLC (mMPLC). As the incidence of lung cancer soars, the diagnoses of patients with multiple primary lung cancers (MPLCs) increase (1, 2). Martini and Antakli et al. (3, 4) proposed the clinical and pathological diagnostic criteria of MPLCs. Furthermore, if MPLC is isolated and has no distant metastasis, surgical resection is still necessary (5). Therefore, invasive mediastinal staging and extrathoracic imaging (head computed tomography/magnetic resonance plus whole-body positron emission tomography or abdominal computed tomography plus bone scan) are recommended for patients with tumors located at different lung lobes.

Multiple primary lung cancers have many characteristics, one of which is that the focus has different histologic types or different molecular genetic characteristics or arises separately from foci of carcinoma *in situ* (3, 5), which provides us with a lot of help for the diagnosis of multiple primary lung cancers in the future. With the discovery of immunohistochemistry and genetic testing, the probability of multiple primary lung cancer detection increases gradually. In order to diagnose lung tumors, especially in cases with similar histopathological types, we can evaluate them by means of genotype or immunoassay, such as epidermal growth factor receptor (EGFR) and tumor protein 53 (TP53). It can provide not only evidence for diagnosis but also direction for follow-up treatment (6).

CASE PRESENTATION

On April 8, 2019, a 56-year-old woman visited our hospital for chronic persistent cough. The patient's symptoms lasted for 2 weeks without sputum or chest suffocation. Physical examination revealed an enlarged right-sided supraclavicular lymph, with a diameter of 2 cm, toughness, and an unclear boundary with the surrounding area. The respiratory sound of both lungs was normal. The patient had a family history of cancer, with his father dying of liver cancer and his mother suffering from bile duct cancer. Contrast-enhanced computed tomography (CT) of the chest showed mass in the lower lobe of the left lung and the right lower lung, which suggested that lung cancer might be considered (**Figures 1A–D**). On April 9, 2019, a lymph node biopsy was performed under ultrasound guidance, and the pathologic results showed small cell lung cancer (SCLC) (**Figures 2A–I**). Later, on April 15, 2019, positron emission tomography/computed tomography (PET/CT) showed positive lesions in the right lower lobe, mediastinal soft tissue, left lower lobe, bilateral hilum, and other sites (**Figure 3**).

According to American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) 8th Tumor Node Metastasis (TNM) staging classification, the patient was initially diagnosed with extensive small cell lung carcinoma (ES-SCLC), which was defined as clinical stage T2aN3M1 and Siewert type IV. Moreover, according to the 2019 National Comprehensive Cancer Network (NCCN) guidelines for SCLC, chemotherapy is the first recommendation. Ruling out the taboo of chemotherapy from April 2019 to May 2019, the patient received 2 cycles of EP chemotherapy regimen with etoposide 100 mg/m^2 on days 1–3 and cisplatin 25 mg/m^2 on days 1–3 in each 3-week period. After 2 cycles of chemotherapy, the efficacy was evaluated as partial response (PR) (**Figure 4**). However, a chest CT taken on May 24, 2019, showed no significant change in the left mass, implying the difference in histological types between the left and right. Therefore, on May 27, 2019, a puncture biopsy of the left lung mass was performed. The pathology showed a low differentiated carcinoma, consistent with adenocarcinoma, with the possibility of complex carcinoma (**Figure 5**). Additional lung cancer common genetic testing with next-generation sequencing (NGS) indicated fusion of EML4 and ALK. Therefore, we modify the diagnosis of the patient with a terminal SCLC in the lower lobe of the right lung (cT2aN3M0, IIIB) and ALK mutation adenocarcinoma of the lower lobe of the left lung (cT4N2M0 IIIB, ALK mutation). According to the NCCN and Chinese Society of Clinical Oncology (CSCO) guidelines in 2019, we reformulated the treatment plan: 1) oral targeted drug treatment (crizotinib, 250 mg bid.); 2) continuous EP chemotherapy regimen; and 3) sequential radiotherapy (from July 19 to August 23, 2019). Sequential radiotherapy began after 4 cycles of chemotherapy. Moreover, the efficacy of the right lung (SCLC) after a 4-cycle chemotherapy was evaluated as PR. The patient received proton radiotherapy (4,500 cGy in total) for the tumors in the right lower lobe, mediastinum, and right supraclavicular lymph node area and then was treated by 6-MV X-ray arc intensity modulation (2,250 cGy) from July 19 to August 23, 2019. The fifth-cycle chemotherapy was completed on July 11, 2019. The efficacy of crizotinib and radiotherapy was evaluated. According to the abnormal signals in the left frontal lobe and cerebellar hemispheres shown by brain enhancement magnetic resonance (MR) (**Figures 6A1, B1**), the possibility of metastases was considered to be high. Just through

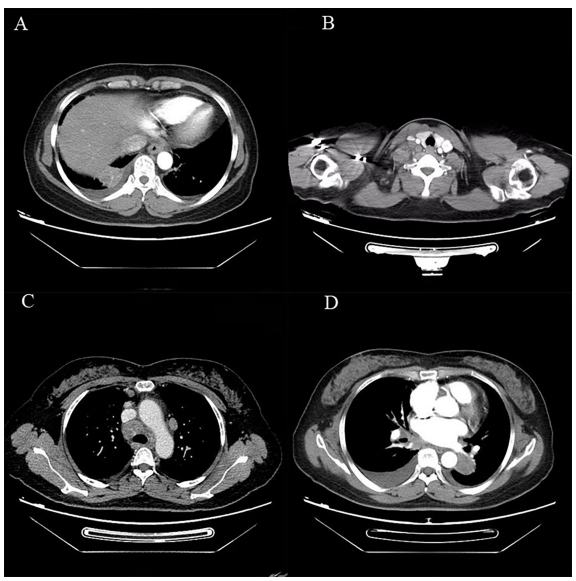


FIGURE 1 | Chest CT of the patient before treatment: **(A–D)** show the range of lesions, respectively.

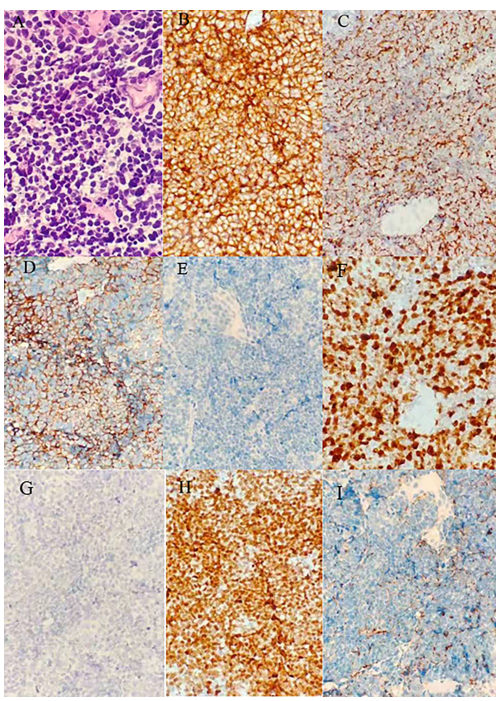


FIGURE 2 | Results of the first puncture: **(A)** Microphotographs of small cell lung cancer; (**B–I**) thymic carcinoma with immunohistochemistry for CD56, CK, Syn, LCA, Ki67, P40, TTF-1, CgA.

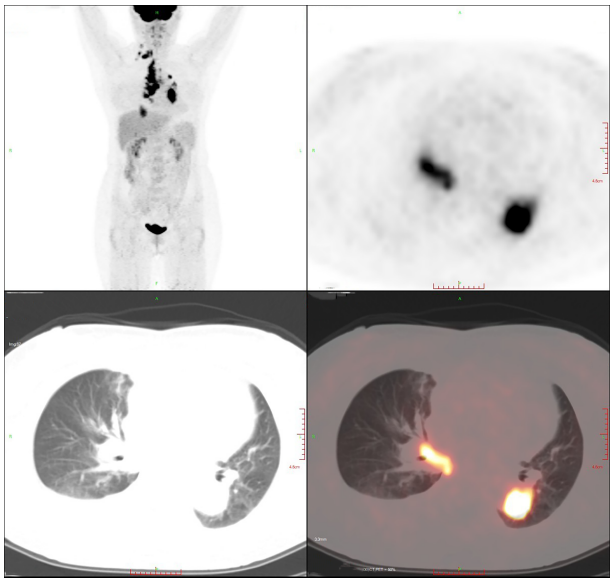


FIGURE 3 | The lesions on positron emission tomography/computed tomography (PET/CT).

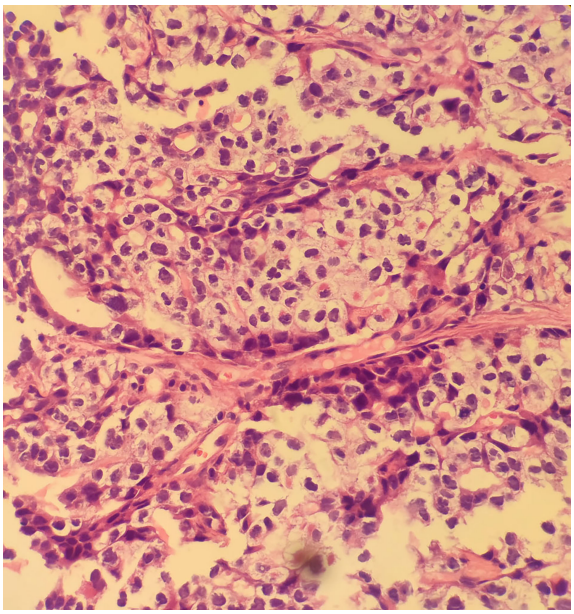


FIGURE 5 | Result of the second puncture: lung adenocarcinoma.

imaging, we cannot judge where the brain metastases lesion came from, and both small cell lung cancer and lung adenocarcinoma with ALK-EML4 are possible. Fortunately, the patient has no symptoms of craniocerebral metastasis, and non-radiotherapy for intervention was considered. As we have known, the low concentration of cerebrospinal fluid is the common cause of crizotinib treatment failure. Moreover, some studies (7, 8) have shown that alectinib has a better effect on craniocerebral metastasis than crizotinib, so we chose alectinib. A month later, we rechecked the brain enhancement MR (**Figures 6A2, B2**) and found that the lesions did not shrink and there were new lesions. Therefore, we

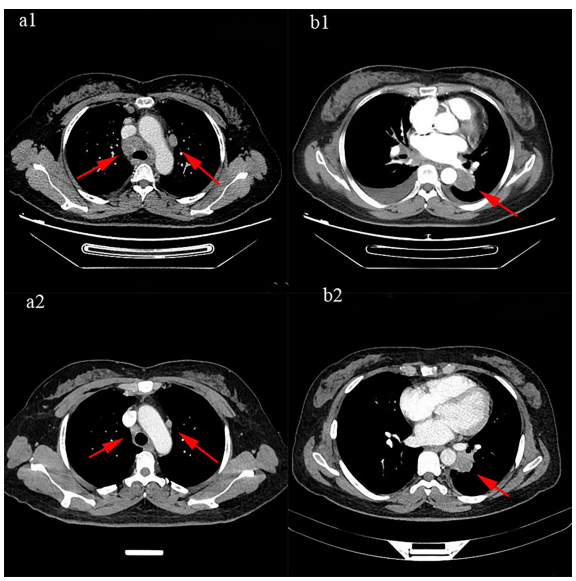


FIGURE 4 | The efficacy was evaluated as partial response (PR): **(a1, b1)** were before treatment, **(a2, b2)** were after 2 cycles of treatment.

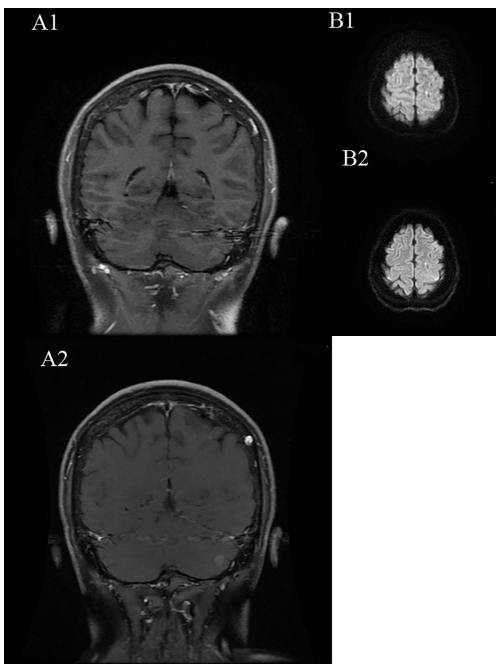


FIGURE 6 | **(A1, B1)** are before treatment of alectinib, **(A2, B2)** are after treatment of alectinib.

considered that the brain's metastases might be from SCLC. Therefore, the patient underwent a 6-MV X-ray whole-brain arc intense-modulated radiotherapy; the metastatic tumor increased starting from July 19, 2019, to August 23, 2019. At the subsequent 2-year follow-up after completion of radiotherapy, this patient was without evidence of locally recurrent or distant disease.

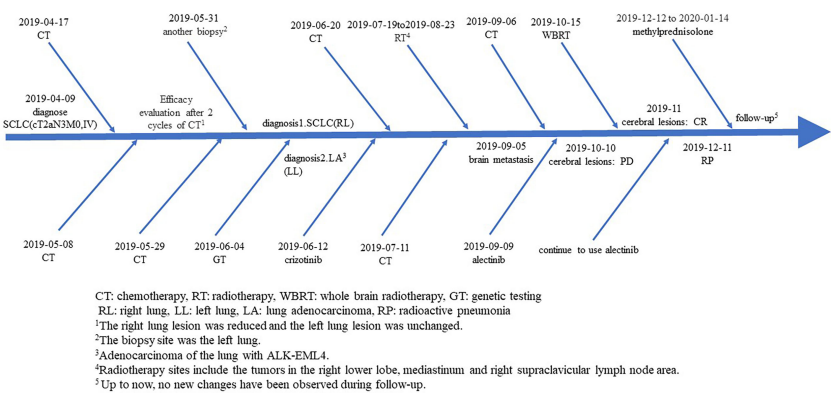
DISCUSSION

Clinically, MPLCs are commonly seen as adenocarcinoma, which often need to be identified with intrapulmonary metastasis (IM) of lung cancer, and the treatment methods of the two are completely different. Studies found that there was a significant difference in prognosis between MPLC and IM. Therefore, it is very important to identify MPLCs, especially sMPLC and IM. In differentiating MPLCs from IM, we can use histopathology, imaging, and molecular genetics. In general, MPLCs have different histological types and have different *in situ* carcinogens, while IM has the same histological type and the same origin. In addition, we can also distinguish between the two based on imaging results (9, 10). Currently, most of the MPLCs reported are mainly multifocal adenocarcinoma, and there are few cases like the one in this case, which is also the unique feature of this case.

In the diagnosis of MPLCs, we still need to distinguish it from combined small cell lung cancer (c-SCLC). C-SCLC is defined by the World Health Organization (WHO) as SCLC combined with additional components that consist of any of the histological types of NSCLC, such as usually adenocarcinoma (ADC), squamous-cell carcinoma (SCC), large-cell carcinoma (LCC), large-cell neuroendocrine carcinoma (LCNEC), or less commonly spindle-cell carcinoma or giant-cell carcinoma (11–15). C-SCLC generally occurs in the same lobe and is mostly interrelated, while multiple primary lung cancers are more likely to occur in different lobes or in different lungs. In this case, two lesions were located in two different lung lobes. During the treatment, different therapeutic effects suggest that the pathological sources of two lesions may be different, and the second biopsy confirmed our hypothesis.

At present, there is still no unified understanding of the treatment of MPLCs. However, the treatment principles of MPLCs in domestic and foreign literature are consistent, and they all believe that as long as there is no absolute contraindication, active local treatment based on surgery should be carried out, combined with the multidisciplinary comprehensive treatment mode of adjuvant radiotherapy and chemotherapy (16–18). Advanced MPLC patients can be treated with radiotherapy, chemotherapy, targeted therapy, interventional therapy, immunotherapy, best support therapy, and other palliative treatments. In this case, multiple mediastinal and supraclavicular lymph node metastases suggest that the disease is at least locally advanced, regardless of the pathological type, so surgery was not one of the first choices. Referring to the 2019 NCCN guidelines and CSCO guidelines, combined with the specific condition of the patient, we adopted chemotherapy for SCLC, TKI-targeted drugs for ALK rearrangement adenocarcinoma, and sequential radiotherapy for right lung lobe lesion, mediastinum, supraclavicular lymph node, and brain (**Figure 7**). Furthermore, in the whole course of treatment, the patient also had some treatment-related adverse reactions, such as grade 1 nausea and vomiting, grade 1 bone marrow suppression, and grade 2 radiation pneumonia. Methylprednisolone was used to treat radioactive pneumonia. Through symptomatic treatment, the patient achieved a good quality of life.

Compared to other cases of MPLCs, our case has a unique feature. In this case, the origin of the brain metastasis (BM) is a matter of consideration, because it determines the treatment plan. Some studies (11, 19, 20) showed that the incidence of BM in NSCLC patients is 30%–40%, and lung cancer is responsible for approximately 50% of all BM. However, the molecular mechanism of BM in lung cancer is still unclear and may be related to the interaction of the blood–brain barrier, cancer stem cells, lung cancer cells, and brain microenvironment (21). Brain radiotherapy is the best treatment for SCLC patients with brain metastasis, and small molecule targeted drugs are another choice for NSCLC patients with gene mutation (11, 22–24). In our case, we cannot estimate where the brain metastases came from just according to MR imaging. Moreover, the patient has no



CT: chemotherapy, RT: radiotherapy, WBRT: whole brain radiotherapy, GT: genetic testing
RL: right lung, LL: left lung, LA: lung adenocarcinoma, RP: radioactive pneumonia
[1]The right lung lesion was reduced and the left lung lesion was unchanged.
[2]The biopsy site was the left lung.
[3]Adenocarcinoma of the lung with ALK-EML4.
[4]Radiotherapy sites include the tumors in the right lower lobe, mediastinum and right supraclavicular lymph node area.
[5]Up to now, no new changes have been observed during follow-up.

FIGURE 7 | Flow chart of patient treatment.

symptoms of craniocerebral metastasis; therefore, we have time to choose another TKI drug, alectinib. Several studies have shown that alectinib has a better effect on craniocerebral metastasis than crizotinib. It is a pity that after a 1-month treatment of alectinib, the craniocerebral lesions did not shrink and new lesions appeared. At this time, we highly suspected that the craniocerebral lesions might be from SCLC. Then, brain radiation was given to the patient and the BM was reduced. Diagnosis and treatment complement each other. Only when the diagnosis is clear can the right medicine be applied.

CONCLUSION

In conclusion, diagnosis is the first priority for the treatment of diseases. With the discovery of driver mutations in lung adenocarcinoma (ADC), next-generation sequencing (NGS) would provide an explicit answer to the key question, whether individual tumors represent intrapulmonary metastases or independent tumors. Only when the diagnosis is correct can we choose the right treatment method and benefit patients more. Moreover, whether the disease is rare or common, patients benefit from systematic treatment. For some rare diseases, we should start with diagnosis, progress step by step, and overcome them one by one. Further study is warranted for the diagnosis and treatment of MPLCs.

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 the Ethics Committee of Affiliated Hospital of Qingdao University Affiliated Hospital of Qingdao University. 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

WJ, YZ, and FL contributed to the conception and design of the study. QQ and YX organized the database. ZH and WX wrote the first draft of the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

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Combining a CDK4/6 Inhibitor With Pemetrexed Inhibits Cell Proliferation and Metastasis in Human Lung Adenocarcinoma

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Background: Recent clinical trials of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in human lung adenocarcinoma (LUAD) have not achieved satisfactory results. The disappointing results of single-drug treatments have prompted studies about synergistic therapies of CDK4/6i with other drugs. We aimed to test the anti-tumor effect of ribociclib (a CDK4/6i) combined with pemetrexed on LUAD and the potential mechanisms.

Methods: Cell lines were exposed to ribociclib and pemetrexed at different doses. Antitumor effects were measured using growth inhibition. Cell cycle distribution and apoptosis were evaluated using flow cytometry. Cell migration and invasion were measured using wound healing and transwell invasion assays, respectively. The expression levels of proteins were analyzed using western blotting. Mice xenograft models were used for validation *in vivo*.

Results: Synergism was associated with a combination of cell cycle effects from both agents. Cell cycle analysis revealed that pemetrexed blocked cells in the S phase, whereas ribociclib arrested cells in the G1 phase. Concomitant treatment with pemetrexed and ribociclib resulted in a significantly stronger antitumor ability than treatment alone. We also found that ribociclib strongly enhanced the pro-apoptotic activity of pemetrexed *via* the caspase/bcl-2 signaling pathway. In addition, we report for the first time that combination treatment with ribociclib and pemetrexed significantly inhibits the migration and invasion of LUAD cells.

Conclusions: Combining ribociclib and pemetrexed showed a powerful ability to inhibit cancer proliferation, invasion, and metastasis, and it holds potential as a novel effective combinative therapy for patients with LUAD.

Keywords: CDK4/6 inhibitor, pemetrexed, cell cycle, synergy, lung adenocarcinoma

BACKGROUND

An increasing number of patients with lung cancer are being diagnosed with lung adenocarcinoma (LUAD) (1). For advanced LUAD without sensitizing mutations, such as EGFR, BRAF, ALK or ROS-1 gene rearrangements, chemotherapy with a platinum-based reagent is the main treatment option if no contraindication exists (2). Unfortunately, not all patients respond to first-line therapy, and even the patients who initially respond are likely to relapse (3). Treatment options for these patients remain an area of significant unmet medical need.

The cell cycle is regulated by multiple evolutionarily conserved process that is required for mammalian cell viability and progression (4). The uncontrolled cell cycle is a common feature of cancer. Cancer cells display unscheduled proliferation and genomic instability (5, 6). Targeting the cell cycle in cancer has been shown to be potential and promising therapeutic strategy (7). Cyclin-dependent kinase 4 (CDK4) and the closely related CDK6 are critical mediators in cellular proliferation, where they help to drive the transition of DNA synthetic phase of the cell-division cycle (8). Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are a novel class of drugs targeting the dysregulated cell cycle in malignant cells, including Palbociclib, Ribociclib, and Abemaciclib. CDK4/6i are now commonly used as approved and investigative treatments across many cancer types. A previous study has demonstrated that Palbociclib treatment alters nucleotide biosynthesis and glutamine dependency in A549 cells (9). The previous study has shown that adenocarcinoma cell lines are more sensitive to CDK4 than squamous cancer cell lines (10).Unfortunately, recent clinical trials of CDK4/6i as single agents in non-small cell lung cancer (NSCLC) have not achieved satisfactory results (11–14). These disappointing results have prompted studies on the combinatorial strategy of CDK4/6i and other agents.

Pemetrexed is a cytostatic antifolate drug that inhibits thymidylate synthase (TS) and several other enzymes in the nucleotide synthesis pathway and is a cornerstone for the treatment of lung cancer (15). Ribociclib is one of the selective CDK4/6i that blocks tumor suppressor retinoblastoma protein (RB) phosphorylation and induces cell cycle arrest (16). Interestingly, a clinical evaluation of the combination therapy of abemaciclib and pemetrexed in a phase Ib trial has demonstrated an acceptable safety profile (17). However, whether the combination of ribociclib and pemetrexed has the same safety and enhanced anti-tumor effect needs further experimental confirmation.

Therefore, this study aimed to evaluate the efficacy and mechanism of action of ribociclib in combination with pemetrexed in LUAD cells. We found that ribociclib plus pemetrexed showed robust cytotoxicity and antitumor effect. Several molecular pathways that appeared to drive the combinatorial antitumor effect cumulatively were identified. Our findings supported clinical testing of this combination therapeutic strategy for lung adenocarcinoma patients.

MATERIALS AND METHODS

Data Sources

The UALCAN (http://ualcan.path.uab.edu/) is a web-based tool for gene expression analysis of cancer OMICS data (18). The RNA sequencing (RNA-seq) information and corresponding clinical data of LUAD patients were downloaded from The Cancer Genome Atlas (TCGA) database (https://www.cancer.gov/tcga). Baseline clinicopathological information and final clinical outcome were recorded for each patient.

Cell Lines and Reagents

The human lung adenocarcinoma cell lines A549, HCC827, NCI-1395, and NCI-H1650 were obtained from the American Type Culture Collection (ATCC). PC9 and NCI-H1975 cells were provided by Dr Fan (Department of Thoracic Surgery, Fourth Military Medical University, Xi'an, China). All cells were grown in Roswell Park Memorial Institute (RPMI) 1640 complete medium (Gibco, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, USA), 100 U/mL penicillin (Thermo Fisher Scientific, MA, USA), and 100 ug/mL streptomycin (Thermo Fisher Scientific, MA, USA). All cells were cultured in a humidified atmosphere with 5% CO_2 at 37°C. Cell lines were routinely authenticated, and mycoplasma tested. Ribociclib was purchased from Selleck, China, and pemetrexed was from Med Chem Express, China. Drugs were dissolved in dimethyl sulfoxide (DMSO, Sigma, USA) and stored at -20°C.

Cell Viability Assay

A549 and PC9 cells were cultivated in RPMI 1640 complete medium. Approximately 2000 cells per well were seeded in 96-well plates. After overnight incubation, cells were exposed to a 10-fold serial dilution of ribociclib ranging from 0.01 to 100 μmol/L and pemetrexed ranging from 0.001 to 10 μmol/L for 6, 24, 48, and 72 h. Cell viability was detected using Cell Counting Kit 8 (CCK-8, Beyotime, China) following the manufacturer's protocol. Cell viability was determined by the percentage of surviving drug-treated cells versus DMSO-treated control cells. The IC50 value was the concentration for 50% of maximal inhibition of cell proliferation. For two drugs combination experiments, cells were treated with indicated doses of ribociclib and/or pemetrexed (1:100) for 72h.

Colony Formation Assay

For colony formation detection, cells were cultured and treated with 0.1 μmol/L pemetrexed and/or 10 μmol/L ribociclib for 72 h. Equal amounts of the solvent (DMSO) were added as a control group. Approximately 1000 single cells per well were seeded in 6-well plates and incubated for 12 days. At the endpoints of the colony formation experiment, the cells were washed twice with PBS, fixed with 4% paraformaldehyde (PFA, Sigma, USA) for 15 min, and stained using 0.2% crystal violet (Sigma, USA) for observation. All relevant assays were independently performed at least three times.

Wound Healing Assay

A density of 1×10^5 cells/mL PC9 or A549 cells were seeded in 6-well plates. After 24h incubation, the cells were either untreated or treated with 10μmol/L ribociclib and/or 0.1μmol/L pemetrexed. When the cell reached about 90–100% confluence, a sterile 200 μL pipette tip was used to scratch a line. The cells were washed twice with PBS and cultured in a fresh medium with 0.1% FBS. Wound healing was observed at 0h and 48 h using a microscope (Olympus, Japan) and analyzed using Image J 1.8.0.

Transwell Migration and Invasion Assay

Cell invasion assays were performed using 24-well transwells (8μm pore size; Corning, USA) and coated with 50μL diluted Matrigel (1:5 in PBS) (BD Biosciences, USA). Cells were either untreated or treated with 10μmol/L ribociclib and/or 0.1μmol/L pemetrexed for 72h. Then, the upper chamber added A549 and PC9 cells (5×10^4 cells/200μL cell suspension in FBS-free medium). The lower chambers filled 500 μL of RPMI 1640 medium containing 10% FBS. After 24h incubation, the cells in the upper chamber were removed with cotton swabs, and the cells adherent to the bottom surface were fixed with cold 4% PFA for 15 min and stained using 0.2% crystal violet. Finally, after washing the filters in water, five random fields/filters were taken and counted under a microscope (Olympus, Japan) with a 100-fold magnification.

Cell Cycle Analysis

Approximately 1×10^5 cells per well Cells were seeded into 6-well plates. After 24h incubation, cells were either untreated or treated with 10μmol/L ribociclib and/or 0.1μmol/L pemetrexed for 72h. Then adherent cells were harvested, washed, and resuspended in cold PBS. Single-cell suspensions were overnight fixed in cold 70% ethanol at 4°C. The fixed cells were washed with PBS and stained with 50 μg/mL propidium iodide (Beyotime, China) containing 50 μg/mL RNase I for 30 min at room temperature and then analyzed using flow cytometry (BD AriaIII, USA) and Flowjo software.

Cell Apoptosis Analysis

According to the manufacturer's instructions(C1062s, Beyotime, China), The apoptotic status of A549 and PC9 cells was tested using flow cytometry *via* the Annexin V-fluorescein isothiocyanate (FITC) and PI double staining method. Briefly, the cells were seeded into six-well plates at a density of approximately 1×10^5 cells per well and treated with 0.1μM pemetrexed and/or 10 μM ribociclib for 72 h. The cells were then collected and resuspended in 500 μL of binding buffer containing 5 μL Annexin V-FITC and 5 μL PI, and then incubated for 15–30 min in the dark at room temperature and analyzed using flow cytometry.

RNA Isolation and qRT-PCR

Total RNA from cells was extracted with Total RNA Kit II (R6934-01, Omega, Georgia, USA). RNA samples were quantified with Nanodrop. cDNAs were synthesized with a Reverse Transcription Kit (RR036A, Takara Biotechnology, Japan),. Quantification of gene expression was performed with SYBR Premix Ex Taq II (RR820A, Takara Biotechnology, Japan). Gene expression levels were quantified using the delta-delta CT method with GAPDH as a housekeeping gene. The primers used to amplify the indicated genes are listed in Supplementary Material (**Supplementary Table 1**).

Western Blotting Analysis

Western blotting was performed as previously described (19). Cells were treated with the drug corresponding to the drug treatment group, DMSO control, 10 μM ribociclib, 0.1μM pemetrexed, 10 μM ribociclib +0.1μM pemetrexed. After 72 hours, cells were harvested and lysed in RIPA buffer (Beyotime, China) in the presence of protease/phosphatase inhibitor (Roche, USA). Protein concentration was quantified using a BCA assay (Thermo Fisher Scientific, Italy). The lysates were mixed with 1x loading buffer (Beyotime, China). A total of 30 μg protein per sample was loaded to 7.5% and 10% SDS-PAGE, which was run for one hour at 150V in the running buffer (25 mM Tris base, 192 mM glycine, 0.1% SDS). Then, the protein from gels was transferred to an activate PVDF membrane (Tanon, Shanghai, China) running for 60 min at 100V in the transfer buffer (25 mM Tris base,192 mM glycine, 10% methanol). Membranes were blocked with 5% BSA for 1h. Subsequently, protein was overnight incubated at 4°C with the following primary antibodies: Antibodies against CDK4 (CST-23972,1:1000 dilution), CDK6 (CST-13331T,1:1000), phospho-Rb ser807/811 (CST-8516T, 1:1000), Cyclin D1 (CST-55506T, 1:1000), E2F1 (CST-3742S, 1:1000), Cleaved Caspase-3 (CST-9664T, 1:1000), Cleaved Caspase-9 (CST-9505T, 1:1000), Cleaved PARP-1 (CST-5625T, 1:1000), Bcl-2 (CST-4223S, 1:1000), Vimentin (CST-5741S, 1:1000), E-cadherin (CST-3195S, 1:1000), β-actin (CST-3700S,1:1000) were purchased from Cell Signal Technology (Danvers, MA, USA). Membranes were incubated with HRP coupled goat anti-mouse or goat anti-rabbit secondary antibody (1:2000 dilution, Proteintech, Wuhan, China) for 60 min at room temperature. The immunoreactive proteins were detected using enhanced chemiluminescence (P0018S, Beyotime, China).

Immunofluorescence (IF) Staining

For immunofluorescence staining, A549 and PC9 cells were seeded on 10 mm confocal dishes and treated with 0.1 μmol/L pemetrexed and/or 10 μmol/L ribociclib. Equal amounts of DMSO were added to control cells. After 72h, cells were fixed in 4% PFA for 30 min, permeabilized in 0.3% Triton X-100 for 20 min, and blocked in 5% normal goat serum for 60 min at room temperature. Sequentially, cells were incubated with primary antibody against CDK4 (1:200 dilution, #ab108357, Abcam, USA) or phosphor-Rb (1:200, #8516T, Cell signalling Technology, USA) at 4°C overnight, then washed with phosphate buffered-saline with Tween-20 (PBST) and incubated with FITC-labelled secondary antibody (1:100 dilution, Proteintech, Wuhan, China) for 1 h at room temperature. The nuclei were labelled using 4′,6-diamidino-2-phenylindole (DAPI) (2 mg/mL) in the dark for 15 min, and imaging was performed on a fluorescence microscope (Olympus IX 73 DP80, Japan).

Immunohistochemistry (IHC)

Immunohistochemical analyses were performed on specimens from xenograft tumors. Formalin-fixed paraffin-embedded tissue sections (4μm thickness) were deparaffinized and rehydrated in graded ethanol solutions (100%, 95%, 80%, 70%). For IHC staining, after antigen repair, the tissue slides were incubated with anti-Ki-67 (1:200, #9027S, Cell signaling, USA) overnight at 4°C, then washed with PBS and incubated with a horseradish peroxidase-labelled secondary antibody for 30 min and stained with diaminobenzidine (DAB) for 5 min. For H&E staining, tissue sections were stained with hematoxylin for 3 min and eosin solution for 30 s. For the TdT-mediated dUTP nick-end labelling (TUNEL) assay, we used a TUNEL *in situ* apoptosis detection kit (Roche, USA) according to the manufacturer's instructions. The stained images were observed using a fluorescence microscope at a 200-fold magnification.

Animal Experiments

Female BALB/C nu/nu mice (6-week-old) were purchased from Vital River Laboratory Animal Technology (Beijing, China), and all animal experiments were approved by the Fourth Military Medical University Animal Care Facility and were performed according to National Institutes of Health guidelines. For the synergic effect test of ribociclib combined with pemetrexed, the method performed is as follows. A total of 5×0^6 A549-luciferase cells were collected in 100 μL PBS and subcutaneously injected into the right flank of each mouse. When the tumor size reached about 100 mm^3, the mice were randomized into 4 groups (n=5 per group). they were treated as described in the following: The first group of mice were intratumorally injected with saline solution as an untreated vehicle (Control), the second was treated with ribociclib (200 mg/kg, oral, 21 d) alone (Ribo), the third received pemetrexed (100 mg/kg) administered alone (PTX), the fourth received ribociclib and pemetrexed combination treatment (Ribo + PTX) and the size of the subcutaneous tumors and weight of the mice were recorded every 4 days. Tumor volume (V) was calculated according to the formula: $\Pi/6 \times \text{length} \times \text{width}^2$.

Statistical Analysis

The expression of CDK4 was recorded as a dichotomous (high vs low) variable by the optimal cut-off value using Z-score. Survival curves according to CDK4 expression were estimated with the Kaplan-Meier method and a log-rank test was used to assess significance. All statistical analyses were performed using SPSS Statistics 21. Unless stated otherwise, all experiments were conducted in triplicate. Data were expressed as the mean ± standard deviation (SD) of at least three independent experiments. The significance of differences between mean values was determined using a two-way analysis of variance (ANOVA) with Tukey's *post hoc* multiple comparisons, depending on the normality of data distribution. Statistical significance was set at a P value less than 0.05.

RESULTS

CDK4 Expression Is Associated With Poor Prognosis in LUAD

We first determined the gene expression levels of CDK4 using The Cancer Genome Atlas (TCGA) datasets. CDK4 mRNA expression levels in LUAD were significantly higher than in normal control tissues ($p < 0.001$, **Figure 1A**). Furthermore, Kaplan–Meier curves analysis of TCGA samples showed that higher CDK4 mRNA expression levels were correlated with poorer overall survival (OS) (p=0.033, **Figure 1B**), strongly suggesting that CDK4 contributes to LUAD progression. Subsequently, we detected the protein expression of CDK4 in a panel of 6 LUAD cells (NCI-H1975, NCI-H1395, HCC827 NCI-U1650, A549 and PC9), and we found that CDK4 was highly expressed in A549 and PC9 cell lines (**Figure 1C**) and thus, A549 and PC9 cell lines were chosen for further studies. Immunofluorescence assay was conducted to assess the subcellular location of CDK4.The result showed that CDK4 was primarily localized in the nucleus with a low expression in the cytoplasm in A549 and PC9 cells. We also detected the protein expression of CDK4 in BEAS-2B, a normal human lung epithelial cell line, and found that CDK4 was low expressed in BEAS-2B (**Figure 1D** and **Supplementary Figure 1**). Taken together, these findings suggest that CDK4 expression is upregulated in LUAD and indicates a poor prognosis. A549 and PC9 cells can be used as suitable cell models for this study.

Ribociclib Combined With Pemetrexed Shows Enhanced Cytotoxicity in LUAD Cells

In our study, the antiproliferative effects of using A549 and PC9 cells of the Ribo and PTX alone groups were concentration- and time-dependent (**Figures 2A, B**). The IC50 values of A549 and PC9 cell lines of the Ribo group were 45.56 ± 0.811 μM (6 h), 15.98 ± 0.1466 μM (24 h), 4.796 ± 0.0637 μM (48 h), and 2.104 ± 0.0539 μM (72 h) and 38.6 ± 0.194 μM (6 h), 23.37 ± 0.1467 μM (24 h), 12.34 ± 0.1144 μM (48 h), and 6.165 ± 0.067 μM (72 h), respectively. The IC50 values of A549 and PC9 cell lines of the PTX group were 1.064 ± 0.07388 μM (6 h), 0.3864 ± 0.0487 μM (24 h), 0.1245 ± 0.02606 μM (48 h), and 0.0499 ± 0.029 μM (72 h) and 1.968 ± 0.134 μM (6 h), 0.5445 ± 0.0543 μM (24 h), 0.206 ± 0.0311 μM (48 h), and 0.0766 ± 0.0315 μM (72 h), respectively. We then evaluated the growth inhibition effect of Ribo + PTX group at different concentrations for 72 h. The results showed that the growth inhibition effect of Ribo + PTX group was more potent than that of Ribo or PTX group at each concentration (**Figures 2C, D**). Colony formation is an important parameter in cancer survival and development, and thus, we next evaluated these effects by conducting colony formation assays. A549 and PC9 cells of Ribo + PTX group inhibited colony formation to a greater extent than Ribo or PTX group (**Figures 2E, F**). These findings suggested that ribociclib combined with pemetrexed shows enhanced cytotoxicity in LUAD cells.

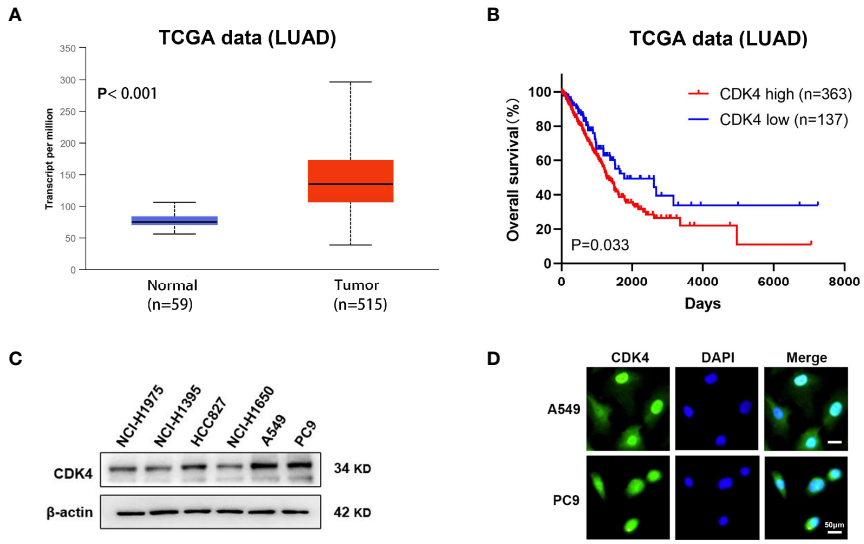

FIGURE 1 | Elevated expression of CDK4 indicates a poor prognosis in patients with LUAD. **(A)** Representative data extracted from TCGA datasets showing the relative expression of CDK4 mRNA in LUAD tissues compared with normal tissues. **(B)** Kaplan–Meier analysis showing the correlation between CDK4 mRNA expression and OS for the patients with LUAD included in TCGA datasets. **(C)** Western blotting analysis was performed using different LUAD cells. **(D)** IF staining for CDK4 in A549 and PC9 cell lines. The scale bars represent 50 μm. LUAD, lung adenocarcinoma; TCGA, The Cancer Genome Atlas; OS, overall survival; IF, immunofluorescence.

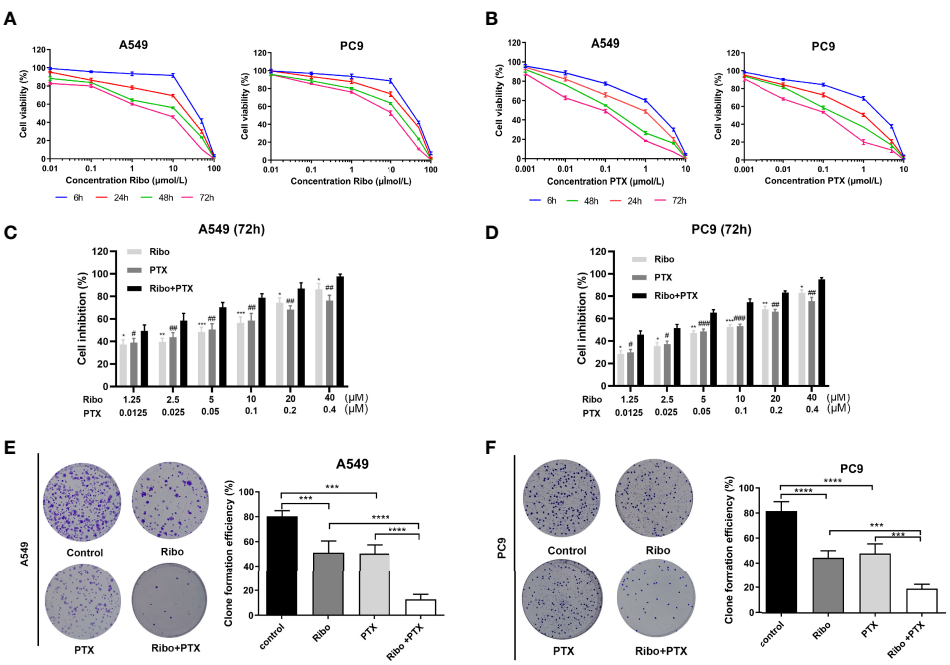

FIGURE 2 | Ribociclib plus pemetrexed enhanced the cytotoxicity *in vitro*. **(A, B)** A549 and PC9 cell lines were exposed to ribociclib and pemetrexed in combination or alone at different doses. **(C, D)** Cell lines were exposed to different combinations of pemetrexed and ribociclib dosages (*p < 0.05, **p < 0.01, and ***p < 0.001, ****p < 0.0001), ribociclib (Ribo) versus Ribo + pemetrexed (PTX) (#p < 0.05, ##p < 0.01, and ###p < 0.001), and PTX versus Ribo + PTX). **(E, F)** Representative images and quantification of colony formation assay. Data are presented as mean ± SD of triplicate experiments (*p < 0.05, **p < 0.01, ***p < 0.001 as ***p < 0.001, ****p < 0.0001). SD: standard deviation.

Ribociclib and Pemetrexed Combination Enhances LUAD Cell Death *Via* the Caspase/Bcl-2 Signalling Pathway

Apoptosis is one of the main mechanisms of cancer cell death. We next decided to examine the effect of ribociclib in combination with pemetrexed on apoptosis. A549 and PC9 cells were treated with 10 μM Ribo and 0.1 μM PTX together or alone for 72 h. Our results showed that a high percentage of cells undergoing apoptosis was observed in the Ribo + PTX group (**Figures 3A, B**). To elucidate the potential molecular mechanisms, we next analyzed the mRNA and protein levels of the caspase family and Bcl-2, which are involved in apoptosis. Our results found that the expression of cleaved caspase 3, cleaved caspase 9, and cleaved PARP were upregulated, whereas the expression of bcl-2 was downregulated, and the changes in the levels of these proteins and mRNA were more obvious in the cells of the Ribo + PTX group than treatment with Ribo or PTX alone (**Figure 3C** and **Supplementary Figure 3**). The results revealed that ribociclib combined with pemetrexed enhances cell death *via* the Caspase/Bcl-2 signalling pathway.

Ribociclib and Pemetrexed Coadministration Leads to Cell-Cycle Arrest

The cell cycle distribution was analyzed in cells of the Ribo, PTX, and Ribo + PTX groups by flow cytometric and western blot analysis. The Ribo group experienced a G1-phase arrest in ~69% of A549 cells and ~65% of PC9 cells. The PTX group experienced an S-phase arrest in ~46% of A549 cells and ~49% of PC9 cells. The Ribo + PTX group experienced a G1-phase arrest in ~95% of A549 cells and ~91% of PC9 cells (**Figures 4A, B**). To further identify the regulatory mechanism and confirm the effect of the drugs on cell cycle distribution, we first conducted an immunofluorescence analysis to visualize the expression and subcellular localization of phosphorylated retinoblastoma (Phos-RB) protein, a vital molecule of the CDK4/Cyclin D/RB/E2F pathway. **Figure 4C** shows that Phos-RB mainly was localized in the nucleus, and treatment with the Ribo and PTX significantly inhibited the phosphorylation of RB. Furthermore, we detected the expression of various cell cycle-related proteins and mRNA levels. We found that the expression levels of CDK4,

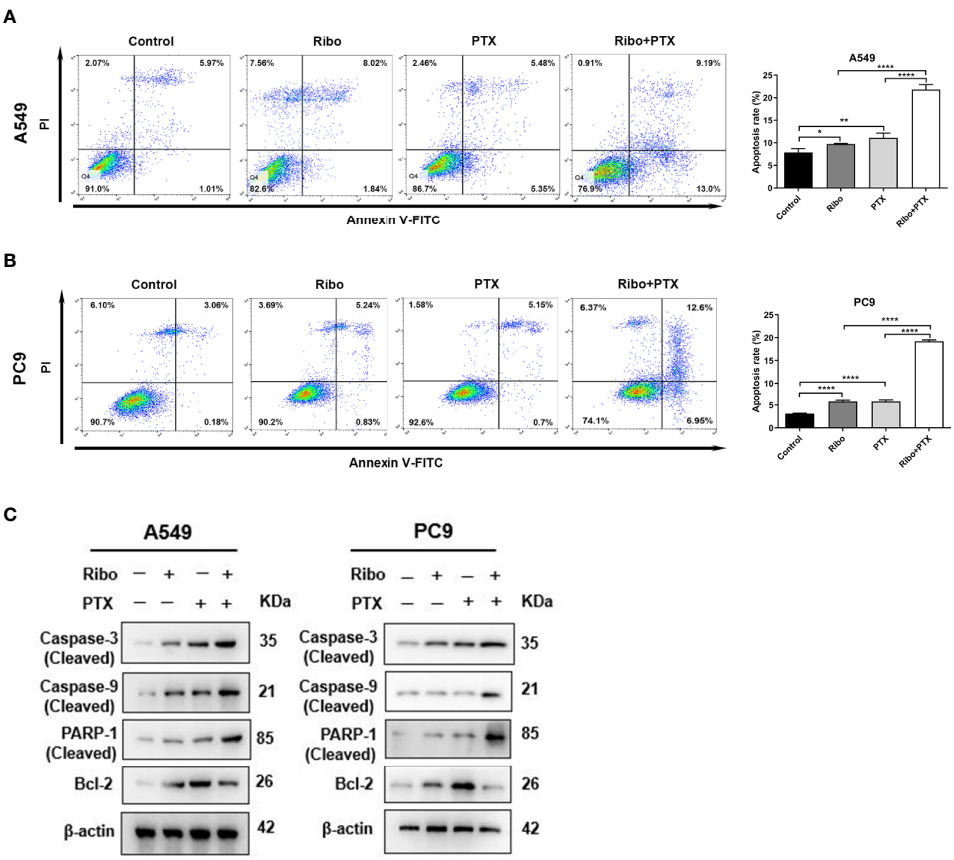

FIGURE 3 | The effect of ribociclib plus pemetrexed on inducing apoptosis of A549 and PC9 cells *in vitro*. **(A, B)** A549 and PC9 cells were treated with ribociclib with or without pemetrexed. The quantitative analysis was shown in the bar graphs. **(C)** The levels of the apoptosis-related proteins were analyzed using western blotting in A549 and PC9 cells treated with or without ribociclib with or without pemetrexed. Data are presented as mean ± SD of triplicate experiments (*$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$). SD, standard deviation.

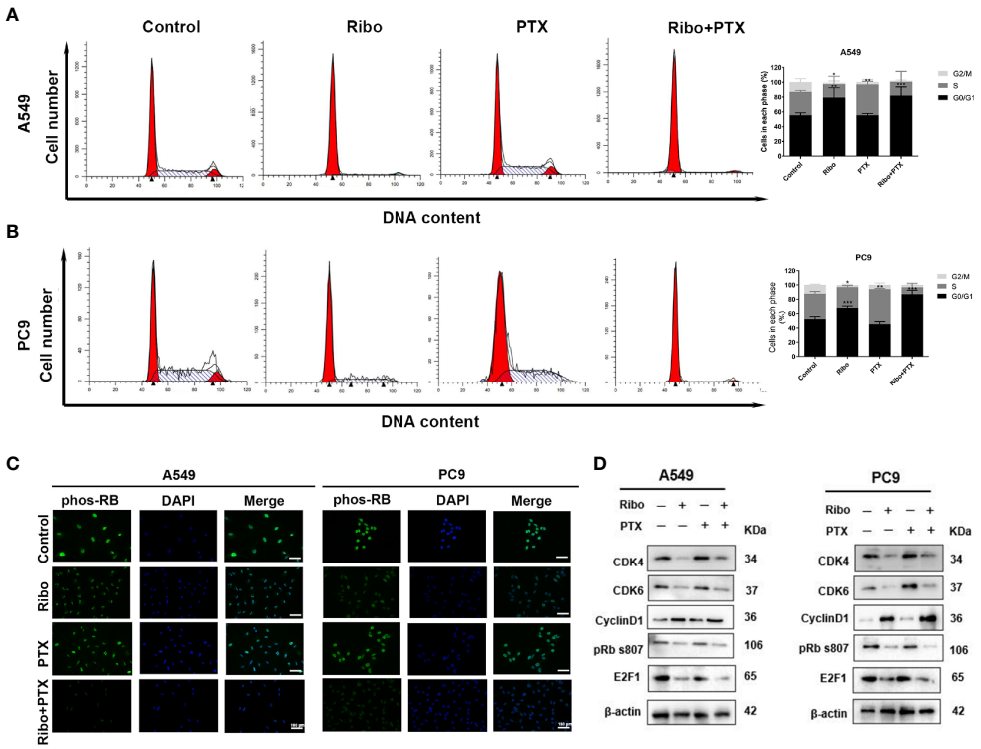

FIGURE 4 | The effect of ribociclib and pemetrexed on cell cycle in A549 and PC9 cells. **(A, B)** The cell cycle distribution of A549 and PC9 cells treated with ribociclib and pemetrexed alone or in combination. **(C)** The expression and subcellular localization of pRB were detected using immunofluorescence analysis in A549 and PC9 cells. **(D)** Western blotting showed the changes in levels of cyclin D1, CDK4/6, pRB, and E2F1. The scale bars represent 100 μm. Data are presented as mean ± SD of triplicate experiments (*p < 0.05, **p < 0.01, and ***p < 0.001). SD, standard deviation.

CDK6, phos-RB, and E2F1 were downregulated and that of cyclinD1 was upregulated, consistent with G1-phase arrest (**Figure 4D** and **Supplementary Figure 3**). These results suggest that concurrent administration of Ribo and PTX results in cell cycle distribution through the CDK4/Cyclin D/RB/E2F pathway.

Ribociclib Combined With Pemetrexed Inhibits Cell Migration and Invasion

Effects of Ribo and PTX on cell migration were detected using wound healing and transwell assays. Our results showed that A549 and PC9 cells treated with combination with Ribo plus PTX were significantly reduced cell migration compared with those of the Ribo group or PTX group (**Figures 5A–C**). The results of transwell invasion assay showed that the cell migration of the Ribo + PTX group was significantly lower than that of Ribo or PTX groups (**Figure 5D**). As epithelial to mesenchymal transition (EMT) is a key process for metastasis, we next examined the expression of EMT-related proteins (E-cadherin and vimentin) using western blotting. Our results showed that vimentin expression was downregulated whereas E-cadherin was upregulated in cells treated with the Ribo or PTX alone, which were statistically significant than those in the Ribo + PTX group (**Figures 5E, F**). These data suggested that ribociclib combined with pemetrexed significantly inhibits cell metastasis.

Ribociclib Combined With Pemetrexed Promotes Antitumor Effect in a Xenograft Mouse Model

Based on the results from *in vitro* studies, we further evaluated whether combined ribociclib and pemetrexed treatment could enhance the anti-tumor effect in LUAD xenograft mouse models. The tumor volume and tumor weight were decreased in groups treated with Ribo or PTX alone compared to the control group, and further decreased in the Ribo + PTX group (**Figures 6A–D**). In addition, no appreciable detrimental effects or abnormal symptoms were observed during the drug treatments based on the body weight (**Figure 6E**). Moreover, damage to the vital organs such as heart, liver, and kidney was not observed using hematoxylin and eosin (HE) staining (**Figure 6F**). We next analyzed the expression of Ki67 (a marker for cell proliferation) in the tumor sections by IHC. Although treatment by ribociclib or pemetrexed alone downregulated the expression of Ki67, the combination therapy was more effective (**Figure 6F**). The TdT-mediated dUTP-biotin nick end labelling (TUNEL) analyses revealed that coadministration of ribociclib and pemetrexed effectively increases apoptosis in xenograft tumors (**Figure 6F**). Taken together, the combination of ribociclib and pemetrexed yielded a superior response in the xenograft LUAD model.

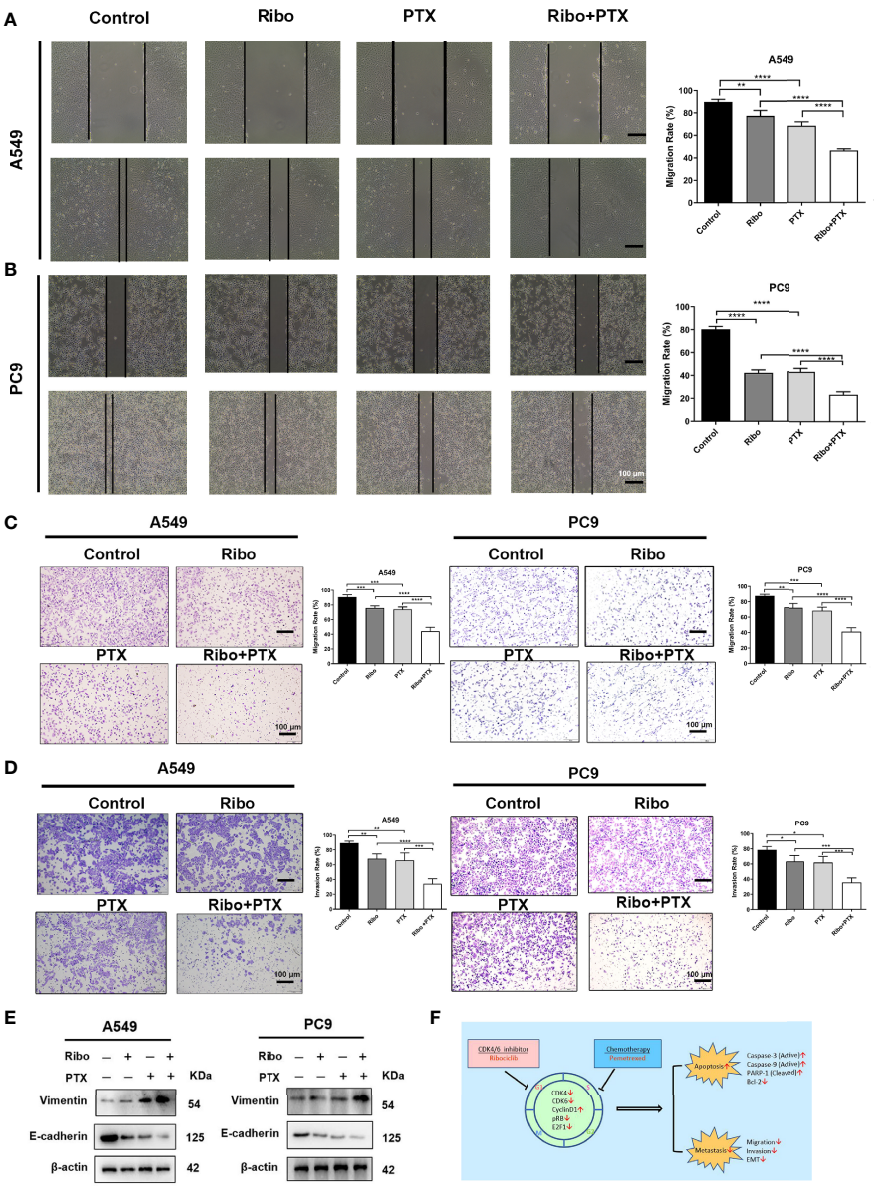

FIGURE 5 | The inhibition effect of ribociclib plus pemetrexed on the migration and invasion of A549 and PC9 cells. **(A, B)** Representative images and quantification of wound healing assay results using A549 and PC9 cells. **(C, D)** Representative images and quantification of transwell migration and invasion assays results using A549 and PC9 cells. **(E)** The EMT-related protein molecules were analyzed using western blotting in A549 and PC9 cells. The scale bars represent 100 μm. Data are presented as mean ± SD of triplicate experiments (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$). **(F)** Summary of the effects of treatments with ribociclib and pemetrexed on their molecular targets and the different observed outcomes. EMT, epithelial to mesenchymal transition; SD, standard deviation.

