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# Reviews in thoracic oncology

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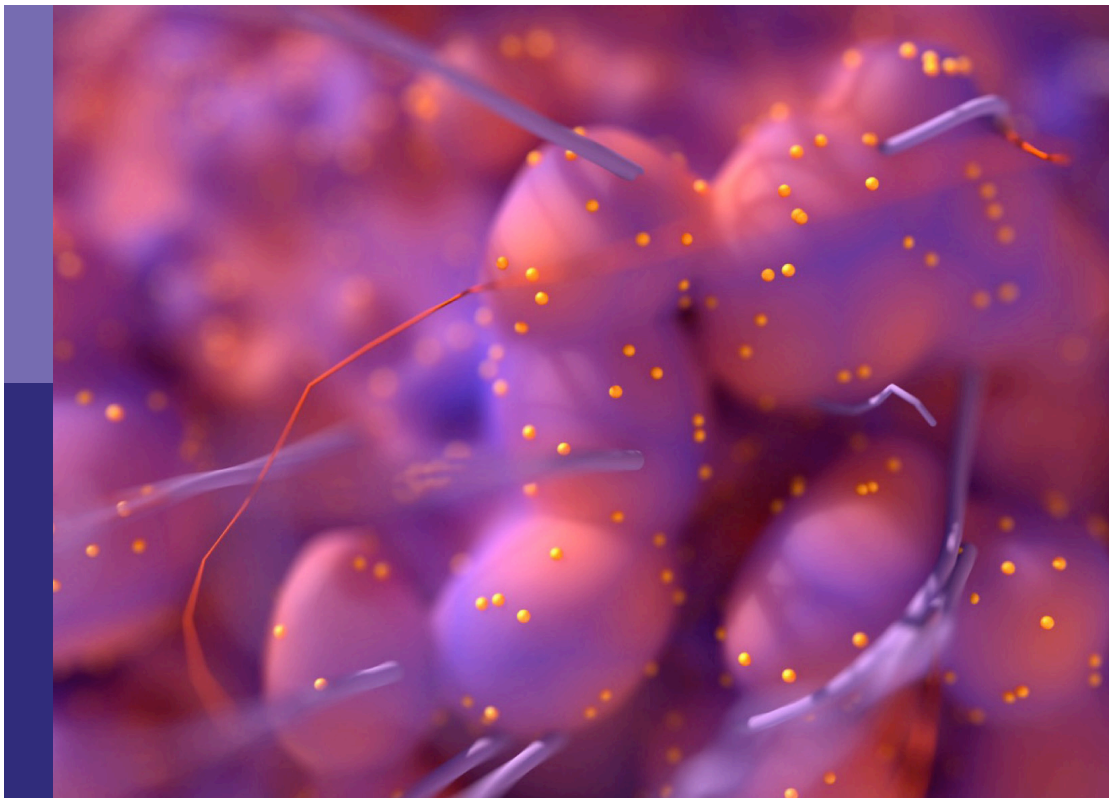

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# Reviews in thoracic oncology

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# Editorial: Reviews in thoracic oncology

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KEYWORDS

**thoracic, cancer, oncology, lung cancer, malignant pleural effusion (MPE)**

Editorial on the Research Topic
Reviews in thoracic oncology

This is a Research Topic on thoracic oncology. Thoracic malignancy is a term used to describe any cancer presented in organs, glands, or structures within the thoracic cavity. Lung cancer is the second most frequent malignancy after breast cancer, accounting for 2.21 million cases annually, and the leading cause of cancer mortality worldwide (1.8 million deaths) for women and men combined (1). Men exhibit almost two times higher lung cancer incidence compared to women. The global patterns of lung cancer incidence and mortality are heterogeneous reflecting the stage of the tobacco epidemic. Lung cancer patients often present with pleural metastases. Pleural involvement signals advanced disease and poor expected prognosis (2).

Better understanding of the disease has advanced and improved lung cancer treatment and clinical management. Patients may receive chemotherapy, radiotherapy, targeted therapy, immunotherapy, and surgery. Chen et al., present the evolution of lung cancer treatments and landmark studies over the last two decades. Lung cancer patient phenotyping and targeted treatments have extended survival and reduced side effects. Brigatinib is an anaplastic lymphoma kinase (ALK) inhibitor and is administered as first-line treatment to ALK-positive metastatic non-small cell lung adenocarcinoma patients. Xing et al., systematically reviewed the efficacy and safety of Brigatinib. Tyrosine kinase inhibitors is another type of lung cancer targeted treatment. Currently, mutation status is determined by examining lung tumor tissue biopsies. Hu et al., discuss the advances of PET/CT in establishing EGFR mutation status in lung cancer and their clinical significance.

The introduction of immune checkpoint inhibitors (ICI) revolutionized cancer treatment and extended survival. However, not all patients respond to ICI therapy and benefit in terms of survival. It is still not clear which is the cohort of patients that would benefit the most. Mizuno et al., discuss the current status and future perspectives of PD-1/PD-L1 immune checkpoint blockade in lung cancer. ICIs may cause immune-related adverse events. Hao et al., present the pathogenesis, risk factors, and clinical presentation of immune checkpoint inhibitor-related pneumonitis. Non-small cell lung cancer patients with mutations on the MET pathway present poor clinical outcomes. The development of targeted tyrosine kinase inhibitors and bispecific antibodies for MET genetic alterations have benefited this cohort of patients. Michaels and Bestvina discuss the evolution and

current state of MET selective therapy. Surgery remains the first-line treatment for early stage lung cancer patients with resectable tumors. The surgical methods have developed resulting to smaller surgical traumas, fewer complications, and quicker post-operational recovery periods. Fuzhi et al., outline the importance of evaluating pulmonary function in individuals who have undergone surgery for lung cancer, as well as the alterations in pulmonary function that occur after surgery. Additionally, they discuss strategies for effective rehabilitation of pulmonary function and factors that may affect the success of such rehabilitation.

Metastasis is a major factor that leads to mortality, and approximately 90% of cancer deaths are attributed to metastases. Malignant pleural effusion (MPE) is a common clinical problem for patients with lung cancer. The conduction of large-scale randomized clinical trials advanced diagnosis and clinical management. However, treatment focuses on symptom relief and control of fluid accumulation (Addala et al., 2022; Zhao et al., 2022). Parotid and gastric metastases for patients with lung cancer are rare and thus not very well studied. Wang et al., and Tang et al., present two reviews on primary lung cancer with parotid and gastric metastases.

Financial toxicity refers to the adverse impact of cancer treatment expenses on a patient's quality of life. Lung cancer survivors often experience a rise in unemployment, psychological stress and a decrease in wages, indicating the persistent impact of financial toxicity. Boulanger et al., reviewed the connection between financial toxicity, quality of life, and survival in high value care.

Carcinogen derived thoracic cancers including lung and oesophageal are amongst the most frequently diagnosed malignancies worldwide. Despite advances like the introduction of ICIs the clinical management of these patients remains challenging. Endotyping of lung cancer patients in combination with targeted treatments has improved survival. Metastases are common and more studies are necessary to understand the underlying biology. Finally, the effect of cancer on the financial sustainability and stability of patients is an important factor we need to investigate and gather more data.

## Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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MINI REVIEW
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# Extracellular Vesicle Derived From Mesenchymal Stem Cells Have Bidirectional Effects on the Development of Lung Cancer

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Mesenchymal stem cell is a kind of pluripotent cells with the ability of self-renewal and multi-directional differentiation, which exist in bone marrow, umbilical cord blood, umbilical cord tissue, placenta tissue, adipose tissue and so on. Extracellular vesicles are membranous lipid vesicles secreted by a variety of cells and widely present in body fluids, which contain proteins, mRNA, microRNA and other substances, and are an important medium of intercellular communication. At present, more and more evidence shows that mesenchymal stem cell-derived extracellular vesicles play an important role in the development of lung cancer. Regulating the levels of proteins, RNAs and other substances in MSC-EVs and then transplanting them into patients may be a new way to alleviate the development of lung cancer. We mainly introduce the role of extracellular vesicles derived from human umbilical cord mesenchymal stem cells, bone marrow mesenchymal stem cells and adipose mesenchymal stem cells in lung cancer, to provide new alternatives for the treatment of lung cancer.

**Keywords: mesenchymal stem cells, extracellular vesicle, lung cancer, promote, inhibition**

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## INTRODUCTION

Lung cancer is the most common cancer in the world and the leading cause of cancer-related deaths. Because early-stage lung cancer is asymptomatic, most cases are detected at an advanced stage. The prognosis of patients with advanced lung cancer is poor, and the 5-year relative survival rate is about 5.2% (1). In 2018, there were more than 2 million cases of lung cancer worldwide, with about 1.76 million deaths, which has become a major burden on health care around the world (2). Environmental factors are one of the main risk factors for lung cancer, such as smoking, air pollution and radiation exposure (3). At present, the development of lung cancer treatments mainly includes radiotherapy, chemotherapy, surgery and so on (2). Accumulating evidence suggests that mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) play an important role in the development of lung cancer. One study found that EVs derived from human umbilical cord mesenchymal stem cells (hUCMSCs-EVs) could transfer miR-130b-3p into lung cancer cells and

promote the occurrence and development of lung cancer through the FOXO3/NFE2L2/TXNRD1 axis (4). Therefore, MSC-EVs may become a new direction for lung cancer treatment.

# MESENCHYMAL STEM CELLS AND EXTRACELLULAR VESICLES

## Sources of Mesenchymal Stem Cells and Their Regulatory Effects

Mesenchymal stem cells (MSCs) are pluripotent cells derived from mesoderm that exist in bone marrow, umbilical cord tissue, placenta, adipose tissue and other tissues, and MSCs have the potential to differentiate into adipocytes, osteoblasts and chondroblasts (5, 6). They have the characteristics of low immunogenicity, multi-directional differentiation and promote tissue regeneration, which make them play a role in anti-inflammation, promoting regeneration and maintaining the stability of the internal environment (7, 8). MSCs, originally discovered in bone marrow (BM), can now be isolated from many organs or tissues, but their origin remains unclear, and growing evidence suggests that MSCs originate from perivascular cells (5). Isolated pericytes express the same set of cell surface markers as MSCs, and perivascular cells with typical pericyte markers *in vivo* also express a novel adipose-derived stem cell surface-specific marker (9). At present, it was found that MSCs mainly express CD73, CD90 and CD105, and negatively express CD14, CD34, CD45 and HLA-DR5, but the source of MSCs cannot be distinguished based on these (6). A study has shown that the anti-inflammatory and immunomodulatory effects of MSCs are mainly mediated by non-contact ways such as the release of extracellular vesicles (7). Some evidence shows that MSCs, through their paracrine effects and their ability to modify the microenvironment, alter the activity of other cells and affect tumor cells and immune cells (10). MSCs have been found to increase the secretion of matrix metalloproteinase 9 (MMP9) by activating ABL kinase in lung cancer cells, thereby promote the metastasis of lung cancer cells (11). When adipose-derived MSCs were co-cultured with A549 cells, the growth rate and metastasis rate of A549 cells were increased (12). Current clinical trials of MSCs involve hundreds of diseases. Due to the strong heterogeneity of its cell products, the clinical therapeutic effect varies with different product batches. Varieties of mesenchymal stem cells are currently used in clinical trials. They are divided into two categories: adult mesenchymal stem cells, including bone marrow, adipose tissue, peripheral blood, and dental pulp, and neonatal tissue-derived mesenchymal stem cells, derived from placenta, amniotic membrane, and umbilical cord. Bone marrow mesenchymal stem cells (BMSCs) are the most widely used stem cells in clinical trials, but which derived from birth-related tissues may possess remarkable biological properties, such as high proliferative capacity, longevity, and differentiation potential (13). Therefore, the functional optimization and product quality control of mesenchymal stem cells are the current research focus in cell therapy (14).

## Biogenesis and Regulation of Extracellular Vesicles

Extracellular vesicles (EVs) are accessible to most cells and are widely present in human body fluids (15). There are three different types of EVs: endosomes invaginate to form multivesicular bodies, which fuse with the cell membrane to form EVs with a size of 30-100 nm; the cell membrane buds to form microvesicles with a size of 50-1000 nm; the release of membrane substances during apoptosis will produce apoptotic bodies, the size of which is vary from 100 nanometers to several micrometers (16). It contains proteins, RNA and other substances, and has a lipid bilayer membrane structure (15) and is an important medium of intercellular communication which can regulate endothelial cell function (17). The communication methods of EVs are diverse, including activation of surface receptors, phagocytosis, and endocytosis or membrane fusion (18). RNA in EVs includes various biotypes that represent selected fractions of the source cell's RNA content, mainly small noncoding RNAs, but also fragmented and intact mRNAs, rRNAs, and lncRNAs (19). The transfer of microRNAs (MiRNAs) regulated by EVs has been shown to affect the progression of all types of cancer, including cancer cell invasion and proliferation, as well as drug resistance. It is reported that EVs secreted by human umbilical cord mesenchymal stem cells with high expression of miR-148B-3p inhibit the development of breast cancer, while extracellular vesicles derived from tumor-associated fibroblasts with low expression of miR-320a inhibit cell proliferation and migration of hepatocellular carcinoma (3). Tumor cell-derived lncRNAs in EVs confer aggressive and chemoresistant phenotypes to adjacent counterparts in the tumor microenvironment. They also mediate the interaction between tumor and stromal cells, thereby remodeling the local environment to promote tumor growth and progression (20).

## Biogenesis of EVs and Their Heterogeneity Based on Mesenchymal Stem Cells

MSCs are one of the most EV-producing cells currently known. Phenotypically, MSC-EVs also expressed CD73, CD90, and CD105, while negatively expressed CD14, CD34, or CD11b (6). Some experiments suggest that MSC-EVs can improve inflammatory diseases by modulating immune function (21). MSC-EVs can inhibit T and B lymphocyte proliferation and induce Treg cell population, and reduce TNF-α expression and increase IL-10 expression by affecting the maturation of macrophages (22). A study showed, MSC-EV-miR-146a plays an anti-inflammatory role by reducing the mRNA and protein levels of TNF receptor-associated factor 6 (TRAF6) and IL-1 receptor-associated kinase 1 (IRAK1), inhibiting the phosphorylation of NF-κ B p65 and I κ B α, reducing the expression of pro-inflammatory factors, and increasing the level of IL-10 (23). Gao et al. co-cultured human umbilical cord mesenchymal stem cell exosomes expressing miR-100-5p with eosinophils treated with oxidized low-density lipoprotein and found that the former can inhibit inflammation through the FZD5/Wnt/β-catenin pathway (24). Because cancer cell lines

differ in cancer type, stage, mutation, and drug resistance, the effects of MSC-EVs on different cancer cells may be completely opposite (25). It has been found that BMSC-derived EVs (BMSC-EVs) promotes the invasion, proliferation and migration of osteosarcoma cells through lncRNA MALAT1/miR-143/NRSN2/Wnt/β-Catenin axis. BMSC-EVs can transfer MALAT1 into osteosarcoma cells, thus increasing the expression of MALAT1 and NRSN2, reducing the expression of miR-143, and activating Wnt/β-catenin pathway in osteosarcoma cells (26). Besides, Feng et al. demonstrated that BMSC-EVs can transfer miR-375 to cervical cancer cells to reduce MELK expression, and inhibit the occurrence and progression of cervical cancer (27). Experiments have demonstrated that miR-16 in mouse BMSCs can down-regulate the expression of VEGF at the mRNA and protein levels in breast cancer cells and inhibit angiogenesis (25). MSCs-EVs are implicated in many lung pathologies, such as acute lung injury, acute respiratory distress syndrome and lung cancer (2). Wang et al. found that Intratracheal and intravenous administration of MSC-EVs attenuates lipopolysaccharide-induced lung injury by increasing miR-27a-3p levels, reducing NFKB1, and promoting alveolar macrophage M2 polarization (28). MSC-EVs also showed protection in COPD. Through chronic cigarette smoke-induced COPD mice model, Guo et al. found MSC-EVs can improve lung function, and reduce pro-inflammatory cytokine production, the total number of macrophages and neutrophils to reduce inflammation (29). Studies have shown that BMSC-EVs can transfer miR-186 into fibroblasts to stop the cells activation by inhibiting the expression of SOX4 and DKK1, thereby alleviating idiopathic pulmonary fibrosis (30). Gao et al. demonstrated that adipose-derived mesenchymal stem cell-derived EVs (AMSC-EVs) could inhibit PM2.5-induced TGF-βRI by transferring let-7d-5p into recipient cells, thereby alleviating lung fibrosis (31). Liu et al. found that MSC-EVs expressing miR-204 could inhibit the migration and invasion of non-small cell lung cancer through the KLF7/AKT/HIF-1α axis (32). (Additional file 1: **Table S1**).

## CHARACTERIZATION AND ISOLATION OF EVS

Currently, there is no globally recognized standardized method for the isolation and purification of EVs, and the method adopted depends on the source of the sample for EV extraction and the volume and application direction of EVs. According to the survey results, the samples for EV isolation and extraction are usually various biological fluids, such as plasma, serum or urine, and conditioned cell culture fluids are also commonly used materials (33). The most common is differential centrifugation. Zhou et al. ultracentrifuged the cells at 300g for 30 minutes, then centrifuge twice at 10,000g for 20 min to obtain EVs. Then, the isolated EVs were washed with 25 ml phosphate buffered saline (PBS), and the supernatant was discarded after spinning again at 100,000 g for 1 h. Finally wash the EV again for immediate use or store at -80°C (30). However, with this method, washing increases the purity, but also leads to a decrease in the number of EVs (34). In addition, sucrose gradient ultracentrifugation is also a very common method. Sucrose concentration gradients can be created using sucrose solutions of different concentrations, including resuspended particles, after centrifugation and PBS dilution to get EV (35). Size exclusion chromatography is increasingly used. First use differential centrifugation to remove cells, debris and apoptotic bodies, then use ultrafiltration to manage the sample volume, and finally use SEC column to separate EVs according to the radius size. The advantages of this method are that the obtained EVs are highly pure and easy to obtain applied to various biological fluids (36). In addition to the above methods, precipitation of EVs by using polyethylene glycol (PEG) is also a good option. Centrifugation followed by mixing with an equal volume of freshly prepared PEG solution can provide EVs of sufficient purity (37). At present, differential centrifugation is still the most commonly used separation method because of its simplicity and economy (38). Finally, the characterization of EVs by different methods is important to evaluate the results of the separation method. The International Society for Extracellular Vesicles (ISEV) recommends quantitative measurement of the source of EVs, as well as to determine the number of EVs as much as possible, and to determine the presence of EV-related components and other non-vesicular, co-separated substances (38) (**Table 1**).

## THE ROLE OF EXTRACELLULAR VESICLE DERIVED FROM MESENCHYMAL STEM CELLS IN LUNG CANCER

Studies have shown that MSC-EVs have a bidirectional effect on lung cancer, which can not only promote the migration and invasion of lung cancer cells (39), but also promote the apoptosis of lung cancer cells or inhibit the growth of lung cancer cells (3). EVs from different mesenchymal stem cells have different effects on lung cancer. We mainly introduce the effect of EVs derived from bone marrow mesenchymal stem cells (BMSCs), EVs derived from adipose mesenchymal stem cells (AMSCs), and

**TABLE 1** | Advantage or disadvantages of isolation methods of extracellular vesicles.

| References | Methods | Advantage | Shortcoming |
|---|---|---|---|
| Konoshenko MY et al. (34) | Differential centrifugation | Easy operation | Less quantity |
| Muraoka S et al. (35) | Sucrose gradient ultracentrifugation | Low cost | Complex operation |
| Monguio-Tortajada M et al. (36) | Size exclusion chromatography | Higher purity | Time consuming |
| | | Higher amounts of EVs protein and RNA | Pollution |
| | | Higher purity | |
| | | Easy to obtain | |

EVs derived from human umbilical cord mesenchymal stem cells (hUCMSCs) in lung cancer.

## Extracellular Vesicle Derived From Human Umbilical Cord Mesenchymal Stem Cells

A study has shown that hUCMSCs-EVs can reduce the survival rate, migration and invasion ability of lung cancer cells, and promote the apoptosis of lung cancer cells. Xie et al. co-cultured H1299 and H460 cells with hUCMSCs-EVs highly express miR-320a, and found that miR-320a-expressing hUCMSCs-EVs were antitumor both *in vivo* and *in vitro*. They also confirmed that sex-determining region Y-box 4 (Sox4) and miR-320a may have a targeting relationship. Therefore, the hUCMSCs-EVs highly expressing miR-320a may inhibit the growth of lung cancer cells through Sox4 (3). Dong et al. found that miR-410 in hUCMSCs-EVS could be transferred to lung adenocarcinoma cells. They also confirmed that miR-410 directly regulates the expression of the tumor suppressor gene PTEN at the post-transcriptional level, and the expression of PTEN protein decreased in lung adenocarcinoma cells treated with hUCMSCs-EVS, but the expression of PTEN mRNA and protein in hUCMSCs-EVS was not detected. These results suggest that hUCMSCs-EVS can reduce the expression of PTEN protein by transferring miR-410 to lung adenocarcinoma cells, thus regulating the growth of lung adenocarcinoma cells (40). Zhao et al. demonstrated that TGF-β1 in hUCMSCs could affect the promotion of epithelial-mesenchymal transition (EMT), migration and invasion of lung cancer cells by hUCMSCs-EVs through Smad2/3, Akt/GSK-3β, MAPK and NF-κB pathways (39). A study has shown that A549 cells were treated with hUCMSCs-EVs expressing miR-130a-3p, and then detected the content of miR-130a-3p in A549 cells. It was found that the level of miR-130a-3p in A549 cells in the experimental group was significantly increased compared with the control group. At the same time, CCK-8 assay was used to measure cell proliferation, Transwell assay was used to detect cell migration and flow cytometry was used to detect cell apoptosis. The results showed that compared with the control group, the proliferation ability and *in vitro* migration ability of A549 cells in the experimental group were significantly decreased, and the apoptosis rate in both early and late stages was significantly increased (41).

## Extracellular Vesicle Derived From Bone Marrow Mesenchymal Stem Cells

BMSCs play an important role in regulating endogenous processes such as hematopoiesis and tumor survival. Extracellular vesicles derived from bone marrow mesenchymal stem cells (BMSCs-EVs) play a significant role in inhibiting the development of lung cancer and improving patient survival rate (2). Liu et al. detected the expression of let-7i, lysine demethylase 3A (KDM3A), bicorticoid kinase 1 (DCLK1) and ion transport regulator 3 (FXYD3) containing FXYD domain in lung cancer tissues, then determined the regulatory relationship among them, and observed the effects of them on lung cancer cells. At the same time, xenogeneic tumors were transplanted into nude mice to evaluate tumor growth in nude mice. The results showed that LET-7i derived from BMSC-EV suppressed the inhibitory effect of DCLK1 on FXYD3 by down-regulating the expression of KDM3A, thus inhibiting the proliferation, migration and invasion of lung cancer cells (2). Wu et al. have shown that BMSCs-EVs rearrangement miR-193a inhibits colony formation, invasion and migration of cisplatin-resistant non-small cell lung cancer cells by decreasing LRRC1 expression, and promotes apoptosis (42). Through *in vitro* and *in vivo* experiments, Liang et al. found that BMSCs-EVs could downregulate CCNE1 and CCNE2 to inhibit cell proliferation and colony formation in non-small cell lung cancer *via* deliver miR-144 (43). Ren et al. treated A549 and H23 cells with hypoxic or non-hypoxic BMSCs-EVs and found that miR-21-5p could mediate the tumor-promoting effects of hypoxic BMSCs-EVs and the M2-polarizing effect of macrophages. Meanwhile, overexpression of PTEN, PDCD4 and RECK in A549 cells significantly reduced the tumor-promoting effect of miR-21-5p in hypoxic BMSCs-EVs, whereas overexpression of PTEN in monocytes significantly reduced M2 polarization in macrophages. These results confirmed that hypoxic BMSCs-EVs promoted the occurrence and development of non-small cell lung cancer cells and the M2 polarization effect of macrophages through miR-21-5p (7). One study confirmed that after treating A549, H358, H460 and LLC cells with hypoxic BMSC-EVs, hypoxic BMSC-EVs could transfer miR-193a-3p, miR-210-3p and microRNA-5100 into lung cancer cells and activate STAT3-induced EMT, thereby promoting metastasis of lung cancer cells (44). Chen et al. first demonstrated that miR-126-3p could regulate protein tyrosine phosphatase non-receptor type 9 (PTPN9). Then, they co-cultured A549 cells with BMSC-EVs expressing miR-126-3p, and detected the expression of PTPN9 in A549 cells and the effect of miR-126-3p in BMSC-EVs on the occurrence and development of tumor cells, and found that overexpressing miR-126-3p -126-3p BMSC-EVs can inhibit the viability, invasion and migration of non-small cell lung cancer by inhibiting PTPN9 (45). Liu et al. first confirmed that Kruppel-like factor 15 (KLF15) was a target gene of miR-190a-5p using dual-luciferase reporter gene assay, and then detected miR-190a-5p by qRT-PCR and Western blotting the expression regulation of KLF15 and the effect of BMSC-EVs on the migration and invasion of lung cancer cells (A549, LK79, H1975 and HCC827) were detected by Transwell assay. The results showed that BMSC-EVs expressing miR-190a-5p could increase the content of miR-190a-5p in lung cancer cells and inhibit the mRNA and protein expression of KLF15, thereby inhibiting the migration and invasion of lung cancer cells (46).

## Extracellular Vesicle Derived From Adipose Mesenchymal Stem Cells

In recent years, more and more attention has been paid to the study of AMSCs in malignant tumor cells. Some studies have shown that AMSC may be a novel approach for targeted therapy of glioma, and AMSC-derived extracellular vesicles (AMSC-EVs) can increase the efficacy of chemotherapy in hepatocellular carcinoma. Circular RNAs (CircRNAs) have been shown to play critical roles in cell growth and tumor

**TABLE 2** | Functions of MSC-derived EVs in preclinical models of lung cancer.

| Reference | Year | EV type | EV source | Isolation method | Mechanisms |
|---|---|---|---|---|---|
| Xie et al.(3) | 2021 | Exosomes | Human UC-MSCs | ExoQuick ULTRA EV isolation kit (SBI, Palo Alto, CA, USA). | EVs suppress lung cancer cell growth *via* the SOX4/Wnt/β-catenin axis by transferring miR-320a |
| Dong et al. (40) | 2018 | Exosomes | Human UC-MSCs | UCF | EVs transfer miR-410 to affect the growth of lung cancer cells by inhibiting the expression of PTEN |
| Zhang et al. (8) | 2021 | Exosomes | Human AMSCs | Exosome Isolation Reagent (Geneseed, China) | EVs carrying circ_100395 increase LATS2 expression by sponging miR-141-3p to regulate Hippo/YAP signaling pathway, and further inhibit malignant transformation |
| Liu et al. (32) | 2021 | Exosomes | MSCs | Not available | |
| | 2020 | and | Human BM-MSCs | UCF | |
| | 2020 | microvesicles | Human BM-MSCs | UCF | EVs carrying miR-204 inhibit KLF7 expression and AKT/HIF-1α pathway activity, resulting in impaired cell migration, invasion, as well as EMT |
| Liu et al. (2) | 2019 | Exosomes | Human hypoxia pre-challenged BM-MSCs | UCF | |
| | 2018 | Exosomes | | UCF | EVs transferring let-7i inhibit lung cancer progression through the KDM3A/DCLK1/FXYD3 axis |
| Wu et al. (42) | 2021 | Exosomes | Human UC-MSCs | ExoQuick-TC Kit (System Biosciences, CA) | |
| | 2019 | Exosomes | | UCF | EVs shuffle miR-193a to suppress the colony formation, invasion, migration, and proliferation as well as advance apoptosis of lung cancer cells by downregulating LRRC1 |
| Liang et al. (43) | 2021 | Exosomes | Human UC-MSCs | UCF | |
| | 2020 | Exosomes | | UCF | |
| Ren et al. (7) | | Exosomes | Human hypoxia pre-challenged BM-MSCs | UCF | EVs transferring miR-144 inhibit cell proliferation, colony formation, and the number of S phase-arrested cells by downregulating CCNE1 and CCNE2 |
| | | Exosomes | | UCF | |
| Zhao et al. (39) | | | Human BM-MSCs | | EVs promote lung cancer cell growth and mobility as well as macrophage M2 polarization *via* miR-21-5p delivery |
| Li et al. (41) | | | Human BM-MSCs | | EVs induce EMT and enhance the migration and invasion of lung cancer cells, which can be reversed by knock-down of TGF-β1 |
| Zhang et al. (44) | | | | | EVs carrying miR-130a-3p can reduce the proliferation ability and *in vitro* migration ability of lung cancer cells while increasing the rate of apoptosis |
| Chen et al. (45) | | | | | EVs can promote lung cancer cell invasion by transferring miR-193a-3p, miR-210-3p, and miR-5100 to activate STAT3 signaling-induced EMT |
| Liu et al. (46) | | | | | EVs overexpressing miR-126-3p can inhibit the viability, invasion and migration of NSCLC by inhibiting PTPN9 |
| | | | | | EVs carrying miR-190a-5p can inhibit the mRNA and protein expression of KLF15, thereby inhibiting the migration and invasion of lung cancer cells |

*MSC, mesenchymal stem cells; EVs-extracellular vesicles; UC, umbilical cord; SOX4, sex determining region Y box 4; AMSCs, adipose derived mesenchymal stem cells; LATS2, large tumor suppressor kinase 2; YAP, yes associated protein; KLF7, kruppel like factor 7; EMT, epithelial mesenchymal transformation; BM, bone marrow; UCF, ultracentrifugation; KDM3A, lysine demethylase 3A; DCLK1, doublecortin like kinase 1; FXYD Domain Containing Ion Transport Regulator 3, FXYD domain containing ion transport regulator 3; LRRC1, leucine rich repeat containing 1; CCNE1, Cyclin E1; CCNE2, Cyclin E2; PTEN, phosphatase and tensin homolog deleted on chromosome ten; TGF-β1, transforming growth factor beta 1; STAT3, signal transducer and activator of transcription 3; PTPN9, protein tyrosine phosphatase non-receptor type 9; KLF15, Kruppel-like factor 15.*

development. Zhang et al. examined the expression of CIRC-100395 in non-small cell lung cancer cells and the interaction among CIRC-100395, miR-141-3p and LATS2, and found that CIRC-100395 in AMSC-EVs could downregulate miR- 141-3p to increase the expression of LATS2, thereby slowing the progression of non-small cell lung cancer. At the same time, they also demonstrated that CIRC-100395 in AMSC-EVs could inhibit the activity of Hippo/YAP signaling pathway in lung cancer cells (8) (**Table 2**).

## CONCLUSION

At present, we still do not have a specific treatment for lung cancer, to find the relevant molecular targets and target therapy is still the focus of our future research. Many studies have shown that proteins, RNAs, and other substances encapsulated in MSC-EVs can inhibit the growth, migration and drug resistance of lung cancer cells in different ways, which may become a new direction in the treatment of lung cancer. We may be able to regulate the levels of proteins, RNA and other substances in MSC-EVs *in vitro*, especially miRNA, and then transplant MSC-EVs into patients to alleviate the development of lung cancer and prolong the life of patients. However, there are still many problems in the application of exosomes. First, there is no globally unified standardized method for the isolation and purification of EVs, and EVs isolated in different laboratories lead to different experimental results. At the same time, the therapeutic dose and injection time will also have an impact on clinical application (47). Second, how to mass-produce MSC-EVs to meet clinical needs is also a great challenge (48). In addition, the content of different MSC-EVs is heterogeneous (49). In conclusion, it is necessary for us to understand the role and mechanism of MSC-EVs in the occurrence and development of lung cancer, and to determine a globally recognized standardized method for the isolation and purification of EVs as soon as possible. It is believed that MSC-EVs will have broad prospects in the diagnosis and treatment of lung cancer, become new anti-tumor targeted drugs or tumor intervention measures, and bring good news to lung cancer patients.

## AUTHOR CONTRIBUTIONS

JW: Manuscript writing. YM: Conception and design, final approval of manuscript. YL: Final approval of manuscript. YC: Final approval of manuscript. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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# Gastric Metastasis of Primary Lung Cancer: Case Report and Systematic Review With Pooled Analysis

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**Background:** Gastric metastasis from lung cancer (GMLC) is a rare occurrence. The clinicopathological characteristics, outcomes, and prognostic factors remain largely elusive.

**Methods:** We conducted a systematic review on case reports and case series of GMLC by scanning MEDLINE, Embase, and ISI Web of Knowledge. Data involving the clinicopathological features, treatment, and outcomes were extracted and analyzed. Survival analysis was performed using Kaplan–Meier method. The Cox proportional hazards regression model was used to identify potential prognostic factors associated with survival. Furthermore, a case of metastatic gastric adenocarcinoma of pulmonary origin with epidermal growth factor receptor (EGFR) L858R+T790M mutation was also described and included.

**Results:** Seventy-eight records involving 114 cases (including ours) were finally included. The median age on admission was 65 years with a male predominance of 79.8%. Lung adenocarcinoma (42.1%), located in the right upper lobe (30.3%), was the most frequent primary tumor. Bleeding (36.7%) and abdominal pain (35.8%) were the two most common symptoms. Endoscopically, gastric lesions were typically presented as elevated lesions with or without volcano-like ulceration, or ulcerative lesions, mostly involving the gastric corpus. The median overall survival time and survival time after diagnosis of metastatic cancer were 11 months [95% confidence interval (CI): 7–14] and 4.5 months (95% CI: 3–9), respectively. The survival analyses revealed that surgical interventions (including lung surgery and/or abdominal surgery) and systemic therapy (including chemotherapy, radiotherapy, and/or targeted therapy) seemed to be positive prognostic factors for both overall survival and survival after diagnosis of metastatic cancer.

**Conclusions:** Clinicians should be alerted to the occurrence of gastric metastasis in lung cancer patients. Comprehensive evaluation and appropriate treatment for specific patients may improve the survival rate of GMLC patients.

**Keywords: gastric metastasis, primary lung cancer, EGFR mutation, clinicopathological features, prognosis**

## INTRODUCTION

Lung cancer is a highly malignant tumor. About half of patients present metastasis at the time of diagnosis (1). The most common sites of extrapulmonary metastases are the liver, bone, brain, and adrenal glands (1). In very rare circumstances, lung cancer may metastasize to the stomach, the incidence of which has been reported to range from 0.19% to 5.1%, with a higher rate reaching 2%–14% in autopsy studies (2). Because of advances in the diagnosis and treatment of cancer, patients' survival has gradually prolonged, making the encounter with gastric metastasis more frequent. However, only limited data have been published focusing on gastric metastasis from lung cancer (GMLC), and its clinical features and treatment strategy remained poorly understood. Especially when targeted therapies including epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been proven to induce a remarkable response in advanced non-small cell lung cancer (NSCLC) with EGFR-activating mutations (3), the effect of targeted therapies on GMLC patients has been barely reported. In the present study, we describe an unusual case of gastric metastasis from primary lung adenocarcinoma that was treated with the third-generation EGFR-TKI osimertinib and conduct a systematic review of previous case reports to study the clinical features, outcomes, and prognostic factors of this rare entity.

## CASE REPORT

A 72-year-old man with a long-term smoking habit (one pack of cigarettes per day for 30 years) was referred to our hospital in April 2021 due to a 1-month history of recurrent fever and discovery of a right lung mass, which showed no change after antibiotic treatment.

His past medical history was significant for hypertension and diabetes mellitus for 5 years, and his medications were nifedipine gastrointestinal therapeutic system (GITS) 30 mg once daily, metformin 50 mg once daily, and acarbose 50 mg three times a day.

On admission, a computed tomography (CT) scan of the chest revealed an irregular mass measuring 3.5 cm × 2.7 cm in the right upper lobe (RUL), with mediastinal mildly enlarged lymph nodes (**Figure 1A**). Additional workup using abdominal CT detected a gastric fundal mass that measured 1.9 cm (**Figure 2A**). The patient denied any abdominal symptoms. Further gastroscopy demonstrated an ulcerated tumor 2.0 cm × 2.0 cm in size located in the gastric fundus (**Figure 2C**).

A CT-guided lung mass biopsy and pathological examination revealed poorly differentiated tumor cells (**Figure 3A**). The immunohistochemical stains showed that the tumor was thyroid transcription factor-1 (TTF-1) (+), CK7 (+), p63 (±), Napsin A (focally+), Ki67 (25%+), CK20 (-), CD56 (-), CK5/6 (-), and p40 (-), which is most consistent with lung adenocarcinoma (**Figure 3B**). Meantime, a gastric mass biopsy revealed poorly differentiated carcinoma with a similar morphological feature to the tumor from the pulmonary biopsy (**Figure 3C**). The immunohistochemical profile of the gastric sample showed TTF-1 (focally+), vimentin (+), Ki67 (40%+), CK7 (-), CK20 (-), Napsin A (-), p40 (-), CEA (-), villin (-), HER2 (-), and MOC31 (-) (**Figure 3D**). Furthermore, genetic studies demonstrated the same EGFR L858R+T790M mutation in both the gastric and pulmonary lesions, while the pulmonary sample also harbored a programmed cell death ligand 1 (PD-L1) Tumor Proportion Score (TPS) of 90%. All these findings supported the metastatic gastric adenocarcinoma of pulmonary origin. Additional brain CT and bone scan identified no abnormalities. The patient was diagnosed with poorly differentiated primary lung adenocarcinoma with gastric metastases (cT2N1M1 stage IV). Hence, oral treatment with osimertinib (80 mg, once a day) was started on May 13, 2021.

After 3 months of treatment (August 2021), a follow-up chest CT scan revealed a reduction in the RUL mass (with the maximum cross section measuring 2.6 cm × 2.2 cm, **Figure 1B**). The gastric mass in the fundus exhibited complete regression in the CT scan (**Figure 2B**) and gastroscopy examination (**Figure 2D**). Meanwhile, an abdominal CT detected a nodule measuring 2.9 cm × 2.0 cm in the right adrenal gland, considered as a new metastatic lesion (**Figure 4A**). The patient's primary lesion and gastric metastatic lesion were reduced, and a new adrenal gland metastasis was observed. According to RECIST 1.1 criteria (4), the efficacy was evaluated as progressive disease (PD). However, considering the effective treatment of primary

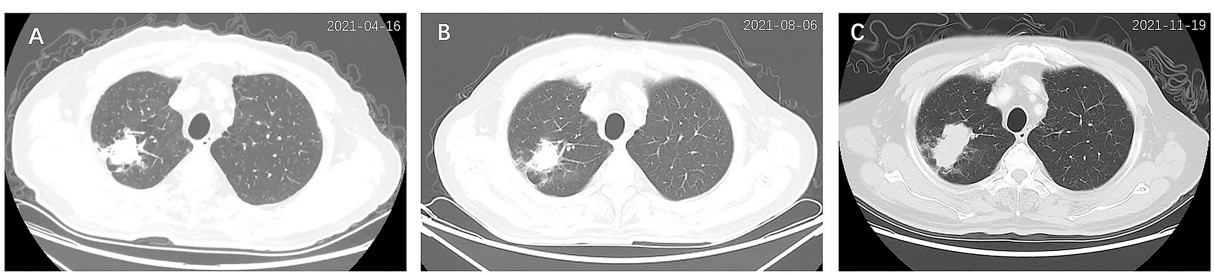


**FIGURE 1** | Chest computed tomography (CT) scan of the primary lung cancer at diagnosis **(A)**, 3 months after treatment **(B)**, and 6 months after treatment **(C)**. An irregular mass (3.5 cm × 2.7 cm) was detected in the right upper lobe **(A)**, which shrunk (2.6 cm × 2.2 cm) after 3 months of treatment **(B)** but enlarged (5.2 cm × 2.6 cm) after 6 months of treatment **(C)**.

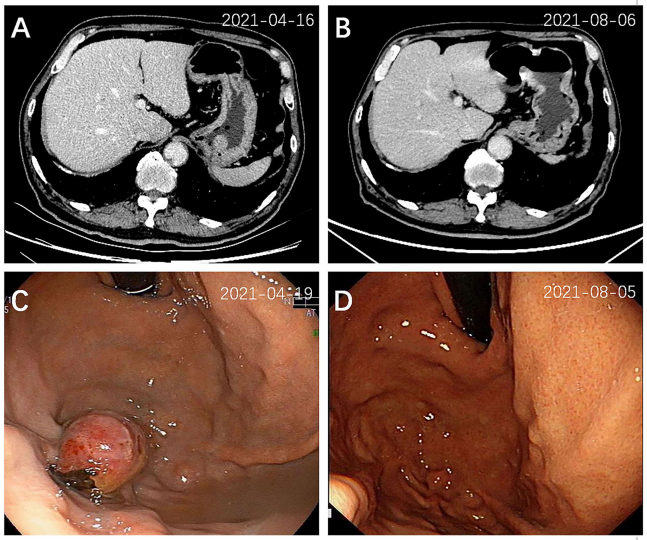


**FIGURE 2** | Abdominal CT scan and endoscopic view of the gastric tumor at diagnosis **(A, C)** and 3 months after treatment **(B, D)**. A mass (2.0 cm × 2.0 cm) located in the gastric fundus was detected by CT **(A)** and gastroscopy **(C)**, which disappeared 3 months after treatment **(B, D)**.

lesions and gastric lesions, the patient chose to continue with osimertinib treatment. Unfortunately, 6 months after the initial diagnosis, the patient showed further disease progression with the enlargement of the primary lung mass (**Figure 1C**) and multiple metastatic lesions involving the bilateral adrenal glands and abdominal cavity (**Figures 4B, C**). The patient was recommended anti-PD-1 immunotherapy, multitargeting TKI (anlotinib), or chemotherapy. After communicating with the patient and his family, the patient opted for anlotinib treatment. At the time of writing, the patient is alive 8 months after the initial diagnosis of lung cancer.

# SYSTEMATIC REVIEW

## Methods

### Search Strategy

A systematic review of the case reports was conducted to examine the clinical features and outcomes of GMLC. Literature search was performed by scanning MEDLINE (through PubMed), Embase, and ISI Web of Knowledge for relevant articles published until September 2021. The search terms included lung cancer-related and gastric metastasis-related index words. The specific search strategy is presented in the **Supplementary Material**. Reference lists of the relevant articles and reviews were carefully scanned to identify other eligible cases.

### Study Selection

Two independent investigators (DT and JL) screened and included the relevant articles if they fulfilled all of the following criteria: 1) case reports or case series including the terms for gastric metastasis from primary lung cancer; 2) published in English or Chinese; and 3) provision of sufficient data on the demographic and/or clinicopathologic outcomes of GMLC cases. Articles were excluded if they were as follows: 1) reviews, meta-analysis, conference abstracts, or comment papers and 2) animal studies. Disparities were resolved with a third investigator (YG).

### Data Extraction

Data such as title, author, publication year, age, gender, smoking habit, primary lung cancer site, pathological histology, interval time between the lung cancer diagnosis and gastric metastasis

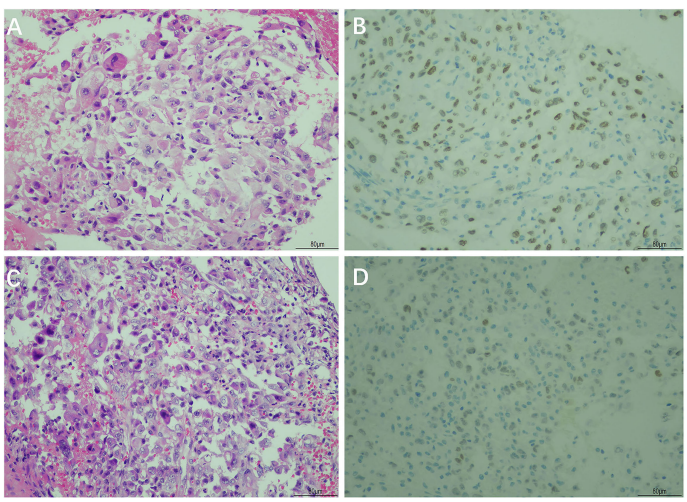


**FIGURE 3** | Hematoxylin and eosin (H&E) and immunohistochemical staining of the primary lung cancer and gastric tumor biopsy. H&E staining showed poorly differentiated adenocarcinoma in the primary lung cancer tissue **(A)** and gastric tumor tissue **(C)**. Immunohistochemical staining showed a positive reaction for thyroid transcription factor-1 (TTF-1) in the primary lung cancer tissue **(B)** and gastric tumor tissue **(D)** (magnification, ×200).

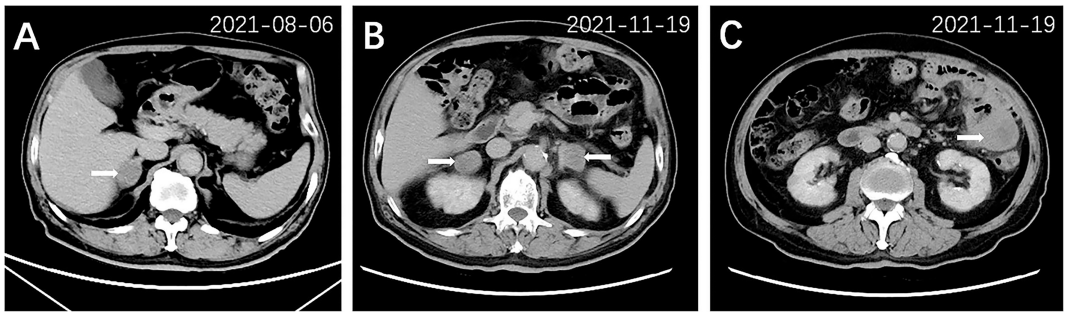


**FIGURE 4** | Abdominal CT scan of other metastatic lesions 3 months after treatment **(A)** and 6 months after treatment **(B, C)**. A nodule (2.9 cm × 2.0 cm) in the right adrenal gland (arrow) was detected after 3 months of treatment **(A)**. Multiple metastatic lesions were shown in bilateral adrenal glands (arrow, **B**) and left lower abdominal cavity (arrow, **C**) after 6 months of treatment.

diagnosis, other metastasis site, clinical presentation, gastric tumor location, endoscopic appearance, treatment, and survival information were extracted by two investigators (JL and ZL) using a predefined form.

### Statistical Analysis

Descriptive data were presented as median (interquartile range) and percentages. Overall survival (OS) was measured from the date of primary lung cancer diagnosis to the date of death. Survival after gastric metastasis was measured from the date of GMLC diagnosis to the date of death. Survival analysis was performed by Kaplan–Meier method. Univariate analysis was performed using Cox proportional hazards regression model, followed by a multivariate Cox regression analysis only including variables with a $P$ value <0.10 during univariate analysis. Variables such as age, gender, number of metastases (solitary vs. multiple), interval (synchronous vs. metachronous), histology type, and treatment strategies were included in the univariate analysis. Synchronous metastasis is when the time interval of diagnosis between lung cancer and gastric metastasis was <1 month, while the time interval ≥1 month was considered as metachronous metastasis (5). Statistical analysis was performed using R software (version 4.0.3; The R Foundation for Statistical Computing, Vienna, Austria). A 2-sided $P < 0.05$ was considered statistically significant.

## Results

A total of 2,078 papers were retrieved, among which 2,064 were obtained through database search (PubMed: 260; Embase: 1,357; Web of Science: 447) and 14 through manual search. After 226 duplications and 1,676 papers were excluded by title and abstract screening, 176 were screened for full text and 78 papers were finally included in this systematic review, as shown in **Figure 5**.

A total of 114 cases were recruited in the present review (113 from the literature plus our case, **Table S1**) (2, 6–84). As shown in **Table 1**, the median age was 65 years (range, 59–71 years). There were 91 men (79.8%) and 23 women (20.2%). Among 54 cases that reported smoking habits, 42 patients (77.8%) were cigarette smokers, 12 (22.2%) had never smoked. NSCLC (99 cases, 86.8%) was the main histological type of GMLC. Adenocarcinoma (48 cases, 42.1%), squamous cell carcinoma (28 cases, 24.6%), and large cell lung cancer (12 cases, 10.5%) were the three most common histological types of NSCLC. Among 76 cases that reported the primary location of the lung cancer, gastric metastases were more commonly from the right lung (46 cases, 60.5%). Also, the most common site was the upper lobe (50%; right upper lobe: 30.3%; left upper lobe: 19.7%), followed by the lower lobe (23.7%; right lower lobe: 15.8%; left lower lobe: 7.9%) and hilum (18.4%; right hilum: 9.2%; left hilum: 9.2%).

In 107 cases that mentioned the number of metastatic sites, 28 cases (26.2%) presented as a single-site metastasis at the time of diagnosis, whereas 79 cases (73.8%) demonstrated other metastatic sites besides the stomach, with the liver, bone, brain, and adrenal gland being the four most prevalent metastatic sites. Moreover, 18 cases (16.8%) showed multiple metastases within the digestive tract, and the duodenum (11 cases, 10.3%) was the

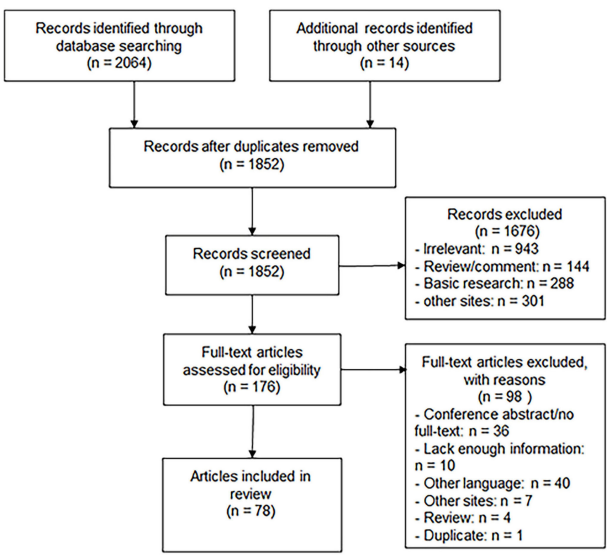


**FIGURE 5** | Flowchart of the selection process.

**TABLE 1** | Demographic and clinicopathologic features of GMLC.

| Characteristics | Value |
|---|---|
| **Age (years)** | 65 (59–71) |
| **Gender** | |
| Men | 91 (79.8) |
| Women | 23 (20.2) |
| **Smoking** | |
| **(54 cases available)** | |
| Smoker | 42 (77.8) |
| Non-smoker | 12 (22.2) |
| **Histological type** | |
| Small cell lung cancer | 15 (13.2) |
| Adenocarcinoma | 48 (42.1) |
| Squamous cell carcinoma | 28 (24.6) |
| Large cell carcinoma | 12 (10.5) |
| Pleomorphic carcinoma | 6 (5.3) |
| Primary lung sarcoma | 2 (1.8) |
| Non-small cell lung cancer | 3 (2.6) |
| **Primary lung location** | |
| **(76 cases available)** | |
| Right upper lobe | 23 (30.3) |
| Right middle lobe | 2 (2.6) |
| Right lower lobe | 12 (15.8) |
| Right hilum | 7 (9.2) |
| Right lung | 2 (2.6) |
| Left upper lobe | 15 (19.7) |
| Left lower lobe | 6 (7.9) |
| Left hilum | 7 (9.2) |
| Left lung | 2 (2.6) |
| Both lung | 1 (1.3) |
| **No. of metastasis sites** | |
| **(107 cases available)** | |
| Solitary | 28 (26.2) |
| Multiple | 79 (73.8) |
| **Interval** | |
| **(113 cases available)** | |
| Synchronous | 54 (47.8) |
| Metachronous | 59 (52.2) |
| **Interval time (m)** | 5 (1.6-13) |
| **(113 cases available)** | |

*Data presented as the number of patients (%) or median (interquartile range).*
*GMLC, gastric metastasis from lung cancer.*

**TABLE 2** | Clinical and endoscopic features of gastric metastatic tumors.

| Characteristics | Value |
|---|---|
| **Clinical presentation** | |
| **(109 cases available)** | |
| Bleeding | 40 (36.7) |
| Abdominal pain | 39 (35.8) |
| Anemia | 11 (10.1) |
| Abdominal discomfort | 5 (4.6) |
| Dysphagia | 6 (5.5) |
| Nausea, vomiting | 4 (3.7) |
| Weight loss | 4 (3.7) |
| Perforation | 3 (2.8) |
| Asymptomatic | 11(10.1) |
| **Stomach location** | |
| **(89 cases available)** | |
| Corpus | 50 (56.2) |
| Fundus | 19 (21.3) |
| Antrum | 13 (14.6) |
| Cardia | 7 (7.9) |
| Whole | 6 (6.7) |
| **Endoscopic appearance** | |
| **(85 cases available)** | |
| **Elevated lesions** | **50 (58.8)** |
| **Without ulcer** | **19 (22.4)** |
| SMT | 8 (9.4) |
| Mass | 2 (2.4) |
| Polypoidal mass | 6 (7.1) |
| Nodules | 3 (3.5) |
| **With ulcer** | **31 (36.5)** |
| SMT with ulcer (volcano-like) | 13 (15.3) |
| Ulcerated mass (volcano-like) | 15 (17.6) |
| Ulcerated nodules | 3 (3.5) |
| **Ulcerated lesions** | **31 (36.5)** |
| Ulceration | 12 (14.1) |
| Bulging ulcerated lesion (volcano-like) | 10 (11.8) |
| Infiltrative ulcerated lesion | 9 (10.6) |
| **Others** | **4 (4.7)** |
| *Linitis plastica* | 3 (3.5) |
| Erosive and atrophic pangastritis | 1 (1.2) |

*Data presented as the number of patients (%) or median (interquartile range).*
*SMT, submucosal tumor.*
*The bold value means the summarized patient numbers (bold numbers) and proportions (bold numbers in brackets) of relevant sub-items.*

main concurrent site with the stomach, followed by the colon (4 cases, 3.7%, including 1 case that showed concurrent stomach, duodenum, and colon metastases), small intestine (3 cases, 2.8%), and esophagus (1 case, 0.9%). Synchronous (54 cases, 47.8%) and metachronous (59 cases, 52.2%) metastases demonstrated similar proportions. The median time between the primary lung cancer diagnosis and gastric metastasis diagnosis was 5 months (interquartile range, 1.6–13 months).

As presented in **Table 2**, bleeding was the most common symptom on admission, which was observed in 40 cases (36.7%; 21 melena; 4 hematemesis; 1 melena and hematemesis; 14 hemorrhage), followed by abdominal pain in 39 cases (35.8%) and anemia in 11 cases (10.1%). Eleven cases showed no symptoms (10.1%), and 3 cases (2.8%) presented with acute abdomen caused by perforation. Some cases also presented with abdominal discomfort, dysphagia, nausea, vomiting, or weight loss.

Metastatic lesions were mainly located in the corpus of the stomach (56.2% in 89 cases with whom the information regarding the metastatic site in the stomach was available), followed by fundus (19 cases, 21.3%), antrum (13 cases, 14.6%), and cardia (7 cases, 7.9%). Thirteen cases had lesions in two or more parts of the stomach.

According to the endoscopic appearance of gastric metastasis that was described in 85 cases, two main types of lesions were observed: the elevated lesions with or without ulceration (50 cases, 58.8%) and ulcerated lesions (31 cases, 36.5%). Moreover, elevated lesions with volcano-like ulceration were more common than that without ulceration (36.5% vs. 22.4%). Some cases also presented with pangastritis or *linitis plastica*-like features.

Immunohistochemical information was available in 58 cases, among which the typical immunophenotype of GMLC diagnosis was positive for TTF-1 (44, 75.9%), cytokeratin 7 (CK7, 31, 53.4%), and negative for CK20 (22, 37.9%), and caudal-related homeodomain transcription 2 (CDX2, 14, 24.1%). Other markers for diagnosis such as p63, CK5/6, CKAE1/AE3(+), and Napsin A were also reported.

As shown in **Table 3**, nearly one-third of cases underwent lung surgery (29.5%, mainly lobectomy) for primary lung cancer and abdominal surgery (31.5%, mainly partial or total gastrectomy) for gastric metastasis. Chemotherapy, radiotherapy, chemoradiotherapy, or targeted therapy were performed in 45.5% and 32.6% cases for primary lung cancer and gastric metastasis, respectively. Only supportive treatment was conducted in 25% and 35.9% of cases for primary lung cancer and gastric metastasis, respectively. The statistics were calculated based on cases with data available.

Survival information was available for 93 cases. A total of 72 cases had succumbed to disease by the end of the study, and 21 cases were alive as reported, considered as censored data. The median OS was 11 months (95% CI: 7–14), with 1- and 3-year survival rates of 41.7% and 17.9%, respectively. The median survival time after diagnosis of metastatic cancer was 4.5 months (95% CI: 3–9), with 1- and 3-year survival rates of 24.9% and 10.5%, respectively.

As for survival after diagnosis of metastatic cancer, univariate Cox analysis revealed that cases with multiple metastatic sites exhibited poorer prognosis than that with solitary gastric metastasis [unadjusted hazard ratio (HR) 2.239, 95% CI: 1.255–3.992, $P = 0.006$], while cases manifested as elevated lesions with or without ulcer in the stomach (unadjusted HR 0.385, 95% CI: 0.195–0.760, $P = 0.006$; unadjusted HR 0.352, 95% CI: 0.150–0.825, $P = 0.016$, respectively) or that underwent surgery treatment for primary lung cancer or gastric metastasis lesions (unadjusted HR 0.178, 95% CI: 0.083–0.383, $P = 0.000$; unadjusted HR 0.171, 95% CI: 0.088–0.332, $P = 0.000$, respectively) or non-surgery therapy (unadjusted HR 0.321, 95% CI: 0.171–0.604, $P = 0.000$ for lung cancer; unadjusted HR 0.223, 95% CI: 0.116–0.432, $P = 0.000$ for gastric metastasis, respectively) demonstrated better outcomes compared with cases with ulcerated lesions in the stomach or underwent only supportive treatment (**Figure 6**). As for OS, similar prognostic factors were discovered, including synchronous, multiple metastasis, ulcerated lesions, supportive treatment that indicated poorer outcome, and metachronous, solitary metastasis, elevated lesions with or without ulcer, lung surgery, abdominal surgery and non-surgery therapy for gastric metastasis that indicated better survival prognosis (**Figure 6**).

In multivariate Cox analysis, after adjustment for prognostic factors, lung surgery for primary lung cancer, abdominal surgery, and non-surgery therapy for gastric metastasis remained prognostic factors for both OS and survival after gastric metastasis, except for synchronous metastasis that indicated a prognostic factor only for OS (**Figure 7**). Other factors were not significant.

**TABLE 3** | Treatment and prognosis features of primary and metastatic tumors.

| Characteristics | Value |
|---|---|
| **Primary lung treatment (88 cases available)** | |
| Lung cancer surgery | 26 (29.5) |
| Non-surgery therapy | 40 (45.5) |
| Supportive treatment | 22 (25) |
| **Gastric metastasis treatment (92 cases available)** | |
| Abdominal surgery | 29 (31.5) |
| Non-surgery therapy | 30 (32.6) |
| Supportive treatment | 33 (35.9) |
| **Survival information (93 cases available)** | |
| Dead | 72 (77.4) |
| Alive | 21 (22.6) |
| Survival after diagnosis of primary cancer, months | 11 (7–14) |
| Survival after diagnosis of metastatic cancer, months | 4.5 (3–9) |

*Data presented as the number of patients (%) or median (interquartile range).*

## DISCUSSION

The occurrence of GMLC is rare. The diagnosis remains challenging especially when the primary lung cancer histology is adenocarcinoma. In this study, we described a case of gastric metastasis originating from lung adenocarcinoma, which was confirmed by tissue biopsy, immunohistochemistry, and mutational analysis. As the EGFR L858R+T790M mutations were detected, the patient was treated with the third-generation EGFR-TKI osimertinib but showing rapid disease progression. To our knowledge, our patient is probably the second reported case of lung cancer with gastric involvement treated with the new-generation EGFR-TKI (8). As there is difficulty in the diagnosis and treatment of gastric metastasis patients, we further systematically analyzed 114 GMLC cases to reveal the clinical features and prognostic factors of the patients.

In the present review, GMLC is more likely to occur in the old, and male is the more susceptible gender. Adenocarcinoma is the most frequent primary histological type resulting in gastric metastasis, which is consistent with previous reports (30, 49, 85–87). However, other certain studies have shown squamous cell carcinoma to be prominent (67, 88). Thus, the dominant primary histological type remains incompletely understood.

At present, the pathway underlying gastric metastasis is not clearly elucidated; however, hematogenous and lymphatic routes are supposed to be most likely involved in GMLC (15, 29, 85, 89). The metastatic tumor cells invade the submucosal layer through blood or lymph and develop into submucosal tumors (SMTs) (30, 34, 82), which remain clinically silent unless the gastric mucosa or serosa is involved or the tumor occupies the lumen (34, 53). Thus, most patients with GMLC are asymptomatic, and detection of gastric abnormality is usually by chance during follow-up or staging procedures of primary lung cancer, like that in our patient. When symptomatic, bleeding (mainly exhibited as melena) and abdominal pain were the two most common symptoms according to our review, all of which are nonspecific and usually misinterpreted as side effects of chemotherapy or indefinite complaints (30, 67, 75). Therefore, attention needs to be paid to gastrointestinal symptoms among lung cancer patients, and endoscopic examination is recommended for further evaluation.

Endoscopically, metastatic lesions most commonly present as a solitary ulcerated lesion located in the gastric corpus (86). The typical morphological appearance has been reported as SMT-like masses with elevation and ulceration at the apex, so-called "volcano-like" lesions (90, 91). Some lesions also appear as ulcers,

polypoid nodules, or thickened walls (29). However, these endoscopic features are nonspecific, and differential diagnosis with primary lesions such as primary gastric cancer (GC) and lymphoma should be considered (14). Furthermore, about 9.4% of GMLC lesions manifested as SMTs with intact overlying mucosa, making conventional endoscopic biopsies frequently inconclusive. Endoscopic ultrasonography (EUS) is thus recommended for further evaluation. In EUS images, the metastatic tumors generally appeared as slightly hypoechoic lesions (more hyperechoic than the muscular tissue) involving the muscularis propria (fourth layer), mimicking primary subepithelial lesions such as gastrointestinal stromal tumors (GISTs), leiomyomas, and schwannomas (92, 93). EUS-guided fine-needle aspiration and biopsy (EUS-FNA/B) is currently the gold standard tissue sampling method for SMTs (92, 93). Hence, biopsies or EUS-FNA/B in conjunction with immunohistochemistry provides a reliable method to identify metastatic gastric tumors.

Several immunohistochemical markers have been reported to be useful for subclassifying tumors of different types and sites, such as TTF-1, Napsin A for lung adenocarcinoma, CDX2 for intestinal-type adenocarcinoma, and p63, CK5/6, CK34βE12/CK903 for squamous cell carcinoma (SCC) (14, 94, 95). Currently, TTF-1 is the most widely used stain for adenocarcinomas of pulmonary origin, with 61.5% sensitivity and 100% specificity in a series of 34 primary and metastatic adenocarcinomas in the lung (96). Also, different expression patterns of CK7 and CK20 are helpful for distinguishing tumor origin, with CK7+/CK20- for primary lung cancer and CK7-/CK20+ for gastrointestinal cancer (41, 62). Thus, a marker panel composed of TTF-1, CK7, CK20, and CDX-2 may be recommended to determine whether a gastric tumor was a primary or a pulmonary metastasis.

At present, there is no standard treatment protocol for GMLC patients, and treatment should be personalized according to pathology and patients' condition. The therapeutic strategy includes surgery, chemotherapy with or without radiotherapy, targeted therapies, and supportive treatment (14).

Generally, the presence of a distant metastasis is a contraindication for surgery. High perioperative mortality and poor outcomes had been observed in surgical gastric and/or duodenal metastatic patients (49). However, our study and some other reports showed that surgery seemed to be a positive prognostic factor for GMLC patients (5, 30, 50). Accordingly, patients with solitary gastric metastasis may exhibit a survival benefit with surgical intervention (29, 50). Also, surgery may be necessary to prevent and/or control life-threatening complications such as massive hemorrhage or perforation (14, 29). Therefore, we considered surgery an option to treat gastric metastasis in properly selected patients, such as patients with unique metastatic lesions in the stomach and generally good condition, or with uncontrolled severe complications. With respect to radical surgery for isolated gastric metastasis, the optimal operating method remains to be clarified. According to our review, among 29 cases that underwent gastric surgical intervention, 5 cases received total gastrectomy, while 14 received partial or subtotal gastrectomy. The extent of gastric resection may depend on the site and size of the tumor. In selected GC patients such as early-stage and distal-third GC, subtotal gastrectomy may provide similar survival rates and better functional outcome compared to total gastrectomy (97). More recently, function-preserving gastrectomies such as proximal gastrectomy and pylorus-preserving gastrectomy have shown the advantages of preserving partial gastric physiologic functions and improving postoperative quality of life while maintaining radicality in early GC patients (98, 99). However, the impact of different surgical strategies including total gastrectomy, subtotal gastrectomy, or function-preserving

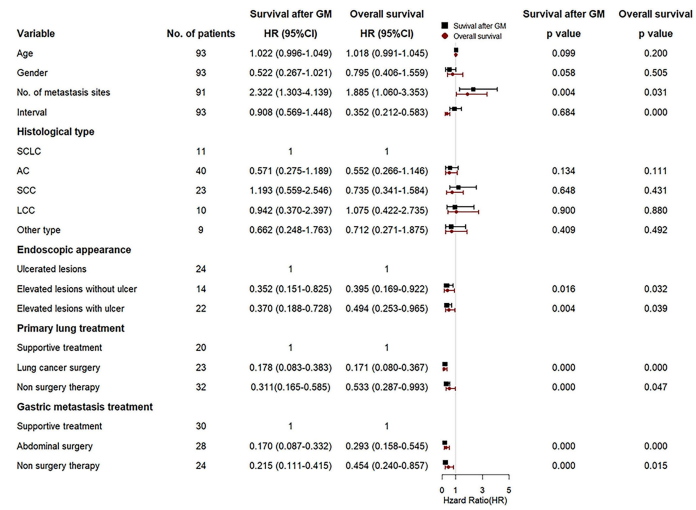


**FIGURE 6** | Forest plot for the univariate Cox regression analyses of variables that may affect survival after gastric metastasis and overall survival of the gastric metastasis from lung cancer (GMLC) patient.

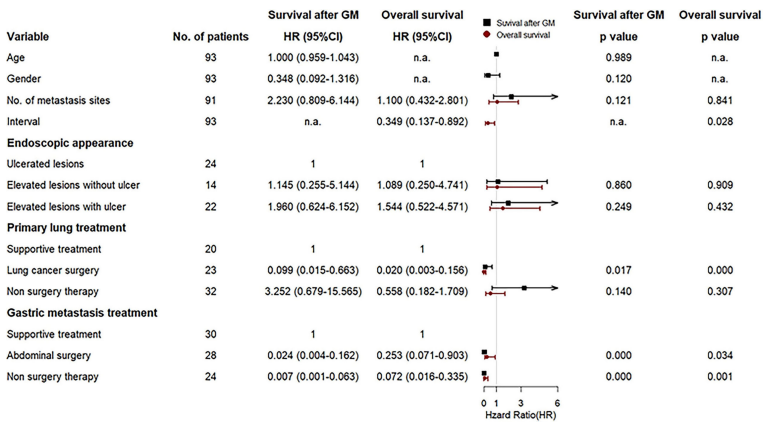


**FIGURE 7** | Forest plot for the multivariate Cox regression analyses of variables that may affect survival after gastric metastasis and overall survival of the gastric metastasis from lung cancer (GMLC) patient.

gastrectomy on isolated metastatic gastric lesions still remains unclear and needs further investigation. In the present case, given the old age and generally poor condition, oral targeted therapy was prescribed other than surgery.

Currently, EGFR-TKIs represent the standard of care for advanced NSCLC patients with activating EGFR mutations, with median progression-free survival (PFS) ranging from 10 to 14.7 months (100). However, the efficacy of EGFR-TKIs on NSCLC with gastric metastasis has been barely reported. According to the present review, three cases were detected with the EGFR exon 19 deletions in gastric metastasis (24, 25, 30), which is the most common EGFR-TKI-sensitive activating mutation (101), and were treated with first-generation EGFR-TKI erlotinib. All of them tolerated the treatment well and were alive at the time of writing the reports (24, 25, 30). Our case harbored both L858R and T790M mutation at diagnosis, the latter of which is perceived as the most common resistance mutation associated with first- and second-generation EGFR-TKIs (101). At present, for NSCLC patients with T790M mutation, the third-generation EGFR-TKI osimertinib is recommended (100, 101). Also, in a randomized phase III FLAURA trial, osimertinib as first-line treatment exhibited improved PFS (18.9 months) and OS (38.6 months) compared with first-generation EGFR TKIs (median PFS of 10.2 months; median OS of 31.8 months) (102, 103). Therefore, our case was started on first-line therapy with oral osimertinib. Nevertheless, the patient experienced disease progression after 3 months of treatment, although the lesions of the lung and stomach exhibited partial response. The reason for the poor response to osimertinib in our case remains unclear. The reported potential mechanisms of resistance to osimertinib include the emergence of on-target resistance mutation such as EGFR C797S, bypass pathway activation such as MET amplification, or histologic small cell transformation (8, 100, 101, 104). Timely rebiopsies with comprehensive genomic profiling following disease progression on osimertinib therapy may be helpful for unraveling the resistance mechanisms (8). The effective therapies after osimertinib resistance still remain elusive. Chemotherapy, immunotherapy, and antiangiogenic therapy, either alone or in combination, may be considered for further treatment (100). Also, the combination of EGFR-TKIs with other therapeutic agents such as chemotherapy or vascular endothelial growth factor (VEGF) inhibitors has emerged as a potential therapeutic approach in the first-line setting to overcome EGFR-TKI resistance (101, 104). Several clinical trials are currently exploring the role of combination approaches with osimertinib (105), which may provide critical information to inform future treatment practice.

In summary, GMLC is a rare entity with poor prognosis. Diagnosis can be challenging as for the nonspecific symptoms and heterogeneous endoscopic appearances. Histological examination with immunohistochemical staining may help to confirm the diagnosis, and genomic profiling may provide valuable information for the diagnosis and therapeutic options. Treatment should be personalized, with surgery and systemic therapy (chemotherapy, radiotherapy, and/or targeted therapy) demonstrating better survival prognosis than only supportive care. The new-generation EGFR TKI osimertinib, either alone or combined with other therapeutic agents, emerges as a promising therapeutic strategy for metastatic NSCLC patients with EGFR-activating mutations. However, more clinical evidence is needed for exploring the efficacy of osimertinib on GMLC patients.

## DATA AVAILABILITY STATEMENT

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

## AUTHOR CONTRIBUTIONS

YG conceived the idea and designed the study. DT collected clinical data, conducted the literature search, and analyzed the literature data. JL collected clinical data, performed the follow up, conducted the literature search, and extracted the literature data. ZL collected pathological data, and extracted the literature data. DT wrote the first version of manuscript. SZ revised the article. All authors have read and approved the final manuscript.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.922016/full#supplementary-material

**Supplementary Figure 1 |** Kaplan–Meier plot of the survival after gastric metastasis and overall survival curve.

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# Rapid Recovery of Postoperative Pulmonary Function in Patients With Lung Cancer and Influencing Factors

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Among malignant tumors, lung cancer has the highest morbidity and mortality worldwide. Surgery is the first-line treatment for early-stage lung cancers, and has gradually advanced from conventional open-chest surgery to video-assisted thoracic surgery (VATS). Additionally, increasingly smaller surgical incisions and less surgical trauma have resulted in reduced pulmonary function damage. Previous studies have found that the level of pulmonary function loss and recovery is significantly correlated with postoperative complications and the quality of life. Thus, an accurate assessment of the preoperative pulmonary function and effective rehabilitation of postoperative pulmonary function are highly important for patients undergoing lung surgery. In addition, pulmonary function assessment after pulmonary rehabilitation serves as an objective indicator of the postoperative pulmonary rehabilitation status and is crucial to facilitating pulmonary function recovery. Furthermore, a complete preoperative assessment and effective rehabilitation are especially critical in elderly patients with pulmonary tumors, poor basic physiological functions, comorbid lung diseases, and other underlying diseases. In this review, we summarize the clinical significance of pulmonary function assessment in patients undergoing lung cancer surgery, postoperative changes in pulmonary function, effective pulmonary function rehabilitation, and the influencing factors of pulmonary function rehabilitation.

**Keywords: lung cancer, pulmonary function, pulmonary rehabilitation, respiratory training, surgery**

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## INTRODUCTION

Among malignant tumors, lung cancer has the highest morbidity and mortality in China and throughout the world (1). Surgery is the first-line treatment for early-stage lung cancers, and the preoperative pulmonary function status and surgical methods are important factors affecting the prognosis and quality of life (2). With an inability to regenerate new tissues from residual pulmonary tissues, the surgical excision of functional tissues and reconstruction of residual thoracic structures results in reduced postoperative pulmonary function (3). In particular, wide ranging complications resulting from reduced respiratory function caused by pneumonectomy are major reasons for poor postoperative quality of life (4). Hence, an accurate assessment of preoperative pulmonary function is crucial in patients undergoing pneumonectomy (5). Here, we

summarize the clinical significance of pulmonary function assessment in patients undergoing lung cancer surgery, postoperative changes in pulmonary function, effective pulmonary function rehabilitation, and the influencing factors of pulmonary function rehabilitation.

## CLINICAL SIGNIFICANCE OF PULMONARY FUNCTION MEASUREMENT IN PATIENTS UNDERGOING LUNG CANCER SURGERY

### Pre-Operative Pulmonary Function Assessment

Among pulmonary function indices, the forced expiratory volume in the 1st second (FEV1) and the diffusing capacity of the lung for carbon monoxide (DLCO) show the best correlations with postoperative morbidity and mortality rates (6). The predicted post-operative FEV1 (ppoFEV1) and forced vital capacity (ppoFVC) are highly correlated with the patient's actual FEV1 and forced vital capacity (FVC) (r= 0.867, 0.832, respectively) (7). Hence, the preoperative measurement of pulmonary function and calculation of predicted postoperative values can be instrumental in effectively evaluating surgical feasibility and predicting postoperative pulmonary function recovery and pulmonary complications. There are several ways to predict postoperative lung function, including counting residual lung lobes, perfusion scintillation to calculate residual lung function, or imaging to calculate the area (8). The American College of Chest Physician's evidence-based clinical practice guidelines (3rd edition) recommend the use of perfusion to calculate and predict lung function, using the following formulas:

Pneumonectomy: ppoFEV1 = preoperative FEV1 × (1 − fraction of total perfusion for the resected lung)

Lobectomy: ppoFEV1 = preoperative FEV1 × (1 − number of functional or unobstructed lung segments to be removed/total number of functional segments)

The same equations can be used to estimate the ppoDLCO. Both a ppoFEV1 and ppoDLCO >60% indicate a low risk for anatomic pneumonectomy (6).

A study by Zhang et al., comprising 805 patients undergoing pulmonary surgery, suggested that two indices, ppoFEV1% and ppoDLCO%, can be used to evaluate surgical feasibility and predict the risk of pulmonary complications, regardless of whether the surgery is open or minimally invasive (9). Furthermore, Khullar et al. indicated that DLCO might be a better predictor of the postoperative quality of life than age (10).

In summary, pre-operative pulmonary function assessment has significant value in predicting surgical feasibility, postoperative complications, and the quality of life. Thus, pulmonary function should be properly assessed preoperatively.

### Postoperative Pulmonary Function Testing

Patients undergoing lung resection surgery usually experience pulmonary function decline to various degrees after surgery. Generally, pulmonary function gradually recovers within 6-12 months postoperatively, depending on the range of the surgical excision and the intensity of postoperative rehabilitation exercise. Pulmonary function testing during hospitalization is conducive to the early detection of pulmonary infections. Gregor et al. performed postoperative pulmonary function testing in patients with lung cancer and found that the FEV1 decline at 4 days postoperatively was more notable in patients with pneumonia than in patients without pneumonia (43.2% VS 32,2%) (11). Hence, regular postoperative pulmonary function testing, combined with other diagnostic assessments such as laboratory testing, radiology, and breathing frequency, could help detect pneumonia. Furthermore, for patients undergoing rehabilitation exercise, pulmonary function assessment can be helpful in objectively evaluating the efficacy of the rehabilitation exercise. In addition, some researchers have found that the decline in postoperative pulmonary function is negatively correlated with the postoperative quality of life (12). However, a study by Ozturk et al. found no significant correlations between pulmonary function test parameters (FEV1, FVC, and FEV1/FVC) and the quality of life (13). Therefore, other cardiopulmonary function indices, such as the six-minute walk test (6MWT), might serve as better indicators of the postoperative quality of life (14).

## POSTOPERATIVE CHANGES IN PULMONARY FUNCTION IN PATIENTS WITH LUNG CANCER

Lung surgery exerts notable short-term and long-term impacts on the postoperative pulmonary function of patients with lung cancer. There are various causes of pulmonary function impairment after pneumonectomy, including the resection of lung tissues and changes in the mechanical structure of the chest wall induced by surgical incisions (15). Conventional open-chest surgery results in a 10%–40% postoperative decrease in pulmonary function (16, 17). Postoperative pulmonary function assessment in a prospective study, comprising 238 patients undergoing muscle-sparing lateral thoracotomy lobectomy, found that the FEV1 and DLCO values at 3 months postoperatively were only 84% and 88.5% of preoperative values, respectively (16). Shiono et al. revealed a significant decrease in pulmonary function at two weeks postoperatively and a significant decrease in pulmonary function and oxygenation at 6 months postoperatively (2). The adoption of VATS within the division of thoracic surgery aids in sparing more chest wall muscle, reducing surgical trauma and pulmonary function loss. A retrospective study by Shibazaki et al., comprising 104 patients who underwent VATS lobectomy reported that the mean FEV1 at 3, 6, and 12 months postoperatively was 85.78%, 87.93%, and 89.22% of preoperative values, respectively (18). Nezu et al. reported a significant decrease in patients' pulmonary function at 3 months after pneumonectomy, and improvement in pulmonary function at 6 months, but with a failure to return to preoperative levels

(19). In a prospective study of patients undergoing unilateral VATS lobe resection, Yokoba et al. found that FVC and FEV1 values at 3-12 months postoperatively were lower than preoperative vales (20).

In brief, a long-term postoperative decline in pulmonary function is inevitable, regardless of whether the surgery is open-chest or VATS. Although pulmonary function gradually improves after surgery, the overall level is still lower than the preoperative level, which affects the postoperative quality of life to varying degrees.

## FACTORS THAT AFFECT POSTOPERATIVE PULMONARY FUNCTION RECOVERY

Pulmonary function recovery after lung cancer surgery is affected by various factors. The choice of surgical method and the range of lung tissue excision are major factors of pulmonary function decline (21). Smoking history and body mass index (BMI) are also important factors affecting postoperative FEV1 (18). Moreover, concomitant pulmonary diseases (4) and effective postoperative rehabilitation (22) can affect pulmonary function recovery.

### General Pre-Operative Condition Factors

General pre-operative condition factors, including age (23), BMI (24), smoking history, concomitant lung diseases, and other underlying diseases, etc.: Pulmonary functions begin to decline at the age of 35 years, with a mean FEV1 decline of approximately 30 mL/year and a mean FVC decline of approximately 20 mL/year (25). Mori et al. found that younger age was related to greater postoperative pulmonary function recovery (26). Elderly patients usually have comparatively poor pulmonary function; thus, special attention should be paid to the preoperative assessment of pulmonary function and postoperative recovery (27).

Compared to normal weight and obesity, underweight status is associated with decreased pulmonary function (24). Good preoperative nutritional status can facilitate postoperative pulmonary function recovery and reduce complications (28). For patients with poor nutritional status, perioperative nutritional support should be strengthened to reduce postoperative complications and facilitate pulmonary function recovery. Central obesity is associated with pulmonary function decline in the Chinese elderly population, with better pulmonary function in patients with moderate obesity (29); proper diet control and postoperative rehabilitation exercise can facilitate the improvement in pulmonary function in such patients.

Long-term smoking is a risk factor for pulmonary complications after pneumonectomy, and smoking cessation can effectively lower the incidence of pulmonary complications (30, 31). However, the level of impact that smoking has on postoperative pulmonary function recovery currently remains unclear and needs to be confirmed by further observations and studies.

The process of pulmonary function recovery after lung cancer surgery is accompanied by various influencing factors, including pulmonary atelectasis, pleural effusion, and postoperative chest pain. After lung cancer surgery, early postoperative rehabilitation and improvement in pulmonary function should be facilitated by the aggressive administration of expectorants, proper use of analgesics, tapping on the back in a prone position (to encourage coughing, facilitate postoperative sputum excretion, and promote re-expansion of collapsed lung lobes), improvement in pulmonary ventilation and gas-exchange function, and aggressive treatment of complications, including pleural effusion and pulmonary infections.

### Choice of Surgical Method

Surgical trauma is an important factor influencing postoperative pulmonary function recovery. Posterolateral incisions are most widely used in conventional open-chest surgery. The incisions are relatively long and the latissimus dorsi muscle needs to be incised. Additionally, intraoperative rib spreading usually damages the ribs and intercostal nerves, which causes persistent postoperative pain and affects pulmonary function recovery. Liu et al. showed greater FVC decline and FVC% decline at 6 months and 2 years postoperatively with pneumonectomy and chest wall resection than with chest wall-sparing pneumonectomy (21). Harada et al. and Macke et al. reported significant pulmonary function decline in patients who underwent chest wall resection, and better pulmonary function recovery in patients receiving VATS lobectomy than in patients who underwent open lobectomy (especially in the early postoperative period); thus, pulmonary function recovery needs to be facilitated in the early period (32, 33). Lung surgery with VATS spares more chest wall muscle, cause less surgical trauma and less respiratory muscle injury, than conventional open-chest surgery, and hence are more conducive to postoperative pulmonary function recovery.

### The Range of Lung Tissue Excision

With the development of minimally invasive techniques, most lung cancer surgeries have been performed by VATS in recent years. The range of lung tissue excision varies depending on the size, amount, and location of the lesions, which are major factors affecting postoperative pulmonary function recovery. Mori et al. demonstrated that, in patients who underwent lung wedge resection, postoperative FVC decreased temporarily, but nearly recovered to the preoperative level after 12 months, whereas the postoperative FEV1 recovered gradually over the course of 12 months, but did not recover to the preoperative level (26). Furthermore, the number of resected lung segments is significantly and positively correlated with the FVC decline (32). FEV1 decline is greater in patients who underwent the resection of 3-5 segments than in patients who underwent the resection of fewer anatomical segments (1-2 segments), suggesting that the resection of less lung tissue results in less pulmonary function loss (33). Saito et al. and Keenan et al. found that decreases in FVC and FEV1 were notably smaller after the resection of pulmonary segments than after pulmonary lobectomy (34, 35). Since a smaller amount of lung tissue is

resected, pulmonary functions are better preserved with pulmonary segmentectomy and lung wedge resection than with pulmonary lobectomy and the resection of multiple pulmonary segments. It is worth mentioning that sleeve lobectomy preserves more lung tissue and pulmonary function than pneumonectomy. In particular, for some patients with poor preoperative pulmonary function, sleeve resection could help preserve pulmonary function.

Therefore, when choosing the surgical method, surgeons should consider retaining normal lung tissues when possible, on the premise of complete tumor resection, in order to facilitate pulmonary function recovery in the early postoperative period and improve the quality of life.

## Comorbid Chronic Obstructive Pulmonary Disease

Changes in pulmonary function are associated with the location, volume, and severity of emphysema (20). Lung volume reduction surgery (LVRS) is a surgical intervention for patients with emphysema to improve lung function. LVRS is a potential option for patients with upper lobe emphysema and low exercise tolerance. The National Emphysema Treatment Trial showed that, compared with thoracotomy lung volume reduction, LVRS leads to better improvements in 6MWT distance, predictive FEV1%, quality of life, and dyspnea. Upper lobe–dominant emphysema and inhomogeneous emphysema showed better recovery of lung function than lower lobe–dominant emphysema and homogeneous emphysema (36). Comorbid COPD is an independent favorable factor for the preservation of FEV1 in the late postoperative phase following lung cancer surgery (4). The postoperative pulmonary function and recovery time in patients who undergo VATS pulmonary lobectomy vary depending on the pulmonary lobectomy itself and the presence of COPD (37). Wei et al. reported that the decline in postoperative FEV1 among patients with lung cancer and comorbid COPD ranged 5%–18.3%, indicating that pulmonary lobectomy did not cause further pulmonary function impairment in patients with lung cancer and comorbid COPD (38). Baldi et al. reported that patients with lung cancer and comorbid COPD exhibited a smaller decrease in pulmonary function during the late postoperative phase after pulmonary lobectomy than in patients without comorbid COPD (39). This phenomenon might be associated with reduced lung volume after pneumonectomy, alleviation of pulmonary hyperinflation, and changes in the mechanical structure of the chest wall. Further studies are required to confirm the specific mechanisms.

## Postoperative Pulmonary Function Compensation

Compensation for reduced pulmonary functions after pneumonectomy can help slow the pulmonary function decline caused by surgery. Physiological compensation after the resection of lung tissues is mainly achieved *via* two mechanisms: enhancement of the diffusing capacity of the residual lung and the generation of new pulmonary gas-exchange units (40). Fisher et al. demonstrated an increase in the mitotic activity of contralateral alveolar cells in rats after unilateral pneumonectomy, suggesting that functional compensation after pneumonectomy is primarily a compensation of the residual lung (41). This compensation is manifested, not by an overexpansion of the pre-existing alveolar septal tissues, but instead by an increase in functioning lung tissue (42). Ueda et al. showed that, despite the removal of more functional pulmonary parenchyma, postoperative pulmonary function after lower lobe resection was not worse than that after upper lobe resection because of greater postoperative compensation with lower lobe resection (5). Postoperative compensation after lower lobe resection is achieved by the expansion of both the contralateral lung and remaining ipsilateral lung. Hence, the postoperative decrease in total lung volume after lower lobe resection is smaller than that after upper lobe resection, even though more pulmonary parenchyma are excised in lower lobe resection (43).

## Preoperative and Postoperative Therapy

For patients with locally advanced lung cancer, neoadjuvant therapies, (including radiotherapy, chemotherapy, targeted therapy, and immunotherapy) can cause some damage to normal lung tissues while treating primary lesions, resulting in pulmonary function decline after treatment. Nomori et al. demonstrated pulmonary function decline in patients who underwent induction radiotherapy and chemotherapy; the pulmonary function decline primarily occurred on the affected side (44), which was probably the result of damage to the surrounding normal lung tissues caused by the radiotherapy. Radiation exposure in radiotherapy can lead to radiation pneumonitis in the early phase of treatment and pulmonary fibrosis in the late phase, which causes progressive dyspnea with decreased lung compliance, and, hence, lower FEV1 and DLCO (45). Shin et al. revealed a notable decrease in DLCO following neoadjuvant chemotherapy (46). Zhu et al. suggested that preoperative neoadjuvant immunotherapy significantly increased FEV1 and FEV1% while treating the primary tumor, enabling pathological remission, but also caused a decline in DLCO% (47). This might be due to damage to normal lung tissues caused by neoadjuvant therapies, resulting in reduced pulmonary gas-exchange function, despite an improvement in ventilation function induced by tumor volume reduction. At present, there remains a lack of studies regarding the impact of postoperative adjuvant therapies on the pulmonary function of patients with advanced lung cancer; thus, this topic requires further studies and discussions. For patients with locally advanced lung cancer, complications of chemotherapy and radiotherapy, including pneumonia and pulmonary fibrosis, should be prevented and treated; furthermore, aggressive rehabilitation treatment is conducive to pulmonary function improvement (45).

## Effective Rehabilitation Exercise

Poor exercise capacity (peak oxygen consumption <15 mL/kg/min) is the major determinant of postoperative morbidity and mortality after pneumonectomy (48). Effective pulmonary rehabilitation can improve cardiopulmonary function and

exercise tolerance, and has positive clinical value in improving long-term survival (49–53). Cesario et al. showed notable improvement in FEV1 at 1 month postoperatively with in-hospital pulmonary rehabilitation than without pulmonary rehabilitation (2.32 Lt vs 1.79 Lt) (22). A randomized controlled trial by Zhou et al. demonstrated higher FEV1 at 28 days postoperatively in patients receiving pulmonary rehabilitation than in the control group (54). A study on patients receiving thoracoscopic lobectomy or segmental resection by Zou et al. found more notable improvement in pulmonary function at 3 months after hospital discharge in patients receiving pulmonary rehabilitation treatment (55). Furthermore, a retrospective analysis of patients who underwent VATS pneumonectomy by Choi et al. revealed better FEV1 preservation in the rehabilitation group than in the non-rehabilitation group (56). These results indicate that effective rehabilitation exercise can facilitate pulmonary function improvement.

However, unlike the above studies, a 20-week trial by Edvardsen et al. showed no difference in FEV1 between the rehabilitation group (who underwent high-intensity endurance and strength training) and the control group; only DLCO was higher in the rehabilitation group (57). Studies by Jonsson et al. and Cavalheri et al. suggested no difference in physical activity and pulmonary function at 8-12 weeks postoperatively between the rehabilitation and control groups (58, 59). This result might be associated with the low exercise intensity in the rehabilitation group. Furthermore, the intervention duration in these studies was short, at less than 3 months. There is currently no standardized procedure for pulmonary rehabilitation; different research institutions have adopted different postoperative rehabilitation programs, and hence might reach different conclusions. In addition, pulmonary function testing alone cannot fully reflect the cardiopulmonary function status. Pulmonary function testing combined with other exercise endurance assessments (such as the 6MWT and stair-climb test) might serve as a more accurate indicator of pulmonary rehabilitation efficacy. Previous studies have shown that pulmonary function recovers in about 6-12 months. In order to better improve the pulmonary function of patients, postoperative rehabilitation exercise should ideally last approximately 1 year. Furthermore, rehabilitation exercises should reach a certain intensity and be personalized to the patient's individual tolerability. Patient compliance is an important factor affecting the execution of rehabilitation programs; thus, rehabilitation therapies should be individualized and tailored to the patient's condition during the process of pulmonary rehabilitation, in order to achieve the best postoperative rehabilitation outcomes.

Clinical experience suggests that postoperative patients should perform proper breathing and aerobic exercises in the early postoperative phase, including deep breathing, pursed-lip breathing, jogging, swimming, stair climbing, etc. In addition, pulmonary function tests should be regularly performed; the exercise intensity can be gradually increased and maintained for 3-6 months, based on the pulmonary function recovery and improvement in respiratory symptoms. These measures can be instrumental in accelerating the postoperative pulmonary function recovery.