DISCUSSION

In this study, we evaluated the response of LUAD cells, A549 and PC9, to ribociclib and pemetrexed. We found that the combination treatment of ribociclib and pemetrexed showed an enhanced effect on cell proliferation, cell cycle distribution, cell migration, cell invasion, and cell death. Our results suggested that the combination of ribociclib and pemetrexed led to a synergistic effect. In addition, we found that the anti-tumor effect is mediated through modulation of the CDK4/Cyclin D/RB/E2F and Caspase/Bcl-2 signal pathways.

Treatment options for patients with metastatic NSCLC on or after first-line treatment are limited considerably after cancer progression. Among the available treatments, historical median progression-free survival is only 2.0–4.5 months for second-line treatment and likely shorter for the subsequent treatment (20), which makes the treatment of these patients challenging.

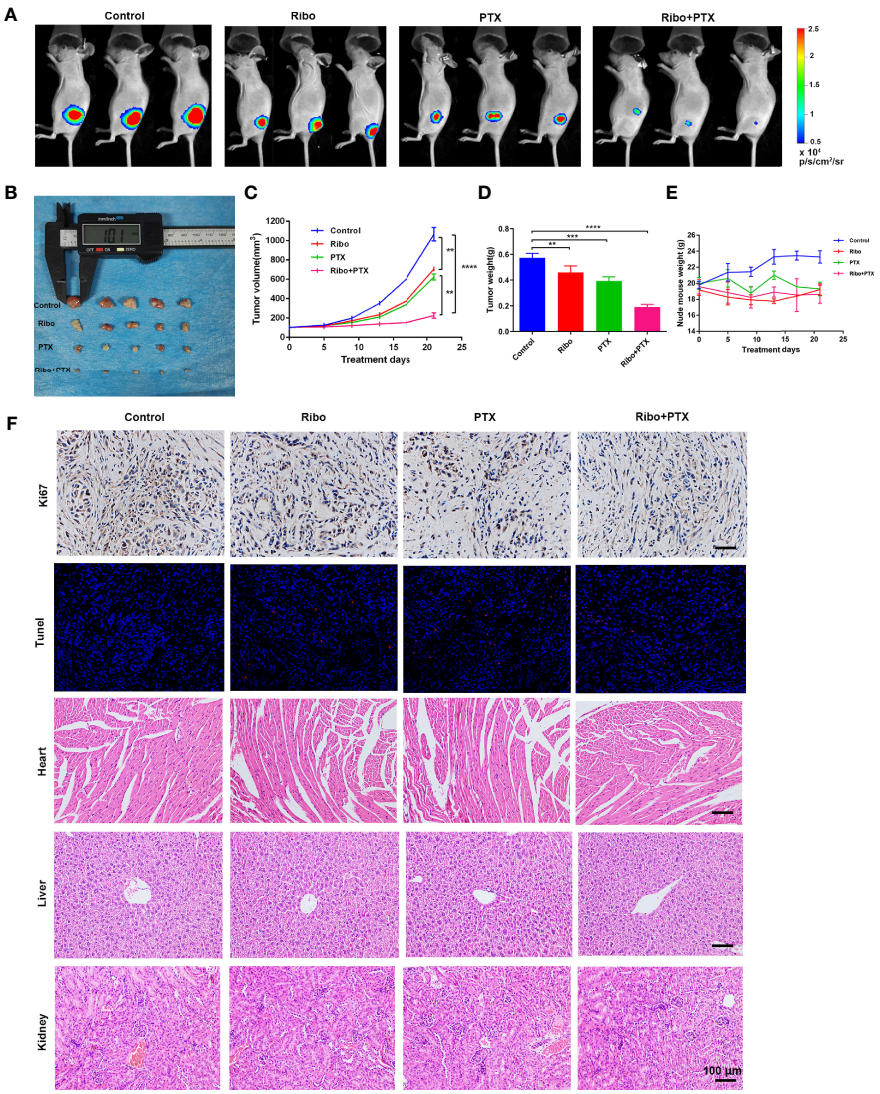

FIGURE 6 | The therapeutic effect of ribociclib plus pemetrexed in a xenograft nude mouse model. **(A)** Representative fluorescence images of luciferase signals captured from subcutaneous tumors are shown. **(B–D)** The change of tumor volume and tumor weights (n = 5 mice per group). **(E)** The effect of body weight. Data are presented as mean ± SD of triplicate experiment (**p < 0.01, ***p < 0.001 and ****p < 0.0001). **(F)** Representative panels of immunohistochemical and HE staining. The scale bars represent 100 μm. SD, standard deviation; HE, hematoxylin and eosin.

The cell cycle dysregulation frequently occurs in lung cancers (7, 21). CDKs are critical cell cycle regulators and drive cellular proliferation through the most complex molecular interactions (22). Aberrant activation of CDKs provided a rationale for CDKs inhibitors to be used as anticancer drugs in advanced NSCLC. Recently, the development of CDK4/6i (palbociclib, ribociclib, and abemaciclib) and the approval of their use by the Food and Drug Administration (FDA) for advanced metastatic breast cancer have resulted in the designing of multiple clinical trials using these agents (23). Many clinical trials of CDK4/6i in several tumor types have achieved promising results (24–26). Unfortunately, CDK4/6i in human NSCLC have demonstrated little clinical activity (11, 12). Due to the unsatisfactory results of single agents for NSCLC, the combination of CDK4/6i and other conventional therapy is being tested in clinical trials to enhance anti-tumor efficacy. A recent study identifies that palbociclib could sensitize lung cancer cells to EGFR-TKI and gefitinib (27). Co-treatment with MEK inhibitor (trametinib) plus palbociclib has shown significant anti-KRAS-mutant and anti-CDKN2A-mutant NSCLC activities in preclinical models (28). In addition, as the critical role in cell proliferation and progression, mTOR inhibitors are considered promising candidates for synergistic inhibitory effects with CDK4/6i (29). Currently, abemaciclib combined with pemetrexed has demonstrated an acceptable safety profile in a clinical evaluation in a phase Ib trial (17). However, practical strategies for formulating rational trial designs have not been identified. Thus, well-planned experiments using suitable animal and cell models are still needed.

CDK4 gene amplification has been found in numerous types of cancer including breast cancer (30), sarcoma (31), cervical cancer (32), and melanoma (33). The effect of CDK4 amplification on CDK4/6i sensitivity remains controversial; although it enhanced sensitivity in liposarcoma (34), it caused resistance in glioblastoma (35). This study found that CDK4 was highly expressed in LUAD cells and is associated with poor patient outcomes in the TCGA dataset. In theory, CDK4/6i could be combined with cytotoxic agents that target the S or M phase of the cell cycle to kill tumor cells. However, recent studies indicated that CDK4/6i and chemotherapeutic drugs might have antagonistic effects. Exposure of RB-intact breast cancer cells to palbociclib prior to cytotoxic agents (doxorubicin or carboplatin) significantly reduced their cytotoxicity (36). Another study demonstrated that the combination of palbociclib and taxanes at clinically available doses in multiple squamous cell lung cancer models enhanced antitumor effects by inhibiting the pRB-E2F signalling pathway (5). Studies of combination therapy of CDK4/6i with cytotoxic chemotherapy using pemetrexed have not been reported. A549 and PC9 cells are typical lung adenocarcinoma cells and express wild-type RB, which harbour a $p16^{INK4A}$ deletion resulting in constitutive RB hyperphosphorylation and inactivation. Our study found that ribociclib combined with pemetrexed shows enhanced cytotoxicity in A549 and PC9 cells. Combining these two classes of drugs did not demonstrate antagonistic effects. Pemetrexed blocked cells in the S phase, whereas ribociclib arrested cells in the G1 phase. Concomitant treatment showed more robust G1 phase arrest and pro-apoptosis effects than treatment with ribociclib or pemetrexed alone. We speculate that the CDK4/6-cyclinD-pRB-E2F pathway regulated the cell cycle; however, more evidence is needed to confirm the same. In addition, we also found that treatment with ribociclib and pemetrexed in combination showed significant inhibitory effects on the migration and invasion of A549 and PC9 cells. In the LUAD xenograft mouse model, the coadministration of ribociclib and pemetrexed amplified the anti-tumor effect without increasing toxicity. Taken together, Our results showed that ribociclib combined with pemetrexed had strong cytotoxicity, antitumor effect and acceptable safety, indicating the potential practicability of combination therapy.

Clinical trials evaluating combinations of CDK4/6 inhibitors with other agents have accumulated in recent years (37). However, the effects of CDK4/6 inhibition are far more wide-reaching. New insights into their mechanisms of action have triggered the identification of new therapeutic opportunities, including the development of new combinations and modification of dosing schedules (38). This will extend the utility of CDK4/6 inhibitor to the treatment of other cancer types.

CONCLUSIONS

Our studies demonstrate that the pharmacologic inhibition of CDK4/6 by ribociclib in combination with pemetrexed leads to improved therapeutic responses. The combinatorial effect of these drugs may be through the modulation of the CDK4/6-cyclinD-pRB-E2F pathway. Although the relevant proteins have undergone significant changes, whether these factors may play a role in ribociclib plus pemetrexed combination treatment warrants further investigation. Currently, only the tolerance and benefit of abemaciclib plus pemetrexed have been investigated clinically. A positive outcome of this study will provide further support for the assessment of ribociclib and pemetrexed combination in LUAD. Meanwhile, this study also supplies potential treatment options for patients with advanced LUAD.

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 authors.

ETHICS STATEMENT

The animal study was reviewed and approved by The Ethics Committee of Air Force Military Medical University.

AUTHOR CONTRIBUTIONS

Conception and design, YK, C-GL, and Z-QZ. Administrative support, L-MK and H-LZ. Collection and assembly of data, YK and R-JL. Data analysis and interpretation, X-ML and H-LZ. All authors contributed to the article and approved the submitted version.

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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.2022.880153/full#supplementary-material

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Anti-Angiogenic Drugs Inhibit Interstitial Lung Disease Progression in Patients With Advanced Non-Small Cell Lung Cancer

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Background: Interstitial lung disease (ILD) is the most serious complication of chemotherapy in lung cancer patients with pre-existing ILD. The effect of anti-angiogenic drugs in lung cancer patients with ILD remains unclear. We examined the effect of anti-angiogenic drugs on reducing the risk of ILD progression in non-small cell lung cancer (NSCLC) patients receiving chemotherapy.

Methods: We analyzed the risk of ILD progression in 52 patients with advanced NSCLC with ILD who received first-line chemotherapy with (anti-angiogenic group, n = 22) and without (non-anti-angiogenic group, n = 30) anti-angiogenic drugs between August 2014 and January 2021.

Results: The incidences of chemotherapy-related ILD progression were significantly lower in the anti-angiogenic than in the non-anti-angiogenic groups (0% vs. 20.0%, p = 0.033). However, there were no differences in other events as the competing risk factors of ILD progression between the two groups. The overall-cumulative incidence of ILD progression during the first-line and subsequent chemotherapy was 30.8% (16 of the 52). The median progression-free survival had no significant difference between the anti-angiogenic and the non-anti-angiogenic groups (10.3 vs. 8.1 months, p = 0.386).

Conclusions: The addition of anti-angiogenic drugs to chemotherapy regimens may reduce the risk of chemotherapy-related ILD progression in patients with NSCLC-ILD.

Keywords: non-small cell lung cancer, interstitial lung disease, acute exacerbation, anti-angiogenic, chemotherapy

BACKGROUND

In recent years, new treatments regimens for non-small cell lung cancer (NSCLC) have developed rapidly, such as targeted therapy and immunotherapy, which can significantly prolong the progression-free survival (PFS) and overall survival (OS) of patients. However, these treatment regimens can induce the occurrence of interstitial lung disease (ILD), and NSCLC patients with pneumonia have a higher incidence of ILD (1–3). In contrast, chemotherapy may be a more

appropriate treatment option. However, our previous meta-analysis indicated that first-line chemotherapy may be associated with a higher rate of acute exacerbation of interstitial lung disease (AE-ILD), the pooled AE-ILD rate was 8.07% (95% CI: 6.12-10.26%) (4). Therefore, there is an urgent need for new strategies to treat such patients.

The development of anti-angiogenic drugs had brought new hope for the treatment of lung cancer patients. A variety of anti-angiogenesis drugs had been developed, including endostar, bevacizumab and apatinib, etc. These drugs were often used in combination with chemotherapy to play a synergistic effect and prolong the survival time of lung cancer patients (5). Among them, the anti-angiogenic drug nintedanib in combination with docetaxel has shown a survival benefit in the second-line treatment of patients with advanced lung adenocarcinoma (6). At the same time, nintedanib has also become a specific drug for the treatment of pulmonary fibrosis. Studies have shown that nintedanib can significantly delay the decline of lung function and improve the life quality of pulmonary fibrosis patients (7, 8). Therefore, anti-angiogenic drugs may have dual effects of anti-cancer and anti-fibrosis.

A recent study showed that first-line chemotherapy combined with bevacizumab can reduce the risk of chemotherapy-related AE-ILD in NSCLC-ILD patients (0% vs 22.6%, P=0.037) (9), so whether anti-angiogenic drugs can inhibit the ILD progression in NSCLC patients with pre-existing ILD is worthy of further exploration.

METHODS

Patients

We reviewed retrospectively medical records of patients with advanced NSCLC and pre-existing ILD who received first-line chemotherapy at Nanjing Drum Tower Hospital between August 2014 and January 2021. We enrolled patients according to the following inclusion criteria: age ≥ 18 years, histological or cytological confirmation of advanced NSCLC, at least 2 cycles chemotherapy in the first-line treatment, diagnosis of ILD, performance status (PS) 0-1 and organ function is sufficient for chemotherapy. Patients who had ILD with known etiology, such as collagen vascular disease, pneumoconiosis and drug-induced pneumonia; had a history of radiotherapy and chemotherapy; had pre-existing histories of AE-ILD and had received antifibrotic agents, such as pirfenidone and nintedanib were excluded from the study.

Definition of ILD and ILD Progression

Pre-existing ILD was diagnosed according to clinical characteristics and pretreatment chest high-resolution computed tomography (HRCT) findings. All patients underwent HRCT according to standard clinical practice, and the presence of ILD was evaluated by two physicians (LYM and QZ). ILD including idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonitis (DIP) and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) was diagnosed according to the international consensus classification of the American Thoracic Society/European Respiratory Society (ATS/ERS) (10). CT findings of pre-existing ILD in our study were classified into two groups: usual interstitial pneumonia (UIP) and non-UIP. The HRCT features of UIP were as follows: the distribution of lesions is usually mainly in the lower lung and subpleura, with grid shadow and honeycomb shadow of the lungs, often accompanied by traction bronchiectasis; ground glass shadow is visible, but the lesion area is smaller than the grid film. When HRCT lacks the above signs, it is classified as non-UIP type (11).

Chemotherapy-related ILD progression was defined as newly developed bilateral ground-glass abnormality and/or consolidation superimposed on pretreatment interstitial shadows within 4 weeks after the last cycle of the first-line chemotherapy; serum lactate dehydrogenase, C-reactive protein, KL-6 or surfactant protein A or D was elevated; no evidence of pulmonary infection and no radiotherapy during the treatment. In addition, if dyspnoea worsens within 30 days, it was defined as chemotherapy-related AE-ILD.

Outcomes

The primary endpoint for comparing the anti-angiogenic and non-anti-angiogenic groups was the cumulative incidence of ILD progression in the observation period. The observation period was defined as the time from the day of initiating first-line chemotherapy to 4 weeks after the end of first-line chemotherapy. Secondary endpoints were progression-free survival (PFS), calculated as the period from day 1 to the date of disease progression or death by any cause. If no disease progression or death occurred, the date of the last imaging examination was used as the study endpoint. The response to chemotherapy was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1.

Data Collection and Statistical Analysis

All clinical and laboratory data were collected from patients' medical records. We performed a descriptive analysis of the count data. The $\chi 2$ test was used for patient count data. Pearson $\chi 2$ test was used when all theoretical numbers ≥ 5, and Fisher's exact test was used when any theoretical number < 5. The survival data PFS adopted the multiplicative limit method, namely the Kaplan-Meier method to estimate the median PFS and draw the survival curve. The Log-rank test was used to analyze the clinical characteristics of PFS by a single factor, and then based on the results of the single factor analysis, P<0.2 and factors considered clinically related to PFS were included in the Cox regression model for multivariate analysis, and the risk ratio (HR) and its 95% confidence interval (CI) were also given. All analyses were performed using R version 3.3.2, with $p < 0.05$ indicating statistical significance.

RESULTS

Patient Characteristics

We collected a total of 203 LC-ILD patients from the oncology department and respiratory department. 151 patients were excluded because they received radiotherapy and antifibrotic

agents, and had ILD with known etiology. We finally enrolled 52 patients in this study and divided them into anti-angiogenic group and non-anti-angiogenic group (**Figure 1**).

Baseline characteristics were summarized in **Table 1**. Median age at the time of first-line chemotherapy was 67 years (IQR, 65.0-73.0), 16 of the 52 (30.8%) patients were never smokers. 29 of the 52 (55.8%) patients had adenocarcinoma. Stage III and IV diseases were observed in 19 (36.5%) and 33 (63.5%) patients, respectively. Most (67.3%) patients received chemotherapy more than 4 circles. Regarding the HRCT findings of ILD, most (84.6%) patients had a non-UIP pattern while the remainder had a UIP pattern. The average CT scan intervals were 6.6 weeks in anti-angiogenic group and 6.9 weeks in non-anti-angiogenic group. There were no significant differences between the anti-angiogenic and non-anti-angiogenic groups.

First-Line Chemotherapy Regimens and Incidence of ILD Progression

First-line chemotherapy regimens are shown in **Table 1**. There is no significant difference between the anti-angiogenic and non-anti-angiogenic groups in the chemotherapy regimen (P=0.176). The most common regimen used for first-line chemotherapy in the anti-angiogenic group was platinum plus gemcitabine, and a total of 9 patients (40.9%) were enrolled. The most common regimen used for first-line chemotherapy in the non-anti-angiogenic group was platinum plus pemetrexed, and a total of 17 patients (56.7%) were enrolled. The risk of ILD progression after chemotherapy were 0% (0 of the 22 patients) and 20% (6 of the 30) in the anti-angiogenic and non-anti-angiogenic groups, respectively, and the difference in ILD progression rate was statistically significant (0% vs 20%, P=0.033; **Table 2**). Furthermore, in patients who received PEM-containing regimens, the risk of ILD progression had no significant difference in the anti-angiogenic and non-anti-angiogenic groups (0% vs 22.2%; P=0.268; **Table 2**).

TABLE 1 | Clinical Characteristics of 52 patients.

Clinical Characteristics	Total	Antiangiogenic group N (%)	Control Group N (%)	P Value
Patients	52(100)	22 (42.3)	30 (57.7)	
Gender				0.442
Male	44 (84.6)	20 (90.1)	24 (80)	
Female	8 (15.4)	2 (9.9)	6 (20)	
Age				0.399
Median	67	67	67.5	
Range	49-80	49-75	54-80	
<65	20 (38.5)	7 (31.8)	13 (43.3)	
>65	32 (61.5)	15 68.2)	17 (56.7)	
Smoke				0.640
Yes	36 (69.2)	16 (72.2)	20 (66.7)	
No	16 (30.8)	6 (27.3)	10 (33.3)	
Stage				0.575
III	19 (36.5)	9 (40.9)	10 (33.3)	
IV	33 (63.5)	13(59.1)	20 (66.7)	
Pathologic Types				0.473
Adenocarcinoma	29 (55.8)	11(50)	18 (60)	
Squamous	23 (44.2)	11(50)	12 (40)	
Carcinoma Classification of ILD				0.782
IPF	6 (11.5)	2 (9.1)	4 (13.3)	
Non-IPF	46 (88.5)	20 (90.9)	26 (86.7)	
ILD pattern				0.708
UIP Type	8 (15.4)	4(18.2)	4 (13.3)	
Non-UIP Type*	44 (84.6)	18(81.8)	26 (86.7)	
Cycle				0.190
<4	17 (32.7)	5(22.7)	12 (40)	
≥4	35 (67.3)	17(77.3)	18 (60)	
Regimens				0.176
AP	24 (46.2)	7 (31.8)	17 (56.7)	
GP	19 (36.5)	9 (40.9)	10 (33.3)	
TP	4 (7.7)	2 (9.1)	2 (6.7)	
PEM	5 (9.6)	4 (18.2)	1 (3.3)	

AP, pemetrexed+cisplatin; GP, gemcitabine+cisplatin; TP, nano albumin paclitaxel +platinum; PEM, pemetrexed.

**Non-IPF including nonspecific interstitial pneumonia (NSIP) (89%), desquamative interstitial pneumonitis (DIP) (4.5%) and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) (6.5%)*

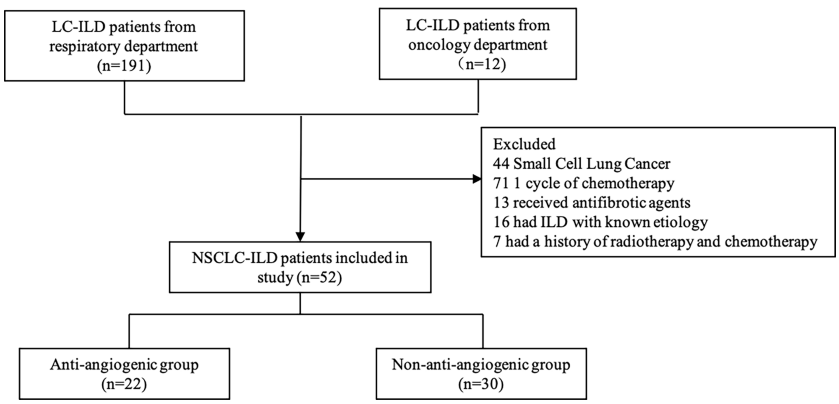

FIGURE 1 | Flow Chart Diagram of Patients Selection.

TABLE 2 | Incidence of ILD progression during frst-line chemotherapy.

Regimens	Antiangiogenic group		Control Group		P Value
	Number	Progress N (%)	Number	Progress N (%)	
AP	7	0 (0)	17	3 (17.7)	
GP	9	0 (0)	10	2 (20)	
TP	2	(0)	2	0 (0)	
PEM	4	0 (0)	1	1 (100)	
All	22	0 (0)	30	6 (20)	0.033
Including PEM scheme	11	0 (0)	18	4 (22.2)	0.268

AP, pemetrexed+cisplatin; GP, gemcitabine+cisplatin; TP, nano albumin paclitaxel +platinum; PEM, pemetrexed.

Risk Factors of Chemotherapy-Related ILD Progression

We compared clinical parameters between 6 patients with and 46 without ILD progression during first-line chemotherapy to evaluate risk factors of ILD progression. Administration of anti-angiogenic drugs (p = 0.033) were significant (**Table 3**).

Comparison of Clinical Outcomes

The survival curves in the anti-angiogenic and non-anti-angiogenic groups are shown in **Figure 2**. PFS had no significant differences between the anti-angiogenic group and the non-anti-angiogenic group (10.3 months; 95% confidence interval [CI], 7.0-13.5 vs 8.1 months; 95% CI, 6.3-9.9; p = 0.386; **Figure 2**). Overall response rate (ORR) and disease control rate (DCR) was not significantly different between the groups (ORR: 45.5% in the anti-angiogenic group vs 36.7% in the non-anti-angiogenic group, p = 0.523; DCR: 90.9% in the anti-angiogenic group vs 90% in the non-anti-angiogenic group, p = 1.00; **Table 4**).

TABLE 3 | Comparison of clinical factors between patients with and without ILD progression.

Clinical Characteristics	ILD progress N(%)	ILD non-progress N (%)	P Value
Patients	6	46	
Gender			0.573
Male	6	38	
Female	0	8	
Age			0.664
Median	67.5	67	
Range	54-75	49-80	
<65	3	17	
>65	3	29	
Smoke			0.160
Yes	6	30	
No	0	16	
Stage			1.00
III	2	17	
IV	4	29	
Pathologic Types			0.682
Adenocarcinoma	4	25	
Squamous Carcinoma	2	21	
Classification of ILD			0.540
IPF	1	5	
Non-IPF	5	41	
ILD pattern			0.573
UIP Type	0	8	
Non-UIP Type*	6	38	
Cycle			0.650
<4	1	16	
≥4	5	30	
Regimens			
Combination of anti-vascular drugs	0	22	0.033
Including pemetrexed	4	25	0.682

**Non-IPF including nonspecific interstitial pneumonia (NSIP) (89%), desquamative interstitial pneumonitis (DIP) (4.5%) and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) (6.5%).*

DISCUSSION

Our retrospective study enrolled 52 NSCLC-ILD patients, including 22 patients in the antiangiogenic group and 30 patients in the control group. The rate of ILD progression related to first-line chemotherapy in the antiangiogenic group was significantly lower than that in the control group (0% vs 20%, P=0.033). Our results suggested that first-line chemotherapy combined with anti-angiogenic drugs can reduce the ILD progression rate for patients with NSCLC combined with pre-existing ILD.

Our result is consistent with the research conducted by Hamada et al. (9), which included a total of 48 patients with advanced NSCLC with ILD. They showed that the incidence of AE-ILD induced by first-line chemotherapy in the bevacizumab group was significantly lower than that in the non-bevacizumab group (0% vs 22.6%, P=0.037). In this study, most patients (83.3%) received pemetrexed-containing chemotherapy regimens, in this part of patients, the incidence of AE-ILD between the two groups also showed a significant difference (0% vs 24%, P=0.044). In our study, only 29 patients (55.7%) were treated with pemetrexed-containing regimens, the ILD progression related to first-line chemotherapy in the antiangiogenic group was lower than the control group (0% vs 22.2%). However, there was no significant difference (P=0.268) between two groups. Notably, the incidence of gemcitabine-induced ILD progression were higher than pemetrexed in our study (**Table 2**), this may explain why in only patients who received PEM-containing regimens, the incidence of ILD progression had no significant difference between two groups. Nevertheless, our results can also indicate that anti-angiogenic drugs can inhibit chemotherapy related ILD progression for NSCLC-ILD patients.

A meta-analysis conducted by Chen et al. (12) included 7 studies with a total of 251 patients. The incidence of AE-ILD related to first-line chemotherapy in NSCLC-ILD patients was 8.47%. Our updated meta-analysis included a total of 684 patients, and our results showed that the incidence of AE-ILD in NSCLC-ILD patients was 8.07%, similar to Chen's study. The incidence of AE-IPF within 1 year in IPF patients is 3.6%-9.6% under natural progression (8), while chemotherapy-related AE-ILD mostly occurs within 4 months. Therefore, chemotherapy

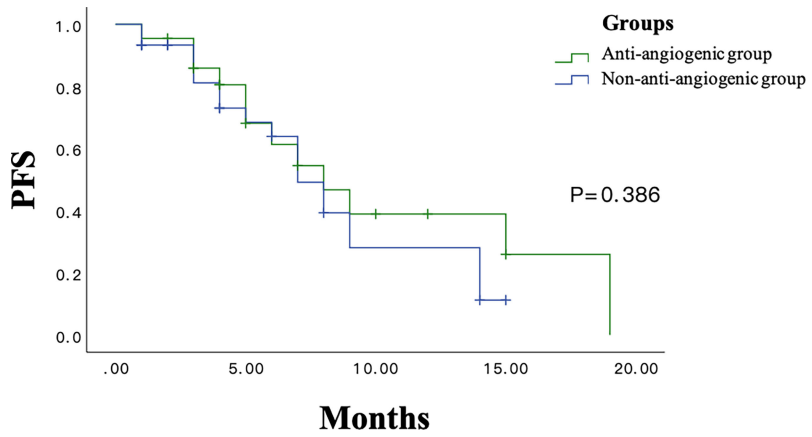

FIGURE 2 | The PFS Survival Curve in Anti-angiogenic Groups and Non-anti-angiogenic Groups.

TABLE 4 | Comparison of the short-term efficacy and mPFS in test group and control group.

Curative effect	Antiangiogenic group	Control group	P value
CR	1	1	
PR	9	10	
SD	10	16	
PD	2	3	
ORR(%)	10 (45.5)	11 (36.7)	0.523
DCR(%)	20 (90.9)	27 (90)	1.00
mPFS (months)	10.3	8.1	0.386

increases the incidence of AE-ILD. Previous studies had shown that the incidence of AE-ILD caused by various chemotherapy regimens was different. Two retrospective studies (13, 14) showed that the incidence of AE-ILD in NSCLC-ILD patients treated with pemetrexed-containing regimen was 12.5-22.6% (**Table S1**). In our study, the ILD progression rate in patients treated with pemetrexed-containing regimen was 17.7%, but no patients had AE-ILD, which may be contributed to the differences in patients' baselines. A retrospective study analyzed 109 LC-ILD patients and found that patients with usual interstitial pneumonia (UIP) had a higher incidence of chemotherapy-related AE-ILD than non-UIP patients (30% vs 8%, P=0.005). Patients with UIP mode had higher AE-ILD mortality rate (15). In the study conducted by Hamada et al, UIP patients accounted for 50%, while UIP patients accounted for only 15.4% in our study, so it was hard to determine its impact on the ILD progression rate. Many studies (16–20) showed that the incidence of AE-ILD in patients adopt the platinum-containing albumin paclitaxel regimen was low, ranging from 0% to 8.3% (**Table S1**). At the same time, our meta-analysis showed that the incidence of AE-ILD in patients adopt this regimen was 4.98% (95%CI: 2.44-8.37%). Therefore, this regimen has the potential to become the most suitable chemotherapy regimen for patients with NSCLC-ILD. In our study, only 4 patients were treated with albumin paclitaxel and platinum-containing chemotherapy, and no patients developed ILD progression. Due to the insufficient sample size of patients enrolled in this regimen, we cannot perform subgroup analysis to verify whether this regimen has a lower ILD progression rate than other chemotherapy regimens. There is an ongoing phase II randomized controlled study (21), which aims to explore whether the nintedanib combined albumin paclitaxel and platinum-containing regimens prolong the interval to AE-IPF, and the results of this study are expected in the future.

In our study, the ORR and DCR had no significant difference between antiangiogenic group and control group (P>0.05). A study included 10 patients with NSCLC-ILD treated with chemotherapy combined with bevacizumab and 11 patients treated with chemotherapy alone (22). The ORR and DCR of the bevacizumab group was 40% and 90%, the ORR and DCR of the chemotherapy group was 27% and 82%. There was no significant difference between the two groups (P>0.05), which was consistent with our results. However, a phase III clinical trial (5, 23, 24) showed that anti-angiogenic drugs combined with chemotherapy can significantly increase the ORR of NSCLC patients (P<0.01). Our study did not show any short-term therapeutic benefit, which may be related to insufficient sample size and case selection bias.

In terms of the long-term efficacy of chemotherapy combined with anti-angiogenic drugs in the treatment of patients with advanced NSCLC, several clinical studies have shown that chemotherapy combined with anti-angiogenic drugs can significantly increase the PFS of patients with NSCLC compared to chemotherapy alone (25, 26). Up to now, a total of 3 studies have evaluated the long-term efficacy of chemotherapy combined with anti-angiogenic drugs in the treatment of NSCLC-ILD (9, 22, 27). The study conducted by Hamada et al. showed that the PFS of NSCLC-ILD in the bevacizumab group was significantly better than the chemotherapy group (8.0 months vs 4.3 months, P=0.026) (9). However, Shimizu et al. showed that the PFS of NSCLC-ILD patients in the bevacizumab group was similar with the

chemotherapy group (5.5 months vs. 4.4 months, P>0.05) (22). In our study, the PFS of the antiangiogenic group and the control group was 10.3 and 8.1 months, respectively. There was no significant difference between the two groups (P>0.05), which did not show the value of long-term benefit. This may be related to insufficient sample size and publish bias.

Significance and Limitations

To our knowledge, this is the first study to explore whether the application of anti-angiogenic drugs combined with chemotherapy can inhibit the ILD progression in NSCLC-ILD patients. The results of the study showed that anti-angiogenic drugs can reduce the progression rate of ILD in such patients, which provides new ideas for the first-line treatment of NSCLC-ILD. This study has several limitations. Firstly, this study was a small-scale retrospective study, giving rise to selection bias. Secondly, this study only includes Chinese patients. Some studies had shown that the incidence of chemotherapy-induced ILD was different in various ethnic groups (28, 29), so further research is needed to verify whether our results are equally applicable to other racial groups. Thirdly, the sample size of IPF and UIP patients in our study was small, so our findings were only applicable to non-IPF and non-UIP patients. Finally, studies had shown that ILD patients with poor basic lung function have higher incidence of AE-ILD and worse prognosis (27). Our study had a small sample size and lacked records of the basic lung function status, so it was hard to determine its impact on the ILD progression rate.

CONCLUSION

This preliminary study suggests that anti-angiogenic drugs had lung protection and can reduce the risk of chemotherapy related ILD progression in NSCLC-ILD patients. Chemotherapy combined with anti-angiogenic drugs is a more appropriate treatment plan for first-line treatment of NSCLC-ILD patients. Further large-scale, randomized controlled studies are needed to confirm the effect of anti-angiogenic drugs on chemotherapy-related ILD progression and to develop better therapeutic managements for patients with lung cancer and pre-existing ILD.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

AUTHOR CONTRIBUTIONS

YW and XG contributed equally to this work. LM and YZ contributed equally to this work. All authors contributed to the article and approved the submitted version.

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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.2022.873709/full#supplementary-material

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Short-Term Surgical Outcomes for Lobectomy Between Robot-Assisted Thoracic Surgery and Uniportal Video-Assisted Thoracoscopic Surgery

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Objectives: To evaluate the short-term outcomes of uniportal video–assisted thoracoscopic surgery (UVATS) and Da Vinci robot–assisted thoracoscopic surgery (RATS) in lobectomy and lymph node (LN) dissection.

Methods: The two groups of patients with primary non-small cell lung cancer (NSCLC; RATS group, UVATS group) were matched by the propensity score to compare LN dissection and recent clinical outcomes. The results were analyzed by univariate analysis. From November 2020 to November 2021, 412 NSCLC patients (54 RATS and 358 UVATS) from a single institution of the Provincial Hospital affiliated with Shandong First Medical University were included in the analysis. Age, sex, lung lobe, surgical resection scope, solid nodules, and core tumor ratios were matched according to different surgical methods.

Results: From November 2020 to November 2021, 412 patients with NSCLC (54 RATS, 358 UVATS) from the Provincial Hospital affiliated with Shandong First Medical University were included in the analysis. According to our matching results, LN dissection was more thorough in the RATS group.

Conclusion: RATS has potential advantages over UVATS in radical lung cancer surgery.

Keywords: RATS, UVATS, lung cancer, lymph node dissection, short-term outcomes

INTRODUCTION

The evolution of technology has gradually promoted the development of minimally invasive surgery, and the prospect of minimally invasive surgery for non-small cell lung cancer (NSCLC) has changed dramatically. Robot-assisted thoracoscopic surgery (RATS) and video-assisted thoracoscopic surgery (VATS) are less-invasive methods for radical lung cancer surgery (1).The minimally invasive surgery provides a better postoperative quality of life, reduced complications, and less length of hospital stay than open-heart surgery (2). After uniportal thoracoscopic surgery

was first used for a wedge resection of the lung (3), more and more thoracic surgeons developed the uniportal thoracoscopic technique. Multiple studies have shown that uniportal video–assisted thoracoscopic surgery (UVATS) incision can shorten the operation time and reduce long-term postoperative pain (1, 4). In 2011, an article described the potential of Da Vinci robotic–assisted thoracoscopy in surgery (5), and a small number of surgeons applied robotic surgery to treat lung cancer.

Currently, a large amount of data support the feasibility, safety, and effectiveness of minimally invasive techniques. In recent years, UVATS and RATS have increased in number and proportion in minimally invasive areas. However, a recent analysis showed that the total number of lymph nodes (LNs) resected by VATS was small. The Da Vinci surgical system (DVSS) offers the benefits of joint forceps, including the three-dimensional (3D) free field of vision, these can improve the accuracy and quality of LNs (6, 7). The composition of pulmonary nodules has not been paid much attention before, so few reports compare pulmonary nodules with different core tumor ratios (CTRs) in RATS and UVATS.

Previously an academic thoracic surgery center with VATS for minimally invasive anatomic pulmonary resection, we now added the RATS program. This study aimed to analyze the cases of patients receiving RATS and UVATS during the same period of the continuous treatment of stage I–IIIA primary NSCLC in our hospital, which compare the short-term efficacy of the two surgical methods in our institution.

MATERIALS AND METHODS

Patient Selection

The Ethics Review Committee approved the study of the Provincial Hospital affiliated with Shandong First Medical University. The data came from 412 patients who underwent lung cancer surgery at the facility in November 2020 and November 2021.

Inclusion criteria included the following: 1. preoperative pulmonary function supported lobectomy, preoperative computed tomography (CT) showed non-pure ground glass density nodules, and there was only one surgical method; 2. pathologically confirmed stage I–IIIA NSCLC, requiring LN dissection; 3. preoperative radiotherapy, chemotherapy, puncture, pulmonary nodule ablation, and other treatments were not performed; and 4. did not undergo any lung surgery. Patients who met the criteria were enrolled in the study.

Excluded criteria included the following: 1. the lung has undergone surgery; 2. extensive adhesion and atresia in the pleural cavity; and 3. intraoperative exploration revealed tumor-infiltrating surrounding organs and invading the pleura, requiring the simultaneous removal of a lung and other thoracic organs. Operative death was defined as death within 30 days of the operation or any time after the operation if the patient did not leave the hospital alive.

The choice of surgical method depends on the patient's will. Patients were retrospectively classified into two groups based on the surgical approach: RATS and UVATS. We made a short flowchart, as shown in **Figure 1**.

Surgical Technique

Preoperative patients undergoing surgery at our center have met the surgical standards recommended by the NCCN guidelines (8) and have undergone a multidisciplinary consultation with physicians in the departments of oncology, thoracic surgery, and respiratory medicine before hospitalization. We have considered the choice of tumor treatment and performed the surgery.

Patients in the RVTS group were in a lateral decubitus position. One surgical incision and three robotic arm incisions were opened while maintaining a distance of 10 cm between each port and 10–15 cm from the operating site; the camera is on the middle port. Patients in the VATS group were in a lateral decubitus position. According to the surgeon's preference, a surgical incision was opened in the 4th or 5th intercostal space. The camera was placed on the side of the incision away from the surgeon and secured by an assistant to expose the field of vision.

All patients received routine preoperative examination and serological examination in our hospital, and several physicians decided the preoperative surgical plan through discussion. General anesthesia was used for surgery, and a one-lung ventilation and incision protector was placed in all incisions. Energy equipment was used to anatomize the lung structure. According to the recommendations of the NCCN guidelines, patients with resectable NSCLC should receive N1 and N2 nodule resection and at least 3 N2 station sampling or LN dissection, including 2, 4, 7, 8, and 9 stations on the right and 5, 6, 7, 8, and 9 on the left (8).

We formulated the extubation conditions by clinical specifications and extubation strategy based on clinical experience: 1. the absence of air leakage;2. the absence of an increased drainage volume every 6 h after surgery;3. the absence of a densely bloody, purulent, or cloudy pleural effusion;4. the absence of atelectasis on

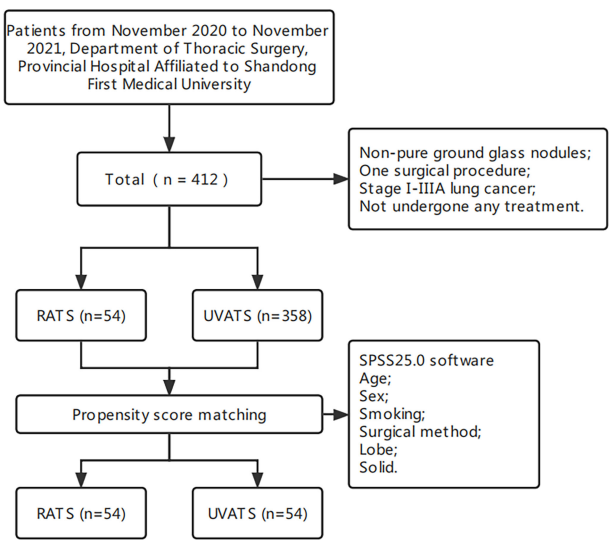

FIGURE 1 | Flow-chart of the study.

postoperative chest radiograph; and 5. the absence of subcutaneous emphysema. Patients meeting the above conditions and having less than 200ml of drainage per day were removed.

Study Variables

We obtained age, sex, procedure, surgical location, and smoking history from medical records. We got the patient's height, weight, postoperative daily drainage volume, and pain score on the first day after surgery from the nursing record paper. Postoperative thoracic drainage volumes were calculated. The characteristics of the target nodules, including solid nodules, subsolid nodules, and ground-glass nodules, were obtained from the imaging reports. According to the Visual Analog Scale for Pain, postoperative pain was scored. CTR is the ratio of solid core-to-length diameter on the maximum tumor section in preoperative CT imaging. TNM staging is based on the Joint Committee on Cancer Staging Manual (8th Edition) (9).

Differences in the characteristics of patients in the surgical group suggest that treatment allocation is affected by selection bias. Therefore, we built the propensity score matching model. Each patient receiving VATS was matched with one RATS (probability <2%) to form a surgical group with a similar probability of being assigned to each surgical type. Propensity score–matched variables are presented in the results, and the objective partially eliminates the bias that usually accompanies treatment assignment in non-randomized studies.

Statistical Analysis

We analyzed all the patients' factors. The continuous variables are summarized as the mean ± standard deviation of normally distributed data and the median [interquartile range (IQR)] of non-normally distributed data. For categorical variables, the Mann–Whitney U test was performed for a comparison between the two groups. All statistical tests were two-tailed tests, and $P < 0.05$ was considered statistically significant. SPSS25.0 software was used for propensity score matching. The graphics were created with the help of GraphPad Prism.

RESULTS

Patient Characteristics in the Unmatched Cohort

A total of 412 patients were collected, and the clinical characteristics of the collected patients were described at baseline according to different surgical methods, as shown in **Table 1**. The patients were divided into two groups according to surgical methods, including 54 RATS and 358 UVATS patients. The median age was 57 years; male patients accounted for 39.3% (n=162). Smoking history accounted for 16% (n=66). Lobectomy accounted for 97.1% (n=400). Patients with stage pI tumor accounted for 93% (n=383). Solid nodules accounted for 90% (n=371). CTR > 0. 5 accounted for 69.2% (n=285). The median postoperative hospital stay was 3 days. The median number of days with a chest tube was 2 days. The median pleural drainage volume was 280 ml. Lung air leakage occurred in 11.9% of patients after surgery (n=49). No perioperative death or open-chest surgery occurred in all patients during the observation period. These results can be seen in **Table 1**.

Patient Characteristics of the Propensity Score–Matched Patients

According to surgical methods, using propensity score matching, all patients' data were matched with SPSS software, and the primary data were age, sex, smoking, operation method, lobe, and solid. In the end, 108 patients were obtained, and the clinical baseline characteristics after matching are shown in **Table 2**. They had similar clinical features.

Matched-cohort RATS had an advantage over UVATS in the number of LN dissections (**Figure 2**). In both groups, the most common postoperative complication is lung leakage. In the VATS group, one patient was recatheterized due to extensive subcutaneous emphysema. The other patient accidentally pulled out the chest tube while going to the toilet, and there were no apparent complications when he was discharged. There was no statistical difference in the postoperative pulmonary air leakage incidence between the two groups (P=0.223). There was no significant difference in pain on the first postoperative day (P=0. 055), but the mean length of stay at UVATS was shorter (P<0.001). The median number of mediastinal LN dissection and the total number of LNs obtained by RATS were higher than those by UVATS (P<0. 001 for both factors). The cost of surgery in the RATS group was higher than that in the UVATS group (P<0. 001). **Table 3** shows the statistics of the short-term outcome of the matched population.

DISCUSSION

According to the GLOBOCAN (Global Cancer) statistics, there were approximately 1 million cases of lung cancer worldwide in 2000 and an estimated 2.09 million new cases in 2018 (10). Surgery is the primary treatment for lung cancer, especially NSCLC. In the initial thoracoscopic surgery, there are more than two surgical ports. Thoracic surgeons have been pursuing the innovation of surgical methods. RATS and UVATS have been widely used in treating lung cancer, and the NCCN guidelines have designated them as the first choice for radical lung cancer surgery. At present, the prospect of minimally invasive surgery in lung cancer treatment has changed dramatically. However, LN dissection plays a vital role in the radical resection of lung cancer, which can clarify postoperative staging, guide postoperative adjuvant therapy, and prolong the disease-free survival time. The quality of LN dissection, including the number of LNs dissected, is an indirect indicator of the surgical thoroughness of lung cancer (11).

In this study, no patients were transferred to thoracotomy or died. Before matching, the pulmonary air leakage complication rate was 7.4% in the RATS group and 12.6% in the UVATS group. After being matched, there was no significant difference in postoperative complications between the two groups. We found a statistical difference in the number of LN dissections between

TABLE 1 | Patient characteristics in the unmatched cohort (N = 412).

Characteristics	Total	RATS (n = 54)	VATS (n = 358)	P
Age (year, IQR)	57 (50–64)	61 (53–67)	57 (49–64)	0.015
Sex male (n, %)	162 (39.3)	23 (42.6)	139 (38.8)	0.598
Lobe (n, %)				0.268
RUL	147 (35.7)	20 (37.0)	127 (35.5)	
LUL	87 (21.1)	16 (29.6)	71 (19.8)	
RML	29 (7)	4 (7.4)	25 (7)	
RLL	66 (16.0)	6 (11.1)	60 (16.8)	
LLL	83 (20.1)	8 (14.8)	75 (20.9)	
Smoking (n, %)				0.592
Never	346 (84.0)	44 (81.5)	302 (84.4)	
Former	66 (16.0)	10 (18.5)	56 (15.6)	
Operation method (n, %)				0.173
Pulmonary segments	12 (2.9)	0 (0)	12 (3.4)	
Pulmonary lobectomy	400 (97.1)	54 (100)	346 (96.6)	
Pathology (n, %)				0.164
Adenocarcinoma	387 (93.9)	53 (98.1)	334 (93.3)	
Squamous	25 (6.1)	1 (1.9)	24 (6.7)	
pT stage (n, %)				0.023
1a	158 (38.3)	13 (24.1)	145 (40.5)	
1b	158 (38.3)	25 (46.3)	133 (37.2)	
1c	67 (16.3)	10 (18.5)	57 (15.9)	
2a	24 (5.8)	3 (5.6)	21 (5.9)	
2b	2 (0.5)	1 (1.9)	1 (0.3)	
3	3 (0.7)	2 (3.7)	1 (0.3)	
pN stage (n, %)				0.091
N0	382 (92.7)	47 (87.0)	335 (93.6)	
N1	14 (3.4)	4 (7.4)	10 (2.8)	
N2	16 (3.9)	3 (5.6)	13 (3.6)	
Solid (n, %)	371 (90)	51 (94.4)	320 (89.4)	0.248
CTR (n, %)				0.075
≤0.5	127 (30.8)	11 (20.4)	116 (32.4)	
>0.5	285 (69.2)	43 (79.6)	242 (67.6)	
Length of tumor (cm, IQR)	13.5 (10–20)	15 (10.8–25)	13 (10–20)	0.053

RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL right lower lobe; LLL, left lower lobe; CTR, core tumor ratio.

the two groups in postoperative observation. The number of LN dissection in the RATS group was significantly higher than that in the UVATS group (the median value of RATS was 11, and the median value of UVATS was 16; $P < 0.001$). Although some previous prospective studies have shown that RATS and VATS can achieve the same tumor outcome, there is no difference in LN dissection between the two surgical approaches. However, recent studies have shown that RATS can remove more LNs and obtain more positive LNs (2, 7).

This study suggested that the total number of dissected LNs in the mediastinal region of RATS was significantly higher than that of the UVATS group. Our study finding is similar to recent studies that RATS have a more significant advantage than VATS in LN dissection at the N2 station (6, 12). In a large retrospective study of 7,452 matched stage I lung cancer patients, the comparison results also suggested that the median number of LNs dissected by robotic surgery was higher than thoracotomy (13). Yang et al. (14) also suggested that RATS has certain advantages over UVATS in treating lung cancer and LN dissection in small-sample-size studies. In contrast, UVATS is often accompanied by a mutual interference of instruments due to the limitation of the fixed-angle field of vision, which makes it challenging to perform LN dissection with UVATS. In this study and similar to our results, we analyze why more LNs may be that the robot surgery has better operative field exposure in the intraoperative, flexible mechanical arm, more thorough cleaning of LNs, and more accurate operation to the mediastinum and hilar LNs in the deeper position.

In terms of postoperative recovery, in this study, we found that the RATS group had more postoperative pleural drainage volume, drainage time, and postoperative hospital stay than the UVATS group. Drainage tube placement is routinely required in chest surgery patients, and the extubation time is closely related to postoperative drainage. The increased pleural drainage volume in the RATS group is as follows: RATS can obtain more LNs in the mediastinal area and destroy more mediastinal regions. RATS has four surgical incisions, which destroy more parietal pleura and affect pleural drainage fluid reabsorption to a certain extent. Some studies have found that age is an independent risk factor for increased total pleural drainage. Lower pneumonectomy is also a factor in increased pleural drainage (15).

Although not all postoperative patients were systematically assessed for pain scores in this study, there were no significant differences in early postoperative pain in lung cancer patients. This result is similar to the study of Van der Ploeg APT (16). We speculate that compared with thoracotomy, the smaller surgical incision in minimally invasive surgery reduces the injury of the intercostal nerve, thus reducing postoperative pain. Compared

TABLE 2 | Patient and disease characteristics of the propensity score–matched groups (N = 108).

Characteristics	RATS (N= 54)	VATS (N= 54)	P
Age (year, IQR)	61 (53–67)	60 (51–65)	0.449
Sex Male (n,%)	23 (42.6)	21 (38.9)	0.697
Lobe (n,%)			0.251
RUL	20 (37.0)	23 (42.6)	
LUL	16 (29.6)	20 (37.0)	
RML	4 (7.4)	2 (3.7)	
RLL	6 (11.1)	5 (9.3)	
LLL	8 (14.8)	4 (7.4)	
Smoking (n,%)			0.809
Never	44 (81.5)	43 (79.6)	
Former	10 (18.5)	11 (20.4)	
Operation method (n,%)			1.000
Pulmonary segments	0 (0)	0 (0)	
Pulmonary lobectomy	54 (100)	54 (100)	
Pathology (n,%)			0.028
Adenocarcinoma	53 (98.1)	47 (87.0)	
Squamous	1 (1.9)	7 (13.0)	
pT stage (n,%)			0.509
1a	13 (24.1)	16 (29.6)	
1b	25 (46.3)	24 (44.4)	
1c	10 (18.5)	8 (14.8)	
2a	3 (5.6)	6 (11.1)	
2b	1 (1.9)	0 (0)	
3	2 (3.7)	0 (0)	
pN stage (n,%)			0.811
N0	47 (87.0)	48 (88.9)	
N1	4 (7.4)	2 (3.7)	
N2	3 (5.6)	4(7.4)	
Solid (n,%)	51 (94.4)	52 (96.3)	0.649
CTR (n,%)			0.809
≤0.5	11 (20.4)	10 (18.5)	
>0.5	43 (79.6)	44 (81.5)	
Length of tumor (cm, IQR)	15 (10.8-25)	15 (10-22)	0.587

RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe; CTR, core tumor ratio.

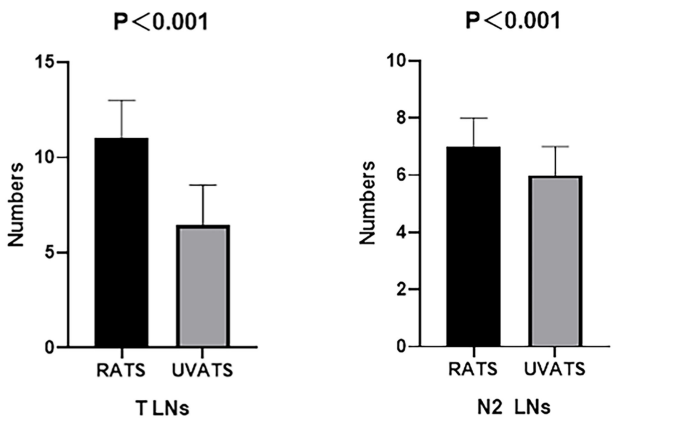

FIGURE 2 | Comparison of the number of lymph node dissection in matched cohort. The model was adjusted for age, sex, smoking, lobe, operation method, solid.

TABLE 3 | Postoperative outcomes of the propensity score–matched groups (N =108).

Characteristics	RATS (N= 54)	VATS (N= 54)	P
T LNs (n, IQR)	11 (10–13)	6 (5–7)	**<0.001**
N2 LNs (n, IQR)	7 (6–8)	6 (5–7)	**<0.001**
Air leakage (n,%)	4 (7.4)	8 (14.8)	0.223
LOS (day, IQR)	4 (3–5)	3 (2–3)	**<0.001**
Drainage time (d, IQR)	2 (2–3)	2 (1–2)	**0.001**
PDV (ml, IQR)	475 (320–757.5)	255 (160–382.5)	**<0.001**
Cost (CNY, IQR)	74,998.5 (65,473.5–75,486.6)	45,180.6 (35,833.1–54,869.4)	**<0.001**
Pain (score, range)	2 (1–4)	2 (1–4)	0.055

TLNs, total lymph nodes; N2 LNs, N2 station lymph nodes; LOS, length of hospital stay; PDV, pleural drainage volume.

with traditional thoracotomy, the small incision of RATS and UVATS surgeries did not have the expansion of an intercostal space. Minimally invasive surgery can significantly shorten the operation time, to a certain extent, reduce the compression and damage time to the intercostal nerve, and reduce postoperative pain. However, this study did not systematically evaluate patients' pain. Currently, our study lacks comparative studies on long-term postoperative pain in patients with UVATS, and more randomized trials are needed to confirm this in the future.

In the study, the hospitalization cost of the robot-assisted thoracoscopic surgery group was significantly higher than that of the UVATS group, which is also one of the problems that robotic surgery faces. Although the benefits of robot-assisted surgery are apparent, RATS is more expensive than other methods. The price of robotic surgical systems and their corresponding surgical instruments is high because technology monopolizes production in this field. Novellis et al. (17) reported that the Da Vinci surgical system costs approximately US$200,000 per year to maintain and $2 million to produce expensive one-off consumable items. Hospital costs will eventually be transferred to patients through higher insurance premiums, which naturally make surgery expensive. Moreover, this part of the cost is not covered by medical insurance, and patients have to bear it themselves, which makes it difficult for the Da Vinci surgical system to be widely used. Rising health spending can be a real problem.

UVATS has become the most exciting new development in minimally invasive thoracic surgery. While ensuring safety and oncology results, the single 4–5-cm surgical approach minimizes surgical trauma, alleviates postoperative pain, and contributes to rapid postoperative recovery (15). The DVSS combines surgical safety with a 3D imaging system, a mechanical arm that can ignore hand tremors, and action lever reduction technology to perform delicate soft tissue dissection (18, 19). RATS can also be applied to surgical cases with more complex anatomy, such as obese patients and after neoadjuvant therapy. The unique advantages of the two surgical methods make them widely used in the treatment of lung cancer in thoracic surgery.

Limitation

There were some limitations in our study. Although we had more cases of UVATS, the number of RATS studied was very small. In addition, our study was limited to our institution and was a single-center study. Our study was done recently, and we did not predict long-term survival. Focusing only on a specific procedure can lead to different results than in previous studies by such bias in studies.

CONCLUSION

For stage I–IIIA NSCLC with solid nodules, in our study, LN dissection can benefit from RATS, which can perform better anatomy and has potential benefits for the postoperative tumor staging of patients.

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 Medical Ethics Commission of Shandong Provincial Hospital SWYX: No. 2022-261. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FZ and GW designed the study and wrote the manuscript. HL and AM are responsible for data collection. LX and GW revised the manuscript and finally approved the submitted and published versions. GW is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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Improved Survival With Surgical Treatment of Primary Lung Lesions in Non-Small Cell Lung Cancer With Brain Metastases: A Propensity-Matched Analysis of Surveillance, Epidemiology, and End Results Database

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Objectives: Non-small cell lung cancer (NSCLC) with Brain metastases (BM) is an advanced disease with poor prognosis and low survival rate. Our study evaluated the survival benefit of primary lung resection with mediastinal lymph node dissection in NSCLC patients with BM using Surveillance, Epidemiology, and End-result (SEER) databases.

Methods: All cases analyzed were from Surveillance, Epidemiology, and End Results database. The data of the patients with BM of NSCLC from 2010 to 2016 was retrospectively analyzed. Patients (N=203) patients who underwent radical surgical treatment for primary lung lesions and patients (N=15500) who did not undergo surgery were compared. We successfully analyzed patients using propensity score matching (PSM). Kaplan-Meier and Cox- regression analyses were applied to assess prognosis.

Results: The median survival in the surgery group was longer than in the control group (27 months vs 5 months; $P < 0.001$) in the overall sample, 21 months longer compared to the control group (27 months vs 6 months; $P<0.001$) in a PSM cohort. Cox regression analysis showed that underwent surgery patients in the propensity-matched sample had a significantly lower risk of mortality (HR:0.243, 95%CI: 0.162-0.365, $P < 0.001$) compared with untreated patients. Multivariate analysis identified the following as independent risk factors for NSCLC with BM: no primary resection surgery, age >65 years, worse differentiation, squamous cell carcinoma, lymphatic metastasis, no systemic therapy. Subgroup analysis revealed that radical resection of the primary lung provided a survival benefit regardless of marital status, tumor size, tumor grade, tumor T stage, and mediastinal lymph node metastasis after PSM.

Conclusion: Radical resection of primary lung can improve the survival of NSCLC patients with BM. Male, age>65years, poorly differentiated tumor, tumor size>5cm, and mediastinal lymph node metastasis were factors for poor survival.

Keywords: non-small cell lung cancer, brain metastases, propensity score matching, surgical treatment, surveillance, epidemiology, and end results

INTRODUCTION

Lung cancer is one of the most common malignancies, accounting for about 85% of non-small cell lung cancer (NSCLC), and the 5-year survival rate is only 16% (1–3). NSCLC with BM are widespread, with an incidence of about 30%-50% (4). NSCLC with BM generally has a poor prognosis, and the median survival time of untreated patients is less than one month (5, 6).Despite some therapeutic advances, such as intracranial surgical resection, whole brain radiotherapy (WBRT), stereoscopic radiotherapy (SRS), and chemotherapy, NSCLC patients with BM still have a poor prognosis. In the past, NSCLC patients who had single BM with resectable lung lesions were considered to be clinically at stage IV. Such patients were considered to have no survival benefit after resection of the lung primary tumor, so no active surgical treatment was required for the lung lesions, so chemotherapy or radiotherapy were generally only given.In recent years, it has been found that selective pulmonary resection can improve the prognosis of NSCLC patients with isolated single BM, whose mOS ranges from 20.5 months to 64.9 months (7–10). In addition, whether the primary lung tumor is completely removed is related to postoperative recurrence and prognosis (10, 11). Although NSCLC with BM is at an advanced stage, the principle of radical treatment should still be followed during lung surgery to maximize the removal of tumor tissue and routine dissection of regional lymph nodes, so as to achieve the best therapeutic effect.

With the improvement of diagnosis and treatment, there is an urgent need for more effective treatment to improve the prognosis of patients. The clinical significance of surgical selective resection of pulmonary primary lesions and brain metastases has attracted attention, but the feasibility and effectiveness of surgical treatment for such patients are still controversial. However, few studies have been reported on the resection of lung primary lesion and conventional mediastinal lymph node dissection, and large sample data are lacking. Therefore, the purpose of this study was to evaluate the survival benefits of pulmonary primary resection with mediastinal lymph node dissection in NSCLC patients with BM based on Surveillance, Epidemiology, and end Results databases.

MATERIALS AND METHODS

Ethics Statement

The data about cancer in the SEER database is continually reported in every state of the United States and retrieved with no need for informed patient consent. The present study complied with the Declaration of Helsinki (as revised in 2013).

Data Source

Data in this population-based study were abstracted from the SEER. SEER*Stat Software version 8.3.4 (https://seer.cancer.gov/seerstat/; Information Management Service, Inc., Calverton, MD, USA) was used to generate the case listing.

Study Population

Our data came from the National Cancer Institute's (NCI) SEER database, andbecause SEER did not record BM information until 2010.Patients diagnosed before that year were excluded. Therefore, a retrospective cohort study was conducted on patients diagnosed from 2010 to 2016. SEER is an open access U.S. cancer database from 18 population-based cancer registries. SEER currently collects and publishes cancer incidence and survival data covering approximately 28% of the U.S. population, which is representative of the population.

Inclusion and Exclusion Criteria

We screened patients from the SEER database with pathologically diagnosed NSCLC, including adenocarcinoma, squamous cell carcinoma, and adenosquamous cell carcinoma, according to the International Classification of Diseases of Cancer Version 3 (ICD-O-3) histological codes 8140, 8070, 8560, 8046. Ethical approval and informed consent were waived because the SEER data were freely available and our investigation was retrospective. The exclusion criteria for NSCLC patients in this study were as follows: (I) no BM; (II) patients with multiple primary malignant tumors; (III) patients with NSCLC whose survival was less than one month or whose survival data were not available were excluded. We excluded patients who did not undergo primary pneumonectomy and mediastinal lymphadenectomy, such as local lobectomy, lymphadenectomy, laser ablation, or cryotherapy. Follow-up was from diagnosis of NSCLC to death or the end of the follow-up period.

Propensity Score Matching (PSM)

The purpose of this study was to compare the benefits of primary lung resection with mediastinal lymph node dissection in patients with NSCLC with BM. This was a retrospective study, so the surgery assignment was not random. Some of the key covariates of patients in the active and control groups were heterogeneous and could have influenced the results. Therefore, we further compared the difference in survival between the surgical and untreated groups by univariate analysis using 1:2

nearest neighbor matching and setting the caliper value to 0.02. The PSM process has been applied to minimize selection bias and roughly balance baseline covariates in an intergroup set of analyses (12).

Statistical Analysis

The primary endpoint of the study was overall survival (OS). Chi-square test was used to compare the characteristics of surgical patients and control patients. Covariates in this study included multilevel factors (such as age, sex, race, marital status, insurance status, tumor tissue type, tumor size, lymph nodes, degree of differentiation, chemotherapy and radiotherapy). SEER data recorded a small number of tumor lesions larger than 20cm. We thought these might be incredible, so we included them in part to understand the participation statistics. Propensity scores are used to reduce selection bias. Kaplan-Meier analysis was used to estimate OS before and after PSM. Log-rank tests were performed to compare survival differences in patients, lesions, and treatment-related characteristics. To perform a multivariate analysis in a matched population, we constructed a Cox proportional risk model to identify predictors ofsurvival. P value<0.05 considered that the difference was statistically significant. All statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA).

RESULTS

Baseline Characteristics

From 2010 to 2016, 188,840 patients with newly diagnosed NSCLC were identified in the SEER data set. A total of 21,811 patients diagnosed with advanced NSCLC with BMs were selected based on inclusion criteria described in the study population. Of these, 15,703 met the inclusion criteria for this study. The surgical and untreated groups included 203 (1.31%) and 15,500 (98.69%) patients, respectively (**Figure 1**).

Survival Before and After PSM

Kaplan-Meier analysis showed that overall survival was significantly improved in patients who underwent surgery compared to the control group (P<0.001, **Figure 2A**). Median survival was 27 months for patients who underwent primary lung resection with mediastinal lymph node dissection at the start of the NSCLC diagnosis, compared with the control group. After matching patients undergoing surgical treatment with the propensity score, we balanced nearly all available covariates between groups, while a few covariates such as age, degree of tumor differentiation, tumor size, and tumor N-stage showed differences. After excluding the mismatched population, 203 surgical patients and 406 untreated patients were matched at 1:2 PSM (**Table 1**). To balance covariates, significant differences in survival time were also observed between patients treated

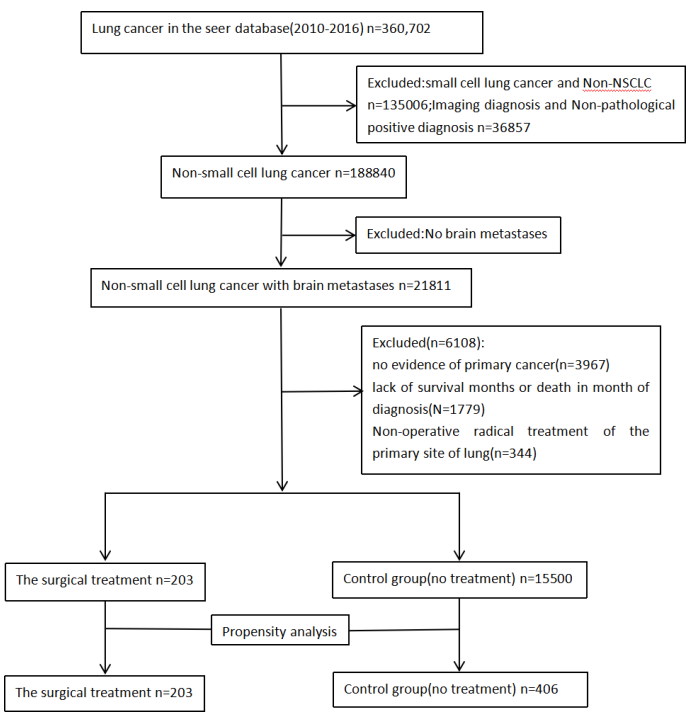

FIGURE 1 | SEER Data extraction and filtering flowchart.

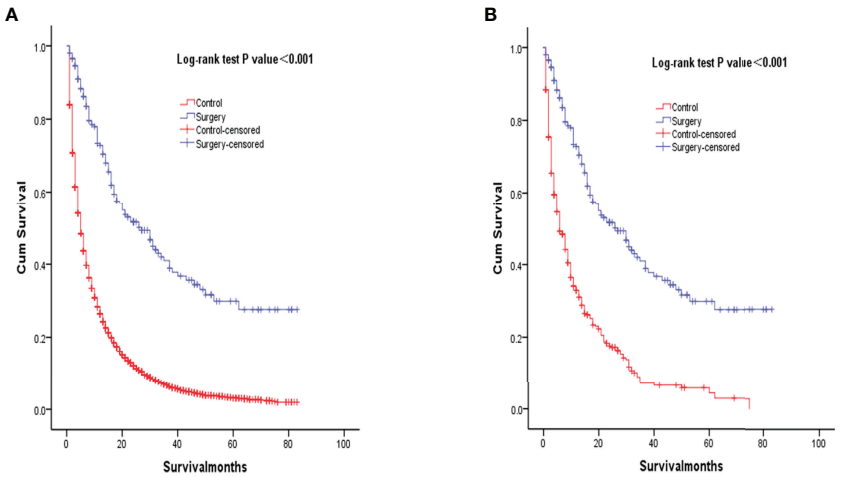

FIGURE 2 | Kaplan-Meier overall survival curves of surgery-treated patients vs control before propensity score matching **(A)** and after propensity score matching **(B)**.

surgically after PSM matching and those who did not receive treatment (P<0.001, **Figure 2B**).

Prognostic Factors

Table 2 lists the median survival results of univariate Kaplan-Meier analysis in the matched population. During surgery (P < 0.001), age (P < 0.001), sex (P = 0.010), marital status (P = 0.014), pathological type (P < 0.001), degree of differentiation (P= 0.001), tumor size (P < 0.001), lymph node (P < 0.001), chemotherapy (P < 0.001). There was significant difference in survival rate among covariables. Patients who did not undergo primary resection with mediastinal lymph node dissection, age >65 years, male, divorced, poorly differentiated or undifferentiated, tumor size >5cm, mediastinal lymph node metastasis, and did not undergo chemotherapy had poor survival. **Table 3** shows the multivariable predictors of mortality for the propensity matched sample. Patients in the propensity matching sample who underwent surgery had a significant reduction in mortality compared with those who did not (HR: 0.243, 95%CI: 0.162-0.365, P < 0.001). Age >65 years, squamous cell carcinoma, mediastinal lymph node metastasis, and no chemotherapy were independentlyassociated with higher mortality (P < 0.001, < 0.001 and < 0.001, **Table 3**). Mortality was higher in male, divorced, poorly differentiated or undifferentiated, and tumor size >5cm than in female, married, well-differentiated or moderate differentiated, and tumor size ≤5cm.

Predictors of Survival Among Surgery-Treated Patients

Multivariate analysis assessed the predictors of survival in surgical patients, and the results were shown in **Table 4**. Patients >65 years of age who received surgical treatment had an increased risk of death compared with patients ≤65 years of age (HR= 1.587, 95%CI: 1.027-2.453, P= 0.034, **Table 4**). Patients who underwent surgery for squamous cell carcinoma had an increased mortality rate compared with those who underwent surgery for adenocarcinoma (HR= 2.009, 95%CI: 1.180-3.420, P = 0.010). Survival was significantly lower in patients undergoing chemotherapy than in patients not undergoing chemotherapy (HR = 2.555, 95%CI: 1.640-3.979, P < 0.001).

Subgroup Analysis After PSM

After PSM matching, differences in age, tumor differentiation, tumor size, and lymph nodes still existed between groups, so subgroup analysis was further performed. By age subgroup analysis, overall survival after PSM was longer in patients who underwent surgery than in patients who did not receive treatment (P < 0.001 and P < 0.001, **Figure 3**). In the subgroup of tumor differentiation degree, the survival rate of surgery group was significantly higher than that of untreated group (P < 0.001 and P < 0.001, **Figure 4**). In the tumor size subgroup, survival was significantly higher in the surgically treated group than in untreated patients (P < 0.001 and P < 0.001, **Figure 5**). Based on subgroup analysis of lymph nodes, patients who underwent surgery had significantly higher survival rates than untreated patients(P < 0.001 and P < 0.001, **Figure 6**).

DISCUSSION

In this study, radical pulmonary resection was independently associated with survival of NSCLC with BM. Primary lung tumor resection could improves survival in patients with BM from NSCLC.

Although relevant treatment guidelines for NSCLC with BM have been issued at home and abroad, there is still a lack of mature consensus due to the diversity and complexity of clinical symptoms and individual differences of patients, and there are still different views on the best treatment methods for concurrent BM of lung cancer in the academic circle. Simultaneous brain-lung resection is not widely used. In the early stage, it was believed that such patients did not benefit from the removal of

TABLE 1 | Summary characteristics of the overall sample stratified by surgery treatment before and after propensity score matching.

Variables	Before PSM			After PSM		
	Surgery (n = 203)	Control (n = 15500)	P value	Surgery (n = 203)	Control (n = 15500)	P value
Age (y)			<0.001			0.013
≤65	140 (69.0)	8,623 (55.6)		140 (69.0)	238 (58.6)	
>65	63 (31.0)	6,877 (44.4)		63 (31.0)	168 (41.4)	
Sex			0.031			1
Male (%)	89 (43.8)	7,979 (51.5)		89 (43.8)	178 (43.8)	
Female (%)	114 (56.2)	7,521 (48.5)		114 (56.2)	228 (56.2)	
Race			0.041			0.263
White (%)	169 (83.3)	11,721 (75.6)		169 (83.3)	315 (77.6)	
Black (%)	18 (8.9)	2,063 (13.3)		18 (8.9)	49 (12.1)	
API (%)	16 (7.9)	1,716 (11.1)		16 (7.9)	42 (10.3)	
Marital status			0.620			0.774
Married (%)	113 (55.7)	8,089 (52.2)		113 (55.7)	217 (53.4)	
Single and unmarried (%)	31 (15.3)	2,844 (18.3)		31 (15.3)	75 (18.5)	
Widowed, divorced, separated (%)	50 (24.6)	3,975 (25.6)		50 (24.6)	99 (84.4)	
Unclear (%)	9 (4.4)	592 (3.8)		9 (4.4)	15 (3.7)	
Insurance status			0.450			0.340
Insured (%)	189 (93.1)	14,589 (94.1)		189 (93.1)	381 (93.8)	
Uninsured (%)	9 (4.4)	693 (4.5)		9 (4.4)	21 (5.2)	
Unclear (%)	5 (2.5)	218 (1.4)		5 (2.5)	4 (1.0)	
Histological type (%)			0.145			0.571
Adenocarcinoma (%)	158 (77.8)	11,385 (73.5)		158 (77.8)	313 (77.1)	
Squamous cell carcinoma (%)	27 (13.3)	2,007 (12.9)		27 (13.3)	47 (11.6)	
NSCLC,adenosquamous carcinoma (%)	18 (8.9)	2,108 (13.6)		18 (8.9)	46 (11.3)	
Grade (differentiated)			<0.001			<0.001
Well/Moderate (%)	73 (36.0)	2,001 (12.9)		73 (36.0)	63 (15.5)	
Poor/Undifferentiated (%)	113 (55.7)	4,672 (30.1)		113 (55.7)	121 (29.8)	
Unclear (%)	17 (8.4)	8,827 (56.9)		17 (8.4)	222 (54.7)	
AJCC N, 7th ed			0.014			0.069
N0 (%)	97 (47.8)	2,800 (18.1)		97 (47.8)	68 (16.7)	
N1-N3 (%)	78 (38.4)	10,547 (68.0)		78 (38.4)	278 (68.5)	
Unclear (%)	28 (13.8)	2,153 (13.9)		28 (13.8%)	60 (14.8)	
Tumor size			<0.001			<0.001
≤5cm (%)	125 (61.6)	6,539 (42.2)		125 (61.6)	180 (44.3)	
>5cm (%)	50 (24.6)	6,808 (43.9)		50 (24.6)	166 (40.9)	
Unclear (%)	28 (13.8)	2,153 (13.9)		28 (13.8)	60 (14.8)	
Chemotherapy			0.759			0.724
Yes (%)	123 (60.6)	9,227 (59.5)		123 (60.6)	252 (62.1)	
No (%)	80 (39.4)	6,273 (40.5)		80 (39.4)	154 (37.9)	
Radiotherapy			0.612			0.953
Yes (%)	163 (80.3)	12,240 (79.0)		163 (80.3)	322 (79.3)	
No (%)	36 (17.7)	2,766 (17.8)		36 (17.7)	75 (18.5)	
Unclear (%)	4 (2.0)	494 (3.2)		4 (2.0)	9 (2.2)	

the lung primary tumor, so they did not need active surgical treatment for the lung lesions.In recent years, for NSCLC patients with isolated single BM, selective resection of pulmonary lesions can improve the prognosis (13–18). Other studies have shown that SRS can also achieve better treatment effect for surgically resectable BM patients, and long-term survival is similar to surgery (7, 19–21). In addition, studies have suggested that whether complete resection of primary lung tumor is related to postoperative recurrence and prognosis (10, 11), but most cases are limited to selective local resection of lung lesions, and radical resection of lung lesions in NSCLC patients with BM is rarely reported on prognosis. HAN et al. (22) believed that lung surgery should still follow the principle of radical treatment and maximize the removal of tumor tissue and routine dissection of regional lymph nodes to achieve the best therapeutic effect. However, due to the small number of cases, the impact of radical surgical treatment on survival and prognosis of NSCLC patients combined with BM has not been fully discussed. In this study, all 203 patients underwent pulmonary primary tumor resection and mediastinal lymph node dissection, which confirmed that this radical surgical method of pulmonary primary tumor resection can prolong survival and have certain long-term survival benefits, and is an independent risk factor for OS.

Previous studies have shown that in addition to surgery, gender, race, adenocarcinoma, marital status, insurance status, mediastinal lymph nodes and other factors are also related to the prognosis of NSCLC patients with BM (19, 23–28). It has also

TABLE 2 | Univariate analysis of prognostic factors for OS.

Variables	After PSM		
	All patients	Survival time (months), median (95% CI)	P value
Group			<0.001
Surgery	203	27 (19.332-34.668)	
Control	406	6 (4.709-7.291)	
Age (y)			<0.001
≤65	378	15 (12.688-17.312)	
>65	231	6 (4.368-7.632)	
Sex			0.010
Male	267	8 (5.821-10.179)	
Female	342	13 (10.600-15.405)	
Race			0.125
White	484	10 (8.297-11.703)	
Black	67	9 (6.941-11.059)	
Yellow	58	22 (17.064-26.936)	
Marital status			0.014
Married	330	14 (11.156-16.844)	
Single and unmarried	106	9 (6.161-11.839)	
Widowed, divorced, separated	149	8 (5.516-10.484)	
Unclear	24	13 (2.833-23.167)	
Insurance status			0.434
Insured	570	10 (8.118-11.882)	
Uninsured	30	12 (9.741-14.259)	
Unclear	9	20 (6.511-33.489)	
Histological type			<0.001
Adenocarcinoma	471	13 (10.846-15.154)	
Squamous cell carcinoma	74	5 (3.489-6.511)	
NSCLC, adenosquamous carcinoma	64	7 (2.712-11.288)	
Grade (differentiated)			0.001
Well/Moderate	136	16 (11.589-20.411)	
Poor/Undifferentiated	234	10 (7.238-12.762)	
Unclear	239	9 (7.313-10.687)	
Tumor size			<0.001
≤5cm	305	14 (11.612-16.388)	
>5cm	216	7 (5.371-8.629)	
Unclear	88	–	
TNM/N			<0.001
N0	165	16 (10.916-21.084)	
N1-N3	356	9 (7.168-10.832)	
Unclear	88	–	
Chemotherapy			<0.001
Yes	375	16 (13.872-18.128)	
No	234	4 (3.270-4.730)	
Radiotherapy			0.053
Yes	485	12 (10.112-13.888)	
No	111	6 (4.048-7.952)	
Unclear	13	4 (2.668-5.332)	

been reported (22, 29) that the prognosis of lung surgery in NSCLC patients with BM is not related to mediastinal lymph node stage and T stage of lung lesions (11, 22). In this study, we performed PSM to minimize selection bias and make no significant differences in these factors when using the same sex, race, marital status, insurance status, histological type, and mediastinal lymph node subsets. So, the patients are evenly distributed. Our results suggest that radical resection of pulmonary lesions, youth (≤65 years), adenocarcinoma, and absence of mediastinal lymph node metastasis are independent prognostic factors for BM patients. Moreover, male, non-Asian race, divorce, poor tumor differentiation, and tumor >5cm were found to be negatively correlated predictors of prognosis in NSCLC patients with BM, which has been widely discussed in numerous studies (24, 29–32). In addition, BM suggests blood metastasis of tumor cells in patients, so it is necessary for NSCLC patients with BM to undergo chemotherapy (33, 34).The results of this group of cases showed that chemotherapy was an independent factor affecting prognosis. Although our study found no significant difference in survival risk between patients who received radiotherapy and those who did not, this may be due to the fact that the radiotherapy site (lung or brain) was not recorded for subgroup analysis. However, we believe that radiotherapy and chemotherapy play an indispensable role in the comprehensive treatment of NSCLC patients with BM.

TABLE 3 | Multivariate analysis of factors predictive of patients OS.

Variables	After PSM	
	HR (95% CI)	P value
Group, control (vs. surgery)	0.243 (0.162-0.365)	<0.001
Age, ≤65 (vs. >65)	1.620 (1.289-2.037)	<0.001
Sex, male (vs. female)	0.761 (0.620-0.934)	0.009
Race, white (vs. black)	1.026 (0.749-1.405)	0.873
Race, white (vs. API)	0.651 (0.453-0.936)	0.020
Marital status, Married (vs. Single and unmarried)	1.215 (0.916-1.611)	0.176
Marital status, Married (vs. Widowed, divorced, separated)	1.427 (1.116-1.825)	0.005
Insurance status, insured (vs. uninsured)	1.091 (0.694-1.713)	0.707
Histological type,Adenocarcinoma (vs. squamous cell carcinoma)	1.729 (1.290-2.318)	<0.001
Histological type,Adenocarcinoma (vs. NSCLC/Adenosquamous carcinoma)	0.960 (0.697-1.322)	0.804
Grade (differentiated),Well/Moderate (vs. poor/undifferentiated)	1.493 (1.141-1.954)	0.004
Tumor size, ≤5cm (vs>5cm)	1.263 (1.010-1.579)	0.040
TNM/N,N0 (vs. N1-N3)	1.716 (1.333-2.209)	<0.001
Chemotherapy, yes (vs. no)	3.041 (2.429-3.809)	<0.001
Radiotherapy, yes (vs. no)	0.913 (0.700-1.191)	0.503

TABLE 4 | Multivariate analysis of predictors of survival among patients with surgery patients.

Variables	HR (95% CI)	P value
Sex, male (vs. female)	0.66 (0.439-0.993)	0.149
Age, ≤65 (vs. >65)	1.587 (1.027-2.453)	0.034
Race, white (vs. black)	1.816 (0.942-3.499)	0.075
Race, white (vs. yellow)	0.676 (0.257-1.78)	0.428
Marital status, Married (vs. Single and unmarried)	1.584 (0.846-2.215)	0.188
Marital status, Married (vs. Widowed, divorced, separated)	1.369 (0.846-2.215)	0.125
Histological type,Adenocarcinoma (vs. squamous cell carcinoma)	2.009 (1.180-3.420)	0.010
Histological type,Adenocarcinoma (vs. NSCLC/Adenosquamous carcinoma)	0.998 (0.461-2.162)	0.996
Grade (differentiated),Well/Moderate (vs. poor/undifferentiated)	1.355 (0.882-2.080)	0.165
Tumor size, ≤5cm (vs>5cm)	1.034 (0.666-1.607)	0.881
TNM/T,T1-T2 (vs. T3-T4)	1.276 (0.794-2.052)	0.314
TNM/T,T1-T2 (vs. unclear)	1.198 (0.161-8.934)	0.86
TNM/N,N0 (vs. N1-N3)	1.388 (0.926-2.080)	0.113
TNM/N,N0 (vs. unclear)	0.496 (0.043-5.774)	0.575
Chemotherapy, yes (vs. no)	2.555 (1.640-3.979)	<0.001

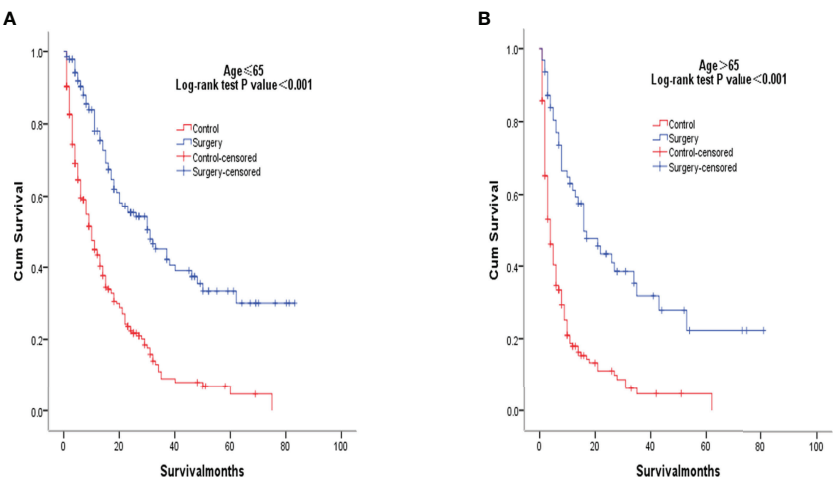

FIGURE 3 | Kaplan-Meier overall survival curves of surgery-treated patients vs control after propensity score matching stratified by age ≤ 65years **(A)**, age> 65 years **(B)**.

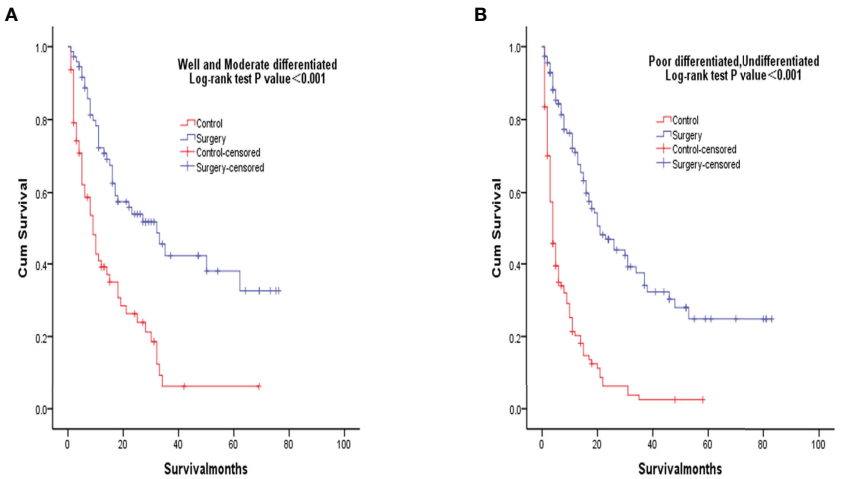

FIGURE 4 | Kaplan-Meier overall survival curves of surgery-treated patients vs control after propensity score matching stratified by well and moderate **(A)**, poor and undifferentiated **(B)**.

Limitations

There are some limitations in this study, which may affect our research results to some extent. The SEER database did not record data on patient complications, smoking history, and physical conditions. It is well known that some factors such as the number of BM, genetic changes and the treatment of BM affect the prognosis and clinical efficacy of patients (30, 35, 36), but the SEER database does not provide relevant information. These limitations may have some effect on overall prognosis, and we hope to refine this section in future prospective studies. Although the database contains specific radiotherapy and surgical methods, the lack of information on specific chemotherapy schemes has a certain impact on surgical evaluation, which is also the limitation of this paper. Therefore, we need more detailed data to assess the efficacy and adverse effects of surgery. Finally, although PSM was used to reduce selection bias in the surgical group, the retrospective nature of this study makes it difficult to avoid bias in other confounding factors.

CONCLUSION

Based on our findings, it is evident that radical resection of primary lung can improve the survival of NSCLC patients with

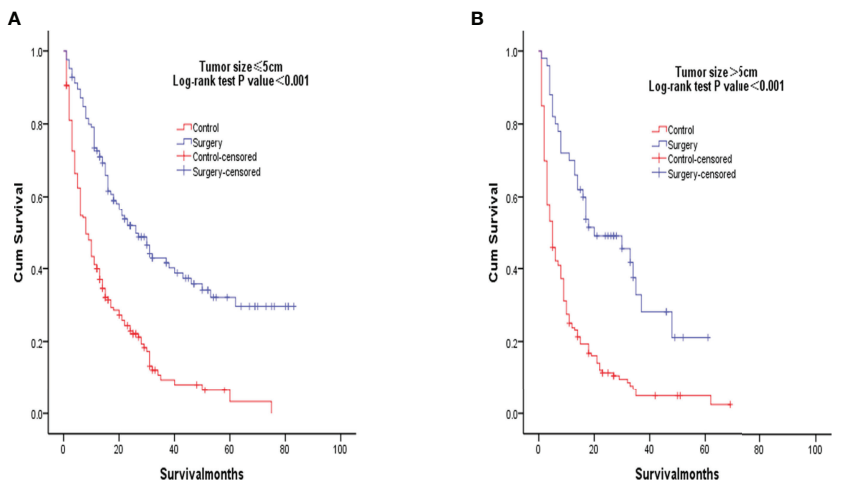

FIGURE 5 | Kaplan-Meier overall survival curves of surgery-treated patients vs control after propensity score matching stratified by Tumor size, ≤5cm **(A)**, >5cm) **(B)**.

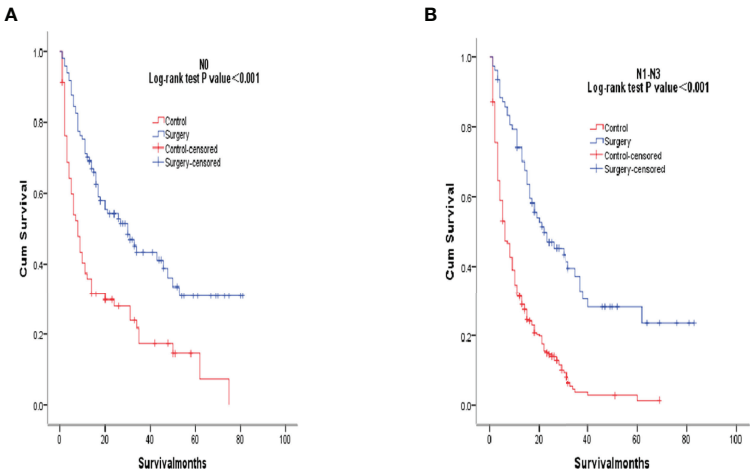

FIGURE 6 | Kaplan-Meier overall survival curves of surgery-treated patients vs control after propensity score matching stratified by N0, **(A)**, N1-N3 **(B)**.

BM. In the future, a study with well-designed, multi-center, prospective randomized design is needed to validate this conclusion.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

QW performed the majority of experiments, acquisition of data, analysis and interpretation of data, statistical analysis, and drafting of the manuscript; JL and XL conducted part of the experiment, analysis and interpretation of data; QZ for critical revision of the manuscript for important intellectual content and study supervision.

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State-of-the-art combination treatment strategies for advanced stage non–small cell lung cancer

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Non–small cell lung cancer (NSCLC) is the most abundant type of epithelial lung cancer being diagnosed after 40% of invasions of excrescence in pulmonary tissues. According to WHO, 30% of NSCLC patients can be cured if diagnosed and treated early. Mutations play an important role in advanced stage NSCLC treatment, which includes critical proteins necessary for cellular growth and replication. Restricting such mutations may improve survival in lung cancer patients. Newer technologies include endoscopic bronchial ultrasonography and esophageal ultrasonography. Currently, policymaking or decision-making for treatment regimens merely depends on the genomic alterations and mutations. DNA sequencing, methylation, protein, and fragmented DNA analysis do NSCLC screening. Achievement of these goals requires consideration of available therapeutics in current anticancer approaches for improving quality of life and treatment outcomes for NSCLC patient. The specific goals of this review are to discuss first-line and second-line therapies for advanced-stage NSCLC and molecularly targeted therapy including thoughtful discussion on precise role of treatment strategies in specific tumors. Also, concerned diagnostics, new clinical trial designs, and pursuing appropriate combinations of radiotherapy and/or chemotherapy with biological therapy for exceptional cases considering resistance mechanisms and palliative care will be discussed.

KEYWORDS

lung cancer, small cell lung cancer, advanced stage, chemotherapy, immunotherapy, targeted therapy

Introduction

Lung cancer has become one of the most widespread and deadliest cancers worldwide with non–small cell lung cancer (NSCLC) as predominating of all lung cancers, approximately 85% lower survival rate (1–6). An insignificant number of patients are detected at initial stage, including 26% and 8% at stages I and II, respectively, whereas later stages, like stage III and stage IV, are diagnosed more as 28% and 38%, respectively (7). It has been expected that $^{2}/_{3}$ of NSCLC is usually on superior tiers of cancer III and IV while they may be diagnosed (8).

Lung cancer classification, 2021, by World Health Organization (WHO) is based on histopathological and molecular subtypes into the following categories: precursor glandular and squamous precursor lesions, squamous cell, adeno-, adeno-squamous, large-cell, and sarcomatoid carcinomas; lung neuroendocrine neoplasm, tumors, and carcinomas; and salivary gland–type tumors (7) (Figure 1). For advanced NSCLC (9), owing to metastasis of the disease, NSCLC is rather aggressive and metastasizes early, involving the liver and brain, and is characterized by rapid tumor growth (10).

The survival rate for NSCLC is comparatively lower than other cancers and was approximately 16.8% and 25.1% for men and women, respectively, from the period of 2012 to 2015. Comparatively, the slow survival rate is because most NSCLC cases, about two-thirds, are detected at later stage or at unresectable IIIB and IV stages (3). For NSCLC, a 5-year survival rate is 25% influenced by multifarious factors, i.e., subtype and disease progress.

Advanced-stage NSCLC is characterized by metastases and is non-treatable with surgical resection if multiple metastatic sites are present. Patients with a single metastatic site are candidates for surgical removal of primary tumor. However, chemotherapy is frontline treatment for most advanced cases of NSCLC. Other two most common treatment options are either radiotherapy or palliative chemotherapy (3). Consistent exposure of lung epithelium to carcinogens leads to dysplasia and, if this persists, mutations arise and altered proteins will be synthesized resulting in disruption of cell cycle and sets stage for carcinogenesis. Genetic mutations most commonly responsible for pathogenesis of NSCLC are epidermal growth factor (EGFR), Kirsten rat sarcoma virus (KRAS), and p16 (7). Furthermore, greater risk of pulmonary embolism (PE) and thromboprophylaxis is associated with surgery. Current standard of care is concurrent chemoradiotherapy followed by immunotherapy (11).

Current treatment strategies of advanced-stage NSCLC

The goal of treating advanced stages of NSCLC is to improve and prolong patient's life and alleviate symptoms. Cancer stage consideration is important for determining treatment choices of NSCLC. According to the Union of International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC), TNM's classification has been considered as the golden standard for staging and subsequent prognosis of solid tumors. The latest guidelines of the eight TNM staging edition recognize multi-model therapy crucial for unresectable stage III NSCLC, considerable superior effects of chemoradiotherapy followed by durvalumab [anti–programmed death ligand 1 (PD-L1) agent], approved by United States Food and Drug Administration (US FDA) over standard chemoradiotherapy (12). Treatment options for stages I and IIA and IIB are surgery and, later, adjuvant chemotherapy. Chemotherapeutics used in NSCLC include primarily platinum analogs (cisplatin and carboplatin) along with mitomycin C, ifosfamide, and vinca alkaloids (vindesine, vinorelbine, and vinblastine), as well as etoposide, gemcitabine, pemetrexed, and taxanes such as paclitaxel and docetaxel (13).

Surgery in advanced-stage NSCLC

Stage III is the most heterogeneous stage due to tumor invasion and involvement of lymph nodes, and therefore, patients are considered for a multidisciplinary treatment approach (14). At stage 0, surgery is the most fruitful treatment option because, at this stage, tumor is neither invasive nor metastatic in nature; segmentectomy is beneficial in this case, while, in case of centrally located lesions, either lobectomy or endobronchial therapy is performed, including electrodynamics therapy, cryotherapy, ND-YAG laser therapy, and electrocautery.

At stages IA and IB, an evidence-based study showed a 4-year survival outcome with lobectomy with complete ipsilateral mediastinal lymph node dissection (CMLND) in comparison to lymph node sampling. This currently holds limitations and rejection as the treatment of choice because of reduced efficacy at all stages. Therapeutic surgery is regarded as the treatment of choice for stage IIIA with N1 lymph nodes. However, a large number of patients are diagnosed with N2 disease (14). Therefore, surgery is followed by adjuvant chemotherapy in current consensus. For stage IIIA1 and IIIA2 patients, a mediastinal lymphadenectomy is often followed by platinum-based adjuvant chemotherapy (5).

First-line systemic treatment in metastasized NSCLC

Postoperative radiation therapy (PORT) is not evidenced as effective in stage I patients and did not improve survival rate. The restricting mutations may improve survival in lung cancer patients. These mutations are EGFR and anaplastic lymphoma kinase (ALK). EGFR is inhibited by tyrosine kinase inhibitors

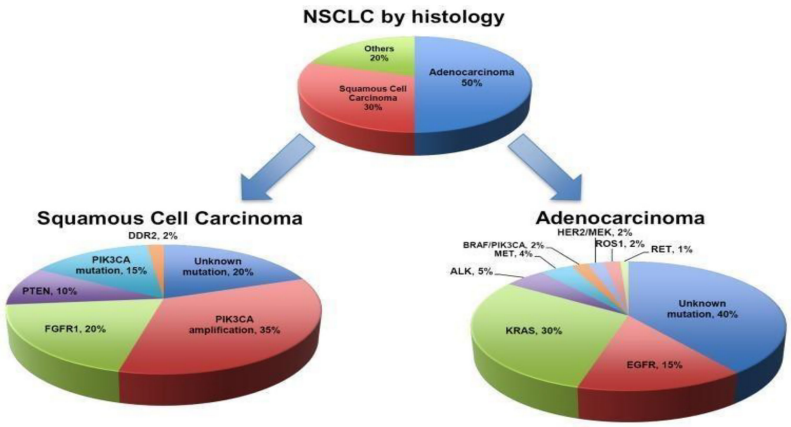

FIGURE 1
Classification of NSCLC (4).

(TKIs) (Figure 2). Novel research in targeted drug therapy showed significant survival benefits to NSCLC patients up until stage IIIA, with EGFRs-sensitizing mutation like ceritinib (80 mg) improved disease-free survival.

Currently, standard for frontline treatment of advanced-stage NSCLC, which is negative for a mutant EGFR or ALK, is platinum-based doublet chemotherapy (PT-DC). Improved clinical outcomes have been observed by incorporation of bevacizumab (Bev) to first-line PT-DC, as compared to chemotherapy alone to treat non-squamous NSCLC (Figure 3).

In case of stage IIIA and IIIA4 patients, with tumors and N2/N3 lymph nodes, conditionally being healthy patient with no weight loss, best outcomes can be achieved with concurrent chemoradiotherapy followed by surgery including platinum-based chemoradiotherapy; however, this may cause severe esophagitis. To reduce local relapse of tumor, PORT can be used without prolonging survival. Nevertheless, meta-analysis of five randomized controlled trails (RCT) of cisplatin-based therapy has resulted in survival benefit (HR for death −0.89, 99% CI; 0.82–0.96) (13, 15).

Stage IV remains incurable and therapy aims at improving quality of life and survival of patient (12, 15). During this stage, only a small percentage of patients, 10%–30%, respond to chemotherapy and few, 1%–3%, survive 5 years after being

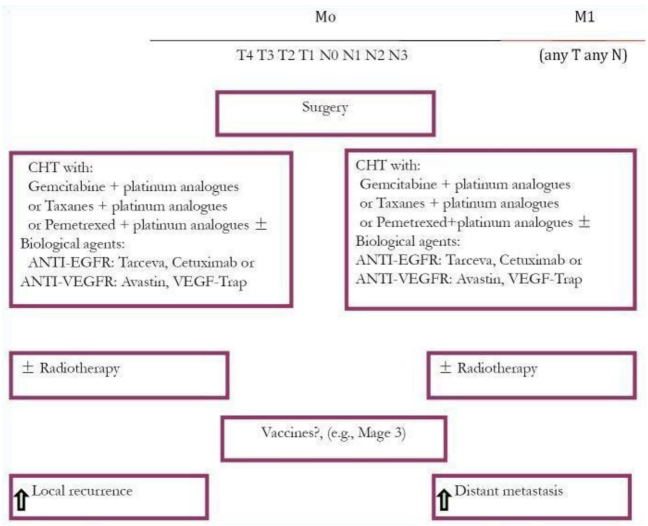

FIGURE 2
Treatment plan for NSCLC (13).

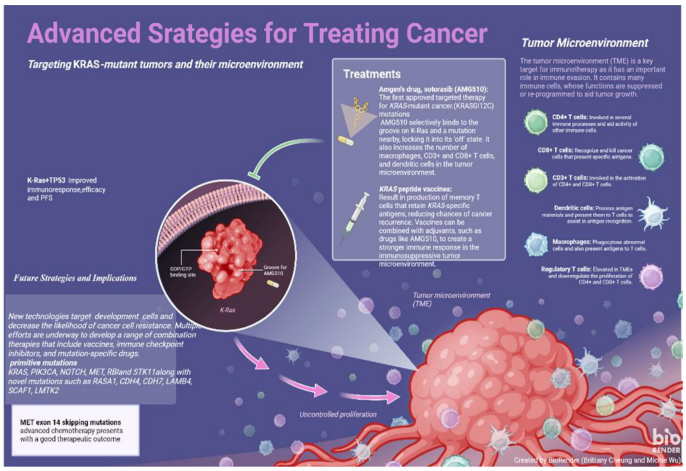

FIGURE 3
Advanced strategies for treating cancer.

diagnosed. Functional patients are offered double drug-based chemotherapy for small survival benefit (15). Numerous randomized trials demonstrated an overall survival (OS) benefit, with more than a hundred patients, by deploying chemotherapy treatment along with best supportive care (BSC) (13).

In elderly population, combination chemotherapy of gemcitabine and vinorelbine failed to show improvement in response rate, TTP, and quality of life. However, this combination has been well tolerated and effective in numerous phase II trials (16). Cisplatin- and carboplatin-based therapies have shown to be tolerable in geriatric population according to retrospective analyses of phase III RCT and multiple phase II studies. Weekly paclitaxel and carboplatin showed improvement in all outcome parameters in comparison to either single-agent vinorelbine or gemcitabine in randomized phase III trials (17). Overall response rate (ORR), survival benefit, progression-unfastened survival (PFS), median survival, and 1-year OS improved with paclitaxel and carboplatin (18). Clinically, non-platinum monotherapy is the first-line treatment for unfit geriatric patients with advanced NSCLC. Those who are physically fit enough have a better option of a carboplatin-based combination. More improvement in survival was observed with combination of Bev and paclitaxel/carboplatin (PCB) as compared to chemotherapy alone. However, this benefit was missing in women over the age of 60 (19, 20). According to two randomized phase III studies, i.e., the ECOG 4599 and AvAil, incorporation of Bev, an anti-angiogenic agent, to carboplatin and paclitaxel regimen in the first study and gemcitabine/cisplatin in the second study improved effectiveness and PFS from 4.5 to 6.2 months, $P < 0.0001$. In comparison to control arm, the arm receiving Bev in ECOG 4599 study had improved OS statistically (HR 0.79; 95%, CI: 0.67–0.92; $P = 0.003$) (21). Hence, results of these two trials indicated that Bev can be recommended to be used in combination with chemotherapy in NSCLC treatment (13).

Pemetrexed-platinum doublet chemotherapy with or without bevacizumab

Pemetrexed-platinum doublet (Pem-Pt) is a combination of platinum-based chemotherapy with Bev and is regarded as category 1 regimen for advanced-stage NSCLC. The addition of Bev to Pem-Pt doublet regimen exhibited longer median PFS and higher ORR in general population ($P = 0.000$). The addition of Bev as maintenance therapy after Pem-Pt plus Bev regimen demonstrated a longer median PFS in comparison to patients without Bev in maintenance therapy. The Pem-Pt plus Bev regimen was associated with an acceptable safety profile, which lacked incidences of hypertension, proteinuria, or excessive bleeding (6) (Table 1). Bev is approved along with chemotherapy in advanced non-squamous NSCLC owing to its antiangiogenic effects, anti–vascular endothelial growth factor (VEGF), and immunomodulatory effects. It enhances efficacy of atezolizumab to reverse VEGF immunosuppression (29).

In a more recent trial, BeTa (Bev/Tarceva) trial, a combination of Bev and erlotinib, as second-line treatment of advanced-stage NSCLC was investigated. Results suggested that the combination doubled PFS (3.4 months) in comparison to monotherapy of erlotinib alone (1.7 months,

TABLE 1 Chemotherapeutics agents in maintenance designed trials.

Trial	Number randomized	First-line agents	Maintenance	Survival in months (Hazard ratio; P-value)
(22)	181	MIC	Vinorelbin	12.3vs.12,3 (HR=1.08;P=0.48)
(23)	206	GC	Gemicitabine	OS13vs.11 (HR=n.r;P=0.195)
(24)	464	GC	Gemicitabine	PFS 3.7vs.2.1 (HR=0.51;P<0.001)
(25)	255	GCb	Gemicitabine	OS 8vs.9.3 (HR=0.97,P=0.84)
(26)	307	GCb	Docetaxel	OS12.3 vs.9.7 (HR=n.r;P=0.0853)
(27)	663	Cb/CG/Pac/D	Pemetrexed	OS13.4 vs.10.6 (HR=0.79; P=0.012)
(28)	539	PemC	Pemetrexed	PFS3.9vs.2.6 (HR=0.64; P=0.002)

P = 0.001) with no improvement regarding OS (13). Other randomized trial of targeted therapy suggested that addition of Bev enhances chemotherapeutic response but no increment in OS (13).

Nivolumab monotherapy as first-line treatment of advanced-stage NSCLC

Nivolumab is an antibody that targets programmed cell death protein 1 (PD-1) as an immune checkpoint inhibitor (ICI). It is shown to improve ORR of 17% in heavily pretreated patients of advanced NSCLC and 1- to 3-year OS rates of 42%, 24%, and 18%, respectively, evidenced through phase I, multi-cohort, and checkmate 0.12 trial. Previous study conducted on 423 patients reported >5% PD-L1 expression and minimal advantage of nivolumab treatment in RR (26% vs. 33%), PFS (4.2 vs. 5.9 months; HR, 1.15; 95% CI, 0.91–1.45; P = .25), or OS (14.4 vs. 13.2 months; HR, 1.02; 95% Q17 CI, 0.80–1.30) were observed (30).

Nivolumab and ipilimumab in combination and monotherapy

Nivolumab is of particular importance and improved survivors to chemotherapy coupled with low toxicity profile and survival rate. It is used as second-line monotherapy for squamous and non-squamous cell metastatic NSCLC. Phase III trial (CheckMate 227) studied the combination therapy of nivolumab and ipilimumab (ICI antibodies) in previously untreated patients of advanced-stage NSCLC (31, 32). PD-1 and PD-L1 inhibitors are currently recommended second-line remedies apart from first-line remedies (33).

Disease progression-free survival was reported to be less than 1% PD-L1 with nivolumab plus chemotherapy versus chemotherapy alone in the first part of the study. Median PFS was observed for 5.6 months with nivolumab and chemotherapy and 4.7 months without nivolumab (95% CI: 0.58–0.94; HR: 0.74) (31). Results of phase II CheckMate 568 trials emphasized that increased TMB, which are not associated with PD-L1 status, showed better response [PD-L1 and tumor mutational burden (TMB); predictors of response to immunotherapy].

Atezolizumab plus chemotherapy and bevacizumab as first-line treatment for advanced-stage NSCLC

Incorporation of atezolizumab to a regimen consisting of Bev and chemotherapy significantly improves PFS in advanced non-squamous NSCLC (34). This result is not influenced by expression of EGFR or ALK. The promising efficacy and reasonable safety profile increased when combined with a platinum doublet chemotherapy in NSCLC cases not treated with chemotherapy before (35).

Monotherapy or combination of ICI as first-line treatment for advanced NSCLC

Incorporation of ICIs shows sustainable anti-tumor activity and increases long-term survival (36). Chemotherapy along with pembrolizumab and then with atezolizumab demonstrated much greater response in comparison to all treatments, for both non-squamous and squamous patients. In non-squamous histology, combining chemotherapy with pembrolizumab and atezolizumab/Bev chemotherapy, seconded with pembrolizumab monotherapy and atezolizumab chemotherapy, has shown to be the best treatment generally in overall cohort (37). Pembrolizumab is being used as a first-line regimen for advanced-stage NSCLC with a PD-L1 expression of ≥50%. On this context, necitumumab along with platinum-based chemotherapy can become an affordable substitute as a first-line treatment protocol. In squamous NSCLC with PD-L1 expression <50%, quadruple schedules of platinum doublet plus pembrolizumab and necitumumab are being used (8).

Second-line agents for advanced-stage NSCLC

The standard second-line agents include pemetrexed, docetaxel, erlotinib, and gefitinib (TKIs). In patients who carry a mutant EGFR, the TKIs are preferred the second-line agent if not used in the first-line therapy. Crizotinib, a newly FDA-approved drug for ROS-1 mutation expressing cancers (36), is an EML4/ALK fusion protein inhibitor (36). MET/ALK inhibitor, crizotinib, is under clinical trials along with a pan-HER inhibitor (dacomitinib). Among ALK inhibitors are ceritinib and alectinib, and crizotinib was granted an FDA approval in 2011 and proved to be superior to second-line chemotherapy in patients who already received platinum doublet with a median PFS of 7.7 months with crizotinib as compared to docetaxel or pemetrexed chemotherapy with PFS of 3 months (HR 0.49; 95% CI, 0.37–0.64, $P < 0.001$) and, therefore, showed greater survival advantage in comparison to patients not receiving crizotinib. It is orally active and works as a small-molecule inhibitor of ALK, MET, and ROS tyrosine kinases (4). Currently, crizotinib is being evaluated as a first-line agent over platinum-pemetrexed chemotherapy in phase III PROFILE 1014 study to treat ALK-positive NSCLC (Table 2). With the NSCLC harboring ALK or ROS1 rearrangements, RET-rearranged lung cancers can respond to pemetrexed-based doublet chemotherapy with an ORR of 45% and PFS of 19 months (38, 39). Erlotinib, another EGFR inhibitor, has shown promising results in randomized phase III trials primarily as second-line and third-line therapy, maintenance therapy, and in patients carrying mutations in EGFR. Brigatinib is first line against crizotinib in advanced ALK +NSCLC and was shown to have better activity than crizotinib in ALTA-1L trial [52, 53]. Another first-line agent, lolatinib, was evaluated against crizotinib (phase III randomized CROWN trial) and resulting ORR was 76%, which was higher than 58% of the crizotinib group [51] [13, 35] (Table 3).

Maintenance therapy in NSCLC

Maintenance therapy is treatment given to a patient after specific chemotherapy cycles when there is no disease progression and this is continued until either undesirable or toxic effects manifest or cancer progresses (41). Consolidation therapy is given following treatment with induction chemotherapy for specified number of cycles.

There are two ways to proceed with treatment: using an agent from induction regimen (continuation maintenance therapy) or incorporation of a different cytotoxic drug with different mechanism which was not included in first-line therapy known as the switch maintenance therapy (41). The drugs included as maintenance therapy in NSCLC are gemcitabine, docetaxel, and pemetrexed, and targeted agents include Bev, cetuximab, and erlotinib (41).

Maintenance therapy for NSCLC can be carried out in multiple ways, for example, continuation of induction therapy until disease progression, continuation of just non-platinum agents or molecularly targeted agent (continuation maintenance), and changing to another cytotoxic or molecularly targeted agent (switch maintenance). Randomized controlled trials show use of chemotherapy, immunotherapy, and molecularly targeted agents for maintenance therapy. The current standard treatment for advanced NSCLC comprises four–six sessions of a platinum-based doublet chemotherapy, which prolongs survival and alleviates symptoms. Another approach is administration of four sessions of cisplatin-based chemotherapy in combination with third-generation anti-EGFR or anti-VEGFR drug. It is not recommended to use platinum-based chemotherapy for advanced NSCLC for more than six cycles, according to ASCO guidelines (42).

Maintenance chemotherapy after first-line therapy

Trials on combination chemotherapy to treat advanced-stage NSCLC

The results of phase III trials of multidrug combinations including newer chemotherapeutics to treat advanced-stage NSCLC are discussed in Table 1 that presents response of using third-generation cytotoxic drugs as monotherapy along with platinum analogs. Novel treatment with atezolizumab significantly increased disease-free survival (43). Adjuvant targeted therapy has the same results as it has at stage IA or IB.

At stage IIIA, surgical resection of the tumor and lymph node that it has spread to, with postoperative chemotherapy, is beneficial. While preoperative chemoradiation therapy may reduce tumor burden, chemoradiation therapy improves only disease-free survival DSF but not OS (13).

Targeted therapy rationale

Targeted therapies consist of either small-molecule inhibitors or mAb or monoclonal antibodies (4). Targeted therapy for NSCLC rationale is based on targeting “driver mutations” which encode important proteins crucial for replication and cell growth. It is hypothesized that restricting mutations may improve survival at stage IVA (recurrent NSCLC).

Combination therapy, i.e., platinum therapy (cisplatin or carboplatin) in combination with paclitaxel, docetaxel

10.3389/fonc.2022.958505

TABLE 2 FDA approved targeted agents for advanced NSCLC (1).