## CONCLUSIONS

With continued progress in minimally invasive concepts and techniques, VATS exerts an increasingly smaller impact on postoperative pulmonary function. Thus, there exists some controversy regarding the pulmonary function changes in patients undergoing lung cancer surgery; it was previously believed that lung cancer surgery can cause an absolute decline in postoperative pulmonary function, affecting postoperative complications and the quality of life. However, in recent years, some researchers have suggested that postoperative pulmonary function in patients with lung cancer can basically recover within 6-12 months after surgery despite a transient decline, without affecting the postoperative quality of life. Such studies mainly focused on patients receiving lung segmental and lung wedge resections, who experience a mild decline in postoperative pulmonary function. After prolonged recovery and compensation for pulmonary function loss, their pulmonary function basically recovers to the preoperative level, with little impact on the postoperative quality of life. In terms of postoperative pulmonary rehabilitation, most studies suggest that cardiopulmonary function and the quality of life can be improved to a certain extent after lung cancer surgery *via* effective pulmonary rehabilitation exercise. However, some studies suggest that pulmonary rehabilitation does not induce a significant improvement in postoperative cardiopulmonary function. Current studies are mostly limited to the assessment of pulmonary function recovery in the early postoperative phase; there are few reports on the recovery of pulmonary functions after long-term pulmonary rehabilitation exercise.

Our research team is conducting a prospective study on long-term postoperative pulmonary rehabilitation based on telemedicine platforms in 500 patients, including a pulmonary rehabilitation remote monitoring group, in which patients are followed up and managed using wearable devices with remote monitoring functions and rehabilitation management systems; and a pulmonary rehabilitation conventional management group, in which patients are followed up and managed using common means of social communication, including phone calls, text messages, and WeChat. In this ongoing study, we are applying digital technologies and multidisciplinary individualized comprehensive interventions to improve respiratory function, relieve postoperative symptoms, improve daily activity endurance, and promote wound healing after thoracic surgery. Remote wearable devices are used for the collection of physiological parameters and data analysis. We also plan to integrate internet technologies into postoperative monitoring and rehabilitation after thoracic surgery, in order to alleviate or control the complications of minimally invasive lung cancer surgery, and eliminate surgery-induced dysfunctions and psychological issues. In addition, we educate patients on how to improve exercise and activity endurance, improve self-care ability,

and reduce the risk of hospitalization. The study is currently mid-stage, and preliminary data have confirmed the feasibility of telemedicine-based post-thoracic surgery rehabilitation. We believe that the results of this study can provide evidence to verify the necessity of postoperative rehabilitation in patients with lung cancer, promote the application of telemedicine techniques in the field of post-tumor surgery rehabilitation, facilitate the introduction and promotion of post-lung cancer surgery telerehabilitation programs in China, and inspire standardized procedures for post-lung cancer surgery telerehabilitation.

## AUTHOR CONTRIBUTIONS

SX and GW provided the initial idea for this review. YF, MN and FW were in charge of data acquisition and drafting of the article. TD, WY and WJ revised the article. All authors read and approved the final manuscript.

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# Immune checkpoint inhibitor-related pneumonitis in non-small cell lung cancer: A review

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Immune checkpoint inhibitors (ICIs) have shown definite therapeutic effects in various types of cancers, especially non-small cell lung cancer (NSCLC). However, ICIs have unique side effects, called immune-related adverse events (irAEs), which can occur in various systems throughout the body. Among such irAEs, immune checkpoint inhibitor-related pneumonitis (ICI-P) is a fatal adverse reaction. In this review, we discussed the risk factors, pathogenesis, clinical characteristics, radiological manifestations, pathological features, diagnosis, grading, and management of ICI-P in NSCLC and the relationship between ICI-P and the efficacy of ICI therapy. In addition, we discussed the predictive factors for ICI-P. This review will play a crucial role in the prediction, evaluation, and management of ICI-P for widespread application of immunotherapy.

KEYWORDS

**immune checkpoint inhibitor, immune checkpoint inhibitor-related pneumonitis, immune-related adverse events, immunotherapy, non-small cell lung cancer**

## Introduction

Lung cancer is one of the most common malignant tumours worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of cases (1, 2). According to the recent population-based cancer incidence and mortality data reported by the American Cancer Society, which is compiled every year, the incidence of cancer is gradually decreasing, and the decline in the number of lung cancer cases is particularly pronounced (3). In addition, the mortality rate of lung cancer has declined significantly, which is related to improved management.

Immune checkpoint inhibitors (ICIs) exert significant clinical therapeutic effects and have accelerated the treatment of advanced cancer in the new era of immunotherapy. The use of ICIs has shown great success in improving the overall survival (OS) and progression-free survival (PFS) rates of NSCLC (4–7). ICIs have been approved as a first-line treatment for

advanced driver gene-negative NSCLC owing to their superior efficacy and no evident side effects compared with conventional chemotherapy (8). However, they can result in systemic reactions called immune-related adverse events (irAEs) (9) that are completely different from adverse reactions resulting from conventional chemotherapy.

IrAEs can affect all organs of the body, including the skin, gastrointestinal tract, liver, kidneys, lungs, endocrine organs, and the central nervous system (9–11). Among irAEs, immune checkpoint inhibitor-related pneumonitis (ICI-P) is a rare but fatal reaction (12, 13). ICI-P is defined as the development of dyspnoea and/or other respiratory symptoms and the appearance of a new infiltrative shadow on chest imaging after the patient has been treated with ICI, except for clinical conditions such as lung infection or tumour progression. According to the data of clinical trials, the incidence of ICI-P is 3%—6.3% in NSCLC, and the mortality rate is <1% (14–16). However, in previous epidemiological studies, the incidence of ICI-P varied greatly, ranging from 2.7% to 19% in NSCLC (17–20) (Table 1). Patients with lung cancer are more likely to develop ICI-P than patients with other types of cancer (17). The onset of ICI-P is earlier in patients with lung cancer (78 days) than in patients with non-lung cancer (186 days) (21). Recent real-world statistical data show that in clinical practice, the incidence of ICI-P is higher than that reported in pivotal trials, leading to the approval of programmed death-(ligand) 1 (PD-[L]1) inhibitors (22) by the United States Food and Drug Administration. High-grade ICI-P is extremely dangerous and often threatens the lives of patients. Therefore, clinicians should make rapid and accurate decisions for providing reasonable and effective treatment for ICI-P.

## Risk factors for ICI-P

Many potential factors can increase the incidence of ICI-P in NSCLC patients treated with ICIs. Among the 97 patients who participated in the subgroup analysis of the Keynote-001 trial, OS was significantly longer after pembrolizumab administration in patients who had previously received radiotherapy than in patients who had not received radiotherapy. However, 3 (3/24, 13%) patients who underwent thoracic radiotherapy had developed ICI-P, whereas only 1 (1/72, 1%) patient who did not receive thoracic radiotherapy had developed ICI-P. Therefore, the probability of treatment-related pulmonary toxicity is higher in patients who have received radiotherapy than in patients who have not received radiotherapy (23). Other clinical studies have reported that patients who have received thoracic radiotherapy are more likely to have ICI-P (24–26) and respiratory failure (24). According to several retrospective studies, pre-existing history of interstitial pneumonitis is also associated with the incidence of ICI-P (27, 28). The development of ICI-P is independently associated with the presence of baseline fibrosis on computed tomography (CT) of the chest, which is a composite measure of obstructive lung disease (29). Cho et al. reported the same phenomenon, indicating that a pre-

TABLE 1 Published meta-analysis and clinical trials on immune checkpoint inhibitor-related pneumonitis.

| Author | Year | Numbers of patients/ trials | ICI type | Tumour type | Incidence (%) | Mortality (%) | Grade≥3 (%) |
|---|---|---|---|---|---|---|---|
| Khunger M(14) | 2017 | 5038/19 | Anti-PD-1<br>Anti-PD-L1 | NSCLC | PD-1: 3.6<br>PD-L1: 1.3 | N/A | PD-1: 1.1<br>PD-L1: 0.4 |
| DeVelasco G (15) | 2017 | 11454/21 | Anti-PD-1<br>Anti-PD-L1<br>Anti-CTLA-4 | NSCLC,SCLC,Melanoma, etc. | All patients: 2.6 | <1 | All patients: 1.1 |
| Nishino M(17) | 2016 | 4496/20 | Anti-PD-1<br>Anti-CTLA-4 | NSCLC,Melanoma,RCC | All patients: 2.7<br>NSCLC: 4.1<br>Melanoma: 1.6<br>Monotherapy: 1.6<br>Combined therapy: 6.6 | NSCLC: 0.4 | All patients: 0.8<br>NSCLC: 1.8<br>Melanoma: 0.2<br>Monotherapy: 0.2<br>Combined therapy: 1.5 |
| Cho JY(18) | 2018 | 167/1 | Anti-PD-1<br>Anti-PD-L1 | NSCLC | All patients: 13.2<br>Monotherapy: 13.6<br>Combined therapy: 10 | All patients: 18.2 | All patients: 4.2<br>Monotherapy: 4.1<br>Combined therapy: 5 |
| Suresh K(19) | 2018 | 205/1 | Anti-PD-1<br>Anti-PD-L1 | NSCLC | All patients: 19.02 | N/A | All patients: 11.7 |
| Ono K(20) | 2021 | 203/1 | Anti-PD-1 | NSCLC | All patients: 13.79 | N/A | All patients: 3.44 |

ICI, immune checkpoint inhibitor; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; RCC, renal cell carcinoma; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1inhibitor; CTLA-4, cytotoxic T lymphocyte associated protein 4; N/A, not applicable.

existing pulmonary disease associated with a significantly higher incidence of ICI-P, which could explain why ICI-P is more common in lung cancer patients than in other cancer types (18).

According to a recent meta-analysis of ICI clinical trials, the total incidence of ICI-P after single and combination therapy is 1.6% and 6.6%, respectively, suggesting that the risk of ICI-P is higher after combination therapy than after single therapy (17). In another study, a higher incidence of ICI-P was seen with the risk ratio of all grades of ICI-P increasing up to 2.92 after combination therapy (30). According to a meta-analysis, ICI-P was the most common cause of anti-PD-1/PD-L1-related fatalities (35%). In addition, toxicity-related fatality rates were higher in patients who received combination therapy of PD-1/PD-L1 plus CTLA-4 (1.23%) than in those who received single therapy with anti-PD-1 (0.36%), anti-PD-L1 (0.38%), or anti-CTLA-4 (1.08%) (31). The incidence of ICI-P was higher in patients treated with sequential therapy with targeted agents (18.8%) within 8 weeks of ICI treatment than in patients treated with cytotoxic agents (7.4%) and in patients not treated with chemotherapy (5.1%). The onset of ICI-P was earlier in patients who received sequential therapy with targeted agents after immunotherapy than in those who received sequential therapy with cytotoxic drugs (35 days versus 62 days, respectively). Patients who received targeted agents within 8 weeks of immunotherapy had a higher chance (100%) of developing ≥grade 3 ICI-P than those treated with cytotoxic agents (0%). Among 23 patients with ICI-P, 16 patients (69.6%) required intravenous steroids. Despite receiving high-dose systemic intravenous steroids, 1 patient with grade 4 pneumonitis recovered, whereas 6 (26.1%) patients died (32). Some findings showed that PD-1 inhibitors were associated with a higher incidence of ICI-P compared with PD-L1 inhibitors (immune monotherapy) (33–35). In a study by Khunger, compared with PD-L1 inhibitors (1.3%), PD-1 inhibitors were associated with a higher risk of ICI-P (3.6%). In addition, the incidence of >grade3 ICI-P was higher in patients receiving anti-PD-1 therapy (1.1%) than in those receiving PD-L1 therapy (0.4%) (14).

A retrospective study enrolling 1826 patients with cancer reported that ICI-P occurred more frequently in men and former or current smokers (64 [3.5%] patients) (36). Nakahama reported that tumour invasion in the central airway (TICA) was associated with an increased risk of ICI-P. Patients with TICA had a higher risk of ICI-P than patients with a history of radiotherapy, which is a well-known risk factor for ICI-P (37). Based on the conclusions of these two studies, the incidence of ICI-P is higher in NSCLC (especially squamous cell lung cancer) than in melanoma (38, 39). Furthermore, a study involving 837 patients showed that 354 (42.3%) patients aged ≥ 65 years had a significantly increased risk of developing ICI-P, compared with 483 (57.7%) patients aged < 65 years, with a risk ratio of 2.12 (40).

In conclusion, patients with the following characteristics: male, former or current smoker, ≥65 years old, previous chest radiotherapy, previous lung disease, combination therapy, and TICA are predisposed to ICI-P after immunotherapy (Table 2). Clinicians should be cautious while using ICIs to treat the aforementioned susceptible populations and keep patients under careful observation after ICI therapy.

TABLE 2 Risk factors of immune checkpoint inhibitor-related pneumonitis.

| |
|---|
| **Patient characteristics:** |
| Λ male |
| Λ ≥ 65 years old |
| Λ former or current smoker |
| Λ previous lung disease |
| **Tumour:** |
| Λ lung cancer > other cancer types |
| squamous cell lung cancer > non-squamous cell lung cancer |
| Λ tumour invading the central airway |
| **Treatment:** |
| Λ previous chest radiotherapy |
| Λ Anti-PD-1 > Anti-PD-L1 |
| Λ combination therapy |
| ICI and targeted drug > ICI and cytotoxic drug> single ICI |
| Anti-PD-1/PD-L1 and Anti-CTLA-4 > immune monotherapy |

PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1 inhibitor; CTLA-4, cytotoxic T lymphocyte associated protein 4; ICI, immune checkpoint inhibitor; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; CT, computed tomography.

## Pathogenesis of ICI-P

The mechanisms of ICI-P remain unclear; however, some theories based on the mechanism of action of ICIs and related studies are described below. Activated T cells, B cells, NK T cells and myeloid cells express PD1 (41). Tumour cells express PD-L1, which is upregulated in macrophages, dendritic cells, fibroblasts and activated T cells (42). The interaction between PD-L1 and PD1 inhibits the function, differentiation and survival of T cell (41). Anti-PD(L)-1 improves the anti-tumour immune response by activating T cells and relieving the inhibition of associated signalling pathways. CTLA-4 is an inhibitory receptor belonging to the CD28 immunoglobulin subfamily, expressed mainly by T-cells, which inhibits binding of CD28 on T cells, to B7 proteins on antigen-presenting cells (APCs), thereby impairing the costimulatory effect of T cells the costimulation on T cells (43, 44). In addition, CTLA4 can also interferes with Treg cell function (45). In a study on a knockout mouse model, mice lacking the CTLA-4 gene died of lymphoproliferation, whereas those lacking PD-1 developed lupus-like autoimmune diseases (46, 47). The occurrence of ICI-P may be associated with excessive T cell activation and tumour microenvironment disturbance. Although ICIs promote

lymphocyte activation against tumours, activated T cells can damage alveolar cells, leading to ICI-P (48, 49). A study by Suresh reported a marked increase in the number of lymphocytes, especially CD4+ T cells, in the bronchoalveolar lavage (BAL) of patients with ICI-P (50). The tumour microenvironment includes both immune cells and associated cytokines. Disturbance in the tumour microenvironment owing to ICI use may also contribute to the development of ICI-P. A study by Catacchio highlighted the significance of the tumour microenvironment (44). ICIs are immunotherapeutic agents with a specific target. Off-target toxicity is a specific mechanism by which targeted therapy causes negative effects (51). CD8+ cytotoxic T lymphocyte-mediated cell lysis induces the release of neoantigens, tumour antigens, and autoantigens from normal tissues. The immune tolerance of normal tissues is reduced as a result of this phenomenon known as "epitope spreading,", which may lead to the development of ICI-P (52).

## Clinical characteristics

ICI-P is a unique toxic reaction that occurs after immunotherapy. Although it is relatively rare, it is one of the most important causes of death caused by ICIs in patients with NSCLC. A meta-analysis by Mizuki Nishino (17) showed that the overall incidence of ICI-P after PD-1 inhibitor monotherapy was 2.7% for all-grades of ICI-P and 0.8% for ≥grade 3 ICI-P. However, the incidence was higher among patients with NSCLC than with melanoma and kidney cancer, for all-grade (4.1%) and ≥grade 3 ICI-P (1.8%). The extent of involvement of the lungs in ICI-P is highest in the lower lungs, followed by the middle and upper lungs. In a clinical study by Myriam Delaunay (53), the average time required for the onset of ICI-P after introducing immunotherapy was 2.3 (0.2-27.4) months. A majority (42.2%) of patients developed ICI-P within < 2 months of introducing immunotherapy; the time to development of ICI-P was 2-4 months in 26.6%, 4-6 months in 17.2% and > 6 months in 14.1% of patients. Another study also showed that the onset of all grades of ICI-P was early, usually within 6 months of initiating immunotherapy, with higher-grade ICI-P occurring earlier than lower-grade ICI-P (19).

ICI-P is non-infectious pneumonitis, and its clinical manifestations are different from ordinary pneumonitis (54). A study by Myriam Delaunay showed that the most common symptoms of ICI-P were dyspnoea (80.3%) and cough (52.5%). Fever (32.8%) and asymptomatic conditions (6.6%) were less common (53). Another clinical study by Tomomi W Nobashi reported that one of the major symptoms of ICI-P was fever, lasting for a few days or more. They found that the symptoms with a higher incidence were fever (30%), dyspnoea (26%), low oxygen saturation (15%) and cough (15%), whereas those with a relatively low incidence were malaise (7%), rash (4%) and anorexia (4%). In addition, thyroid dysfunction and rashes were common in patients with and without ICI-P; however, the frequency of incidence was significantly higher in patients with ICI-P (21).

## Radiological manifestations

When ICI-P is suspected, clinicians should make accurate and rapid decisions, because ICI-P has characteristics that demand urgency in treatment. However, the clinical manifestations of ICI-P are diverse, and it is difficult to predict the occurrence of ICI-P before initiating treatment. CT of the chest plays a significant role in the diagnosis of ICI-P. Understanding the features of CT of the chest in ICI-P is important for prompt treatment. At present, the imaging classifications are mainly divided into the following categories: organising pneumonitis (OP), non-specific interstitial pneumonitis (NSIP), hypersensitivity pneumonitis (HP) and diffuse alveolar damage (DAD). DAD is also called acute respiratory distress syndrome (ARDS). The severity of these conditions is graded as follows: DAD>NSIP/HP>OP. In terms of incidence rate, OP has the highest incidence (65%), NSIP has a lower incidence (15%) and HP and DAD have the lowest incidence (10%) (55, 56). The radiological features of cryptogenic organising pneumonitis (COP) may be a sign of enhanced efficacy of ICIs (57). In addition, signs of ground-glass opacity (GGO), consolidations, traction bronchiectasis, nodular lesions, and reversed halo can be observed on CT. Among the five major types of signs, GGO is observed in a majority of patients, followed by consolidations. Although the reversed halo sign is rare, it is a typical finding in OP (18).

## Pathological features

Pathological methods are becoming increasingly essential for the diagnosis of ICI-P. They can be used to rule out infectious pneumonitis and tumour progression. However, BAL and lung biopsy are not routinely performed in patients with ICI-P. In a retrospective study by Brandon T on 9 patients with ICI-P (58), OP was the most common histological pattern (7 patients). Among the 9 patients, 3 had concomitant ambiguous non-necrotising granulomas in the airway, and 2 presented with more acute symptoms, with histological changes indicating severe acute lung injury. In addition, 1 patient showed a pattern of acute fibrinous pneumonitis, and 1 patient with acute respiratory failure showed a pattern of acute and organising DAD. All 9 patients showed patchy accumulation of foamy macrophages in the airway and vacuolisation of type II pneumocytes. BAL has been used in a few studies on patients with NSCLC with ICI-P. Sabino Strippoli (59) analysed the characteristics of BAL in patients with melanoma with ICI-P and showed that cellular analysis using BAL revealed typical and homogeneous features with increased lymphoid population,

relevant enrichment of CD8 + T cells and consequent inversion of the CD4/CD8 ratio. Moreover, the proportion of activated CD3 + HLA-DR + T cells was associated with the grading of adverse events. It has been reported that a major feature of BAL analysis in ICI-related NSCLC is an increase in the proportion of lymphocytes (60). The proportion of BAL lymphocytes, mainly CD4 + T cells, increases in ICI-P. An increase in the number of BAL central memory T (Tcm) cells, evidence of type I polarisation, and decreased expression of CTLA-4 and PD-1 in BAL Tregs indicate both activation of pro-inflammatory subpopulations and a weakened inhibitory phenotype. In a study, the myeloid immune population in BAL supernatants in ICI-P showed increased expression of IL-1β and decreased counter-regulation of IL-1RA expression, with increased levels of Tcm chemoattractants. These dysregulated immune cell subsets may represent possible targets for the treatment of pathological irAEs (50). Bronchoscopy plays an important role in the diagnosis of acute lung injury and fibrosis (61).

## Diagnosis

The diagnosis of ICI-P requires a comprehensive consideration of the clinical symptoms, as well as general bloodwork, CT imaging, and invasive evaluation (BAL or lung biopsy). Exclusion diagnosis is also an important strategy. Infectious pneumonitis, radiation pneumonitis (RP), tumour progression, carcinomatous lymphangitis, and pulmonary oedema caused by heart failure or myocarditis are common differential diagnoses. Establishing a diagnosis of ICI-P requires the exclusion of diseases mentioned in Table 3 (62–64). Among them, the presentation of RP and ICI-P is similar to that of interstitial pneumonitis. Therefore, it is difficult to distinguish clinically RP from ICI-P in patients who have undergone both radiotherapy to the chest and immunotherapy. However, there are some differences in terms of CT location distribution between the two types of pneumonitis. On CT of the chest, RP usually shows sharp margins; thin, dense plaques or streak-like changes in the lung ipsilateral to a lesion consistent with the extent of irradiation and to a lesion that is not consistent with the normal lung tissue structure (not distributed based on lung field or lung segment) (65). However, ICI-P is usually bilateral, involves multiple lung lobes and shows no sharp borders on CT, and the ICI-P area usually does not cross the lung fissures (66).

## Grading and management of ICI-P

### Grading

According to the latest National Comprehensive Cancer Network (NCCN) guidelines, ICI-P is divided into three levels and four grades as follows: mild (G1), moderate (G2) and severe (G3-4) (Table 4). Grade G1 refers to asymptomatic disease; ICI-P is confined to one lobe or < 25% of the lung parenchyma. Grade G2 marks the appearance of new symptoms such as shortness of breath, cough, chest pain, fever, and hypoxia; with the involvement of multiple lung lobes, affecting 25%-50% of the lung parenchyma; It affects daily life and requires drug intervention. Grade G3 refers to the appearance of serious new symptoms. It involves all lung lobes or > 50% of the lung parenchyma. Patients with G3 ICI-P have limited self-care ability and require oxygen supplementation. Grade G4 refers to life-threatening respiratory system damage, such as acute respiratory distressyndrome (ARDS), which requires emergency care (67).

### Management

Steroid therapy is a routine strategy for the management of ICI-P. Regular and sufficient use of steroids can help to treat 70—80% of patients with ICI-P (16). According to the current consensus on ICI-P treatment, steroid therapy should be initiated after a confirmed diagnosis of ≥G2 ICI-P. Patients with G1 ICI-P can be temporarily observed, and the use of ICIs should be suspended (1-2 weeks). However, if there are signs of progress of ICI-P, steroid therapy should be initiated. For patients with G2 ICI-P, prednisone/methylprednisolone at a dose of 1—2 mg/kg/day (Treatment until symptoms improve to ≤ grade 1, then taper over 4-6 weeks) is usually administered. For patients with G3-4, methylprednisolone at a dose of 1—2 mg/kg/day (taper over ≥6 weeks) is usually administered (67). Some patients are not sensitive to steroid therapy (no improvement after 48 hours for G3-4 ICI-P). This condition is usually called steroid-refractory pneumonitis (68), the criterion of which is mainly based on clinical symptoms and chest CT. In this case, the following treatments can be considered: 1) Intravenous administration of infliximab at a dose of 5 mg/kg, which can be repeated after 14 days at the discretion of a physician; 2) Intravenous injection of immunoglobulin; 3) Mycophenolate mofetil at a dose of 1-1.5 g twice daily (BID); the dosage can be gradually decreased over time (67, 69, 70). During treatment, the efficacy should be continuously monitored. If the infection has not been completely ruled out, empirical use of antibiotics should be considered. In terms of supportive treatment, clinicians should provide corresponding respiratory and systemic support to patients and actively deal with their complications. For reinitiating ICI treatment, a cohort study showed that after re-challenge with the same ICI, the recurrence rate of the same irAE associated with the discontinuation of ICI therapy was 28.8%. In such cases, clinicians can consider resuming ICI treatment for selected patients, who should be monitored appropriately (71, 72).

TABLE 3 Differential diagnosis of immune checkpoint inhibitor-related pneumonitis.

| Differential diagnosis | Description |
|---|---|
| Infectious pneumonitis | • Most patients have symptoms of fever and expectoration, and antibiotic treatment is effective.<br>• Elevation of serum inflammatory response indicators (including WBC, CRP, PCT, IL-6, etc.).<br>• Positive results of pathogen detection (including nasal swab, sputum culture, blood culture and BAL).<br>• CT findings: consolidation, air bronchogram sign, silhouette sign, tree-in-bud sign, etc. Usually distributed by lung fields or segments. |
| Radiation pneumonitis | • Typically develops 4 to 12 weeks after completing radiotherapy.<br>• CT findings: patchy lesions, diffuse ground-glass opacity, traction bronchiectasis and scar-like lesions in the irradiated field. |
| Tumour progression or carcinomatous lymphangitis | • Metastasizes in the lungs or grows and spreads along the lymphatic vessels.<br>• CT findings: new nodules, ground-glass opacities, reticular nodules, thickened bronchial bundles and beaded thickening of interlobular septa.<br>• Exfoliative cytology, BAL and lung biopsy will play an important role in the diagnosis. |
| Pulmonary oedema due to heart failure or myocarditis | • Specific clinical manifestations: paroxysmal nocturnal dyspnea, dyspnea after exercise, pink foam sputum, etc.<br>• CT findings: interlobular septums, fissures, peribronchovascular interstitium thickening, cardiomegaly, pleural effusion, Kerley B lines and increased artery to bronchus ratio. |

WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; BAL, bronchoalveolar lavage; CT, computed tomography.

# Discussion

## Association between the occurrence of ICI-P and the outcome of cancer treatment

Some scholars have compared a large amount of research data and concluded that the occurrence of irAEs is directly proportional to the prognosis (73). The occurrence of irAEs indicates that immunotherapy has activated the immune system of patients. Patients with greater toxicity to immune drugs can attain better curative effects, leading to prolonged PFS and OS (20). In a meta-analysis (74), irAEs, especially endocrine, dermatologic and low-grade irAEs, were significantly associated with better ICI outcomes in patients with cancer. In addition, the development of irAEs was associated with the beneficial effects of treatment on survival in patients with cancer treated with PD-1 inhibitors but not in those treated with CTLA-4 inhibitors. Patients receiving immune monotherapy have more significant benefits than patients receiving combination therapy. Syed Hussaini reported a similar conclusion (75). In patients treated with ICIs, the occurrence of irAEs is positively correlated with objective response rate (ORR), PFS and OS but is not associated with the site of disease, type of ICIs and irAEs. Patients with ≥grade 3 ICI-P have better ORR but worse OS. However, some studies have reported more positive results, indicating that the OS of patients with multiple irAEs is significantly better than that of patients with a single irAE (76). Although studies have shown that endocrine, skin, and low-grade irAEs are associated with the efficacy of immunotherapy, some studies have reported that ICI-P can significantly improve recurrence-free survival (RFS) (77). Studies have also shown that the ORR and PFS of patients with ICI-P are significantly better than those of patients with irAE-non-ICI-P and non-irAEs (27). In a study by Shankar B, the PFS and OS of the ICI-P group were better than those of the non-ICI-P group (76). The incidence of low-level ICI-P can prolong PFS and OS, and increase ORR. High-grade ICI-P does not benefit OS but can help in achieving better ORR (75) (Table 5)

TABLE 4 Grading of immune checkpoint inhibitor-related pneumonitis.

| Level | Grade | Description |
|---|---|---|
| Mild | G1 | Λ asymptomatic |
| | | Λ ICI-P is confined to one lobe or < 25% of the lung parenchyma |
| Moderate | G2 | Λ the appearance of new symptoms such as shortness of breath, cough, chest pain, fever, and hypoxia |
| | | Λ multiple lung lobes are involved, affecting 25%—50% of the lung parenchyma |
| Severe | G3 | Λ the appearance of serious new symptoms |
| | | Λ involves all lung lobes or > 50% of the lung parenchyma |
| | G4 | Λ life-threatening respiratory system damage |
| | | Λ ARDS |

ICI-P, immune checkpoint inhibitor-related pneumonitis; ARDS, acute respiratory distress syndrome.

TABLE 5 Published researches on association between the occurrence of ICI-P and the outcome of immunotherapy in NSCLC.

| Author | Year | Numbers of patients/ trials | ICI type | Incidence of ICI-P (%) | ORR(%) | PFS(months) | OS(months) |
|---|---|---|---|---|---|---|---|
| Ono K (20) | 2021 | 203/1 | Anti-PD-1 | 14 | ICI-P: 68<br>Non-ICI-P: 20 | ICI-P: 18.9<br>Non-ICI-P: 3.9 | ICI-P: 27.4<br>Non-ICI-P: 14.8 |
| Sugano T (27) | 2020 | 130/1 | Anti-PD-1<br>Anti-PD-L1 | 12 | ICI-P: 63<br>Other irAEs: 43<br>Non-irAEs: 22 | ICI-P: 15.9<br>Other irAEs: 5.4<br>Non-irAEs: 3.3 | N/A |
| Haratani K (73) | 2018 | 134/1 | Anti-PD-1 | 4 | N/A | IrAEs: 9.2<br>Non-irAEs: 4.8 | IrAEs: NR<br>Non-irAEs: 11.1 |
| Shankar B (76) | 2020 | 623/1 | N/A | Monotherapy: 12<br>Combined therapy: 9 | N/A | Single irAE: 10.9<br>Multisystem irAEs: 5.1<br>Non-irAEs: 2.8 | Single irAE: 21.8<br>Multisystem irAEs: 12.3<br>Non-irAEs: 8.7 |
| Hussaini S (75) | 2021 | 2859/19 | Anti-PD-1<br>Anti-PD-L1 | N/A | IrAEs: 41.49<br>Non-irAEs: 18.01 | IrAEs: 8.97<br>Non-irAEs: 3.06 | IrAEs: 19.07<br>Non-irAEs: 7.45 |

NSCLC, non–small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1inhibitor; CTLA-4, cytotoxic T lymphocyte associated protein 4; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; NR, not reached; OS, overall survival; PFS, progression free survival; ORR, bjective response rate; N/A, not applicable.

## Markers predicting the occurrence of ICI-P

The incidence of serious ICI-P after immunotherapy adversely affects the survival and quality of life of patients. The discovery and optimisation of predictive factors through laboratory tests can help clinicians to predict the occurrence of ICI-P, discontinue the use of ICIs in time or administer steroids early and may help in prolonging the survival of patients. A study showed that the expression of PD-L2 may be related to the incidence of irAEs in patients with NSCLC treated with PD-1 inhibitors. In addition, pre-existing autoimmunity markers such as the rheumatoid factor have been identified as independent predictors of skin reactions caused by ICIs (78). Thyroid dysfunction is more common in patients with anti-thyroid antibodies (79). However, to the best of our knowledge, studies have not reported the specific predictors of ICI-P. Therefore, relevant fundamental research is warranted to guide the application of clinical immunotherapy.

# Conclusion

Clinicians should be cognizant of adverse reactions caused by ICIs, especially ICI-P. It is important to make an assessment before administering medications and pay attention to high-risk groups. After the administration of immunotherapeutic drugs, clinicians should pay close attention to changes in the condition of patients. Based on the combination of clinical manifestations, imaging data, and pathological characteristics of patients, ICI-P can be easily diagnosed, considering that infectious pneumonitis is excluded. ICI-P is mild in most cases and can be cured by appropriate treatment such as discontinuing immunotherapy or using steroids. If severe ICI-P occurs, immunotherapy should be promptly discontinued, and steroids and immunosuppressive therapy should be administered. Early intervention has a great impact on the survival and quality of life of patients. More studies are required for steroid-refractory pneumonitis, because, at present, an effective standard treatment plan is not available. In addition, further investigation is warranted to identify the predictors of ICI-P in the future.

# Author contributions

All authors planned and wrote the manuscript and contributed to the article and approved of the submitted version.

# Conflict of interest

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

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# Evolutions in the management of non-small cell lung cancer: A bibliometric study from the 100 most impactful articles in the field

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**Objective:** The study was designed to explore the evolution of non-small cell lung cancer (NSCLC) management in the last 20 years.

**Methods:** The top 100 most-cited papers on NSCLC treatment were retrieved from the Web of Science Core Collection database. R and VOSviewer were used to extract bibliographic information, including the year of publication, countries/regions, institutions, authors, journals, keywords, impact factor, and total citations. The topic and type of papers were checked independently by authors. Bibliometric analysis was conducted and visualized with R, CiteSpace, Excel and VOSviewer to identify output dynamics, research forces, topics, hotspots, and frontiers in the field.

**Results:** The average citation of each retrieved top 100 most-cited NSCLC management papers was 1,725 (range: 615-7,340). Fifty-seven corresponding authors were from the United States. This country contributed the most papers (n=76), followed by Germany (n=34), France (n=33), and South Korea (n=32). The top contributors were Paz-Ares L. (n=12) and Reck M. (n=12). The Memorial Sloan Kettering Cancer Center published the largest number of papers (n=20). There were two significant citation paths, indicating publications in medicine/medical/clinical journals primarily cited journals in molecular/biology/genetics fields, partly cited health/nursing/medicine fields. Top-cited papers mainly came from the New England Journal of Medicine (n=33, citations=80,427), followed closely by the Journal of Clinical Oncology (n=28, citations=32,408). "Chemotherapy" (n=36) was the keyword with the greatest frequency of co-occurrence. "Open-label" was the keyword with the strongest burst strength (=4.01), followed by "nivolumab" (=3.85), "blockade" (=2.86), and "efficacy" (=2.85).

**Conclusions:** The United States as a nation and the Memorial Sloan Kettering Cancer Center as an institute contributed the most to this field. The New England Journal of Medicine is the most eye-catching journal. Hotspots of NSCLC management have almost undergone an evolution from chemotherapy and radiotherapy to targeted therapy to immunotherapy. Molecular/biological/genetic fields become the main research base for NSCLC treatment. Immunotherapy and combination therapy are research frontiers.

KEYWORDS

**non-small cell lung cancer (NSCLC), management, treatment, bibliometric, R, VOSviewer, Citespace**

## Introduction

Lung cancer is the second most prevalent cancer and the most common cause of cancer-related deaths, with approximately 2.2 million new cases and 1.8 million deaths each year, accounting for one-tenth of diagnosed cancers and one-fifth of cancer deaths globally. This cancer has become the leading burden on worldwide health care (1). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of all lung cancer cases, which is further subdivided into three types: adenocarcinoma, squamous carcinoma, and large cell lung carcinoma (2, 3). The most common type is adenocarcinoma, which occurs in the peripheral bronchi and accounts for approximately 40% of all lung cancers. This is followed by squamous carcinoma, which arises in the main bronchi and comprises 25-30% of all diagnosed lung cancers. Large cell carcinoma accounts for 10%, occurring in the proximal part within the thorax (3, 4). NSCLC is a heterogeneous malignancy harboring a wide variety of driver genetic mutations. Over the past few decades, tremendous advances in NSCLC treatment, especially the advent of targeted and immunotherapy, have changed the landscape of NSCLC management. Individualized precision medicine based on genetic characteristics is gaining popularity. Currently, the options for NSCLC management mainly include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. Among them, surgery has become a greatly recommended choice for resectable NSCLC, stereotactic ablative radiotherapy (SABR) techniques make radiotherapy more precise and less damaging, platinum-based chemotherapy remains the standard regimen for some advanced NSCLC patients, while small molecular tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) have brought unprecedented benefit in particular patients (5–7). The emergence of new technologies and the obsolescence of old ones have been ongoing.

However, the evolution of NSCLC treatment over the last 20 years is not well defined previously. Textbook-style chapter summaries and systematic reviews fail to fully demonstrate a time-based research progress and to effectively analyze a large amount of data. In fact, it is difficult for scholars to perform an exhaustive analysis in the face of the vast amount of NSCLC treatment research findings over the last 20 years. It is even more challenging to assess the evolution of the subject according to its temporal dynamics. Bibliometric analysis is one of the best tools for studying temporal trends in a certain area, which offers more comprehensive and objective results (8–11). Therefore, bibliometrics may provide meaningful insight into NSCLC management. We have innovatively applied this approach in the field of NSCLC treatment. The volume of citations in a paper signifies the significance of the study, indicating the impact it has had on the understanding and treatment of the disease (12). To make the study representative, we filtered the 100 most-cited articles in NSCLC treatment based on bibliometric citation analysis. These articles stand for the most impressive achievements in NSCLC treatment. In the 21st century, when the treatment of NSCLC is rapidly evolving, all research is inseparable from the foundation of previous generations. We can gain a lot of inspiration and experience from the evolution of NSCLC treatment. The study may help clinicians and researchers quickly understand the evolution of NSCLC management and grasp research status quo. The data visualization can help them to have a more intuitive understanding of the 100 most-cited NSCLC papers. To our knowledge, this is the first comprehensive bibliometric study about the evolution of NSCLC treatment in the last 2 decades.

## Materials and methods

### Data acquisition

The relevant data used in this study were downloaded from the Science Citation Index Expanded (SCI-EXPANDED) of Clarivate Analytics Web of Science Core Collection (WoSCC).

The WoSCC is the most commonly used database for various bibliometric studies (8, 13). As the most prestigious global database, it can provide detailed information needed for bibliometric software and ensure the quality of research (14).

Literature in WoSCC published from January 2000 to December 2021 was systematically searched. The search terms were partly selected from the Medical Subject Headings (MeSHs) offered by the PubMed. We mainly refer to papers to expand the search terms (8). In addition, we consulted experts and physicians to add supplementary concept. The search topic terms were "non-small cell lung cancer" and "treatment". The summary of the search strategy is presented in Supplementary Table S1. Guidelines, editorials, and statements were all excluded. Only original articles and reviews with full manuscripts regarding the management of NSCLC were reserved, and no language restrictions were applied. It has been demonstrated that bibliometric analysis using original articles and reviews is effective (15). To select the papers with the highest academic impact in the field, two authors (S.C. and Y.Q.) identified the top 100 articles based on total citation (TC) independently. If there was any dissensus, it was discussed with a corresponding expert (Y.H.) until a consensus was reached. To avoid errors caused by the database update, all data acquisition was completed on December 2, 2021. We download the 100 most influential articles' records, in the "Full Record and Cited References" form from WoSCC in.txt format (Figure 1).

## Data analyses and visualization

R is a unique language and environment for statistical calculation and plotting (16). It offers a wide diversity of statistical and charting techniques and is highly extensible and useful in ever-changing fields, such as bibliometrics (11, 17). The "bibliometrix" R-package provides a range of flexible tools for quantitative research in bibliometrics and scientometrics while it can also be integrated with other R packages (11). We mainly rely on the "bibliometrix" package in the R software to convert, analyze, and visualize data.

VOSviewer, a computer program developed by Leiden University, used to build and view bibliometric maps, has exceptional capabilities in exploring and visualizing network-based data (18). It was chosen because it delivers concise, information-rich charts that meet the research needs.

CiteSpace, a JavaScript-based application developed by Drexel University, was designed as a powerful tool for identifying and mapping potential trends and dynamics of a scientific field over time (19). The program has been commonly applied for bibliometric analysis in numerous subjects, such as oncology, immunology, and regenerative medicine (9, 13, 20, 21).

The results of the bibliometric analysis are always manifested through science mapping, which is complex and frequently requires a combination of various software for the creation (11). The above applications were utilized in combination to achieve enriched results. We used the "bibliometrix" package

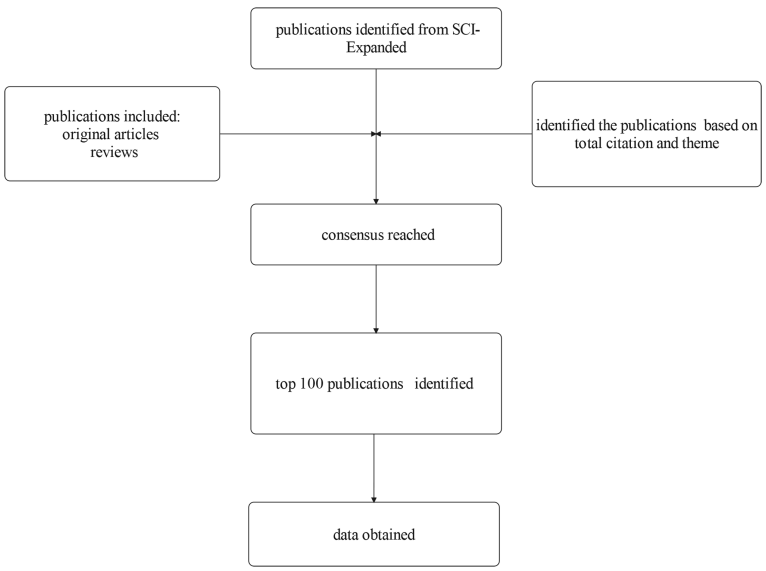


FIGURE 1
Flow chart of literature screening.

(Version 3.1.4) in R software (Version 4.1.1) and VOSviewer (Version 1.6.17) to extract the bibliographic information of the selected papers, including the year of publication, countries/regions, institutions, authors, journals, keywords, impact factor (IF, from Web of Science InCites Journal Citation Reports, JCR Year 2020), and TC. To ensure the accuracy of the data, we also finalized the papers' topic and type by reading titles, abstracts, and even the full texts. After that, we combine R and Microsoft Office Excel (Version 2019) to create the map concerning the annual distribution of publications, the proportion of international cooperation, the annual output of the top 10 authors, and the annual growth trends of the journals. VOSviewer was also used for graph generation of the overlay visualization map of the top-cited publications, the cooperation relationships of countries/regions, the item density visualization map of major institutions, the cooperation relationships of major authors, and the overlay visualization map of keywords co-occurrence. CiteSpace (Version 5.8.R3) was adopted to draw the dual-map overlay of journals and to identify the keywords with the strongest burst strength. Excel was used to manage the database.

# Results

## Output of publications

More than 300,000 articles (published between January 2000 and December 2021) related to the treatment of NSCLC were retrieved from WoSCC. The result shows that the TC varied from 615 to 7,340 and the average citations per publication were 1,725. These papers, including 97 original articles and 3 reviews, were published by a sum of 1,940 authors, with an average of 19.7 authors per publication, and none of the papers were solely authored.

As is displayed in Figure 2A, the selected most influential papers were published from 2000 to 2019, with annual output ranging from 1 to 10. The high-yield years were 2005 (n=10), 2015 (n=9) and 2018 (n=9) and the lowest yield year was 2001 (n=1).

Figure 2B reflects that the single papers published by Paez JG, Mok TS, and Borghaei H had the top 3 TC, with 7,340, 5,931, and 5,453 respectively. In addition, there was a wide citation relationship between the top papers. The detailed information about the 100 most influential publications was recorded in Supplementary Table S2.

## Countries/regions analysis

As is shown in Figure 3A, the 100 top-cited articles were from 44 countries/regions. Among these countries/regions, the United States possesses the largest weight (n=76), meaning the number of papers involving authors from the United States was 76. The densest connecting lines surrounding "Unites States" suggests the strongest cooperation between the United States and other countries/regions. The highly cooperative countries/regions also include Germany (n=34), France (n=33), South Korea (n=32), Spain (n=29), Italy (n=27), Japan (n=27), United Kingdom (n=25), Canada (n=24), Australia (n=22) and China (n=21) (shown in the Supplementary Table S3).

Figure 3B demonstrates the distribution of corresponding authors. The level of scientific research in a country/region depends to a large extent on the number of experts in the field. Generally, the corresponding author is the leader in charge of the research and the gatekeeper of the final quality of academic papers. To further explore leading countries/regions in the area, we analyze the distribution of corresponding authors. The majority of the article's corresponding authors are from the United States (n=57), followed by China (n=10), Japan (n=7), France(n=5), Italy (n=4), Canada (n=4), Spain (n=3), Germany (n=3) and Korea (n=2).

## Institutions analysis

As is noted in Figure 4, The Memorial Sloan Kettering Cancer Center holds the largest weight (n = 20), which signifies that the institution was involved in publishing 20 papers, followed by the Massachusetts General Hospital, the AstraZeneca, the Dana-Farber Cancer Institute, and the Sungkyunkwan University, with 16, 12, 12 and 12 respectively. TC/publication is the ratio of TC to number of publications and is equal to the average TC per paper, reflecting the average impact of papers in the journal.

As is listed in Table 1, the Dana-Farber Cancer Institute had the highest TC/publication (2,635.00), followed by the AstraZeneca (1,909.00), the Chinese University of Hong Kong (1,760.20), and the Memorial Sloan Kettering Cancer Center (1,747.15).

## Authors analysis

In Figure 5A, major authors were divided into 4 clusters, which can help us identify the core research teams. The researchers formed a collaborative network with Paz-Ares L., Reck M., Wu Yl., Von Pawel J., and Felip E. as the core, each publishing 12, 12, 11, 10, and 9 articles.

As is shown in Figure 5B, there was a large gap (nearly 10 years) between the two top articles published by Herbst R. whereas some authors, like Paz-Ares L. and Reck M., had been publishing articles for years in a row.