Actionable mutation	FDA approved therapy (citation)	Clinical trial (phase)	Comparator	ORR (%)	mPFS (months)	mOS (months)	Adverse effects
KRAS	Sotorasib	CodeBreaK 100 (I)	No	32%	6.3	12.5	Diarrhea, nausea, elevated LFT's, fatigue
EGFR	Erlotinib	EURTAC (III)	Chemotherapy	64%	9.7	22.9	Fatigue, rash, diarrhea
	Gefitinib	NEJ002 (III)	Carboplatin/ Paclitaxel	74%	10.8	27.2	Rash, diarrhea
	Afatinib	LUX-Lung 3 (III)	Cis/Pemetrexed	56%	11.1	28.2	Rash, diarrhea, paronychia
	Dacomitnib	ARCHER 1050 (III)	Gefitinib	75%	14.7	34.1	Diarrhea, paronychia, rash
	Osimertinib	FLAURA (III)	Erlotinib/ Gefitinib	80%	18.9	38.6	Rash, diarrhea, pneumonitis
ALK	Crizotinib	PROFILE 1014 (III)	Platinum/ Pemetrexed	74%	10.9	NR	Vision disorder, diarrhea, edema
	Certinib	ASCEND-4 (III)	Platinum/ Pemetrexed	73%	16.6	51.3	Diarrhea, nausea, vomiting
	Alectinib	ALEXALEX (III)	Crizotinib	83%	25.7	Immature	Elevated LFT's, CPK elevation, anemia
	Brigatinib	ALTA 1L (III)	Crizotinib	74%	24	47.6	Elevated CPK and LFT's
	Ensartinib‡	eXALT-3 (III)	Crizotinib	75%	25.8	Immature	Rash, pruritis, edema
	Lorlatinib	B7461006 (III)	Crizotinib	76%	NR	Immature	Hyperlipidemia, edema, increased weight
MET Exon 14 skipping mutation	Capmatinib	GEOMETRY-mono-1 (II)	No	41% (68%) *	5.4 (12.4)*	NA/NA	Peripheral edema, nausea
	Tepotinib	VISION (II)	No	46%	8.5	Immature	Peripheral edema
MET amplification	Capmatinib	GEOMETRY-mono-1 (II)	No	29% (40%)*	4.1 (4.2)*	NA/NA	Peripheral edema, nausea
BRAF mutations	Dabrafenib + Trametinib	BRF113928 (II)	No	64% (68%)*	10.8 (10.2)*	17.3 (18.2)*	Pyrexia, LFT elevation, HTN
RET	Selparcatinib	LIBRETTO-001 (II)	No	64% (85%) *	16.5 (NR)	NR/NR	Dry mouth, diarrhea, HTN
	Pralsetinib	ARROW (II)	No	61% (70%)*	16.5 (13)*	NA/NA	LFT elevation, anemia
ROS1	Crizotinib	PROFILE 1001 (I)	No	72.40%	19.3	51.4	Vision disorder, nausea, edema
	Certinib	NCT01964157(II)	No	62% (67%)*	9.3 (19.3)*	24	Diarrhea, nausea, anorexia
	Lorlatinib	NCT01970865 (I-II)	No	41% (62%)*	8.5 (21)*	NA	Dyslipidemia
	Entrectinib	STARTRK-1, STARTRK-2, ALKA-372–001 (I-II)	No	77%	19	NR	Weight gain, neutropenia
NTRK	Larotrectinib	LOXO-TRK-14001 (I-II)	No	70%	NA	NA	LFT elevation, neutropenia, anemia
	Entrectinib	ALKA, STARTRK-1, STARTRK-2 (I-II)	No	70%	NA	NA	Dysgeusia, constipation, fatigue
HER2	T-DM1‡	NCT02675829 (II)	No	44%	5	NA	Infusion reactions, thrombocytopenia
	T-DXd‡	DESTINY-Lung01 (II)	No	62%	14	NA	Neutropenia, anemia, ILD

*Indicates data for treatment naïve patient.

TABLE 3 Effects of first-line and second-line treatments in NSCLC (67).

Overall Population		EGFR mutation		KRAS mutation		BRAF mutation		HER2 mutation		PIK3CA mutation		ALK rearrangement		Full WT
(n = 17664)		(n = 1,787)		(n = 4,588)		(n = 230)		(n = 92)		(n = 157)		(n = 340)		(n = 2,769)
		All	Adapted[$]	All	Adapted[$]	All	Adapted[$]	All	Adapted[$]	All	Adapted[$]	All	Adapted[$]	All
First-line Treatment														
Number with data %	8,448 (48%)	1,128 (63%)	662 (37%)	2,085 (45%)	979 (21%)	146 (64%)	64 (28%)	62 (67%)	28 (30%)	73 (47%)	29 (19%)	236 (69%)	120 (35%)	1,214 (44%)
Pemetrexed-based regimen	2,747 (33%)	188 (17%)	57 (9%)	792 (38%)	525 (54%)	51 (35%)	34 (53%)	31 (50%)	18 (64%)	17 (23%)	11 (38%)	111 (47%)	55 (46%)	401 (33%)
Vinorelbine-based regimen	504 (6%)	39 (3%)	9 (1%)	128 (6%)	68 (7%)	5 (4%)	2 (3%)	0	0	7 (10%)	3 (10%)	13 (6%)	9 (8%)	80 (7%)
Taxane-based regimen	1,064 (13%)	60 (5%)	18 (3%)	261 (13%)	166 (17%)	20 (14%)	12 (19%)	8 (13%)	4 (14%)	11 (15%)	7 (24%)	17 (7%)	11 (9%)	188 (16%)
EGFR-TKI	684 (8%)	543 (48%)	520 (79%)	26 (1%)	9 (1%)*	3 (2%)*	2 (3%)*	0	0	1 (1%)*	1 (3%)*	4 (2%)*	2 (12%)*	17 (1%)
Crizotinib	18 (<1%)	0	0	0	0	0	0	0	0	0	0	18 (8%)	18 (15%)	0
Trial[£]	253 (3%)	36 (3%)	31 (5%)	63 (3%)	48 (5%)	8 (6%)	5 (8%)	3 (5%)	1 (4%)	0	0	16 (7%)	12 (10%)	36 (3%)
Other[§]	709 (8%)	27 (2%)	9 (1%)	171 (8%)	77 (8%)	11 (8%)	3 (5%)	5 (8%)	3 (11%)	10 (14%)	5 (17%)	6 (3%)	3 (4%)	131 (11%)
BSC only	2,469 (29%)	235 (21%)	18 (3%)	644 (31%)	86 (9%)	48 (33%)	6 (9%)	15 (24%)	2 (7%)	27 (37%)	2 (7%)	51 (22%)	10 (8%)	361 (30%)
Second-line Treatment														
Number with data %	5,518 (31%)	698 (39%)	381 (21%)	1,358 (30%)	566 (12%)	106 (46%)	37 (16%)	43 (47%)	22 (24%)	48 (34%)	12 (8%)	157 (46%)	102 (30%)	797 (29%)
Taxane	782 (14%)	46 (7%)	34 (9%)	236 (17%)	203 (36%)	16 (15%)	8 (22%)	6 (14%)	4 (18%)	5 (10%)	2 (17%)	5 (3%)	4 (4%)	119 (15%)
Pemetrexed	612 (11%)	125 (18%)	97 (26%)	136 (10%)	105 (19%)	8 (8%)	6 (16%)	5 (12%)	4 (18%)	4 (8%)	2 (17%)	13 (8%)	10 (10%)	81 (10%)
Erlotinib	776 (14%)	231 (33%)	218 (57%)	125 (9%)	94 (17%)	9 (9%)	4 (11%)	5 (12%)	4 (18%)	2 (4%)	2 (17%)	10 (6%)	6 (6%)	96 (12%)
Crizotinib	73 (1%)	0	0	0	0	0	0	0	0	0	0	73 (46%)	73 (72%)	0
Trial[£]	116 (2%)	8 (1%)	7 (2%)	33 (2%)	27 (5%)	5 (5%)	5 (14%)	3 (7%)	2 (9%)	2 (4%)	1 (8%)	4 (3%)	4 (4%)	25 (3%)
Other[§]	442 (8%)	10 (1%)	6 (2%)	90 (7%)	60 (11%)	8 (8%)	7 (19%)	8 (18%)	8 (36%)	2 (4%)	2 (17%)	5 (3%)	3 (3%)	79 (10%)
BSC only	2,711 (49%)	272 (39%)	15 (4%)	738 (54%)	77 (14%)	60 (57%)	7 (19%)	16 (37%)	0	33 (69%)	3 (25%)	47 (30%)	2 (2%)	397 (50%)

*: Patients with tumors exhibited two molecular alterations including EGFR mutation. $: Selection of treatment based on the molecular analyses. £: Based on targeted therapy.
§: Including, but not limited to, another type of chemotherapy.

gemcitabine, or premetrexed, is the treatment of choice (44). Addition of baclizumab (monoclonal antibody that targets endothelial vascular growth factor) to first-line treatment provides survival benefits.

For patients with EGFR-sensitizing mutations, EGFR TKIs are utilized that enhanced PSF profile of patient. Osimertinib is a drug of choice due EGFR and tyrosine kinase inhibition. Also, ALK inhibitors with ALK translocation, including crizotinib or alectinib, have greater PSF rate (45). The mutated protein kinases or receptors set off a cascade of signaling pathways such as PI3K-AKT-mTOR, MAPK or RAS-RAF-MEK-ERK, and JAK-STAT pathways, all of these play a major role in the uncontrolled growth and proliferation of tumor cells (Figure 4).

Anti-EGFR monoclonal antibodies as targeted therapy

Monoclonal antibodies targeting mutant EGFR and hinder receptor's signaling through which bind to extracellular domain of receptor and form antibody-receptor complexes that undergo endocytosis and subsequent degradation cetuximab,

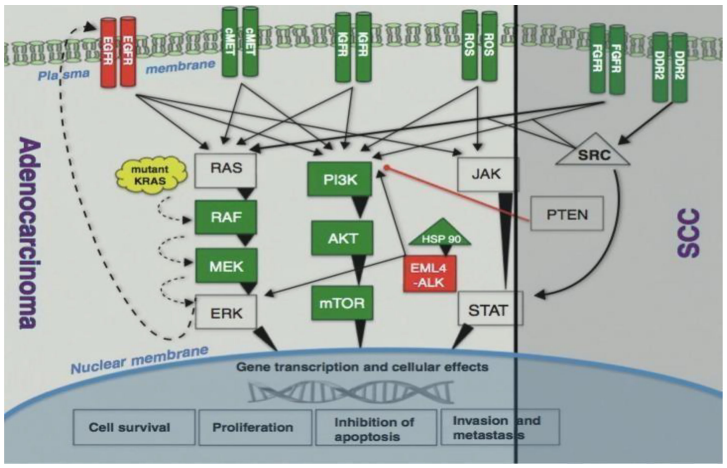

FIGURE 4
Signaling pathways (4).

necitumumab, panitumumab, and matuzumab are representative (46) (Figure 5). Two phase III studies have evaluated the effect of combining cetuximab along with platinum doublet chemotherapy to treat advanced NSCLC and exhibited a slight improvement in median OS (11.3 months with cetuximab vs. 10.1 months without cetuximab) (4, 48).

Currently, necitumumab is being studied in two phase II clinical studies: INSPIRE on non-squamous NSCLC and SQUIRE on squamous NSCLC to evaluate cisplatin-gemcitabine in combo with necitumumab. From the SQUIRE study, an improved OS was observed. Panitumumab and matuzumab are other mAbs currently in phase II trials (4). Monoclonal antibodies also exert immunologic mechanism inducing ADCC (antibody-dependent cellular cytotoxicity) (49).

Necitumumab is anti-EGFR recombinant mAb and induces fewer allergic reactions due to the absence of murine systems and induction of antibody-dependent cell-mediated cytotoxicity (ADCC) in most cancer cells expressing EGFR (8). Antitumor effect of necitumumab was studied by Topper et al. as monotherapy and in combination therapy, the latter showing synergistic anti-tumor effects (50) and higher toxicity profile than other EGFR-directed monoclonal antibodies.

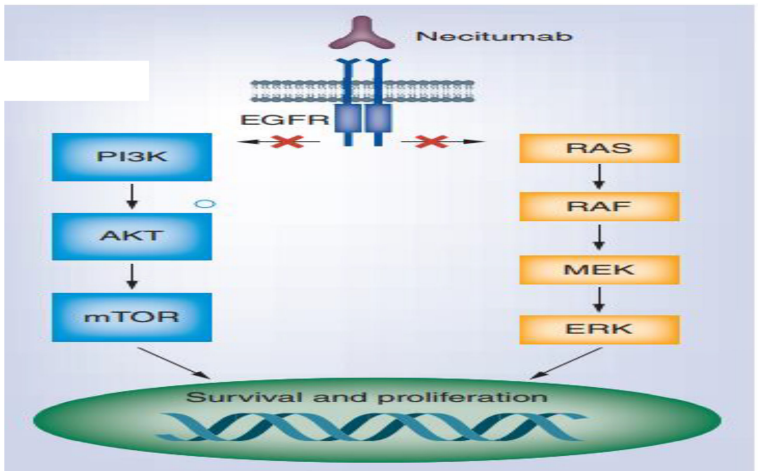

FIGURE 5
Necitumumab for the treatment of advanced (47).

Targeted therapy efficacy

Osimertinib is a kinase inhibitor, which falls under this category of targeted therapy as it targets EGFR gene, thereby halting carcinogenesis in NSCLC patients with a mutation in EGFR gene. The side effects of osimertinib include nausea, vomiting, abdominal pain, decreased blood counts, and rarely cardiotoxicity. However, these symptoms disappear upon cessation of drug therapy (51). In the IPASS trial, non-smokers were randomly assigned to receive the EGFR inhibitor gefitinib or carboplatin with paclitaxel (CP) that reflected a better and superior PFS (progression free survival) in the gefitinib as compared to the later (HR 0.74; 95%, CI: 0.65–0.85; $P < 0.0001$) and ORR (43% vs. 32.2%; $P = 0.0001$). The OS was observed as median 18.6 and 17.3 (13). The patients with mutated EGFR showed better response from gefitinib with a 51% reduction in progression (HR 0.48; $P < 0.0001$). The patients who do not carry a mutated EGFR show a better response to chemotherapy ($P < 0.0001$) (13).

Approaches of resistance to targeted therapy

Despite the fact that EGFR TKIs have dramatically improved treatment approach for EGFR-mutant NSCLC, most responses in many patients do not withhold after 7–12 months. Resistance can develop *de novo* or after body's exposure to targeted agents and can thrive as resistant clones, both within the same tumor or in different ones in the same patient. Most patients get acquired resistance either by EGFR mutations that follow a primary mutation or *via* activation of EGFR-independent pathways (Figure 6). The mechanism of resistance for EGFR activation includes increased EGFR expression and increased subsequent ligand production on malignant cells and, lastly, the presence of mutations of EGFR in malignant/tumor cells. EGFR is a primary therapeutic target and, currently, it is inhibited by TKI and a targeted monoclonal antibody both reversibly and competitively inhibits the ATP for tyrosine kinase domain of EGFR which inhibits all resultant downstream pathways. The EGFR incidence of mutation is high in Asian: up to 50% adenocarcinomas bearing EGFR mutations (Figure 7).

Therefore, it is advised to re-biopsy a patient as disease progresses to assess latest tumor biology. In about 50% of resistance cases, basic mechanism is developing a mutation in exon 20 of EGFR which codes for T790M. As a result, methionine replaces threonine and thereby changing kinase domain's configuration and increasing its affinity for ATP, as compared to wild-type, and decreasing its affinity for first-generation TKIs (4). Another mechanism, which is present in 5%–20% of cases, is based on amplification of MET to overcome EGFR inhibition *via* PI3L-AKT-mTOR signaling. Other resistance mechanisms comprise mutations at PIK2CA, HER2, BRAF, STAT3, AXL kinase, and CRKL amplification. A transformation into small cell lung cancer is also observed in 5% of cases. However, empirical cytotoxic chemotherapy still holds as the treatment of choice because about 30% of resistance has unknown mechanisms (4). The targeted therapy focusing on EGFR tyrosine kinase is used to treat lung cancer (10%–20%) but resistance develops due to mutations (53).

For advanced NSCLC, the NRF2 or NEF2L2 is important in cancer advancement (54), metastasis, and exhibiting resistance to immunotherapy (55). NRF2 is usually exploited by way of most cancer cells in order to lessen oxidative strain and perhaps lead to chemo-resistance. One of the strategies is to target NRF2 and its downstream molecules as interfering with most cancer metabolism, including glutaminolysis and fatty acid synthesis.

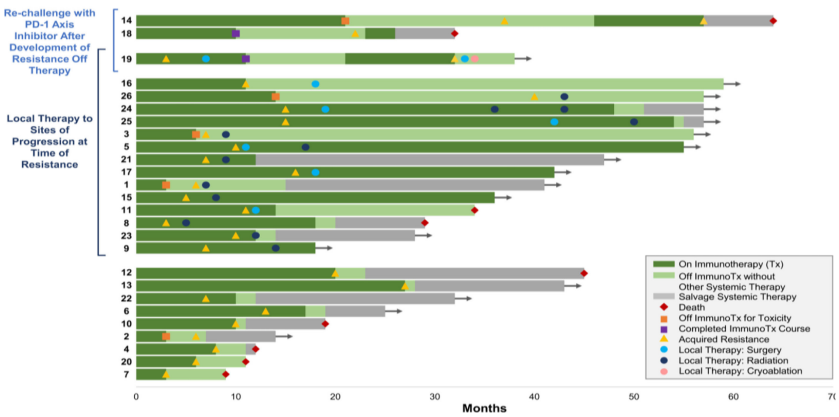

FIGURE 6
Treatment and resistance (52).

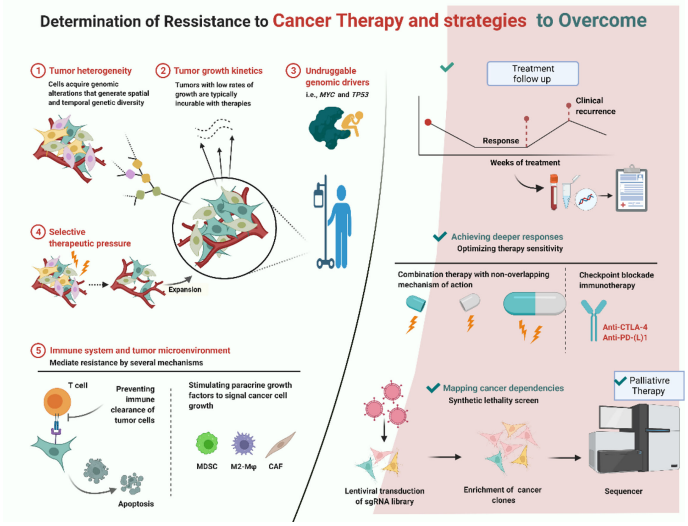

FIGURE 7
Stages of resistance development and therapeutic strategies.

Similarly, TP53 tumor suppressors are the most abundant mutations genes and can cause resistance (56). An NRF2 activation is an extraordinary event in EC, related to NFE2L2 or KEAP1 mutations that studies clinical benefits provided by large-scale adoption of molecular profiling in lung cancer.

Screening is essential to routinely assess cancer. The molecular screening, involving the largest sample 17,664 patients within advanced-stage NSCLC patients [71], enabled detection of at least one actionable molecular alteration in almost 50% of analyses and affected treatment plans for 51% of patients. Improving median standard survival was 4–7 months longer without causing genetic mutation.

Among one of the studies in 37 patients with drug resistance in NSCLC is through either EGFRT790M or MET gene amplification. Resistant cancer occasionally reflects gene mutation and amplification through gene of PIK3CA or epithelial cells leading to mesenchymal transition. In the study, 14% of tumors were sensitive to standard treatments since transformation from NSCLC to SCLC. The selective pressure of EGFT inhibitor treatment [imatinib (Gilotrif), dacomitinib (Vizimpro), entrectinib (Rozlytrek), erlotinib (Tarceva), gefitinib (Iressa), and osimertinib (Tagrisso)] led to resistance and genetic mutations (57).

It is important to first identify aberrant pathways. In order to quickly identify significant mutations and resistance mechanisms at tumor tissue and circulating tumor DNA, next-generation sequencing is performed with advanced NSCLC patients. Reducing DNA repair increases the sensitivity of treatment in case of drug resistance to platinum-based chemotherapy and vice versa. Variations at ERCCI and ERCC2 enhance response to platinum chemotherapy but their overexpression will reduce patient survival with gemcitabile-cisplatin treatment.

PD-1 ligand inhibitors develop resistance with approximately 88% recurrence, and 58% of patients were treated with local therapy in contrast to systemic therapy where improved survival rate was observed for 2 years (58). Long-term survival in some patients referred as LTLC may occur due to invasive procedures like lung resection, RT, and differential chemotherapy, leaving patients with high risk of disease reoccurrence and developing comorbidities (1) (Figure 8).

MET inhibitors

The advanced chemotherapy for tumors exhibiting MET exon 14 skipping mutations presents with a good therapeutic outcome. Mechanism involves activation of oncogenic driver MET protein and reducing degradation. In 2020, FDA has approved lapatinib, an inhibitor of MET protein for adult therapy, and is preferred over chemotherapy and immunotherapy. Another inhibitor, tepotinib, is underway for conditional approval after confirmatory trial response (1).

RT combined with chemoradiation to treat locally advanced NSCLC

The two important aspects to remember when treating locally advanced NSCLC include the effect of local tumor control on the OS in patients at risk for metastatic spread and the toxic effects of radiation on chest hosting extensive tumor

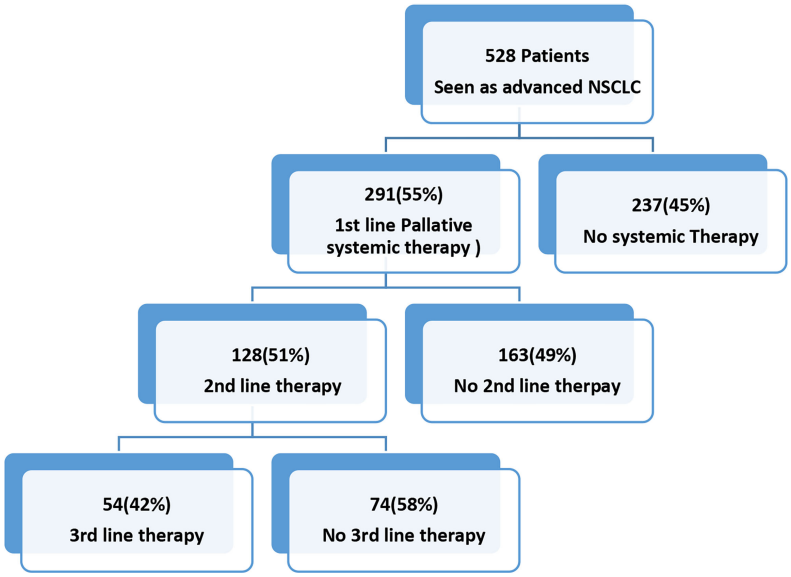

FIGURE 8
Systemic therapy uses in patients with advanced NSCLC (59, 60).

growth, and, whether or not, a high-dose RT would improve patient's survival rate and quality of life (61). An analysis of 11 RTOG trials consisting of 1,356 patients demonstrated a 2-year survival rate of 38% and 5-year survival rate of 15% with chemoradiation (62). The local failure rate (LFR) was reported to be 46% and 52% for 2 and 5 years, respectively.

Chemoradiation consisting platinum-based chemotherapy concurrent with radiation remains the standard protocol for locally advanced-stage NSCLC; however, local tumor control and OS are poor. Socinski et al. reported initial local failure in 46% of patients following neoadjuvant and concurrent chemotherapy (63). Overall, an escalation in radiation dose is believed to improve local control and OS in stage III NSCLC patients according to non-randomized trials and a secondary analysis of RTOG of over 1,300 patients undergoing chemoradiation (64). Genomic profiling

Current advanced treatment of NSCLC is being guided by genomic profiling and genotyping, providing efficient information on fundamental biological and molecular mechanisms, confirming multiplexity of NSCLC. It led to adjustments in the treatment selection, based on pharmacologic and clinical outcome selection of biomarkers based totally on molecular profile (65). The existence of genomic alterations and tumor suppressor genes has arisen as principal precept and pattern can capture complexity regarding tumor development, metastasis, immune microenvironment, and therapeutic susceptibility to TP53 and NFE2L2.

Advanced strategies

A limited portion of patients with NSCLC responds well to immunotherapy. Biologics therapy also called immunotherapy uses interleukin-2 (IL-2) and is in current medical expertise (66) being the standard care for advanced NSCLC along with monoclonal antibodies addressing the need of treatment by improving response and survival of NSCLS patients (66). Formerly unanticipated long-term responses in advanced stages of NSCLC have been done, with 5- to 12-month OS of 20%–40% in unselected versus patients expressing high PD-L1 levels (67).

The other advanced therapies include the use of checkpoint inhibitors for PD-1 and CTLA-4 pathways. Examples are pembrolizumab, nivolumab, and ipilimumab. Pembrolizumab is advanced first-line treatment for advanced-stage NSCLC and more than 50% of cells express PD-L1 in those cases where driver mutations are non-existent (68). Targeted treatments through tyrosine kinase and ICI are recent advances (69). Treatment with pembrolizumab improved RR (45% vs. 28%), PFS (10.3 vs. 6 months; P <.001; 95% CI, 0.37–0.68; HR, 0.50), and OS (30 vs. 14.2 months), making pembrolizumab as the standard care for these types of patients (19). The targeted therapy with IL-2 is administered orally as well as intravenously.

Some TKI molecules poziotinib, pyrotinib, and mobocertinib have been studied to improve their effect on NSCLC. Furthermore, a currently posted ADVERT HOC, a secondary analysis (LUX-Lung 8 trial), has discovered that position of ERBB mutations is among vital biomarkers, in particular HER2 mutations (49).

In a recent study, mutation in TP53 and KRAS resulted in better response to immunotherapy and efficacy in NSCLC and improved PFS as compared to without co-mutations (70). The environmental factors of smoking with BMI and the presence of

expression of estrogen receptor in epithelial cells are key regulators for mutation.

Precision treatments

Another targeted therapy for NSCLC is use of RET inhibitors, i.e., pralsetinib and selpercatinib, gaining recent approval from FDA, for adult treatment instead of immunotherapy and/or chemotherapy. Serious toxicities, 45%–58% for both drugs, include hypertension, high-level aspartate aminotransferase, hyponatremia, and lymphopenia (71). But numerous critical parameters are crucial for consideration, i.e., inadequate response, resistance to pralsetinib and selpercatinib ($\approx^1/_3$ of RET-altered cancers), and acquired resistance to RET TKIs *via* secondary on-target and/or driver mutations. Mutation burden of tumor with excessive TMB, with accompanying elevated neoantigen expression, performs a crucial position in antitumor immunity. The following are illustration development and control of obtained resistance to programmed loss of life with axis inhibitor therapy., 7

Improvement in survival rate

Twenty-six percent of all patients with NSCLC live ≥ 5 years after diagnosis (72). The annual survival rate of NSCLC has been improved from 2.4% to 5% overall, while simultaneous incidence has been reported to decrease (2.2%–2.3%). The comparisons were made for two-drug and three-drug regimens for chemotherapy and the latter proved significant benefit in progression-free survival. The improvement in trends from 1.8% to 4.4% in women and 3.1% (2009–2013) to 5.5% (2014–2018) in men has been reported and was distinct in women and all races and ethnic groups (73). Visual decline in lung cancer mortality doubled (from 3.1% from 2009 to 2013 to 5.5% from 2014 to 2018) in men and (1.8%–4.4%) in women with 2.4%–5% overall decline. This trend coincides with steady declines in occurrence (2.2%–2.3%) but rapid gain in survival in NSCLC.

The relative survival rate in NSCLC increased from 34% to 42% from 2009 to 2016 with an estimated 6% for each stage of lung cancer attributed to targeted therapy, while, at the same time, survival of SCLC remained 14%–15%. Therefore, there is a decrease in overall mortality to 3.1%. The studies revealed an improved disease prognosis with a patient exhibiting BRAF V600 E mutations and an improved OS rate (3 years). This contrasted with patients without RAF V600 mutations (24%) (73).

For instance, 2-year NSCLC relative survival rate increased from 34% to 42% (2009 and 2010–2015 and 2016, respectively), including absolute increase of 5%–6% at every stage with only 14%–15% survival for small cell lung cancer patients. Improved treatment showed excellent response against lung cancer and provided record decline in overall cancer mortality (74).

BRAF mutation in NSCLC exhibits less therapeutic improvement but appears to be responsive to immunotherapy due to aggressive clinical features of three distinct functional classes. The evidence did not exist for combination therapy explaining the use of BRAF or MEK inhibitors against non-V600E BRFA mutant NSCLC (73).

The sotorasib is among the targeted therapeutic agents approved by US FDA for NSCLC of local and advanced metastatic lung cancer with KRAS mutations (75). The drugs exhibit extensive adverse drug reactions. In a recent study, 88% improved response rate in NSCLC was observed with sotorasib with PFS of 6.3 months and less than 5% adverse effects each in LFT abnormalities, diarrhea, anemia, hepatitis, and hyponatremia (76). Another related molecule is adagrasib having a 45% response rate. The resistant refractory to other standard therapy is treated preferably by trastuzumab-based regimen, e.g., trastuzumab-druxtecan, showing 55% response rate and PFS of 8.2 months with 17.8 months of OS (77).

Any significant association between HER2 mutations and HER2 amplification could not be found. Initial clinical studies exhibited no results for targeted therapy in HER2-amplified NSCLC. Interim analysis of DESTINY-Lung-01 study demonstrated 24.5% response rate using various genotypes such as P13K and CTNNB1, and also tumor suppressors STK11, KEAP1, and NFE2L2. Alterations in genes do not lead to sensitivity to the targeted therapy. The STK11 alterations demonstrate relative resistance to immunotherapy and KEAP1 mutations increase resistance to radiotherapy (78). Siglec-15 antibody is an immunoglobulin-like protein in lots of human cancers that works as critical immune suppressor and is, at the same time, unique to PD-L1 (79).

Palliative chemotherapy and outcomes

Palliative chemotherapy is directed to enhance the quality of life and survival; however, some patients still remain untreated (59). Studies suggest not a great fee of development in survival through the use of aggregate therapies. The palliative care of NSCLS is focused on provisions of suitable treatments and symptomatic treatment of pain, dyspnea, nausea/vomiting, and fatigue. The chemotherapeutic drugs lead to pulmonary toxicity and require management in palliative care (59). Still, a fragment of patients of advanced NSCLC gets hold of any form of systemic treatment.

Palliative treatment options for endobronchial tumors include chemotherapy, radiotherapy, endobronchial laser resection, or stent placement. As a rule, cough improves if directed therapy reduces impact of cancer. However, symptom improvement with endobronchial brachytherapy, radiotherapy, or palliative chemotherapy can take multiple weeks. Mild cough options include patient counseling, use of linctus such as honey,

cough suppression techniques, and/or breathing exercises. If they are useless, patient is then prescribed peripherally performing antitussive (e.g., benzonatate). If symptoms do not improve with a peripherally acting antitussive, a centrally acting antitussive is indicated, as for patients with a more severe cough.

The nebulization with lidocaine and bupivacaine is also used in serious cases for specialized palliative care clinics. There has been limited efficacy of dextromethorphan as a cough suppressant in cancer patients. Opioids are first-line treatment for palliative care patients with severe cough with intrathoracic cancer. Addiction is a rare concern. The opioids used are morphine, codeine, and dihydrocodeine. Higher efficacies were observed at high doses. The patients already receiving opioids are being prescribed with 25%–50% higher dose than the current dose to alleviate symptoms. Morphine is the preferential treatment of choice (80). Due to development of P450 cytochrome enzyme, the Asian population are at greater risk of developing codeine adverse effects.

The evidence from trial indicates that opioids reduce cough severity and frequency to improve quality of life. The monitoring is done for sedation which declines after 1–3 days. Other side effects are peripheral edema, weakness, nystagmus, nausea, somnolence, tremor, and emotional lability. Gabapentin has been used to relieve cough refractory to gastroesophageal reflux with dose of 300 mg/day to reduce occurrence of sedation and dizziness. Adjunctive therapies in palliative care include expectorants for thickening of sputum. Examples include guaifenesin and nebulized nasal saline and acetylcysteine as mucolytic.

Bronchospasm symptoms are treated with ipratropium bromide and inhaled ibuterol. Pharmacologic therapies for excess secretions include anticholinergics and most used are intravenous preparations of glycopyrrolate. Glycopyrrolate is also given subcutaneously and sublingually to reduce excess secretions.

Hemoptysis is frequently observed in patients with lung cancer due to elevated bronchial secretions. Approximately 20% NSCLC patient exhibit hemopytysis at any stage in life of cancer patients exhibit hemoptysis at any stage in life. Palliative treatments of hemoptysis include management of bleeding: use darker shades of accessories (such as towel, dressings, sheets, blankets, and absorptive dressings), avoid using white cups at bedside and red-streaked white tissues and environmental management. The management of life-threatening hemoptysis is adjusting position of patients to prevent non-bleeding lung from spillage of blood, which can cause blockage of gases with clots or filling alveoli with blood. Supportive care with blood and platelet transfusions is administered for reversal of anticoagulation and administration of procoagulant.

Therapeutic bronchoscopy performed by balloon tamponade and infusion of adrenaline is successfully used. Oral and nebulized antifibrinolytics are used. Nebulized vasopressin and tranexamic acid have been reported with response rates of 60%–100%. Nebulized tranexamic acid has been helpful in case reports. If the area of bleeding is directly visualized, bronchoscopy techniques (laser coagulation/electrocautery) may be used with response rates of 60%–100%. Numerous phase III clinical studies proved that palliative strategy for advanced NSCLC may improve outcomes. This includes extended survival and enhanced life quality with lung cancer prevalence of 11.4% (81).

Complications

Complications of treatments are enhanced with aged and medically ill patients. The aged patients are the majority among NSCLC. Furthermore, malnutrition and depression have been reported and associated to increased mortality, indeed in aged patients, with progression-free tumors with less adherence to treatment and poor lungs performance (82). Definitive radiotherapy is advised as a suitable choice of treatment for aged patients (≥75 years) with inoperable or unresectable NSCLC. The consecutive chemoradiotherapy or radiotherapy alone is applicable for senior patients. Still, increased toxicity is a consideration. Retreatment after initial response led complications of colitis (17%), rash (16%), pneumonitis (19%), and liver enzyme abnormalities (10%). Retreated patients had resolution of irAEs or improvement to approximately grade 1 in comparison to those with discontinued treatment (97 vs. 76, P = 0.01). Overall, among the 48 patients, exhibited PFS and OS improved with retreatment. The retreatment with ICI led to grade 3 or grade 4 toxicity (83). Relapse after definitive remedy may pose predominant patterns of failure, making an argument for chemotherapy either sequentially or concurrently (84).

Local management of metastasis

Advancements in OS with multimodality regimens, i.e., chemotherapy with surgery and/or radiation, have shown decreased prevalence in preventing brain metastases of advanced NSCLC. Locally advanced NSCLC poses greater threat in development of brain metastases. It may identify a definite group of patients, benefiting from aggressive management strategies, to address this issue after completion of local therapy (85). Avoidance of EGFR impediments for patients with EGFR wild type/mutated NSCLC is normally characterized by “uninflamed” tumor microenvironment, weak immunogenicity, and immunological tolerance (86).

Conclusion

In this review, we have discussed the latest staging and treatment strategies of advanced-stage NSCLC. The NSCLC treatment has gained great concern in modern research due to multiple problems faced during the treatment including

diagnosis of stage and resistance to conventional therapy. Different therapies have been utilized to effectively treat NSCLC like platinum-based chemotherapy, chemo-immunotherapy, and, most importantly, the targeted therapy. NSCLC if diagnosed and treated at early stages can be treated effectively; materials were discussed in our review. Furthermore, due to unique effects of chemo-immunotherapy and targeted therapy, the occurrence of disease has been improved in many studies. Moreover, NSCLC treatment strategies need to be further investigated to establish safe and effective treatment options without resistance being caused.

Author contributions

RF, AZ, YY, and MR contributed to the conceptualization of the study. The design by RF, AZ and MR. Data collection by TH, KS analysed and interpreted the data. RF and AZ wrote the first draft of the manuscript. YD and MR revised the article for important intellectual content. All authors read and approved the final manuscript.

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

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Current treatments for non-small cell lung cancer

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Despite improved methods of diagnosis and the development of different treatments, mortality from lung cancer remains surprisingly high. Non-small cell lung cancer (NSCLC) accounts for the large majority of lung cancer cases. Therefore, it is important to review current methods of diagnosis and treatments of NSCLC in the clinic and preclinic. In this review, we describe, as a guide for clinicians, current diagnostic methods and therapies (such as chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy, and combination therapy) for NSCLC.

KEYWORDS

NSCLC, diagnosis, chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy

1 Introduction

Lung cancer, as a common malignant cancer, presents a serious threat to human life. Lung cancers can be divided into NSCLC and small cell lung cancer (SCLC), based on differences in histology and origin (1). NSCLC predominates, accounting for almost 85%, of lung cancer cases. NSCLC is further subdivided into two main subtypes: lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). The two types have different gene expression profiles, especially of *NECTIN1*, a cadherin biomarker (2). In addition, LUSC proliferates faster than LUAD (3).

The causes of lung cancer are diverse, but smoking is considered to be the primary reason. In some lung cancer patients with no smoking history, the disease can be attributed to exposure to radon (^{222}Rn), usually from building materials (4). The incidence of lung cancer is also related to genetics and demographic characteristics (5). The link with

demographic characteristics may be attributable to differences in health care systems in different countries. For example, differences in the physical examination of patients may affect the stage at which lung cancer is diagnosed (the development of NSCLC can be divided into four stages: I, II, III, and IV) (6). The main reason for the high mortality rate among lung cancer patients is that only 15% of patients are diagnosed at an early stage (7), and in most patients (70%) the disease is not diagnosed until it is at an advanced stage, perhaps because symptoms are relatively slight in the early stages, and patients may ignore them.

It appears that NSCLC does not metastasize in the early stages and, therefore, surgery could extend the life of patients provided the disease is diagnosed at this stage (8). However, surgery will not benefit those patients, the majority, in whom the disease is diagnosed at an advanced stage. Therefore, the low rate of diagnosis of NSCLC in the early stages remains a problem.

The use of positron emission tomography (PET) could increase the proportion of patients in whom lung cancer is diagnosed in the early stages and thereby reduce lung cancer mortality. The problem is how to increase the number of patients who undergo PET. Common symptoms of lung cancer, such as coughing, chest pain, and wheezing, are often ignored by patients, and hemoptysis, although more likely to be worrying to patients, is experienced by only 20% of lung cancer patients (9). As a result, many patients miss out on the opportunity for early diagnosis and effective treatment.

Treatments for lung cancer include chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy, and combination therapy. Treatment of stage II–IV disease also involves adjuvant therapy and neoadjuvant therapy, in addition to the therapies mentioned above. In some cases, these therapies can be used to confirm the success or otherwise of surgery or combined with surgery to give better results. Besides, surgery is the main treatment for stage I disease. In this review, we describe the biological features of lung cancer, diagnostic methods, and drugs or other compounds currently used in chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy, and combination therapy (Figure 1). We hope that this review will act as guidance for the clinical treatment of lung cancer.

2 The biological features of lung cancer

Lung cancer is a heterogeneous cancer, which means that the tumor contains different subpopulations of cells. Heterogeneity is correlated with chemoresistance and the probability of metastasis (10). Diagnostic methods, therapeutic methods, and the identification of novel biomarkers would also benefit from the further study of lung cancer biology. It is therefore important to summarize the biological features of lung cancer.

2.1 Oncogene mutations in NSCLC patients

Oncogene mutations are found in most NSCLC patients and, therefore, targeted drugs are associated with fewer side effects, higher response rates (RRs), and longer progression-free survival (PFS) than cytotoxic drugs. A mutation in the gene coding for *epidermal growth factor receptor (EGFR)* is common in NSCLC patients (found in 10%–30% of patients), and downstream signaling pathways such as MAPK/ERK, PI3K/AKT and Bax/Bcl-2 are also potential targets (11). Almost 90% of *EGFR* mutations in NSCLC patients are exon 19 deletions or *L858R* substitutions in exon 21. In addition, mutation of the *T790M* gene occurs in 50%–60% of NSCLC patients with the *EGFR* mutation, and this mutation is associated with acquired resistance (12). Acquired resistance to the EGFR tyrosine kinase inhibitor (TKI) in NSCLC patients is correlated with overexpression of osteopontin (OPN), upregulation of integrin αVβ3, and activation of downstream signaling pathways such as FAK/AKT and ERK (13). Activation of the PI3K/AKT/mTOR signaling pathway is also associated with acquired resistance to *EGFR* TKIs in NSCLC patients (14). The PI3K/AKT/mTOR signaling pathway is linked to the proliferation and invasion of cancer cells, affecting the likelihood of success of chemotherapy.

Rearranged during transfection (RET) rearrangements are found in 1%–2% of NSCLC patients, and the downstream signaling pathways of *RET*, such as PI3K/AKT, JAK-STAT, and RAS/MAPK, are associated with cell proliferation, invasion, and migration (15, 16). *MET* mutations could result in the abnormal expression of MET axis, and the MET/HGF (hepatocyte growth factor) signal pathway play an important role in the MET axis, and this signal pathway leads to tumor cell migration, invasion, and metastasis (17) and are associated with resistance to treatment with *EGFR* and vascular endothelial growth factor receptor (VEGFR) inhibitor. Mutations in exon 14 are the most common *MET* mutations found in NSCLC patients (18). The majority of *MET* exon 14 mutations are point mutations, but indels, insertions, and deletions are also found (19).

Rearrangement of the anaplastic lymphoma kinase gene (*ALK*) has been identified in 5%–6% of younger NSCLC patients (20). Overexpression of ALK in A549 cells can induce epithelial–mesenchymal transition (EMT), and increase migration and invasion, phenomena that are correlated with the upregulation of signal transducer and activator of transcriptions 3 (STAT3) (21). Many NSCLC patients with an *ALK* mutation develop drug resistance after taking drugs for a few years. In the case of ALK inhibitors, the most common mutation associated with acquired resistance is F1174L (22). In addition, some studies have confirmed that drug resistance in NSCLC is associated with signal transducer and activator of transcriptions (STATs), especially the STAT3/ZEB1 signaling

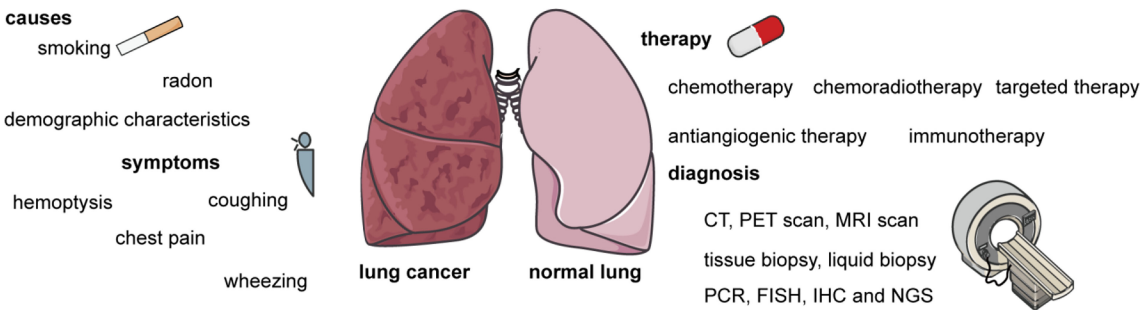

FIGURE 1
The main causes and symptoms of lung cancer, as well as methods of diagnosis and therapies. The causes of lung cancer include smoking, radon, genetics, and demographic characteristics. The symptoms of lung cancer including hemoptysis, coughing, chest pain, and wheezing. Therapies include chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy, and combination therapy. Diagnostic methods include computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), tissue biopsy, liquid biopsy, polymerase chain reaction (PCR), fluorescence *in situ* hybridization (FISH), immunohistochemistry (IHC), and next-generation sequencing (NGS).

pathway (23). These findings are a reminder that combination therapies targeting both ALK and STAT3 could perhaps overcome the resistance associated with the use of ALK inhibitors.

Mutations in the gene encoding human epidermal growth factor receptor 2 (*HER2*) is the mutation of exon 20, and these mutations are found in 2%–4% of NSCLC patients, especially women, besides, the patients with *HER2* mutations easily appear brain metastases (24). Activation of *HER2* induces the phosphorylation of tyrosine residues, leading to the activation of downstream signaling pathways such as MEK/ERK and PI3K/AKT, which in turn increases the migration and proliferation of lung cancer cells (25). Around 4% of NSCLC patients have a mutation in the *B-Raf proto-oncogene* (*BRAF*), but the *V600E* mutation is present in only half of such patients, who as a result are resistant to *BRAF* inhibitors (the *V600E* mutation is associated with a better response to *BRAF*-targeted therapy) (26). $BRAF^{V600E}$ mutation is usually accompanied by MAPK signaling pathway activation, and, therefore, combination therapy with two different drugs, one targeting *BRAF* and the other targeting *MEK* (27), may give better results.

c-Ros oncogene 1 (*ROS1*) rearrangement is found in around 1%–2% of NSCLC patients (28). There are several different ROS1 rearrangements, including *CD74-ROS1, SLC34A2-ROS1, YWHAE-ROS1, TFG-ROS1*, and *CEP85L-ROS1*, but *CD74-ROS1* (44%) is the most common *ROS1* rearrangement found in NSCLC patients (29). ROS1 is a kind of tyrosine kinase; its ligand is neural epidermal growth factor-like 2 neural EGFL-like 2 (30). Just as the other oncogene we mentioned above, such as HER2, BRAF, when ROS1 is activated by its ligands, downstream signaling pathways such as the PI3K/AKT/mTOR, JAK/STAT, and MAPK/ERK signaling pathways are also activated, leading to the proliferation of lung cancer cells and tumor invasion (31).

Among NSCLC patients tested, 13% were found to have the *Kirsten rat sarcoma viral oncogene* (*KRAS*) *p.G12C* mutation (32). *KRAS* mutations, like mutations of other oncogenes, are associated with drug resistance and poorer outcomes in NSCLC (33).

KRAS mutations are also known to be present in 90% of smokers. *KRAS* is related to inflammation, and *KRAS* mutation is found in the most smokers, therefore, it may be some sort of inflammatory reaction in lung cells by smoking (34). The drug resistance induced by *KRAS* mutations is usually intrinsic. However, *KRAS* mutations are heterogeneous, i.e., there is more than one type, and different *KRAS* mutations lead to activation of different downstream signaling pathways. *KRAS* mutations do not result in changes in the phosphorylation of the AKT signaling pathway (35).

Fusion of the *neurotrophic tropomyosin receptor kinase (NTRK)* gene is a relatively rare oncogene mutation, which occurs in less than 1% of NSCLC patients. The detection of *NTRK* fusions relies on RNA-based next-generation sequencing (NGS) (36). The downstream signaling pathways include the MEK/ERK and PI3K/AKT signaling pathways. As mentioned above, these signaling pathways are related to cancer cell proliferation and migration, and the PI3K/AKT signaling pathway is also involved in apoptosis, which is induced by chemotherapy (36). In early-stage NSCLC with *NTRK* gene fusions (Figure 2), patients have a high RR to TKIs (37).

Moreover, the immune checkpoint development also benefits NSCLC patients. If the mutation in patients does not concern the mutations above, then the *programmed death ligand 1 (PD-L1)* mutation maybe a better choice, but there are still some limits, for example, the mutation of PD-L1 at least appears 50% mutation in the lung cancer patients (38). The combination of programmed death 1 (PD-1) and PD-L1 would decrease immune response; therefore, the tumor cells will escape the

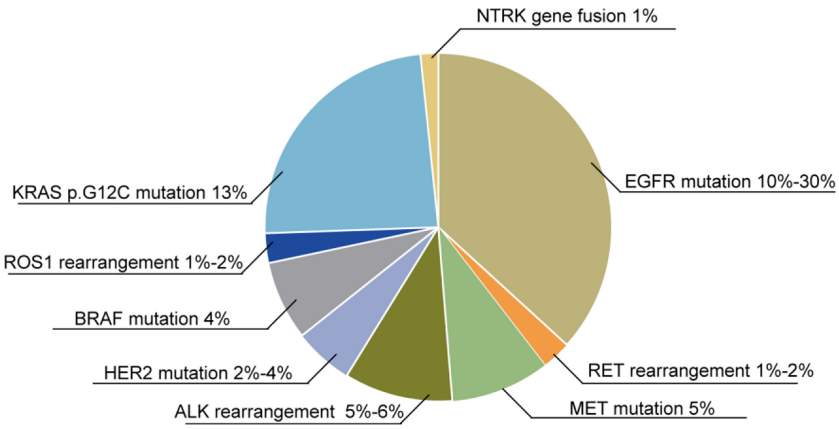

FIGURE 2
Oncogene mutations in NSCLC patients. Various oncogene mutations are found in NSCLC patients: 10%–30% of NSCLC patients exhibit *EGFR* mutations, 1%–2% have *RET* rearrangements, 5% have a *MET* mutation, 5%–6% have an *ALK* rearrangement, 2%–4% have a *HER2* mutation, 4% have a *BRAF* mutation, 1%–2% have *ROS1* rearrangements, 13% have the *KRAS p.G12C* mutation, and 1% have *NTRK* gene fusions.

surveillance of immune cells such as T cells. There are also some studies reported that the *EGFR* mutation in NSCLC could increase the expression of PD-L1 protein, and TKIs could reduce the amount of PD-L1 protein, the signaling pathways referring to this phenomenon are PI3K-AKT, STAT3, NF-κB, and MEK-ERK signaling pathways (39). Furthermore, *ALK* and *KRAS* mutations could improve the expression of *PD-L1*; therefore, if the patients are harboring *PD-L1* and *EGFR* or *ALK* or *KRAS* at the same time, patients will have a higher RR when the interaction between PD-1 and PD-L1 is blocked (40). However, there is still no study that can verify the results for NSCLC patients harboring several mutations at the same time. The high PD-L1 expression is also associated with smoking, and PD-L1 usually appears in the early stage of NSCLC, and could become a biomarker in the diagnosis of lung cancer (41).

Apart from the targets mentioned above, there are also some signaling pathways abnormally expressed in NSCLC that could become new biomarkers in diagnosis and therapy, but these signaling pathways still stand in the preclinical stage.

2.2 long non-coding RNAs, microRNAs, and abnormal proteins in NSCLC

The long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are non-coding RNAs existing in the cells, and these non-coding RNAs are correlated with tumor progression and tumor features, for example, its proliferation, migration, invasion, resistance, and recurrence. In NSCLC, these non-coding RNAs also show a more important role, and some results in preclinical studies could give rise to new biomarkers or targets in the diagnosis and treatment of NSCLC.

2.2.1 lncRNAs and NSCLC

lncRNA H19 and miRNA-21 overexpress in the NSCLC tumor, and these could become biomarkers in the diagnosis and treatment of NSCLC (42). Circular RNAs (circRNAs) hsa_circ_0058357 overexpress in NSCLC, and the abnormal expression of hsa_circ_0058357 is associated with migration, proliferation, and apoptosis through increasing AVL9 accompanied by the inhibition of miR-24-3p (43). LncRNA SNHG14 is a cancer-promoting lncRNA, and it is upregulated in the lung cancer tissue; lncRNA SNHG14 could promote the migration, proliferation, and invasion of NSCLC cells; and lncRNA SNHG14 could inhibit the miR-206 expression; therefore, the downstream targets of miR-206 such as G6PD are upregulated (44). lncRNA ABHD11-AS1 is overexpressed in NSCLC, and it could upgrade the Warburg effect and proliferation of NSCLC. There is m6 A methyltransferase-like 3 (METTL3) in the upstream of lncRNA ABHD11-AS1, which could promote the expression of ABHD11-AS1, and the prognosis for NSCLC patients will get worse (45). lncRNA DUXAP8, an oncogenic lncRNA, could induce the proliferation, EMT, and aerobic glycolysis in lung cancer cells. Its effects will be studied further. Moreover, the overexpression of lncRNA DUXAP8 in NSCLC patients is correlated with the poor prognosis. The mechanisms here are diverse including transcriptional, post-transcriptional, and epigenetic regulation (46). The overexpression of lncRNA CCDC144NL-AS1 in NSCLC patients could promote the proliferation, migration, and invasion of NSCLC cells (H1299, A549, NCI-H650, and HCC827 cells). Mechanically, lncRNA CCDC144NL-AS1 could directly bind to miR-490-3p (47). There are also some other examples showing that lncRNA could be a biomarker in NSCLC, one is LncRNA HOTAIR that could promote the proliferation,

invasion, and migration in NSCLC cells by regulating the CCL22 signaling pathway (48). lncRNA UFC1 could promote the progression of NSCLC by downregulating the expression of PTEN through zeste homolog 2 (EZH2) (49). LncRNA WTAPP1 could promote the invasion and migration of NSCLC cells by suppressing the expression of lncRNA HAND2-AS1 (50).

In addition, there are also some lncRNAs that play an inhibitor role in the progression of NSCLC. LncRNA NBR2 is downregulated in NSCLC patients, and the overexpression of lncRNA NBR2 could inhibit the migration of lung cancer cells (SPC-A1 cells) and the Notch signaling pathways are also suppressed, and the EMT-related genes are also reduced (51). lncRNA LINC00261 is downregulated in the lung cancer tissues, and the overexpression of lncRNA LINC00261 in A549 and SPC-A1 cells would inhibit metastasis *in vitro* and *in vivo* through regulating the miR-1269a/FOXO1 signaling pathway (52). There is a novel lncRNA BRCAT54 that is overexpressed in the lung cancer tissue, but this lncRNA benefits the patients, and its knockdown could promote the migration, proliferation, and apoptosis inhibition of lung cancer cells, which concern the regulation of JAK-STAT and calcium-related signaling pathways (53).

2.2.2 microRNAs and NSCLC

The microRNA functions in NSCLC are different. Some microRNAs show promotion in the progression of lung cancer, and others show inhibition in the progression of lung cancer.

Radiotherapy is useful for most NSCLC patients in the early stage, but radiotherapy is usually accompanied by acquired resistance. Acquired resistance has been proven to be correlated with the overexpression of miR-410 in NSCLC. Mechanically, miR-410 could induce EMT and target the PTEN/PI3K/mTOR signaling pathway (54). miR-10b aberrantly expresses in multiple malignant cancers, such as breast cancer, esophageal cancer, pancreatic cancer, and lung cancer, and it is related to proliferation and invasion (55). miRNA-21 is overexpressed in NSCLC and is related to the poor survival and prognosis of patients, especially with miRNA-21 being correlated with the radiation resistance of NSCLC. Therefore, the inhibition of miRNA-21 in NSCLC cells (A549 cells) could suppress proliferation and improve sensitivity to radiation through increasing apoptosis (56). miR-142-3p, on the one hand, could improve the sensitivity of NSCLC by downregulating the high-mobility group box-1 (HMGB1) protein and inhibiting autophagy. On the other hand, it could also play as an oncogene, and its overexpression is correlated with the poor outcome of NSCLC patients in clinical treatment, and promotes the migration and proliferation of NSCLC cells by downregulating TGFβR1 (57).

In the NSCLC tissues, miR-936 is at a low expression, and the overexpression of miR-936 could block the cell cycle, and inhibit the proliferation and invasion of NSCLC cells. At the same time, the downstream target E2F transcription factor 2 (E2F2) that could promote the invasion of NSCLC is downregulated (58). The overexpression of miR-221–3p could decrease the resistance of paclitaxel by inducing apoptosis accompanied by the inhibition of MDM2/p53 signaling pathway (59). miR-340 is at a lower expression of NSCLC tissues, and its overexpression could inhibit the migration and invasion of NSCLC cells through targeting RAB27B. In addition, the overexpression of miR-340 could suppress proliferation and induce apoptosis through regulating p27 (60). The level of miRNA-597 in the NSCLC tissues is lower than the normal tissue, and the downregulated miRNA-597 is related to the stage and poor prognosis of NSCLC patients. The overexpression of miRNA-597 could inhibit progression by regulating CDK2 (61). miR-4732-5p expression is inhibited in NSCLC; its downregulation is related to metastasis, late stage, and poor outcome of NSCLC patients. Its overexpression could suppress the proliferation, migration, and invasion of NSCLC cells (A549, HCC827, H23, and H1975 cells) by regulating TSPAN13 (also known as NET-6 and TM4SF13) that has been proven to inhibit proliferation and invasion in breast cancer (62, 63).