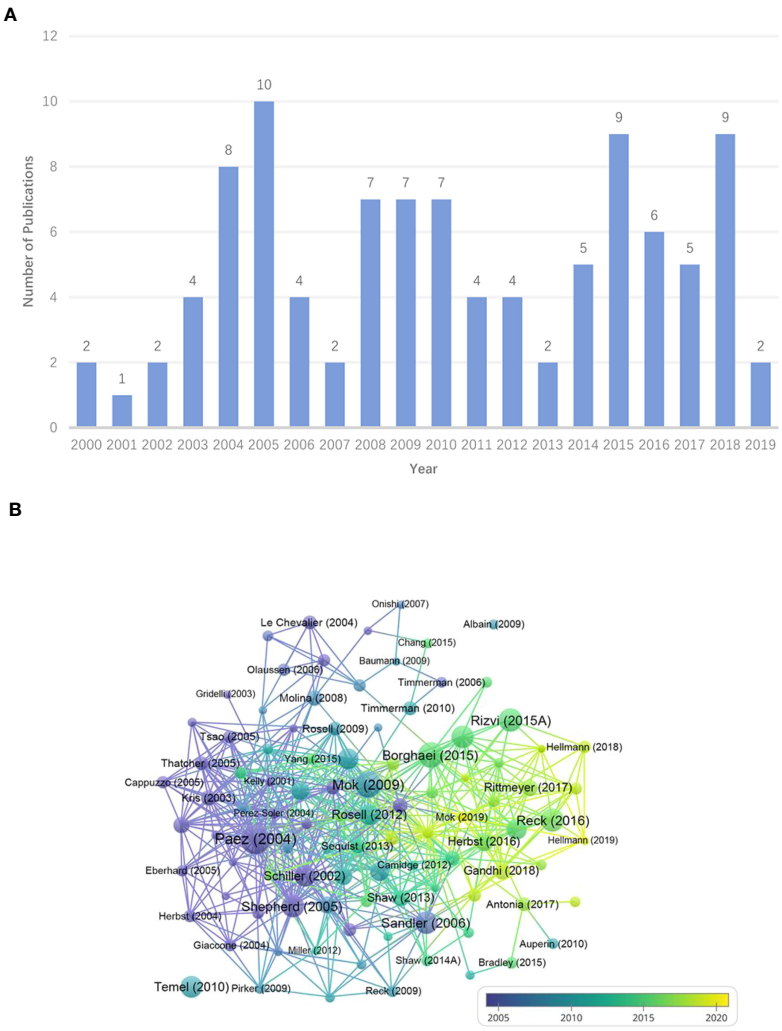


FIGURE 2
**(A)** Annual distribution of publications. **(B)** The overlay visualization map of the top-cited publications. Each node means an article. The size of circles and fonts is proportional to TC. The more purple the node, the earlier the year of publication, and the yellower the node, the more recent the publication date. The node name shows the first author and the publication year of a paper. The connecting line suggests that there is a citation relationship between the papers.

## Distribution of journals

Figure 6A conveys the category distribution of the journals (22). Two significant citation paths were identified and marked in green. The first green path indicates publications in medicine/medical/clinical journals primarily cited journals in molecular/biology/genetics fields and the second means publications in medicine/medical/clinical journals partly cited health/nursing/medicine journals. Immunology and computer-related journals also appear in the citation path marked in yellow and green.

From Figure 6B, the 100 most impactful papers were published in 14 journals. Source dynamics show that most of relevant papers (n=33) were published in the New England Journal of Medicine and had an exponential-like growth in recent years (2012–2019), followed by the Journal of Clinical Oncology (n=28), the Lancet Oncology (n=15) and the Lancet (n=10).

The details are listed in Table 2. The New England Journal of Medicine had the highest IF (=91.253) and TC (=80,427). The 3 journals with the ratio of TC to publication over 2,000 were the Science (=5,933.00), the New England Journal of Medicine (=2,437.18), and the Mayo Clinic Proceedings (=2,049.00).

## Keywords, topics and frontiers

The theme of a paper is reflected in the keywords, and by analyzing them, researchers can get an idea of the topic of the

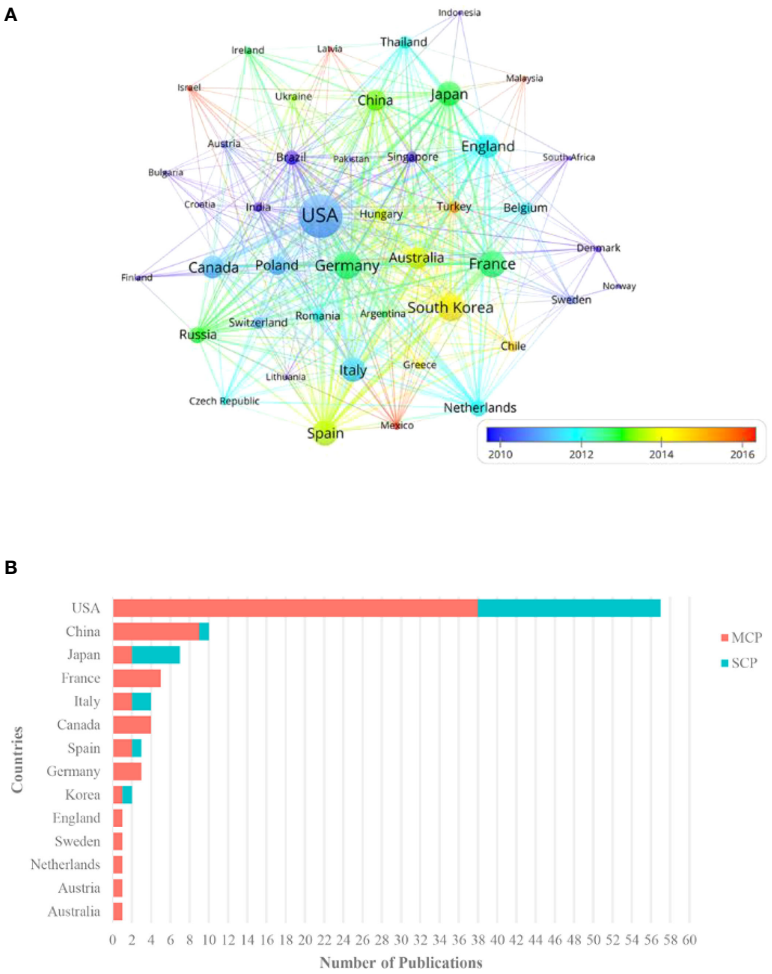


FIGURE 3
**(A)** The cooperation relationships of countries/regions. Each node represents a country/region. The size of circles and fonts symbolizes the number of articles in certain countries/regions, and the thickness of the linking line between countries/regions indicates the frequency of collaborations. The distance between the two circles demonstrates the relatedness of their link. **(B)** The proportion of international cooperation. The length of the bar is determined by the number of corresponding authors in the country/region. MCP is intercountry collaboration indices, denoting the number of papers issued collaboratively by multiple countries/regions. SCP is intra-country collaboration indices, indicating the number of papers published independently by a single country/region.

article (23). The presence of two keywords from a certain field in the same article, called co-occurrence, reflected that there is some internal relationship between them, and the more they appear, the closer the relatedness is (24).

The keyword co-occurrence network (Figure 7A), based on the above principles, can detect the research dynamic and structure of the discipline (25). Keyword plus terms of WoS are effective and more broadly descriptive (26). We chose it to perform keyword analysis. The densest connecting lines around the keyword "chemotherapy" indicate that it is most closely related to other keywords.

As is listed in Table 3, the keywords with the highest frequency were "chemotherapy" (n=36), followed by "clinical-trials" (n=28), "phase-iii" (n=24), and "gefitinib" (n=22).

Figure 7B shows the keywords with the strongest burst strength. Burst-detection algorithms can recognize emerging terms regardless of the number of citations in the host articles, so that burst terms can sensitively and accurately capture the research frontiers (19). Keywords burst earlier indicate that researchers focused on this area in early years, while burst closer to the present denote the topic has suddenly attracted attention recently. The top 5 keywords identified are "open-label", "nivolumab", "blockade", "efficacy" and "phase iii", with the burst strength of 4.01, 3.85, 2.86, 2.85, and 2.77, respectively. "Quality of life" is the earliest keyword to burst, and the most recent burst keywords include "phase iii" and "nivolumab". Keywords with the longest duration of burst are "trial" and "open label".

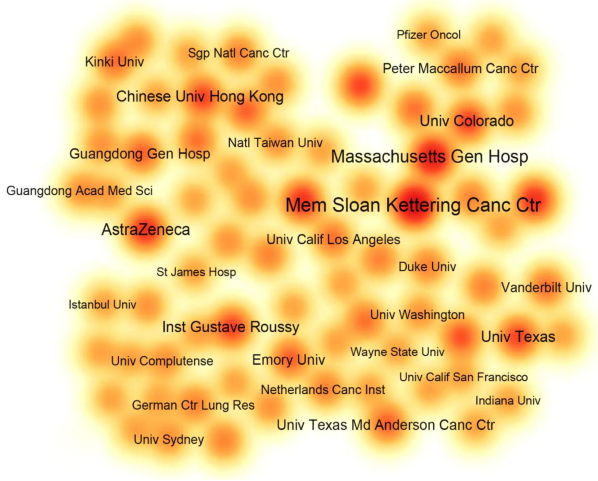


FIGURE 4
The item density visualization map of major institutions. Each node represents an institution. The larger the size of the fonts and the closer the color around the node to red, the more papers the institution is involved in.

## Clinical application

Figure 8A exhibits the principles and landscape of NSCLC management. Chemotherapy, radiotherapy, surgery, targeted therapy and immunotherapy are the main regimens of current NSCLC treatment and have been widely used in clinical practice.

As shown in Figure 8B, ICIs, as new therapeutic agents, have unique advantages, and the mechanism of the ICIs is more in line with the future research direction.

# Discussion

With the significant advancements and rapid changes in NSCLC treatments in the last 20 years, it is crucial to understand the progress and evolution of NSCLC management in the new era where many therapies coexist (5). However, available textbooks and papers lack such information. We selected 100 most impactful papers in this field as research data and applied the bibliometric analysis to systematically explore the output dynamics, research forces, topics, hotspots, and frontiers in the field of NSCLC treatment. It can help scholars quickly learn the basics, clarify study ideas, and learn the research status quo.

As can be seen from Figure 3, top articles evidenced the merits of international cooperation and witnessed a multi-national cooperation network with the United States as the core. Half of the top 10 institutions are from the United States (rank 1, 2, 4, 9, 10 in Table 1). There are 57 corresponding authors belonging to the United States, reflecting the United States is the originator of most top papers and has the most specialists. Additionally, some European countries such as Germany, Britain, and Italy, Canada in North America, and China, Japan, and Korea in Asia, also have

TABLE 1 Top 10 institutions with the most articles.

| Rank | Institutions | Country/Region | Publication | TC | TC/Publication |
|---|---|---|---|---|---|
| 1 | The Memorial Sloan Kettering Cancer Center | USA | 20 | 34943 | 1747.15 |
| 2 | The Massachusetts General Hospital | USA | 16 | 27151 | 1696.94 |
| 3 | The AstraZeneca | England | 12 | 22908 | 1909.00 |
| 4 | The Dana-Farber Cancer Institute | USA | 12 | 31620 | 2635.00 |
| 5 | The Sungkyunkwan University | South Korea | 12 | 19163 | 1596.92 |
| 6 | The Chinese University of Hong Kong | China | 10 | 17602 | 1760.20 |
| 7 | The Institute Gustave Roussy | France | 10 | 16688 | 1668.80 |
| 8 | The Seoul National University Hospital | South Korea | 10 | 13958 | 1395.80 |
| 9 | The University of Colorado | USA | 10 | 15836 | 1583.60 |
| 10 | The University of Texas | USA | 10 | 12761 | 1276.10 |

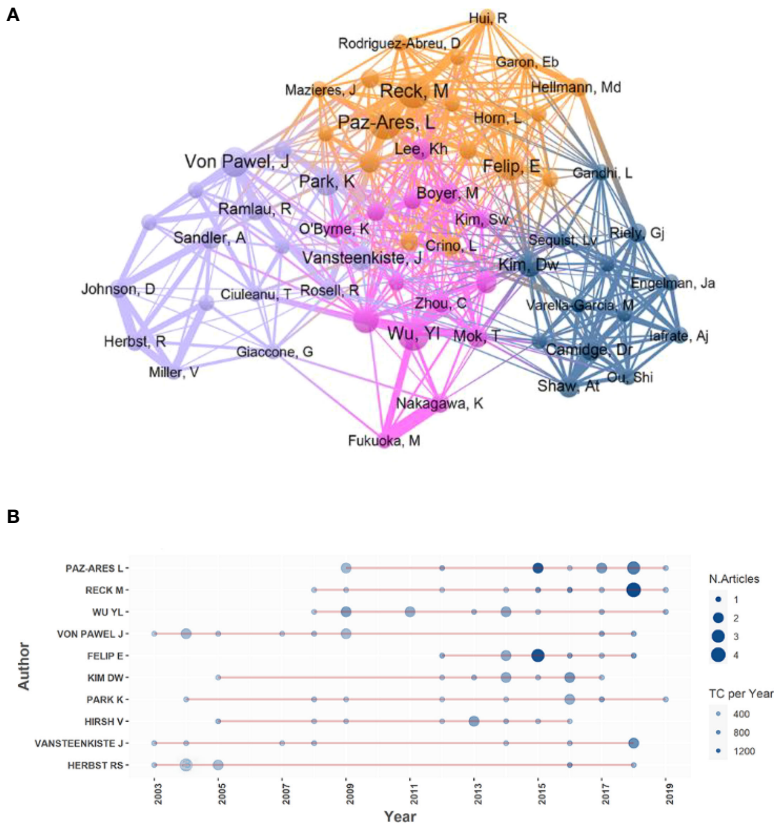


FIGURE 5
**(A)** The cooperation relationships of major authors. Each node stands for an author. The size of circles and fonts means the articles' counts of the author. The colors of the nodes represent clusters. The thickness of the connecting line between authors shows the frequency of collaborations. The distance between the two circles expressed the relatedness of their link. **(B)** Annual output distribution of the top 10 authors. The bigger the node, the more papers published in that year, and the bluer the node, the more annual average TC of the authors' papers in that year.

outstanding performance in the field In 2000, a phase III clinical trial conducted in the United States demonstrated for the first time that docetaxel monotherapy versus vinorelbine/ifosfamide could provide clinical benefit for patients with advanced NSCLC who had relapsed or progressed after receiving platinum-based chemotherapy (27). A phase II study performed in the United States in 2004 investigated the clinical efficacy of erlotinib and found that rash might be a clinical marker for efficacy prediction (28). About a decade ago, this country explored the toxicity and efficacy of stereotactic body radiation therapy in patients with early-stage inoperable NSCLC and concluded that the therapy had high local control rates and moderate adverse events (29). In recent years, the country has also made significant achievements in immunotherapy, such as a single-arm clinical trial covering 27 sites in the United States, France, Germany, and Italy, which revealed favorable efficacy and safety of nivolumab in previously treated patients with refractory advanced squamous NSCLC (30). The United States leads all areas of NSCLC treatment in the world.

As illustrated in Figure 4, the Memorial Sloan Kettering Cancer Center is the foremost research institution for NSCLC management, with the most top-notch papers and highest TC, followed closely by Massachusetts General Hospital. AstraZeneca, the Dana-Farber Cancer Institute, and the Sungkyunkwan University also with exceptional academic results. These institutions all have a long history of distinguished contributions to the field of NSCLC therapy. We found that the major studies in which the Memorial Sloan Kettering Cancer Center was involved were divided into two parts: before 2015 the theme of research was targeted therapy, and after 2015 the topic was immunotherapy. In 2003, the institution participated in a phase II clinical trial that further demonstrated the benefit of gefitinib in improving post-chemotherapy NSCLC symptoms and inducing radiographic cancer regressions (31). In 2015, it was involved in a randomized, open-label, international phase III study comparing the efficacy of nivolumab and docetaxel in patients

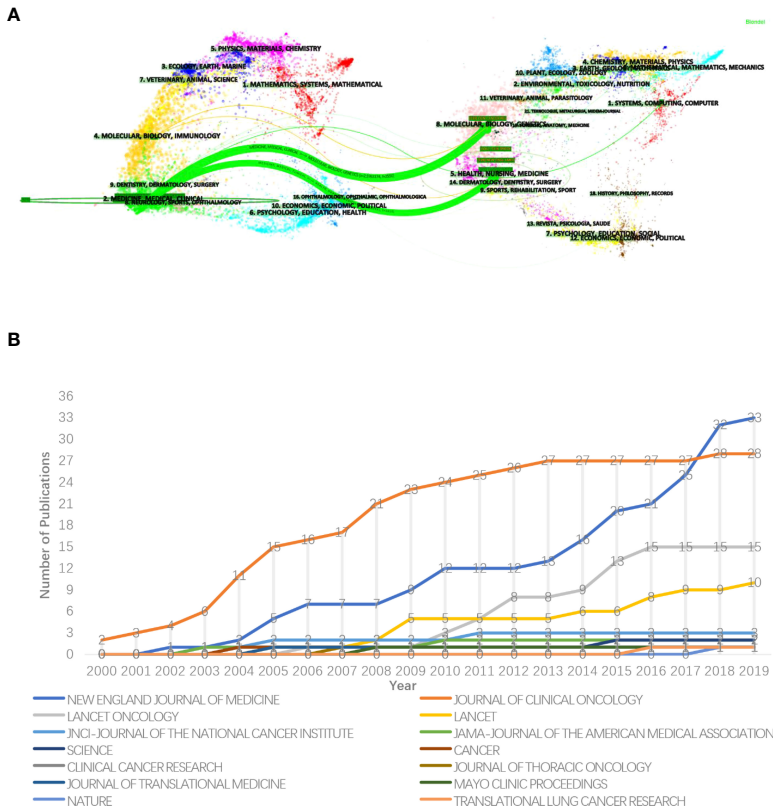


FIGURE 6
**(A)** The dual-map overlay of journals. The citing papers are listed on the left while the cited papers are laid on the right, between them was the curve that presents the citation relationship. Different colors denote journals from different subjects. The length of the vertical axis of the ellipse is proportional to the papers' counts published in the journal and the horizontal length is to authors. **(B)** The annual growth trends of the journals.

TABLE 2 Journals that published the most-cited 100 publications.

| Journal | Publication | IF | TC | TC/Publication |
|---|---|---|---|---|
| New England Journal of Medicine | 33 | 91.253 | 80427 | 2437.18 |
| Journal of Clinical Oncology | 28 | 44.544 | 32408 | 1157.43 |
| Lancet Oncology | 15 | 41.316 | 20771 | 1384.73 |
| Lancet | 10 | 79.323 | 14156 | 1415.60 |
| JNCI-Journal of the National Cancer Institute | 3 | 13.506 | 2672 | 890.67 |
| JAMA-Journal of the American Medical Association | 2 | 56.274 | 3824 | 1912.00 |
| Science | 2 | 47.728 | 11866 | 5933.00 |
| Cancer | 1 | 6.86 | 623 | 623.00 |
| Clinical Cancer Research | 1 | 12.531 | 685 | 685.00 |
| Journal of Thoracic Oncology | 1 | 15.609 | 688 | 688.00 |
| Journal of Translational Medicine | 1 | 5.531 | 628 | 628.00 |
| Mayo Clinic Proceedings | 1 | 7.619 | 2049 | 2049.00 |
| Nature | 1 | 49.962 | 1112 | 1112.00 |
| Translational Lung Cancer Research | 1 | 6.498 | 623 | 623.00 |

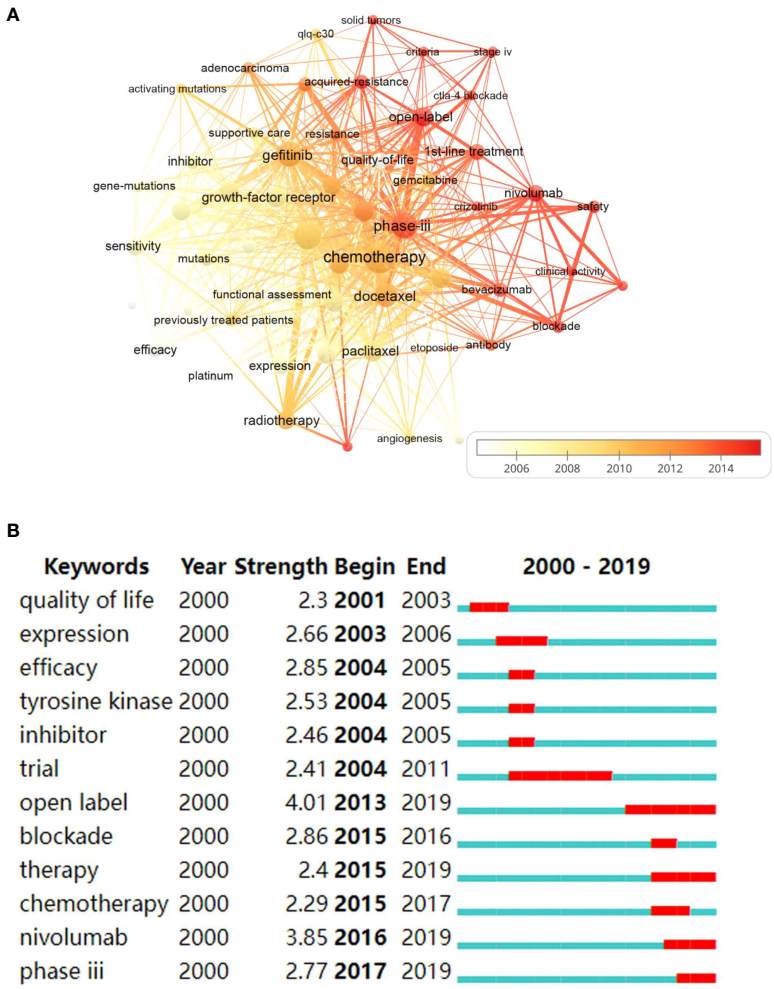


FIGURE 7
**(A)** The overlay visualization map of keywords co-occurrence. Each node represents a keyword. The size of circles and fonts is proportional to the frequency of keywords. The thickness of connecting lines stands for the co-occurrence frequency. The whiter the node is, the earlier the focus on this topic, and the redder is, the more attention it gets nowadays. **(B)** Keywords with strongest burst strength. The red bars indicate the sudden increase of occurrence frequency of the keyword in this period and the blue ones denote the unpopular period.

TABLE 3 Top 20 keywords with the most occurrence.

| Rank | Keywords | Counts | Rank | Keywords | Counts |
|---|---|---|---|---|---|
| 1 | Chemotherapy | 36 | 11 | Erlotinib | 14 |
| 2 | Clinical-trials | 28 | 12 | Combination | 13 |
| 3 | Phase-iii | 24 | 13 | Survival | 13 |
| 4 | Gefitinib | 22 | 14 | Tyrosine kinase inhibitor | 13 |
| 5 | Docetaxel | 19 | 15 | Open-label | 12 |
| 6 | Growth-factor receptor | 15 | 16 | Multicenter | 11 |
| 7 | Paclitaxel | 15 | 17 | Radiotherapy | 11 |
| 8 | Carboplatin | 14 | 18 | Sensitivity | 10 |
| 9 | Cisplatin | 14 | 19 | Nivolumab | 9 |
| 10 | EGFR | 14 | 20 | 1st-line treatment | 8 |

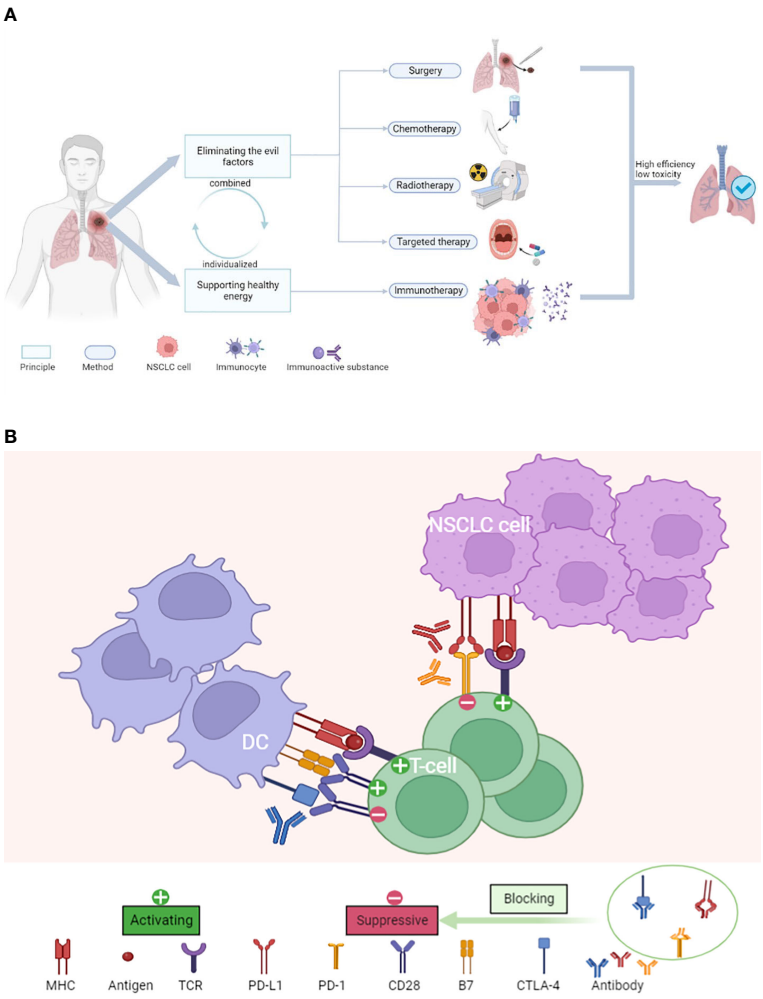


FIGURE 8
**(A)** The principles and landscape of NSCLC management. **(B)** The major mechanism of ICIs for the treatment of NSCLC.

with non-squamous NSCLC that progressed during or after platinum-based dual chemotherapy, proved that nivolumab had longer overall survival (32). The study has been cited more than 5,000 times.

The major contributors (shown in Figure 5), such as Paz-Ares L., Reck M., and Wu Yl., come from different countries and are affiliated with different institutions. It is their long-lasting efforts and closer global collaboration that have driven the development of NSCLC treatment. We found that the distribution of the authors' top papers seemed no correlation with time. Interestingly, both Paz-Ares L. and Reck M. had published remarkable results in 2018, and the topics were both centered on immunotherapy for NSCLC (33, 34). It was also in 2018 that the Nobel Prize in Physiology or Medicine Prize was granted to scientists James P. Allison (United States) and Tasuku Honjo (Japan) for their pioneering work in tumor immunotherapy. Thus, we assume that 2018 was an important time-point for NSCLC immunotherapy.

The distribution of the journals (Figure 6A) demonstrates the treatment of NSCLC is increasingly reliant on molecular, biological, and genetic fields. Thanks to breakthroughs in targeted therapeutic pathways, different targeted regimens have been applied to patients with different genetic mutations, such as EGFR-positive and ALK-positive mutations. Furthermore, that advancement can predict efficacy, safety, and prognosis of targeted therapy (35–37). The molecular mechanism of immune checkpoint blockade has been partially elucidated. Tumor mutation burden and PD-l expression levels were utilized to predict the outcome of immunotherapy (38, 39). The citations in journals related to immunology and computer science indicate that the field has moved toward multidisciplinary integration. Increasingly routine clinical application of targeted next-

generation sequencing technology, immunohistochemical techniques, and comprehensive genomic profiling enables more precise NSCLC management and makes personalized management possible (38, 40, 41). Clinical trials and basic experiments are becoming growingly inseparable today, inaugurating the century of rapid advancement in NSCLC management.

From Figure 6B, the most authoritative journal in the field is the New England Journal of Medicine, which has the most top-cited papers, the fastest papers growth rate, the highest IF and TC, followed by Journal of Clinical Oncology, Lancet Oncology, etc. Papers published in these journals are likely to be of higher academic quality. The most cited paper in the New England Journal of Medicine is about 6,000 times. The paper reported an open-label, phase III trial for non-smoking or formerly lightly smoking untreated patients with adenocarcinoma in East Asia. It demonstrated superior progression-free survival with gefitinib as initial treatment over carboplatin-paclitaxel in this population (42).

As is presented in Figure 7A, chemotherapy and targeted therapy have been studied in a lot of top papers, while the counts of immunotherapy-related keywords, such as nivolumab, were relatively small, probably because it as an emerging regimen has not been heavily cited yet. Of note, the earliest article was published in 2000 on the topic of chemotherapy in NSCLC (27), and the most recent 3 publications published in 2018 and 2019, all focused on immunotherapy (33, 43, 44). The timeline of the keywords illustrated that the hotspots of NSCLC management have evolved from chemotherapy and radiotherapy to targeted therapy and then to immunotherapy.

Surgery and cytotoxic drugs were introduced to treat NSCLC in the 1960 and 1970, making the first leap forward in NSCLC treatment. Surgery is currently the most recommended method for NSCLC patients with stage I-II, yet 70% of patients are in advanced stage III-IV at the time of diagnosis. Cytotoxic drugs, targeted therapy, and immunotherapy are critical for patients with advanced NSCLC (41). Among 100 highly cited papers, there is no research with the theme of surgery for NSCLC, which may be related to the high maturity and effectiveness of video-assisted thoracic surgery (VATS) (45, 46). SABR is considered as a standard care for inoperable peripheral type early-stage NSCLC, showing meaningful clinical benefit (47). Over the past 21 years, the common cytotoxic chemotherapy, such as paclitaxel and docetaxel, remains the predominant therapy for advanced NSCLC to some extent, but with the development of targeted therapy, TKIs have become the first-line treatment for some driver gene mutation-positive NSCLC patients.

TKIs such as gefitinib, and anti-angiogenic agents such as bevacizumab, were approved by the Food and Drug Administration (FDA) for NSCLC treatment. New targeted therapeutics are continually being approved by the FDA. In 2003, gefitinib was granted for treatment of second-line, unselected advanced NSCLC (48). Then in 2006, bevacizumab plus paclitaxel and carboplatin became the first-line regimen for non-squamous NSCLC, approved by the FDA. Using ALK-TKIs and EGFR-TKIs as first-line in the 2010 updates the options for the therapy of NSCLC (41). Third-generation targeted agents, such as osimertinib, and new combination regimens, for example EGFR-TKI erlotinib in combination with anti-angiogenic agent ramucirumab approved for EGFR-mutant NSCLC in 2020, were also gradually being used in the clinical practice (5, 41). Along with the application of targeted therapies, researchers were also more devoted to studying gene mutations and growth-factor receptors, which are inextricably linked to the effectiveness of targeted therapy (40). There is no doubt that targeted therapy is a milestone in the treatment of NSCLC.

In Figure 7A, the large number of lines between treatment modalities implied combination application to different degrees, and the density of the lines did not decrease over time, pointing that combination medication has always been a concern for researchers and remains a hot academic topic, based on which we recommend scholars make more attempts on combination therapy for NSCLC. Keywords with higher burst strength may become the new turning point (49, 50), which can lead us to find emerging hotspots and frontiers of the field. Figure 7B show that after the research boom of targeted therapy represented by TKIs, immune checkpoint blockade represented by programmed cell death-1 (PD1) and programmed cell death ligand-1 (PD-L1) blockade, such as “nivolumab” with the burst strength of 3.85, may become turning points in NSCLC treatment. Actually, cytotoxic T-lymphocyte antigen-4 (CTLA-4) and PD-1/PD-L1 blockade are research frontiers. In 2015, the FDA authorized nivolumab for the treatment of patients whose tumor had progressed on or after platinum-based regimens, a dramatic breakthrough in the treatment of advanced NSCLC that foreshadowed an immune era in lung cancer treatment (5, 51). In 2016, pembrolizumab was approved as monotherapy for first-line treatment of NSCLC with PD-L1 ≥ 50%. Pembrolizumab combined with chemotherapy as first-line treatment for advanced non-squamous NSCLC, granted in 2017, provides survival benefit for patients without target gene mutations (41). Furthermore, durvalumab became a new treatment option for adjuvant therapy in 2018. In 2020, first-line treatment using nivolumab plus ipilimumab and double-platinum chemotherapy for advanced NSCLC also proved the effectiveness of ICIs therapy (52). Another PD-1 inhibitor, such as cemiplimab-rwlc, was approved for first-line treatment in 2021, further confirming the rise of immunotherapy (41). Immunotherapy is perhaps the most significant breakthrough in NSCLC treatment in the last 20 years. It has profoundly changed our treatment landscape and research outlook. More immunologic agents will be available for NSCLC management, while the comparison between different immunologic agents may be worth the attention of researchers. Indeed, immunotherapy has shown excellent anti-tumor effects and a better prognosis than conventional therapy for patients with advanced NSCLC without EGFR or ALK mutations. Although

patients can benefit from ICIs, most of patients may develop resistance after use, and combination therapy is considered a viable approach to overcome acquired resistance (53, 54). At present, ICIs are being explored as combination or monotherapy in neoadjuvant or adjuvant settings for NSCLC management and the results were promising (34, 39, 44). New immunotherapies, such as tumor vaccines, are being developed (3, 55). Researchers are also paying more attention to issues such as drug safety and resistance (30, 56). In terms of trial design, "open label" trials with the burst strength of 4.01, and "phase iii" clinical trials, 2.77, were widely used in the top articles. The large sample size, multicenter, international collaborative RCTs and experiments are necessary to derive reliable studies. Top researchers preferred to explore the efficacy of the combination of various regimens in different types of NSCLC while are more passionate about seeking effective first-line treatment alternatives. Recently, in top-cited papers, immunotherapy and chemotherapy were often combined to treat NSCLC patients or used separately to compare clinical value (33, 43), which is also consistent with Figure 7B, where "chemotherapy" and "nivolumab" red bars overlap in some years.

As shown in Figure 8, the treatment principles of diseases can be divided into two parts: eliminating the evil factors and supporting healthy energy, which is complementary to each other. We think that the management of lung cancer may also be divided based on this principle. Traditional therapy methods (surgery, chemotherapy, radiotherapy, targeted therapy) (54) kill tumor cells directly, in keeping with the principle of eliminating harmful factors. On the other hand, immunotherapy destroys tumor cells indirectly by triggering or improving the immune function of the body, supporting healthy energy. The search for more effective, safer, and sustainable first-line treatment options using a combination of chemotherapy, radiotherapy, surgery, targeted therapy, and immunotherapy is the focus of researchers and clinicians in nowadays. The potential of immunotherapy has not yet been fully explored, and a new therapeutic leap after it is yet to come. Nevertheless, researchers should actively consider what the next epoch-making breakthrough after immunotherapy will be and conceive the future landscape of NSCLC treatment. We speculate that this breakthrough should be based on genetic and molecular technology, relying on the body's inherent anti-tumor ability rather than the direct killing of tumors, in line with the principle of supporting healthy energy.

## Limitation

This study has certain limitations. First, although we identified the most influential papers in NSCLC management based on bibliometric citation analysis and the broad search terms we have formulated, there is still a possibility of missing articles, such as recently published papers that may be widely cited at a future date but do not currently accumulate enough citations to be included in our data. To minimize information omission caused by publication time, we discussed the latest papers to derive the new research progress in NSCLC treatment. Second, our data are all from the WoSCC, so some publications indexed in other databases may be omitted. Databases such as Scopus or PubMed can be used in further research. Third, bibliometric tools inevitably exclude some secondary topics when mapping despite our combination of multiple tools to counteract this effect, and this information probably is also important. Nonetheless, unlike most papers using single tools, we innovatively combined R software, CiteSpace, VOSviewer, and Excel, which may help us achieve comprehensive insights from multiple viewpoints. To our knowledge, the study is the first comprehensive bibliometric assessment of the evolution of NSCLC treatment in the 21$^{st}$ century.

# Conclusion

We found that the United States is the strongest research nation and the Memorial Sloan Kettering Cancer Center is the most prominent institution over the last 20 years. Core authors, such as Paz-Ares L. and Reck M., have developed extensive international collaborations. The New England Journal is the most authoritative journal in the field. Molecular, biological, and genetic research plays a progressively important role in the treatment of NSCLC, while immunology and computer science have also been widely applied to this field. Hotspots of NSCLC management have almost undergone an evolution from chemotherapy and radiotherapy to targeted therapy to immunotherapy, while the exploration of combination therapy has never stopped. Immunotherapy and combination therapy are research frontiers. Encouraging progress has been made in the management of NSCLC in the last 2 decades, and more breakthroughs are sure to be explored in the future.

Overall, our study revealed leading countries, core institutions, distinguished authors, authoritative journals, citation relationships, topic dynamics, and research frontiers in the field of NSCLC management. That information may help researchers quickly sort out the historical progress of NSCLC treatment, provide insight into the future advancement of the field, and guide future research practice.

# Data availability statement

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

# Author contributions

ZL and SC designed the study. SC wrote the manuscript. SC, YH, and YQ selected the 100 most impactful papers and did the

bibliometric analysis. YQ and JC guided the use of the software. SC, YQ, and JC framed the article. YL, JX, and PC proposed constructive opinions. ZH, DH, and YG helped retrieve data. ZL and YH led the team and revised the paper. All authors conducted the literature search and analyzed the data. All authors contributed to the article and approved the submitted version.

## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.939838/full#supplementary-material

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# Parotid metastases from primary lung cancer: Case series and systematic review of the features

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Most parotid metastases have been reported to come from the head and neck; however, cases metastasized from the lung are extremely rare. Missed diagnoses and misdiagnoses occurred quite a few times. Thus, accurately identifying the clinical features of parotid metastasis of lung cancer is important. However, current studies about this issue are mostly case reports, and little is known about the detailed and systematic aspects. We reported three cases of parotid metastases from lung cancer and then systematically searched similar cases through "Pub-Med" and "Web of Science". Finally, twenty-three patients were included in the study. Eighty-three percent of which were males, and 19 patients were over 50 years old. In all cases with smoking history mentioned, 93% were smokers. The predominant pathological type was small cell lung cancer (SCLC, 13 patients, 56%). Seventeen combined with other site metastasis, while more than half of which were brain metastases. The survival time ranged from 3months-17years, and as for SCLCs, it was only 3months-40months. It can be concluded that clinical features, such as sex, age, smoking history, pathological types, and metastasis patterns, could provide valuable evidence for diagnosis. The lung seems to be the most common primary site of parotid metastases except for head and neck tumors. The two circumstances, SCLC coexisting with Warthin's tumor and parotid small cell carcinoma with lung metastasis, should be differentiated from parotid metastasis of lung cancer with caution For cases presented as SCLC, more aggressive strategies, such as chemotherapy with immunotherapy and maintenance therapy, may be more suitable. Due to the greater tendency of brain metastasis in such diseases, whole-brain radiation therapy, stereotactic radiosurgery or prophylactic cranial irradiation should be applied to corresponding patients in time. Additionally, lung cancer parotid metastases may be a marker of poor prognosis.

KEYWORDS

**small cell lung cancer, metastasis, parotid, feature, diagnose, treatment**

## Introduction

Lung cancer is one of the most common malignant tumors, accounting for the leading cause of cancer death worldwide (1). Pathologically, it can be divided into small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) (2). SCLC, although accounting for only approximately 15%, is extremely malignant (3). Even after effective treatment, the median overall survival is still only approximately 1 year, especially for stage IV diseases (4). Distant metastasis is a major feature of lung cancer, but metastasis to parotid gland is really rare (5). The majority of metastatic malignant parotid diseases originate from head and neck tumors, and as a result, most of the pathological types are squamous cell carcinomas or malignant melanomas. Other pathologic types, such as small cell carcinomas, are rare (6).

Owing to the superficial location, parotid masses frequently appear as the initial symptom of lung cancer parotid metastases. Such situations often lead to parotid gland tumors being misdiagnosed as primary lesions, while ignoring the diagnosis and treatment of the real primary site (7). On the other hand, for the inherent benign impression of parotid tumors, misdiagnosis of metastatic parotid tumors also occurs quite a few, especially when lung cancer presents with parotid mass (8). Therefore, great attention should be given to when parotid pathology reveals an uncommon type. Another concern is that the treatment and prognosis of limited and extensive tumors are different, so accurately identifying features of lung cancer parotid metastases matters. However, current studies about this issue are mostly case reports, and little is known about the detailed and systematic aspects. Here, we reported three cases of parotid metastases from SCLC in our institution and reviewed cases regarding parotid metastasis of lung cancer that published previously, in order to provide some references for the management of such disease. To our knowledge, this is the first study to systematically analyze the characteristics of parotid metastasis in lung cancer.

## Materials and methods

We reported three consecutive cases of parotid metastases from lung cancer treated at our institution and then conducted a literature search with no restrictions on the year of publication. According to the following search strategies: ("bronchial carcinoma" OR "lung carcinoma" OR "lung cancer" OR "lung neoplasms" OR "lung adenocarcinoma" OR "lung squamous" OR "small cell lung cancer" OR "NSCLC" OR "SCLC") AND ("parotid" OR "salivary") AND ("metastasis"), the databases "Pub-Med" (http://www.ncbi.nlm.nih.gov/pubmed) and "Web of Science" (https://www.webofscience.com/wos/alldb/basic-search) were fully checked. The latest search date was July 4, 2022. All the identified relevant articles were examined independently by two investigators. Once discrepancies arose, the two reviewers discussed and analyzed the data together and reached a consensus. Studies that did not fit the topic, or were duplicated, or were not full text, or were deficient in clinical information were excluded. In addition, we checked the references within the included studies to avoid any omissions. Since all the articles involved were case reports, the risk bias assessment tool was abandoned in this study. Then, the following information was extracted: the first author, publication year, gender, age, initial symptoms, smoking history, pathological type, primary tumor lesions and size, parotid metastasis lesions and size, other accompanying metastases, treatment, and survival time. Finally, we summarized the above data and analyzed the characteristics.

## Results

### Case Reports

#### Case 1

A 42-year-old male came with the painless hard mass that appeared in front of his left ear. He complained that he had little discomfort except occasional cough. Based on the five-year history of heavy smoking, he was arranged for a chest computed tomography (CT), which found a 6.4 cm x 5.2 cm mass at the right hilum (Figures 1A, B), suggesting central lung cancer. Subsequent lung biopsy and immunohistochemistry confirmed it was SCLC. Further head magnetic resonance imaging (MRI) showed a preauricular mass located at the parotid gland (Figures 1C, D). It is known that tumor metastasis from the lung to the parotid is rare, so there is a big question about the nature of the parotid mass. Hematoxylin and eosin staining of biopsy of the preauricular mass revealed a large number of oat-shaped heteromorphic cells with deep nuclear staining at high magnification, suggesting metastasis of SCLC (Figures 2A–D). Additionally, head MRI and abdominal CT showed that the head and the right adrenal were also affected (Figures 1E, F). Then, he accepted a standard etoposide and cis-platinum (EP) regimen for 6 cycles, as well as the head and chest radiotherapy. Subsequent reviews showed that the patient entered a partial state of remission. Unfortunately, nine months after the completion of treatment, he died due to the progression of brain metastasis.

#### Case 2

A 61yearold man presented to our hospital because of persistent cough and confusion about a progressive growth mass at the left parotid. He was a heavy smoker (44-year history of 20 cigarettes per day). The chest and another neck CT showed a large mass at the left hilar and a 2.8 cm x 2.5 cm mass at the left parotid. The lung biopsy confirmed that he suffered from SCLC. Further examination found that the

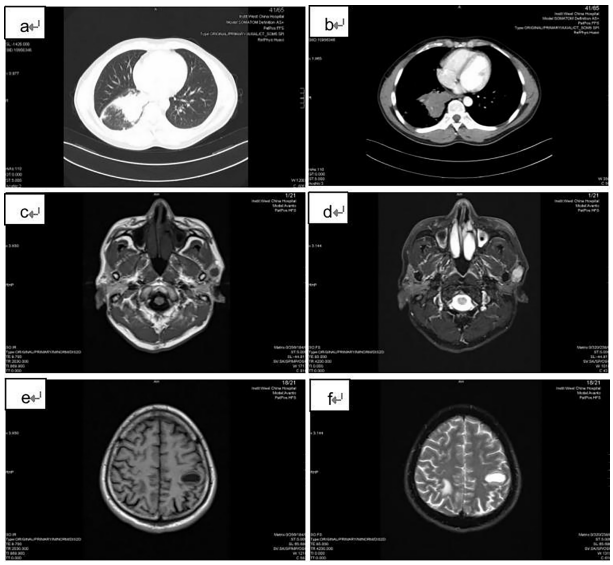


FIGURE 1
Imaging findings of the patient. **(A)** and **(B)**: the chest CT showed a 6.4 cm x 5.2 cm mass at the right hilar; **(C)** and **(D)**: T1 and T2 weighted head MRI images showed the preauricular mass located at the parotid gland; **(E)** and **(F)**: T1 and T2 weighted head MRI images revealed the brain metastases.

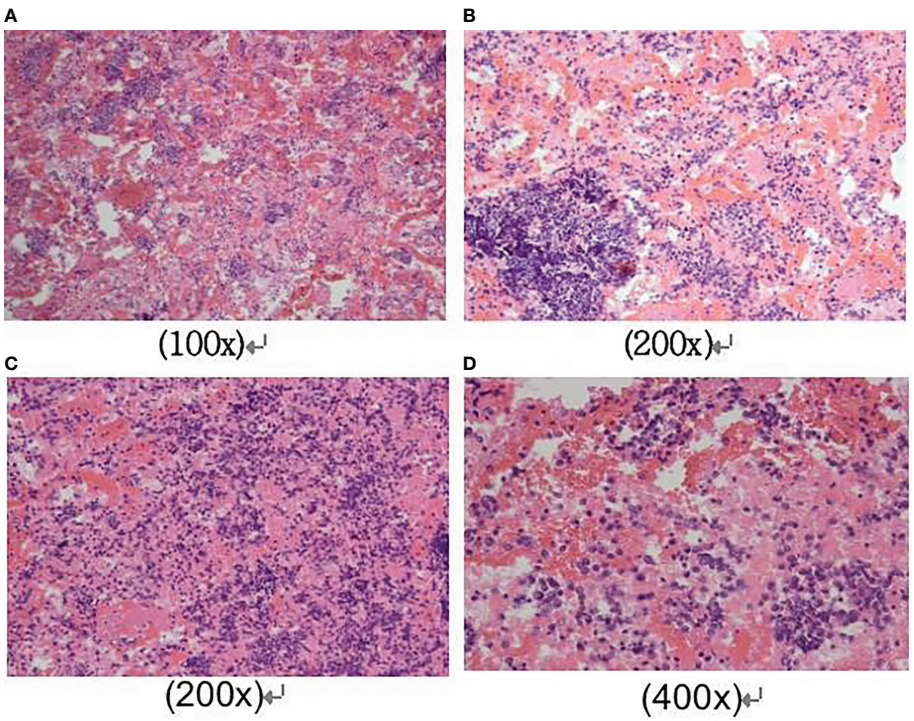


FIGURE 2
Cytological findings of parotid mass biopsy. Hematoxylin and eosin staining of the fine-needle aspiration biopsy of the preauricular mass revealed a large number of oat-shaped heteromorphic cells with deep nuclear staining at high magnification, distributed in the shape of chrysanthemum nests. The magnification was as follows respectively: **(A)** was 100x magnification; **(B)** and **(C)** were 200x magnification; **(D)** was 400x magnification.

bilateral lung, left axillary, left adrenal and head all had metastatic nodules. The otolaryngology suggested that the parotid mass might be Warthin's tumor, so it was not examined further. Then, he was included in a multicenter double-blind clinical study (Identifier NCT01450761) and received a standard treatment of etoposide and carboplatin with ipilimumab/placebo. After two cycles of treatment, the tumors were all shrunken, especially the parotid mass, suggesting that the parotid mass was also the metastasis of lung. Due to the previous wrong evaluation of parotid metastasis, the pathological biopsy of parotid gland was not carried out, resulting in the failure to obtain a correct diagnosis. Since the patient has already entered the extensive stage, the choice of treatment scheme has not been significantly affected. However, after four cycles of treatment, the brain metastases progressed, leading to his death. It was only three months since his diagnosis.

### Case 3

A 50-year-old male underwent the surgery for early left SCLC in April 2012, subsequently underwent 6 cycles of treatment with a standard EP regimen. Then, he followed up regularly. Unfortunately, the recurrence of neck lymph nodes appeared in 2014. Traditional Chinese medicine and chemotherapy (both EP and TP (paclitaxel and cis-platinum) regimen) had little effect. Thankfully, cervical lymph node radiotherapy resulted in a significant mass reduction in March 2015. However, subsequent follow-up found metastatic tumors in the head, parotid and parapharyngeal space. The biopsy of the parotid proved that it was a SCLC metastasis. Then, the patient received a single irinotecan chemotherapy regimen and whole-brain radiation therapy (WBRT). After two cycles of treatment, the tumors remained stable. However, after four cycles of treatment, the patient lost contact with us. It was only less than five months since the parotid mass was founded.

## Literature review

Then, we reviewed previously published similar cases and summarized the characteristics. We originally identified 913 relevant articles. After removing the 323 duplicate records, 590 were left. According to the exclusion criteria, 562 studies which did not fit the topic [including 2 with parotid lymph node metastasis (9, 10)], 1 without full text, and 7 with deficient clinical information were excluded. Ultimately, 20 articles comprising 20 patients were selected for our study (the detailed filtering process is shown in Figure 3). Adding the three patients discovered at our institution, for a total of 23 [Table 1 (5, 11–26)]. Among the 23 patients, 19 (83%) were males, and 4 (17%) were females. Most patients were over 50 years old (19/23 patients, 83%), with a median age of 59 years old. Fifteen (65%) presented with parotid gland mass as their initial symptom. In all cases with smoking history mentioned, 13 (93%) were smokers and only 1 (7%) was a nonsmoker. The predominant pathological type was SCLC (13 patients, 56%), followed by adenocarcinoma (7 patients, 30%), and squamous carcinomas (3 patients, 13%). Ten of the primary sites were left lungs, and thirteen were right lungs. Twelve (52%) cases presented with left parotid metastasis, 8 (35%) cases with right parotid metastasis, 2 (9%) cases with bilateral parotid metastasis, and 1 case not mentioned. Seventeen (74%) had other site metastases, while more than half (9 patients) had brain metastases. Most patients received chemotherapy, a few combined with radiotherapy or parotidectomy, and one patient obtained lung surgery for misdiagnosis of the parotid tumor. The survival time ranged from 3 months-17 years, and for SCLCs, it was only 3 months-40 months. The above features are summarized in Table 2.

# Discussion

Metastatic malignant parotid diseases, accounting for only 6-8% of parotid tumors (30), mostly originate from head and neck tumors, while non-head and neck parotid metastases may originate from the gastrointestinal tract, breast, pancreas and lungs (6). Lung cancer metastasis to the parotid gland is particularly rare (5). Due to the superficial location and benign impression of the parotid (31), missed diagnosis of primary tumors or misdiagnosis of parotid metastasis tumors occurs as common (7, 8). However, there is no appropriate way to avoid the above problems thus far. With regard to different properties and stages, the treatment and prognosis of tumors are also different. To achieve better diagnosis, differential diagnosis, and more effective treatment, we analyzed the characteristics of such patients and attempted to provide reference opinions on their management.

## Diagnosis

As shown in Tables 1, 2, this disease seemed more likely to occur in elderly smoking men in general, which was consistent with the prone crowd of lung cancer (32). Most patients with parotid metastasis of lung cancer had no obvious pulmonary symptoms (5, 12–15, 21–23, 25, 27). The initial clinical manifestation was always a rapidly expanding parotid gland mass, with or without pain, but usually did not invade the skin, sometimes accompanied by facial paralysis, suggesting no specificity. Imaging examination, especially MRI, could provide evidence for the differentiation of benign and malignant tumors, such as boundary and surrounding infiltration (33). Fine needle biopsy is the most commonly

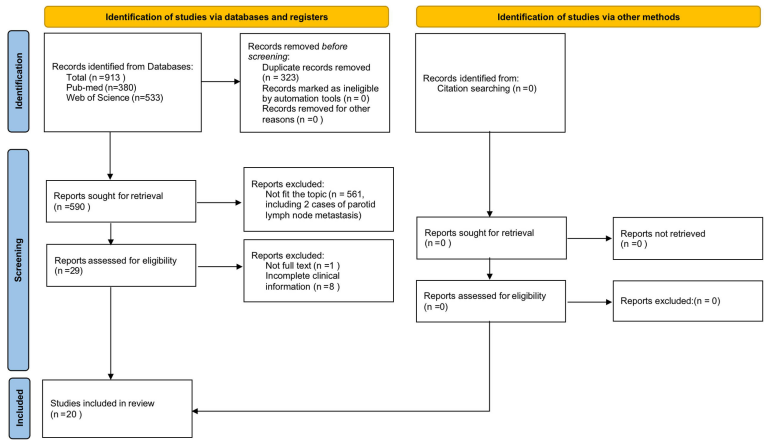


FIGURE 3
The flow diagram according to PRISMA shows the detailed filtering process.

used diagnostic technique (7, 34). Usually, the discovery of an unusual pathological type is the initial cause of the suspicion of metastatic parotid tumor. According to the literature reports, parotid metastases can originate from the gastrointestinal tract, breast, pancreas and lungs (6), but the lung seems to be the most common primary site except for head and neck tumors (6, 7) (34, 35). Therefore, when secondary parotid malignancy is suspected and primary lesions are not found at the head and

TABLE 1 the literature review of all cases of the parotid metastasis of the lung cancer.

| Author/ year | Age/ sex (years) | Initial symptoms | Smoking | Pathological type | primary tumor (cm) | Parotid metastasis tumor (cm) | Other metastases | Treatment | Survival |
|---|---|---|---|---|---|---|---|---|---|
| MF/2004 (5) | 72/M | parotid masses | yes | SCC | left apical lung (NM) | left side (3x4) | No | radiotherapy | 3 years |
| Boeger et al/2005 (11) | 54/M | right parotid swelling | NM | SCLC | Left lung (NM) | right side (NM) | Left adrenal | parotidectomy | NM |
| Cantera et al/1989 (12) | 40/M | bilateral painless parotid masses | yes | SCLC | main left bronchus (NM) | bilateral side (5x4;2x1.5) | bone | chemotherapy | 4months |
| Yu et al/ 2018 (13) | 64/M | peripheral facial paralysis | NM | SCLC | right upper, middle lobes (NM) | right side (2x2) | liver | Parotidectomy, chemotherapy | >10 months |
| Katsurago et al/2006 (14) | 72/M | NM | NM | AC | right upper and left lower lobes (NM) | Left side (NM) | Adrenal, brain | parotidectomy, radiotherapy, chemotherapy | 17 years |
| Lawande et al/2017 (15) | 52/M | facial swelling, chest pain | yes | SCLC | right upper lobe (8.7x6.5) | right side (3.5x3) | Left subdiaphragmatic, adrenal | Radiotherapy, chemotherapy | NM |
| Lenouvel/ 2006 (16) | 59/M | right preauricular swelling | yes | AC | Right lung (NM) | right side (2x2.5) | renal and multiple bony metastases. | No | deteriorated rapidly |
| Shalowitz et al/1988 (17) | 54/M | facial weakness, dry cough | yes | SCLC | Left hilar and left lower lobe (NM) | Left side (0.5x0.5) | Liver and adrenal | Radiotherapy, chemotherapy | > 3 months |

*(Continued)*

TABLE 1 Continued

| Author/ year | Age/ sex (years) | Initial symptoms | Smoking | Pathological type | primary tumor (cm) | Parotid metastasis tumor (cm) | Other metastases | Treatment | Survival |
|---|---|---|---|---|---|---|---|---|---|
| Shi et al/ 2006 (18) | 61/M | right parotid swelling | yes | SCLC | right upper lobe (6.3x5.4) | right side (1.3x1.3) | No | Parotidectomy, chemotherapy | 4 months |
| Ulubas/ 2010 (19) | 59/M | right parotid mass | NM | SCLC | Right lung (9) | right side (NM) | Liver, bone | chemotherapy | 10 months |
| Debnath/ 2015 (20) | 50/M | NM | NM | AC | left lung (NM) | right side (2.5x2) | NM | NM | NM |
| Hisa et al/ 2010 (21) | 61/M | left parotid swelling | NM | SCLC | right lung (NM) | bilateral side (NM) | No | parotidectomy, radiotherapy, chemotherapy | 17 months |
| Takats et al/2010 (22) | 48/F | left parotid swelling | NM | SCLC | right hilar (NM) | left side (3x2) | Pituitary gland, lumber spinal cord | Radiotherapy, chemotherapy | 13 months |
| Norton et al/2020 (23) | 65/F | Breathlessness, left parotid swelling | NM | AC | right lung (NM) | left side (NM) | large intra-abdominal lymph node | Refuse treatment | NM |
| Elena et al/ 2020 (24) | 65/M | left parotid gland mass | yes | SCLC | left lower lobe (5) | left side (2.4) | Brain, cervical vertebrae | chemotherapy | 3 months |
| Yang et al/ 2017 (25) | 66/M | blood-stained sputum, pain near left ear | yes | AC | left upper lobe (4.6) | left side (1x1) | No | Lung cancer operation, chemotherapy | >6 months |
| Wang et al/2016 (26) | 56/F | Parotid swelling, intracranial hypertension | NM | SCC | left upper lobe (3.4x3.3) | right side (2.4x2.4) | Brain | chemotherapy | NM |
| Sankalp et al/2020 (27) | 60/M | Parotid and scalp swelling | yes | SCC | Right upper lobe (5.6x5.4) | right side (3.1x2.6) | Scalp | Chemotherapy, radiotherapy | 9 months |
| Claire et al/2021 (28) | 48/F | Parotid swelling | yes | AC | Right lower lobe (2.3x1.5) | left side (2.5) | Brain, retroperitoneal | Parotidectomy, brain metastases resection | NM |
| NA et al/ 2022 (29) | 79/M | No symptom | yes | AC | Right upper and lower lobe left lower lobe (<3) | left side (1.5) | No | radio-therapy, Parotidectomy | 2 year |
| Present case 1 | 42/M | left parotid mass | yes | SCLC | right hilar (6.4x5.2) | left side (1.5x1.5) | Brain, adrenal | Chemotherapy, radiotherapy | 13 months |
| Present case 2 | 61/M | Cough, left parotid mass | yes | SCLC | left hilar (NM) | Left side (2.8x2.5) | lung, axillary, adrenal, brain | Chemotherapy | 3 months |
| Present case 3 | 50/M | No symptom | No | SCLC | Left lung (NM) | Left side (NM) | Brain, arotid | Chemotherapy, radiotherapy | 40 months |

M, male; F, female; SCLC, small cell lung cancer; SCC, squamous cell carcinoma; AC, adenocarcinoma; NM, not mentioned.

TABLE 2 Summary of the characteristics of lung cancer parotid metastases.

| total | sex | Age (years old) | smoking | Pathological type | Parotid metastasis relative position | Combined with other site metastasis | Survival |
|---|---|---|---|---|---|---|---|
| 23 | M:19<br>F:4 | Rang:40-79<br>Average:58.2<br>Median: 59<br>≥50: 19 | Yes:13<br>No:1<br>NM: 9 | SCLC:13<br>AC:7<br>SCC:3 | Ipsilateral :12<br>opposite:8<br>Bilateral:2<br>NM:1 | Total: 17<br>brain metastasis: 9 | 3months-17years<br>(SCLC:3months-40months) |

M, male; F, female; SCLC, small cell lung cancer; SCC, squamous cell carcinoma; AC, adenocarcinoma; NM, not mentioned.

neck, the possibility of lung origin should be considered first. Indeed, positron emission tomography CT may be a pretty choice (29).

## Differential diagnosis

Due to the rarity of parotid metastases of lung cancer, differential diagnosis should be made carefully. The following situations should be handled with caution: (1) Lung malignancy with parotid gland benign tumor, especially Warthin's tumor, a common benign tumor of the parotid. The majority of parotid gland tumors are benign, but the 2-[18F]-fluoro-2-deoxy-d-glucose (FDG) uptake values of some types, such as warthin's tumor and pleomorphic adenoma, are pretty high, and even equivalent to that of salivary gland malignant tumors (31, 36). As a result, the misdiagnosis of secondary parotid malignancy occurs frequently. Furthermore, because smoking is an identical risk factor for lung cancer (2) and Warthin's tumor (37), lung cancer coexisting with Wartin's tumor is not puzzling (38–41). It is reported that there is a significant correlation between the occurrence of parotid gland warthin's tumor and lung cancer (38, 42). About 19% of patients with warthin's tumor in parotid gland also have lung cancer (38). False recognition of the nature of parotid tumors can lead to different tumor stages and treatment. For example, present case 2 mistook parotid metastasis as Warthin's tumor, and the case of Yang et al. (25) reported accepted the lung cancer operation owing to the wrong judgment of the parotid mass nature. Therefore, accurately discriminating the characteristics of parotid gland masses is particularly important. Parotid benign tumors have a long course of disease and develop slowly (31). Moreover, parotid benign tumors are usually located in the superficial lobe of the parotid gland (43), with no surrounding tissue infiltration and a clear border (31). In contrast, parotid malignant tumors usually grow rapidly (31). Significantly, they are usually discovered at the deep lobe or across the superficial and deep lobe (43), with invasion of the facial nerve or surrounding tissues, and have unclear boundaries (31). Emerging imaging technologies, such as apparent diffusion coefficient (44), diffusion-weighted imaging (45), and dynamic contrast-enhanced magnetic resonance imaging (46), can provide effective help. Therefore, a detailed history and imaging studies are essential for the differential diagnosis. However, the above characteristics still cannot accurately distinguish lung cancer parotid metastasis and lung cancer coexisting with Warthin's tumor. Thus for patients with lung mass and parotid gland mass at the same time, it is very important to perform pathological biopsy for both. (2) Primary malignant tumors of the parotid gland, especially parotid gland small cell carcinoma (PGSmCC), with lung metastasis. In the current study, small cell carcinoma accounted for the priority (65%) of lung cancer parotid metastases. Distinguishing the parotid metastases of SCLC from lung metastases of PGSmCC is the key diagnostic challenge. Primary PGSmCC, accounting for less than 1% of salivary tumors (47), has a 5-year survival rate of 37%, which is much better than that of SCLC (48). Pathologically, primary PGSmCC can be divided into ductal type, Merkel type and pulmonary type. For the ductal type and pulmonary type, cytokeratin 20 (CK20) staining is negative, but for the Merkel type, CK20 staining is strongly positive (49). In general, Servato et al. suggested that approximately 79% of PGSmCCs were CK20 positive (47). However, SCLC has no ductal morphology, and CK20 expression is negative (50). In view of the above, SCLC with parotid metastases and PGSmCC with lung metastases can be preliminarily differentiated. However, there is still no reliable method to distinguish pulmonary-type PGSmCC from SCLC parotid metastasis because the immunophenotype of the two diseases widely overlaps (50). The order of tumor occurrence may be helpful to solve this dilemma. On the other hand, a study comprising 344 cases of primary PGSmCC observed that distant metastasis in such disease was rare (rate 7.3%) (48). However, for SCLC, distant metastasis is universal. Moreover, there is no literature report of lung metastasis from PGSmCC at present. Regardless, either of the two situations should be treated more radically.

## Treatment

According to the study, many patients (75%) had metastases in multiple parts of the body. Shi et al. (18) reported that this phenomenon implies the disease has progressed to extensive stage, which is a reason for the poor prognosis (32). In particular, SCLC is more malignant than any other pathological type of lung cancer (4). Thus, the survival is rarely more than one year. Therefore, for such patients, more aggressive treatment strategies should be adopted. Chemotherapy combined with immunotherapy has brought the treatment of extensive SCLC into a new era (51, 52). Many studies have confirmed that such a treatment strategy can prolong survival by 2-3 months (4, 53), implying that it might be a more suitable method for such patients in the current study. Furthermore, maintenance therapy seems to have no obvious survival benefit (54–56), but it is also worth trying (57, 58). In addition, among patients with the extensive stage, brain metastasis accounted for 53%. Oikawa et al. (59) analyzed the probability of distant metastasis sites of lung cancer and found that there was a specific pattern of lung cancer distant metastasis, that was when one site had metastasis, there was another subsequent site with a relatively high probability of metastasis (59). From the data of this study, there may be a similar relationship between parotid metastasis and brain metastasis of lung cancer. In other words, patients with lung cancer parotid metastasis seem to show a greater tendency of brain metastasis. Previous studies concluded that WBRT (60, 61), stereotactic radiosurgery (SRS) (62, 63), and

prophylactic cranial irradiation (PCI) (62, 64, 65) can improve the prognosis of these patients and bring survival benefits. Therefore, for patients for whom brain metastasis already appears, WBRT or SRS should be performed as soon as possible. More importantly, for patients who have not yet developed brain metastasis, PCI should be applied in time (62). Furthermore, several studies (66, 67) have shown that parotidectomy seems to have no improvement in the prognosis of metastatic parotid tumors. However, for patients with parotid pain, parotidectomy is helpful to ameliorate their quality of life (30, 68).

### Outcome

Only a few studies reported the survival time in the current study, and the prognosis of SCC and AC was better than that of SCLC. Even after multiple treatments, the survival of SCLC patients with parotid metastasis is still short. Notably, as shown in present case 3, initially diagnosed at an early stage, the SCLC patient experienced a long disease-free survival after operation, but the condition deteriorated rapidly once parotid gland metastasis occurred. The case revealed the consistent viewpoint put forward by many previous studies that lung cancer parotid metastasis may be a marker of poor prognosis (13, 18, 24).

## Limitations

Our study has several limitations. First, due to the retrospective nature of the present study, the credibility needs to be verified. Second, for the rarity of parotid metastasis of lung cancer, the number of cases included in the current study is small; Owing to the superficial location and benign impression of parotid tumors, misdiagnosis of metastatic parotid tumors occurs quite a few, which may be another reason for the small samples; Moreover, we were unable to obtain the detailed clinical information of patients from some retrospective studies on secondary parotid metastasis, so these data were excluded from this study. Thus the current conclusion needs to be confirmed by a larger multicenter study. Third, the medical history and relevant data provided in many included cases are limited, and we cannot identify the clinical features, imaging features and survival time more specifically. Last, the metastasis of parotid gland in case 2 was not confirmed by pathological biopsy and was only a clinical diagnosis. Therefore, the value of the current study needs to be further inspected by prospective clinical research.

## Conclusions

The lung seems to be the most common primary site of parotid metastases except for head and neck tumors. Therefore, when secondary parotid malignancy is suspected and primary lesions are not found at the head and neck, the possibility of lung origin should be considered first. Clinical features, such as sex, age, smoking history, pathological types, and metastasis patterns, could provide valuable evidence for diagnosis. The two circumstances, SCLC coexisting with Warthin's tumor and parotid small cell carcinoma with lung metastasis, should be differentiated from parotid metastasis of lung cancer with caution. For cases presented as SCLC, more aggressive strategies, such as chemotherapy with immunotherapy and maintenance therapy, may be more suitable. Due to the greater tendency of brain metastasis in such disease, WBRT, SRS or PCI should be applied to corresponding patients in time. Additionally, lung cancer parotid metastasis may be a marker of poor prognosis.

## Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

## Author contributions

(I) Guarantor of integrity of the entire study: QZ; (II) Study concepts and design: QZ; (III) Literature research: RW, TW; (IV) Clinical studies: RW, TW; (V) Experimental studies/data analysis: RW, TW; (VI) Statistical analysis: RW, TW; (VII) Manuscript preparation: All authors; (VIII) Manuscript editing: All authors. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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# Emerging PD-1/PD-L1 targeting immunotherapy in non-small cell lung cancer: Current status and future perspective in Japan, US, EU, and China

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Non-small cell lung cancer (NSCLC), one of the deadliest types of cancers worldwide, has been the target of immunotherapy due to its high immune antigenicity. With the addition of immune-checkpoint inhibitors (ICIs), including anti-PD-1/PD-L1 antibodies, as an indispensable and powerful regimen for the treatment of this lethal disease, the median survival time for patients with stage IV NSCLC is approximately 2 years. In contrast, the response rate to ICIs remains less than 50%, even if the patients are selected using biomarkers such as PD-L1. Pharmaceutical companies have begun to develop additional anti-PD-1/PD-L1 antibodies to overcome resistance and are devising further immunotherapy combinations. More than 20 anti-PD-1/PD-L1antibodies have been approved or are currently in development. Numerous combination therapies are under development, and several combination therapies have provided positive results in randomized controlled trials. This review aimed to examine the current status of approved and investigational anti-PD-1/PD-L1antibodies for NSCLC in Japan, the United States, the European Union, and China. Further, this review discusses the challenges and future perspectives for developing new ICIs in alignment with the global developments in Japan.

KEYWORDS

**non-small cell lung cancer, immunotherapy, anti-PD-1 antibody, anti-PD-L1 antibody, clinical trial**

# 1 Introduction

Nivolumab was approved as a treatment for malignant melanoma by the United States (US) Food and Drug Administration (FDA) in 2014. With this approval, immune-checkpoint inhibitors (ICIs), mainly anti-programmed cell death-1 (PD-1) antibodies, have rapidly revolutionized cancer treatment. ICIs and anti-PD-1 antibodies have become the main component of cancer therapy and are used in all types of cancer (1). In Japan, since the approval of the first anti-PD-1 antibody nivolumab in 2015, pembrolizumab; the anti-PD ligand (PD-L)1 antibodies atezolizumab, durvalumab, and avelumab; and the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab have also been approved and reimbursed by the National Health Insurance system. Among all the drugs available in Japan in terms of sales as of 2021, pembrolizumab and nivolumab rank first and second, respectively, with each drug generating more than $1 billion in sales (2).

In non-small cell lung cancer (NSCLC), according to the NCCN Guidelines (version 1.2022) (3) and the Japanese Lung Cancer Society Guidelines for NSCLC (2021 edition) (4), combination therapy with an anti-PD-1/PD-L1 antibody and platinum-based chemotherapy is recommended as first-line therapy for patients with advanced NSCLC without driver gene mutations. Even if an anti-PD-1/PD-L1 antibody is not used in the initial therapy, it is recommended as a second-line or subsequent therapy. In locally advanced lung cancer, durvalumab is recommended as maintenance therapy after chemoradiation therapy, based on the results of the PACIFIC trial (5). In terms of postoperative adjuvant chemotherapy, sequential atezolizumab after adjuvant chemotherapy was approved on October 2021 by the FDA and recommended in the NCCN guidelines as the first perioperative ICI for PD-L1-positive (≥1%) stage II-IIIA NSCLC after radical resection based on the results of the IMpower010 trial (6). In Japan, an application for partial changes to atezolizumab as adjuvant therapy was submitted in July 2021 and approved in May 2022. The ICIs must be considered in all patients with NSCLC, except for those with a positive driver gene mutation, poor performance status, autoimmune disease, or interstitial lung disease.

Currently, ICIs primarily target PD-1/PD-L1, which are immune-checkpoint molecules that inhibit the priming phase (activation of antigen-presenting cells and T cells) and effector phase (direct damage to cancer cells) of the cancer-immunity cycle (7). In 2011, 3 years prior to the approval of nivolumab, an antibody drug targeting CTLA-4 (ipilimumab: another immune-checkpoint molecule primarily involved in the priming phase), was developed and approved by the FDA for the treatment of unresectable or metastatic malignant melanoma (approved in Japan in 2015) (8, 9) (Figure 1). Ipilimumab is currently approved in the United States (US), European Union (US), and Japan in combination with nivolumab (with or without platinum combination chemotherapy) as first-line treatment for NSCLC, regardless of the PD-L1 expression status (7, 13, 14). The Japan Clinical Oncology Group is currently conducting a phase III study (JCOG2007, NIPPON study) to evaluate the superiority of nivolumab plus ipilimumab plus platinum combination chemotherapy over pembrolizumab plus platinum combination chemotherapy, which has attracted research attention as an optimal first-line treatment for patients with NSCLC (15).

Currently, multiple ICIs are approved, and other pharmaceutical companies have developed their own anti-PD-1/PD-L1 antibodies as monotherapy and combination immunotherapy for new indications. However, no study has provided a summary of the entire picture of the early and late phase of ICI development from a global perspective. This review aimed to provide a comprehensive overview and a better understanding of the emerging anti-PD-1/PD-L1 antibodies for NSCLC. We also aimed to discuss the current challenges and future perspectives on the development of ICIs in Japan.

# 2 Immunotherapies in development

## 2.1 Novel PD-1/PD-L1 pathway inhibitors

The anti-PD-1 antibodies nivolumab and pembrolizumab and the anti-PD-L1 antibodies atezolizumab, durvalumab, and avelumab (not indicated for NSCLC) are available worldwide, and pharmaceutical companies are developing more anti-PD-1/PD-L1 antibodies with the aim of obtaining additional indications for diseases for which anti-PD-(L)1 antibodies are not available or as combined immunotherapies with compounds that they are developing. The details of the anti-PD-1/PD-L1 antibodies currently under development are presented in Table 1.

### 2.1.1 Cemiplimab

Cemiplimab is an anti-PD-1 antibody approved by the FDA in September 2018 for the treatment of cutaneous squamous cell carcinoma (cSCC), and in February 2021 for cutaneous basal cell carcinoma (cBCC) and for first-line treatment of NSCLC with PD-L1 expression of ≥50% (47, 48). The approval of its use was based on the results of the EMPOWER-Lung 1 study, a phase III trial that compared the efficacy of cemiplimab alone with that of platinum-based chemotherapy in patients with advanced NSCLC with tumor PD-L1 (22C-3) expression of ≥50% with overall survival (OS) and progression-free survival (PFS) as the primary endpoints. The median OS times of the cemiplimab and chemotherapy group were 22.1 months (95% confidence interval [CI], 17.7–NE) and 14.3 months (95% CI, 11.7–19.2), respectively, with a hazard ratio (HR) of 0.68 (95% CI, 0.53–

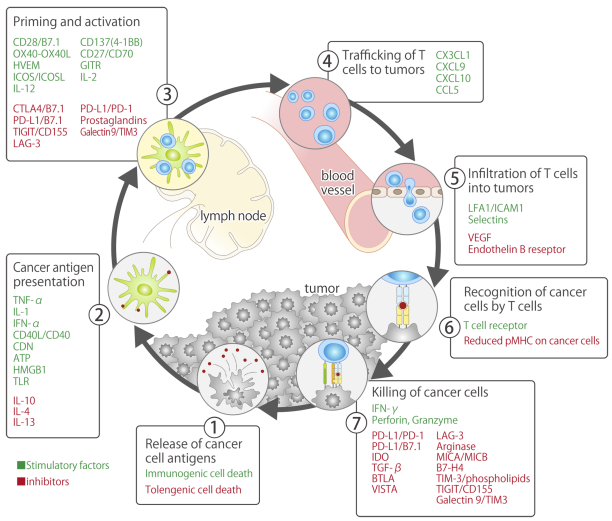


FIGURE 1
Cancer-immunity cycle and immune-checkpoint overview (8, 10–12).

TABLE 1 Anti-PD-1/PD-L1 antibody monotherapy currently approved and under development (data on March 31, 2022).

| Drug name | Target | Approval status in NSCLC | | | | Other major approved indications | Pivotal trial | R&D institutions | Country | Business partner | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FDA | EMA | PMDA | NMPA | | | | | | |
| Pembrolizumab | PD-1 | ○:1L (TPS ≧ 1%), 2L | | | | Melanoma, HNSCC, cHL, urothelial cancer, gastric cancer, cervical cancer, PMBCL, HCC, MCC, esophageal cancer, cSCC, MSI-H/dMMR/TMB-H solid tumor, RCC* | KEYNOTE-024, KEYNOTE-042, KEYNOTE-010 | Merck | Germany | | (16–19) |
| Nivolumab | PD-1 | | | ○:2L | | Melanoma*, RCC, cHL, gastric cancer, HNSCC, urothelial cancer, MSI-H/dMMR CRC, HCC, esophageal cancer* | CheckMate-017, CheckMate-057 | Ono Pharmaceutical | Japan | Bristol-Myers Squibb | (20–22) |
| Atezolizumab | PD-L1 | ○:1L (TC3 or IC3), 2L (adjuvant use is approved by the FDA and the PMDA) | | | | Urothelial cancer | IMpower-110, IMpower-010 | Roche | Switzerland | Chugai Pharmaceutical | (6, 23, 24) |
| Durvalumab | PD-L1 | ○:stage III after CRT | | | | SCLC | PACIFIC | MedImmune | US | AstraZeneca | (5, 25) |
| Cemiplimab | PD-1 | ○:1L (TPS ≧ 50%) | | × | × | cSCC, basal cell carcinoma | EMPOWER-Lung 1 | Regeneron | US | Sanofi | (26, 27) |
| Sintilimab | PD-1 | × | × | ○:Sq 2L | cHL, HCC | ORIENT-3 | Innovent Biologics | China | Eli Lilly | (28) | |
| Tislelizumab | PD-1 | × | × | × | ○:2L | cHL, HCC, esophageal cancer, nasopharyngeal cancer, urothelial cancer, MSI-H/dMMR solid tumor | RATIONALE 303 | BeiGene | China | Novartis | (29) |
| Sugemalimab | PD-L1 | × | × | × | ○:stage III after CRT | – | GEMSTONE 301 | CStone Pharmaceuticals | China | Pfizer | (30, 31) |
| Camrelizumab | PD-1 | × | × | × | × | cHL, HCC, esophageal cancer | | Jiangsu Hengrui Pharmaceuticals | China | LSK BioPharma | (32) |

*(Continued)*

TABLE 1 Continued

| Drug name | Target | Approval status in NSCLC | | | | Other major approved indications | Pivotal trial | R&D institutions | Country | Business partner | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FDA | EMA | PMDA | NMPA | | | | | | |
| Toripalimab | PD-1 | × | × | × | × | Melanoma, nasopharyngeal cancer, urothelial cancer | | Shanghai Junshi Biosciences | China | Coherus BioSciences | (33) |
| Dostarlimab | PD-1 | × | × | × | × | dMMR solid tumor, endometrial cancer | | GlaxoSmithKline | UK | | (34) |
| Avelumab | PD-L1 | × | × | × | × | MCC, urothelial cancer | | Merck | Germany | Pfizer | (35) |
| Zimberelimab | PD-1 | × | × | × | × | cHL | | WuXi Biologics/ Gloria Pharmaceutical | China | Arcus Bioscience/Taiho Pharmaceutical | (36) |
| Penpulimab | PD-1 | × | × | × | × | cHL | | Akesobio | China | | (37) |
| Serplulimab | PD-1 | × | × | × | × | MSI-H/dMMR solid tumor | | Shanghai Henlius Biotech | China | PT Kalbe Genexine Biologics | (38) |
| Balstilimab | PD-1 | × | × | × | × | – | | Agenus | US | Betta Pharmaceuticals | (39) |
| Geptanolimab | PD-1 | × | × | × | × | – | | CBT Pharmaceuticals | US | Genor Biopharma | (40) |
| Cosibelimab | PD-L1 | × | × | × | × | – | | Checkpoint Therapeutics | US | | (41) |
| Tagitanlimab | PD-L1 | × | × | × | × | – | | Sichuan Kelun Pharmaceutical | China | | (42) |
| Envafolimab | PD-L1 (subcutaneous) | × | × | × | × | MSI-H/dMMR solid tumor | | Alphamab Oncology | China | TRACON Pharmaceuticals, 3D Medicines | (43, 44) |
| Sasanlimab | PD-1 (subcutaneous) | × | × | × | × | – | | Pfizer | US | | (45) |
| Nivolumab | PD-1 (subcutaneous) | × | × | × | × | – | | Bristol-Myers Squibb | US | | (46) |

cHL, classical Hodgkin's lymphoma; CRC, colorectal cancer; CRT, chemoradiotherapy; cSCC, cutaneous squamous cell carcinoma; dMMR, deficient mismatch repair; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; IC, tumor-infiltrating immune cells; MCC, Merkel cell carcinoma; MSI-H, microsatellite instability-high; NMPA, National Medical Products Administration; PMBCL, primary mediastinal B-cell lymphoma; PMDA, Pharmaceuticals and Medical Devices Agency; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TC, tumor cell; TPS, tumor proportion score; TMB-H, tumor mutational burden.
*Also approved as adjuvant therapy.

0.87; p = 0.002), while the median PFS times were 8.2 months (95% CI, 6.1–8.8) and 5.7 months (95% CI, 4.5–6.2) months, respectively, with an HR of 0.54 (95% CI, 0.43–0.68; p < 0.0001), leading to the early discontinuation of the trial due to its significant superiority (26). The EMPOWER-Lung 3 trial (NCT03409614), a phase III trial that evaluated the superiority of cemiplimab over platinum-based chemotherapy, was also discontinued early as it already showed substantial evidence of cemiplimab's significant superiority over other therapy; hence, an application for the approval of its use as first-line treatment for NSCLC has been submitted to the FDA (49). However, pivotal studies of cemiplimab for cBCC, cSCC, and NSCLC did not include Japanese patients; hence, cemiplimab has not yet been approved in Japan. Several studies on cemiplimab are underway in Japan (NCT03257267 and NCT03969004), and the results of these trials are expected to contribute to its approval.

### 2.1.2 Sintilimab

In China, which has been a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use since 2017 and became a member of the Management Board in 2018, several anti-PD-1/PD-L1 antibodies developed by domestic companies have been tested in clinical trials and approved for reimbursement. Anti-PD-1 antibodies, such as sintilimab, tislelizumab, toripalimab, zimberelimab, penpulimab, and camrelizumab, and anti-PD-1 antibodies, such as sugemalimab and socazolimab, have been approved in China at relatively lower prices compared with those developed by pharmaceutical companies outside China, and are cost-effective compared with chemotherapies (50–53). In recent years, several Chinese companies have collaborated with overseas companies to expand their businesses worldwide.

In the ORIENT-11 study, a phase III trial that evaluated the superiority of sintilimab plus platinum-based chemotherapy

over platinum-based chemotherapy as first-line treatment for advanced non-squamous NSCLC, the PFS times were 8.9 months (95% CI, 7.1–11.3) in the sintilimab group and 5.0 months (95% CI, 4.8–6.2) in the platinum combination chemotherapy group, with an HR of 0.482 (95% CI, 0.36–0.64; $p < 0.00001$), showing the superiority of sintilimab combination therapy over platinum-doublet therapy (54). Based on the results of a biomarker analysis reported at the 2021 World Conference on Lung Cancer, the abundant expression of genes in the major histocompatibility complex class II antigen-presenting pathway was predictive of the response to sintilimab plus chemotherapy, regardless of the PD-L1 expression status, and is a predictor of treatment response, in addition to tumor PD-L1 expression and tumor mutational burden (55). For patients with squamous NSCLC, the Phase III ORIENT-12 trial compared the efficacy of sintilimab plus gemcitabine plus platinum-based chemotherapy with that of platinum-doublet therapy as first-line treatment, with PFS times of 5.5 months and 4.9 months and an HR of 0.536 ($p < 0.00001$), showing the significant superiority of the sintilimab combination (56). Based on the results of these trials, Eli Lilly and Sintilimab's development partners were in the process of submitting an application to the FDA for the approval of its use. However, on February 2022, the FDA dismissed this request and required additional clinical studies because these trials used PFS rather than OS as their primary endpoint; trials conducted only in China did not reflect the racially diverse population of the US, and the FDA was previously consulted regarding the study design, endpoints, and control group selection (57).

### 2.1.3 Tislelizumab

Tislelizumab, another anti-PD-L1 antibody that has shown efficacy in phase III trials, was designed to minimize macrophage binding to the Fc gamma receptor. This mechanism is believed to suppress the antibody-dependent cell-mediated phagocytosis, which can lead to T-cell elimination and resistance to PD-L1 inhibitors (58–60). The RATIONALE 304 study, an open-label phase III trial conducted in China, evaluated the superiority of tislelizumab plus pemetrexed plus platinum-based chemotherapy over standard platinum-doublet therapy as first-line treatment of non-squamous NSCLC, which reported significantly better median PFS in the tislelizumab group (9.7 months) compared with that in the control arm (7.6 months), with an HR of 0.645 ($p = 0.0044$) (61). In the RATIONALE 307 study, a three-arm, open-label phase III trial conducted in China for the first-line treatment of squamous NSCLC, the experimental arms received paclitaxel plus carboplatin or nab-paclitaxel plus carboplatin combined with tislelizumab, while the control arm received chemotherapy with paclitaxel plus carboplatin or nab-paclitaxel plus carboplatin. The median PFS times were 7.6 months, 7.6 months, and 5.5 months, respectively, with a significantly better HR in the tislelizumab combination group compared with that in the control arm, indicating that tislelizumab is effective regardless of the PD-L1 expression status (62). A biologics license application for tislelizumab was submitted to the FDA on September 2021 by Novartis, which has development and commercialization rights in North America, Europe, and Japan, based on the results of the RATIONALE 302 study, a global phase III trial on esophageal squamous cell cancer (63). However, the tislelizumab trial on NSCLC was conducted only in China, and it may be difficult to obtain an FDA approval based solely on the current results, similar to the case of sintilimab. A global phase III study (NCT04746924) evaluating the superiority of tislelizumab in combination with ociperlimab (an anti-TIGIT antibody) over pembrolizumab in advanced NSCLC patients with PD-L1 expression of ≥50% and a phase III study (NCT04866017) evaluating the superiority of tislelizumab in combination with ociperlimab over durvalumab after chemoradiotherapy are underway, and further developments are anticipated.

### 2.1.4 Subcutaneous PD-1/PD-L1 inhibitors

As some patients with cancer who received ICIs achieve long-term survival and are able to continue receiving them for extended periods of time, companies are also developing ICIs that can be administered subcutaneously in the pursuit of improving convenience during long-term administration and to gain approval for alternative routes of administration. Not only the subcutaneous formulations of approved ICIs, such as nivolumab (NCT03656718), pembrolizumab (NCT04956692), atezolizumab (NCT03735121), and durvalumab (NCT04870112), but also newer agents such as sasanlimab and envafolimab have completed phase I trials and are in further development without any notable safety differences compared with the intravenous formulations, and it will not take long before they are approved and become part of our treatment options (43, 45, 64).

## 2.2 Novel combination therapies with PD-1/PD-L1 pathway inhibitors

Cancer immunotherapies with monoclonal antibodies that inhibit the PD-1 pathway have significantly impacted the treatment of patients with cancer in recent years. However, despite the remarkable clinical efficacy of these agents, anti-PD-(L)1 monotherapies are not actively used in many patients. Evidence from the combined inhibition of PD-1 and CTLA-4 in melanoma and NSCLC underscores the potential of combining drugs with synergistic mechanisms of action to further enhance the clinical efficacy of monotherapies, which has encouraged the ongoing development of combination therapies with ICIs, including anti-CTLA-4 antibodies and

chemotherapy (65). The currently approved and investigated anti-PD(L)1 combination therapies are listed in Table 2.

### 2.2.1 CTLA-4 inhibitors

The most advanced combination therapy with anti-PD-(L)1 antibodies is ipilimumab, an anti-CTLA-4 antibody developed by Bristol-Myers Squibb. Ipilimumab is currently approved in Japan for use in combination with nivolumab for the treatment of NSCLC, malignant pleural mesothelioma, malignant melanoma, renal cell carcinoma, and colorectal cancer with high-frequency microsatellite instability. It is the only anti-CTLA-4 antibody approved for NSCLC patients in Japan and other countries based on the results of CheckMate-227 and -9LA studies (69, 70). The CheckMate-227 randomized, open-label, phase 3 trial, enrolled patients with stage IV or recurrent NSCLC. Patients with a PD-L1 expression level of 1% were randomly assigned in a ratio of 1:1:1 to receive nivolumab plus ipilimumab, nivolumab alone, or chemotherapy. Patients with a PD-L1 expression level of less than 1% were randomly assigned in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone. The median OS times in the nivolumab plus ipilimumab combination group were significantly superior to those in the chemotherapy group, regardless of PD-L1 expression level. In the CheckMate-9LA randomized, open-label, phase 3 trial, patients with treatment-naïve advanced NSCLC were assigned to receive nivolumab (360 mg intravenously every 3 weeks) plus ipilimumab (1 mg/kg intravenously every 6 weeks) combined with histology-based, platinum-doublet chemotherapy (intravenously every 3 weeks for two cycles; combination group), or chemotherapy alone (every 3 weeks for four cycles; control group). The median OS was 15.6 months (95% CI, 13.9-20.0) in the experimental group versus 10.9 months (95% CI, 9.5-12.6) in the control group (HR=0.66 [95% CI, 0.55-0.80]). In contrast, tremelimumab, an anti-CTLA-4 antibody, has been granted an Orphan Drug Designation for malignant pleural mesothelioma by the FDA in 2015 and has been primarily used in combination with durvalumab as treatment for advanced cases. However, in the

TABLE 2 Anti-PD-1/PD-L1 antibody combination therapy currently approved and under development (data on March 31, 2022).

| Drug combination | Target | Approval status in NSCLC | | | | Other major approved indications | Pivotal trial | R&D institutions | Country | Business partner | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FDA | EMA | PMDA | NMPA | | | | | | |
| Pembrolizumab + chemotherapy | PD-1 | ○ | ○ | ○ | ○ | RCC, endometrial cancer, esophageal cancer, gastric cancer, cervical cancer, breast cancer* | KEYNOTE-189, KEYNOTE-407 | Merck | Germany | | (19, 66, 67) |
| Atezolizumab + chemotherapy | PD-L1 | ○ | ○ | ○ | ○ | SCLC, HCC, melanoma | IMpower-130 | Roche | Switzerland | | (24, 68) |
| Nivolumab + ipilimumab | PD-1 | ○ | ○ | ○ | ○ | Melanoma, RCC, MSI-H/dMMR CRC, HCC, malignant mesothelioma | CheckMate-227 | Ono Pharmaceutical | Japan | Bristol-Myers Squibb | (22, 69) |
| Nivolumab + ipilimumab + chemotherapy | PD-1 | ○ | ○ | ○ | × | – | CheckMate-9LA | Ono Pharmaceutical | Japan | Bristol-Myers Squibb | (22, 70) |
| Nivolumab + chemotherapy | PD-1 | ○* | × | × | × | Gastric cancer | CheckMate-816 | Ono Pharmaceutical | Japan | Bristol-Myers Squibb | (71) |
| Cemiplimab + chemotherapy | PD-1 | ×: submitted | × | × | × | – | EMPOWER-Lung 3 | Regeneron | US | Sanofi | (49) |
| Sintilimab + chemotherapy | PD-1 | × | × | × | ○ | HCC | ORIENT-11, ORIENT-12 | Innovent Biologics | China | Eli Lilly | (55, 56) |
| Camrelizumab + chemotherapy | PD-1 | × | × | × | ○ | Nasopharyngeal cancer | Camel, Camel-Sq | Jiangsu Hengrui Pharmaceuticals | China | | (72, 73) |
| Tislelizumab + chemotherapy | PD-1 | × | × | × | ○ | HCC, esophageal cancer, nasopharyngeal cancer | RATIONALE 304, RATIONALE 307 | BeiGene | China | Novartis | (61, 62) |
| Sugemalimab + chemotherapy | PD-L1 | × | × | × | ○ | – | GEMSTONE 302 | CStone Pharmaceuticals | China | Pfizer | (74) |
| Toripalimab + chemotherapy | PD-1 | × | × | × | ×: submitted | Esophageal cancer | CHOICE-01 | Shanghai Junshi Biosciences | China | Coherus BioSciences | (75) |

*(Continued)*

TABLE 2 Continued

| Drug combination | Target | Approval status in NSCLC | | | | Other major approved indications | Pivotal trial | R&D institutions | Country | Business partner | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FDA | EMA | PMDA | NMPA | | | | | | |
| Avelumab + chemotherapy | PD-L1 | × | × | × | × | RCC | | Merck | Germany | Pfizer | (76, 77) |
| Penpulimab + chemotherapy | PD-1 | × | × | × | × | – | | Akeso | China | | (78) |
| Retifanlimab + chemotherapy | PD-1 | × | × | × | × | – | | MacroGenics | US | Incyte | (79) |
| Serplulimab + chemotherapy | PD-1 | × | × | × | × | – | | Shanghai Henlius Biotech | China | PT Kalbe Genexine Biologics | (80, 81) |
| Cosibelimab + chemotherapy | PD-L1 | × | × | × | × | – | | Checkpoint Therapeutics | US | | (82) |
| Ezabenlimab + investigational drugs | PD-1 | × | × | × | × | – | | Boehringer Ingelheim | Germany | | (83–85) |
| Spartalizumab + investigational drugs | PD-1 | × | × | × | × | – | | Novartis | Switzerland | | (86) |
| Geptanolimab + fruquintinib | PD-1 | × | × | × | × | – | | Genor Biopharma | China | Apollomics | (87) |
| Sasanlimab + investigational drugs | PD-1 (subcutaneous) | × | × | × | × | – | | Pfizer | US | | (88) |
| Pembrolizumab + chemotherapy | PD-1 (subcutaneous) | × | × | × | × | – | | Merck | Germany | | (89) |

CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; dMMR, deficient mismatch repair; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; MSI-H, microsatellite instability-high; NMPA, National Medical Products Administration; PMBCL, primary mediastinal B-cell lymphoma; PMDA, Pharmaceuticals and Medical Devices Agency; RCC, renal cell carcinoma; SCLC, small-cell lung cancer; TMB-H, tumor mutational burden-high.
*Approval as neoadjuvant therapy.