2.2.3 Abnormal proteins and NSCLC

There are also some proteins that overexpress in the NSCLC patients, which could become new targets in clinical trials. Fibulin2 (FBLN2) is decreased in the lung cancer cell lines, and the overexpression of FBLN2 would inhibit the activation of MAPK/ERK and AKT/mTOR signaling pathways, accompanied by the decreased migration and invasion of cells (64). This means that FBLN2 could be a potential biomarker for detecting NSCLC in the clinic. The abnormal expression of nuclear factor kappa B (*NF-κb*) is correlated with chemoresistance and radio-resistance in lung cancer therapy, and the inhibition of NF-κβ signaling pathway will decrease the resistance given by chemotherapy and radiotherapy (65). *NF-κb* is related to multi-signaling pathways such as apoptosis, angiogenesis, and inflammation; therefore, *NF-κb* is a relatively difficult oncogenic mutation compared with other oncogene mutations such as *EGFR* and *KRAS* (66). Nuclear factor erythroid 2-related factor 2 (Nrf2) is increased and Keap1 in cytoplasmic is decreased, and these changes in Nrf2 and Keap1 are correlated with the poor outcome of NSCLC patients, and increased Nrf2 may contribute to chemoresistance when using platinum-related chemotherapy (67). Almost 25% of patients with NSCLC appear to have brain metastases, and there are several aberrant proteins arising in this process. NFATc1 and NFATc3 are listed in these biomarkers, and the expression of these two proteins is decreased in patients with brain metastases, at the same time, the downstream targets such as IL-11 (correlated with JAK-STAT3 signaling pathways), CDH5 (correlated with metastasis), and CCL2 (correlated with proliferation and apoptosis) are also regulated by NFATc1 and NFATc3 (68). Tripartite motif (TRIM) protein is a type of

protein correlated with multiple malignant cancers including lung cancer, and takes part in various signaling pathways regulation including p53, NF-κB, and PI3K/AKT. In NSCLC, TRIM could play as an oncogene or suppressor. As disintegrins and metalloproteinases with thrombospondin motifs (ADAMTS8) are downregulated in NSCLC cells (H460 and A549 cells), the overexpression of ADAMTS8 could inhibit proliferation and induce apoptosis of lung cancer cells. Mechanically, the vascular endothelial growth factor A (VEGFA) and CD31 are suppressed (69). Neurexophilin 4 (NXPH4) is overexpressed in NSCLC tissues, and its knockdown could suppress the proliferation and migration of NSCLC cells (A549, H226, H2106, and HCC827 cell line), and trigger cell cycle arrest in phase S1. EZH2 was in the upstream of NXPH4, and could activate the expression of NXPH4; then, the activated NXPH4 could downregulate the expression of CDKN2A, and the downregulated CDKN2A could regulate the cyclinD-CDK4/6-pRB-E2F signaling pathway resulting in the cell cycle activation and the promotion of proliferation and migration of lung cancer cells (70).

2.3 CSCs and lung cancer

Cancer stem cells (CSCs) are considered to be the root of cancer, and evidence confirm that CSCs are related to chemoresistance and recurrence and the survival of lung cancer patients. Therefore, there are many compounds targeting CSCs in preclinical or clinical trials. There are also other strategies that inhibit the stemness of cancer cells. More specifically, targeting signaling pathways such as Wnt, hippo, and notch could inhibit the stemness of cancer cells or the biomarkers correlated with CSCs (71). CSCs also exist in NSCLC, and lung cancers also have the feature of stemness; therefore, these facts confirm that targeting CSCs in NSCLC is crucial (72, 73).

Lung cancer stem cells (LCSCs) with high chemo-resistance were obtained from the NSCLC patients; the subpopulation of LCSCs show self-renewal, resistance, invasion, and tumorigenic potential in the *in vitro* experiments, and the CDKN1A, ITGA6, and SNAI1that were selected by different expression levels between LCSCs and the adherent-cultured cells could become biomarkers for indicating the different stages of lung cancer in patients (74). The LCSC biomarkers in humans include $CD133^+$, $CD90^+$, $CD44^+$, $CD87^+$, ABCG2, SP, and ALDH (75). Forkhead box C1 (*FOXC1*) is correlated with the CSC features, and is elevated in NSCLC. The knockdown of FOXC1 could decrease the subpopulation of $CD133^+$ cells, and the associated genes, such as *NANOG, ABCG2, SOX2*, and *Oct4*, are also downregulated, and the chemo-sensitivity for cisplatin, docetaxel, and gefitinib is also increased (76). m6A demethylase *ALKBH5* is upregulated in LCSCs, and its knockdown could contribute to the E-cadherin upregulation and stem markers such as NANOG and Oct4 are downregulated. Mechanically, there is a positive relationship between *ALKBH5* and *p53*, and the knockdown of *p53* would make *ALKBH5* downregulate, and the tumor formation ability and invasion are also suppressed (77). Nerve injury-induced protein 1 (Ninj1) is upregulated in NSCLC cells and tissues; the subpopulation of $Ninj1^{high}$ LCSCs exhibits the CSC-related features such as the increase of $ALDH^+$ subpopulation, sphere-forming ability, and stemness markers; and the downstream signaling pathway Wnt/β-Catenin is also activated by Frizzled2-LRP6 assembly (78). Histamine N-methyltransferase (HNMT) is overexpressed in NSCLC tissues as found in clinical trials, and is related to a poor prognosis for patients. Moreover, HNMT has a positive relationship with HER2 that could improve the features of CSCs. The knockdown of HNMT could decrease the tumorsphere formation ability, and reduce the expression of CSC markers such as NANOG, CD133, OCT4, and KLF4 through the Nrf2/HO-1/HER2 signaling pathway increasing the accumulation of reactive oxygen species (ROS) (79). The stemness markers ALDH and CD133 are well-verified in LCSCs; p53 is a cancer suppressor, the mutation which is found in 47% of NSCLC cases, and the knockdown of the three genes could reduce the CSC characteristics and prolong the survival of NSCLC patients (80). This study is a reminder that the stemness markers may have some therapeutic effect in NSCLC patients. Heat shock protein 90 (hsp90) inhibitors show better results in clinical use, but in therapy, there is resistance that maybe correlated with CSCs in lung cancer. However, there is a new Hsp90 inhibitor named NCT-80 that could reverse CSCs resulting to resistance by regulating STAT3/Wnt/β-catenin signaling pathways (81). RNF168, a E3 ubiquitin ligase, is downregulated in lung adenocarcinoma, but upregulated in squamous cell carcinoma; the overexpression of RNF168 could inhibit the CSC features (such as sphere-formation ability, stemness markers ALDH) of NSCLC cells. Mechanically, the RNF168 could ubiquitylate RhoC and cause its degradation (82). Non-muscle myosin heavy chain 9 (MYH9) is upregulated in lung cancer, and correlated with the worst prognosis in NSCLC patients, and the overexpression of MYH9 in lung cancer cells could improve the expression of stemness markers (such as SOX2, OCT4, Nanog, CD133, and CD44) and sphere-formation ability by regulating the mTOR signaling pathway (83). The Orai3 channel is a calcium channel related to the chemoresistance of lung cancer, and the overexpression of Orai3 could improve metastasis in NSCLC. LCSCs, derived from NSCLC cells with cisplatin resistance, has a higher expression of Orai3, and the silence of Orai3 could worsen metastasis, accompanied by a sensitivity to cisplatin. Moreover, stemness markers such as Sox2 reduced through regulating the PI3K/AKT signaling pathway (84).

Overall, there are still many stemness markers of NSCLC studied in the preclinical and clinical trials, and the development of small molecular markers could become the new targets or diagnostic markers for the different stages of lung cancer.

3 The diagnosis of lung cancer

Except for the symptom of coughing appearing in the early stage of lung cancer, most lung cancer patients are asymptomatic in the early stage; therefore, early diagnosis and treatment could be missed. The development of technology in diagnosis could save majority of patients and could prolong their lives. Diagnostic methods mainly include image test, biopsy test, and biomarker test.

3.1 Image test

Image tests, such as computed tomography (CT), PET scan, and magnetic resonance imaging (MRI) scan, play an important role in the diagnosis of lung cancer. CT is the most common diagnostic means in lung cancer, which could determine tumor size (≥ 6 mm) and the number of nodules in lung cancer patients. It also could test the metastases, especially the mediastinal lymph nodes in the lung cancer patients (85–87). CT could also detect if the nodules are benign or malignant, but for further determination, biopsy is still needed (88). PET has more sensitivity and specificity than CT because the PET scan uses fluorine-18 fluorodeoxyglucose (F-18 FDG) as the biomarkers. It could locate in the malignant lesions with aberrant glucose metabolism (89). PET could also test if the lesions are benign or malignant, and it also differentiates the different types and staging (especially the distant metastases) of lung cancer by the uptake degree of FDG (90, 91). MRI scan has been used in NSCLC patients with brain and bone metastases because the dye used in MRI scan is not suitable for tissues that can move. With the development of high-performance gradient systems, phased-array receiver coil, and optimized imaging sequences, MRI could also detect nodules in lung tissues; the lowest size of nodules that can be detected is 3 mm (92).

3.1.2 Biopsy test

Furthermore, the identification of lung cancer also needs biopsy (93), which could be tissue or liquid biopsy. Tissue biopsy is a type of invasive mean, and liquid biopsy is a non- invasive mean. Tissue biopsy is the gold standard to test lung cancer in the clinic. The determination of different histological types of lung cancer relies on tissue biopsy (94). Tissue biopsy could also test the mutations in lung cancer, but lung biopsy usually has complications (95). With the limitations of liquid biopsy, its application is restricted. In liquid biopsy, the sample used is the peripheral blood of the NSCLC patients, and the common testing indicators are circulating tumor DNA (ctDNA), circulating tumor cells (CTCS), and exosomes (96). In addition, it could also detect miRNA, circRNAs, circulating tumor vascular endothelial cells (CTECs), and tumor-educated blood platelets (TEPs) (97). Compared with tissue biopsy, liquid biopsy is more sensitive, effective, practical, and acceptable, and it could provide different mutations in the tumor (98).

3.1.3 Biomarker test

Regarding the development of targeted therapy in NSCLC, if patients are diagnosed with NSCLC, then they are advised to take molecular testing to verify possible mutations. The methods are diverse. For example, polymerase chain reaction (PCR) could identify signal gene mutation, mostly used in determining the mutation of *EGFR* in the clinic (99). Fluorescence *in situ* hybridization (FISH) was approved by the food and drug administration (FDA) to test *ALK* rearrangements by fixing the tissue in formalin and embedding in paraffin (20). FISH could also diagnose the aberrant expression of *ROS1, RET, HER2, and MET* (100). Immunohistochemistry (IHC) analysis is suitable for testing the mutations of *PD-L1* (approved by FDA), *ROS1, EGFR, BRAF-V600E*, and *RET* (101). Moreover, IHC could be used in testing the mutation of *ALK* (approved by FDA) (102). NGS is suitable for almost all of mutations appearing in the NSCLC, such as *EGFR, RET, MET, ALK, HER2, BRAF, ROS1, KRAS*, and *NTRK*, also including some new biomarkers such as *PIK3CA* (103). The NGS efficiency is high, the needed sample is small, and the cost is relatively low; therefore, there are more applications of NGS in the clinic.

The development of diagnostic methods in lung cancer (Table 1) could help most patients diagnosed in the early stage; therefore, the treatments for lung cancer could work.

4 Treatments for lung cancer

4.1 Chemotherapy and chemoradiotherapy

4.1.1 Chemotherapy

Before targeted therapy, chemotherapy dominated the clinical treatment for lung cancer. After the gene types of NSCLC have been identified in the clinic, chemotherapy was gradually replaced by targeted therapy, but chemotherapy also concerns cisplatin combination therapy. Currently, chemotherapy in NSCLC mostly involves cisplatin and carboplatin plus gemcitabine, taxanes, and pemetrexed plus some targeted therapy drugs such as VEGFR inhibitor (bevacizumab) or EGFR inhibitor (erlotinib) (104). The mechanism of chemotherapy is diverse. Cisplatin, carboplatin, and gemcitabine could disturb the DNA repair system, create DNA damage, and induce apoptosis in the cancer cell (105, 106). Taxanes could interfere with microtubule dynamics, trigger cell cycle arrest, and induce apoptosis (107, 108). Pemetrexed, an antifolate drug, could cause cell cycle arrest in the S phase (109).

The limitations of chemotherapy in lung cancer treatment mainly involve intrinsic resistance even though the compounds could have some effects at the first early treatment, but the tumor can acquire resistance rapidly (110). This disturbs the process of chemotherapy in the lung cancer treatment. There are various mechanisms of resistance in lung cancer. CSCs are correlated with the resistance of chemotherapy and radiation therapy as

TABLE 1 Diagnostic methods in lung cancer.

Diagnostic method		Details
Image test	CT	Determines the size (≥ 6 mm) and number of nodules
	PET scan	With more sensitivity and specificity than CT, using F-18 FDG
	MRI	Used in NSCLC patients with brain and bone metastases, the lowest size of nodules could be 3 mm
Biopsy test	Tissue biopsy	Invasive mean, could test mutations
	Liquid biopsy	Non-invasive mean, testing indicators: ctDNA, CTCS, miRNA, circRNAs, CTECs, TEPs, and exosomes
Biomarker test	PCR	Determines the mutation of *EGFR*
	FISH	Tests the mutation of *ALK, ROS1, RET, HER2*, and *MET*
	IHC	Tests the mutation of *PD-L1*, *ROS1, EGFR, BRAF-V600E, ALK*, and *RET*
	NGS	Tests the mutation of *EGFR, RET, MET, ALK, HER2, BRAF, ROS1, KRAS*, PIK3CA, and *NTRK*

some compounds directly targeting CSCs could reduce the resistance in lung cancer therapy and improve the outcome of chemotherapy and radiosensitivity. The compounds target CSCs, mostly targeting the representative signaling pathways in the CSCs, such as Notch, MYC. RO4929097 (an inhibitor of Notch signaling pathway, γ-secretase inhibitor) combined with erlotinib could improve the efficiency of erlotinib in advanced NSCLC with chemoresistance and the PFS was up to 5 years (*NCT01193881 (first posted: 2 September 2010), NCT01193868 (first posted: 2 September 2010)*). In preclinical research, sulforaphane could inhibit the properties of LCSCs, such as sphere-forming ability, biomarkers of LCSCs, which could combine with cisplatin and doxorubicin to reduce the chemoresistance of NSCLC (111). Additionally, there are also some signaling pathways related to the resistance of lung cancer, which could provide a combined strategy for chemotherapy to overcome the resistance further. For example, Acetyl-11-keto-β-boswellic acid (AKBA) could improve the sensitivity of cisplatin in NSCLC through targeting P21, which maybe correlated with the increase of apoptosis and the inhibition of autophagy (112). This study reminds us that AKBA could become a new combination therapy in the clinic, even though it is still in preclinical research. The regulation of cell death such as autophagy, apoptosis, and ferroptosis could provide a new perspective to reducing resistance in chemotherapy (71).

Moreover, chemotherapy and radiotherapy have a function in neoadjuvant or adjuvant therapy in stage III NSCLC patients. Chemotherapy could help ensure that surgery goes well and could also serve as supplement after surgery (113). For example, patients with nodal metastases after surgery could benefit from adjuvant cisplatin-based therapy, and induction therapy could serve as a precondition for surgery (114, 115).

4.1.2 Chemoradiotherapy

Radiotherapy is usually used in the local control of different stages of lung cancer, especially stage III unresectable NSCLC, which accounts for 30% in NSCLC patients (104). Moreover because of the development of four-dimensional computed tomography (4DCT), stereotactic body radiotherapy (SBRT), and intensity-modulated radiotherapy (IMRT), the side effects of radiotherapy are reduced (116). However, even though radiotherapy is the standard therapy for stage III NSCLC patients, the survival rate of patients has not improved. After the application of sequential radiotherapy to patients, the overall survival (OS) improved, but elderly patients still have not benefited from it. Therefore, combination therapy with radiotherapy may be of benefit to diverse patients with different states of health (117).

The mechanism of radiotherapy is mainly the damage of DNA, and damaged DNA could induce immune responses in the lung cancer; therefore, the combination therapy of radiotherapy and immunotherapy could produce a better result in the treatment of lung cancer (118). This combination has been verified by clinical trials. For example, in a phase III trial (*NCT02125461 (first posted: 29 April 2014)*), the conventional chemoradiotherapy (platinum-based chemotherapy and radiotherapy) plus durvalumab (an immune checkpoint inhibitor of PD-L1) could significantly prolong OS (up to 4 years) in stage III NSCLC patients compared with chemoradiotherapy alone, and the PFS of patients was also up to 3 years (119).

Chemoradiotherapy (CRT) mostly adjusts to the limited-stage SCLC. In addition, CRT also offers benefit for the lung cancer without metastasis. The chemotherapy in chemoradiotherapy generally includes cisplatin–etoposide (120) and carboplatin plus etoposide (121).

4.2 Targeted therapy

The lung cancer is driven by mutation of multiple oncogenes, the targetable alterations in the clinic provide probability for targeted therapy (122). In order to conduct targeted therapy in lung cancer patients, the molecular mutations in the tumor must be confirmed by diagnostic assays (123). The development of NGS provides a method to test the mutations appearing in lung cancer patients, which could help them get precision and personalized treatment in the clinic (124).

4.2.1 Drugs approved by FDA

The targets that have drugs approved by FDA include *EGFR* (gefitinib (brand name: Iressa, company: ASTRAZENECA, London, the UK), erlotinib (brand name: Tarceva, company: OSI PHARMS, Ardsley, the USA), afatinib (brand name: Gilotrif, company: BOEHRINGER INGELHEIM, southwest Washington, the USA), dacomitinib (brand name: Vizimpro, company: PFIZER, New York City, the USA) and osimertinib (brand name: Tagrisso, company: ASTRAZENECA,London, the UK)), *ALK* (crizotinib (brand name: Xalkori, company: PF PRISM CV, Netherlands), alectinib (brand name: Alecensa, company: HOFFMANN-LA ROCHE, Basel, Switzerland), brigatinib (brand name: Alunbrig, company: TAKEDA PHARMS USA, Lexington, the USA), ceritinib (brand name: Zykadia, company: NOVARTIS, Basel, Switzerland), and lorlatinib (brand name: Lorbrena, location and company: PFIZER, New York City, the USA), *ROS1* (crizotinib (brand name: Xalkori, company: PF PRISM CV, Netherlands), lorlatinib (brand name: Lorbrena, company: PFIZER, New York City, the USA), entrectinib (brand name: Rozlytrek, company: GENENTECH INC, Pennsylvania, the US) and brigatinib (brand name: Alunbrig, company: TAKEDA PHARMS USA, the USA), *RET* (pralsetinib (brand name: Gavreto, company: GENENTECH INC, Pennsylvania, the US) and selpercatinib (brand name: Retevmo, company: LOXO ONCOLOGY INC, Massachusetts, the USA)) (123, 125–127). Some targets such as *HER2, KRAS, BRAF, NTRK*, and *MET* in the clinical trials benefit from the development of genomic profiling (128). The drugs target *HER2* mainly including TKIs (pyrotinib and tucatinib), mono-antibody (trastuzumab), and antibody–drug conjugates (trastuzumab deruxtecan) (129, 130), target *KRAS* contain adagrasib (MRTX849) and sotorasib (AMG510) (122), target BRAF (dabrafenib plus trametinib) (*NCT04452877 (first posted: 1 July 2020)*), target *NTRK* (larotrectinib and entrectinib) (*NCT02576431 (first posted: 15 October 2015), NCT02568267 (first posted: 5 October 2015)*), and target *MET* (crizotinib) (*NCT04084717 (first posted: 10 September 2019)*). The drugs approved by FDA significantly improved the OS of patients, such as gefitinib that improved the median PFS (mPFS) by almost 10.8 months, erlotinib increased mPFS by nearly 14 months, afatinib improved PFS by approximately 48 months, and dacomitinib increased mPFS up to 14.7 months (131–133). The mPFS of patients after taking osimertinib increased 18 months (134). The mPFS of patients with *ALK*-positive or *ROS-1*-positive NSCLC was increased 8.2 months after taking crizotinib and the OS was up to 114 months after taking lorlatinib (135, 136). The mPFS of *ALK*-positive metastatic NSCLC patients improved by 34.8 months after taking alectinib, and 7.8 months for ceritinib (135, 137). Brigatinib for NSCLC patients with *ALK-positive, ROS-1-positive, or EGFR* mutation-positive could also improve PFS by almost 11.0 months (138). Pralsetinib and selpercatinib for NSCLC patients with metastatic *RET* fusion-positive could also improve mPFS by almost 17.1 months and 16.5 months, respectively (139).

4.2.2 Drugs still in preclinical and clinical trials

There are some drugs that are still in clinical trials, but also show significant effects on prolonging the OS of NSCLC patients. These drugs could give more hope to patients. For example, pyrotinib for advanced NSCLC with *HER2* mutation was proved to prolong the PFS of patients for 6.9 months and the median OS for 14.4 months in clinical trial (*NCT02834936 (first posted: 15 July 2016)*). Moreover, the new biomarkers found in the preclinical stage also provide targets for the treatment of lung cancer, for example, the mutations of the *PIK3CA* gene (140) and overexpression of VEGF in lung cancer driven by smoking (141).

Even though targeted therapy could produce high RR and improve the OS of patients, the special targets, such as *EGFR, ALK*, and *ROS1*, only account for a very small part (<20%) in the lung cancer patients (142). Hence, there is an urgency to develop more nonspecific therapies so they can be used to treat more lung cancer patients. The high cost of targeted therapy in the clinical treatment of lung cancer still limits its usage (143). Additionally, there are also some questions such as chemo-resistance in clinical therapy with the wide use of targeted drugs. The mechanism of acquired resistance in NSCLC after treatment with *EGFR* TKIs for several months mainly includes the hepatocyte growth-factor receptor amplification. Currently, deoxypodophyllotoxin (DPT) has been reported to reduce the resistance of HCC827GR cells by targeting *EGFR* and the hepatocyte growth-factor receptor, and induce apoptosis. This study could provide a combination therapy for the use of *EGFR* TKIs to reduce acquired resistance in the clinic (144). Furthermore, there are other therapies combined with targeted drugs that are in clinical trial.

The combination of erlotinib (an *EGFR* inhibitor) and bevacizumab (a monoclonal antibody targeting VEGF) could prolong the PFS of NSCLC patients (*NCT02759614 (first posted: 3 May 2016)*) (145). This reveals the probability of VEGF and *EGFR* double inhibition in the untreated metastatic *EGFR*-mutated NSCLC. Apatinib (a *VEGFR* inhibitor) plus gefitinib (a first-generation *EGFR* TKI) could prolong the mPFS for 19.2 months in advanced NSCLC with *EGFR* mutation, but this combination therapy also has some side effects and the quality of life (QoL) did not change (*NCT02824458 (first posted: 6 July 2016)* (146). The use of osimertinib (a third generation of *EGFR* TKI) is usually accompanied by chemo-resistance in the terminal treatment of advanced *EGFR*-mutated NSCLC patients; the reason maybe because the second-site mutations appear in the *EGFR*. Therefore, osimertinib plus dacomitinib (a pan-HER inhibitor) could reduce drug resistance appearing in therapy, in a phase I/II trial *(NCT03810807 (first posted: 22 January 2019)*) (147). Moreover, the combination of osimertinib and navitoclax (an inhibitor of BCL-2 that could increase apoptosis and reduce chemo-resistance) was feasible in patients with *EGFR*-mutated NSCLC in a phase IB trial (*NCT02520778 (first posted: 13 August 2015)*) (148). The

inhibitors targeting *KRAS* mostly through targeting *KRAS p. G12c*, for example, AMG510 and MRTX849 are still in the clinical study (149). AMG15 was used to treat patients with advanced metastatic NSCLC patients with *KRAS p. G12c* mutation in a phase 3 study (*NCT04303780, first posted: 11 March 2020*). MRTX849 showed better results in NSCLC patients, but had more side effects compared with AMG510. However, for clinical studies such as *NCT04613596 (first posted: 3 November 2020), NCT04685135 (first posted: 28 December 2020), and NCT04330664 (first posted: 1 April 2020)* results are yet to be obtained. AMG510 had already been approved by FDA. ARS-1620, an inhibitor of *KRAS* p. G12c is still in the preclinical stage but shows better anti-cancer ability in NSCLC through targeting his95 amino acid on *KRAS* p. G12c (150).

However, there are also some combination therapies that did not reach the expected results. For example, the combination of binimetinib (a *MEK* inhibitor), cisplatin, and pemetrexed did not improve anti-tumor activity compared with the chemotherapy of cisplatin and pemetrexed in advanced NSCLC with *KRAS* mutation (151). In a phase II study (*NCT03133546 (first posted: 28 April 2017)*), the combination of osimertinib (an *EGFR* TKI) and bevacizumab (a monoclonal antibody targeting VEGF) did not prolong the PFS in patients with advanced NSCLC with *EGFR and T790M* mutations; instead, the side effects increased (152). However, these trials also provide a guidance for clinical therapy (Table 2).

4.3 Antiangiogenic therapy

The abnormal growth of tumor is always accompanied by angiogenesis to supply nutrition for the cancer (153). Molecular markers such as hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), and VEGF receptor (VEGFR) play an important role in this process, and the most used targets are VEGF and VEGFR in cancer therapy (154). In addition, VEGF in the tumor microenvironment (TME) could inhibit the immune reaction of the immune cells. Therefore, VEGF inhibitors could also increase the capacity of immune cells (155). This reminds us that antiangiogenic therapy could combine with immunotherapy to benefit cancer patients. In clinical therapy, using antiangiogenic strategy usually involves two ways, namely, using the antibody to block the reaction between VEGF and VEGFR and using TKIs to inhibit the VEGFR and corresponding signaling pathways (156).

Bevacizumab (brand names: Avastin, Mvasi, Zirabev, company: GENENTECH, AMGEN INC, PFIZER INC), a monoclonal antibody targeting VEGF, has been approved by FDA and could play a role in the NSCLC treatment. The most widely explored use of bevacizumab is in combination therapy. Bevacizumab could increase the PFS (up for 4.4 months) and median OS compared with chemotherapy, but there is no difference of OS between the two therapies (*NCT00318136 (first posted: 26 April 2006), NCT00806923 (first posted: 11 December 2008)*), and the combination therapy of antiangiogenic therapy plus chemotherapy (bevacizumab plus cisplatin and gemcitabine) could prolong the median OS more than 13 months (157). Bevacizumab and atezolizumab are confirmed to be a potential therapy for the non-squamous NSCLC patients with higher *PD-L1* expression (≥50%) but without *EGFR/ALK/ROS1* mutations, in a phase II study (*NCT03836066 (first posted: 11 February 2019)*) (158). In a phase III trial (*NCT02366143 (first posted: 19 February 2015)*), bevacizumab combined with immunotherapy atezolizumab and chemotherapy (carboplatin and paclitaxel) could act as the first-line treatment in NSCLC patients with *KRAS* and *STK11* mutations and/or *STK11, KEAP1, TP53* mutations and/or high *PD-L1* expression (≥50%) (159), and the PFS of patients was up to 29 months and the OS of patients was prolonged by almost 53 months. Moreover, the biosimilars of bevacizumab, such as FKB238 and LY01008 have also shown the same efficiency and safety in non-squamous NSCLC patients, and the patients' PFS and OS were almost 30 months after taking these drugs. These trials were in the phase III (*NCT02810457 (first posted: 23 June 2016), NCT03533127 (first posted: 22 May 2018)*) (160, 161).

VEGFR includes VEGFR1, VEGFR2, and VEGFR3. Even though VEGFR1 and VEGFR2 correlated with angiogenesis, the affinity between VEGFR1 and VEGF is relatively weak. In addition, VEGFR3 regulates lymphangiogenesis (162, 163). Therefore, the target used in anti-angiogenesis in the clinic is usually VEGFR2. Apatinib, a VEGFR2 TKI, has been confirmed to significantly increase the PFS in advanced NSCLC patients with *EGFR* mutation combined with gefitinib, but the QoL did not change (*NCT02824458 (first posted: 6 July 2016)*) (146). In a phase IB clinical trial (*NCT04670107 (first posted: 17 December 2020)*), anlotinib, a multitarget receptor of TKI, plus PD-1 inhibitor camrelizumab showed some efficiency in advanced NSCLC patients who are resistant to the first-line therapy (164).

4.4 Immunotherapy

Immunotherapy in NSCLC usually uses some antibodies to block the recognize between the antigens in immunocytes and ligands in tumor cells (165). Immune checkpoint inhibitors (ICIs) are usually used in advanced and metastatic NSCLC (166). The most widely used targets in NSCLC include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death receptor 1 (PD-1), and programmed death-ligand 1 (PD-L1) (167).

The corresponding monoclonal antibodies that are well-developed include anti-CTLA-4 antibody (ipilimumab (brand names: Yervoy, company: BRISTOL MYERS SQUIBB)), anti-PD-1 antibodies (pembrolizumab (brand names: Keytruda, company: MERCK SHARP DOHME), and nivolumab (brand names: Opdivo, company: BRISTOL MYERS SQUIBB)), and

TABLE 2 Drugs used in chemotherapy and targeted therapy.

Therapy	Compounds	Application	Phase	NCT number	Improved survival time
Chemotherapy	RO4929097 plus erlotinib	Advanced NSCLC	Phase I, phase II	*NCT01193881NCT01193868*	PFS: 5 years
Chemotherapy	Sulforaphane plus Cisplatin and doxorubicin	NSCLC	Preclinical		
Chemotherapy	AKBA plus cisplatin	NSCLC	Preclinical		
Chemoradiotherapy plus immunotherapy	conventional chemoradiotherapy (platinum-based chemotherapy and radiotherapy) plus durvalumab	Stage III NSCLC	Phase III	*NCT02125461*	PFS: 3 years, OS: 4 years
Targeted therapy	Gefitinib, erlotinib, afatinib, and dacomitinib	NSCLC with *EGFR* mutation (exon 19 deletions, exon 21 substitution mutations)	Approved		mPFS: 10.8 months (gefitinib) (131), mPFS: 10-14 months (erlotinib) (132), PFS: 48 months (afatinib), and mPFS: 14.7 months (dacomitinib) (133)
Targeted therapy	Osimertinib	Metastatic NSCLC with *EGFR* mutation (*T790M* mutation)	Approved		mPFS: 18 months (134)
Targeted therapy	Crizotinib, lorlatinib	*ALK*-positive or *ROS-1*-positive NSCLC	Approved		mPFS: 8.2 months (crizotinib) (135), OS: 114.0 months (lorlatinib) (136)
Targeted therapy	Alectinib, ceritinib	*ALK*-positive metastatic NSCLC	Approved		mPFS: 34.8 months (alectinib) (137), mPFS: 7.8 months (ceritinib) (135)
Targeted therapy	Brigatinib	NSCLC with *ALK-positive, ROS-1-positive, or EGFR* mutation-positive	Approved		PFS: 11.0 months (138)
Targeted therapy	Dabrafenib plus trametinib	*BRAF V600E* Mutant metastatic NSCLC	Phase II	*NCT04452877*	Completion date: 28 December 2023
Targeted therapy	Larotrectinib	metastatic NSCLC harboring an *NTRK* fusion without acquired mutation for resistance	Phase II	*NCT02576431*	Completion date: 29 August 2025
Targeted therapy	Entrectinib	Metastatic *ROS-1*-positive NSCLC	Approved		
Targeted therapy	Entrectinib	NSCLC harboring an *NTRK1/2/3, ROS-1*, or *ALK* gene fusion	Phase II	*NCT02568267*	Completion date: 1 April 2025
Targeted therapy	Crizotinib	*ROS-1* or *MET* mutated NSCLC	Phase II	*NCT04084717*	Completion date: June 2025
Targeted therapy	Pralsetinib, selpercatinib	metastatic *RET* fusion-positive NSCLC	Approved		mPFS: 17.1 months (pralsetinib), mPFS,16.5 months (selpercatinib) (139)
Targeted therapy	Pyrotinib	Advanced NSCLC with *HER2* mutation	Phase II	*NCT02834936*	PFS: 6.9 months, median OS: 14.4 months
Targeted therapy	Tucatinib	*HER2*-expressing NSCLC	Phase II	*NCT05091528*	Completion date: April 2023
Targeted therapy	Trastuzumab	NSCLC	Phase II	*NCT00758134*	No results posted
Targeted therapy	Trastuzumab deruxtecan	*HER2*-mutated metastatic NSCLC	Phase II	*NCT04644237*	Completion date: September 2023
Targeted therapy	Adagrasib	NSCLC harboring the *KRASG12C* mutation	Phase III	*NCT04685135*	Completion date: July 2024
Targeted therapy	Sotorasib	Stage IV NSCLC with *KRAS p.G12C* mutation	Phase II	*NCT04933695*	Completion date: 21 February 2028
Targeted therapy	DPT plus gefitinib	NSCLC	Preclinical		
Targeted therapy plus antiangiogenic therapy	Erlotinib plus bevacizumab	Untreated metastatic *EGFR*-mutated NSCLC	Phase III	*NCT02759614*	No results posted

(Continued)

TABLE 2 Continued

Therapy	Compounds	Application	Phase	NCT number	Improved survival time
Targeted therapy plus antiangiogenic therapy	Gefitinib plus apatinib	Advanced NSCLC with *EGFR* mutation	Phase III	*NCT02824458*	mPFS: 19.2 months
Targeted therapy	Osimertinib plus dacomitinib	Advanced *EGFR* mutant lung cancer	Phase I/II	*NCT03810807*	Completion date: January 2023
Targeted therapy	Osimertinib and navitoclax	*EGFR*-mutated NSCLC	Phase IB	*NCT02520778*	Completion date: 30 July 2022

anti-PD-L1 antibodies (atezolizumab (brand names: Tecentriq, company: GENENTECH INC), durvalumab (brand names: Imfinzi, company: ASTRAZENECA UK LTD), and avelumab (brand names: Bavencio, company: EMD SERONO INC)) (168). Recently, immunotherapy in NSCLC has been further developed and plays an even more important role in NSCLC. The drugs approved by FDA in immunotherapy could improve the survival of patients. For example, ipilimumab could improve the patients' PFS up to 0.84 years, and these are patients normally with PD-L1 overexpression and no *EFGR or ALK* mutation (169). Patients with metastatic NSCLC with high PD-L1 expression (≥50%) and without EGF) or *ALK* mutation could improve mPFS for 10.3 months and median OS for 15.5 months after taking pembrolizumab and atezolizumab (170, 171). Patients with metastatic NSCLC with *EGFR- or ALK-positive* mutation could acquire a better mPFS (4.2 months) and median OS (14.4 months) (172). Avelumab could improve the PFS almost 907 days in patients with PD-L1 positive and after failure of a platinum-based doublet (*NCT02395172 (first posted: 20 March 2015)*). Durvalumab was proved to increase the PFS up to 907 days and OS up to 1,420 days after chemotherapy and radiotherapy failed for patients with unresectable stage III NSCLC in a phase III trial (*NCT02395172 (first posted: 20 March 2015)*). Sugemalimab, an anti-PD-L1 monoclonal antibody, was used in stage IV NSCLC (*NCT03789604 (first posted: 28 December 2018)*) (173). In a phase III trial, sugemalimab had the same OS and better PFS compared with durvalumab (174). Toripalimab, an anti-PD-1 antibody, was reported to play a role in the limited-stage small cell lung cancer, which has no reaction to the current chemotherapy (*NCT04418648 (first posted: 5 June 2020)*). In a phase II study (*NCT04304248 (first posted: 11 March 2020)*), toripalimab combined with platinum-based doublet chemotherapy could produce higher MPR/pCR rates in stage III NSCLC (175).

Other immunotherapies for NSCLC usually takes combination therapy and not limited to the monoclonal antibody alone. The combination therapy including immunotherapy plus chemotherapy (chemo-immunotherapy), immunotherapy plus radiotherapy, chemo-immunotherapy and radiotherapy. In a phase III trial (*NCT02492568 (first posted: 8 July 2015), NCT02444741 (first posted: 14 May 2015)*), pembrolizumab (an anti-PD-1 antibody) with radiotherapy could significantly increase the outcome of metastatic NSCLC patients (176). In a phase III trial (*NCT02477826 (first posted: 23 June 2015)*), nivolumab (an anti-PD-1 antibody) plus ipilimumab has a long-term efficacy in patients who have advanced NSCLC (177), but this combination could not prolong the OS in extensive-disease SCLC patients, in a phase III trial (*NCT02538666 (first posted: 2 September 2015)*) (178). Furthermore, nivolumab plus ipilimumab combined with chemotherapy such as platinum doublet (179) or two cycles of chemotherapy (180) could extend the OS of patients in advanced stages compared with chemotherapy alone. Durvalumab, an anti-PD-L1 antibody, also combined with other monoclonal antibodies, chemotherapy or radiotherapy, has a better outcome compared with durvalumab alone. The most common combination is durvalumab and tremelimumab (an anti-CTLA-4 antibody) plus radiotherapy or chemotherapy. In a phase II study (*NCT03373760 (first posted: 14 December 2017)*), the combination of durvalumab and tremelimumab has some activity in patients with advanced NSCLC with resistance to PD-(L)1 therapy, and the OS of patients was 7 months (181). Durvalumab and tremelimumab plus chemotherapy such as platinum had no marked improvement on the OS of patients with advanced NSCLC (182). Furthermore, durvalumab and/or tremelimumab plus radiotherapy improves the efficacy and tolerance of NSCLC patients who are not suited for chemotherapy (*NCT05000710 (first posted: 11August 2021)*). Therefore, the optimum combination with durvalumab still needs more research to explore. However, current research also provides an option for the patients. Camrelizumab is an investigational PD-L1 inhibitor. The combination therapy involving camrelizumab has also been a research interest. In a phase III trial (*NCT03668496 (first posted: 12 September 2018)*), camrelizumab plus chemotherapy such as carboplatin and paclitaxel could dramatically extend the PFS (9.1 months) and median OS (18.2 months) in patients with advanced NSCLC (183). The same result was also found in another phase III trial (*NCT03134872 (first posted: 1 May 2017)*). The combination of camrelizumab and chemotherapy including carboplatin and pemetrexed could also ameliorate the mPFS (11 months) of NSCLC patients without *EGFR and ALK* mutations (184). More interestingly, in a phase Ib/II study (*NCT03268057 (first posted: 31 August 2017)*), pepinemab that mainly treats Alzheimer's

disease and Huntington's disease in combination with avelumab (an anti-PD-L1 antibody) was proved well-tolerated in NSCLC patients (185). Even though the patients' mPFS was only 8.4 weeks in this trial (Table 3), this clinical study provides a new option for the treatment of NSCLC (Figure 3).

5 Conclusion

Lung cancer is already becoming a worldwide threat to human life. NSCLC is a major type of lung cancer. In this review, we described the causes, biological features, (especially

TABLE 3 Drugs used in antiangiogenic therapy and immunotherapy.

Therapy	Compounds	Application	Phase	NCT number	Improved survival time
Antiangiogenic therapy	Bevacizumab	Unresectable, locally advanced or recurrent non-squamous NSCLC	Approved		PFS: 4.4 months (186)
Antiangiogenic therapy plus chemotherapy	Bevacizumab plus carboplatin and paclitaxel	Unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC	Phase II	*NCT00318136*	No results posted
Antiangiogenic therapy plus chemotherapy	Bevacizumab plus cisplatin and gemcitabine	Locally advanced, metastatic, or recurrent non-squamous NSCLC	Phase III	*NCT00806923*	median OS>13 months
Antiangiogenic therapy plus Immunotherapy	Bevacizumab and atezolizumab	Non-squamous NSCLC patients with higher PD-L1 expression (≥50%) but without *EGFR/ ALK/ROS1* mutations	Phase II	*NCT03836066*	Completion date: 30 January 2024
Antiangiogenic therapy plus immunotherapy and chemotherapy	Bevacizumab combined with atezolizumab and chemotherapy (carboplatin and paclitaxel)	NSCLC patients with *KRAS and STK11* mutations and/or *STK11, KEAP1, TP53* mutations and/or high PD-L1 expression	Phase III	*NCT02366143*	PFS: 29 months, OS: 53 months
Antiangiogenic therapy	FKB238, LY01008	Non-squamous NSCLC	Phase III	*NCT02810457, NCT03533127*	PFS: 30 months, OS: 30 months
Antiangiogenic therapy plus Immunotherapy	Anlotinib plus camrelizumab	Advanced NSCLC patients who are resistant to the first-line therapy	Phase IB	*NCT04670107*	No results posted
Immunotherapy	Ipilimumab	Metastatic NSCLC with PD-L1 overexpression and no *EFGR or ALK* mutation	Approved		PFS: 0.84 years (169)
Immunotherapy	Pembrolizumab, atezolizumab	Metastatic NSCLC with high PD-L1 expression (≥50%) and without EGF) or *ALK* mutation	Approved		mPFS: 10.3 months (170), median OS: 15.5 months (171)
Immunotherapy	Nivolumab	Metastatic NSCLC with *EGFR- or ALK-positive* mutation	Approved		mPFS: 4.2 months, median OS: 14.4 months (172)
Immunotherapy	Durvalumab	Unresectable stage III NSCLC after failed chemotherapy and radiotherapy	Phase III	*NCT02395172*	PFS: 907 days, OS: 1,420 days
Immunotherapy	Avelumab	PD-L1 positive, NSCLC after a failed platinum-based doublet	Phase III	*NCT02395172*	PFS: 907 days
Immunotherapy	Sugemalimab	Stage IV NSCLC	Phase III	*NCT03789604*	Completion date: 31 August 2024
Immunotherapy	Toripalimab	Limit-stage small cell lung cancer that has no reaction to the current chemotherapy	Phase III	*NCT04418648*	Completion date: 31 May 2024
Immunotherapy plus chemotherapy	Toripalimab plus platinum-based doublet chemotherapy	Stage III NSCLC	Phase II	*NCT04304248*	Completion date: 30 July 2026
Immunotherapy plus radiotherapy	Pembrolizumab plus radiotherapy	Metastatic NSCLC patients	Phase III	*NCT02492568, NCT02444741*	Completion date: 17 September 2022
Immunotherapy	Nivolumab plus ipilimumab	Stage IV NSCLC	Phase III	*NCT02477826*	Completion date: 30 August 2024
Immunotherapy	Durvalumab plus tremelimumab	Advanced NSCLC with resistance of PD-(L)1 therapy	Phase II	*NCT03373760*	OS: 7 months
Immunotherapy plus radiotherapy	Durvalumab and/or tremelimumab plus radiotherapy	Metastatic or locally advanced NSCLC	Phase II	*NCT05000710*	Completion date: December 2026
Immunotherapy plus chemotherapy	Camrelizumab plus chemotherapy such as carboplatin and paclitaxel	Stage IV squamous NSCLC	Phase III	*NCT03668496*	PFS: 9.1 months, median OS: 18.2 months
Immunotherapy plus chemotherapy	Camrelizumab and chemotherapy including carboplatin and pemetrexed	NSCLC patients without *EGFR and ALK* mutations	Phase III	*NCT03134872*	mPFS: 11 months
Immunotherapy	Avelumab plus pepinemab	Advanced NSCLC	Phase Ib/ II	*NCT03268057*	mPFS: 8.4 weeks

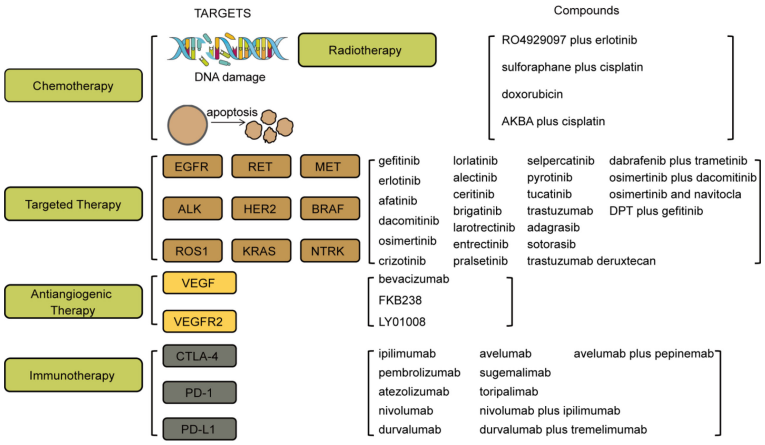

FIGURE 3
Targets and compounds in the treatment of NSCLC. Therapies in use are chemotherapy, targeted therapy, antiangiogenic therapy, and immunotherapy. Targets in chemotherapy include DNA damage and apoptosis. Targets in targeted therapy are EGFR, RET, MET, ALK, HER2, BRAF, ROS1, KRAS, and NTRK. Targets in antiangiogenic therapy are VEGF and VEGFR2. Targets in immunotherapy are CTLA-4, PD-1, and PD-L1. The corresponding drugs or compounds are listed on the right.

the mutations (*EGFR* mutation, *T790M* mutation, *RET rearrangements, MET* mutation, *ALK rearrangement, HER2* mutation, *BRAF* mutation, *ROS1 rearrangement, KRAS* mutation, *NTRK fusions*, and *PD-L1* mutation)), abnormal signaling pathways (MAPK/ERK, Bax/Bcl-2, FAK/AKT, ERK, PI3K/AKT/mTOR, JAK-STAT, RAS/MAPK, MDM2/p53, PTEN/PI3K/mTOR, MAPK/ERK, and NF-κβ signaling pathways), diagnostic methods (such as CT, PET scan, MRI scan, tissue biopsy, liquid biopsy, PCR, FISH, IHC, and NGS), and therapies for lung cancer, such as chemotherapy, chemoradiotherapy, targeted therapy, antiangiogenic therapy, immunotherapy, and some combination therapy. More specifically, we reviewed current drugs used in the clinic, including chemotherapy (RO4929097 plus erlotinib, sulforaphane plus cisplatin and doxorubicin, AKBA plus cisplatin), targeted therapy (gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, crizotinib, lorlatinib, alectinib, ceritinib, brigatinib, dabrafenib plus trametinib, larotrectinib, entrectinib, pralsetinib, selpercatinib, pyrotinib, tucatinib, trastuzumab, trastuzumab deruxtecan, adagrasib, sotorasib, DPT plus gefitinib, osimertinib plus dacomitinib, osimertinib, and navitoclax), antiangiogenic therapy (bevacizumab, FKB238, LY01008), immunotherapy (ipilimumab, pembrolizumab, atezolizumab, nivolumab, durvalumab, avelumab, sugemalimab, toripalimab, nivolumab plus ipilimumab, durvalumab plus tremelimumab, avelumab plus pepinemab), combination therapy, such as chemoradiotherapy plus immunotherapy (conventional chemoradiotherapy (platinum-based chemotherapy add radiotherapy) plus durvalumab, toripalimab plus platinum-based doublet chemotherapy, camrelizumab plus chemotherapy such as carboplatin and paclitaxel, camrelizumab and chemotherapy including carboplatin and pemetrexed), targeted therapy plus antiangiogenic therapy (erlotinib plus bevacizumab, gefitinib plus apatinib), antiangiogenic therapy plus chemotherapy (bevacizumab plus carboplatin and paclitaxel, bevacizumab plus cisplatin and gemcitabine), antiangiogenic therapy plus immunotherapy (bevacizumab and atezolizumab, anlotinib plus camrelizumab), antiangiogenic therapy plus immunotherapy and chemotherapy (bevacizumab combined with atezolizumab and chemotherapy (carboplatin and paclitaxel)), and immunotherapy plus radiotherapy (pembrolizumab plus radiotherapy, durvalumab and/or tremelimumab plus radiotherapy). These diagnostic methods may also undergo further development accompanied by the application of deep learning artificial intelligence (AI) (187). From the drugs used in clinical treatment, we could find that combination therapy and targeted therapy or immunotherapy play an even more important role in the treatment of lung cancer. In addition, with increasing understanding of the pathogenesis of lung cancer and the development of sequencing, the novel targets in lung cancer could be found, and take a role in clinical drug development. Moreover, combination therapy with multi-types of treatment will benefit more patients with lung cancer.

Author contributions

QG, LL, YF, YZ, and ZY reviewed the literature and drafted the article. ZC organized the figures and tables. QG, LL, ZY, and

WZ finalized the paper and provided suggestions for improvement. All authors participated in designing the concept of this manuscript. 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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Adjuvant chemotherapy is not a decisive factor in improving the overall survival of pulmonary sarcoma: A population-based study

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Objective: This study aimed to investigate the impact of adjuvant chemotherapy on overall survival (OS) for pulmonary sarcomatoid carcinoma (PSC) and non-small-cell lung cancer (NSCLC) cohorts and to identify its potential risk factors.

Methods: A retrospective analysis was performed by querying the Surveillance, Epidemiology, and End Results (SEER) database for patients diagnosed as having PSC (n=460) and NSCLC (n=140,467) from 2004 to 2015. The demographics, tumor characteristics, treatment modes, and survival were included in the scope of statistical analysis. Confounding factors were controlled by propensity score matching (PSM) analysis. Kaplan–Meier survival curves were performed to compare the effects of adjuvant chemotherapy on OS of the patients in the two cohorts (PSC *vs*. NSCLC). A multivariable Cox regression model was constructed, and Kaplan–Meier analysis on each variate was applied to predict risk factors associated with OS.

Results: When adjuvant chemotherapy approach was applied in the treatment of patients with PSC or adjusted NSCLC, respectively, an improved OS could be observed in the NSCLC cohort (p=0.017). For the entire PSC cohort, 1-, 3-, and 5-year OS were 25.43%, 13.04%, and 6.96%, respectively, compared with 41.96%, 17.39%, and 10.00%, respectively, for the new adjusted NSCLC cohort after PSM, which were statistically significant difference (p<0.001). Multivariable Cox regression analysis was performed on OS covering prognostic factors such as primary site (p=0.036), first malignant indicator (p<0.001), age at diagnosis (p<0.001), marital status at diagnosis (p=0.039), and high school education (p=0.045). Additionally, patients with the following parameters had the worse impact on OS: a poorly differentiated pathology (Grade III/IV, p=0.023), older age (p<0.001), liver or lung metastasis (p=0.004, p=0.029), and the number of lymph nodes removed <4 (p<0.001).

Conclusions: Adjuvant chemotherapy did not play a decisive role in improving the OS of PSC, while it was associated with improved OS of NSCLC.

KEYWORDS

pulmonary sarcomatoid carcinoma, non-small-cell lung cancer, adjuvant chemotherapy, overall survival, risk factors

Introduction

Pulmonary sarcomatoid carcinoma (PSC) is associated with the characteristics of rarity and more aggressive behavior in all non-small-cell lung cancer (NSCLC) subtypes, which accounts for 0.1%–0.4% of all lung malignancy (1). Compared with other subtypes of NSCLC, the clinical symptoms and classical morphology of PSC are non-specific to distinguish. Current reports on these tumors are mostly limited to the clinical data with small sample size and retrospective analysis extracted from shared databases (2, 3).

Due to the traits of easy invasion and distant metastasis, patients with PSC typically have a poor prognosis even in the early stages of the disease (4). A study using the National Cancer Database (NCDB) reported that PSC is significantly associated with worse survival outcomes compared with conventional NSCLC (5), and the significance of this contrasting survival curve exists across all stages of the disease. The American Cancer Society estimates that the 5-year survival rate of PSC is only 15%–20.1% (6). To date, there are no consensus on guiding PSC patients for standard management strategies. Surgical resection is considered a feasible and effective treatment modality for this rare cancer. However, the benefit of adjuvant chemotherapy pre-/post-operative is still controversial (7–9).

At present, there are few clinical studies on the survival outcomes and prognostic factors for PSC, leading to the treatment regime not fully figured out. We investigated whether adjuvant chemotherapy played a positive role on overall survival (OS) for PSC and NSCLC cohorts. Kaplan–Meier survival curves and multivariable Cox proportional hazard analysis were used to screen for risk factors with an impact on OS. This knowledge will be useful to better understand the progression, prevention, and treatments in PSC disease.

Abbreviations: SEER, the Surveillance, Epidemiology, and End Results; OS, overall survival; PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small cell lung cancer; PSM, propensity score matching.

Methods

Data source

The Surveillance, Epidemiology, and End Results (SEER) database is a large tumor database established by the National Cancer Institute (http://seer.cancer.gov/), which records the incidence, mortality, and prevalence of millions of cancer patients in the United States. The data that we utilized were derived from the SEER database. The dataset includes a detailed patient information such as basic demographic characteristics, survival time, treatment mode, distribution of the lesion, pathological type, and degree of differentiation. The content of this study complies with the relevant provisions of the Declaration of Helsinki, which establishes the ethical principles concerning medical research on human subjects, is a limitation for biomedical research involving people as subjects, and is the second international document on human trials, which is more comprehensive, concrete, and perfect than the Nuremberg Code.

Study population

We extracted lung-cancer-related data from the SEER database for a retrospective analysis study; the detailed screening flowchart is shown in Figure 1. We set the filtering conditions for the cohorts pathologically diagnosed with NSCLC and PSC from 2004 to 2015. NSCLC (squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and others) was chosen as the comparator for PSC (giant-cell carcinoma, small-cell carcinoma, epithelioid carcinoma, undifferentiated carcinoma, and desmoplastic carcinoma), as these tumors are morphologically indistinguishable.

Data elements

Our study aimed to explore the impact of adjuvant chemotherapy on the 1-, 3-, and 5-year survival rates of PSC and NSCLC cohorts and to identify the independent prognostic factors that have an impact on OS, which was defined as the time period from the diagnosis of the disease to the date of death. A complete list of data information on patients are available online. The effect of each covariate on OS was analyzed independently,

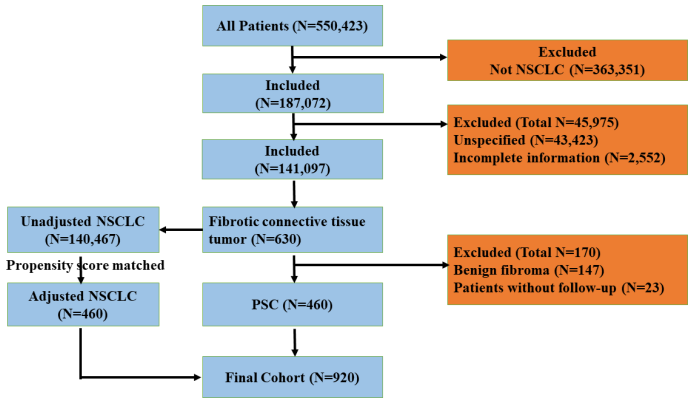

FIGURE 1
The flowchart of exclusion criteria and study design. PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small-cell lung cancer.

including race, sex, age at diagnosis, regional distribution, primary site of lesions, tumor grade, laterality, histopathological subtype, the number of lymph nodes surgical removed, radiation, chemotherapy, bone/brain/liver/lung metastasis, first malignant indicator, insurance status, marital status, high school education, and median household income.

Statistical analysis

All the data in this study were analyzed by using IBM SPSS 25.0 version (IBM Corp, Armonk, NY, USA). The chi-square test was applied for the analysis of categorical variables. In the univariate analysis, a non-parametric test was used to detect the effect of each variable on OS. A multivariable Cox proportional hazards regression model was constructed to further determine the independent predictors of survival. The method of log-rank test was used for the comparison of the survival curves. Kaplan–Meier survival curves were created to compare survival time of the subtypes, which include grade, age at diagnosis, liver metastasis, lung metastasis, and lymph nodes removed. The means of propensity score matching (PSM) was applied to bridge the differences when comparing the survival time between PSC and NSCLC cohorts and to estimate the effect of chemotherapy on these two cohorts. Two-tailed p-values of <0.05 were considered statistically significant.

Results

Baseline cohort characteristics

A total of 460 patients in the PSC study group were compared with 140,467 NSCLC patients enrolled in the statistical analysis during the same study period. All patients' data were extracted from the SEER database. PSC patients, of which 83.0% were white and 63.0% were male, were compared with NSCLC patients, of which 82.3% were white and 60.3% were male, and the proportions of race and gender did not differ between the two cohorts (p=0.421; p=0.233). Notably, a greater fraction of tumors in the PSC and NSCLC cohorts were located in the upper lobe of the lungs. Meanwhile, the proportion of lesions in the upper lung lobe in the PSC cohort was less than that in the NSCLC cohort (p<0.001). Furthermore, patients diagnosed with PSC were more inclined to be younger than 45 years, live in the northwest region, have a poorly differentiated or undifferentiated lesion (Grade III/IV), have laterality to the left, have 0–3 lymph nodes removed, have less selection of radiation and chemotherapy, and have higher levels of median household income compared with the NSCLC cohort of patients. Other demographic variables such as the year of diagnosis, insurance, and marital status of patients showed no statistically significant differences between the two groups. All the data are summarized in Table 1.