MYSTIC study, a phase III trial on NSCLC, the efficacy of combination of durvalumab and tremelimumab was compared with that of platinum doublet chemotherapy but failed to achieve the co-primary endpoints, with median OS times of 11.9 months (95% CI, 9.0–17.7) and 12.9 months (95% CI, 10.5–15.0), respectively, with an HR of 0.85 (98.77% CI, 0.61–1.17; p = 0.20), and median PFS times of 3.9 months (95% CI, 2.8–5.0) and 5.4 months (95% CI, 4.6–5.8), respectively, with an HR of 1.05 (99.5% CI, 0.72–1.53; p = 0.71); it has not yet been approved for use in Japan or any other country (90). The results of a phase III trial (POSEIDON study) that evaluated the superiority of tremelimumab in combination with durvalumab and platinum-based chemotherapy over platinum-based chemotherapy as first-line treatment for NSCLC was presented at the 2021 World Conference on Lung Cancer, with favorable outcomes: median OS times of 14.0 months (95% CI, 11.7–16.1) and 11.7 months (95% CI, 10.5–13.1), respectively, with an HR of 0.77 (95% CI 0.65–0.92; p = 0.00304), and median PFS times of 6.2 months (95% CI, 5.0–6.5) and 4.8 months (95% CI, 4.6–5.8), respectively, with an HR of 0.72 (95% CI, 0.60–0.86; p = 0.00031) (91). The primary endpoints tremelimumab in combination with durvalumab and chemotherapy were PFS and OS. The OS was not met, and the efficacy of durvalumab in combination with tremelimumab and chemotherapy was analyzed as the pre-specified key secondary endpoint. In its press release, AstraZeneca stated, "We look forward to discussing these data with regulatory authorities." However, whether an application was actually filed remains unclear (92). Other drugs targeting CTLA-4, including an open-label phase II study of NSCLC patients treated with KN046, a recombinant humanized PD-L1/CTLA-4 bispecific antibody, were reported during the 2021 meeting of the American Society of Clinical Oncology (ASCO). Based on the hypothesis that the limited peripheral distribution of KN046 would reduce the incidence of treatment-related toxicity, KN046 was added to platinum combination chemotherapy as a treatment for squamous and non-squamous NSCLC and showed good safety and promising efficacy (93). KN046 is currently under phase III trials in combination with carboplatin plus paclitaxel (NCT04474119) as a first-line treatment for squamous NSCLC and in combination with lenvatinib (NCT05001724) for NSCLC after ICI resistance, and is expected to show efficacy and safety as a novel CTLA-4 inhibitor.

### 2.2.2 LAG-3 inhibitors

In 2021, a phase III study (RELATIVITY-047 trial) comparing the efficacy of nivolumab combined with the anti-lymphocyte-activation gene 3 (LAG-3) antibody relatlimab with that of nivolumab alone as first-line treatment for malignant melanoma was the first to show the significant benefit of adding an anti-LAG-3 antibody to standard immunotherapy. The median PFS times, the primary endpoint of the study, were 10.1 months (95% CI, 6.4–15.7) and 4.6 months (95% CI, 3.4–5.6), respectively, with an HR of 0.75 (95% CI, 0.60–0.90; p = 0.0055) (94). The results were presented at ASCO 2021, and relatlimab was approved by the FDA as treatment for unresectable or metastatic melanoma on March 18, 2022, and were included in the PD-1/PD-L1 and anti-CTLA-4 antibody immunotherapy lineup (95). LAG-3 is a cell surface molecule that is expressed in effector and regulatory T cells and regulates the T-cell response, activation, and proliferation. Inhibition of the LAG-3 pathway restores the exhausted T-cell function and promotes antitumor responses, and the use of LAG-3 with PD-1/PD-L1 pathway inhibitors as combination therapy is expected. In NSCLC, several potential novel drug combinations are currently under investigation, including phase II trials of platinum-based chemotherapy plus nivolumab in combination with relatlimab as first-line therapy (NCT04623775); eftilagimod alpha, a soluble fusion protein of LAG-3 and the human IgG Fc moiety, in combination with pembrolizumab as treatment for patients who showed resistance to anti-PD-1/PD-L1 therapy (NCT03625323); and favezelimab, an anti-LAG-3 antibody, in combination with pembrolizumab (NCT03516981).

### 2.2.3 TIGIT inhibitors

Along with LAG-3, T-cell immunoreceptors with immunoglobulin and ITIM domains (TIGIT) are new candidate ICIs. TIGIT suppresses T-cell activation, exhausts T cells, and is highly expressed in tumor-infiltrating T cells. The inhibition of TIGIT promotes cytotoxic T-cell proliferation and antitumor responses, leading to the development of combination therapy with anti-PD-1/PD-L1 antibodies (96, 97). The FDA granted the breakthrough therapy designation to tiragolumab, an anti-TIGIT antibody, in combination with atezolizumab for the treatment of NSCLC with high PD-L1 expression on January 2021 according to the results of the CITYSCAPE trial, a randomized, double-blind, placebo-controlled phase II trial that examined the efficacy and safety of tiragolumab in combination with atezolizumab as first-line therapy in NSCLC patients with PD-L1 expression of ≥1%, which was presented at ASCO 2020 (98). Tiragolumab plus atezolizumab was able to achieve the co-primary endpoints in the intention-to-treat population, showing an improvement in the overall response rate (ORR) (37% *vs.* 21%) and PFS (median PFS, 5.6 *vs.* 3.9 months; HR, 0.58; 95% CI, 0.38–0.89) compared with atezolizumab alone. In the PD-L1 expression of ≥50% subpopulation, the ORRs were 66% and 24%, while the PFS times were not reached and 4.1 months, respectively, with an HR of 0.30 (95% CI, 0.15–0.61), showing very favorable results in the combination therapy group with an acceptable safety profile. Based on these results, Roche conducted a phase III trial (SKYSCRAPER-01, NCT04294810) to evaluate the superiority of tiragolumab plus atezolizumab over atezolizumab in treatment-naïve patients with advanced NSCLC expressing PD-L1; however, the recently released results of the interim analysis showed that the trial did not meet the PFS; hence, the study will continue investigating the OS until the next planned analysis (99). Currently, other phase III studies of anti-TIGIT antibodies are underway, and the competition to develop anti-TIGIT antibodies is starting to intensify. Phase III studies on domvanalimab combined with zimberelimab, an anti-PD-1 antibody (ARC-10 study, NCT04736173), and durvalumab as maintenance therapy after chemoradiotherapy (PACIFIC-8, NCT05211895) are ongoing, while the efficacy of adding vibostolimab to pembrolizumab or pembrolizumab plus platinum combination chemotherapy as first-line treatment is being examined in phase III trials (NCT04738487, NCT05226598) based on the promising results of a phase I study (100).

### 2.2.4 Angiogenesis inhibitors

Following the success of the IMpower150 trial on bevacizumab in addition to platinum-based chemotherapy and atezolizumab as first-line treatments for patients with advanced NSCLC, a number of clinical trials have been conducted combining angiogenesis inhibitors and ICIs (101). A placebo-controlled phase III trial (ONO-4538-52/TASUKI-52) was conducted to evaluate the superiority of nivolumab plus carboplatin plus paclitaxel plus bevacizumab over carboplatin plus paclitaxel plus bevacizumab in patients with advanced non-squamous NSCLC and PD-L1 expression of ≥1%; the median PFS times were 12.1 months (96.37% CI, 9.8–14.0) and 8.1 months (96.37% CI, 7.0–8.5), respectively, with an HR of 0.56 (96.4% CI, 0.43–0.71; p < 0.0001), with significantly better outcomes in the nivolumab arm regardless of tumor PD-L1 expression status (102). The median OS was similar, but the HR showed a favorable trend, indicating that this combination strategy could be a potential first-line treatment for non-squamous NSCLC. A multicenter, open-label, single-arm phase II study (@Be trial) that evaluated the efficacy and safety of atezolizumab plus bevacizumab as first-line therapy in 39 non-squamous NSCLC patients with a PD-L1 tumor proportion score of ≥50% was conducted by the West Japan Oncology Group, and the results were reported at the 2020 European Society for Medical Oncology conference (103). The ORR was 64.1%, with tumor shrinkage observed in most patients, and the safety was comparable to the previously reported data. The West Japan Oncology Group is planning to conduct a @Be-F1rst

study, a parallel-group, three-arm phase III trial, to compare the efficacy of atezolizumab and bevacizumab with that of the IMpower150 regimen and atezolizumab monotherapy. More recently, two trials evaluating the efficacy of angiotensin inhibitors to overcome immunotherapy resistance have been reported. One was an open-label, two-stage phase II trial evaluating the efficacy of bevacizumab plus atezolizumab in NSCLC patients who experienced disease progression following atezolizumab monotherapy (104). This trial enrolled ICI-naïve pretreated NSCLC patients whose disease progressed after at least one line of platinum-based chemotherapy. Patients received atezolizumab until the detection of disease progression on radiographic evaluation (stage I, n = 42). Bevacizumab was combined with atezolizumab (stage II, n = 24). The disease control rate in patients with stage II disease was 87.5% (95% CI, 67.6–97.3) including 12.5% of those who achieved partial response, suggesting that ICI resistance was overcame by adding bevacizumab. Another phase I trial investigating the safety of combining BI 836880, a bispecific nanobody targeting angiopoietin-2 in addition to vascular endothelial growth factor, and ezabenlimab, an anti-PD-1 antibody, has been reported (105). Forty patients with NSCLC, whose disease had progressed after treatment with ICIs, were treated with this combination therapy, showing an ORR of 10% with acceptable safety. The possible use of this regimen in the front-line setting to overcome ICI resistance is being considered.

### 2.2.5 TIM-3 inhibitors

Although it lags behind LAG-3 and TIGIT, anti-T-cell immunoglobulin and mucin domain 3 (TIM-3) therapy is expected to be developed because the co-expression of TIM-3 and PD-L1 adversely affects the immune system and is effective as a combination therapy (106). In 2018, the results of a phase I trial of a combination of cobolimab, an anti-TIM-3 antibody, and dostarlimab, an anti-PD-1 antibody, showed that in 25 NSCLC patients who developed resistance to anti-PD-1 antibodies, cobolimab combined with dostarlimab produced a response in 3 of 20 evaluable patients; hence, further development of this combination therapy is expected to overcome ICI resistance (107). A phase II/III trial (COSTAR Lung Study, NCT04655976) is currently performed to evaluate the superiority of cobolimab plus dostarlimab plus docetaxel and dostarlimab plus docetaxel over docetaxel alone in NSCLC, with an expected completion date of 2024. Meanwhile, sabatolimab, an anti-TIM-3 antibody, was granted a fast-track designation by the FDA and Orphan Medical Product designation by the European Medicines Agency for the treatment of myelodysplastic syndrome based on the results of a phase I trial on myelodysplastic syndrome and acute myeloid leukemia presented at the 2019 American Society of Hematology conference (108). However, for solid tumors, the combination of cobolimab and anti-PD-1 antibody spartalizumab yielded a response rate of only 6% as reported in a phase I trial; another phase I trial showed a modest response rate of 4% for LY3321367 (an anti-TIM-3 antibody) combined with LY300054 (an anti-PD-L1 antibody), making it difficult to decide the necessity of developing anti-TIM-3 therapies in the future (109, 110).

## 2.3 Other anti-PD-1/PD-L1 antibody combination therapies

### 2.3.1 Lenvatinib

Combination therapy with the multi-kinase inhibitors lenvatinib and pembrolizumab has been approved by the FDA, European Medicines Agency (EMA), and Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of uterine cancer and/or renal cell carcinoma. Basic studies have shown that the combination of lenvatinib and pembrolizumab improves the immune microenvironment in hepatocellular carcinoma, and several clinical trials are underway to expand its indication to other types of cancer (111, 112). Several phase III trials using lenvatinib in NSCLC are being examined the efficacy of pembrolizumab in combination with pemetrexed plus platinum in the first-line treatment of non-squamous NSCLC patients (LEAP-006, NCT03829319), in combination with pembrolizumab in the first-line treatment of PD-L1-positive patients (LEAP-007, NCT03829332), in combination with docetaxel in the second-line setting (LEAP-008, NCT03976375), and in combination with KN046, a recombinant humanized PD-L1/CTLA-4 bispecific fusion protein, after ICI resistance (NCT05001724). Ongoing phase I and II trials are using lenvatinib combination therapy with pembrolizumab in the perioperative treatment (NCT04875585), pembrolizumab plus pemetrexed plus carboplatin following treatment with epidermal growth factor receptor-tyrosine kinase inhibitors in epidermal growth factor receptor mutation-positive patients with NSCLC (NCT05258279), GI-101, a bispecific fusion protein of CD80 and interleukin (IL)-2 mutants (NCT04977453), IBI318, a bispecific antibody of PD-1 and PD-L1 (NCT04777084), and envafolimab, a subcutaneous anti-PD-1 antibody formulation (NCT05024214). It might not be long before lenvatinib becomes available in the clinical setting for patients with thoracic malignancies following the approval for thymic cancer in Japan (113).

### 2.3.2 Canakinumab

The inflammatory cytokine IL-1β is believed to be involved in cancer invasion, progression, and metastasis. A subgroup analysis of the CANTOS trial showed that canakinumab, an IL-1β inhibitor with an anti-inflammatory effect on atherosclerosis that inhibits the recurrence of myocardial infarction, also reduces the incidence of lung cancer and death (114). Based

on these findings, the efficacy of canakinumab in NSCLC was validated by multiple phase III trials; however, the addition of canakinumab to standard therapy as first-line (CANOPY-I) and second-line or later-line (CANOPY-II) treatments failed to meet the primary endpoint, as reported in 2021 (115, 116). Canakinumab is currently under a phase II trial as a preoperative treatment (CANOPY-N, NCT03968419) and a phase III trial as a postoperative treatment (CANOPY-A, NCT03447769), being expected to improve the immune microenvironment through IL-1β inhibition in early stage NSCLC.

### 2.3.3 Other novel immunotherapy agents

Other new agents in the early stages of development for combination therapy with ICIs include MK-4830, an IgG4 monoclonal antibody that targets the immunoglobulin-like transcript 4 receptor. The preliminary results of a phase I trial, which was first presented at the 2020 European Society for Medical Oncology conference and published in 2021, showed a promising ORR of 24% in a dose-escalation cohort treated with pembrolizumab; notably, five of the eleven patients who were resistant to anti-PD-1/PD-L1 antibody therapy had an objective response (117). The efficacy and safety of MK-4830 are verified further in a substudy of the phase II KEYMARKER trial (NCT04165083 and NCT04165096). MK-5890, an anti-CD27 agonist, has also been evaluated in the KEYMARKER trial; according to the phase I results presented at the 2019 Society for Immunotherapy of Cancer conference, combination therapy with pembrolizumab showed an ORR of 10.5%. Of the 14 patients who switched to combination therapy with pembrolizumab after experiencing disease progression following MK-5890 monotherapy, 5 patients, including 2 who achieved complete response, showed a favorable response (ORR, 35.7%), which was a very promising result (118).

## 3 Future perspective

PD-1/PD-L1 antibodies are generally approved for NSCLC and can be used in clinical practice in Japan as well as in the US and EU, except for cemiplimab. However, in solid tumors other than NSCLC, pembrolizumab for cervical cancer was approved by the FDA in 2018, cemiplimab and pembrolizumab for cSCC in 2018 and 2020, respectively, and cemiplimab for cBCC in 2021; however, none of these agents were approved for in Japan because Japanese patients were not enrolled in pivotal trials (119–121). In addition, a number of PD-1/PD-L1 antibodies developed in China have not been approved by the PMDA, FDA, or EMA, which is thought to be due in part to the rise of emerging biopharma companies (EBPs)–those with an estimated expenditure on research and development (R&D) of less than $200 million and less than $500 million in revenue–which contributed more than 70% of the FDA regulatory submission for approval (122, 123). Most EBPs are located in the US, EU, or China and do not own any Japanese corporations or domestic administrators, which has led to an increasing number of cases that have not been conducted in Japan. This "decentralized drug development" in oncology field is expected to expand and accelerate in the near future, and certain drugs that can be used in other countries might not be available in our own countries. These problems are so complex that they are difficult to solve without establishing relevant policies (124).

In the past two decades, "drug lag" (i.e., the delay in time required for the approval of oncology drugs) was an issue in Japan compared with that in the US or EU. Efforts have been made to eliminate the "drug lag" with other countries using several approaches such as expediting the regulatory approval, establishment of the Strategy of SAKIGAKE, which allows the accelerated approval of drugs as breakthrough therapies and addressing unmet medical needs in Japan attracting foreign drug trials including orphan drugs, and launching of the Advanced Medical Care Program to enable patients to gain access to promising unapproved drugs or medical devices through the National Health Insurance (NHI) coverage (125–129). In fact, review periods for new drugs have been shortened, with the median periods in 2018 being 10.0 months for the PMDA, 10.4 months for the FDA, and 13.7 months for the EMA (130). Although the review period gap with overseas countries is beginning to shorten, the number of unapproved drugs in Japan has reached 70% due to the rise of EBPs and the negative impact of the expected shrinking of the Japanese pharmaceutical market and the biennial revision of Japanese drug prices (122, 129–132). Currently, although no specific national policies or measures that can attract foreign EBPs to Japan are prominently practiced, our institution has opened its doors to domestic and foreign entrepreneurial ventures, providing online consultation by experts with experience in regulatory review and clinical trial initiatives (133). In addition to promoting the understanding of Japan's strengths, such as NHI coverage, which covers the medical expenses for treatment and medical testing, and Japan's market value (once approved, the drug always carries a drug price and is likely to be delivered to patients), further political support is needed to promote drug development in Japan, such as encouraging more Japanese participation in international joint clinical trials (134–136). To maximize the benefits of "decentralized drug development" for Japanese patients, the Japanese industry, government, and academia should cooperate and catch up with the global market.

## 4 Discussion

The ICI therapy has drastically rewritten the history of cancer treatment. The development of novel agents, and use of combination therapies will continue to accelerate cancer

treatment. In addition to the clinical trials reported to date, numerous drug combinations, such as antibody-drug conjugates, bispecific antibodies targeting multiple immune-checkpoint molecules, and other immune-related molecules in combination with ICIs, have been used. Although several compounds for immunotherapy are being developed, the effectiveness of immunotherapy often depends on the immune and systemic status of the host, and results from early phase trials are not often reflected in later phase trials. Although some treatments are effective in certain patients, there is also a need for measures to address the disadvantages associated with such treatments, such as the increasing medical costs, the need to implement scientific approaches to narrow down the population that will benefit from the treatment (or identifying those who will not benefit), and the duration of treatment for patients who do benefit. In a randomized post-marketing trial of NSCLC patients (CheckMate-153 study), the PFS and OS were significantly shorter after nivolumab discontinuation (137). However, the impact of discontinuation cannot be concluded in this trial alone as it was not planned to address a specific statistical hypothesis: patients who showed exacerbation were included, the number of patients who responded to nivolumab was much larger in the continuation arm, and the important patient characteristics were imbalanced between the treatment arms. The Japan Clinical Oncology Group is currently conducting the JCOG1701 trial (SAVE study), a randomized controlled phase III trial that aimed to evaluate the non-inferiority of treatment suspension to continued treatment in NSCLC patients who have benefited from anti-PD-1/PD-L1 antibody treatment for at least 12 months (138). The prognostic and predictive roles of circulating tumor DNA will be explored in this study. Another randomized phase II–III trial for NSCLC compared the outcomes of discontinuation and continuation of pembrolizumab after six months of treatment with chemotherapy plus pembrolizumab combination therapy (139). These trials will elucidate the optimal management of NSCLC patients treated with ICIs from the perspective of not only safety and better biomarkers, but also cost-effectiveness.

As it has become common for multiple departments to collaborate in the treatment of immune-related adverse events, further development of strategies is warranted to provide optimal treatment to cancer patients through a global collaboration between industry, the government, and academia worldwide.

## Author contributions

This review was drafted by TM and NY, and critically revised by YK, JS, TK, and TS. All authors contributed to the article and approved the submitted version

## Conflict of interest

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

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# Acupuncture for adult lung cancer of patient-reported outcomes: A systematic review and meta-analysis

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**Purpose:** This systematic review and meta-analysis aims to assess the effects of acupuncture on patient-reported outcomes (PROs) in adults with lung cancer.

**Methods:** Electronic databases including PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CQVIP), Wanfang Data, SinoMed, and gray literatures were retrieved from inception to 1 July 2022 for randomized controlled trials (RCTs). Acupuncture was defined as an experimental intervention, and the patients of the control groups included either treatment including conventional therapy (usual care, sham/placebo acupuncture, pharmacotherapy including Western medicine and Chinese traditional medicine). PROs for this study were measured by seven scales of primary outcomes including the Karnofsky Performance Status (KPS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Functional Assessment of Cancer Therapy-Lung, Functional Assessment of Cancer Therapy Lung Cancer Subscale, Leicester Cough Questionnaire (LCQ score), the Medical Outcomes Study (MOS) item short form health survey (SF-36), and the St George's Respiratory Questionnaire, and 12 scales of secondary outcomes. Cochrane Collaboration's tool was used to assess the risks of bias. Data were combined and analyzed with RevMan 5.4 and Stata/SE 16.0.

**Results:** We retrieved 3,002 lung cancer patients from 33 trials. KPS included with 1,000 patients showed that acupuncture could significantly improve the quality of life (QOL) compared with the control group regardless of different tumor–node–metastasis stages or the different stages of disease. The study showed that acupuncture significantly improved lung cancer–related symptoms in the QOL, pain, nausea and vomiting, insomnia, anxiety and depression, fatigue, and constipation compared with the control group. Eight RCTs reported the occurrence of adverse events, whereas four reported none and four RCTs reported that the events in the observation group were significantly less than those in the control group.

**Conclusion:** Acupuncture proved to be a promising intervention, both postoperatively and after chemotherapy, and should be recommended as a beneficial alternative strategy to promote PROs in lung cancer patients at all stages of application. Considering the low quality, we suggest more rigorous clinical trials of acupuncture for lung cancer in the future and more emphasis on the effect of acupuncture in patients with lung cancer on their PROs, mainly in the aspect of the QOL.

**Systematic review registration:** https://www.crd.york.ac.uk/prospero/display_record.php?, identifier [CRD42021274122].

KEYWORDS

**acupuncture, lung cancer, PROs = patient-reported outcomes, systematic review, meta-analysis**

## Introduction

Lung cancer remains the most common cancer and the leading cause of cancer deaths (1). The overall 5-year survival rate for lung cancer diagnosed from 2010 to 2014 was in the range 10%–20% in most countries around the world, still being dismal (2). According to the latest global statistical analysis of International Agency for Research on Cancer, approximately 2.2 million new cases were diagnosed worldwide in 2020, with a mortality rate of 18% in the same year (3). Furthermore, the cost of drugs imposes a heavy social and economic burden on individuals, families, communities, and countries, thus posing substantial challenges (4). Studies have been conducted on patients after lung cancer surgery, commonly showing a significant decline in the quality of life (QOL) scores (5, 6).

Patient-reported outcomes (PROs) are the measurements of any aspect of a patient's health obtained by a self-report, which means that there is no need for physician or any others to interpret the patient's reactions (7). PROs are becoming increasingly important in the evaluation of cancer treatment modalities (8). PROs provide valuable insight into the patient experience and allow the measurement of preoperative and postoperative QOL (9). QOL is a critical outcome measure in lung cancer surgery and is of great significance, especially in treating patients with early-stage lung cancer (10). It has been reported that PRO-based active symptom monitoring intervention is feasible and demonstrates encouraging preliminary efficacy for reducing symptoms and the readmission risk (11), and more to the point, resulting in superior QOL (12).

Recent advances in clinical research show that acupuncture, as an effective, safe, and cost-effective treatment for cancer and cancer-related symptoms, may provide clinical benefits for oncology patients in symptom control and supportive care (13, 14). Acupuncture also alleviates side effects induced by chemotherapy or radiotherapy such as nausea and vomiting (15), cancer-related pain (16), fatigue (17), insomnia (18), and the QOL. Oncology acupuncture has become a new research field with great prospects (19). It is anticipated that as a growing number of evidence continues to emerge, oncology acupuncture will eventually be integrated into standard oncology practice (20).

Despite growing attention to acupuncture as an alternative medicine for lung cancer treatment, the evidence of its impact on the PROs of lung cancer patients is scanty (21). Moreover, there are no systematic reviews of acupuncture improving PROs in lung cancer patients. To fill this gap, we undertake systematic retrieval and analysis to summarize the existing evidence of acupuncture therapy in improving PROs among the lung cancer patients. Our study will provide more reliable evidence from the perspective of PROs and the implementation details of acupuncture therapies in the clinical practice of lung cancer, as well as contribute to optimizing a clinical acupuncture regimen and trial design in the future.

## Methods

This study is performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (22). The protocol of this study has been registered in International Prospective Register of Systematic Reviews (PROSPERO), and the registration number is CRD42021274122.

## Search strategy

Electronic databases including PubMed, Embase, Cochrane Library, Web of science, CNKI, CQVIP, Wanfang Data, SinoMed, and gray literatures including ClinicalTrials.gov Database (www.clinicaltrials.gov), Chinese Clinical Trial Register (www.chictr.org.cn), and conference literatures were retrieved from inception to 1 July 2022. The language is limited to Chinese and English. In addition, the reference lists of eligible articles were also checked to identify additional studies. The searches were performed using the following mesh terms plus keywords, such as "acupuncture", "lung cancer", "PROs", and "Randomized Controlled Trial", including their synonyms. Supplementary Tables 1, 2 in the Supplementary Materials show the complete search strategy for English and Chinese databases above.

## Inclusion criteria

The eligible criteria included:

a. Adult patients (age ≥ 18 years) who were diagnosed with lung cancer through pathology with any tumor stage with no gender restrictions
b. Randomized controlled trials (RCTs) on acupuncture treatment among lung cancer patients with the outcomes of PROs
c. Acupuncture is a method to treat diseases by stimulating meridians and acupoints. It includes manual acupuncture, electroacupuncture (EA), moxibustion, transcutaneous electrical acupoint stimulation (TEAS), auriculotherapy, acupoint application, acupoint injection, fire needle, plum-blossom needle, and acupressure. Acupuncture used alone or in combination was defined as an experimental intervention.
d. The comparison groups included either treatment as follows: usual care, sham/placebo acupuncture, and pharmacotherapy including Western medicine (WM) and Chinese Traditional medicine (TCM).

## Exclusion criteria

The eligible criteria included:

a. Combined with other cancers
b. Quasi-randomized control trial, cohort studies, case–control studies, and articles that have not been peer-reviewed
c. The same acupuncture therapy was conducted in both groups.

It deserves to be mentioned that the acupuncture group has no restriction on the needle size, acupoint selection, stimulation frequency, retention time, and treatment course.

## Outcome measures

We divided the different PRO outcome indicators into two categories: QOL and patient-perceived symptoms. The primary outcome measures were QOL scales commonly used in the efficacy evaluation of lung cancer patients, such as the Karnofsky Performance Status (KPS) (23), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (24), Functional Assessment of Cancer Therapy-Lung (FACT-L) (25), Functional Assessment of Cancer Therapy Lung Cancer Subscale (FACT-LCS), Leicester Cough Questionnaire (LCQ score) (26), the MOS item short form health survey (SF-36) (27), and the St George's Respiratory Questionnaire (SGRQ) (28).

Secondary outcomes were patient-perceived symptoms, including pain, nausea and vomiting, insomnia, fatigue, and constipation, as well as adverse events to be recorded. Pain intensity was measured by four measurement tools including the numerical rating scale (NRS) score (29), Visual Analog Scale (VAS) pain scales (30), pain score in EORTC QLQ-C30, and Brief Pain Inventory-Chinese Version (BPI-C) (31). Nausea and vomiting were measured by three measurement tools including the MASCC (Multinational Association of Supportive Care in Cancer) Antiemesis Tool (MAT) (32), Index of Nausea and Vomiting and Retching (INVR) (33), and nausea and vomiting score in EORTC QLQ-C30. Insomnia was measured by three measurement tools including the Pittsburgh Sleep Quality Index (PSQI) (34), Athens Insomnia Scale (AIS) (35), and sleep score in EORTC QLQ-C30. Fatigue was measured by the following four measurement tools: Revised Piper Fatigue Scale (PFS-R) (36), Brief Fatigue Inventory-Chinese Version (BFI-C) (37), and fatigue score in EORTC QLQ-C30. The secondary outcome anxiety and depression was measured by two measurement tools including the Self-Rating Anxiety Scale (SAS) (38) and Self-Rating Depression Scale (SDS) (39). Constipation was measured by following one measurement tool constipation score in EORTC QLQ-C30.

## Study selection and data extraction

Two researchers (X.Q. W and Z.Q. X) independently extracted and managed data by Excel software (16.59, Microsoft excel for Mac). Any disagreement was resolved by

discussion until a consensus was reached or by consulting a third researcher (K W). The data extraction elements included the authors, year, sex, age, stage, randomization, intervention details, main acupoint, course of treatment, results, follow-up, and outcomes. For RCTs with multiple time points to evaluate outcomes, the data at the end of treatment were extracted. The selection process was presented in a PRISMA flow diagram.

## Risk of bias assessment

Methodological quality and reporting biases were evaluated by two reviewers independently. Cochrane Collaboration' s tool was used to assess the risks of bias (40). We assessed from the following seven dimensions: random sequence generation, allocation concealment, the blinding of participants and patients, the blinding of outcome evaluators, incomplete outcome data, and selective reporting. Divergence would be conquered by the adjudication of the corresponding author.

## Statistical analysis

Data were combined and analyzed with RevMan 5.4.1 (The Cochrane Collaboration) and Stata/SE 16.0. Dichotomous data were reported as the relative ratio (RR), whereas continuous data were reported as the mean difference (MD) or standardized mean difference (SMD), with 95% confidence interval (CI). The MD was used for PROs with the same measures; otherwise, the SMD was chosen. The fixed-effect model was employed when the study of heterogeneity ($I^2$) was <50%; otherwise, a random-effect model was used. Sensitivity analysis was performed by excluding each RCT out sequentially to test the robustness of the result. Subgroup analysis was applied to explore the source of heterogeneity. Meta regression analysis was used to clarify the sources and value of heterogeneity and to further explain the influence of variables on the combined effect. A random-effect model was used for meta regression analysis. The funnel plot was conducted to detect publication bias.

# Results

## Search results

A total of 499 trials were retrieved in the literature search. After a preliminary screening of the titles and abstracts of the articles, we used EndNoteX9 (X9.3.3, Thomson Reuters (Scientific) LLC Philadelphia, PA, USA) and manual checking to remove duplicate and non-standard studies and identified 96 studies from the database. We evaluated the full text of the 96 studies, and only 33 of them met our inclusion criteria. Figure 1 shows the process of the literature search and the screening process used in this study (22).

## Descriptions of the included trials

Of all included 33 RCTs, 27 were published in Chinese and 6 were published in English. Seven trials used auricular acupoint (41–47), seven trials used acupoint application (45, 46, 48–52), six trials used manual acupuncture (41, 46, 53–56), four trials used moxibustion (43, 48, 57, 58), three trials used electroacupuncture (EA) (51, 59, 60), three trials used transcutaneous electrical acupoint stimulation (TEAS) (61–63), two trials used acupoint injection (49, 64), two trials used a fire needle (65, 66), two trials used acupressure (67, 68), and only one trial for each used plum-blossom needle tapping (69), low-frequency pulse (49), catgut-embedding therapy (70), thunder-fire moxibustion (71), thermal moxibustion (72), and Mongolian medicine warm acupuncture (73). All RCTs provided the details of the treatment acupoints. The auricular acupoint sessions ranged from 3 to 5 min. Plum-blossom needle tapping sessions ranged from 5 to 10 min. Acupressure sessions ranged from 10 to 18 min. Thunder-fire moxibustion sessions ranged from 20 to 30 min. Low-frequency pulse sessions ranged from 25 min. Moxibustion, EA, TEAS, manual acupuncture, and Mongolian medicine warm acupuncture sessions ranged from 30 min, and acupoint application sessions ranged from 4 to 6 h. Fire needle sessions were done three times at each point.

Twenty trials used Western medicine or traditional Chinese medicine (TCM) as a control intervention, 9 trials used usual care as a control intervention, and only 4 trials used sham or placebo acupuncture.

Nineteen trials covered the primary outcomes, 8 of which also included secondary outcomes. The remaining 14 trials only with secondary outcomes. The characteristics of the included studies and acupuncture details of included studies are shown in Supplementary Tables 3 and 4 in the Supplementary Materials.

## Risk of bias in individual trials

All of the RCTs reported the generation of random sequences. Twenty-three trials used the random number table method, five trials used random number produced by computer, two trials used lottery, two trials used random number produced by SPSS (20.0 and 22.0) and the remaining one trial used regional random grouping method. The major sources of risk of bias correlated with allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. twenty-nine trials were judged to have a high risk of bias with respect to the blinding of participants given that it was not possible to blind the acupuncturists and most patients in

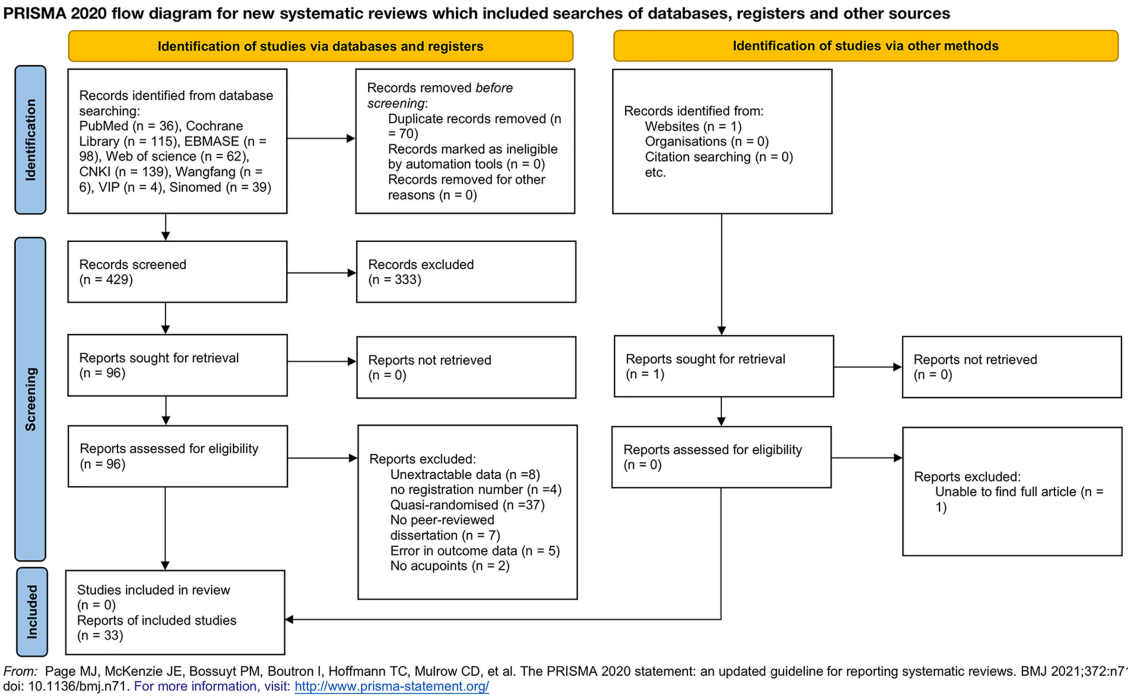


FIGURE 1
Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 flow diagram for new systematic reviews that included the searches of databases, registers, and other sources. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.doi:10.1136/bmj.n71. For more information, visit http://www.prisma-statement.org/.

a study of acupuncture intervention. Other bias in two trials (67, 70) were identified as high risk because these two trials did not report baseline data for age comparison of patient in both control group and observation group. We judge that only two trials (60, 61) had a relatively low risk of bias. The individual risk of bias for each trial is presented in Figure 2.

## Outcome measures

### Quality of life

Seventeen RCTs (41, 42, 45–50, 53, 54, 57, 58, 61, 64–66, 69) reported QOL scales, including KPS (42, 45–50, 53, 61, 64–66, 69), EORTC QLQ-C30 (41, 57), FACT-L (61, 65), FACT-LCS (54), SF-36 (58), LCQ (50), and SGRQ (68). Among these 17 trials, 7 trials used ST36; 4 trials used BL13, LI4, and TF4; 3 trials used PC6 and AH6a; and 2 trials used AT4. Higher scores were considered better in all PROs except SGRQ in which a higher score indicates a poorer QOL. In terms of the QOL measured by KPS, 11 of which used continuous variables and two original studies referred to the criteria of KPS and transformed it into a dichotomous variable. We combined these trials in two different ways: different tumor–node–metastasis (TNM) stage or different stage of disease. A study (74) has shown that KPS appeared to be a more reliable predictor of survival than the results of the QOL questionnaire. This again suggests that KPS is more informative when used to evaluate older and more impaired patients. It was found that the QOL of patients who received acupuncture-related treatment improved significantly compared with those who only received Western medicine treatment and usual care using continuous variables (MD 6.75, 95%CI, 5.82 to 7.68, P<0.00001, $I^2$ = 0%) Two trials (46, 64) concluded that patients experienced a higher effect on QOL in the acupuncture-related group compared with those in the WM/TCM group using dichotomous variables (RR 1.24, 95%CI, 1.09 to 1.41, P=0.001 $I^2$ = 0%). The pooled analysis results of the changes in the mean scores of each scale are listed in Tables 1 and 2.

On two EORTC QLQ-C30 measures of QOL (41, 57), patients receiving acupuncture-related treatment had remarkably higher mean scores than patients from the control group (MD 10.68, 95%CI, 4.56 to 16.81, P=0.0006, $I^2$ = 51%). For the QOL measured by FACT-L, the TEAS and fire needle used by Sun Y et al. (61) and Pei WY et al. (65) worked better (MD 4.65, 95%CI, 1.67 to 7.63,

TABLE 1 The QOL of acupuncture with continuous variables versus comparators for lung cancer treatment–related symptoms.

| Outcome | Participants | End of treatment | | | Meaning of higher scores |
|---|---|---|---|---|---|
| | | IV, Fixed, 95% CI | P-value | Heterogeneity | |
| **KPS** (42, 45, 47–50, 53, 61, 65, 66, 69) | | | | | |
| **1. Different TNM stage** | | | | | |
| 1.1 Early and middle stage (61) | 120 | MD 5.96 [1.79, 10.12] | P=0.005 | / | Better |
| 1.2 Late stage (47, 48) | 170 | MD 7.00 [5.65, 8.35] | P<0.00001 | $I^2$ = 0% | Better |
| 1.3 Middle and late stage (42, 45, 50, 65, 66) | 434 | MD 6.75 [5.12, 8.37] | P<0.00001 | $I^2$ = 31% | Better |
| 1.4 Not mentioned (49, 53, 69) | 276 | MD 6.28 [3.55, 9.01] | P<0.00001 | $I^2$ = 0% | Better |
| **2. Different stage of disease** | | | | | |
| 2.1 Postsurgery (61, 69) | 192 | MD 6.12 [3.30, 8.93] | P<0.0001 | $I^2$ = 0% | Better |
| 2.2 Undergoing chemotherapy (49, 53, 65, 66) | 324 | MD 7.09 [4.53, 11.25] | P<0.00001 | $I^2$ = 18% | Better |
| 2.3 Not mentioned (42, 45, 48, 50) | 396 | MD 6.84 [5.67, 8.01] | P<0.00001 | $I^2$ = 0% | Better |
| **EORTC QLQ-C30** (41, 57) | | | | | |
| **1. Different TNM stage** | | | | | |
| 1.1 T1–4 stage (41) | 118 | MD 13.00 [8.91, 17.09] | P<0.00001 | / | Better |
| **2. Different stage of disease** | | | | | |
| 2.1 Undergoing surgery (57) | 96 | MD 6.47 [-1.54, 14.48] | P<0.05 | / | Better |
| **FACT-L** (61, 65) | | | | | |
| **1. Different stage of disease** | | | | | |
| 1.1 Postsurgery (61) | 120 | MD 3.64 [0.32, 6.96] | P=0.03 | / | Better |
| 1.2 Undergoing chemotherapy (65) | 60 | MD 8.76 [2.05, 15.47] | P=0.01 | / | Better |
| **FACT-LCS** (54) | 28 | MD 5.80 [4.63, 6.97] | P<0.00001 | / | Better |
| **SF-36** (58) | 100 | MD 10.36 [6.17, 14.55] | P<0.00001 | / | Better |
| **LCQ** (50) | 120 | MD 20.21 [15.61, 24.81] | P<0.00001 | / | Better |
| **SGRQ** (68) | 60 | MD -31.69 [-36.58, -26.80] | P<0.00001 | / | Worse |

QOL, quality of life; TNM, tumor–node–metastasis; KPS, Karnofsky Performance Status; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-LCS, the Functional Assessment of Cancer Therapy Lung Cancer Subscale; SF-36, the MOS item short form health survey; LCQ, Leicester Cough Questionnaire; FACT-L, Functional Assessment of Cancer Therapy–Lung; SGRQ, St George's Respiratory Questionnaire.

P=0.002, $I^2$ = 26%). For the QOL measured by FACT-LCS, a significant reduction in the FACT-LCS score was observed in the 14 participants who received active acupuncture compared with those receiving the placebo (MD 5.80, 95%CI, 4.63 to 6.97, P<0.00001). In terms of the QOL measured by LCQ, Ma HX et al. (50) concluded that the improvements in the LCQ score in the treatment group were better than the control group (MD 20.21, 95%CI, 15.61 to 24.81, P<0.00001). Based on the QOL measured by SF-36 (58), the scores of physiological function, physiological function, general health, social function, emotional intelligence, and mental health in the observation group were significantly higher than those in the control group (MD 10.36, 95%CI, 6.17 to 14.55, P<0.00001). For the QOL measured by SGRQ (68), the intervention group's life quality scores significantly decreased (MD -31.58, 95%CI, -36.58 to -26.80, P<0.00001).

## Pain

Eleven RCTs (41, 42, 45, 56–60, 62, 69, 70) reported on pain by patients, and used four pain measures including the NRS score (42, 56, 58, 59, 69, 70), VAS (45, 60, 62), and PA score in EORTC QLQ-C30 (41, 57) or BPI-R (41). Among these 11 trials, 6 trials used LI4, 4 trials used ST36, 3 trials used TF4 and AH6a, and 2 trials used BL13, PC6, and AT4. Higher scores were considered worse in all these PROs. We combined the data of two pain scales, VAS and NRS, and classified them according to different stages of the disease. We reached the conclusions that for patients of cancer pain (42, 45, 56, 59), compared with those receiving Western medicine treatment and usual care, patients receiving acupuncture-related treatment improved significantly (SMD -1.69, 95%CI, -2,49 to -0.90, P<0.0001, $I^2$ = 90%). However, for patients of postoperative pain (60, 62, 69), the results showed no statistical significance (SMD -1.20, 95%CI, -2.26 to 0.22, P = 0.11, $I^2$ = 92%). There were two trials (58, 70) measured by the NRS that used dichotomous variables with the patients of cancer pain, showing that the pain relief efficiency in the observation group was significantly higher than that of the control group (RR 0.50, 95%CI, 0.30 to 0.82, P=0.006, $I^2$ = 0%) (Figure 3).