A univariate survival analysis in PSC cohort

We identified each covariate such as primary site (χ^2 = 16.648, p=0.023), radiation (χ^2 = 11.366, p=0.01), chemotherapy (χ^2 = 24.171, p<0.001), bone metastasis (χ^2 = 6.202, p=0.045), liver metastasis (χ^2 = 6.202, p=0.045), lung metastasis (χ^2 = 9.314, p=0.009), first malignant indicator (χ^2 = 8.504, p=0.004), age at diagnosis (χ^2 = 28.230, p<0.001), and marital status at diagnosis (χ^2 = 10.773, p=0.005) and were shown to be significantly associated with OS by adopting the method of non-parametric test analysis, while race (χ^2 = 1.186, p=0.553), sex (χ^2 = 0.734, p=0.392), region (χ^2 = 1.015, p=0.798), grade (χ^2 = 8.444, p=0.077), laterality (χ^2 = 4.025, p=0.259),

TABLE 1 Baseline cohort characteristics.

Basic characteristics	PSC (n = 460, %)	NSCLC (n = 140,467, %)	χ^2	p
Race			1.728	0.421
White	382 (83.1)	115,615 (82.3)		
Black	48 (10.4)	16,966 (12.1)		
Others	30 (6.5)	7,886 (5.6)		
Sex			1.448	0.233
Male	290 (63.0)	84,693 (60.3)		
Female	170 (37.0)	55,774 (39.7)		
Age (year)			118.002	**<0.001**
<45	34 (7.4)	2,126 (1.5)		
≥45, <55	40 (8.7)	9,801 (7.0)		
≥55, <65	90 (19.6)	29,853 (21.3)		
≥65, <75	119 (25.9)	49,078 (34.9)		
≥75	177 (38.5)	49,608 (35.3)		
Year of diagnosis			1.262	0.532
2004–2007	159 (34.6)	45,356 (32.3)		
2008–2011	154 (33.5)	47,488 (33.8)		
2012–2015	147 (32.0)	47,622 (33.9)		
Region			29.350	**<0.001**
East	173 (37.6)	67,316 (47.9)		
North	43 (9.3)	15,980 (11.4)		
Southwest	15 (3.3)	4,006 (2.9)		
Northwest	229 (49.8)	53,164 (37.8)		
Primary site			73.78	**<0.001**
Upper lobe	190 (41.3)	71,481 (50.9)		
Middle lobe	19 (4.1)	5,308 (3.8)		
Lower lobe	125 (27.2)	40,101 (28.5)		
NOS	95 (20.7)	13,617 (9.7)		
Overlapping lesion	12 (2.6)	1,954 (1.4)		
Main bronchus	17 (3.7)	7,693 (5.5)		
Trachea	2 (0.4)	312 (0.2)		
Grade			1,560.434	**<0.001**
Grade I	8 (1.7)	7,429 (5.3)		
Grade II	15 (3.3)	33,911 (24.1)		
Grade III	106 (23.0)	42,419 (30.2)		
Grade IV	147 (32.0)	3,669 (2.6)		
Unknown	184 (40.0)	53,038 (37.8)		
Laterality			11.498	**0.009**
Right	228 (49.6)	77,507 (55.2)		
Left	207 (45.0)	57,997 (41.3)		
Bilateral	11 (2.4)	1,573 (1.1)		
Others	14 (3.0)	3,389 (2.4)		
Lymph nodes removed			27.893	**<0.001**
0–3 lymph nodes removed	367 (79.8)	103,359 (73.6)		
≥4 lymph nodes removed	64 (13.9)	27,174 (19.3)		
Regional biopsy or aspiration	7 (1.5)	6,371 (4.5)		
Sentinel lymph nodes biopsy	2 (0.4)	260 (0.2)		
Others	20 (4.3)	3,302 (2.4)		
Radiation			235.141	**<0.001**

(Continued)

TABLE 1 Continued

Basic characteristics	PSC (n = 460, %)	NSCLC (n = 140,467, %)	χ^2	p
Beam radiation	120 (26.1)	84,385 (60.1)		
Rad not specified	3 (0.7)	709 (0.5)		
Unknown	333 (72.4)	53,113 (37.8)		
Refused	4 (0.9)	1,837 (1.3)		
Beam with plants or isotopes	0 (0.0)	1,91 (0.1)		
Implants or isotopes	0 (0.0)	231 (0.2)		
Chemotherapy			43.545	**<0.001**
No	325 (70.7)	77,724 (55.3)		
Yes	135 (29.3)	62,742 (44.7)		
First malignant indicator			18.485	**<0.001**
No	147 (32.0)	32,934 (23.4)		
Yes	313 (68.0)	107,532 (76.6)		
Insurance status			3.263	0.353
Medicaid	43 (9.3)	14,432 (10.3)		
Insured or no specifics	273 (59.3)	87,231 (62.1)		
Uninsured	9 (2.0)	2,632 (1.9)		
Blanks or unknown	135 (29.3)	36,171 (25.8)		
Marital status			4.663	0.097
Married or domestic partner	256 (55.7)	72,121 (51.3)		
Divorced or separated or single or windowed	182 (39.6)	62,543 (44.5)		
Unknown=3	22 (4.8)	5,802 (4.1)		
High school education (Score)			11.390	**0.01**
≤1,000	78 (17.0)	28,284 (20.1)		
1,000–2,000	239 (52.0)	72,424 (51.6)		
2,000–3,000	137 (29.8)	35,283 (25.1)		
>3,000	6 (1.3)	4,475 (3.2)		
Median household income ($/month)			11.729	**0.008**
≤5,000	43 (9.3)	18,426 (13.1)		
>5,000, ≤7,000	222 (48.3)	68,110 (48.5)		
>7,000, ≤9,000	147 (32.0)	36,887 (26.3)		
>9,000	48 (10.4)	17,043 (12.1)		

PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small-cell lung cancer.
A p-value of <0.05 represents a significant statistical difference.
Bold indicate p values < 0.05 are statistically significant.

histological type (χ^2 = 5.141, p=0.526), brain metastasis (χ^2 = 4.256, p=0.119), insurance state (χ^2 = 5.193, p=0.158), high school education (χ^2 = 6.778, p=0.079), and median family income (χ^2 = 4.319, p=0.229) were not significantly associated with OS in PSC cohort (as summarized in Supplementary Table S1).

A total of 11 factors comprising primary site, grade, radiation, chemotherapy, bone/liver/lung metastasis, first malignant indicator, age at diagnosis, marital status, and high school education were screened out in utilizing univariate survival analysis (p<0.1). Next, a multivariable Cox regression analysis model was constructed to further evaluate the independent risk factors on OS.

Multivariable Cox proportional hazards analysis of OS in PSC cohort

Within the multivariable Cox proportional hazards analysis, important prognostic factors for OS constitute of primary site (p=0.036), first malignant indicator (p<0.001), age at diagnosis (p<0.001), marital status at diagnosis (p=0.039), and high school education (p=0.045). The predictors of OS by Cox regression analysis did not include grade (p=0.061), radiation (p=0.507), chemotherapy (p=0.260), bone metastasis (p=0.255), liver metastasis (p=0.091), and lung metastasis (p=0.309). Several covariates such as age, marital status, and high school education were further stratified for survival analysis; patients

over 55 years old remained independently associated with lower OS compared with younger patients (HR of 1.725, 95% CI 1.040–2.861, p=0.035 for age ≥55; HR of 2.233, 95% CI 1.376–3.624, p=0.001 for age ≥65; HR of 3.053, 95% CI 1.889–4.936, p<0.001 for age ≥75). Being divorced, separated, singled, or windowed was independently associated with lower OS compared with being married or having a domestic partner (HR, 1.337; 95% CI, 1.069–1.672, p=0.011). Patients who received higher school education were more likely to have PSC compared with those who received lower school education (HR, 1.605; 95% CI, 1.151–2.238, p=0.005) (as summarized in Table 2).

TABLE 2 Multivariable Cox proportional hazards analysis of OS in PSC cohort.

Covariate	HR	95% CI	p
Primary site			**0.036**
Upper lobe	Reference		
Middle lobe	1.227	0.721 – 2.089	0.452
Lower lobe	0.967	0.745 – 1.256	0.803
NOS	1.539	1.158 – 2.044	0.003
Overlapping lesion	1.186	0.606 – 2.320	0.618
Main bronchus	0.751	0.408 – 1.384	0.359
Trachea	0.654	0.085 – 5.015	0.683
Grade			0.061
Grade I	Reference		
Grade II	1.421	0.431 – 4.682	0.564
Grade III	2.746	0.988 – 7.629	0.053
Grade IV	2.523	0.916 – 6.952	0.073
Unknow	2.104	0.765 – 5.784	0.149
Radiation			0.507
Beam radiation	Reference		
Not specified	0.352	0.085 – 1.455	0.149
Unknown	0.961	0.722 – 1.279	0.784
Refused	0.716	0.214 – 2.395	0.587
Chemotherapy			0.260
No	Reference		
Yes	0.869	0.680 – 1.110	0.260
Bone metastasis			0.255
No	Reference		
Yes	1.527	0.905 – 2.575	0.113
Others	1.395	0.474 – 4.109	0.546
Liver metastasis			0.091
No	Reference		
Yes	2.129	1.018 – 4.454	**0.045**
Others	0.535	0.127 – 2.248	0.393
Lung metastasis			0.309
No	Reference		
Yes	1.407	0.906 – 2.187	0.129
Others	1.375	0.337 – 5.603	0.657
First malignant indicator			**<0.001**
No	Reference		
Yes	1.543	1.219 – 1.952	**<0.001**
Age at diagnosis(year)			**<0.001**
<45	Reference		

(Continued)

TABLE 2 Continued

Covariate	HR	95% CI	p
≥45, <55	1.748	0.984 – 3.106	0.057
≥55, <65	1.725	1.040 – 2.861	**0.035**
≥65, <75	2.233	1.376 – 3.624	**0.001**
≥75	3.053	1.889 – 4.936	**<0.001**
Marital status			**0.039**
Married or domestic partner	Reference		
Divorced or separated or single or windowed	1.337	1.069 – 1.672	**0.011**
Unknown	1.140	0.673 – 1.930	0.626
High school education (score)			**0.045**
≤1,000	Reference		
1,000 – 2,000	1.379	1.015 – 1.872	**0.040**
2,000 – 3,000	1.605	1.151 – 2.238	**0.005**
>3,000	1.076	0.418 – 2.768	0.879

PSC, pulmonary sarcomatoid carcinoma; OS, overall survival; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.
A p-value <0.05 represents a significant statistical difference.
Bold indicate p values < 0.05 are statistically significant.

Kaplan–Meier analysis of survival curves between the PSC and NSCLC cohorts

Patients with a well or moderately differentiated PSC (Grade I/II) had better OS compared with those with a poorly differentiated or undifferentiated lesion (Grade III/IV) (p=0.023, as shown in Figure 2A). Among patients of different age stages, younger subjects clearly have a longer OS compared with older individuals (p<0.001, as shown in Figure 2B). Patients with liver or lung metastasis were closely associated with inferior OS compared with those without metastasis (p=0.004, p=0.029, respectively, as shown in Figure 3). Patients with four or more lymph nodes removed have improved OS compared with those managed with zero to three lymph nodes removed (p<0.001, as shown in Figure 4).

For the entire cohort in PSC, 1-, 3-, and 5-year OS were 25.43%, 13.04%, and 6.96%, respectively; when calculated according to differentiated grades, OS were 47.83%, 3.91%, and 4.35% for grade I/II, respectively, and 20.55%, 9.49%, and 6.72% for grade III/IV, respectively. The 3- and 5-year OS in grade III/IV were significantly higher than that in grade I/II (p=0.006). For

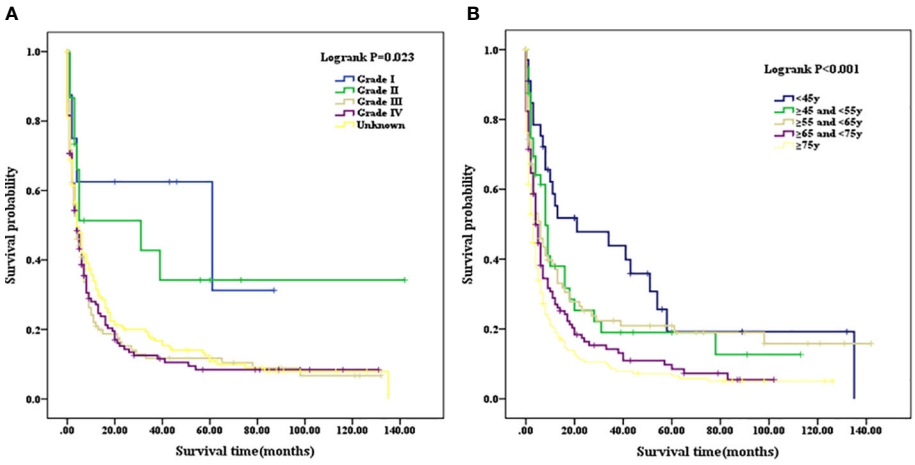

FIGURE 2
(A) Kaplan–Meier analysis of survival curves stratified by grade in PSC cohort. **(B)** Kaplan–Meier analysis of survival curves stratified by age stages in PSC cohort. PSC, pulmonary sarcomatoid carcinoma.

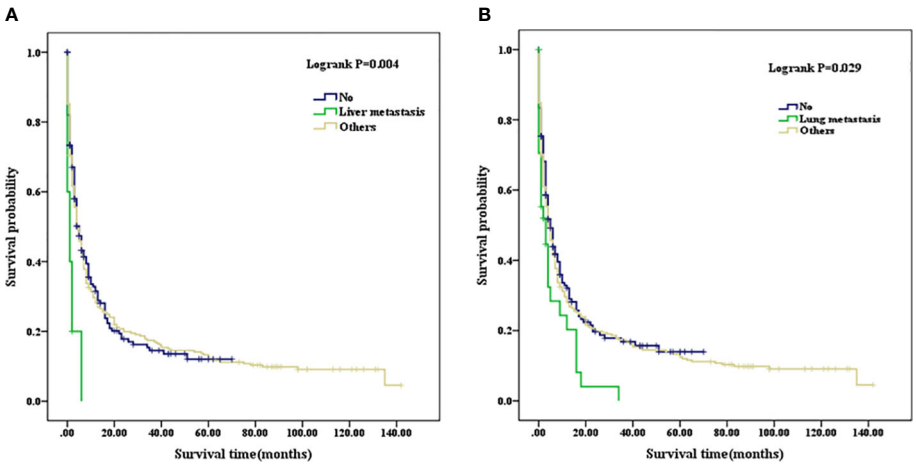

FIGURE 3
(A) Kaplan–Meier analysis of survival curves stratified by liver metastasis in PSC cohort. **(B)** Kaplan–Meier analysis of survival curves stratified by lung metastasis in PSC cohort. PSC, pulmonary sarcomatoid carcinoma.

the entire cohort in unadjusted NSCLC, 1-, 3-, and 5-year OS were 40.70%, 16.38%, and 8.66% respectively, which were significantly higher than that in the PSC cohort (p<0.001). A new NSCLC cohort was created after PSM with PSC cohort. We calculated that the 1-, 3-, and 5-year OS were 41.96%, 17.39%, and 10.00%, respectively, for the new adjusted NSCLC cohort, which were also significantly higher than the PSC cohort (p<0.001) (as summarized in Table 3).

Comparison of median survival time and adjuvant chemotherapy between the PSC and NSCLC cohorts

The mean OS of PSC was 21.549 months (95% CI, 17.536–25.562), and the median OS of the patients was 4 months (95% CI, 3.034–4.966). The mean OS of unadjusted NSCLC was 28.599 months (95% CI, 28.353–28.844), and the median OS was 10

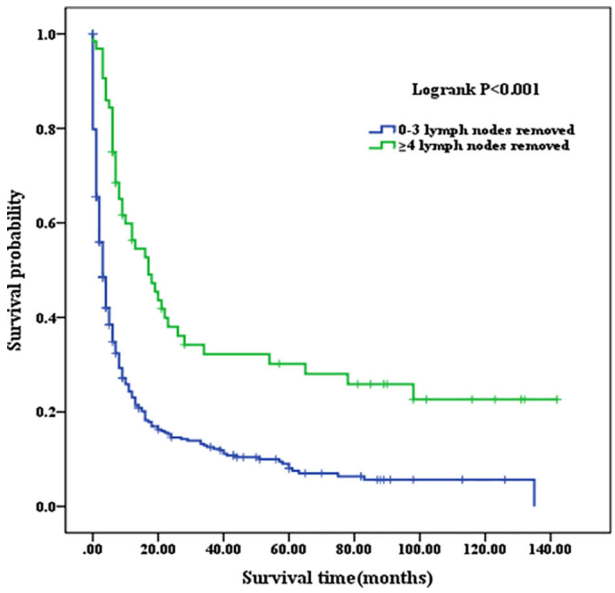

FIGURE 4
Kaplan–Meier analysis of survival curves stratified by the number of lymph node removed in PSC cohort. PSC, pulmonary sarcomatoid carcinoma.

TABLE 3 Comparison of 1, 3, and 5-year OS between the PSC and NSCLC cohorts.

PLS	1-year OS (n/N, %)	3-year OS (n/N, %)	5-year OS (n/N, %)	p
Overall	117/460 (25.43)	60/460 (13.04)	32/460 (6.96)	**0.006**
Grade I/II	11/23 (47.83)	9/23 (3.91)	1/23 (4.35)	
Grade III/IV	52/253 (20.55)	24/253 (9.49)	17/253 (6.72)	
Unknown	54/184 (29.35)	27/184 (14.67)	14/184 (7.61)	
Unadjusted NSCLC	57,172/140,467 (40.70)	23,010/140,467 (16.38)	12,160/140,467 (8.66)	**<0.001**
Adjusted NSCLC	193/460 (41.96)	80/460 (17.39)	46/460 (10)	**<0.001**

PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small-cell lung cancer; OS, overall survival.
A p-value of <0.05 represents a significant statistical difference.
Bold indicate p values < 0.05 are statistically significant.

months (95% CI, 9.888–10.112). The mean OS of adjusted NSCLC was 29.913 months (95% CI, 25.668–34.159), and the median OS was 11 months (95% CI, 8.698–13.302) (as summarized in Table 4). OS in unadjusted NSCLC was significantly higher than that in PSC patients (p<0.001); the same comparable trends were also presented after the NSCLC cohort was adjusted (p<0.001). Survival curves are shown in Figure 5.

The mean OS of the patients who did not receive chemotherapy in the PSC cohort was 21.990 months (95% CI, 16.982–27.000), and the median OS was 3 months (95% CI, 2.298–3.702) compared with the patients who received chemotherapy, whose mean OS was 19.921 months (95% CI, 13.918–25.924) and median OS was 8 months (95% CI, 6.805–9.195). In the adjusted NSCLC cohort, the mean OS was 27.886 months (95% CI, 22.343–33.428), and the median OS was 7 months (95% CI, 4.929–9.071) for the patients who did not receive chemotherapy compared with the patients who received chemotherapy whose mean OS was 30.793 months (95% CI, 24.974–36.612) and median OS was 15 months (95% CI, 12.329–17.671) (as summarized in Table 5). When chemotherapy was applied in the treatment of patients with PSC, there was no improved OS compared with those who did not receive chemotherapy (p=0.03, Figure 6A). We considered that the main reason for this phenomenon was that the proportion of patients with well- and moderately differentiated pathological types was low, and chemotherapy can have a better positive therapeutic effect for the above pathological types, while it may have a negative effect on poorly differentiated or undifferentiated pathological types. As a comparison cohort, when chemotherapy was applied in the treatment of patients with adjusted NSCLC, there was statistically significant improvement on OS compared with those patients who did not receive chemotherapy (p=0.017, Figure 6B).

Discussion

We exploited the SEER database to systematically study the impact of clinicopathological characteristics and treatment modalities on the OS of 460 patients with PSC, and a multivariable Cox regression model was constructed to further explore the risk factors for OS. Our results demonstrated that patients with PSC are associated with a higher incidence in younger patients (<45 years), are more likely to live in the northwest, and have a poorly differentiated or undifferentiated lesion compared with the NSCLC cohort of patients. In order to reduce the statistical differences of survival time between the PSC and NSCLC cohorts, an analysis of PSM was performed. A poorer prognosis of patients with PSC was clearly shown compared with that of their NSCLC counterparts by using a well-matched group. Another study (10) also proved a similar outcome in patients with PSC when compared with other NSCLC patients.

Multivariate Cox regression was performed to further analyze risk factors associated with OS. Variables, including primary site, first malignant indicator, age at diagnosis, marital status, and high school education, were independent predictors for OS in patients with PSC. As an independent risk factor, the influence of age at diagnosis on OS has been investigated in previous research (11). Studies have reported that patients with advanced age may have a high likelihood of poor prognosis and

TABLE 4 Comparison of mean and median survival time between the PSC and NSCLC cohorts.

Groups	Mean OS (months)	95%CI	Median OS (months)	95%CI
PLS	21.549	17.536 – 25.562	4.0	3.034 – 4.966
Unadjusted NSCLC	28.599	28.353 – 28.844	10.0	9.888 – 10.112
adjusted NSCLC	29.913	25.668 – 34.159	11.0	8.698 – 13.302

PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small cell lung cancer; OS, overall survival; CI, confidence interval.

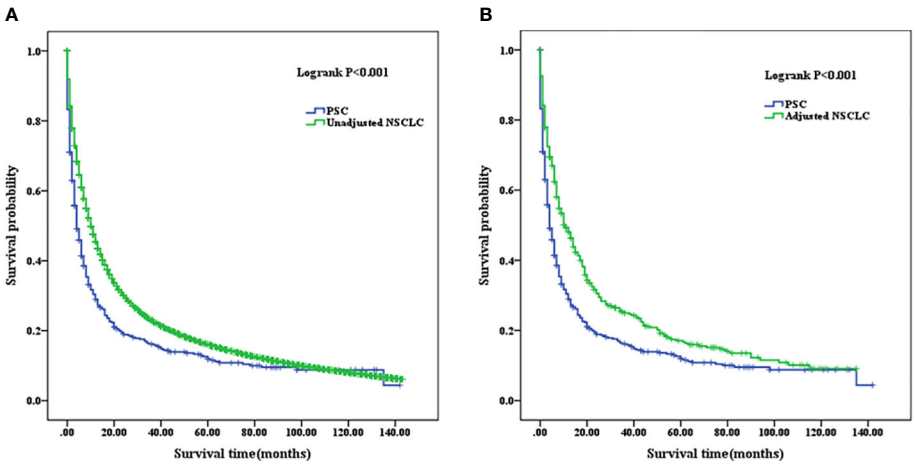

FIGURE 5
(A) Comparison of Kaplan–Meier analysis of survival curves between PSC and unadjusted NSCLC cohorts. **(B)** Comparison of Kaplan–Meier analysis of survival curves between PSC and adjusted NSCLC cohorts. PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small-cell lung cancer.

increased risk of mortality (12, 13). In our research, age beyond 55 years old was also demonstrated to act as an independent risk factor for OS. Histologically identified lung cancer in younger patients typically shows advanced tumor stages, with more symptoms (14, 15). A recent SEER database examined the effect of age on lung cancer patients, with better overall and cancer-specific survival in younger patients than in the older cohort even though under the condition of presenting with stage IV disease (16). Some community-based and national registries analyze the OS of miscellaneous bronchogenic carcinoma to form the view of improved outcomes in younger cohorts (17, 18). The odds of developing comorbidities achieved a substantial accumulation with increasing age. It has been reported that comorbidity is also an independent predictor affecting patient mortality, which has a direct or indirect impact on OS (19, 20).

At present, surgery seems to be an appropriate choice for PSC treatment (21, 22). Such tumors are often characterized by slow growth and presented at advanced stages when discovered. Endobronchial tumors have a better prognosis compared with peripheral tumors, which are more prone to metastasis and invasion to neighboring tissue structures and the vasculature. After surgery, 1-, 3-, and 5-year survival rates for PSC have been reported in some studies to be worse than those for NSCLC (10, 23, 24). The conclusion is supported in our study as evidenced by the significantly lower 1-, 3-, and 5-year OS compared with those of the NSCLC patients. The number of lymph nodes removed, as an important contributor, has been consistently reported to be associated with prognosis of PSC patients (25–27). The OS of PSC patients with four or more lymph nodes removed was significantly higher compared with that of PSC patients with less than four lymph nodes removed in our analysis. Of course, the location of the lymph node was a prognostic factor for overall survival in lung cancer (28). However, it is a pity that SEER database does not record the details about the station of lymph nodes but instead records the number. Considering the practical application value of this issue, we plan to further analyze the association of the location of the lymph nodes with survival time in PSC in future clinical data acquisition.

TABLE 5 Comparison of mean and median survival time after adjuvant chemotherapy between the PSC and NSCLC cohorts.

Groups	Chemotherapy	Mean OS (months)	95%CI	Median OS (months)	95%CI
PLS	No	21.990	16.982 – 27.000	3	2.298 – 3.702
	Yes	19.921	13.918 – 25.924	8	6.805 – 9.195
	Overall	21.549	17.536 – 25.562	4	3.034 – 4.966
Adjusted NSCLC	No	27.886	22.343 – 33.428	7	4.929 – 9.071
	Yes	30.793	24.974 – 36.612	15	12.329 – 17.671
	Overall	29.913	25.668 – 34.159	11	8.698 – 13.302

PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small cell lung cancer; OS, overall survival; CI, confidence interval.

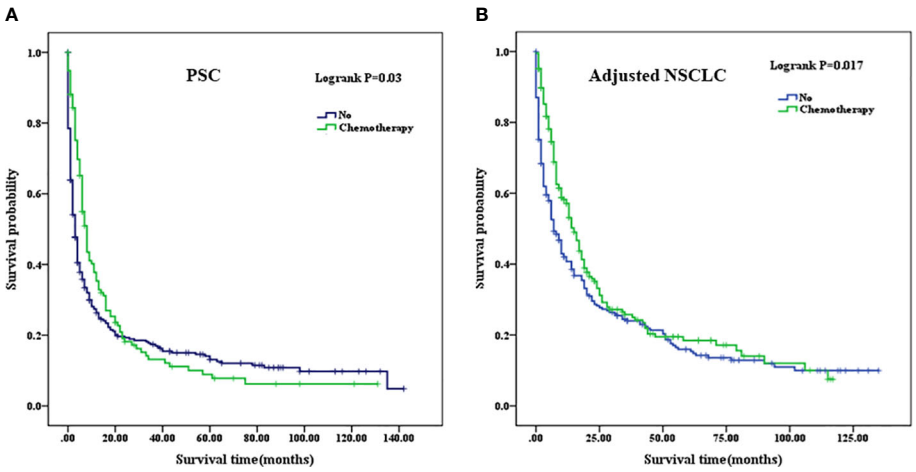

FIGURE 6
(A) Comparison of Kaplan–Meier analysis of survival curves after adjuvant chemotherapy in PSC cohort. **(B)** Comparison of Kaplan–Meier analysis of survival curves after adjuvant chemotherapy in adjusted NSCLC cohort. PSC, pulmonary sarcomatoid carcinoma; NSCLC, non-small-cell lung cancer.

Another interesting point of comparison refers to adjuvant chemotherapy being associated with improved OS for NSCLC but not for PSC in the SEER database. One of the main reasons for this phenomenon is that PSC presented with poorly differentiated pathological morphology. These rare, histologically highly malignant tumors have been described to be associated with poor prognosis in relevant literature reports (29, 30). Among many previous studies, numerous papers have verified that adjuvant chemotherapy did not play a positive role in prolonging the OS in the course of the intervention of treatment for PSC (31–33). Nonetheless, a small fraction of studies has shown that some survival benefits could be obtained from adjuvant chemotherapy, which leads to blurred boundaries in physicians' decision-making regarding whether to take chemotherapy.

Not surprisingly, adjuvant chemotherapy offered different survival benefits in patients with PSC at different stages. When patients with a higher stage disease (stage II and III), the therapeutic effect was particularly pronounced and the OS will be extended after receiving adjuvant chemotherapy compared with the lower stage (stage I). The future directions of pharmacological treatment for PSC might have tendencies toward targeted therapy or immunotherapy (34–36). Undoubtedly, developing a more rational and specific regime plan for each patient instead of general treatment will improve OS of PSC patients (37, 38).

It is also important to consider the potential limitations that affect the analysis of the results in our study. First, a small sample size and the possibility of data bias in this retrospective analysis are difficult to exclude. The finding that PSC patients are more likely to receive a higher degree of school education background and higher levels of salary treatment than NSCLC patients may allude to a referral bias. In addition, the SEER database did not capture the pathological stage for PSC, and therefore, an effective program of staging analysis was not available for all patients. Finally, the specific details on various treatment modalities including chemotherapy regimens were not recorded in SEER database, which comprises the contents of chemotherapeutic drugs, the agents used, biological half-life, toxicity, target genes for the treatment, and the course of taking medication, may impact the final results analysis.

Conclusions

In conclusion, adjuvant chemotherapy is not an appropriate treatment option for patients with PSC but is certainly effective in patients with NSCLC. Age at diagnosis, an independent risk factor, must be used as an important consideration to weigh whether a chemotherapy regimen should be performed and the dose of chemotherapy drugs. This study also predicted other risk factors affecting OS by building a multivariate regression model, which provides us useful information on prevention and treatment strategies for PSC patients.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contribution

Conception and design: LL, ZL, SX, and CW. Acquisition, statistical analysis, or interpretation of the data: all authors. Drafting of the manuscript: LL, ZL, SX, and CW. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.940839/full#supplementary-material

SUPPLEMENTARY TABLE 1
Univariate survival analysis using a non-parametric test on each covariate in PSC cohort. PSC, pulmonary sarcomatoid carcinoma; A p-value of less than 0.05 represents a significant statistical difference.

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Cost-effectiveness analysis of adjuvant therapy with atezolizumab in Chinese patients with stage IB-IIIA resectable NSCLC after adjuvant chemotherapy

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Background: Atezolizumab was first shown to significantly improve progression-free survival (PFS) after platinum-based chemotherapy in early-stage non-small cell lung cancer (NSCLC) in the IMpower010 Phase 3 trial. However, the cost-effectiveness and potential economic impact of atezolizumab treatment in Chinese patients are unknown.

Methods: Markov models were constructed based on follow-up data from the IMpower010 trial and assessed separately in the programmed cell death receptor ligand-1 (PD-L1) tumor cells (TC) ≥ 1% stage II – IIIA group, all stage II – IIIA groups, and the intention-to-treat (ITT) group (stage IB–IIIA). Efficacy and safety data were obtained from the IMpower010 trial, and costs and utility values were derived from the literature and local surveys to estimate their incremental cost-effectiveness ratios (ICERs) compared with willingness-to-pay (WTP) thresholds in scenarios implementing patient assistance programs (PAP) or drug price negotiations. Univariate sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed to investigate the stability of the model results.

Results: Compared with best supportive care (BSC), atezolizumab produced an additional 0.45 quality-adjusted life-years (QALYs), 0.04 QALYs, and -0.0028 QALYs in the PD-L1 TC ≥ 1% stage II – IIIA group, all stage II – IIIA groups, and the ITT group, and the ICERs were 108,825.37/QALY, 1,028,538.22/QALY, and -14,381,171.55/QALY, respectively. The ICERs all exceeded the WTP threshold of $27,354 per QALY (three times the per capita gross domestic product of China in 2022), and univariate sensitivity analysis showed that the price of atezolizumab played a crucial role in the model results. PSA showed that the probability of cost-effectiveness of atezolizumab in the PD-L1 TC ≥ 1% stage II – IIIA group, all

stage II – IIIA groups, and the ITT group increased with the increasing WTP threshold.

Conclusion: From the perspective of China's health care system, in the PD-L1 TC ≥ 1% stage II – IIIA group, all stage II – IIIA groups, and the ITT group, the use of atezolizumab in the adjuvant treatment of patients with early-stage NSCLC after platinum-based chemotherapy is unlikely to be cost-effective. The implementation of PAP or price reduction negotiations for atezolizumab might be among the most effective measures to improve its cost-effectiveness.

KEYWORDS

atezolizumab, non-small-cell lung cancer, cost-effectiveness, adjuvant therapy, China

Introduction

Lung cancer is the most common type of cancer and a leading cause of cancer death worldwide (1, 2). In China, the incidence and mortality of lung cancer have ranked first (3). In 2015, the medical costs of treating lung cancer in China accounted for approximately 0.6% of total health costs (4), and approximately 85% of lung cancers are non-small-cell lung cancer (NSCLC), mostly at an advanced stage at the time of diagnosis, with a 5-year survival rate less than 18% (5–7). As early as 15 years ago, platinum-based adjuvant chemotherapy changed the standard treatment for completely resected early-stage NSCLC (stage IB-IIIA) (8– 9–11). In recent years, with the development of immune checkpoint inhibitors (ICIs), immunotherapy has been increasingly used in clinical practice, and the reactivation of T-cell antitumor function has been demonstrated by inhibiting the programmed cell death-1 (PD-1) and programmed cell death receptor ligand-1 (PD-L1) pathways (12–15). Due to the good clinical efficacy and safety of immunotherapy in preventing postoperative recurrence and metastasis, increasing the effect in combination with chemoradiotherapy, and maintaining treatment in lung cancer, the treatment mode for patients with early, non-metastatic NSCLC has been changed (16–23)

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1, which binds to PD-L1 and allows PD-1 to bind to other ligands (PD-L2) – a process important in preventing severe adverse immunity events (such as pneumonia) are important (24). In 2020, the State Food and Drug Administration of China officially approved atezolizumab combined with chemotherapy as a first-line treatment for extensive-stage small cell lung cancer (25), and in 2022, it officially approved atezolizumab for the detection of adjuvant therapy in patients with stage II-IIIA NSCLC who are assessed to have ≥ 1% tumor cells (TC) positive PD-L1 staining, after surgical resection, and platinum-based chemotherapy. This is the first and only drug approved for post-operative adjuvant immunotherapy of NSCLC in China. However, there are few relevant studies on the efficacy and prognosis of atezolizumab in NSCLC in China. The prognosis analysis of patients with NSCLC treated with atezolizumab combined with chemotherapy found that the response rate of intervention was higher than that of the control group, and the difference had statistical significance (P< 0.05). There was no significant difference in the incidence rate of adverse reactions between the intervention group and the control group (P > 0.05). After treatment, the Karnofsky performance status (KPS) and quality of life (FACT-L) scores in the intervention group were higher than those in the control group, and the differences had statistical significance (P< 0.05). Atezolizumab combined with chemotherapy in the treatment of NSCLC has a significant effect, less adverse reactions, and can effectively improve the quality of life of patients (26). The IMpower010 Phase III study showed that treatment with atezolizumab improved disease-free survival compared with best supportive care (BSC) in stage II-IIIA patients with tumor cell expression (PD-L1) of 1% or more (HR 0.66; 95% CI 0.50-0.88; p = 0.0039) and improved PFS in all stage II-IIIA patients compared with BSC (0.79; 0.64–0.96; p = 0.020), with an HR for disease-free survival of 0.81 (0.67-0.99; p = 0.040) in the intention-to-treat (ITT) group. Fifty-three of 495 patients (11%) had grade 3 and 4 adverse events related to atezolizumab, and 4 patients (1%) had grade 5 adverse events (27).

Abbreviations: NSCLC, Non-small cell lung cancer; PFS, Progression-free survival; PD-L1, Programmed cell death receptor ligand-1; ITT, Intention-to-treat; ICER, Incremental cost-effectiveness ratio; WTP, Willingness to pay; PAP, Patient assistance programs; BSC, Best supportive care; QALYs, Quality-adjusted life years; LYs, Life years; ICIs, Immune checkpoint inhibitors; Tc, Tumor cells; KPS, Karnofsky performance status; IPD, Individual patient data; AIC, Akaike information criterion; SAEs, Severe adverse events; CEAC, Cost-effectiveness acceptability curve; GDP, Gross domestic product; PSA, Probabilistic sensitivity analysis.

Although atezolizumab has been shown to be effective in the patient group after adjuvant chemotherapy for stage IB-IIIA resectable NSCLC, the cost-effectiveness associated with this drug treatment has also received much attention, reflecting whether its high cost has potential value and effects in resource-limited China (28, 29). The aim of our analysis was to evaluate the cost-effectiveness of atezolizumab versus BSC as adjuvant therapy after platinum-based chemotherapy for stage IB-IIIA resectable NSCLC from the perspective of the Chinese health care system.

Materials and methods

Model structure

It is assumed that the target group cohort is patients with stage IB-IIIA NSCLC after complete resection and 1-4 cycles of platinum-based chemotherapy, consistent with the patient characteristics of the IMpower010 trial (27). We followed the guidelines for pharmacoeconomic evaluation in China, and a decision tree model was constructed, clearly demonstrating the decision-making process and assessing the cost-effectiveness of adjuvant treatment strategies (30). In a hypothetical group cohort, a Markov model was used to predict the course of resectable NSCLC in stage IB-IIIA, including three mutually exclusive health states: progression-free survival (PFS), progressed disease (PD) and death (Figure 1). The initial health status of all patients was PFS with a Markov cycle length of 3 weeks, consistent with the treatment plan reported for the IMpower010 trial, and the time frame of the model was 10 years. During each Markov cycle, patients either remained in their assigned health state or were reassigned to a new health state based on the time-dependent probability of metastasis based on the IMpower010 trial results, assuming that subsequent treatments for patients in PD include chemotherapy, targeted therapy, and immunotherapy (31)

The main outputs of the model were assessed, including costs, life years (LYs), and quality-adjusted life years (QALYs). According to Chinese Guidelines for Pharmacoeconomic Evaluation, costs were expressed at the 2022 exchange rate (1 USD = 6.3 RMB), and costs and effects were calculated at an annual discount rate of 5%. According to the guidelines for pharmacoeconomic evaluation in China and the recommendations of the World Health Organization, three times the gross domestic product (GDP) per capita in China in 2022 ($ 27,354/QALY) was used as the willingness-to-pay (WTP) threshold; the ICER was estimated, expressed as the cost per increased QALY; and the ICER was compared with the WTP threshold to determine the cost-effectiveness of the two

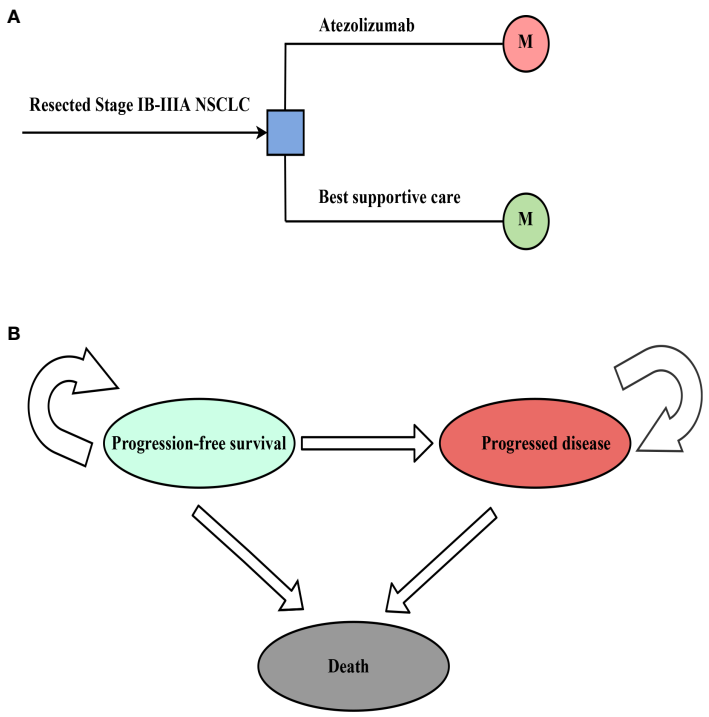

FIGURE 1
The structure of the **(A)** decision tree and **(B)** Markov model. NSCLC, non-small-cell lung cancer.

treatments. This study used TreeAge Pro 2018 software (https://www.treeage.com/) to construct and analyze the model.

Clinical data

Clinical efficacy and safety data in the PD-L1 TC ≥ 1% stage II – IIIA group, all stage II – IIIA groups, and the ITT group was obtained from the IMpower010 trial. The PFS and OS curves were extrapolated over the time frame of the model based on standard statistical analysis developed by Guyot et al. (32). Since the extrapolated curves are not parallel, there is an intersection, we reject the assumption of proportional hazards (PH), giving parametric accelerated failure time (AFT) models that are not affected by the PH hypothesis (33). A single-parameter AFT model was fitted to Stata 16 to reconstruct individual patient data (IPD). First with GetData Graph Digitizer software (version 2.26; using http://www.getdata-graphdigitizer.com/index.php), Data points were extracted separately from the PFS and OS curves for each treatment group, followed by data analysis with R software (version 3.6.1, http://www.rproject.org), IPD were restored, PFS and OS curves were fitted with parametric survival functions using STATA software version 16: exponential, gamma, Weibull, log-logistic, log-normal, and Gompertz and their advantages and disadvantages were judged by the Akaike information criterion (AIC). The AIC values of the three groups are listed in Supplementary Information Table 1. The model used for atezolizumab versus BSC and the estimated survival parameters associated with PFS and OS curves are presented in Table 1. A comparison of the fitted curves with the Kaplan-Meier curves from the IMpower010 trial is shown in Figure 2.

Transition probabilities

The survival parameters and survival functions for each PFS and OS curve were calculated based on the manual instructions for parameterization of survival functions in TreeAge Pro and Stata software, and then the survival parameters and survival functions for each PFS and OS curve were used to calculate the time-dependent transfer probability in a Markov process. We assumed that the probability of PFS to death ($P_{PFS\ to\ death}$) transfer is equal to the natural mortality rate and that the probability of PFS to PFS transfer $P_{PFS\ to\ PFS} = \frac{S_{(t)}}{S_{(t-\mu)}}$; μ is the cycle length of the Markov process, so the probability of PFS to PD transfer ($P_{PFS\ to\ PD}$) is $1-P_{PFS\ to\ Death}-P_{PFS\ to\ PFS}$. Similarly, the transition probability of survival (including PFS and PD patients) to survival ($P_{S\ to\ S}$) can be calculated. After the above parameters are obtained, we can obtain the transition probability of PD to PD ($P_{PD\ to\ PD}$) according to the following formula: $\frac{[(n_{PFS}+n_{PD})*P_{S\ to\ S}-n_{PFS}*P_{PFS\ to\ PFS}-n_{PFS}*P_{PFS\ to\ PD}]}{n_{PD}}$ where n_{PFS} and n_{PD} denote the number of patients in the PFS and PD states, respectively, in the previous Markov cycle (42). The probability of metastasis from PD to Death $P_{PD\ to\ Death}=1-P_{PD\ to\ PD}$

Cost and utility values

The model only calculates the direct medical costs related to cancer treatment, that is, drug costs, BSC costs, subsequent treatment costs for disease progression (including chemotherapy, targeted, immunotherapy, etc.) routine follow-up costs, treatment-related severe adverse events (SAEs, grade ≥ 3) management costs, and hospice costs.

Based on the IMpower010 trial, patients in the atezolizumab group received atezolizumab at a dose of 1200 mg every 3 weeks for 16 cycles, and patients in the BSC group received BSC (observation, periodic scanning for disease recurrence, etc.). The cost of atezolizumab was obtained from the China Health Industry Big Data Service Platform (https://db.yaozh.com/), and the BSC and subsequent treatment costs were derived from the published literature. To simplify the model, we only considered SAE costs with ≥ 1% incidence of SAEs associated with both treatment regimens, assuming that all costs associated with SAEs occurred in the first cycle, and we tested the incidence and costs of SAEs in a sensitivity analysis. The implementation of the PAP for patients with atezolizumab is conducive to improving patients' tolerance for the drug; patients need only pay for the first two cycles and then receive three cycles of atezolizumab treatment free of charge. Currently, PAP is only indicated for patients in China with extensive-stage small cell lung cancer or unresectable hepatocellular carcinoma, and this study used PAP as a scenario analysis to explore the economic impact that PAP might have on patients with resectable NSCLC in stage IB-IIIA.

The utility value of the PFS health status of 626 Chinese lung cancer patients was investigated using the EQ-5D-5L scale, and the utility of PD status was obtained from the published literature (41). The utility values of PFS and PD were 0.827 and 0.321, respectively, and the utility of death was zero. The disutility caused by SAEs was also calculated in the model, and the model parameters are presented in Table 1.

Statistical analysis

Univariate sensitivity analysis and probabilistic sensitivity analysis (PSA) were used to verify the stability of the model results. In the one-way sensitivity analysis, based on data from the published literature, it was assumed that the estimated range of each parameter was ± 25% of the baseline value, as shown in Table 1, to test which parameter had a greater impact on the model results. The results of the one-way sensitivity analysis are presented as a tornado diagram. In PSA, each parameter was set

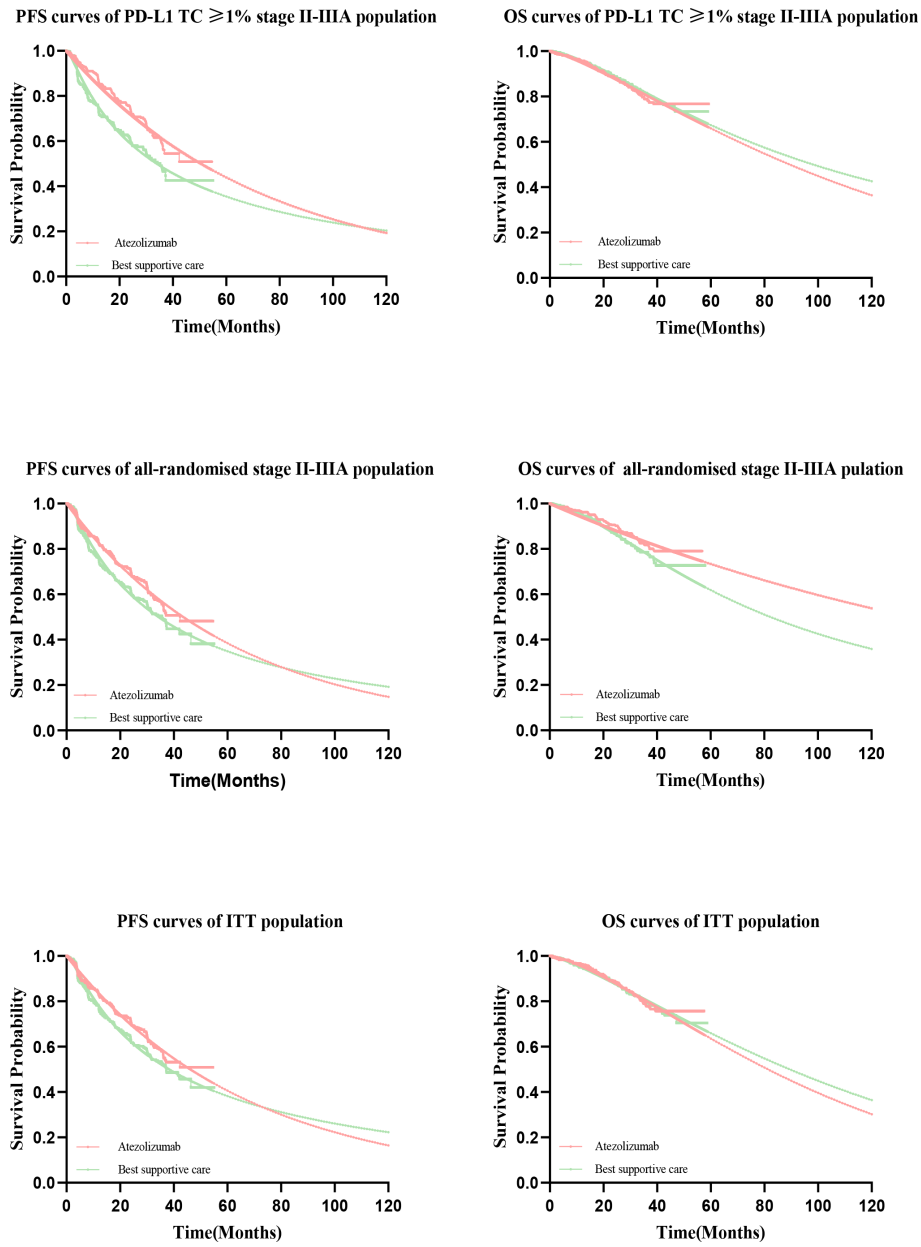

FIGURE 2
Comparison of Kaplan-Meier curves with fitted curves in the IMpower010 trial. PFS, progression-free survival; OS, overall survival.

to change according to its specific distribution (Table 1), and 10,000 Monte Carlo simulations were performed (43), randomly sampled from the statistical distribution to generate 10,000 evaluable cost and QALY estimates for each treatment strategy to test the stability of the study results. Results for PSA were stable and presented as a cost-effectiveness acceptability curve (CEAC). Assuming that costs follow a lognormal or triangular distribution, utility values and SAE incidence followed a beta distribution. The CEAC indicated an acceptable probability of cost-effectiveness for atezolizumab at different willingness-to-pay thresholds.

To explore the impact of economic and health policies with Chinese characteristics on the results of this study, we conducted the following 2 scenario analyses: first, we assumed PAP for resectable NSCLC stage IB-IIIA; and second, to reduce the economic burden of cancer patients in China, many anticancer drugs have been reduced in price by 30-70% through negotiations on anticancer drugs by the National Health

TABLE 1 Model parameters: baseline values, ranges, and distributions for sensitivity analysis.

Parameter	Value	Range	Distribution	Ref
Survival				
Atezolizumab group				
Exponential PFS curve of PD-L1 TC ≥ 1% stage II-IIIA group	λ= 0.01373	–	-	(27)
Exponential PFS curve of all-randomised stage II-IIIA group	λ= 0.01593	–	-	(27)
Exponential PFS curve of ITT group	λ= 0.01502	–	-	(27)
Exponential OS curve of PD-L1 TC ≥ 1% stage II-IIIA group	λ= 0.00516	–	-	(27)
Weibull OS curve of all-randomised stage II-IIIA group	λ= 0.00146; P = 1.40082	–	-	(27)
Weibull OS curve of ITT group	λ= 0.00222; p = 1.27815	–	-	(27)
Best supportive care		–	-	
Lognormal PFS curve of PD-L1 TC ≥ 1% stage II-IIIA group	σ= 1.52190; μ = 3.52507	–	-	(27)
Lognormal PFS curve of all-randomised stage II-IIIA group	σ= 1.50079; μ = 3.64405	–	-	(27)
Lognormal PFS curve of ITT group	σ= 1.50079; μ = 3.64405	–	-	(27)
Loglogistic OS curve of PD-L1 TC ≥ 1% stage II-IIIA group	λ= 0.01216; γ = 0.65240	–	-	(27)
Weibull OS curve of all-randomised stage II-IIIA group	λ= 0.00222; P = 1.27815	–	-	(27)
Loglogistic OS curve of ITT group	λ= 0.01018; γ = 0.67737	–	-	(27)
Costs ($)				
Atezolizumab (1200 mg/cycle)	4218.61	3163.93-5273.18	Lognormal	(34)
Best supportive care (every cycle)	299.47	224.58-374.27	Lognormal	(35)
Progression Subsequent therapy	736.35	552.26-920.43	Lognormal	(36)
Cost of alanine aminotransferase elevation/aspartate aminotransferase elevation treatment (per cycle)	75.67	56.70-94.58	Triangle	(37)
Routine follow-up fee (per cycle)	76.05	56.96-95.03	Lognormal	(38)
End-stage palliative care	2331.70	1748.78–2914.59	Lognormal	(39)
Pyrexia therapy	845.61	634.21-1056.98	Lognormal	(40)
Utilities				
PFS state	0.827	0.620-1.000	Beta	Local
PD state	0.321	0.240-0.401	Beta	(41)
Disutility for pyrexia	0.420	0.315-0.525	Beta	(41)
Risk for treatment-related AEs				
Neutropenia in the atezolizumab Arm	0.01	0.007-0.012	Beta	(27)
Alanine aminotransferase increased in the atezolizumab group	0.02	0.015-0.025	Beta	(27)
Aspartate aminotransferase increased in the atezolizumab group	0.01	0.007-0.012	Beta	(27)
Other				
Discount Rate (%)	5	0-8	Fixed in PSA	(30)

PFS, progression-free survival; PD, progressed disease; BSC, best supportive care; AEs, adverse events.

Security Agency (NHSA) since 2017. Therefore, we paid closer attention to the impact of NHSA negotiations on the results of this study and hypothesized an atezolizumab price 30–70% less to perform scenario analysis.

Results

Base-case analysis

From the perspective of the Chinese health care system, atezolizumab is expected to generate an additional 5.72 LYs, 5.08 LYs, and 5.23 LYs in the PD-L1 TC ≥ 1% stage II – IIIA group (SP263), all stage II – IIIA groups, and the ITT group, with incremental costs and incremental QALYs of $48,971.42 and 0.45 QALYs, $41,141.53, and 0.04 QALYs, and $41,370.46 and -0.0028 QALYs, respectively, compared with BSC. The results showed that the ICERs of atezolizumab with BSC were $108,825.37/QALY in the PD-L1 TC ≥ 1% stage II – IIIA group, $1,028,538.22/QALY in all stage II – IIIA groups, and $-14,381,171.55/QALY in the ITT group (Table 2).

Sensitivity analyses

Univariate sensitivity analysis showed that, whether in the PD-L1 TC ≥ 1% stage II – IIIA group, all stage II – IIIA groups,

TABLE 2 Base-case results.

Strategies and Scenarios	Total cost, $	LYs	QALYs	ICER ($/QALY)
Without PAP				
PD-L1 TC ≥ 1% stage II-IIIA group				
Atezolizumab	96, 105.57	5.72	3.81	108, 825.37
Best supportive care	47, 134.15	5.11	3.36	–
All-stage randomised II-IIIA group				
Atezolizumab	90, 675.89	5.08	3.45	1, 028, 538.22
Best supportive care	49, 534.36	5.28	3.41	–
ITT group				
Atezolizumab	91, 477.59	5.23	3.562	-14,381,171.55
Best supportive care	50, 107.13	5.43	3.565	–
With PAP				
PD-L1 TC ≥ 1% stage II-IIIA group				
Atezolizumab	63, 616.58	5.72	3.81	36, 627.60
Best supportive care	47, 134.16	5.11	3.36	–
All-stage randomised II-IIIA group				
Atezolizumab	58, 779.39	5.08	3.45	231, 125.92
Best supportive care	49, 534.36	5.28	3.41	–
ITT group				
Atezolizumab	59, 337.94	5.23	3.562	-3,208,807.97
Best supportive care	50, 107.13	5.43	3.565	–
Price Reductions				
Reduce price to 70% of original price				
PD-L1 TC ≥ 1% stage II-IIIA group				
Atezolizumab	76, 667.57	5.72	3.81	65, 725.84
Best supportive care	47, 134.15	5.11	3.36	–
All-stage randomised II-IIIA group				
Atezolizumab	71466.86	5.08	3.45	693, 104.99
Best supportive care	49534.36	5.28	3.41	–
ITT group				
Atezolizumab	72, 174.52	5.23	3.562	-7, 671, 042.54
Best supportive care	50, 107.13	5.43	3.565	–
Reduce price to 60% of original price				
PD-L1 TC ≥ 1% stage II-IIIA group				
Atezolizumab	70, 188.23	5.72	3.81	51, 306.25
Best supportive care	47, 134.15	5.11	3.36	–
All-stage randomised II-IIIA group				
Atezolizumab	65, 063.85	5.08	3.45	490, 758.81
Best supportive care	49, 534.362	5.28	3.41	–
ITT group				
Atezolizumab	65, 740.16	5.23	3.562	-5, 434, 336.94
Best supportive care	50, 107.13	5.43	3.565	–
Reduce price to 50% of original price				
PD-L1 TC ≥ 1% stage II-IIIA group				
Atezolizumab	63, 708.90	5.72	3.81	36, 886.65
Best supportive care	47, 134.15	5.11	3.36	
All-stage randomised II-IIIA group				
Atezolizumab	58, 660.84	5.08	3.45	288, 412.62
Best supportive care	49, 534.36	5.28	3.41	

(Continued)

TABLE 2 Continued

Strategies and Scenarios	Total cost, $	LYs	QALYs	ICER ($/QALY)
ITT group				
Atezolizumab	59305.81	5.23	3.562	-3, 197, 634.42
Best supportive care	50107.13	5.43	3.565	
Reduce price to 40% of original price				
PD-L1 TC ≥ 1% stage II-IIIA group				
Atezolizumab	57, 229.56	5.72	3.81	22, 467.05
Best supportive care	47, 134.15	5.11	3.36	
All-stage randomised II-IIIA group				
Atezolizumab	52, 257.83	5.08	3.45	86, 066.43
Best supportive care	49, 534.36	5.28	3.41	
ITT group				
Atezolizumab	52, 871.45	5.23	3.562	-960, 928.81
Best supportive care	50, 107.13	5.43	3.565	
Reduce price to 30% of original price				
PD-L1 TC ≥ 1% stage II-IIIA group				
Atezolizumab	50, 750.23	5.72	3.81	8, 047.48
Best supportive care	47, 134.15	5.11	3.36	
All-stage randomised II-IIIA group				
Atezolizumab	45, 854.82	5.08	3.45	-116, 279.74
Best supportive care	49, 534.36	5.28	3.41	
ITT group				
Atezolizumab	46, 437.09	5.23	3.562	1, 275, 776.78
Best supportive care	50, 107.13	5.43	3.565	

or the ITT group, the key parameters with the greatest impact on ICERs were the cost per 1200 mg of atezolizumab and the utility of PFS, and other parameters had little effect on the model results. By changing the model input within a certain range to run the probability sensitivity analysis, it was found that ICER was insensitive to AE cost. When PAP is not implemented, the cost of atezolizumab, the utility value of PFS status has the greatest impact on the model (Figure 3), however implementing PAP, the cost of atezolizumab still has a large impact on the three types of patient group models (Supplementary Figure 1). And the ICER was above the WTP threshold (every additional QALY requires an investment of $27,354) regardless of whether PAP was implemented for the three types of group.