For pain measured by the PA score in EORTC QLQ-C30, Wang X et al. (41) and Wang LQ et al. (57) compared the PA scores of patients in the observation group after treatment with those in the control group, but the differences were not statistically significant in both two trials (P>0.05) (MD -3.90, 95%CI, -9.33 to

TABLE 2 The QOL of acupuncture with dichotomous variables versus comparators for lung cancer treatment–related symptoms.

| Outcome | Participants | End of treatment | | | Meaning of higher scores |
|---|---|---|---|---|---|
| | | M-H, Random, 95% CI | P-value | Heterogeneity | |
| **KPS** | | | | | |
| **Different TNM stage** | | | | | |
| Late stage (46) | 142 | RR 1.19 [1.00, 1.41] | P=0.009 | / | Better |
| Middle and late stage (64) | 80 | RR 1.30 [1.07, 1.59] | P<0.05 | / | Better |

QOL, quality of life; KPS, Karnofsky Performance Status; TNM, tumor–node–metastasis.

1.54, P=0.16, $I^2$ = 58%). One RCT (41) using BPI-R showed that there was significant difference in the pain intensity between the observation group and the control group after treatment and between the observation group after treatment and before treatment (Table 5).

## Nausea and vomiting

Four RCTs (41, 51, 55, 57) reported on nausea and vomiting by patients and used three NA measures including the NV score in EORTC QLQ-C30 (41, 57), MAT (51) and INVR (55). Among these four trials, two trials used LI4 and ST36, one trial used TF4, AH6a, PC6, and AT4. Two (51, 55) of the trials were for nausea and vomiting after chemotherapy; one (57) was postoperative, and one (41) was not specified. Higher scores were considered worse in all these PROs. For NV measured by the NV score in EORTC QLQ-C30, Wang X et al. (41) and Wang LQ et al. (57) compared the NV scores of patients in the observation group after treatment with those in the control group; scores in the observation group were significantly lower than those in the control group for both postoperative and routine patients (MD -14.73, 95%CI, -23.88 to -5.59, P=0.002, $I^2$ = 81%). In terms of INVR scores (55), there was no statistical difference between the POG and the control group on the first day of chemotherapy, but the prechemotherapy acupuncture group (PRG) differed significantly from the postchemotherapy acupuncture group (POG) and control group (P<0.05). On the second-to-seventh day of chemotherapy, the difference between the three groups was statistically significant (MD -1.18, 95%CI, -1.89 to -0.47, P=0.001).

One RCT (51) measured by MAT using dichotomous variables showed that the severity of acute vomiting in the observation group was significantly lower than that in the control group at the end of treatment (RR 0.59, 95%CI, 0.41 to 0.86, P=0.006) (Table 5).

## Sleep disturbances

Seven RCTs (41, 43, 44, 52, 59, 71, 73) reported on sleep disturbances by patients and used three sleep disturbance measures including the SL score in EORTC QLQ-C30 (41), PSQI (43, 52, 59, 71, 73), and AIS (44). Among these seven trials, three trials used TF4, AT4, and ST36; two trials used AH6a and LI4; and one trial used BL13. Three (43, 71, 73) of the trials were for sleep disturbances after chemotherapy, three (41, 52, 59) were cancer-related sleep disturbances, and one (44) was for radiotherapy. Higher scores were considered worse in this PRO. Five trials used PSQI to measure patients' sleep quality, one of which (43) used four arms, so the results are not easy to be combined and will be analyzed separately. Guo et al. showed that there were statistically significant differences in the PSQI factor scores of the four groups, suggesting that the auricular acupoint combined with the moxibustion treatment group had the most obvious effect. The remaining four trials showed that the score of PSQI in the observation group was significantly lower than those

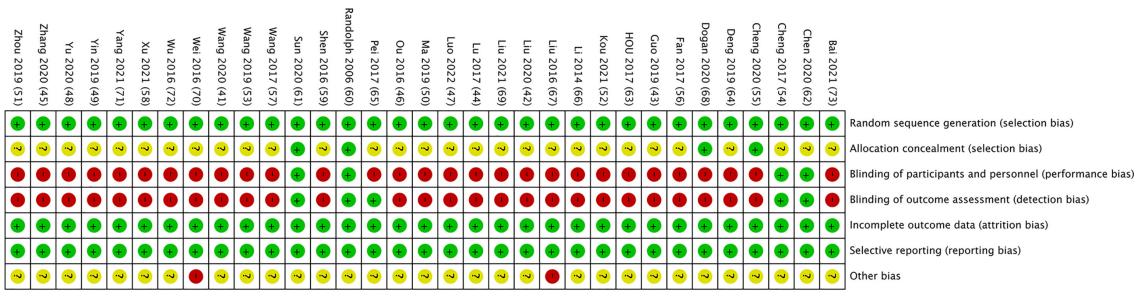


FIGURE 2
Risk of bias assessment by individual trials.

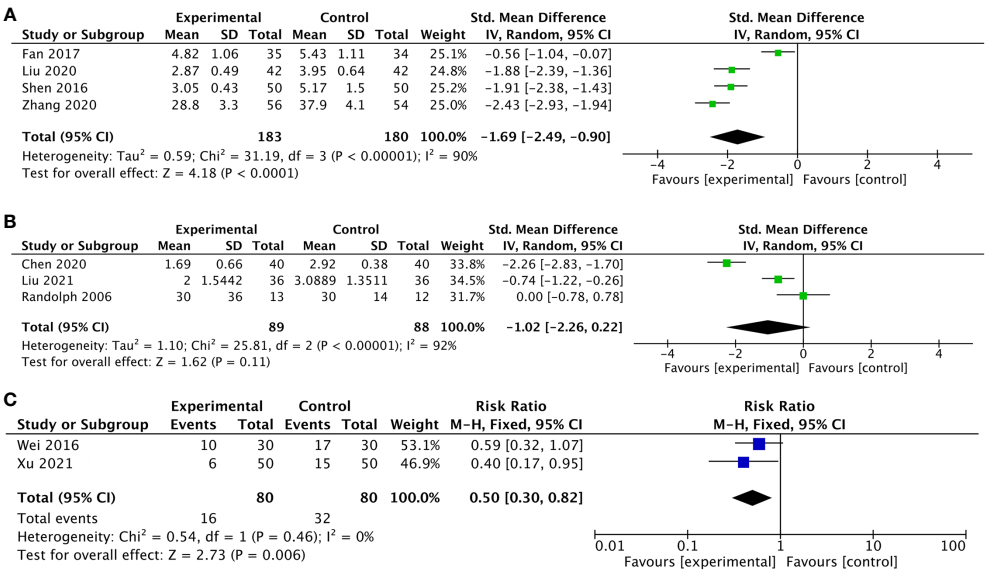


FIGURE 3
Forest plot of the pain in lung cancer patients treated with acupuncture and control. **(A)** The changes measured by the combination of the Numerical Rating Scale (NRS) score and Visual Analog Scale (VAS) pain scales in lung cancer patients with cancer pain treated with acupuncture-related intervention versus control from the baseline to the end of treatment; **(B)** the changes measured by the combination of NRS and VAS scores in lung cancer patients undergoing surgery treated with acupuncture-related intervention versus control from the baseline to the end of treatment; **(C)** the changes measured by the combination of the NRS score in lung cancer patients with cancer pain treated with acupuncture-related intervention versus control from the baseline to the end of treatment using dichotomous variables. IV, inverse variance; CI, confidence interval.

in the control group and the total improvement rate of sleep quality was also superior to the patients in the control group for both chemotherapy-induced and cancer-related sleep disturbances (MD -3.73, 95%CI, -5.99 to -1.48, P=0.001, $I^2$ = 97%) (Figure 4). For the SL score in EORTC QLQ-C30 (41), a comparison between groups after treatment showed that the SL scores in the observation group after acupuncture observation were lower than those in the control group (MD -14.16, 95%CI, -20.91 to -7.41, P<0.001). One RCT (44) using AIS showed that AIS scores in the observation group and the control group were not statistically significant (P>0.05) (MD -0.17, 95%CI, -1.93 to 1.59, P=0.85) (Table 5).

## Fatigue

Eight RCTs (41, 42, 54, 57, 63, 67, 71, 72) reported on fatigue by patients and used four fatigue measures including the FA score in EORTC QLQ-C30 (41, 57), PFS-R (42, 63, 71, 72), and BFI-C (54, 67). Among these eight trials, five trials used ST36; three trials used LI4; two trials used AT4, BL13, TF4 and AH6a; and one trial used PC6. Three (63, 67, 71) of the trials were for fatigue after chemotherapy and five (41, 42, 54, 57, 72) were cancer-related fatigue. Higher scores were considered worse in all these PROs. Four RCTs used PFS-R to measure fatigue, including two (63, 71) trials of chemotherapy-induced fatigue and two (42, 72) trials of cancer-related fatigue. After weeks of

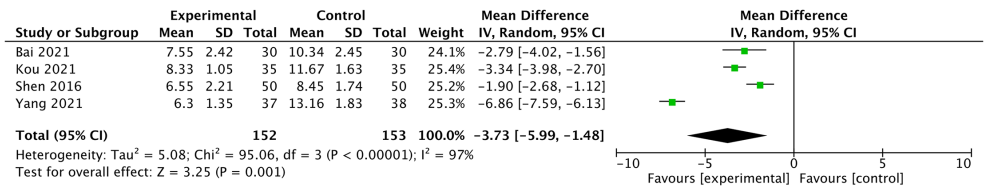


FIGURE 4
Forest plot of the sleep disturbances measured by Pittsburgh Sleep Quality Index in lung cancer patients treated with acupuncture and control.

intervention, the PFS score of the two groups was significantly lower than those before the intervention, and the decrease in the observation group was more significant than that in the control group for both chemotherapy-induced and cancer-related fatigue (MD -1.18, 95%CI, -1.93 to -0.43, P<0.00001, $I^2$ = 92%) (MD -0.94, 95%CI, -1.16 to -0.72, P = 0.34, $I^2$ = 0%) (Figure 5).

For FA measured by the FA score in EORTC QLQ-C30, Wang X et al. (41) and Wang LQ et al. (57) compared the FA scores of patients in the observation group after treatment with those in the control group; scores in the observation group were significantly lower than those in the control group (MD -12.81, 95%CI, -24.50 to -1.12, P=0.01, $I^2$ = 84%). There were two trials measured by BFI-C using continuous variables and dichotomous variables, respectively. Cheng et al. (54) showed that patients who received active acupuncture had significantly lower BFI-C scores compared to those who received placebo (MD -1.40, 95% CI, -1.62 to -1.18, P<0.00001). Liu (67) showed that the degree of fatigue in the observation group was significantly lower than that of the control group (RR 0.84, 95%CI, 0.73 to 0.97, P=0.02) (Table 5).

## Anxiety and depression

Two RCTs (45, 59) reported on anxiety and depression by patients and used two AD measures including SAS (45, 59) and SDS (45, 59). Among these two trials, BL13, TF4, AH6a, LI4, and ST36 were all used only once. Higher scores were considered worse in all these PROs. Shen et al. and Zhang et al. showed that compared with the control group, both SAS scores in the observation group were lower than those in the control group after treatment (MD -4.74, 95%CI, -6.66 to -2.82, P=0.51, $I^2$ = 0%) and so were SDS scores (MD -6.02, 95%CI, -8.11 to -3.94, P=0.58, $I^2$ = 0%) (Figure 6).

## Constipation

Only one RCT (41) reported on anxiety and depression by patients and used the CO score in EORTC QLQ-C30. This trial used acupoints including LI4, LR3, AT4, TF4, and AH6a. Higher scores were considered worse in all these PROs. Wang et al. showed that the CO score of patients in the study group after treatment was lower than that in the control group (Table 5).

## Side effect

Eight trials (42, 44, 46, 49, 50, 68, 70, 71) reported on side effects including dizziness, encephalalgia, fatigue, somnolence, gastrointestinal reaction, erythra, or respiratory depression. Three trials (46, 50, 71) reported no serious side effects in both groups. One trial (68) concluded that there were no serious side effects, but no data were available. Four trials reported that side effects in the observation group were lower than those in the control group and two (44, 70) of which had statistical significance (P<0.05), while the other two (42, 44) had no statistical significance (P>0.05). Since one patient could be associated with multiple side effects, and the author did not report in detail, the data were not convenient for statistics.

# Subgroup analysis

When we combined two secondary outcomes of pain, VAS and NRS, in the trials of cancer pain, the heterogeneity was up to 90%. Then, we compared the effects between subgroups according to the following methods: acupuncture technique, acupoint combination, frequency of treatment session, duration time, and TNM stage. The results are shown in Table 3.

Subgroup analysis showed that studies with all types of the methods above had significant effect on alleviating cancer pain. In

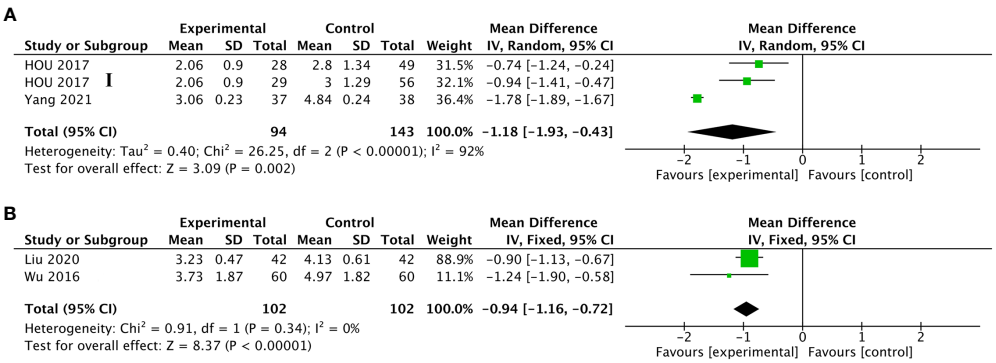


FIGURE 5
Forest plot of the fatigue in lung cancer patients treated with acupuncture and control. **(A)** The changes measured by the Revised Piper Fatigue Scale (PFS-R) in lung cancer patients undergoing chemotherapy treated with acupuncture-related intervention versus control from the baseline to the end of treatment; **(B)** the changes measured by PFS-R in lung cancer patients with cancer-related fatigue treated with acupuncture-related intervention versus control from the baseline to the end of treatment. IV, inverse variance; CI, confidence interval. The Roman numerals "I", followed by the study ID, represented the comparison of acupuncture versus no intervention in the study that had three arms.

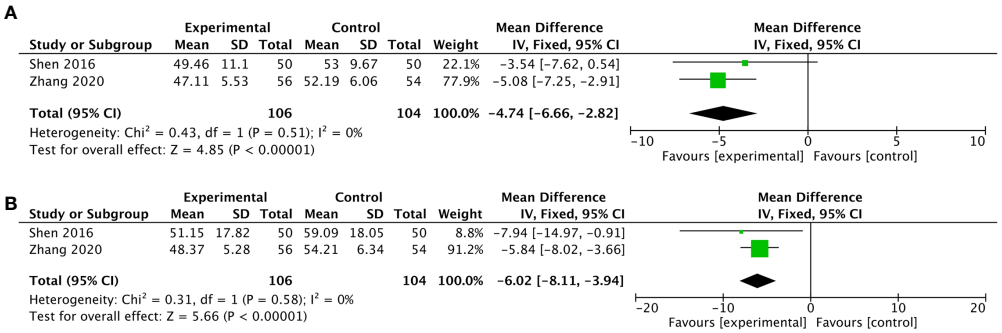


FIGURE 6
Forest plot of the fatigue in lung cancer patients treated with acupuncture and control. **(A)** the changes measured by the Self-Rating Anxiety Scale in lung cancer patients treated with acupuncture-related intervention versus control from the baseline to the end of treatment; **(B)** the changes measured by Self-Rating Depression Scale in lung cancer patients treated with acupuncture-related intervention versus control from the baseline to the end of treatment. IV, inverse variance; CI, confidence interval.

the analysis of acupuncture technique treatment, auricular acupoint treatment showed lower heterogeneity and increased effect size on reducing cancer pain (SMD -2.16, 95%CI, -2.70 to -1.62, P<0.00001, $I^2$ = 57%). In the analysis of the TNM stage, treatments in the studies of late stage showed significant improvement in patients with lung cancer–related pain and lower heterogeneity (SMD -2.07, 95%CI, -2.43 to -1.72, P<0.00001, $I^2$ = 34%). In the analysis of acupoint combination, studies showed a significant effect on cancer pain reduction but could not explain the heterogeneity (SMD -1.62, 95%CI, -2.37 to -0.51, P<0.00001, $I^2$ = 93%). In the analysis of the frequency of treatment session, studies showed no statistical difference at reducing cancer pain (SMD -1.37, 95%CI, -2.38 to

TABLE 3 Subgroup analysis of the combination of NRS and VAS in patients with cancer pain.

| Outcome | Subgroup | Participants | End of treatment | | |
|---|---|---|---|---|---|
| | | | IV, Random, 95% CI | P value | Heterogeneity ($I^2$) |
| **Pain** | **Acupuncture technique** | | | | |
| | Manual acupuncture (56) | 69 | MD -0.61 [-1.12, -0.10] | P=0.02 | / |
| | TEAS (59) | 100 | MD -2.12 [-2.55, -1.69] | P<0.00001 | / |
| | Auricular acupoints (42, 45) | 194 | SMD -2.16 [-2.70, -1.62] | P<0.00001 | $I^2$ = 57% |
| | **Acupoint combination** | | | | |
| | Cancer pain (42, 45, 56) | 263 | SMD -1.62 [-2.73, -0.51] | P<0.00001 | $I^2$ = 93% |
| | sSeep disturbances and cancer pain (59) | 100 | MD -2.12 [-2.55, -1.69] | P<0.00001 | / |
| | **Frequency of treatment session** | | | | |
| | 1/d (56, 59) | 169 | MD -1.37 [-2.38, 0.11] | P=0.07 | $I^2$ = 95% |
| | 2/d (45) | 110 | MD -0.91 [-1.05, -0.77] | P<0.00001 | / |
| | 6/d (42) | 84 | MD -1.08 [-1.32, -0.84] | P<0.00001 | / |
| | **Duration time** | | | | |
| | 3–5 min (42) | 84 | MD -1.08 [-1.32, -0.84] | P<0.00001 | / |
| | 20 min (56) | 69 | MD -0.61 [-1.12, -0.10] | P=0.02 | / |
| | 30 min (59) | 100 | MD -2.12 [-2.55, -1.69] | P<0.00001 | / |
| | Not mentioned (45) | 110 | MD -2.43 [-2.93, -1.94] | P<0.00001 | / |
| | **TNM stage** | | | | |
| | Late stage (42, 45, 59) | 294 | SMD -2.07 [-2.43, -1.72] | P<0.00001 | $I^2$ = 34% |
| | Middle and late stage (56) | 69 | MD -0.61 [-1.12, -0.10] | P=0.02 | / |

TNM, tumor–node–metastasis.

TABLE 4 The effect of acupuncture on the QOL compared to different comparators.

| Outcome | Participants | End of treatment | | | Meaning of higher scores |
|---|---|---|---|---|---|
| | | IV, Random or Fixed, 95% CI | M-H, Fixed, 95% CI | P-value | |
| **1. Acupuncture vs. WM/TCM** | | | | | |
| KPS (42, 45, 48–50, 53, 65, 66, 69) | 792 | MD 6.88 [5.88, 7.89] | | P<0.00001 | better |
| KPS (46, 64) | 222 | | RR 1.26 [1.10, 1.44] | P=0.001 | better |
| SF-36 (58) | 100 | MD 10.36 [6.17, 14.55] | | P<0.00001 | better |
| FACT-L (65) | 60 | MD 8.76 [2.05, 15.47] | | P=0.01 | better |
| LCQ (50) | 120 | MD 20.21 [15.61, 24.81] | | P<0.00001 | better |
| **2. Acupuncture vs. placebo** | | | | | |
| FACT-LCS (54) | 28 | MD 5.80 [4.63, 6.97] | | P<0.00001 | better |
| **3. Acupuncture vs. usual care** | | | | | |
| KPS (47, 61) | 208 | MD 5.93 [3.43, 8.44] | | P<0.00001 | better |
| FACT-L (61) | 120 | MD 3.64 [0.32, 6.96] | | P=0.03 | better |
| EORTC QLQ-C30* (41, 57) | 214 | MD 10.68 [4.56, 16.81] | | P=0.0006 | better |
| SGRQ (68) | 60 | MD -31.69 [-36.58, -26.80] | | P<0.00001 | worse |

*Random-effect model was used for the high heterogeneity ($I^2$>50%). QOL, quality of life; KPS, Karnofsky Performance Status; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-LCS, the Functional Assessment of Cancer Therapy Lung Cancer Subscale; SF-36, the MOS item short form health survey; LCQ, Leicester Cough Questionnaire; FACT-L, Functional Assessment of Cancer Therapy–Lung; WM, Western medicine; TCM, traditional Chinese medicine; SGRQ, St George's Respiratory Questionnaire.

0.11, P = 0.07, $I^2$ = 95%). In the analysis of duration time, because of the different duration time of all four studies, heterogeneity could not be explained.

After further subgroup analysis, we found that Fan LY et al. (56) was the main source of heterogeneity. This trial was focused on the effect of manual acupuncture in improving patients with lung cancer–related pain at middle and late stage; therefore, the most difference between it and other trials lied in the different TNM stage. Additionally, we performed another subgroup analyses of all the outcomes based on the different control strategies used, and the results are shown in Tables 4 and 5.

## Sensitivity analysis

In order to explore the stability of the results and the sources of heterogeneity in our meta-analysis, we pooled all studies for sensitivity analysis by excluding each study individually.

In terms of the cancer pain measured by the combination of VAS and NRS, there were significant changes in the outputs after excluding each study. After removing the study conducted by Fan LY et al. (56), the heterogeneity was significantly reduced and the result did not alter (SMD -2.07, 95%CI, -2.43 to -1.72, P<0.00001, $I^2$ = 34%). In terms of the postoperative pain measured by the combination of VAS and NRS, the heterogeneity did not alter but the result changed to statistically significant after removing the study of Randolph et al. (60) (SMD -1.49, 95%CI, -2.98 to -0.01, P<0.05, $I^2$ = 94%). After removing the study of Chen et al. (62), the heterogeneity decreased from 92% to 60% but with no statistical significance.

In terms of the sleep disturbances measured by PSQI, the heterogeneity decreased from 97% to 74% after removing the study of Yang H et al. (71).

In terms of the fatigue measured by PFS, after removing the study of Yang H et al. (71), the heterogeneity was significantly reduced to 0% and the result did not alter (MD -0.91, 95%CI, -1.10 to -0.73, P = 0.70, $I^2$ = 0%).

## Meta regression

We used meta regression analysis to clarify the sources and value of heterogeneity, and to further explain the influence of variables on the combined effect. We explored heterogeneity by taking acupuncture technique, course of treatment, frequency of treatment, year of publication, country of publication, duration time, TNM stage as variables. The results showed that the duration time in the sleep disturbances measured by PSQI was the main source of heterogeneity (p=0.017) and the other results showed that the variables were insignificant under meta regression (p>0.05). Supplementary Tables 5–8 in the Supplementary Material.

## Publication bias

The funnel plot of 11 trials measured by KPS of the primary outcome QOL showed approximate symmetry (Figure 7). Because of the limited number of trials included for the remaining comparison measured by other PROs in the meta-analysis, funnel plots were not feasible. Therefore, we could not fully evaluate publication bias.

TABLE 5 The effect of acupuncture on the secondary outcomes compared to different comparators.

| Outcome | Participants | End of treatment | | | Meaning of higher scores |
|---|---|---|---|---|---|
| | | IV, Random, 95% CI | M-H, Fixed, 95% CI | P-value | |
| **1. Acupuncture vs. WM/TCM** | | | | | |
| 1.1 Pain | | | | | |
| NRS (56, 58, 59, 70) | 329 | | RR 0.47 [0.29, 0.75] | P=0.001 | worse |
| NRS + VAS (42, 45, 56, 58, 59, 69, 70) | 435 | SMD -1.16 [-1.55, -0.76] | | P<0.00001 | worse |
| 1.2 Nausea and vomiting | | | | | |
| MAT (51) | 160 | | RR 0.59 [0.41, 0.86] | P=0.006 | worse |
| INVR (55) | 96 | MD -1.18 [-1.89, -0.47] | | P=0.001 | worse |
| 1.3 Insomnia | | | | | |
| PSQI (43, 52, 59, 73) | 346 | MD -2.68 [-3.49, -1.86] | | P<0.00001 | worse |
| 1.4 Fatigue | | | | | |
| PFS-R (42, 63) | 246 | MD -0.88 [-1.08, -0.69] | | P<0.00001 | worse |
| 1.5 Anxiety and depression | | | | | |
| SAS (45, 59) | 210 | MD -4.74 [-6.66, -2.82] | | P<0.00001 | worse |
| SDS (45, 59) | 210 | MD -6.02 [-8.11, -3.94] | | P<0.00001 | worse |
| **2. Acupuncture vs. placebo** | | | | | |
| 1.1 Fatigue | | | | | |
| BFI-C (54) | 28 | MD -1.40 [-1.62, -1.18] | | P<0.00001 | worse |
| **3. Acupuncture vs. sham acupuncture** | | | | | |
| 1.1 Pain | | | | | |
| VAS (60, 62) | 105 | MD -1.08 [-1.87, -0.29 | | P=0.007 | worse |
| **2. Acupuncture vs. usual care** | | | | | |
| 1.1 Pain | | | | | |
| QLQ-C30 PA (41, 57) | 214 | MD -3.90 [-9.33, 1.54] | | P=0.16 | worse |
| BPI (41) | 118 | MD -3.22 [-3.66, -2.78] | | P<0.00001 | worse |
| 1.2 Nausea and vomiting | | | | | |
| QLQ-C30 NV (41, 57) | 214 | MD -14.73 [-23.88, -5.59] | | P=0.002 | worse |
| 1.3 Insomnia | | | | | |
| PSQI (71) | 75 | MD -6.86 [-7.59, -6.13] | | P<0.00001 | worse |
| AIS (44) | 60 | MD -0.17 [-1.93, 1.59] | | P=0.85 | worse |
| QLQ-C30 SL (41) | 118 | MD -14.16 [-20.91, -7.41] | | P<0.00001 | worse |
| 1.4 Fatigue | | | | | |
| BFI-C (67) | 105 | | RR 0.84 [0.73, 0.97] | P=0.02 | worse |
| PFS-R (71, 72) | 195 | MD -1.61 [-2.10, -1.12] | | P<0.00001 | worse |
| 1.5 Constipation | | | | | |
| QLQ-C30 CO (41) | 118 | MD -12.70 [-19.52, -5.88] | | P=0.0003 | worse |

QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; NRS, Numerical Rating Scale; VAS, Visual Analog Scale; BPI-C, Brief Pain Inventory–Chinese Version; MAT, MASCC (Multinational Association of Supportive Care in Cancer) Antiemesis Tool; INVR, Index of Nausea and Vomiting and Retching; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; AIS, Athens Insomnia Scale; PSQI, Pittsburgh Sleep Quality Index; BFI-C, Brief Fatigue Inventory–Chinese Version; PFS-R, The Revised Piper Fatigue Scale; WM, Western medicine; TCM, traditional Chinese medicine.

# Discussion

## Interpretation of the results

This study, including 33 RCTs, showed that acupuncture had a marked beneficial effect on improving PROs in different dimensions and different cancer stages or conditions. Compared with control groups such as usual care and pharmacotherapy, using acupuncture alone or in combination with other treatments can effectively relieve PROs, including postoperative chronic pain, and reduce anxiety and depression, so as to improve their QOL, which has a certain clinical application value.

Among 33 trials, 15 trials used ST36, and 7 trials used BL13, LI4, and PC6. One trial used only one acupoint (ST36) and five trials used two acupoints, showing significant efficacy in patients with lung cancer. It followed that ST36 can tonify qi and/or blood deficiency, increases stamina and energy, and it is the most

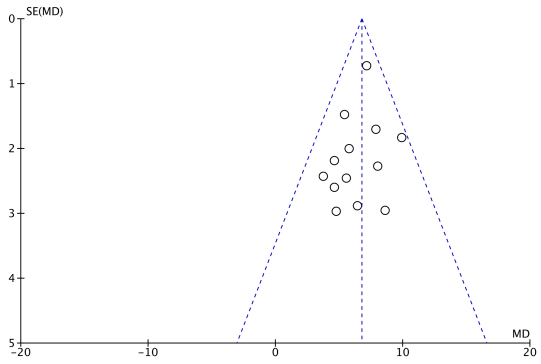


FIGURE 7
The funnel plot of quality of life measured by the Karnofsky Performance Status in lung cancer patients treated with acupuncture and control.

important point to promote general wellness. Auricular acupoints were used in 7 of the 33 trials, among which TF4 was used in 6 trials, AT4 was used in 5 trials, and AH6a was used in 4 trials. It suggested that AT4 was a reference point for the diagnosis of nervous system diseases, tumors, insomnia, lethargy, and other diseases, which was of great importance for the diagnosis of malignant tumors (75). We also divided 33 trials into 4 different types to observe the commonness of acupoint selection. Of all five surgery-related trials, three used LI4 and two used ST36, SP6, and SP10. Of all 12 chemotherapy-related trials, 8 used ST36 and 4 used RN12 and PC6. One radiotherapy-related trial used auricular acupoints. The remaining trials were about lung cancer itself, and six of them used BL13 and five used LI4 and ST36. Thus, ST36 was useful in all types of trials except for the radiotherapy trials because of the selection of auricular acupoints. This study also provides a reference for the selection of effective acupoints for remedying various disorders in the PRO outcome of lung cancer patients, including the QOL, pain, nausea and vomiting, sleep disturbances, fatigue, anxiety and depression, constipation, and side effect. For example, sleep disturbance is a prominent concern in lung cancer patients, which is linked to worse prognosis and a poorer QOL (76, 77). In our study, the following acupoints were selected for sleep disorders in these trails: TF4, AT4, ST36, AH6a, LI4, BL13. However, one study found that the top 10 most frequently selected acupoints for sleep disorders were HT7, SP6, PC6, KI1, GV20, EM5, EX-HN3, EX-HN16, KI3, and MA-TF1 and also suggested that the acupoints of EX-HN3, EX-HN16, GV20 integrated with HT7, KI1, PC6 are the kernel acupoint combination in the field of acupuncture therapies for sleep disorders based on an association rule analysis (78). These acupoints are completely inconsistent with our findings. The selection of acupoints during treatment is one of the main factors affecting the efficacy of acupuncture treatment. Thus, according to the different dimensions of the QOL of lung cancer patients, optimizing and screening acupoints should be the focus of future studies.

Among 33 trials, only five trials involved follow-up, and the longest one lasted only a month. The sustained and long-term effect of acupuncture on the RPOs of patients with lung cancer is unknown since most included trials ranged in duration from 4 to 8 weeks.

Eight trials reported side effects but did not state in detail whether they were caused by acupuncture or chemotherapy. However, all the trials reported that the side effects of involved acupuncture groups were lower than those of the control group. This indicated that conventional Western medicine combined with acupuncture had the advantage of reducing toxicity and increasing effects in the treatment of lung cancer, reflecting the advantages of acupuncture in lung cancer such as safety, effectiveness, urgency, acceptability, and applicability.

Eighteen trials were about the treatment of chemotherapy-induced lung cancer-related symptoms by acupuncture, and five were about postoperative. It shows that acupuncture has more opportunities to be used in the above two situations, reflecting the advantages of acupuncture. The results showed that the scores with PROs of acupuncture on patients were also higher than that of the control group, indicating that acupuncture had a significant effect on both the QOL and other patients' self-conscious symptoms. Acupuncture could improve the PRO of lung cancer patients at different TNM stages and under different treatments of disease.

## Exploration of heterogeneity from the patient-reported outcomes

Among the 33 included RCTs, the heterogeneity obtained by approximately half of the trials was low, which meant maybe unimportant (less than 40% according to the Cochrane Handbook for Systematic Reviews of Interventions), while obvious heterogeneity was shown in several results of meta. Among them, heterogeneity 58% and 81% was derived from two secondary outcomes in pain and insomnia. The reason for the high heterogeneity of these two groups of data after the combination was that we highly suspected the existence of problems in the original data from the same trial (57). Wang LQ et al. (57) stated in the study that two secondary outcomes QLQ-C30 NV and FA in the observation group were significantly decreased compared with the control group ($P<0.05$), but the data showed totally opposite results that the scores of the observation group were dramatically higher than the control group (higher scores were considered worse in these two PROs). Judging from the data, the quality of this study is debatable and should be removed. However, the primary

outcome in this study was the QOL of patients with the QLQ-C30, so we chose to retain the data in this study.

Heterogeneity 90% and 92% came from the cancer pain and postoperative pain measured by the combination of VAS and NRS. After subgroup and sensitivity analysis, we found the heterogeneity based on Fan LY et al. (56) in the patients of cancer pain. This may be due to the different TNM stage of patients in this trial compared with others. However, among patients of postoperative pain, Randolph et al. (60) stated that there was a trend for lower average VAS pain scores from postoperative day 2 to day 6 in the EA group, but this did not reach statistical significance. This is most likely secondary to the error from the small sample size. When we removed the study of Chen et al., the heterogeneity decreased to 60%. The major difference between this group was that patients in this trial received TEAS for 30 min before anesthetic induction and continuous stimulation throughout the whole surgical procedure.

Heterogeneity 97% from PSQI was based on Yang H et al. (71) and Kou XW et al. (52). Heterogeneity 94% from PFS was based on the same trial, Yang H et al. (71). After meta regression, we found that the duration time in the sleep disturbances measured by PSQI was the main source of heterogeneity (p=0.017), and the heterogeneity decreased from 97% to 30% after removing these two studies. The remaining two trials (59, 73) had the same duration time of treatment due to their similar interventions, which was treated by warm acupuncture and EA. Therefore, the heterogeneity was lower compared with the other two trials using thunder-fire moxibustion and acupoint application, respectively. The male patients included in Yang H et al. (71) accounted for 81.3%, which was the four times the number of women. Moreover, the majority of patients are in the stage of I and II, which may lead to the better effect of treatment. The most significant difference was evidenced by the type of the intervention, which was the only one among the 33 included trials that used thunder-fire moxibustion as the observation group for treatment in lung cancer chemotherapy patients. A study showed that thunder-fire moxibustion has anti-inflammatory effects (79). Currently, the mechanism of cancer-related fatigue is the inflammatory hypothesis that has attracted the most attention of scholars (80). The authors suggested that thunder-fire moxibustion could relieve the fatigue symptom and improve the QOL of lung cancer patients.

We combined the trials of QOL in the different TNM stages or different stages of disease and in different comparators including WM/TCM, usual care, and placebo. The results showed that the heterogeneity was low and even no heterogeneity. After subgroup and sensitivity analysis, we found that heterogeneity varied within a small range, which did not influence the stability of results. We analyzed the possible reasons as follows: first, we strictly formulated the inclusion and exclusion criteria, so the included articles were of high homogeneity; second, this represented no statistical heterogeneity, which may exist in clinical and methodological heterogeneity; third, there were still individual differences in patients' stages of disease.

## Risk of bias

First, for selection bias. 29 of the 33 RCTS included in this study did not mention allocation concealment. During the treatment, due to the particularity of acupuncture, it is obviously impractical and difficult to blind the experimenter as well as the patients. However, for efficacy assessors and statistical analysts, blinding can be performed to minimize possible detection bias, and no one except four studies took this factor into account. Furthermore, some PROs such as the QOL instruments are often used as non-primary outcomes in studies; authors often do not present detailed numerical or exact results (as mentioned above) or even only provide bar chart results without extracting specific numbers for statistics, which may lead to publication bias.

## Clinical implications

In this study, different acupuncture interventions were used as study objects for evaluation, and it was found that manual acupuncture, acupoint application, and auricular point were most frequently used in clinical practice. Acupoint application and the auricular point had good curative effects and, meanwhile, could be treated anytime and anywhere, which was worthy of clinical application and promotion.

The advantage of our study is that we only focused on PROs with lung cancer patients, while other studies used scales that were not PROs or not just PROs to assess the treating effects of lung cancer such as the index of immunomodulation. Compared with other studies of the same type, we not only paid attention to the change of QOL with lung cancer patients by acupuncture but also to the change of lung cancer–related symptoms, which made the results more comprehensive and effective.

In addition, some trials were of poor quality and were not reported according to the reporting specifications of CONSORT (81). For instance, the lack of follow-up of PROs and side effect reports of patients were not conducive to the judgment of the QOL of lung cancer patients. We believed that the long-term follow-up of patients to assess their subsequent PRO is clinically significant. We suggested that we should pay more attention to PROs clinically in order to judge the most real situation of the patient fully and comprehensively. Moreover, the lack of research reports on the qualifications of acupuncturists indicates a lack of attention to them. Randomized controlled trials have proven that acupuncturists with different

qualifications have different therapeutic effects on acupuncture (82), so we suggest that studies at home and abroad should focus on relevant information reports.

Research on acupuncture for cancer pain has been proven. Acupuncture and/or acupressure were significantly associated with reduced pain in cancer patients compared with sham surgery controls, according to a study published in JAMA Oncology (83). In other words, acupuncture is effective in reducing cancer pain and the use of opioid painkillers. With the improvement of early screening technology and treatment of lung cancer, the survival rate of lung cancer patients will be improved, and the advantages of acupuncture in early lung cancer as well as in surgery, radiotherapy and chemotherapy, immunotherapy, and other situations will be increasingly obvious. Additionally, the synergistic optimization effect of acupuncture and targeted therapy needs further research in the future.

On this basis, the pursuit of the treatment concept of prolonging the life of lung cancer patients and constantly improving the QOL of patients with lung cancer has become the research direction of more and more researchers. In this study, we evaluated the evidence from published RCTs and found that acupuncture for lung cancer and its treatment-related symptoms has the advantages of high acceptability and safety, as well as good effects on PROs with lung cancer patients. Among the main outcome measures included in this study, the most frequently used scales were KPS, QLQ-C30, and FACT-L. We hope to popularize the PRO-scale clinical trials of acupuncture for LC in the future in order to focus on the effect of acupuncture in patients with lung cancer on their PROs, mainly in the aspect of QOL.

### Limitation of evidence

Considering that various designs and techniques of acupuncture were included in this study, there is a potential risk of heterogeneity in the results. A total of 15 different interventions were included in this study, including a combination of two or three acupuncture-related interventions or just one intervention. Different experimental interventions are different in the frequency and cycle of treatment. For the same interventions, there are slight differences in therapeutic efficacy due to different acupuncturists. Second, since a rigorous search and screening strategy was used to obtain available studies, the sample size of the included studies was not particularly large. Controversial academic dissertations that have not been peer-reviewed, as well as trials that have been found to reuse data during data extraction, were excluded, resulting in only 27 trials in Chinese and 6 trials in English. Due to the inclusion of trials, which were mostly published in Asia, there are bias and limited generalizability of the conclusions to some extent. Additionally, due to the limited sample size included and the low quality of the original study, Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was not used to construct the system of evidence. Furthermore, considering that acupuncture may be applied to the various stages of lung cancer and situations, we did not restrict the inclusion of specific population conditions. The age of the population we included was concentrated around 50 years old and was not representative of all adults, especially the elderly, which was mainly limited by the age of the population in the original studies and the epidemiological characteristics of lung cancer.

## Conclusion

Our study indicates that acupuncture therapies is a promising intervention in promoting PROs in lung cancer patients with all stages and regardless of postsurgery or postchemotherapy. Acupuncture should be recommended as a beneficial alternative strategy for lung cancer patients on clinic. High-quality, large-sample, multicenter original RCTs of acupuncture that focus on PROs are needed in the future.

## 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

KW and JZ conceived and designed the study. KW, XW, and ZX searched the databases and screened the articles. ZX, XW, and ZY were involved in data extraction and the assessment of methodological quality. ZX and XW analyzed the data. All the authors contributed to the composition of the manuscript. All the authors have checked manuscripts and approved the publication of the study.

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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.2022.921151/full#supplementary-material

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# Recent and current advances in PET/CT imaging in the field of predicting epidermal growth factor receptor mutations in non-small cell lung cancer

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Tyrosine kinase inhibitors (TKIs) are a significant treatment strategy for the management of non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation status. Currently, EGFR mutation status is established based on tumor tissue acquired by biopsy or resection, so there is a compelling need to develop non-invasive, rapid, and accurate gene mutation detection methods. Non-invasive molecular imaging, such as positron emission tomography/computed tomography (PET/CT), has been widely applied to obtain the tumor molecular and genomic features for NSCLC treatment. Recent studies have shown that PET/CT can precisely quantify EGFR mutation status in NSCLC patients for precision therapy. This review article discusses PET/CT advances in predicting EGFR mutation status in NSCLC and their clinical usefulness.

KEYWORDS

**PET/CT, prediction model, epidermal growth factor receptor, non-small cell lung cancer, radiogenomics**

## 1 Introduction

Lung cancer has the highest incidence and mortality worldwide (1), with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancer cases and adenocarcinoma (ADC) being the most prevalent pathological type (2). The emergence of targeted therapy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) paradigms has radically changed advanced NSCLC treatment and improved

patient survival rates, especially for advanced lung adenocarcinoma (3). Accurate and rapid quantification of EGFR mutation status in NSCLC patients is crucial to selecting the most effective management strategy for individualized therapy and precision medicine to improve patient prognosis.

The gold standard assessment of EGFR mutation status is based on tumor tissue acquired by fine-needle aspiration, biopsy, or resection (4). However, acquiring a representative biopsy is not necessarily feasible with inherent limitations, including sampling bias due to the intratumoral heterogeneous tissue samples that are not readily available, and the invasive methods have low repeatability, may cause patient discomfort, and are time-consuming and costly, with inadequate samples or poor-quality tissue samples leading to inconclusive results (5). Despite liquid biopsy's convenience, rapidity, and affordability, its sensitivity and stability are not ideal (6). Therefore, it is critical to develop a high-throughput and ideally non-invasive longitudinal method for EGFR mutation detection in NSCLC.

Image-based phenotyping is a promising clinical method for precision medicine, as it provides a non-invasive approach to visualizing tumor phenotypic characteristics (7). CT imaging combined with clinical characteristics has been systematically analyzed to predict EGFR mutations in NSCLC (8), with positron emission tomography/computed tomography (PET/CT) now widely applied to assess NSCLC patients undergoing targeted treatment. PET images capture the molecular tumor phenotypes indicating somatic mutations (9); thus, there is increasing interest in whether PET/CT can predict EGFR mutation status in NSCLC patients to develop individualized treatment. This review article discusses PET/CT advances in predicting EGFR mutation status in NSCLC and their clinical usefulness.

## 2 Association of $^{18}$F-FDG uptake PET/CT with epidermal growth factor receptor mutation status in non-small cell lung cancer

The EGFR signaling pathway maintains aerobic glycolysis in EGFR-mutated lung cancer cells, and EGFR TKIs have an early and profound influence on aerobic glycolysis, as they activate and promote increased oxidative phosphorylation (10), consequently indicating that EGFR mutation status is closely related to glucose metabolism in lung cancer cells. $^{18}$F-FDG PET/CT is increasingly used for cancer diagnosis and image-guided therapy, as it can characterize tumor cell proliferation and glucose metabolism. Accordingly, $^{18}$F-FDG metabolic parameters, for instance, maximum standardized uptake value (SUVmax), total lesion glycolysis (TLG), and metabolic tumor volume (MTV) may, in part, reflect EGFR mutation status in NSCLC. Numerous studies have assessed the association between $^{18}$F-FDG uptake and EGFR mutation status in NSCLC (Figure 1) but have conflicting results (Table 1).

Na et al. evaluated the relationship between the EGFR mutation status and the SUVmax of $^{18}$F-FDG uptake by reviewing 100 patients with NSCLC (11), reporting that patients with a low SUVmax were more likely to have an EGFR mutation as compared to patients with a high SUVmax. Mak et al. (12) assessed 100 patients with NSCLC (24 EGFR mutants and 76 wild types), demonstrating that high FDG uptake in the primary tumor is related to a very low risk of an EGFR mutation. Subsequently, increasing evidence demonstrated that EGFR mutation status is associated with a lower SUVmax in NSCLC (9, 13). Chen et al. (14) showed that patients with an *EGFR* mutation showed decreased SUVmax values and subsequently reported that decreased FDG uptake associated with EGFR mutation status was *via* NOX4/ROS/GLUT1 axis. Yang et al. (15) analyzed 200 patients with lung adenocarcinoma, demonstrating that MTV of wild-type and mutant *EGFR* was significantly different. Furthermore, a study by Liao et al. (16) demonstrated that low primary MTV (pMTV) (<8.13 cm) was a strong and independent predictor and could be combined with female sex and gastrin-releasing peptide levels (proGRP, ≥38.44 pg/ml) to determine EGFR mutation status. In addition, decreased FDG uptake was shown to be a significant predictor of *EGFR* mutation status (17–22). Interestingly, EGFR mutation status was reported to be associated with a higher SUVmax (23, 24). Ko et al. (23) demonstrated a tendency of higher SUVmax in NSCLC patients with an EGFR mutation, and higher SUVmax could be combined with never smoking, carcinoma embryonic antigen (CEA) level, and a non-spiculated tumor margin to obtain a higher area under the receiver operating characteristic (ROC) curve for EGFR mutation status. A similar conclusion was reached by Kanmaz et al. (24).

However, multiple studies have shown no association between $^{18}$F-FDG uptake and EGFR mutation status. Chung et al. found no significant differences in $^{18}$F-FDG PET/CT parameters (SUVmax, MTV, and TLG) of EGFR mutation-positive and mutation-negative lung adenocarcinoma cases (25). Other studies confirmed that $^{18}$F-FDG metabolic parameters of PET/CT in NSCLC had no significant clinical value in predicting EGFR mutation status (26–29). The low diagnostic OR and the likelihood ratio scatter plot indicated that $^{18}$F-FDG PET/CT might be useless for predicting EGFR mutation status in NSCLC as indicated by a meta-analysis of Du et al. (30). According to a recent meta-analysis (31), SUVmax of the primary tumor had a moderate predictive value for EGFR mutation status in NSCLC. Due to this dispute, further high-quality studies are required to explore the predictive value of EGFR mutation status in NSCLC.