The results of this study were stable after performing PSA, the cost-effectiveness acceptance curve (Figure 4) showed that, when the WTP threshold in China was $27,354/QALY, the probability of cost-effectiveness of treatment with atezolizumab over BSC was 0% in the three groups. When the WTP threshold of atezolizumab in the PD-L1 TC ≥ 1% stage II – IIIA group, all stage II – IIIA groups, and the ITT group was approximately $79,859.15 /QALY, $266, 197.20 /QALY, and $310,563.40/ QALY, respectively, there was a 50% probability of cost-effectiveness. In the implementation of PAP scenario, atezolizumab had an increased probability of cost-effectiveness in PD-L1 TC ≥ 1% stage II – IIIA group, All stage II – IIIA, or Intention-to-treat group (stage IB – IIIA), i.e. with an increased probability of cost-effectiveness reaching approximately 94.9%, 60%, and 50%, respectively, at a cost-effectiveness threshold of $27,354/QALY. It means that implementing PAP may be one of the most effective measures to improve its cost-effectiveness (Figures 4). After the price of atezolizumab was reduced by 30–70%, the probability of cost-effectiveness increased in the three types of groups, especially in the PD-L1 TC ≥ 1% stage II – IIIA group; when the price of atezolizumab (1200 mg) was reduced to 50% of the original price, the probability of cost-effectiveness in PD-L1 TC ≥ 1% stage II – IIIA group reached more than 54%; and When it is reduced to less than 45% of the original price, in the all stage II – IIIA groups and the intention-to-treat group (IB – stage II – to-treat group) the probability of cost-effectiveness in the IIIA group reached more than 50% (Figures 4, 5).

Discussion

This study is the first to evaluate the cost-effectiveness of atezolizumab versus BSC as an adjuvant treatment strategy after postoperative platinum-based chemotherapy for early-stage NSCLC (PD-L1 TC ≥ 1% stage II – IIIA group, all stage II – IIIA groups, or the intention-to-treat group (stage IB – IIIA))

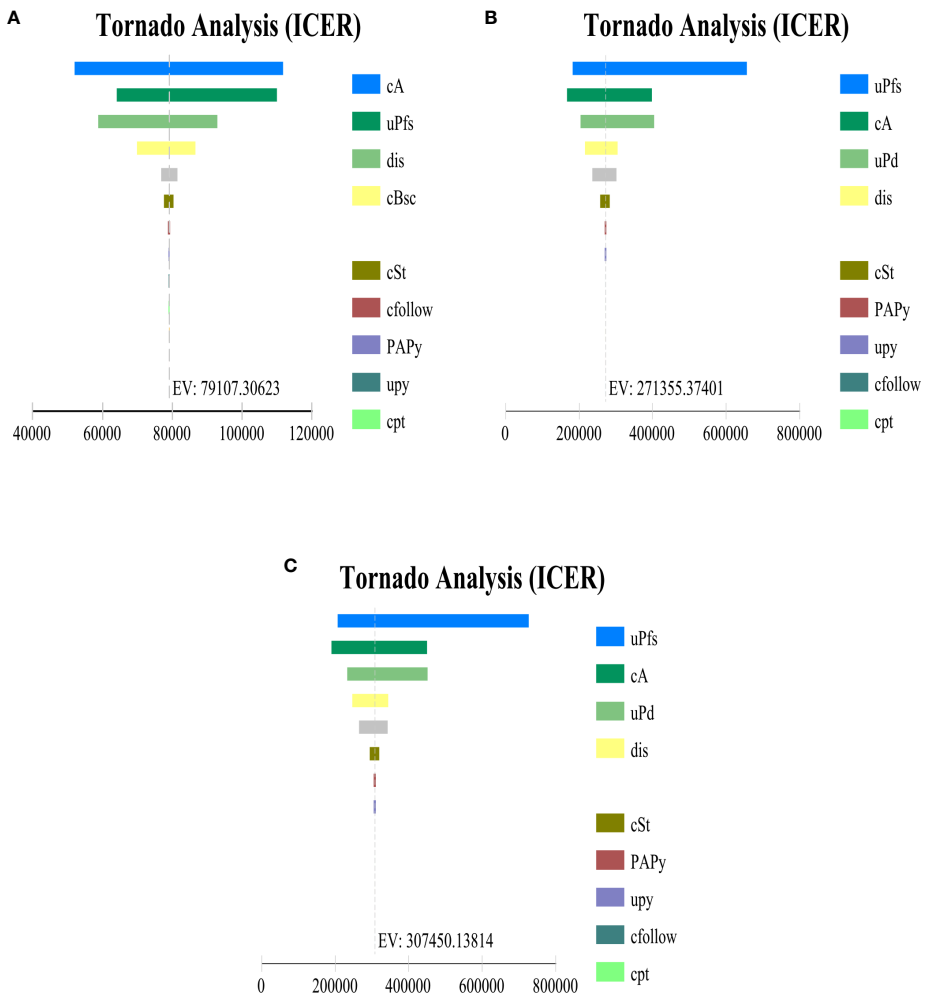

FIGURE 3
Tornado diagram indicating the most influential parameter in **(A)** PD-L1 TC ≥ 1% stage II – IIIA group (SP263), **(B)** All stage II – IIIA, **(C)** Intention-to-treat group (stage IB – IIIA) when PAP is not applicable. cA, cost per cycle of atezolizumab treatment; uPfs, health utility of disease-free survival status; dis, discount rate; cBsc, cost per cycle of best supportive care; cSt, cost per cycle of subsequent therapy for progression status; cfollow, routine follow-up costs per cycle; PAPy, incidence of fever with atezolizumab; cpt, cost of palliative care in end-stage disease; cal, cost of alanine aminotransferase/aspartate aminotransferase elevation treatment; cpy, cost of Pyrexia treatment; PAAl, incidence of alanine aminotransferase elevation with atezolizumab; uPd, utility values for progressive disease status.

from the perspective of the Chinese health care system, Unlike studies using proportional hazards models (44, 45), parametric curves in this study were fitted to each treatment group separately (46, 47), and the reason for the crossover of the PFS curves may be due to the fact that atezolizumab showed a pretreatment advantage of different groups at different times. Our analysis showed that the use of atezolizumab as adjuvant therapy after platinum-based chemotherapy resulted in a higher ICER compared with the WTP threshold $(27,354/QALY) for the PD-L1 TC ≥ 1% stage II-IIIA group, all stage II-IIIA group, or the ITT group, making atezolizumab less likely to be cost-effective in patients after postoperative platinum-based chemotherapy for early NSCLC. The results of our one-way sensitivity analysis and PSA showed that this result has good stability.

Currently, atezolizumab is mainly used for the treatment of small cell lung cancer in China. No domestic and foreign scholars have found the health economic evaluation of atezolizumab versus BSC as adjuvant therapy after platinum-based chemotherapy for stage IB-IIIA resectable NSCLC. A recent study assessed the economic outcomes of atezolizumab versus platinum-based chemotherapy for first-line treatment of EGFR and ALK wild-type metastatic NSCLC in a group with high, high or intermediate PD-L1 expression and in any group with PD-L1 expression from a Chinese health authority perspective, based on the IMpower110 trial. The incremental cost of atezolizumab compared with

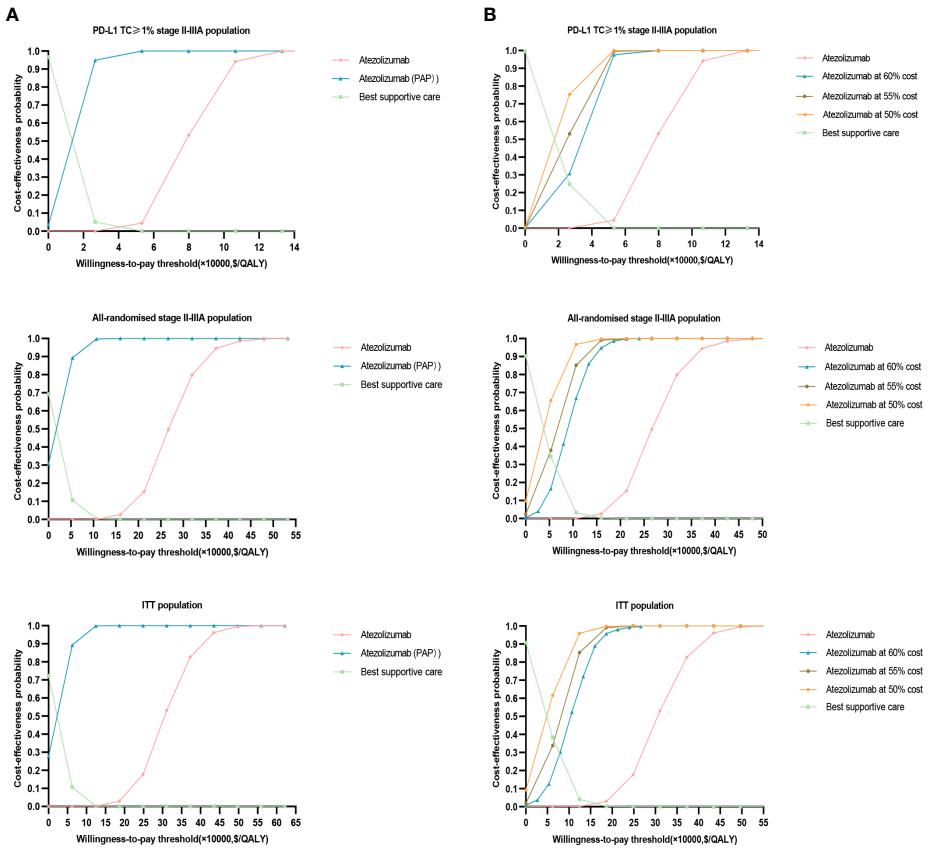

FIGURE 4
Probability sensitivity analysis acceptance curve. **(A)** When PAP is applicable, the probability sensitivity analysis of atezolizumab versus best supportive care in the PD-L1 TC ≥ 1% stage II – IIIA group (SP263), all stage II – IIIA groups, or the intention-to-treat group (stage IB – IIIA) can be compared with the acceptable curve. Atezolizumab, atezolizumab without PAP; Atezolizumab (PAP), atezolizumab after PAP strategy; Best supportive care, whether best supportive care of PAP is performed or not. **(B)** Probability sensitivity analysis of atezolizumab after price reduction versus best supportive care in the PD-L1 TC ≥ 1% stage II – IIIA group (SP263), all stage II – IIIA groups or the intention-to-treat group (stage IB – IIIA) can be compared with the acceptable curve. Atezolizumab, atezolizumab at 100% cost; Best supportive care, best supportive care at 100% cost.

chemotherapy was reported to be $112,744.35, and 0. 91QALYs, $81, 831.03,and 0. 57QALYs, $70,346.51, and 0. 42QALYs in groups with high, high, or intermediate PD-L1 expression, respectively, and in any group with PD-L1 expression. The results of univariate sensitivity analysis of the above studies were consistent with the results of this study, indicating that the cost of atezolizumab and the utility of PFS were the factors that had the greatest impact on the model results. It is worth noting that the ICERs of the above studies were much lower than those of the all-randomized stage II-IIIA group in this study and were similar to those of our PD-L1 TC ≥ 1% stage II-IIIA group, which could be due to the following causes. First, the control strategy in the study was different; the above study used chemotherapy, and this study used the BSC, and the risk of SAEs and management costs that occur with different drugs are quite different, so the estimated incremental costs of the two studies were also different. Second, the utility value of health status is different, and the PFS in the above study was 0.804, while the PFS in our model was 0.827. Third, the group and order of administration of atezolizumab in the study were different, and the clinical effects on patients were also different. In the above study, atezolizumab was used as a first-line drug for metastatic lung cancer with different PD-L1 expression statuses (high PD-L1 expression group, high or medium PD-L1 expression group and any PD-L1 expression group), producing 1.80 QALYs, 1.47 QALYs and 1.32 QALYs, respectively. In this study, atezolizumab was used as an adjuvant drug for the treatment of patients with early NSCLC after postoperative platinum-based chemotherapy (PD-L1 TC ≥ 1% II-IIIA group, all-stage II-IIIA group, ITT group), producing 3.81 QALYs. Therefore, we believe that the conclusions of the above studies are not comparable to those of our study.

In recent years, relying on pharmacoeconomic evidence, the Chinese government has reduced the prices of many anticancer drugs by 30-70% in price negotiations with pharmaceutical

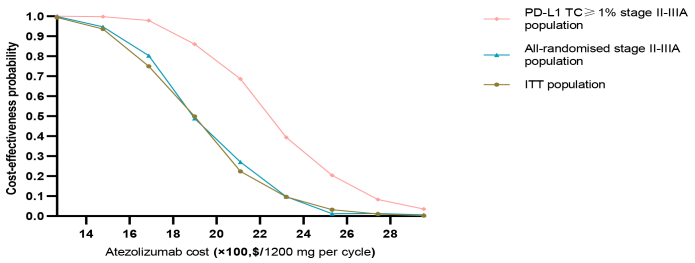

FIGURE 5
Acceptable probability of cost-effectiveness achievable in PD-L1 TC ≥ 1% stage II – IIIA group (SP263), All stage II – IIIA, or Intention-to-treat group (stage IB – IIIA) with different proportion of atezolizumab price reductions.

companies. The latest results of national health insurance negotiations in 2020 showed that the average price reduction of drugs with successful negotiations was 50.64%, so we explored the effect of price reduction on the model results. When PAP was not available, the price of atezolizumab was reduced to 50%, 55%, and 60% of the original price, the probability that atezolizumab being cost-effective was equal to or greater than 30% in the PD-L1 TC ≥ 1% II-IIIA group and less than or equal to 20% in all-stage II-IIIA group and ITT group. its price reduction was Markov models were constructed based on follow-up data from the IMpower010 trial and assessed separately in the PD-L1 TC ≥ 1% stage II – IIIA group, all stage II – IIIA groups, and the ITT group, cost-effectiveness of adjuvant atezolizumab to the acceptable probability of cost-effectiveness, with the most significant effect in the PD-L1 TC ≥ 1% stage II-IIIA group, but less effective in all stage II-IIIA groups or the ITT group. In patients with resectable NSCLC, the effect of the PAP strategy was the most significant in the stage II–IIIA subgroup whose tumors expressed PD-L1 TC≥1%. Therefore, to make atezolizumab cost-effective compared with BSC, this study recommends the implementation of the PAP strategy for the PD-L1 TC ≥ 1% stage II – IIIA group in patients after postoperative adjuvant chemotherapy for stage IB-IIIA resectable NSCLC; reducing the price of atezolizumab to less than 45% of the original price through price negotiations might make the drug cost-effective for patients with stage IB-IIIA resectable NSCLC. These findings have certain reference value for guiding policy makers in rationally allocating health resources.

Our study had several limitations. First, the KM survival curve was obtained from the IMpower010 trial to extrapolate the long-term clinical effect of the drug by fitting a parameter function, and the extrapolation time exceeded the real follow-up time of the trial, incurring inevitable limitations and perhaps lead to deviations between the model results and the actual situation. Second, some key clinical costs were derived from the literature rather than survey data from this study (34–40), such as the subsequent treatment cost of PD, considering only the cost of grade III/IV adverse events reported by ≥ 1% of patients in the IMpower010 trial, this may lead to inaccurate estimates of AE costs. By changing the model input within a certain range to run the probability sensitivity analysis, it was found that ICER was not sensitive to AE cost. Third, there was uncertainty in the long-term survival prediction of the IMpower010 trial, and the data must be continuously updated to validate our model results. Despite these limitations, we believe that this study accurately reflects the clinical treatment of resectable NSCLC in stage IB-IIIA in China.

Conclusion

From the perspective of the Chinese health care system, it is unlikely that the use of atezolizumab in the adjuvant treatment of Chinese patients with stage IB-IIIA resectable NSCLC after adjuvant chemotherapy (PD-L1 TC ≥ 1% stage II-IIIA group, all-stage randomized II-IIIA group, ITT group) is cost-effective. Implementing PAP or reducing drug prices might be the most effective measure to increase the cost-effectiveness of atezolizumab.

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

This cost-effectiveness analysis was based on a literature review and modeling techniques, the study did not require approval from an Institutional Research Ethics Board.

Author contributions

Conception and design, PC and QY. Analysis and interpretation, PC and QY. Data collection, PC and QY. Writing the article, PC. Critical revision of the article, PC, QY, JC, XJ, and YL. Final approval of the article, PC and QY. Overall

responsibility, PC and QY. 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.2022.894656/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Tornado diagram indicating the most influential parameter in **(A)** PD-L1 TC ≥ 1% stage II – IIIA group (SP263), **(B)** All stage II – IIIA, **(C)** Intention-to-treat group (stage IB – IIIA) when PAP is applicable. cA, cost per cycle of atezolizumab treatment; uPfs, health utility of disease-free survival status; dis, discount rate; cBsc, cost per cycle of best supportive care; cSt, cost per cycle of subsequent therapy for progression status; cfollow, routine follow-up costs per cycle; PAPy, incidence of fever with atezolizumab; cpt, cost of palliative care in end-stage disease; cal, cost of alanine aminotransferase/aspartate aminotransferase elevation treatment; cpy, cost of Pyrexia treatment; PAAI, incidence of alanine aminotransferase elevation with atezolizumab; uPd, utility values for progressive disease status.

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The efficacy and safety of anlotinib combined with platinum-etoposide chemotherapy as first-line treatment for extensive-stage small cell lung cancer: A Chinese multicenter real-world study

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Background: Patients with extensive-stage small-cell lung cancer (ES-SCLC) have high recurrence rates and bleak prognosis. This multicenter real-world study aimed to explore the efficacy and safety of anlotinib combined with platinum-etoposide chemotherapy as the first-line treatment of ES-SCLC.

Methods: Pathologically confirmed ES-SCLC patients receiving anlotinib plus platinum-etoposide chemotherapy as the first-line treatment were enrolled in this retrospective study. The primary endpoint of this study was progression-free survival (PFS), and secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse reactions. The Cox regression analyses were employed to investigate the independent prognostic factors for OS and PFS of these individuals.

Results: In total, 58 patients were included in this study. The median PFS was 6.0 months [95% confidence interval (CI): 3.5-8.5], and the median OS was 10.5 months (95%CI 8.7-12.3). Thirty-four patients achieved partial response (PR), 18 patients achieved stable disease (SD), and 6 patients achieved progressive disease (PD). The ORR and DCR were 58.6% and 89.6%. The main treatment-related adverse reactions were generally tolerated. Myelosuppression (44.8%) was the most common adverse reaction, followed by hypertension (41.4%), fatigue (34.5%), gastrointestinal reaction (32.7%), and hand-foot syndrome (24.1%). Multivariate analysis showed that post-medication hand-foot syndrome [PFS 8.5 *vs.* 5.5 months, Hazards Ratio (HR)=0.23, 95%CI 0.07-

0.72, P =0.012] was the independent predictor of PFS, and hypertension (OS 15.9 *vs.* 8.3 months, HR=0.18, 95%CI 0.05-0.58, P =0.005) was the independent predictor of OS.

Conclusion: Anlotinib combined with platinum-etoposide chemotherapy as the first-line treatment for ES-SCLC appears to be effective and well-tolerated in the real-world. Well-designed large-scale prospective studies are urgently needed in the future to verify our findings.

KEYWORDS

small cell lung cancer, anlotinib, chemotherapy, real-world data, efficacy, safety

Introduction

Lung cancer is the most frequent cause of tumor death worldwide. Small cell lung cancer (SCLC) is a highly aggressive and deadly malignant tumor, accounting for approximately 10% to 15% of all lung cancers (1–3). SCLC comprises an estimated 250,000 new cases and at least 200,000 deaths worldwide each year (4). Approximately 70% of the patients are diagnosed with extensive-stage SCLC (ES-SCLC) with poor overall survival (OS) (5). It has been reported that the median OS for ES-SCLC patients without systemic therapy is 2 to 4 months (6, 7).

As the gold standard for SCLC therapy, platinum-etoposide chemotherapy has been widely used in the past 40 years. The median progression-free survival (PFS) of platinum-etoposide chemotherapy as the first-line treatment is about 5 months, and the median OS is about 10 months (8). In recent years, the rapid rise of immunotherapy has broken the unshakable position of platinum-etoposide chemotherapy. Atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, was studied in IMpower133 clinical trial in combination with platinum-etoposide chemotherapy as the first-line treatment for ES-SCLC. The combined regimen brought survival benefits: the median OS was prolonged for 2 months (12.3 *vs.* 10.3 months), and the 1-year OS rate was increased by 13.5% (51.7% *vs.* 38.2%) compared with platinum-etoposide chemotherapy (9). Durvalumab, another PD-L1 inhibitor, was also found to have a similar OS benefit (13.0 *vs.* 10.3 months) in CASPIAN clinical trial (10). PD-L1 plus platinum-etoposide chemotherapy has become the new first-line therapy for ES-SCLC.

Angiogenesis is a complex process that plays an essential role in tumor growth, invasion and metastasis. Vascular endothelial growth factor (VEGF) is the most critical proangiogenic protein (11). Previous studies found that about 80% of SCLC tissues were positive for VEGF expression, and the VEGF level was an independent prognostic factor in SCLC (12). However, the efficacy of antiangiogenic therapy in SCLC is limited. Bevacizumab, a monoclonal antibody directed against VEGF, showed a promising activity in combination with platinum-etoposide as the first-line treatment of patients with ES-SCLC, and two randomized studies confirmed that bevacizumab improved PFS, but failed to prolong OS (13, 14). Instead, disappointing results have been observed with endostar, sunitinib, sorafenib, vandetanib, and thalidomide in combination with chemotherapy in the first-line setting. Only anlotinib improved PFS and OS as third-line therapy in Chinese patients with SCLC (15). As an oral antiangiogenic tyrosine kinase inhibitor (TKI), anlotinib targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptors (PDGFR), fibroblast growth factor receptor (FGFR), and c-kit (16). Based on ALTER 1202 study, anlotinib was approved by the China Food and Drug Administration (CFDA) in 2019 as the third-line and above treatment for SCLC (17). Additionally, some small sample size clinical trials in China have shown the favorable efficacy of anlotinib combined with platinum-etoposide chemotherapy (18–20). The 2021 American society of clinical oncology (ASCO) meeting announced the preliminary result of a phase II clinical study on the efficacy and safety of anlotinib combined with platinum-etoposide chemotherapy in the first-line treatment of ES-SCLC. Twenty patients could evaluate the efficacy, of which the median PFS was 10.0 months, the median OS was 15.0 months, the objective response rate (ORR) was 90%, and the disease control rate (DCR) was 100% (18). It was significantly higher than that of traditional chemotherapy.

In clinical trials, patients are strictly screened. Thus, patients with poor conditions, such as the elderly, combined brain metastases, and the Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2, are often excluded. Therefore, we conducted this multicenter retrospective study to investigate the real-world efficacy and safety of anlotinib combined with platinum-etoposide chemotherapy as the first-line treatment for ES-SCLC.

Methods

Study design and patients

This research is a multicenter, non-intervention, retrospective real-world study. ES-SCLC patients receiving anlotinib combined with platinum-etoposide chemotherapy as the first-line treatment in the First Affiliated Hospital of Xi'an Jiaotong University, Xijing Hospital of Air Force Military Medical University, Xianyang Central Hospital, Shaanxi Nuclear Industry 215 Hospital, Hanzhong Central Hospital, and Baoji Traditional Chinese Medicine Hospital were eligible for retrospective analysis between December 1, 2018, and July 31, 2021. These tertiary hospitals are located in Shaanxi, China. The characteristics of patients were collected, including age, sex, smoking status, ECOG PS, age-adjusted Charlson comorbidity index (aCCI), TNM stage, number and location of metastases, anlotinib initial dose, imaging and laboratory examination, and adverse reaction.

Inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (1) age ≥18 years; (2) patients with ES-SCLC diagnosed by pathology have measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 standard; (3) receiving anlotinib combined with platinum-etoposide chemotherapy as the first-line treatment; (4) ECOG PS ≤2; (5) without surgery. The exclusion criteria for patients were as follows: (1) severe lack of clinical records or loss of follow-up; (2) imaging efficacy evaluation cannot be performed; (3) patients with active bleeding or serious systemic diseases.

Therapeutic methods

Each patient was treated with 2 to 8 21-day cycles of anlotinib (12mg/10mg, day 1 to 14 of each cycle), etoposide (100mg/m^2 of body surface area, day 1 to 3 of each cycle), and carboplatin (area under the curve of 5mg/mL/min, day 1 of each cycle) or cisplatin (25mg/m^2 of body surface area, day 1 to 3 of each cycle), followed by anlotinib maintenance every 3 weeks. The actual dosage was adjusted by qualified physicians according to patients' situation. Treatment was continued until disease progression, death, or unacceptable toxicity.

Efficacy and safety evaluation

According to the RECIST version 1.1 standard, two qualified physicians independently evaluated the efficacy through computed tomography (CT) or magnetic resonance imaging (MRI). The responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). When there was disagreement on the assessment, a third physician was requested to reevaluate. Follow-up data were collected up to October 31, 2021. PFS was defined as the time from the start of treatment until tumor progression or death from any cause before disease progression or last follow-up. OS was defined as the time from the treatment initiation to death or last follow-up. Respectively, ORR or DCR was calculated as the addition of CRs plus PRs or CRs plus PRs plus SDs. The adverse reactions were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The primary endpoint of this study was PFS, and secondary endpoints included OS, ORR, DCR, and adverse reactions.

Statistical analysis

Patients' baseline characteristics were summarized as proportions for categorical variables and medians (range) for continuous variables as appropriate. The median PFS, OS, and 95% confidence interval (CI) were estimated using the Kaplan–Meier method. Cox proportional hazards regression was used for the univariable and multivariable analyses and to calculate the hazard ratios (HR) with 95% CIs. All statistical analyses in this study were performed using SPSS version 18.0 for Windows 64.0 and GraphPad Prism version 6.0. A two-tailed P-value <0.05 was considered statistically different.

Results

Baseline clinical characteristics of patients

In total, 58 patients were included in the present study. Among them, 11 (19.0%) patients were from the First Affiliated Hospital of Xi'an Jiaotong University, 12 (20.7%) patients were from Xijing Hospital of Air Force Military Medical University, 21 (36.2%) patients were from Xianyang Central Hospital, 7 (12.1%) patients were from Shaanxi Nuclear Industry 215 Hospital, 4 (6.9%) patients were from Hanzhong Central Hospital, and 3(5.1%) patients were from Baoji Traditional Chinese Medicine Hospital. The median follow-up duration was 7.9 months. Details of the patients' baseline clinical characteristics were shown in Table 1. The median age of the patients was 59 years (range, 36 to 81 years). A total of 47 patients were male (81.0%). Former smokers and non-smokers were noted in 41 (70.7%) and 17 (29.3%) patients. ECOG PS 0-1 were observed in 38 (65.5%) patients. Forty-three (74.1%) patients were initially diagnosed in the TNM IV stage. Among them, 24 (41.4%) patients received thoracic radiotherapy during the treatment. In addition, patients with post-medication

TABLE 1 Baseline clinical characteristics of patients.

Characteristics	N (%)
Age (years)	
Median (range)	59 (36-81)
<65	41 (70.7)
≥65	17 (29.3)
Sex	
Male	47 (81.0)
Female	11 (19.0)
Smoking status	
Ever	41 (70.7)
Never	17 (29.3)
ECOG PS	
0-1	38 (65.5)
2	20 (34.5)
aCCI	
<8	26 (44.8)
≥8	32 (55.2)
TNM stage	
III	15 (25.9)
IV	43 (74.1)
T stage	
T1-2	23 (39.7)
T3-4	35 (60.3)
N stage	
N0-2	9 (15.5)
N3	49 (84.5)
Number of metastatic sites	
<2	33 (56.9)
≥2	25 (43.1)
Brain metastases	
Yes	5 (8.6)
No	53 (91.4)
Hepatic metastases	
Yes	16 (27.6)
No	42 (72.4)
Osseous metastases	
Yes	14 (24.1)
No	44 (75.9)
Pleural metastases/pleural effusion	
Yes	20 (34.5)
No	38 (65.5)
Lung metastases	
Yes	19 (32.8)
No	39 (67.2)
Baseline NSE	
≤20ng/ml	19 (32.8)
>20ng/ml	39 (67.2)
Anlotinib initial dose	
10mg	4 (6.9)
12mg	54 (93.1)
Plus thoracic radiotherapy	
Yes	24 (41.4)
No	34 (58.6)
Post-medication hypertension	
Yes	24 (41.4)
No	34 (58.6)
Post-medication hand-foot syndrome	
Yes	14 (24.1)
No	44 (75.9)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; aCCI, age-adjusted Charlson comorbidity index; NSE, neuron specific enolase.

hypertension and hand-foot syndrome were observed in 24 (41.4%) cases and 14 (24.1%) cases, respectively.

Clinical efficacy

The median PFS was 6.0 months (95%CI 3.5-8.5), and the median OS was 10.5 months (95%CI 8.7-12.3) (Figure 1A, B). The 6-month PFS rate was 47.9%, the 6-month OS rate was 72.5%, and the 1-year OS rate was 28.9%. Among them, 34 (58.6%) patients achieved PR, 18 (31.0%) patients achieved SD, and 6 (10.4%) patients achieved PD. Respectively, the ORR and DCR were 58.6% and 89.6%. The waterfall plot of tumor best response compared with measurable baseline lesions was shown in Figure 2. A 52-year-old female patient without metastasis reached the longest PFS of 16.8 months.

Univariate analysis (Table 2) showed that female (9.3 vs. 5.5 months, P =0.002), ECOG PS 0-1 (8.5 vs. 3.1 months, P <0.001), aCCI <8 (8.0 vs. 5.5 months, P =0.044), T1-2 (8.5 vs. 5.4 months, P =0.007), no hepatic metastases (8.0 vs. 4.7 months, P =0.010), baseline neuron specific enolase (NSE) ≤20ng/ml (8.5 vs. 5.4 months, P =0.006), plus thoracic radiotherapy (8.3 vs. 4.2 months, P =0.002), post-medication hypertension (8.5 vs. 5.4 months, P =0.008), and post-medication hand-foot syndrome (8.5 vs. 5.5 months, P =0.040) might have longer PFS benefits. Age <65 (15.0 vs. 8.3 months, P =0.005), female (16.8 *vs.* 9.1 months, P =0.009), never smoking (16.8 *vs.* 9.1 months, P =0.024), ECOG PS 0-1 (15.0 *vs.* 4.0 months, P <0.001), aCCI < 8 (15.9 vs. 8.5 months, P =0.013), N0-2 (17.5 vs. 9.2 months, P =0.043), no hepatic metastases (15.0 *vs.* 5.4 months, P <0.001), plus thoracic radiotherapy (16.8 *vs.* 7.7 months, P <0.001), and post-medication hypertension (15.9 *vs.* 8.3 months, P <0.001) might have longer OS benefits. Factors with P < 0.050 in univariate analyses were included in multivariate Cox regression analysis. Multivariate analysis revealed that sex (male *vs.* female: HR=6.05, 95%CI

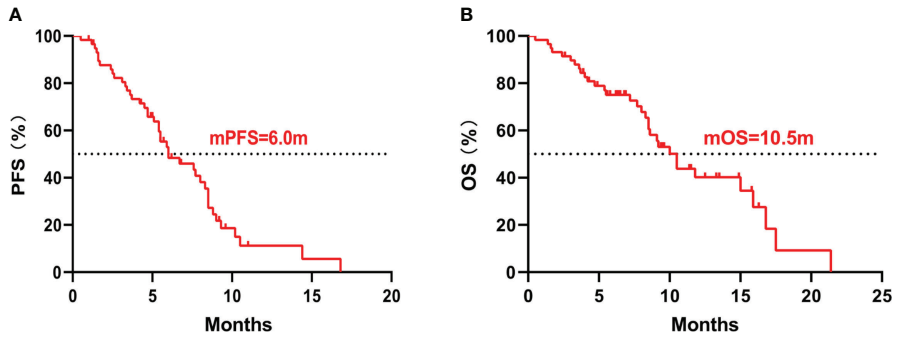

FIGURE 1
Kaplan–Meier curves of all patients. **(A)** The Kaplan–Meier curve of PFS; **(B)** The Kaplan–Meier curve of OS. PFS, progression-free survival; OS, overall survival.

1.74-20.98, *P* =0.005), ECOG PS (2 *vs.* 0-1: HR=8.34, 95%CI 2.54-27.39, *P* <0.001), T stage (T3-4 *vs.* T1-2: HR=3.82, 95%CI 1.59-9.18, *P* =0.003), and post-medication hand-foot syndrome (yes *vs.* no: HR=0.23, 95%CI 0.07-0.72, *P* =0.012) were the independent predictors of PFS (Table 3). Age (≥65 *vs.* <65: HR=4.87, 95%CI 1.71-13.82, *P* =0.003), ECOG PS (2 *vs.* 0-1: HR=11.26, 95%CI 2.49-50.84, *P* =0.002), hepatic metastases (yes *vs.* no: HR=3.83, 95%CI 1.41-10.41, *P* =0.008), and post-medication hypertension (yes *vs.* no: HR=0.18, 95%CI 0.05-0.58, *P* =0.005) were the independent predictors of OS (Table 4). The Kaplan–Meier curves of PFS and OS in multivariate Cox regression analysis were presented in Figures 3, 4.

Patients with ECOG PS ≥2 are often excluded in clinical trials. But 20 (34.5%) patients with ECOG PS 2 were included in this study. In univariate and multivariate Cox regression analysis, we found that ECOG PS was the independent predictors of PFS and OS. Similar with other clinical trials, patients with ECOG PS 0-1 had longer PFS (8.5 *vs.* 3.1 months, *P* <0.001) and OS (15.0 *vs.* 4.0 months, *P* <0.001) than patients with ECOG PS 2 (Figure 3B, Figure 4B). Of all 38 patients with ECOG PS 0-1, the 6-month PFS rate was 75.9%, the 6-month OS rate was 100.0%, and the 1-year OS rate was 62.5%. Among them, 28 (73.7%) patients achieved PR, 9 (23.7%) patients achieved SD, and 1 (2.6%) patient achieved PD. Respectively, the ORR and DCR were 73.7% and 97.4% (Table 5).

Safety

All of the 58 patients were available for safety profile. The incidence of treatment-related adverse reactions was 70.7% (41/58), and the incidence of grade 3 and above adverse reactions was 24.1% (14/58) among the participants. Dose reductions due to adverse reactions were required for 16 (27.6%) patients, and 7

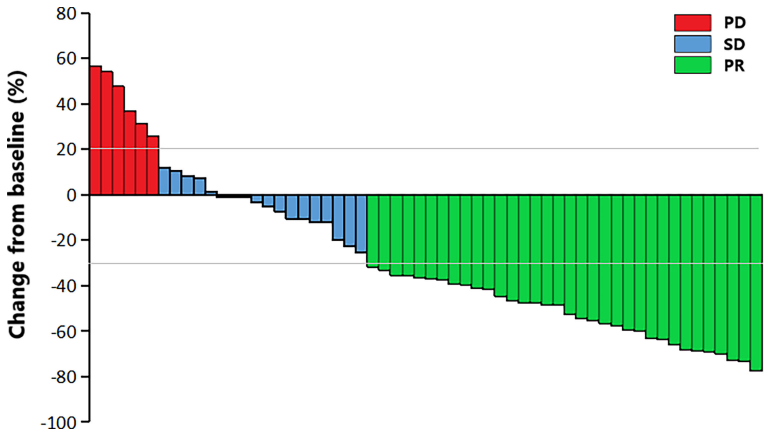

FIGURE 2
The waterfall plot of tumor best response compared with baseline measurable lesions. PR, partial response; SD, stable disease; PD, progressive disease.

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TABLE 2 Univariate analysis of factors associated with PFS and OS.

Factors	mPFS (months)	95% CI	*P*-value	mOS (months)	95% CI	*P*-value
Age (years)			0.262			**0.005**
<65	6.0	3.3-8.7		15.0	9.8-20.2	
≥65	5.9	2.7-9.1		8.3	7.6-9.0	
Sex			**0.002**			**0.009**
Male	5.5	4.6-6.4		9.1	8.0-10.2	
Female	9.3	8.1-10.5		16.8	10.5-23.1	
Smoking status			0.084			**0.024**
Ever	6.0	5.3-6.7		9.1	8.0-10.2	
Never	8.5	4.0-13.0		16.8	5.6-28.0	
ECOG PS			**< 0.001**			**< 0.001**
0-1	8.5	7.9-9.1		15.0	9.7-20.3	
2	3.1	1.3-4.9		4.0	2.9-5.1	
aCCI			**0.044**			**0.013**
<8	8.0	7.1-8.9		15.9	9.1-22.7	
≥8	5.5	3.2-7.8		8.5	6.5-10.5	
TNM stage			0.217			0.663
III	8.3	7.8-8.8		8.5	5.1-11.9	
IV	5.4	4.1-6.7		10.5	8.7-12.3	
T stage			**0.007**			0.631
T1-2	8.5	7.4-9.6		9.2	6.6-11.8	
T3-4	5.4	4.3-6.5		11.8	9.1-14.5	
N stage			0.129			**0.043**
N0-2	9.3	4.4-14.2		17.5	8.6-26.4	
N3	6.0	5.3-6.7		9.2	7.5-10.9	
Number of metastatic sites			0.114			0.226
<2	8.3	7.6-9.0		11.8	6.2-17.4	
≥2	5.4	4.9-5.9		9.2	7.7-10.7	
Brain metastases			0.851			0.506
Yes	6.7	3.3-10.1		8.6	1.0-16.2	
No	6.0	3.0-9.0		10.5	8.8-12.2	
Hepatic metastases			**0.010**			**< 0.001**
Yes	4.7	3.2-6.2		5.4	1.2-9.6	
No	8.0	6.1-9.9		15.0	9.8-20.2	
Osseous metastases			0.238			0.287
Yes	5.4	4.9-5.9		9.1	4.4-13.8	
No	7.7	5.1-10.3		10.5	6.6-14.4	
Pleural metastases/pleural effusion			0.132			0.700
Yes	5.4	4.0-6.8		9.2	–	
No	8.0	5.5-10.5		10.5	7.9-13.1	
Lung metastases			0.849			0.912
Yes	5.1	3.0-7.2		10.5	3.6-17.4	
No	6.7	4.1-9.3		9.2	7.0-11.4	
Baseline NSE			**0.006**			0.051
≤20ng/ml	8.5	7.8-9.2		21.4	–	
>20ng/ml	5.4	4.6-6.2		9.2	7.1-11.3	
Anlotinib initialdose			0.970			0.534
10mg	2.6	0.0-6.9		8.6	1.9-15.3	
12mg	6.7	4.3-9.1		10.5	7.5-13.5	

(Continued)

TABLE 2 Continued

Factors	mPFS (months)	95% CI	*P*-value	mOS (months)	95% CI	*P*-value
Plus thoracic radiotherapy			**0.002**			**<0.001**
Yes	8.3	6.6-10.0		16.8	14.7-18.9	
No	4.2	1.9-6.5		7.7	3.9-11.5	
Post-medication hypertension			**0.008**			**<0.001**
Yes	8.5	6.1-10.9		15.9	14.0-17.8	
No	5.4	3.4-7.4		8.3	3.3-13.3	
Post-medication hand-foot syndrome			**0.040**			0.115
Yes	8.5	7.4-9.6		15.9	9.9-21.9	
No	5.5	4.2-6.8		9.2	7.1-11.3	

PFS, progression-free survival; OS, overall survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; aCCI, age-adjusted Charlson comorbidity index; NSE, neuron specific enolase.
Bold value represents P-value < 0.05.

TABLE 3 Multivariate Cox regression analysis of factors associated with PFS.

Factors	HR	95%CI	*P*-value
Sex (Male *vs.* Female)	6.05	1.74-20.98	**0.005**
ECOG PS (2 *vs.* 0-1)	8.34	2.54-27.39	**<0.001**
aCCI (≥8 *vs.* <8)	1.51	0.74-3.06	0.257
T stage (T3-4 *vs.* T1-2)	3.82	1.59-9.18	**0.003**
Hepatic metastases (Yes *vs.* No)	0.67	0.30-1.49	0.323
Baseline NSE (>20ng/ml *vs.* ≤20ng/ml)	1.39	0.47-4.06	0.551
Plus thoracic radiotherapy (Yes *vs.* No)	0.98	0.30-3.23	0.979
Post-medication hypertension (Yes *vs.* No)	0.72	0.31-1.68	0.450
Post-medication hand-foot syndrome (Yes *vs.* No)	0.23	0.07-0.72	**0.012**

PFS, progression-free survival; HR, Hazard ratio; CI, Confidence inter; ECOG PS, Eastern Cooperative Oncology Group Performance Status; aCCI, age-adjusted Charlson comorbidity index; NSE, neuron specific enolase.
Bold value represents P-value < 0.05.

TABLE 4 Multivariate Cox regression analysis of factors associated with OS.

Factors	HR	95%CI	*P*-value
Age (≥65 *vs.* <65)	4.87	1.71-13.82	**0.003**
Sex (Male *vs.* Female)	0.88	0.13-5.83	0.891
Smoking status (Ever *vs.* Never)	2.52	0.51-12.49	0.258
ECOG PS (2 *vs.* 0-1)	11.26	2.49-50.84	**0.002**
aCCI (≥8 *vs.* <8)	1.89	0.69-5.13	0.213
N stage (N3 *vs.* N0-2)	0.90	0.18-4.57	0.899
Hepatic metastases (Yes *vs.* No)	3.83	1.41-10.41	**0.008**
Plus thoracic radiotherapy (Yes *vs.* No)	0.73	0.17-3.04	0.662
Post-medication hypertension (Yes *vs.* No)	0.18	0.05-0.58	**0.005**

OS, overall survival; HR, Hazard ratio; CI, Confidence inter; ECOG PS, Eastern Cooperative Oncology Group Performance Status; aCCI, age-adjusted Charlson comorbidity index.
Bold value represents P-value < 0.05.

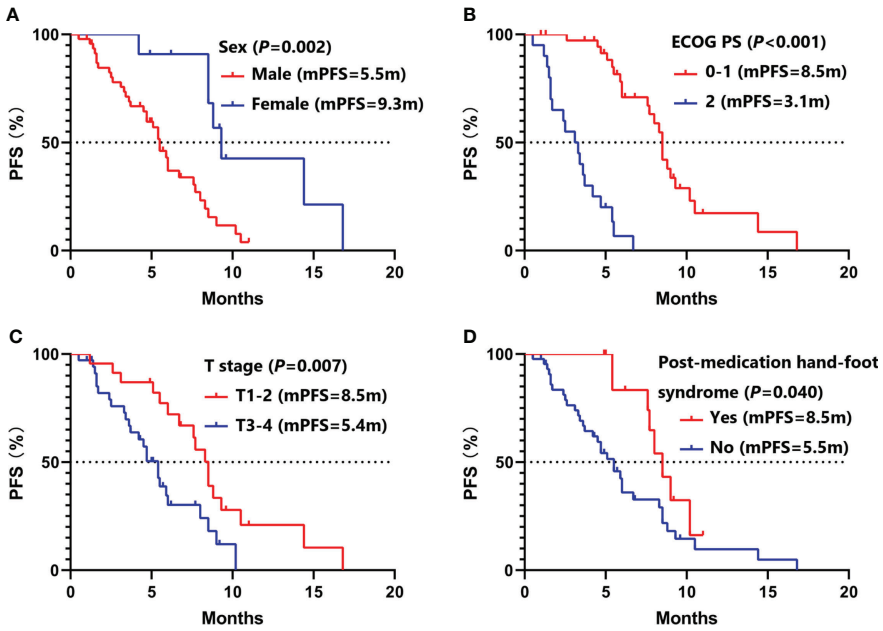

FIGURE 3
Kaplan–Meier curves of PFS in multivariate Cox regression analysis. **(A)** stratified by sex; **(B)** stratified by ECOG PS; **(C)** stratified by T stage; **(D)** stratified by post-medication hand-foot syndrome. PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

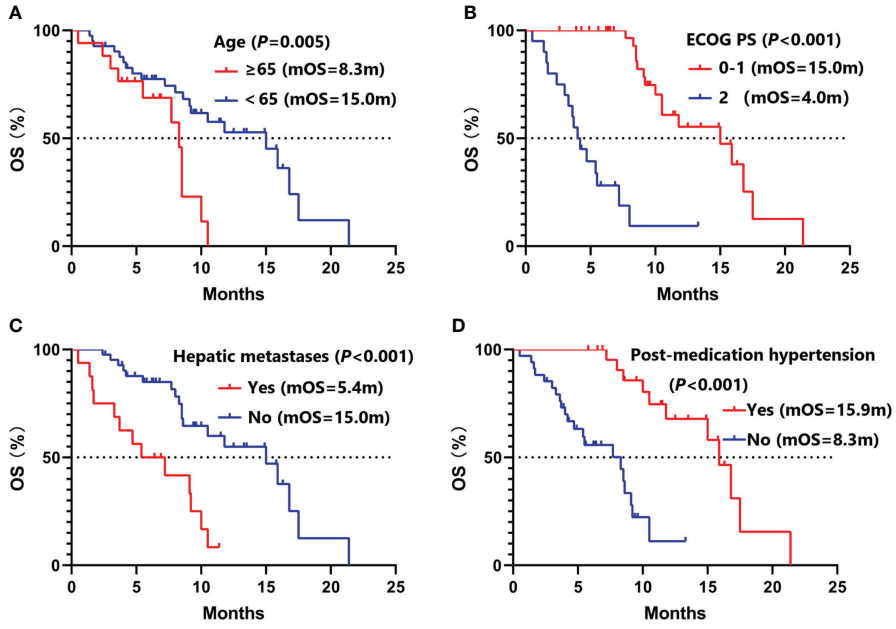

FIGURE 4
Kaplan–Meier curves of OS in multivariate Cox regression analysis. **(A)** stratified by age; **(B)** stratified by ECOG PS; **(C)** stratified by hepatic metastases; **(D)** stratified by post-medication hypertension. OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

TABLE 5 Efficacy in patients with different ECOG PS.

	Overall (n=58)	ECOG PS 0-1 (n=38)	ECOG PS 2 (n=20)
PR, n(%)	34 (58.6)	28 (73.7)	6 (30.0)
SD, n(%)	18 (31.0)	9 (23.7)	9 (45.0)
PD, n(%)	6 (10.4)	1 (2.6)	5 (25.0)
ORR, %	58.6	73.7	30.0
DCR, %	89.6	97.4	75.0
mPFS (months)	6.0	8.5	3.1
mOS (months)	10.5	15.0	4.0
6-month PFS, %	47.9	75.9	5.3
6-month OS, %	72.5	100.0	22.2
1-year OS, %	28.9	62.5	5.9

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

(12.1%) patients discontinued the treatment. There were no treatment-related deaths in this research. As shown in Table 6, the most common adverse reaction was myelosuppression (44.8%), followed by hypertension (41.4%), fatigue (34.5%), gastrointestinal reaction (32.7%), and hand-foot syndrome (24.1%). Notably, most of the adverse reactions were grade 1-2.

Discussion

SCLC has an abnormally high proliferation rate, a strong tendency for early metastasis, and a bleak prognosis (4). As the first-line standard treatment for ES-SCLC in the past 40 years, the PFS of platinum-etoposide chemotherapy is about 5 months, and the median OS is about 10 months (8). Based on the IMpower133 and CASPIAN clinical trials, PD-L1 plus platinum-etoposide chemotherapy has become the new first-line standard therapy in recent years. Although, it only brought the OS benefit for 2 to 3 months (9, 10). Angiogenesis serves a pivotal role in tumor occurrence, invasion, and metastasis (21). However, the efficacy of antiangiogenic therapy in SCLC is limited, such as bevacizumab, sorafenib, sunitinib and so on, except for anlotinib (15, 22–24). In China, anlotinib has been approved by CFDA as the third-line and above treatment for SCLC based on the ALTER 1202 study (17). Several small sample size single arm phase II clinical trials of anlotinib

TABLE 6 Summary of adverse reactions.

Toxicity	All grades (%)	Grade 1-2 (%)	Grade ≥3 (%)
Myelosuppression	26 (44.8)	17 (29.3)	9 (15.5)
Hypertension	24 (41.4)	21 (36.2)	3 (5.2)
Fatigue	20 (34.5)	20 (34.5)	0 (0.0)
Gastrointestinal reaction	19 (32.7)	17 (29.3)	2 (3.4)
Hand-foot syndrome	14 (24.1)	13 (22.4)	1 (1.7)
Hyperlipemia	11 (19.0)	11 (19.0)	0 (0.0)
Hemorrhage	9 (15.5)	6 (10.3)	3 (5.2)
Transaminase elevation	6 (10.3)	5 (8.6)	1 (1.7)
Hyponatremia	6 (10.3)	6 (10.3)	0 (0.0)
Hyperbilirubinemia	6 (10.3)	4 (6.9)	2 (3.4)
Hypophosphatemia	5 (8.6)	4 (6.9)	1 (1.7)
Mucositis oral	5 (8.6)	4 (6.9)	1 (1.7)
Rash	4 (6.9)	4 (6.9)	0 (0.0)
Thyroid dysfunction	3 (5.2)	3 (5.2)	0 (0.0)
Hypokalemia	3 (5.2)	3 (5.2)	0 (0.0)
Proteinuria	3 (5.2)	3 (5.2)	0 (0.0)
Hoarseness	1 (1.7)	1 (1.7)	0 (0.0)
Arthralgia	1 (1.7)	1 (1.7)	0 (0.0)

combined with platinum-etoposide chemotherapy as the first-line treatment for ES-SCLC are being carried out in China and the preliminary results have shown the favorable clinical efficacy (18–20).

Antiangiogenic therapy can improve drug delivery efficiency by opening the vascular normalization window, thus exerting a synergistic effect when combined with other regimens (25). In addition, the non-overlapping toxicity spectrum and excellent tolerance of anlotinib allow it to be used in combination with other drugs. In a clinical trial conducted by Kong T et al., 20 ES-SCLC patients received anlotinib plus platinum-etoposide chemotherapy as the first-line therapy, the median PFS was 10.0 months, and the median OS was 15.0 months (18). Similarly, in Deng P's study, the median PFS and OS were 9.4 and 13.9 months, respectively (20). Supported by these encouraging preliminary results, phase III clinical trials have already begun in China. In this real-world study, the median PFS was 6.0 months, the median OS was 10.5 months, the ORR was 58.6%, and the DCR was 89.6%. Our results are similar to the efficacy of traditional platinum-etoposide chemotherapy. But 20 (34.5%) patients with ECOG PS 2 were included in this study. In contrast, there were no patients with ECOG PS >1 in these clinical trials. The median PFS and OS of patients with ECOG PS 0-1 in this study were 8.5 and 15.0 months, respectively. The 6-month PFS rate was 75.9%, the 6-month OS rate was 100.0%, and the 1-year OS rate was 62.5%. Respectively, the ORR and DCR were 73.7% and 97.4%. Multivariate Cox regression analysis showed that ECOG PS was the independent influencing factor of PFS and OS. This result showed better efficacy compared with traditional chemotherapy and PD-L1 plus chemotherapy, and the OS was similar to the clinical studies of anlotinib plus platinum-etoposide chemotherapy. Since there is no control group in our study, the efficacy of combination therapy still requires further verification by prospective studies with larger sample size.

ES-SCLC patients first receive chemotherapy to control the spread of metastasis. Subsequently, chest radiotherapy is recommended to control local lesions for patients who achieve CR or PR after chemotherapy (26). Some studies found that antiangiogenic therapy can increase the local oxygen partial pressure and oxygen content of tumor tissue, inhibit the angiogenesis induced by radiotherapy, and play the role of radiotherapy sensitization (27). In our study, patients combined with thoracic radiotherapy had more extended PFS (8.3 *vs.* 4.2 months, P =0.002) and OS (16.8 *vs.* 7.7 months, P <0.001) benefits in univariate analysis. However, there were no statistical differences in multivariate analysis.

Hypertension and hand-foot syndrome are the most common adverse reactions of anlotinib. Interestingly, more extended PFS benefits were observed in ES-SCLC patients with post-medication hypertension or hand-foot syndrome in Song PF's study (28). In this research, patients with post-medication hypertension (8.5 vs. 5.4 months, P =0.008) and hand-foot syndrome (8.5 vs. 5.5 months, P =0.040) had longer PFS benefits in univariate analysis. Additionally, we also found that patients with post-medication hypertension (15.9 vs. 8.3 months, P <0.001) had longer OS benefits. Multivariate analysis showed that post-medication hand-foot syndrome (yes vs. no: HR=0.23, 95%CI 0.07-0.72, P =0.012) was the independent predictor of PFS, and post-medication hypertension (yes vs. no: HR=0.18, 95%CI 0.05-0.58, P =0.005) was the independent predictor of OS. Hypertension might be attributed to the mechanism that inhibition of VEGFR in vascular endothelial cells decreased the production of nitricoxide and prostacyclins, thus leading to increased blood pressure (29). Hand-foot syndrome might be induced by decreased reconstruction of skin after restriction of vessels (30). Therefore, hypertension or hand-foot syndrome induced by anlotinib could partly reflect the inherent host biology that caused differences in VEGF/VEGFR blockade (31).

Furthermore, we observed that sex (male vs. female: HR=6.05, 95%CI 1.74-20.98, P =0.005) and T stage (T3-4 vs. T1-2: HR=3.82, 95%CI 1.59-9.18, P =0.003) were the independent influencing factors of PFS. Age (≥65 vs. <65: HR=4.87, 95%CI 1.71-13.82, P =0.003) and hepatic metastases (yes vs. no: HR=3.83, 95%CI 1.41-10.41, P =0.008) were associated with OS in multivariate Cox regression analysis. However, only 11 (19.0%) female patients were included in our study, which might influence the result.

In this research, the toxicity of anlotinib plus platinum-etoposide chemotherapy was generally well tolerated. The grade 3 and above adverse reactions were manageable with dose reduction or drug discontinuation. Similar to previous research, myelosuppression was the most frequent adverse reaction (18–20). As the most common adverse reactions of anlotinib, the incidence of hypertension and hand-foot syndrome were 41.1% and 24.1%, respectively. There were no new anlotinib-related adverse reactions observed in this study, and the toxic profile was similar to other studies of anlotinib in SCLC (17). The incidence of adverse reactions in this research might be lower than actual data in the real world because of the bias of the retrospective study.

This study provided real-world data of anlotinib combined with platinum-etoposide chemotherapy as the first-line treatment for ES-SCLC at the first time. Despite the advantages of this work, there are several inevitable shortcomings in our study. First, as a real-world study, the Chinese undiversified population and small sample size might affect the universality of the results. Thus, well-designed large-scale prospective studies are urgently needed in the future to provide more profound insights into this field. Second, due to the retrospective design of this study, selection bias and information bias could not be avoided. For instance, the majority of patients included in this study are male, which may affect the representation of the study population. Besides, although we identified that post-medication hypertension and foot-hand syndrome may correlated with favorable prognosis after treatment, the sample size of these patients is small and some adverse effects are not well recorded. This

further emphasizes the importance of conducting relevant studies in the future. Last but not least, since the dosage was determined by different physicians according to the actual situation of patients, and this may affect the efficacy.

Conclusion

To sum up, our study revealed that anlotinib combined with platinum-etoposide chemotherapy as the first-line treatment for ES-SCLC appears to be effective and well-tolerated in the real-world setting, especially in patients with ECOG PS 0-1. Patients with post-medication hypertension and hand-foot syndrome may confer superior survival benefits. However, well-designed large-scale prospective studies are urgently needed in the future to verify our findings.

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 Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YY contributed to the concept and design of the research; H-RZ established the database; H-RZ, A-MJ, and HG conducted statistical analysis; H-RZ and A-MJ wrote the first draft of the manuscript; HG, NL, X-QZ, XF, Z-PR, TT, XL and YY reviewed and edited the manuscript. All authors participated in the revision of the manuscript, read 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

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Chinese herbal injections versus intrapleural cisplatin for lung cancer patients with malignant pleural effusion: A Bayesian network meta-analysis of randomized controlled trials

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Background: Malignant pleural effusion (MPE) is a common complication in patients with advanced lung cancer that can severely compromise the quality of life and limit life expectancy. Randomized controlled trials (RCTs) have shown that Chinese herbal injections (CHIs) may be beneficial in improving quality of life. This network meta-analysis (NMA) aims to explore several CHIs used for lung cancer patients with MPE.

Methods: Seven databases were systematically searched for eligible RCTs from inception to November 2021. The primary outcome was the clinical effective rate. Secondary outcomes were the improvement rate of Karnofsky performance status (KPS) score and incidence of adverse events (AEs). The Cochrane risk of bias 2 tool was used to assess the quality of included studies. Data analysis was performed using STATA 16.0 and R software 4.1.0. Both pairwise meta-analysis and Bayesian NMA were conducted. Competing interventions were ranked using the surface under the cumulative ranking (SUCRA) probabilities. Evidence grading was evaluated using the Confidence in Network Meta-Analysis online software (https://cinema.ispm.unibe.ch/).

Results: A total of 44 studies involving 2,573 patients were included. The combined Huachansu injection (HCS) with intrapleural cisplatin (cis-diamminedichloro-platinum, DDP) had the highest probability of improving the clinical effective rate (SUCRA, 84.33%). The Kangai injection (KA) combined with DDP had the most improvement rate of KPS score (SUCRA, 80.82%), while the Fufangkushen injection (FFKS) alone was more likely to reduce AEs

including gastrointestinal reactions (SUCRA, 89.92%), leukopenia (SUCRA, 91.85%), and chest pain (SUCRA, 98.17%). FFKS combined with DDP ranked the best in reducing the incidence of fever (SUCRA, 75.45%).

Conclusions: Our NMA showed that CHIs alone or combined with DDP could improve clinical effectiveness and quality of life and reduce AEs, compared to DDP alone. HSC and KA, combined with DDP, may be the most effective considering clinical effective rate and improvement of KPS score, respectively. FFKS, either used alone or in combination therapy with DDP, may be the best in reducing AEs. However, high-quality RCTs with larger sample sizes are needed to further support the evidence.

Systematic review registration: PROSPERO https://www.crd.york.ac.uk/prospero/, identifier CRD42021285275.

KEYWORDS

malignant pleural effusion (MPE), lung cancer, Chinese herbal injections, cisplatin, network meta-analysis

1 Introduction

With an estimated crude death rate of 23% (per 100,000), lung cancer was the leading cause of cancer-related death worldwide in 2020, resulting in 1.79 million deaths (1). Throughout the disease progression, approximately 40% of patients develop pleural effusions (2). Malignant pleural effusion (MPE) usually signifies advanced-stage disease or metastasis, which is a criterion for stage IV, M1a in the TNM staging system (3), with an average survival of 4 to 7 months (2). Patients may be asymptomatic at presentation but eventually develop debilitating symptoms of dyspnea, chest pain, and cough, which severely compromise their quality of life (4).

With no cure for MPE, the main goal of current management has remained predominantly palliative to alleviate symptoms and improve quality of life (5, 6). Many treatment options include chest drainage alone or with the instillation of a pleurodesis agent, semi-permanent indwelling pleural catheter, and intracavitary chemotherapy (7). For patients with poor performance status that cannot tolerate systemic chemotherapy, intrapleural chemotherapy has been proven to be a safe and effective alternative to locally control the effusion in addition to treating the underlying malignancy (8). The most used pleural injection drug is cisplatin (cis-diamminedichloro-platinum, DDP) which can kill tumor cells and reduce the generation of pleural effusion. However, the therapeutic effect of DDP is not sufficient if used alone. Furthermore, its toxic adverse effects also need to be considered (9). Complementary and alternative treatment modalities have also been critical in cancer management. Traditional Chinese medicine (TCM) has been widely used in contemporary Chinese medical practice as an adjuvant to chemotherapy, radiotherapy, targeted therapy, and immunotherapy (10). With a number of pharmacological studies demonstrating their antitumor effects, accumulating research evidence has indicated that many medicinal plants could be used alone or in combination with commonly used chemotherapy drugs for patients with MPE, as they can increase efficiency and reduce adverse reactions (11, 12). Various kinds of Chinese herbal injections (CHIs) have been developed in recent years, containing substances extracted from single materials or compound formulas of TCM (13). Due to their extensive biological activity and low toxicity in animal studies, these drugs have been used as therapeutic options for MPE (14). Numerous randomized controlled trials (RCTs) have reported advantageous results for synergy and attenuation when CHIs have been used as adjuvant or alternative treatments when compared to DDP for lung cancer patients with MPE. While there is a diverse range of CHIs, there is insufficient evidence available to determine their effectiveness. Our study aims to conduct a systematic review and network meta-analysis (NMA) on the estimated relative effects of multiple CHIs as an adjuvant for intrapleural cisplatin (DDP) in lung cancer patients with MPE.

2 Methods

Our protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO)

(registration number CRD42021285275). The full review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMA (15). The PRISMA checklist is provided in Supplementary File S1.

2.1 Search strategy

The following seven databases were searched from inception to November 2021: MEDLINE (*via* PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (*via* OVID), China National Knowledge Infrastructure (CNKI), WanFang Database, Chinese Scientific Journals Database (VIP), and Chinese Biomedical Literature database (SinoMed). Literature was searched using the combination of medical subject headings (MeSH), free-text words, and publication types. Only Chinese and English articles were retrieved. Reference lists of relevant systematic reviews and meta-analysis identified through screening were also checked manually. Full details of the search strategies used for each database are provided in Supplementary File S2.

2.2 Eligibility criteria

2.2.1 Types of studies

Only RCTs reported in English and Chinese were included. Clinical trials described to be randomly allocated were all considered eligible, but studies with a considerable high risk of bias in the generation of the randomization sequence, for example, by date of admissions, were excluded.

2.2.2 Types of patients

Adult patients over the age of 18 and diagnosed with MPE caused by lung cancer (of any type and stage), confirmed by histological or cytological findings, were included. There were no restrictions on patient gender, race, and histological types of lung cancer.

2.2.3 Types of interventions

Studies that compared CHIs combined with or without DDP by intrapleural perfusion to intrapleural DDP alone were included. The following 10 CHIs, categorized as antitumor agents within the inventory of Chinese patent drugs authorized by the National Healthcare Security Administration (NHSA) of the People's Republic of China (http://www.nhsa.gov.cn/), were considered eligible: Aidi injection (AD), Huachansu injection (HCS), Fufang Kushen injection (FFKS), Tongguanteng injection (TGT), Yadanzi injection (YDZ), Shenqi Fuzheng injection (SQFZ), Polyporus umbellatus polysaccharide injection (PUP), Kangai injection (KA), Kanglaite injection (KLT), and Astragalus polysaccharide (APS). Patients who received systemic or intravenous chemotherapy other than intrapleural DDP, or oral TCM formulas, or other TCM interventions in addition to the above 10 CHIs were excluded.

2.2.4 Types of outcomes

We used the following dichotomous outcomes for easier interpretation into clinical guidance. The primary outcome was the clinical effective rate for MPE, defined as the proportion of patients achieving complete response (CR) and partial response (PR) after treatment according to the World Health Organization criteria (16, 17), which could be computed as the number of patients achieving CR and PR divided by the total number of patients treated. Secondary outcomes were the rate of Karnofsky performance status (KPS) improvement (referring to KPS score increasing more than 10 points after treatment) and incidence of adverse events including gastrointestinal reactions, leukopenia, chest pain, and fever.

2.3 Study selection and data extraction

EndNote (EN) X9.3.3 was used to manage literature. One review author (YFX) excluded ineligible studies first by screening titles and abstracts. This was followed by two review authors (YRC and YFX) independently identifying eligible studies through full-text review. Disagreements were resolved through discussion or by referral to a third author (ZLL).

Two review authors (YFX and YXS) independently extracted data from eligible studies. Data were cross-checked for accuracy, and disagreements were resolved through discussion. The following data items were extracted: (1) publication information including first author and year of publication; (2) study characteristics including sample size, follow-up duration, randomization procedure, and blinding procedure; (3) patient characteristics including age and sex; (4) intervention and comparator characteristics including dose and course; and (5) outcome measurements.

2.4 Risk of bias assessment

Two authors (YXS and CYL) independently assessed risk of bias for each study using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (18). The following five domains were assessed within each included study under the official guidance document (19): (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. An overall risk-of-bias judgment was

made on each study as "low risk of bias", "some concerns", or "high risk of bias". Disagreements were resolved through discussion or by consulting a third author (DMQ) for consensus.

2.5 Quality of evidence assessment

Two review authors (BFL and YBH) independently assessed the confidence in the body of evidence using the Confidence in Network Meta-Analysis (CINeMA) web application, recommended by the Cochrane handbook for undertaking NMA (20). Disagreements were discussed mutually or by inviting a third author (JPL) to reach a consensus. The methodological framework of CINeMA evaluates confidence in the NMA findings based on the contribution matrix of included studies with consideration of the following six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (21).

2.6 Statistical analysis

We performed a standard pairwise meta-analysis using STATA 16.0. A Bayesian NMA was conducted using R software 4.1.0 *via* Just Another Gibbs Sampler (JAGS). The BUGSnet package was used in R (22). We calculated the risk ratio (RR) with 95% confidence intervals (CIs) for the rate of clinical effectiveness, KPS improvement, and AEs. A random-effects model was analyzed to estimate effects among multiple comparisons using the Markov chain Monte Carlo (MCMC) method. We set an uninformative prior distribution for four Markov chains running 250,000 iterations (burn-in iterations = 50,000, thinning factor = 1). Convergence was assessed by the Brooks-Gelman-Rubin diagnosis plot and potential scale reduction factor (PSRF), with a PSRF value close to 1 indicating convergence (23). For the dichotomous outcome measurements among mixed comparisons, RR with 95% credible intervals (CrIs) were presented within league tables. We also calculated surface under the cumulative ranking curve (SUCRA) probability values to estimate rankings of competing interventions. The BUGSnet R package was used to draw SUCRA plots. In our study, higher SUCRA values reflect a higher associated clinical effective rate, higher KPS improvement rate, and a lower rate of adverse events. A network geometry plot was drawn to summarize the treatment network using STATA. Each node represents an intervention, and each edge represents a head-to-head comparison between two different interventions (24). The sizes of nodes and edges display the numbers of patients receiving the treatment and the number of studies for the comparison, respectively (24). We split three-arm studies into two pairwise comparisons by equally dividing the number of patients receiving DDP. Since there were no "closed loops" in the network plot, we were unable to assess inconsistency among direct and indirect comparisons. Statistical heterogeneities were tested using the $\chi 2$ test with a significance level of 0.1 and quantified using I^2 statistics. Substantial heterogeneities were considered with I^2 greater than 50%. There was insufficient information in included studies for conducting subgroup analysis considering different lung cancer subtypes or treatment duration. A subgroup analysis considering different doses of DDP was conducted to identify substantial sources of clinical heterogeneity. Comparison-adjusted funnel plots were presented to assess small study effects and potential publication bias using STATA.

3 Results

3.1 Search results

A total of 7,456 citations were identified from seven databases. After removing 1,364 duplicates, a further 5,778 were excluded due to irrelevancy based on their titles and abstracts. The full text of the remaining 314 studies was screened, of which 44 RCTs were deemed eligible. The PRISMA flow diagram for the study selection process is shown in Figure 1.

3.2 Characteristics of included studies

A total of 2,573 lung cancer patients and 6 kinds of CHIs were involved in the 44 RCTs in which all the patients were in advanced stage. The average age of patients in the vast majority of included studies fluctuated between 50 and 70. All patients received treatment for at least 2 weeks. In terms of treatment, 1,258 patients used DDP alone, 1,096 patients were treated with CHIs combined with DDP, and 219 patients received only CHIs. For the outcomes, 43 studies (97.7%) reported clinical effective rate, 30 studies (68.2%) evaluated the improvement rate of KPS score, and 33 studies (75.0%), 25 studies (56.8%), 26 studies (59.1%), 21 studies (47.7%) assessed the incidence of gastrointestinal reactions, leukopenia, chest pain, and fever, respectively. Details of the baseline characteristics of the studies are shown in Table 1.

Of the 44 RCTs included, all were two-arm studies except for one (51) three-arm study. The three-arm study administered YDZ combined with DDP, DDP alone, and YDZ alone. The interventions for all the two-arm studies were either combined therapies of CHIs and DDP or CHIs alone, compared to DDP alone. Among the combined therapies, there were six kinds of CHIs: AD combined with DDP [10 RCTs (25–30, 43, 46, 60, 61)], FFKS combined with DDP [11 RCTs (31–37, 42, 45, 48, 59)], HCS combined with DDP [one RCT (38)], KA combined

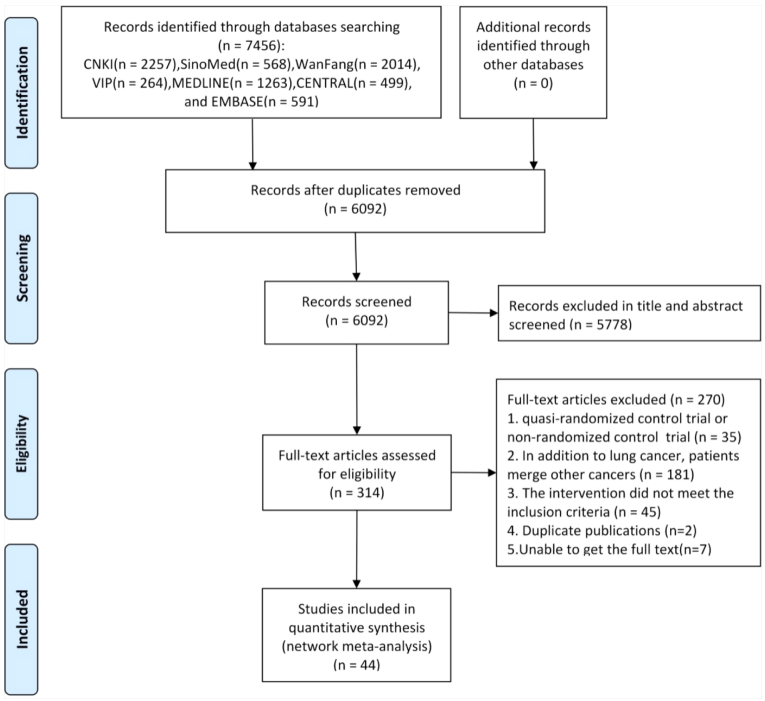

FIGURE 1
Flowchart of the search for eligible studies. Note: n, number of articles. CNKI, China National Knowledge Infrastructure; SinoMed, the Chinese Biomedical Literature Database; WanFang, the WanFang Database; VIP, the Chinese Scientific Journals Full-Text Database. n, number of articles. CNKI, China National Knowledge Infrastructure; SinoMed, the Chinese Biomedical Literature Database; WanFang, the WanFang Database; VIP, the Chinese Scientific Journals Full-Text Database.

with DDP [two RCTs (39, 40)], KLT combined with DDP [one RCT (41)], and YDZ combined with DDP [12 RCTs (44, 47, 49–58)]. As for the studies that used CHIs alone, there were four kinds of CHIs: KLT [one RCT (62)], AD [three RCTs (63, 65, 68)], FFKS [two RCTs (64, 66)], and YDZ [two RCTs (51, 67)]. The detailed information about compositions, indications, and mechanisms of the CHIs is described in Supplementary File S3.

3.3 Risk of bias assessment

Considering the bias generated by the randomization process, all studies had adopted a randomized approach, and reported that the baselines of the two groups were comparable. However, due to the lack of specified methods for generating allocation sequence and concealment, 41 of 44 RCTs were assessed as "some concerns". Two RCTs (45, 56) were classified as low risk with envelopes for concealment and double-blind procedure mentioned, respectively. One RCT (60) was classified as high risk because of collecting data retrospectively. About the bias due to deviations from intended interventions, all included studies reported no deviations from allocated interventions and used an appropriate method to analyze treatment effects. Thus, all studies were regarded as "low risk". In terms of bias due to missing outcome data and bias in measurement of the outcome, we could get complete data in all studies; moreover, the measurement or determination of the outcomes in the two groups is consistent and objective; hence, all studies were evaluated as "low risk". As for the bias in selection of the reported results, there were no pre-reported study protocols identified; thus, all RCTs were rated as "some concerns". Details of the risk of bias assessment are shown in Supplementary File S4.

3.4 Pairwise meta-analysis

We performed a direct comparison of interventions with different CHIs compared with DDP in the six outcomes. The forest plot and detailed information of the heterogeneity analysis for the six outcomes are shown in Supplementary File S5. Most of the comparisons between the two groups showed no significant heterogeneity, except for FFKS compared to DDP for clinical effective rate (I^2 = 69%), YDZ compared to DDP for the improvement rate of KPS score (I^2 = 90.9%), and FFKS

TABLE 1 Characteristics of the included studies.

Study ID	Sample size (E/C)	Mean/median age (E/C)	Sex (M/F) (E/C)	Treatment of experiment group†	Treatment of control group†	Course	Outcomes
Zhu Y, 2011 (25)	43/30	58.4/58.2	(30/13)/(20/10)	DDP 30 mg/m^2 + AD 70 ml	DDP 30 mg/m^2	Once a week/×3	①②③⑤⑥
Wang XH, 2010 (26)	30/30	/	(22/8)/(25/5)	DDP 40 mg + AD 50 ml	DDP 40 mg	Once a week/×4	①④
Sun SL, 2012 (27)	21/19	62/60	(14/7)/(13/6)	DDP 20–30 mg/m^2 + AD 50–80 ml	DDP 20–30 mg/m^2	Once a week/×4	①②③④⑤⑥
Meng ZL, 2009 (28)	22/20	68	(14/8)/(14/6)	DDP 20–30 mg/m^2 + AD 50–80 ml	DDP 20–30 mg/m^2	Once a week/×4	①②③④⑤⑥
Wang Y, 2017 (29)	32/32	(56.7 ± 4.3)/(56.1 ± 4.4)	(22/10)/(23/9)	DDP 20–30 mg/m^2 + AD 50–80 ml	DDP 20–30 mg/m^2	Once a week/×4	①②③④⑤⑥
Zhang ZL, 2010 (30)	38/36	46–75	43/31	DDP 40–60 mg + AD 50–70 ml	DDP 40–60 mg	Twice a week/×4	①③⑤⑥
Han ZQ, 2012 (31)	28/28	(62 ± 3)/(58 ± 12)	35/21	DDP 20–40 mg + FFKS 30–50 ml	DDP 20–40 mg	Once a week/×(2–4)	①②③④③
Tang XQ, 2018 (32)	30/30	(55.6 ± 2.1)/(53.2 ± 1.8)	/	DDP 40 mg + FFKS 60 ml	DDP 40 mg	Twice a week/×6	①②③④
He L, 2010 (33)	24/20	58/60	(16/8)/(9/11)	DDP 40 mg/m^2 + FFKS 40 ml	DDP 40 mg/m^2	Once a week/×3	①③④
Li YP, 2009 (34)	30/30	55/56	(25/5)/(24/6)	DDP 40 mg + FFKS 20 ml	DDP 40 mg	Once a week	①③④③⑥
Wu CY, 2019 (35)	25/25	(53.48 ± 4.26)/(55.14 ± 5.32)	(16/9)/(14/11)	DDP 40–60 mg + FFKS 40–60 ml	DDP 40–60 mg	Once or twice every 2 weeks	①②③
Liu L, 2017 (36)	30/30	56.4/54.2	/	DDP 40 mg + FFKS 20 ml	DDP 40 mg	Once a week/×4	①②③④
Shi WJ, 2017 (37)	30/30	(56.8 ± 5.7)/(56.4 ± 5.8)	(18/12)/(21/9)	DDP 40 mg + FFKS 20 ml	DDP 40 mg	Once a week/×4	①②③④
Liu SY, 2017 (38)	32/32	(56 ± 1)/(55 ± 1)	(18/14)/(17/15)	DDP 60 mg + HCS 20 ml	DDP 60 mg	Once a week/×2	①③④③⑥
Qu DM, 2012 (39)	24/22	63	(15/9)/(12/10)	DDP 40–60 mg + KA 50 ml	DDP 40–60 mg	Once a week/×3	①②
He JY, 2011 (40)	20/20	58.2	24/16	DDP 80 mg + KA 60 ml	DDP 80 mg	Once a week/×6	①③④
Li HH, 2012 (41)	30/30	35–78	38/22	DDP 50 mg + KLT 100 ml	DDP 50 mg	Once a week/×2	①②
Pan JJ, 2007 (42)	36/34	60 ± 21	(22/14)/(21/13)	DDP 40 mg + FFKS 30 ml	DDP 40 mg	Once a week/×3	①③④
Yang DF, 2015 (43)	25/25	(62.2 ± 2.6)/(61.2 ± 2.3)	(16/9)/(17/8)	DDP 25 mg + AD 75 ml	DDP 25 mg	Once a week/×5	③④
Shen SL, 2017 (44)	40/40	(64.6 ± 4.7)/(62.5 ± 5.2)	(23/17)/(29/11)	DDP 50 mg/m^2 + YDZ 50 ml	DDP 50 mg/m^2	Once a week/×4	①②③④⑤⑥
Liu D, 2015 (45)	46/42	60.2 ± 8.2	48/40	DDP 40–60 mg + FFKS 20 ml	DDP 40–60 mg	Once a week/×3	①②③⑤⑥
Wu MB, 2020 (46)	18/18	(67.37 ± 3.5)/(65.33 ± 4.1)	(11/7)/(14/4)	DDP 25 mg/m^2 + AD 50 ml	DDP 25 mg/m^2	Once a week/×(12–18)	①③④③⑥
Jing Y, 2017 (47)	30/33	63.84 ± 1.59	(18/12)/(16/17)	DDP 40 mg/m^2 + YDZ 60 ml	DDP 40 mg/m^2	Once a week/×2	①②
Peng HY, 2020 (48)	25/25	(57.2 ± 2.1)/(56.9 ± 1.9)	(14/11)/(15/10)	DDP 30 mg/m^2 + FFKS 40 ml	DDP 30 mg/m^2	Three times every 2 weeks/×2	①③⑤⑥
Mo SX, 2009 (49)	28/28	50.3/51.8	(17/11)/(18/10)	DDP 80–100 mg + YDZ 60–80 ml	DDP 80–100 mg	Once a week/×3	①②③④⑤⑥
Liu Y, 2014 (50)	14/14	45–85	18/10	DDP 40 mg + YDZ 40 ml	DDP 40 mg	Five times a week/×4	①②

(Continued)

TABLE 1 Continued

Study ID	Sample size (E/C)	Mean/median age (E/C)	Sex (M/F) (E/C)	Treatment of experiment group†	Treatment of control group†	Course	Outcomes
Song YJ, 2011 (51)	30/30/30	56 ± 11.5	53/37	DDP 40 mg/m^2 + YDZ 50 ml; YDZ50 ml	DDP 40 mg/m^2	Once a week/×4	①②
Wang HM, 2007 (52)	35/35	58	45/25	DDP 20–30 mg/m^2 + YDZ 80–100 ml	DDP 20–30 mg/m^2	Once every 5–7 days/×4	①②③④⑤⑥
Zhang SF, 2009 (53)	27/23	72	(19/8)/(16/7)	DDP 20–30 mg/m^2 + YDZ 50–100 ml	DDP 20–30 mg/m^2	Once every 5–7 days/×4	①②③④⑤⑥
Liu B, 2012 (54)	32/32	57.2	31/33	DDP 40 mg/m^2 + YDZ 100 ml	DDP 40 mg/m^2	Once every 5–7 days/×4	①②③④⑤⑥
Guo YF, 2013 (55)	34/28	63/68	(24/10)/(22/6)	DDP 60–80 mg + YDZ 60 ml	DDP 60–80 mg	Once a week/×(2-3)	①②
Zhang H, 2013 (56)	34/30	62.5/56	(28/6)/(24/6)	DDP 40–60 mg + YDZ 40–50 ml	DDP 40–60 mg	Once a week/×3	①⑤
Wang CY, 2016 (57)	30/30	(60.25 ± 1.64)/(63.84 ± 1.59)	(18/12)/(16/14)	DDP 40 mg/m^2 + YDZ 60 ml	DDP 40 mg/m^2	Once a week/×2	①②
Chen SL, 2015 (58)	30/30	(56.6 ± 11.9)/(57.7 ± 12.5)	(18/12)/(17/13)	DDP 20–30 mg/m^2 + YDZ 60–90 ml	DDP 20–30 mg/m^2	Once a week/×3	①②③④⑤⑥
Huang XM, 2007 (59)	20/18	55/56	(15/5)/(13/5)	DDP 40 mg + FFKS 20 ml	DDP 40 mg	Once a week	①③④⑤⑥
Wang XC, 2014 (60)	32/32	68	46/18	DDP 60 mg + AD 40 ml	DDP 60 mg	Once a week/×4	①③④⑤
Liu CX, 2013 (61)	56/56	(62.18 ± 8.95)/(62.05 ± 9.05)	(28/28)/(29/27)	DDP 30 mg + AD 100 ml	DDP 30 mg	Once a week/×4	①②③④⑤
Zhang HZ, 2015 (62)	32/26	45–72/47–76	(23/9)/(18/8)	KLT 200 ml	DDP 30 mg	Five times a week/×4	①③⑤⑥
Sun LH, 2005 (63)	25/25	32–74	23/27	AD 50 ml	DDP 40 mg	Twice a week/×4	①②③⑤⑥
Hu Q, 2008 (64)	20/20	(64.5 ± 2.3)/(64.3 ± 2.1)	(13/7)/(12/8)	FFKS 20 ml	DDP 30 mg	Once a day/×3	①②③④⑤⑥
Fu J, 2005 (65)	20/20	35–74	/	AD 50 ml	DDP 40 mg	Twice a week/×4	①
Xing HM, 2013 (66)	45/42	(60.2 ± 7.9)/(62.5 ± 8.4)	(28/17)/(24/18)	FFKS 20 ml	DDP 40–60 mg	Once every 3–5 days/×4	①②③⑤⑥
Wang K, 2010 (67)	21/21	32–75	/	YDZ 50 ml	DDP 40 mg	Once 2 weeks/×2	①②③
Wang JH, 2013 (68)	26/26	58.85/58.88	(15/11)/(14/12)	AD 100 ml	DDP 80–100 mg	Once a week/×(2–4)	①②③⑤

†All treatments were administered through intrapleural injection. E, experiment group; C, control group; M, male; F, female; DDP, cisplatin; AD, Aidi injection; FFKS, Fufangkushen injection; HCS, Huachansu injection; KA, Kangai injection; KLT, Kanglaite injection; YDZ, Yadanzi injection. ① Clinical effective rate; ② The improvement rate of KPS score; ③ Incidence of gastrointestinal reactions; ④ Incidence of Leukopenia; ⑤ Incidence of chest pain; ⑥ Incidence of fever.

+DDP compared to DDP for the incidence of gastrointestinal reactions (I^2 = 59.5%). Thus, the fixed-effects model for meta-analysis was used. Subgroup analysis and sensitivity analysis was conducted when there was heterogeneity. Since the tumor stages included in this study were all stage IV, which were consistent and had no obvious clinical heterogeneity, and different doses and courses of chemotherapy may be substantial sources of clinical heterogeneity, a subgroup analysis conducted on the total dose of DDP with sufficient studies indicated that the dose was the likely cause of the heterogeneity. Changing the effect model and eliminating the literature effect size one by one revealed that the original results were not changed ($p < 0.05$), indicating that the sensitivity analysis results were negative, and the results were relatively robust and reliable. The details of subgroup analysis and sensitivity analysis are shown in Supplementary File S6.

3.5 Network meta-analysis

Network graphs comparing CHIs for lung cancer patients with MPE in each of the six outcomes are shown in Figure 2. The network graphs were generated using Stata 16.0. Each intervention was shown by a circular node, and each connection represented a contrast. The diameter of the circular node was positively correlated with the number of

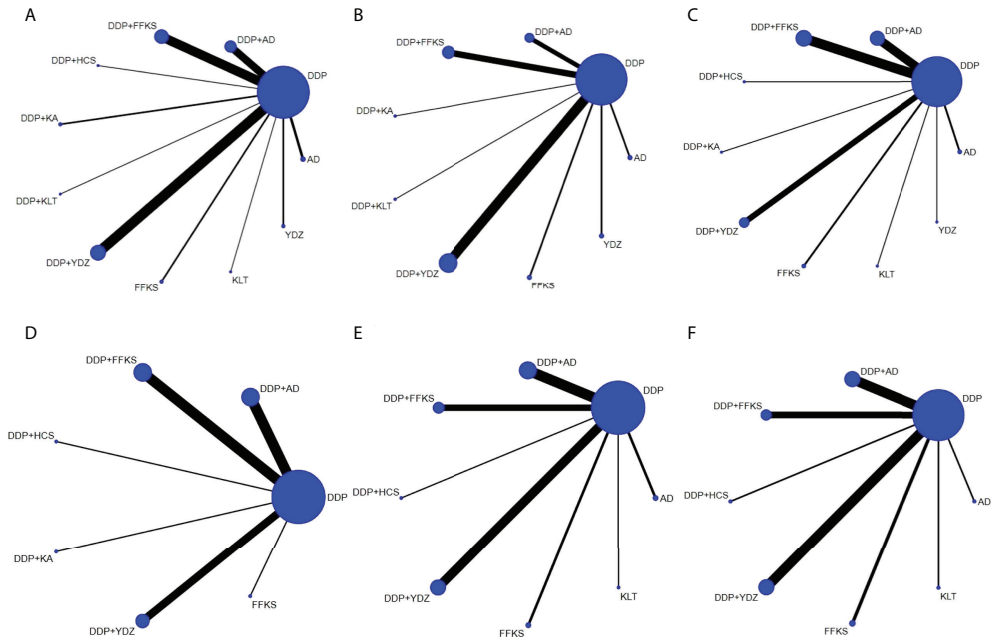

FIGURE 2
The network graphs comparing CHIs for lung cancer with MPE. **(A)** Clinical effective rate. **(B)** The improvement rate of KPS score. **(C)** Incidence of gastrointestinal reactions. **(D)** Incidence of leukopenia. **(E)** Incidence of chest pain. **(F)** Incidence of fever. Each node represents an intervention, and each edge represents a head-to-head comparison between two different interventions. The sizes of nodes and edges display the numbers of patients receiving the treatment and the number of studies for the comparison, respectively. AD, Aidi injection; DDP, cisplatin; FFKS, Fufang Kushen injection; HCS, Huachansu injection; KA, Kangai injection; KLT, Kanglaite injection; YDZ, Yadanzi injection.

patients included, and line thickness was positively related to the number of direct comparisons.

It can be seen from Figure 2 that DDP was used as the comparator arm in all studies, but as there was no direct comparison between any two interventions, no closed loop existed. As a result, an inconsistency test was not required for this study. Based on the heterogeneity results and the baseline data of the studies shown in Table 2, we believe that the homogeneity and similarity assumptions between the studies were sufficient in the NMA, and therefore, the consistency model and random-effects model were chosen to build Bayesian models. The maximum number of iterative calculations during the model building process was 250,000.

RRs (95% CrIs) of all interventions for the six outcomes in our NMA are shown in Table 2. The results of the ranking probabilities based on SUCRA are shown in Table 3 and Figure 3. We also provided the rankograms in Figure S7.

3.5.1 Clinical effective rate

A total of 43 studies reported the clinical effective rate, including the three-arm study. There were 11 interventions involved in this NMA where DDP was used as a common control to indirectly compare the clinical effectiveness of different CHIs.

Table 2A details the effectiveness of the comparison of different interventions by RRs and the corresponding 95% CrIs in NMA. The combination therapy of CHIs and DDP was significantly more effective in improving the clinical effective rate than DDP alone. However, CHIs alone did not show statistical significance compared with DDP alone. The results of the SUCRA showed that the combination of HCS and DDP might be associated with the highest probability of being the best choice for improving the clinical effective rate (84.33%) and DDP alone showed the lowest probability (7.06%). The probability ranked in the middle was the CHIs alone.

3.5.2 The improvement rate of KPS score

There were 30 studies that informed the improvement rate of KPS score, including the three-arm study, and nine related interventions. The network comparisons displayed in Table 2B suggested that there were four interventions (AD, DDP+AD, DDP+FFKS, and DDP+YDZ) that could improve KPS compared to DDP alone, though other interventions showed no statistical significance.

TABLE 2 League table of NMA estimations.

Table 2A Network meta-analysis comparisons for clinical effective rate

DDP										
0.91 (0.73,1.13)	**AD**									
0.72 (0.63,0.80)	0.79 (0.62,1.01)	**DDP+AD**								
0.73 (0.65,0.81)	0.80 (0.63,1.03)	1.02 (0.87,1.20)	**DDP +FFKS**							
0.60 (0.38,0.87)	0.65 (0.40,1.02)	0.83 (0.52,1.24)	0.81 (0.51,1.21)	**DDP+HCS**						
0.71 (0.48,1.00)	0.78 (0.50,1.18)	0.99 (0.66,1.43)	0.97 (0.65,1.40)	1.19 (0.69,2.09)	**DDP+KA**					
0.63 (0.41,0.89)	0.69 (0.43,1.05)	0.89 (0.57,1.27)	0.87 (0.56,1.24)	1.06 (0.61,1.87)	0.89 (0.52,1.50)	**DDP+KLT**				
0.69 (0.62,0.77)	**0.76 (0.60,0.97)**	0.96 (0.82,1.13)	0.94 (0.81,1.10)	1.16 (0.78,1.84)	0.97 (0.68,1.45)	1.09 (0.76,1.69)	**DDP +YDZ**			
0.82 (0.64,1.04)	0.90 (0.65,1.25)	1.15 (0.87,1.50)	1.12 (0.85,1.47)	1.38 (0.87,2.29)	1.16 (0.75,1.83)	1.30 (0.84,2.11)	1.19 (0.90,1.55)	**FFKS**		
0.78 (0.51,1.14)	0.86 (0.53,1.33)	1.09 (0.70,1.61)	1.07 (0.69,1.58)	1.32 (0.74,2.31)	1.10 (0.64,1.88)	1.24 (0.71,2.14)	1.13 (0.73,1.67)	0.95 (0.58,1.49)	**KLT**	
0.92 (0.66,1.26)	1.01 (0.69,1.48)	1.29 (0.91,1.80)	1.26 (0.89,1.76)	1.55 (0.93,2.63)	1.30 (0.80,2.12)	1.46 (0.90,2.47)	1.34 (0.95,1.86)	1.13 (0.74,1.67)	1.18 (0.72,1.99)	**YDZ**

Table 2B Network meta-analysis comparisons for the improvement rate of KPS score

DDP										
0.63 (0.43,0.89)	**AD**									
0.68 (0.56,0.81)	1.07 (0.73,1.65)	**DDP+AD**								
0.67 (0.56,0.79)	1.06 (0.72,1.62)	0.99 (0.76,1.26)	**DDP +FFKS**							
0.51 (0.21,1.02)	0.81 (0.32,1.79)	0.76 (0.30,1.54)	0.77 (0.31,1.55)	**DDP+KA**						
0.73 (0.50,1.04)	1.17 (0.69,1.97)	1.08 (0.71,1.62)	1.10 (0.72,1.63)	1.43 (0.65,3.71)	**DDP+KLT**					
0.68 (0.60,0.76)	1.08 (0.75,1.63)	1.00 (0.80,1.25)	1.01 (0.83,1.25)	1.33 (0.66,3.27)	0.92 (0.64,1.38)	**DDP+YDZ**				
0.79 (0.54,1.12)	1.26 (0.76,2.12)	1.17 (0.77,1.73)	1.19 (0.79,1.77)	1.56 (0.71,3.98)	1.08 (0.65,1.81)	1.17 (0.79,1.69)	**FFKS**			
0.76 (0.44,1.30)	1.21 (0.63,2.37)	1.12 (0.63,1.99)	1.14 (0.64,2.01)	1.50 (0.62,4.08)	1.04 (0.54,2.02)	1.12 (0.64,1.94)	0.96 (0.51,1.85)	**YDZ**		

Table 2C Network meta-analysis comparisons for incidence of gastrointestinal reactions

DDP									
12.79 (2.92,105.93)	**AD**								
2.46 (1.46,4.28)	**0.19 (0.02,0.94)**	**DDP+AD**							
2.40 (1.55,3.96)	**0.19 (0.02,0.90)**	0.97 (0.48,2.01)	**DDP +FFKS**						
0.97 (0.19,4.89)	**0.07 (0.01,0.68)**	0.39 (0.07,2.14)	0.40 (0.07,2.13)	**DDP+HCS**					
3.25 (0.55,29.52)	0.25 (0.02,3.56)	1.32 (0.20,12.66)	1.35 (0.21,12.67)	3.41 (0.30,50.31)	**DDP+KA**				
1.65 (0.88,3.24)	**0.13 (0.01,0.66)**	0.67 (0.29,1.57)	0.69 (0.31,1.53)	1.71 (0.30,9.91)	0.51 (0.05,3.45)	**DDP+YDZ**			
16.81 (3.83,130.04)	1.32 (0.10,16.24)	**6.85 (1.40,56.08)**	**7.00 (1.46,56.24)**	**17.89 (1.92,230.72)**	5.27 (0.37,77.49)	**10.24 (1.99,85.75)**	**FFKS**		
6.92 (1.26,61.22)	0.54 (0.04,7.39)	2.82 (0.46,26.16)	2.89 (0.48,26.26)	7.29 (0.67,105.90)	2.14 (0.13,35.16)	4.21 (0.66,40.02)	0.41 (0.03,5.78)	**KLT**	
4.90 (1.26,22.92)	0.38 (0.03,3.23)	2.00 (0.45,10.10)	2.05 (0.47,9.99)	5.12 (0.61,46.95)	1.51 (0.11,15.89)	2.98 (0.65,15.57)	0.29 (0.03,2.47)	0.71 (0.05,7.06)	**YDZ**

(Continued)

TABLE 2 Continued

Table 2D Network meta-analysis comparisons for incidence of leukopenia

DDP						
1.69 (1.31,2.35)	**DDP+AD**					
2.02 (1.51,2.80)	1.20 (0.78,1.80)	**DDP+FFKS**				
3.87 (1.23,18.55)	2.28 (0.69,11.03)	1.91 (0.58,9.37)	**DDP+HCS**			
2.98 (1.15,10.21)	1.76 (0.64,6.17)	1.48 (0.54,5.20)	0.78 (0.13,4.13)	**DDP+KA**		
2.30 (1.58,3.47)	1.36 (0.82,2.20)	1.14 (0.69,1.88)	0.60 (0.12,2.03)	0.77 (0.21,2.18)	**DDP+YDZ**	
10.24 (1.74,236.98)	**6.07 (1.00,138.93)**	5.06 (0.84,116.98)	2.66 (0.25,71.19)	3.40 (0.39,88.58)	4.48 (0.72,104.55)	**FFKS**

Table 2E Network meta-analysis comparisons for incidence of chest pain

DDP						
2.48 (1.09,6.42)	**AD**					
1.88 (1.08,3.09)	0.76 (0.25,1.96)	**DDP+AD**				
1.99 (1.01,4.16)	0.80 (0.25,2.43)	1.06 (0.46,2.69)	**DDP +FFKS**			
2.41 (0.92,7.07)	0.97 (0.25,3.75)	1.28 (0.45,4.40)	1.21 (0.36,4.27)	**DDP+HCS**		
1.15 (0.70,2.06)	0.46 (0.16,1.27)	0.61 (0.30,1.41)	0.58 (0.24,1.42)	0.48 (0.15,1.50)	**DDP+YDZ**	
9.44 (3.39,35.14)	3.83 (0.94,17.82)	**5.04 (1.64,20.84)**	**4.75 (1.34,20.55)**	3.93 (0.88,19.99)	**8.24 (2.48,32.83)**	**FFKS**
2.45 (0.79,8.66)	0.99 (0.22,4.49)	1.30 (0.38,5.26)	1.23 (0.32,5.16)	1.01 (0.21,4.94)	2.13 (0.58,8.05)	0.26 (0.05,1.33)

Table 2F Network meta-analysis comparisons for incidence of fever

DDP						
3.78 (0.26,143.83)	**AD**					
1.19 (0.48,4.99)	0.32 (0.01,7.11)	**DDP+AD**				
3.24 (1.04,17.45)	0.87 (0.02,21.53)	2.72 (0.51,15.21)	**DDP +FFKS**			
1.65 (0.27,10.50)	0.43 (0.01,11.05)	1.41 (0.12,9.14)	0.52 (0.04,3.83)	**DDP+HCS**		
1.15 (0.48,3.54)	0.31 (0.01,5.71)	0.97 (0.19,3.63)	0.36 (0.06,1.58)	0.69 (0.10,6.17)	**DDP+YDZ**	
2.86 (0.76,11.87)	0.76 (0.02,15.88)	2.42 (0.31,11.64)	0.89 (0.10,4.93)	1.74 (0.18,17.00)	2.50 (0.42,12.45)	**FFKS**
1.82 (0.26,13.67)	0.47 (0.01,13.65)	1.54 (0.12,11.98)	0.56 (0.04,5.01)	1.10 (0.08,16.15)	1.58 (0.16,13.18)	0.63 (0.06,7.02)

The differences between the compared groups were deemed as significant when the 95% CrI of the RR did not contain 1.00, which is marked as bold font. The data are the RR (95% CrI) of the column intervention compared to the row intervention, i.e., for the clinical effective rate, DDP alone was significantly less effective than DDP plus AD (RR 0.72, 95% CrI 0.63–0.80). DDP, cisplatin; AD, Aidi injection; FFKS, Fufangkushen injection; HCS, Huachansu injection; KA, Kangai injection; KLT, Kanglaite injection; YDZ, Yadanzi injection.

According to the SUCRA probabilities, the ranking of interventions to improve the KPS score is as follows: DDP+KA (80.82%) > AD (68.37%) > DDP+FFKS (60.87%) > DDP+AD (58.02%) > DDP+YDZ (57.93%) > DDP+KLT (44.95%) > YDZ (41.52%) > FFKS (33.46%) > DDP (4.03%). As with clinical effective rate, DDP alone might show the lowest probability of improving KPS scores.

3.5.3 Incidence of gastrointestinal reactions

In terms of the incidence of adverse events, 33 studies involving 10 interventions reported incidence of gastrointestinal reactions. Network comparisons suggested that six types of treatment (DDP+AD, DDP+FFKS, AD, FFKS, KLT, and YDZ) were better than DDP alone in reducing the incidence of gastrointestinal reactions.

TABLE 3 Ranking probability of interventions.

Intervention	Clinical effective rate		The improvement rate of KPS score		Incidence of gastrointestinal reactions		Incidence of leukopenia		Incidence of chest pain		Incidence of fever	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
DDP+AD	62.80	4	58.02	4	43.88	6	25.98	6	46.68	6	33.19	6
DDP+FFKS	57.34	6	60.87	3	42.79	7	42.34	5	50.36	5	75.45	1
DDP+HCS	84.33	1	–	–	14.56	9	72.64	2	59.97	3	47.95	5
DDP+KA	61.25	5	80.82	1	51.43	5	63.62	3	–	–	–	–
DDP+KLT	78.15	2	44.95	6	–	–	–	–	–	-	–	-
DDP+YDZ	71.45	3	57.93	5	26.80	8	53.17	4	17.08	7	31.00	7
KLT	46.90	7	–	–	72.26	3	–	–	59.45	4	51.21	4
AD	21.24	10	68.37	2	85.67	2	–	–	62.05	2	69.87	3
YDZ	21.41	9	41.52	7	64.91	4	–	–	–	–	–	–
FFKS	38.09	8	33.46	8	89.92	1	91.85	1	98.17	1	70.67	2
DDP	7.06	11	4.03	9	7.77	10	0.42	7	6.21	8	20.67	8

DDP, cisplatin; AD, Aidi injection; FFKS, Fufangkushen injection; HCS, Huachansu injection; KA, Kangai injection; KLT, Kanglaite injection; YDZ, Yadanzi injection.

As the results of SUCRA show, four CHIs (FFKS, AD, KLT, and YDZ) when used alone might have minimal incidence of gastrointestinal reactions, and CHIs combined with DDP could reduce the incidence of gastrointestinal reactions compared to DDP alone.

3.5.4 Incidence of leukopenia

A total of 25 studies involving seven interventions showed incidence of leukopenia. Regardless of whether CHIs were combined or used by itself, the use of CHIs showed a lower incidence of leukopenia than DDP alone.

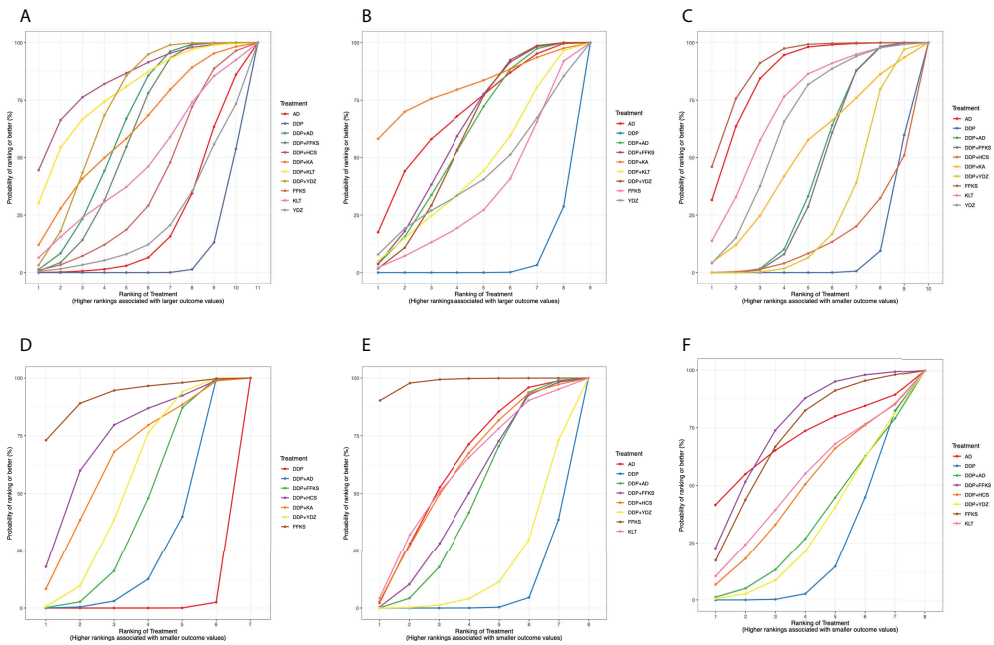

FIGURE 3
Surface under the cumulative ranking curve (SUCRA) probabilities of different interventions for six outcomes. **(A)** Clinical effective rate. **(B)** The improvement rate of KPS score. **(C)** Incidence of gastrointestinal reactions. **(D)** Incidence of leukopenia. **(E)** Incidence of chest pain. **(F)** Incidence of fever. The area under each curve corresponds to the probability of each treatment being the best treatment. AD, Aidi injection; DDP, cisplatin; FFKS, Fufang Kushen injection; HCS, Huachansu injection; KA, Kangai injection; KLT, Kanglaite injection; YDZ, Yadanzi injection.

Similar to the incidence of gastrointestinal reactions, the lowest incidence of leukopenia was seen when using FFKS, and CHIs combined with DDP could reduce adverse events. The rank probability was as follows: FFKS (91.85%), DDP+HCS (72.64%), DDP+KA (63.62%), DDP+YDZ (53.17%), DDP+FFKS (42.34%), DDP+AD (25.98%), and DDP (0.42%).

3.5.5 Incidence of chest pain

A total of 26 studies involving eight interventions, reported incidence of chest pain. Four types of treatment (AD, DDP+AD, DDP+FFKS, and FFKS) showed a lower incidence of chest pain than DDP alone, while other treatments did not show statistical significance compared with DDP alone.

According to the rank probabilities, FFKS might have the highest possibility of showing less incidence in chest pain (98.17%), while DDP alone might be the least improved treatment (6.21%).

3.5.6 Incidence of fever

A total of 21 studies involving eight interventions reported incidence of fever. Table 2E reveals that DDP combined with FFKS showed a lower incidence of fever than DDP alone (RR = 3.24, 95% CrI: 1.04–17.45), while others did not show statistical significance compared with DDP alone.

With the incidence of fever, DDP+FFKS might have the highest possibility of showing less incidence in fever (75.45%), and the DDP alone still might be the worst performer (20.67%).

3.6 Publication bias

Comparison-adjusted funnel plots were used to detect whether there was publication bias in the six outcomes and are provided in Supplementary File S8. It can be seen in Figure S8 that there are different angles between the calibration auxiliary line and the center line, indicating that this study may have potential publication bias and small study effects in the six outcomes.

3.7 Confidence in evidence

The grading of the comparisons with CINeMA displayed mainly "low" to "very low" confidence ratings. This was due to the network without closed loops of evidence (without mixed evidence); hence, inconsistency cannot be assessed. Thus, the "Incoherence" levels were all illustrated as "Some concerns". There were "Major concerns" about "Imprecision," usually related to the low numbers of trials available for some comparisons in this study. Details are provided in Supplementary File S9.

4 Discussion

CHIs are commonly used as a complementary treatment in China. However, due to the lack of direct comparison between different types of CHIs, it is often difficult for clinical physicians to choose the optimal therapy for patients with MPE. As a result, this NMA was undertaken to understand the best available evidence on the comparisons of different types of CHIs, to assist physicians in clinical practice.

4.1 Summary of evidence

This NMA evaluated six types of CHIs as adjuvant and four types of CHIs as alternative treatments when compared to DDP alone for lung cancer patients with MPE. The CHIs included AD, FFKS, HCS, KA, KLT, and YDZ. The six outcomes assessed included clinical effective rate, the improvement rate of KPS score, and the incidence of gastrointestinal reactions, leukopenia, chest pain, and fever. The overall heterogeneity between the different comparisons of drugs was found to be low in our NMA. With respect to improvements in clinical effective rate, the NMA results concluded that HCS combined with DDP performed the best. Modern pharmacological studies have shown that cininobufosin and its active compounds (such as bufalin and cininobufosin) have significant antitumor activities and can reverse the regulation of multidrug resistance and immune response. Moreover, some clinical data have indicated that cinocobalamin may have effective anticancer activity, with low toxicity and few adverse effects (69). In the aspect of KPS score, KA combined with DDP might be the best choice. KA is an intravenous fluid made from an extraction of three Chinese herbs (ginseng, astragalus, and matrine), which has a variety of pharmacological effects including antitumor, reductions in adverse reactions caused by chemotherapy, and improvements in the body's immune function (70). In relation to reducing the incidence of adverse reactions, FFKS alone showed the best results in reducing gastrointestinal reactions, leukopenia, and chest pain, and FFKS combined with DDP demonstrated the best safety when it comes to fever. The main components of FFKS are oxymatrine, matrine, and other alkaloids, which could induce cell apoptosis and enhance the effects of DDP in non-small-cell lung cancer (NSCLC) cells (71), and prevent or reduce chemotherapy- and/or radiotherapy-induced toxicity when combined with chemotherapeutic drugs (72). Apart from this, other CHIs are able to exert their antitumor and reduce side effects through various mechanisms. The AD contains multiple active ingredients, including astragaloside (Re, Rb1, and Rg1), ginsenoside, cantharidin, eleutheroside E, and syringin, which significantly inhibit the proliferation of various tumor cells, induced cell apoptosis, and have shown outstanding antitumor

properties, immune regulation functions, and decrease in chemotherapy-related ADRs (73). Coixenolide is the main active ingredient of KLT, which exhibits anticancer and immunomodulatory properties. The induction of NF-κB-mediated gene transcription in CD4+ T cells participates in the immunomodulatory activity of KLT (74). Research has shown that YDZ could induce the death of cancer cells through a variety of mechanisms, and exhibited higher activity and a broader antitumor spectrum *in vitro* (75).

As the rank probability of six outcomes suggested, CHIs combined with DDP or single-use CHIs were superior than the use of DDP alone in improving the effective rate and KPS score and reducing the incidence of adverse reactions. However, several CHIs did not show statistical significance when compared with DDP alone in the pairwise meta-analysis. Moreover, because of the wide confidence intervals in the NMA due to the small sample size of included patients and the low incidence of adverse events, the rank results need to be carefully considered. One previous simulation study found that the rank probability of the treatment was underestimated when being tested in the largest number of studies in a given network and overestimated for the treatment included in the smallest number of studies. The results can only be reliable when each treatment involved in the analysis has direct evidence or has obvious advantages in effectiveness (76). In this NMA, there was only one RCT of HCS combined with DDP, one RCT of KA combined with DDP, and two RCTs of FFKS alone included where analysis lacked direct comparisons between certain interventions. The grading of the comparisons with CINeMA showed primarily "low" to "very low" confidence ratings, and as a result, the conclusions based on this NMA may not be trustworthy. We suggest clinicians should choose different treatment methods according to the specific requirements of their patients.

4.2 Strengths and limitations

In comparison with published research, this is the first NMA, to our knowledge, that compares different CHIs as an adjuvant or alternative treatment to DDP in the treatment of lung cancer patients with MPE (77, 78). Our research has ascendency. Firstly, strict eligibility criteria were used, particularly inclusion of only patients with pleural effusion caused by lung cancer, and DDP as a fixed control. This ensured consistency of the disease conditions and interventions included in the RCTs, which could decrease clinical heterogeneity. Only antitumor drugs listed by the NHSA in the catalog of Chinese patent medicines were included, to ensure conformity with actual clinical usage and provide relevancy for future clinical practice. Furthermore, the six outcome indicators, clinical effective rate, improvement rate of KPS score, and the incidence of gastrointestinal reactions, leukopenia, chest pain, and fever, were chosen on the basis of whether they could provide comprehensive information to recommend as realistic treatment recommendations.

Nevertheless, limitations and shortcomings existed in our research. Firstly, the overall risk of bias was assessed as some concerns. Secondly, the sample size of included studies was relatively small, and the number of qualified studies included were not sufficient. We believe that the credibility of the NMA could be improved if the sample size was increased, and more eligible studies and more RCTs of different types of CHIs were included. In addition, more ranking comparison on dosage and treatment duration could also be considered. Thirdly, as indicated by our results, the network diagram does not form a typical closed loop, such that the research inconsistencies and credibility of our conclusions cannot be checked. Fourthly, long-term survival outcomes are critical for clinical decision-making, and most studies included in our MNA were primarily focused on the short-term therapeutic outcomes due to the relatively limited treatment course and follow-up time. Finally, owing to the limited scope of application of CHIs, all included studies were carried out in China and all patients were Chinese, which may introduce some degree of selection bias to the results. Notably, the Food and Drug Administration (FDA) of the United States approved the clinical trial of KLT in 2001, and a phase II study in patients with advanced pancreatic cancer has been completed in 2014 (79). The Russian Federation approved the clinical trial of KLT in 2002, and KLT has been marketed in Russia since 2005 with a positive response (80). However, the clinical application of KLT still seems limited outside of China with little information being reported officially, and there is no international multicenter study concerning the effect of KLT on MPE. The conclusions drawn from the results, therefore, cannot be generalized on a large scale worldwide.

5 Conclusions

Our NMA evaluated the effectiveness and safety of CHIs as an adjuvant or alternative therapy for DDP in the treatment of lung cancer patients with MPE. To our knowledge, this is the first comprehensive NMA study of its kind. The results showed that CHIs alone or combined with DDP could improve clinical effectiveness and quality of life and reduce AEs, compared to DDP alone. HSC and KA, combined with DDP, may be the most effective considering clinical effective rate and improvement of KPS score, respectively. FFKS, either used alone or in combination therapy with DDP, may be the best in reducing AEs. However, high-quality RCTs with larger sample sizes are needed to further corroborate the 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 authors.

Author Contributions

Y-FX and Y-RC: conceptualization, methodology, formal analysis, and writing the original draft. F-LB and Y-BH: methodology and supervision. Y-XS and C-YL: visualization and review editing; JS: language editing and supervision. J-PL: methodology and supervision. Z-LL and D-MQ: conceptualization, funding, and project administration. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.942941/full#supplementary-material

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