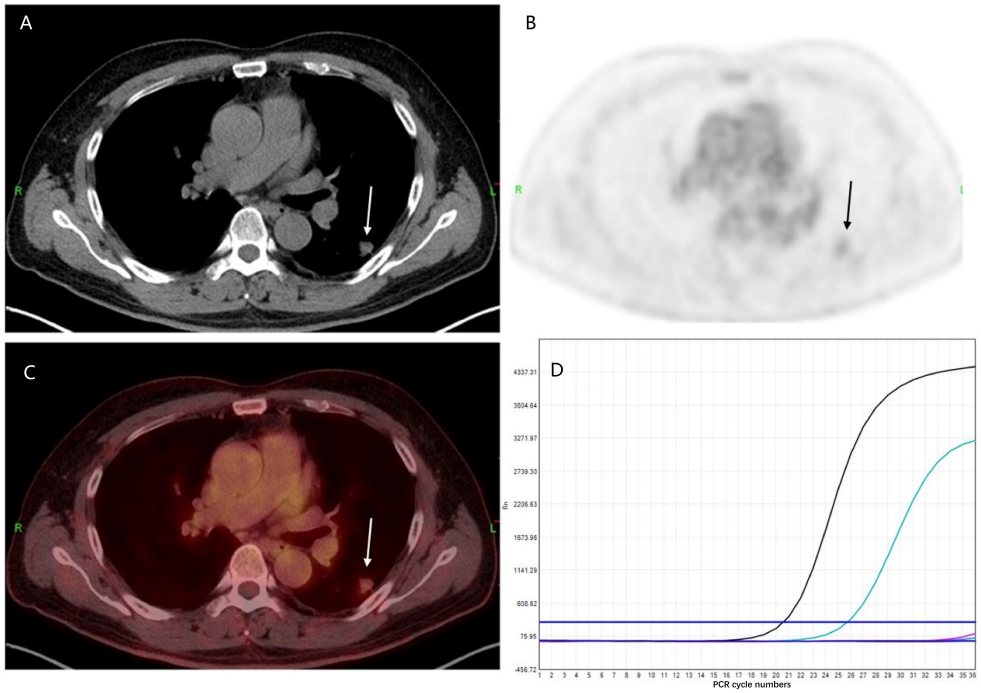


FIGURE 1
Representative epidermal growth factor receptor (EGFR) status and $^{18}$F-FDG PET/CT finding. A 53-year-old man with EGFR wild-type lung adenocarcinoma. **(A)** CT, **(B)** PET, and **(C)** PET/CT fusion images show a 1.0-cm-sized mild $^{18}$F-FDG uptake mass in the dorsal segment of the left lower lobe (SUVmax = 2.3) (arrow). **(D)** Genetic testing demonstrates wild-type EGFR status.

## 3 Predictive value of $^{18}$F-FDG PET/CT-derived radiomics with epidermal growth factor receptor mutation status in non-small cell lung cancer

Radiomics texture is an emerging field of interest in medical imaging and is a high-throughput and quantitative extraction of imaging features based on a computational approach (32). The rapid advance of emerging radiomics analysis could help discriminate the disease type, predict survival, and monitor the response to therapy using large datasets and artificial intelligence techniques (33). Radiomics also has various logistic advantages, for instance, offering nearly real-time results and being non-invasive (34). Additionally, compared with standard biopsy, radiomics can provide a comprehensive analysis of one lesion and multiple lesions within the examined area (35). The growing applications of $^{18}$F-FDG PET/CT radiomics have therefore attracted extensive interest in recent years, especially in lung cancer (36). The radiomics analysis of $^{18}$F-FDG PET/CT data comprises five steps: 1) data acquisition, 2) image segmentation, 3) feature extraction, 4) feature selection, and 5) model construction (Figure 2). Indeed, $^{18}$F-FDG PET/CT radiomics estimates of the tumor imaging phenotype extracted from PET/CT images facilitate the management of lung cancer, including differential diagnosis of benign/malignant solitary pulmonary nodules, NSCLC subtypes, lymph node metastasis, and distant metastases, as well as response evaluation and survival prediction (34, 37, 38). Increasing studies have confirmed the feasibility and potential superiority of $^{18}$F-FDG PET/CT radiomics to predict EGFR mutation status in NSCLC (Table 2).

To our knowledge, studies demonstrating the relationship between $^{18}$F-FDG PET/CT imaging textures and EGFR mutation status are limited. However, they have proved that prediction models based on $^{18}$F-FDG PET/CT imaging features can help differentiate EGFR mutation status in NSCLC, which is crucial in clinical practice to identify candidates for targeted therapy (39–44). Yang et al. (45) used $^{18}$F-FDG PET/CT-based radiomics features integrated with clinical features and $^{18}$F-FDG PET/CT metabolic parameters (MTV, TLG, SUVmax, and SUVmean) of 174 lung adenocarcinoma patients to establish prediction models and achieved an area under the curve (AUC) of 0.71–0.77. Shiri et al. (46), Zhang et al. (47), and Zhang et al. (48) reached a similar conclusion.

Li et al. (49) showed that radiomics signatures derived from $^{18}$F-FDG PET/CT images were significantly more predictive of EGFR mutations than those derived from CT or conventional

TABLE 1 Recent publications about the association of $^{18}$F-FDG metabolic parameters of PET/CT with epidermal growth factor receptor mutation status in non-small cell lung cancer.

| Authors | No. of patients | Aspect evaluated | Main results |
|---|---|---|---|
| Na et al. | 100 | SUVmax | A low SUVmax were more likely to possess EGFR mutation compared with patients with a high SUVmax. |
| Mak et al. | 100 | SUVmax | High FDG avidity in the primary tumor was associated with a very low chance of harboring an EGFR mutation. |
| Usuda et al. | 148 | CT imaging features and SUVmax | The EGFR mutation was significantly associated with pure or mixed GGO, lower SUVmax, and smaller tumor diameter. |
| Qiang et al. | 97 | SUVmax | Lower SUVmax was significantly correlated with the EGFR mutation group. |
| Guan et al. | 360 | SUVmax | Lower SUVmax values (SUVmax ≤ 8.1) were significantly associated with EGFR mutations. |
| Chen et al. | 157 | SUVmax | The SUVmax values were significantly lower in patients with EGFR mutations compared with patients with wild-type EGFR. |
| Takamochi et al. | 734 | SUVmax | EGFR mutations were more frequent in tumors with lower SUVmax. |
| Lv et al. | 849 | pSUVmax, nSUVmax, and mSUVmax | Low pSUVmax, nSUVmax, and mSUVmax were significantly associated with EGFR mutations. |
| Gu et al. | 210 | CEA, CT imaging features, and SUVmax | Higher CEA levels (CEA ≥ 7.0 ng/ml) and lower SUVmax (SUVmax < 9.0) were significant predictors of EGFR mutations. |
| Zhu et al. | 139 | SUVmax, SUVmean, SUVpeak, and SUVratio | SUVmax, SUVmean, SUVpeak, and SUVratio were lower in EGFR-mutated than in wild-type tumors. |
| Ko et al. | 132 | CEA, CT imaging features, and SUVmax | High SUVmax, CEA levels, and a non-spiculated tumor margin were independent predictors of the EGFR mutation. |
| Kanmaz et al. | 218 | TTF-1 and SUVmax | High SUVmax was positively correlated with EGFR mutation. |
| Caicedo et a | 102 | SUVpeak, SUVmax, and SUVmean | No significant differences were observed in $^{18}$F-FDG uptake between EGFR-mutated and EGFR wild type. |
| Lee S M et al. | 206 | SUVmax | $^{18}$F-FDG avidity of NSCLC had no significant clinical value in predicting EGFR status. |
| Lee E Y et al. | 71 | pSUVmax, mSUVmax, and dSUVmax | No statistically significant difference was observed in SUVmax of the primary tumors and EGFR mutation status. |
| Du et al. | 3574 | SUVmax | SUVmax has low sensitivity and specificity in predicting EGFR mutations. |
| Guo et al. | 4024 | SUVmax, SUVmean | SUVmax and SUVmean had pooled sensitivity and specificity to predict EGFR mutation status. |
| Chung et al. | 106 | SUVmax, MTV, and TLG | No significant differences were found in FDG PET/CT parameters for EGFR mutation-negative and EGFR mutation-positive patients. |
| Cho et a | 61 | SUVmax, MTV, and TLG | SUVmax and TLG were significantly lower with EGFR mutation-positive lesions compared with EGFR wild type. |
| Liu et al. | 82 | SUVmax, MTV, TLG, clinicopathologic | Lower MTV combined with non-smokers and a peripheral tumor location were more likely to have EGFR mutations. |
| Yang et al. | 200 | SUVmax, SUVmean, MTV, and TLG | MTV demonstrated a significant difference between wild-type and mutant *EGFR* mutation status. |
| Liao et al. | 191 | SUVmax, MTV, TLG, CA199, and proGRP | Low MTV, proGRP, and female sex were independent significant predictors for EGFR mutation. |

NSCLC, non-small cell lung cancer; SUV, standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; CT, computed tomography; EGFR, epidermal growth factor receptor; TTF-1, thyroid transcription factor 1; CA199, carbohydrate antigen 199; proGRP, recombinant pro-Gastrin releasing peptide.

PET images. In addition, a recent study found that PET/CT radiomics model has a better capability (AUC = 0.76) to predict EGFR mutation status than the PET radiomics model (AUC = 0.71) and the CT radiomics model (AUC = 0.74) in NSCLC (50). A meta-analysis by Abdurixiti et al. (51) revealed that PET/CT-based radiomics signatures could be used as a diagnostic index for EGFR mutation status in patients with NSCLC.

The reachable results in the literature are definitely promising; $^{18}$F-FDG PET/CT-based radiomics has the potential to replace classic approaches based on biopsy and histopathology to detect EGFR mutation status in NSCLC. However, the results should be interpreted with caution, as there is a lack of reproducibility and a basic deficiency of normalization methods and settings (52), so further studies are essential to establish a consistent approach. Furthermore, a high-quality predictive model depends on a large amount of data, so additional studies involving larger multicenter cohorts will be needed to develop this method into a clinical tool.

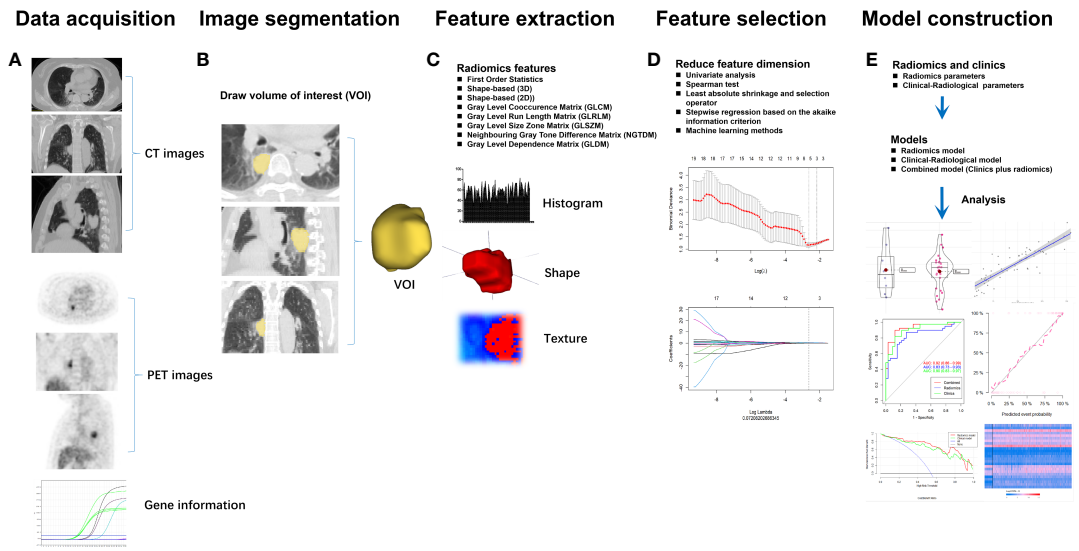


FIGURE 2
The workflow for radiomics analysis of $^{18}$F-FDG PET/CT data comprises five steps: **(A)** data acquisition, **(B)** image segmentation, **(C)** feature extraction, **(D)** feature selection, and **(E)** model construction.

TABLE 2 Recent publications about the predictive value of $^{18}$F-FDG PET/CT-derived radiomics with epidermal growth factor receptor mutation status in non-small cell lung cancer.

| Authors | No. of patients | Aspect evaluated | Main results |
|---|---|---|---|
| Yip et al. | 348 | PET radiomics features | 19 novel PET radiomics features were strongly associated with EGFR mutation status. |
| Park et al. | 183 | Heterogeneity of textural parameters of PET/CT | Heterogeneity textural parameters acquired from pretreatment FDG-PET/CT had clinical implications for identifying a high-risk subpopulation for EGFR TKI treatment. |
| Jiang et al. | 80 | PET and CT radiomics features | 35 selected features were significantly associated with EGFR mutation status. |
| Koyasu et al. | 138 | Random forest (RF), gradient tree boosting (XGB) | In the classification of EGFR mutation status, the AUC values were as follows: RF, 0.625; XGB, 0.617. |
| Mu et al. | 616 | PET/CT-based deep learning model | Deep learning model to predict EGFR mutation status with AUCs of 0.86, 0.83, and 0.81 in the training, validation, and independent test cohorts, respectively. |
| Abdurixiti et al. | 973 | PET/CT-based radiomics | The ICC for summed RQS was 0.986 [95% confidence interval (CI): 0.898–0.998]. |
| Yang et al. | 174 | PET/CT radiomics features, | The mutant/wild-type model was identified in the training (AUC, 0.77) and validation (AUC, 0.71) groups. |
| Zhang J et al. | 248 | PET/CT-based radiomics features | AUC is equal to 0.79 in the training set and 0.85 in the validation set, compared with 0.75 and 0.69 for the clinical model. |
| Zhang M et al. | 173 | PET/CT radiomics prediction model | Four CT and two PET radiomics features were finally selected to build the PET/CT radiomics model. |
| Shiri et al. | 150 | Low-dose CT, diagnostic CT, and PET radiomics | Multivariate machine learning-based AUC performances were significantly improved to 0.82 for EGFR. |
| Li et al. | 115 | PET/CT, CT radiomics features, conventional PET parameters | Wild-type of EGFR− cases with an AUC of 0.805, an accuracy of 80.798%, a sensitivity of 0.826, and a specificity of 0.783. |
| Chang et al. | 583 | PET/CT, CT, and PET radiomics models | The PET/CT radiomics–clinical combined model has better performance (AUC = 0.84) to predict EGFR mutation. |

PET/CT, positron emission tomography/computed tomography; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

# 4 A new type of molecular PET/CT probe to evaluate epidermal growth factor receptor mutation status in non-small cell lung cancer

$^{18}$F-FDG metabolic parameters associated with EGFR mutation status in NSCLC reflect the tumor cell glucose metabolism of tumor cells, which have poor sensitivity and are limited by many factors. Therefore, the targeting moiety or ligand must be attached with an applicable labeling agent for the imaging modality to accurately evaluate EGFR mutation status or guide EGFR-TKI treatment. Antibodies are often used due to their sufficient high-affinity specific EGFR (wild and mutated) binding. Currently, the molecular imaging modalities employed for detecting EGFR mutations are SPECT, PET, and PET/CT. Isotopic labeling substances may be combined with monoclonal antibodies to EGFR or EGFR-TKI molecular probes to reflect EGFR mutation status according to radioactive uptake in PET/CT images. Previous studies mainly used radioactive nuclides such as $^{86}$Y, $^{64}$Cu, and $^{89}$Zr to label anti-EGFR monoclonal antibodies (including cetuximab and panitumumab) and $^{11}$C and $^{18}$F to label EGFR-TKI (involved PD153035, gefitinib, erlotinib, and afatinib). However, current research focuses on cell and animal experiments with little clinical application (Table 3).

## 4.1 Monoclonal antibody probes

Monoclonal antibodies directly target the extracellular domain of EGFR to prevent the binding of EGFR to ligands, thus blocking downstream signal transduction pathways. Monoclonal antibodies are all large molecules that need to be labeled with radionuclides with a long half-life, such as $^{64}$Cu, $^{11}$C, and $^{89}$Zr, as they infiltrate tissue very slowly. PET/CT using $^{89}$Zr-cetuximab allowed the visualization and quantification of tumor $^{89}$Zr-cetuximab uptake in cells and animals (53) or other malignancies (54) with EGFR mutations. Van Loon et al. studied head and neck cancer (NHC) and NSCLC patients using $^{89}$Zr-cetuximab PET/CT but showed that SUVmax and SUVmean had no direct relationship between EGFR immunohistochemistry (IHC) score and tumor-to-background ratio (TBR) (55). $^{89}$Zr-DFO-panitumumab PET/CT imaging assessed EGFR expression at a cellular level and in animals (56, 57).

## 4.2 Epidermal growth factor receptor–tyrosine kinase inhibitors molecular probes

Radiolabeled EGFR-TKI can bind specifically to the tyrosine kinase domain of the mutant protein, and the uptake levels can

TABLE 3 Recent publications about the new type of molecular probe of PET/CT in use for the detection of epidermal growth factor receptor mutation status in non-small cell lung cancer.

| Authors | No. of patients | New type of molecular probe | Main results |
|---|---|---|---|
| Lui et al. | 11 | $^{11}$C-PD153035 | EGFR expression in NSCLC primary tumors with $^{11}$C-PD153035 uptake, and the SUVs were also correlated with the EGFR expression level. |
| Meng et al. | 21 | $^{11}$C-PD153035 | $^{11}$C-PD153035 uptake is close to the EGFR expression level in NSCLC. |
| Sun et al. | 75 | $^{18}$F-MPG | $^{18}$F-MPG uptake is significantly accelerated in NSCLC tumors harboring EGFR-activating mutations. |
| Van Loon et al. | 6 | $^{89}$Zr-cetuximab | No direct significant association was found between SUVmax, SUVmean, and EGFR IHC score. |
| Memon et al. | 30 | $^{11}$C-Erlotinib | Variation in $^{11}$C-erlotinib accumulation between different malignant lesions in the same patient. |
| Bahce et al. | 10 | $^{11}$C-Erlotinib | $^{11}$C-Erlotinib accumulated in tumors that expressed high levels of EGFR and were sensitive to TKI therapy. |
| Bahce et al. | 10 | $^{11}$C-Erlotinib | Tumor $^{11}$C-erlotinib uptake in NSCLC patients after erlotinib therapy was reduced and further illustrated the $^{11}$C-erlotinib binding specificity of EGFR mutation. |
| Song et al. | 3 | $^{18}$F-IRS | PET/CT imaging with $^{18}$F-IRS showed a potential to diagnose NSCLC EGFR mutation. |
| Stadt et al. | 10 | $^{18}$F-Afatinib | $^{18}$F-Afatinib can potentially be used in evaluating EGFR mutation-positive patients. |
| Stadt et al. | 12 | $^{18}$F-Afatinib | $^{18}$F-Afatinib PET/CT could provide methods to identify EGFR mutation-positive patients who benefit from afatinib therapy. |

$^{11}$C-PD153035, $^{11}$C-labeled 4-N-(3-bromoanilino)-6,7-dimethoxyquinazoline; $^{18}$F-MPG, $^{18}$F-labeled2-(2-(2-(4-(3-chloro-4-fluorophenylamino)-6-methoxyquinazolin-7-yl)oxy) ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate; $^{18}$F-IRS, $^{18}$F-N-(3-chloro-4-fluorophenyl)-7-(2(2-(2-(2-(4-fluorine)ethoxy)ethoxy)-ethoxy)-6-(3-morpholinopropoxy) quinazoline-4-amine.

reflect EGFR expression and mutation status. Therefore, EGFR-TKI molecular probes have many obvious advantages over monoclonal antibodies. EGFR-TKI molecular probes are labeled with radionuclides of short circulating half-life, such as $^{11}$C and $^{18}$F, which can penetrate tissues quickly because they are small molecules.

### 4.2.1 $^{11}$C-PD153035

4-*N*-[3-bromoanilino]-6,7-dimethoxyquinazoline (PD153035) is a reversible inhibitor of EGFR tyrosine kinase and a potent ATP-competitive TKI of EGFR (58). Additionally, $^{11}$C-labeled PD153035 has been assessed *in vivo* as a PET/CT agent to estimate EGFR expression in multiple tumors (59). Liu et al. studied the distribution of $^{11}$C-PD153035 in PET/CT imaging of 11 patients with NSCLC, finding that SUVs were correlated with expression levels of EGFR (60). Meng et al. analyzed $^{11}$C-PD153035 PET/CT images of 21 NSCLC patients revealing that $^{11}$C-PD153035 uptake is closely related to EGFR expression (61). Dai et al. demonstrated that $^{11}$C-PD153035 PET/CT imaging can be used as a simple and efficient method to detect NSCLC patients who are sensitive to EGFR-TKIs (62). Furthermore, the synthesis of polyethylene glycol (PEG)-modified (PEGylated) anilinoquinazoline derivative, 2-(2-(2-(2-(4-(3-chloro-4-fluorophenylamino)-6-methoxyquinazolin-7 yl)oxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (T-MPG) derived from the known EGFR-TKI PD153035 has been reported by Sun et al. (63). Not only their preclinical research but also clinical research that involved 75 NSCLC patients has suggested that $^{18}$F-MPG uptake is dramatically accelerated in *EGFR*-mutated NSCLC.

### 4.2.2 $^{11}$C-Erlotinib

$^{11}$C-Erlotinib is a PET imaging tracer with great promise for evaluating EGFR expression in NSCLC patients and has been reported in animal models and human subjects, but only a limited number of clinical PET/CT studies have been conducted. Bahce et al. illustrated that $^{11}$C-erlotinib accumulated in tumors that highly expressed EGFR by reviewing $^{11}$C-erlotinib PET/CT images of 10 patients with NSCLC (64). A study by Bachce et al. analyzed 10 NSCLC patients with EGFR mutation status, demonstrating that $^{11}$C-erlotinib uptake in tumors reduces after erlotinib therapy (65). However, Petrulli et al. showed a lack of association between EGFR mutation status and $^{11}$C-erlotinib uptake in an analysis of 10 NSCLC patients *via* dynamic multi-bed PET/CT scan using $^{11}$C-erlotinib, suggesting disease heterogeneity and low tracer uptake for the lack of association (66).

### 4.2.3 $^{11}$C-/$^{18}$F-Gefitinib

Gefitinib is a small-molecule EGFR kinase inhibitor that binds to the intracellular tyrosine kinase domain and disrupts EGFR kinase activity with nanomolar affinity (67). $^{11}$C- and $^{18}$F-radiolabeled gefitinib could be applied to image EGFR expression and pharmacokinetics non-invasive study of gefitinib in patients. However, a few studies have been conducted at the cell and animal levels, and human tumor xenografts have not shown EGFR-specific concentrations (68). However, a novel radiotracer, $^{18}$F-*N*-(3-chloro-4-fluorophenyl)-7-(2(2-(2-(4-fluorine)ethoxy)ethoxy)-ethoxy)-6-(3-morpholinopropoxy)quinazoline-4-amine ($^{18}$F-IRS) based on gefitinib has been designed and synthesized, with $^{18}$F-IRS PET/CT showing potential to diagnose NSCLC EGFR mutation according to higher $^{18}$F-IRS uptake in NSCLC with EGFR mutations (69).

### 4.2.4 $^{18}$F-Afatinib

Afatinib is a second-generation irreversible 4-anilinoquinazoline EGFR kinase inhibitor (70). In mouse models bearing NSCLC xenografts [EGFR-mutated (HCC827 and H1975) xenografts and EGFR wild-type (A549)], Slobbe et al. suggested accumulation of $^{18}$F-afatinib in NSCLC tumors with EGFR mutation status (71, 72), justifying the further evaluation of NSCLC tumor EGFR mutations. Stadt et al. (73) quantified $^{18}$F-afatinib tumor uptake in NSCLC patients, suggesting that $^{18}$F-afatinib could potentially be used to evaluate EGFR mutation-positive patients. Furthermore, Stadt et al. (74) also evaluated whether $^{18}$F-afatinib uptake could predict the response to afatinib therapy by evaluating $^{18}$F-afatinib PET/CT images of 12 patients with NSCLC, showing that $^{18}$F-afatinib PET/CT could serve as a method for precise quantification of EGFR mutation status in NSCLC patients who would benefit from afatinib therapy.

The possibilities of protein molecular probes targeting EGFR have been demonstrated in *in vivo* imaging cell, animal, and clinical studies, especially EGFR-TKI-type molecular probes. Although these studies showed that molecular probes targeting EGFR for PET/CT imaging can identify EGFR mutation status in NSCLC, they tend to produce high background noise because of high lipophilicity, which leads to poor imaging quality. The short half-life of $^{11}$C also limits its widespread use in clinical practice, and $^{18}$F labeling requires many procedures to label the TKIs.

## 5 Conclusion

EGFR is a significant target for lung cancer diagnosis and treatment; thus, non-invasive, accurate, and rapid methods for EGFR mutation detection should be developed in NSCLC. Due to recent advances in molecular imaging and analytic platforms, PET/CT may play a crucial role in identifying EGFR mutation status. The relatively new $^{18}$F-FDG PET/CT-derived radiomics to predict EGFR mutations has attracted much attention, with studies revealing promising results. PET/CT imaging with

radiolabeled monoclonal antibodies and EGFR TKIs is particularly attractive and may be better than $^{18}$F-FDG PET/CT-derived radiomics in detecting EGFR mutation status in NSCLC because it can be repeatedly operate and reflect receptor status in real-time. However, since most of the research to date has been performed at the cellular level or in animals, further clinical studies are needed in the future.

## Author contributions

Conceptualization: NH, PGL, and PL. Writing (original draft preparation): NH, GY, YHW, and PGL. Writing (review and editing): PGL, YW, LW, and YNX. All the authors have read the manuscript and have approved it before submission.

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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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# Financial toxicity in lung cancer

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In the United States, lung cancer is the third most common cancer and the overall leading cause of cancer death. Due to advances in immunotherapy and targeted therapy, 5-year survival is increasing. The growing population of patients with lung cancer and cancer survivors highlights the importance of comprehensive cancer care, including recognizing and addressing financial toxicity. Financial toxicity is a term used to contextualize the negative effects of the costs of cancer treatment in terms of patient quality of life. The American Society of Clinical Oncology (ASCO) Value Framework places emphasis on high-value care as it evaluates cancer treatments "based on clinical benefit, side effects, and improvements in patient symptoms or quality of life in the context of cost". Prior studies have shown that risk factors for financial toxicity in patients with lung cancer include lower household income or savings, inability to afford basic necessities, higher than anticipated out of pocket expenses, and taking sick leave. Among lung cancer survivors, patients experience increased unemployment and lower wages compared to the general population underscoring the lasting effects of financial toxicity. Financial toxicity is associated with increased psychosocial distress and decreased quality of life, and bankruptcy is an independent predictor of mortality in patients with cancer. Despite the negative implications of financial toxicity on patients, standardized screening practices and evidence-based interventions are lacking. The "COmphrensive Score for financial Toxicity (COST)" tool has been validated for assessing financial toxicity with correlation with health-related quality of life. Further research is needed to understand the utility of incorporating routine screening for financial toxicity into clinical practice and the efficacy of interventions. Understanding the relationship between financial toxicity and quality of life and survival is critical to providing high-value cancer care and survivorship care.

KEYWORDS

**financial toxicity, lung cancer, ASCO value framework, quality of life, survivorship care**

# Introduction

Despite a consistent decline in incidence and mortality over the past two decades, lung cancer continues to remain the leading cause of cancer-related deaths among both men and women in the United States (1). With only a 22% 5-year survival rate (1), great effort has been focused on the development of new treatment approaches and detection strategies. While many of these advancements offer hope for improved patient outcomes, unforeseen physical and socioeconomic side effects often emerge.

Financial toxicity refers to issues caused by the cost of medical care (2) and is characterized by the monetary burden, poor outcomes, and psychological distress impacting patients (3). Financial difficulties not only stem from high-cost medical treatment and diagnostics, but also non-medical costs such as transportation, parking, lodging and caregiving, as well as indirect costs from lost income and wages (4). While the concept of financial toxicity is not new, its impact has become increasingly prominent as the cost of living and cancer care continues to rise. Based on estimates from the National Cancer Institute, overall cancer-related medical costs will increase greater than 34% from the year 2015 to 2030 (4). While private and government-funded insurance programs will absorb much of this cost, higher deductibles, co-payments and out-of-pocket (OOP) expenses will undoubtedly fall to the patient. OOP expenses in 2018 accounted for 5%, or 5.6 billion dollars, of total cancer-related treatment expenses (4). The annual per-patient cost of medical services for patients with lung cancer ranges from 12.2 to 118 thousand dollars annually, with the greatest financial burden occurring at the time of initial diagnosis and the last year of life (5).

Financial hardship does not impact all patients equally and may wax and wane throughout a lifetime. Those more likely to suffer include patients of younger age, minority status, minimal educational experience, and those with decreased household savings and inability to afford basic necessities (4, 6). Because of this financial instability, negative outcomes can be seen on physical, mental, emotional, and economic levels (4). Physical health may be sacrificed in an effort to save money by delaying medical appointments or foregoing medications (7). In addition, significant stress and worry regarding individual health and finances can result in poor mental health outcomes, and accrual of monetary debt may lead to food and housing insecurity along with bankruptcy (8). These effects take a significant toll on individual quality of life (QOL) and wellbeing with the potential to worsen symptom burden and hasten patient mortality (6, 8). Focused attention at the patient, clinician, professional society and governmental level is needed to address and counteract this complex area of medical care. The focus of this review will be to highlight prior research, contributing factors, and potential interventions to address financial toxicity in patients with lung cancer.

# Discussion

## Financial toxicity in patients with cancer

As the United States (US) population ages alongside increasing cancer survival rates, a growing number of individuals with cancer will be impacted by financial toxicity. A study conducted by Mariotto et al. offered projections of increasing cancer prevalence and estimated care costs from the years 2010 to 2020. They estimated a rise in cancer prevalence from 13.7 million to 18 million, with a projected 27% increase in national expenditure solely based on the growing and aging US population, while keeping current cancer incidence, survival and cost constant (9). It is not surprising that cost varies by disease and throughout an individual disease course, which was also considered in the above estimation. For instance, colorectal cancer produces the highest cost during the initial phase of the disease, with lung cancer accounting for the highest costs during the final year of life, and prostate/breast cancers creating the highest expenditure during the middle, continuing phase of care (9). With an ever-growing increase in cancer prevalence, understanding the impact and determining ways to combat the effects of financial toxicity is imperative.

Various outcomes of previous financial toxicity research among the general population with cancer were nicely summarized by Altice et al. in a systematic review of 45 studies between 1990-2015. The estimated monthly OOP costs for patients ranged from $316 to $741, and most studies emphasized that those with a cancer diagnosis faced significantly higher OOP costs compared to those without (10). Not only were direct costs higher, but indirect costs from lost days at work or decreased productivity ranged from $380 to $8,236, annually (10). Additionally, 2-3% of individuals diagnosed with cancer filed bankruptcy claims within the first two years of diagnosis, and a vast majority of patients utilized income or savings to pay for medical expenses while 7-10% increased credit card debt or borrowed money from family or friends (10). Multiple studies found that effects of financial instability led to difficulty affording necessities such as clothes, food, and home utilities (10). Patients with cancer were also more apt to avoid spending on other areas or healthcare including prescription refills and experienced increased rates of stress with a greater risk of depression compared to the general population (10). Lack of transportation leads to delays in care, especially in patients who are single, have lower income, are underinsured, or have self-reported physical limitations (11). Furthermore, the cumulative costs of parking alone for cancer related appointments is burdensome, with median parking cost

of $2 per hour or $5 per day at National Cancer Institute-Designated Cancer Treatment Centers (12). Only 54% of NCI-Designated Treatment Centers have free parking available for chemotherapy appointments (12).

A survey study of 1,202 adult cancer survivors in the US explored material and psychological hardship associated with cancer. One fifth of survivors experienced material financial hardship, and almost a quarter of survivors experienced psychological hardship. Younger patients, defined as between 18 to 64 years, experienced a statistically significant increase in both material and psychological hardship related to financial toxicity compared to patients ≥ 65 years (13). Among younger patients, material hardship was associated with female gender and undergoing more recent treatment (13). Interestingly, psychological hardship was more common in younger patients who were uninsured compared to private insurance but did not vary by type of insurance in the older patients (13).

## Measures of financial toxicity

While greater attention has been paid to financial toxicity in recent years, identifying and validating standardized means of measurement remains an area of ongoing research. A systematic review conducted by Witte et al. evaluated 43 studies plus six systematic reviews from 2006 to 2018 highlighting various measurement tools. Most studies hailed from the United States with a majority encompassing all cancer types, with six studies focusing solely on lung cancer (14). Primary means of measurement were in the form of patient-reported questionnaires (14). Three broad domains of financial toxicity and their subtypes were described: material conditions, further broken down into active spending and the passive utilization of personal financial resources; psychological response represented by the patient's affect; and coping behaviors, further divided into support seeking behaviors, care plan adjustments, and lifestyle modifications (14).

Some individual studies within the Witte et al. review focused their questionnaire on overall health-related quality of life (HRQoL) with only a subset of questions targeting the patient's financial situation. These included the European Organization for Research and Treatment of Cancer Core Quality of Life Survey (EORTC QLQ-C30), Cancer Care Outcomes Research and Surveillance Consortium Patient Survey (CanCORS), Social Difficulties Inventory (SDI) and the Patient Satisfaction Questionnaire (PSQ-18) (14). EORTC QLQ-C30 is one of the most frequently used tools to assess cancer-related QOL (15) *via* 30 questions focusing on functional status, physical symptoms and perceived QOL, with only one question addressing financial difficulties (14). Similarly, the CanCORS patient survey also incorporates one question regarding financial burden (14). Specifically, it asks, "If you lost all of your current sources of income (for example, paycheck, Social Security, pension, public assistance) and had to live off of your savings, how long could you continue to live at your current address and standard of living?" (16). Unlike EORTC QLQ-C30, this survey has only been studied among patients with lung and colorectal cancers and the above question has shown an independent association between low levels of financial reserve and poorer QOL along with higher symptom burden (16). The SDI is a 21-question survey developed to measure a variety of social issues impacting patients diagnosed with cancer including personal care, work, family matters, communication, etc. with two questions focusing on financial issues (17). While the EORTC QLQ-C30, CanCORS and SDI are all cancer-specific questionnaires, the PSQ-18 is often used to assess a broad patient population including but not limited to those with cancer (14). The PSQ-18 is an 18-item questionnaire addressing overall patient satisfaction among various facets of care with one domain being "financial aspects" (18). One study, not included in the Witte et al. review, evaluated financial toxicity among patients with cancer utilizing the following PSQ-18 item; "You have to pay for more medical care than you can afford" with corresponding Likert scale responses of strongly agree, agree, uncertain, disagree, and strongly disagree (18). Those who chose strongly agree or agree were deemed to exhibit financial toxicity (18). Results from this study showed similar patient demographics and overall prevalence of financial toxicity among the study population compared to previously reported data, suggesting that this question may be an appropriate screening tool to quickly identify at-risk patients (18). Developing efficient, valid and reliable means of screening is an important aspect of financial toxicity to allow for early intervention at, or before, the initiation of treatment. Future studies comparing individual questions, such as those utilized in the above questionnaires, are needed to help better address this area.

Other studies within the Witte et al. review utilized multi-item questionnaires which were designed to specifically assess subjective financial distress including The Comprehensive Score for Financial Toxicity (COST), Breast Cancer Finances Survey Inventory (BCFS), Socioeconomic Wellbeing Scale (SWBS) and InCharge Financial Distress/Financial Well-Being Scale (IFDFW) (14). The IFDFW is the only generic tool among those listed and focuses on psychosocial affect, financial resources, and coping strategies (14). This scale is identified as a valid and reliable tool to measure financial distress among individuals in a vast array of settings including healthcare (19). However, due to the unique financial burdens of those with cancer compared to those with other chronic medical conditions and moreover, the general population, a more focused means of measurement is preferable. The BCFS tool has questions encompassing all three financial toxicity domains but only four of the six subtypes outlined by Witte et al., including financial spending, utilization of financial resources, patient affect and lifestyle modifications (14). BCFS was developed specifically for utilization among patients with breast cancer,

making its generalizability to other cancer types – such as lung cancer – limited (19). The SWBS was originally developed as a subscale for other questionnaires focused on overall HRQoL, however it can be used independently as well (14). The questions are skewed toward the material domain of financial toxicity including financial spending and utilization of financial resources with questions regarding care plan adjustments and psychosocial affect also included (14); utilization of this measurement tool is limited.

Lastly, the COST tool, developed in 2014, is one of the most widely used instruments to assess financial toxicity in patients with cancer (20). It is an 11-item patient-reported outcome measure with a large focus on the psychosocial domain of financial toxicity followed by financial resource utilization and financial spending (14). Due to significant need for a tool measuring financial toxicity at the time, COST was deployed in both research and clinical domains upon its development, even prior to establishing validity and reliability (21). COST measurements were significantly associated with employment status, race, income, psychological distress along with the number of inpatient admissions (22). This study was the first to demonstrate a positive association between financial toxicity and the frequency of inpatient admissions (22). Additionally, this study indicated a statistically significant correlation to HRQoL making this a clinically relevant tool as well (22). Not only has COST been validated in the United States but it has been validated in other countries with varying healthcare financing models (23–25). Scores for COST range from 0-44 with lower scores correlating to greater financial toxicity. While some studies have set COST thresholds based on percentiles obtained from their unique study population (21), De Souza et al. defined a grading system for financial toxicity utilizing the COST tool which has been studied among patients with various types of cancer demonstrating consistent validity (26). Grade 0 indicates absence of financial toxicity with a score of greater than or equal to 26 points. Grade 1 indicates mild financial toxicity with a score between 14-25. Grade 2 indicates moderate financial toxicity with a score 1-13, and grade 3 indicates severe financial toxicity with a score of zero (26). While the COST tool appears to be the most widely used and studied cancer-specific instrument to measure financial toxicity, it is not specific to lung cancer. In fact, only nine of the 100 patients involved in the initial assessment and analysis of this questionnaire had lung cancer diagnoses (27). It is, however, the most frequently used tool among studies specifically assessing financial toxicity in patients with lung cancer.

## Implications of financial toxicity in lung cancer care

Prior studies have described the risk factors for and consequences of financial toxicity in lung cancer care. Friedes and Hazell et al. conducted a prospective longitudinal study of 215 patients with stage II-IV lung cancer between July 2018 to May 2020 assessing COST at diagnosis and six-month follow up (28). At diagnosis, household income less than $40,000, having less than one month of savings, and inability to afford basic necessities were associated with financial toxicity (28). At six-month follow up, having less than one month of savings and inability to afford basic necessities were still associated with financial toxicity, as well as being on sick leave and paying more than anticipated for OOP costs. Interestingly, most patients at diagnosis over-estimated their OOP costs, with median reported costs $2496 compared to median estimates of $3000. At six-month follow up, 27.7% of patients reported making sacrifices to pay for medical care, including using personal savings or selling assets, borrowing money, or changing housing. Furthermore, 17.9% were unable to afford basic necessities, which was defined as "ability to pay for gas, electricity, bills, food, prescription medication, or other monthly structure payments". However, only 4.5% reported withholding medical care due to cost. Only 9.8% of patients saw a financial counselor at diagnosis and 14.6% retrospectively reported that they wished they had. Overall, there was a small, statistically significant improvement in financial toxicity from diagnosis to the six-month mark, though 27.4% of patients did not have six-month follow up data due to research limitations during the COVID-19 pandemic. Friedes and Hazell et al. importantly demonstrated the evolution of financial toxicity in lung cancer treatment (28).

Financial toxicity is associated with decreased HRQoL in patients with stage III-IV lung cancer (29). Furthermore, financial distress requiring bankruptcy is a risk factor for early mortality (hazard ratio 1.79; 95% CI, 1.64 to 1.96) across a broad range of malignancies (8). While no patients in the study by Friedes and Hazell et al. declared bankruptcy, a study by Chino et al. conducted in 245 patients with solid tumors including 39 patients with lung cancer, found that 49% reported willingness to declare bankruptcy to afford medical care at baseline assessment and 42% at three-month follow up (30). Patients with lung cancer at 5-years from diagnosis had the highest cumulative incidence of bankruptcy and lowest overall survival compared to survivors of other malignancies (8). Among lung cancer survivors, patients experience increased unemployment and lower wages compared to the general population underscoring the lasting effects of financial toxicity (31).

Weaver et al. evaluated 6,602 adult cancer survivors (including breast, cervical, melanoma, prostate, or multiple cancers) and 104,364 individuals with no cancer history and demonstrated that among cancer survivors, 7.8% forego medical care and 9.9% forego prescription medications compared to 5.2% and 7.2% in the general population, respectively (32). Additionally, cancer survivors under age 65 were more likely to forego care. While this study was evaluating non-lung malignancies, it highlights the need to further characterize financial toxicity in lung cancer by age. The study by Friedes

and Hazell et al. evaluating patients with lung cancer included only 7% of patients under 50 years old, highlighting a gap in current research in younger patients with lung cancer. Younger patients with cancer experience bankruptcy at higher rates among all cancer types, and patients with lung cancer were 3.8 times more likely to go bankrupt than controls in a study by Ramsey et al. While most patients diagnosed with lung cancer are age 65 or older (33), as lung cancer screening increases, we anticipate a decrease in the average age at diagnosis.

Meeker et al. evaluated overall distress and financial distress in 119 patients with solid malignancies, stratifying by age groups (defined as young <50, middle-age 50–64, and elderly ≥ 65 years of age) (34). The types of solid malignancies included were not specified. Overall distress was evaluated using the National Comprehensive Cancer Network (NCCN) distress thermometer and financial distress was measured by the IFDFW (34). In multivariable analysis, overall distress was most strongly associated with financial distress in middle aged patients (34).

While many of the advancements in lung cancer treatment based on cancer genomics offer incredible hope for improved survival, they can come at a high financial cost. Genomic testing alone can cost $300-$10,000 (35). Although testing with next generation sequencing is standard of care, the cost to patients is not readily available. Improved transparency about coverage of testing and OOP costs is needed for patients and clinicians. Furthermore, there is limited research regarding the cost of targeted therapies in patients with lung cancer. Skinner et al. evaluated 364 patients with advanced non-small cell lung cancer on tyrosine kinase inhibitors (TKI) (36). The mean monthly cost of systemic cancer therapy was $8,530 (95% CI $7,141–$9,919) for those who received TKI, accounting for 42.4% of their total mean monthly healthcare costs (36). Kaisaeng et al. evaluated patients with Medicare part D on oral cancer treatment, including 96 patients on erlotinib. Median OOP costs per day for erlotinib were $28.35, or $850.50 per month (37). For each $10 increase in OOP costs per month, the odds of discontinuation or delay increased 13.8% for those on erlotinib (37). Paying more than anticipated for OOP costs is associated with financial toxicity, and the lack of available information for patients regarding costs serves as a barrier to mitigating this risk.

Financial toxicity has major implications in terms of clinical trial enrollment. Although clinical trials are sometimes the best available treatment options for patients, only 5% of patients with cancer enroll in a clinical trial (38). Clinical trials often involve frequent travel, relocation, interruption of unemployment, and insufficient support to match expenses (38). Patients with lower income are less likely to participate in clinical trials (38). In order to provide equitable clinical trial access, appropriate financial incentives are needed to minimize the increased costs that may come with clinical trial participation. ASCO has called for improving the policy environment regarding coverage for clinical trials, targeted financial support, and greater transparency regarding the costs of clinical trial participation (39).

Numerous barriers to alleviating financial toxicity exist on a clinical, institutional, and systematic level. Lack of clinician expertise regarding costs of care and lack of time are important clinical limitations (40). Involvement of multidisciplinary teams, including financial counselors, social workers, case managers, nurse navigators, and pharmacists, is essential for comprehensive cancer care. The American Society of Clinical Oncology (ASCO) has called attention to high-value care through the Value Framework which evaluates cancer treatments "based on clinical benefit, side effects, and improvements in patient symptoms or quality of life in the context of cost" (41). Policy-level changes incentivizing high-value care are likewise needed to address financial toxicity in cancer care.

## Future directions

Despite the negative implications of financial toxicity on patients, standardized screening practices and evidence-based interventions are lacking. Further research is needed to understand the utility of incorporating routine screening for financial toxicity into clinical practice. The COST tool has been validated for assessing financial toxicity and also correlates with HRQoL (22). Utilizing the COST tool for screening in conjunction with targeted interventions by multidisciplinary teams to mitigate financial toxicity should be evaluated in both patients receiving active cancer treatment and cancer survivors. Additionally, continued research is needed to further understand financial toxicity differences among varying types of malignancies and treatment regimens with the potential for more targeted assessment tools. Furthermore, establishment of a cancer-specific instrument that equally accounts for all three domains and corresponding subtypes of financial toxicity, proposed by Witte et al., may be of great value.

Understanding and addressing the relationship between financial toxicity, QOL, and survival is critical to providing high-value cancer care and survivorship care. A longitudinal study of financial toxicity in patients with lung cancer is imperative to understanding the pervasive impact of cancer on patients. This is particularly relevant to understanding the experience of middle-aged patients, who are more likely to forego medical care and declare bankruptcy (32, 42). Additionally, research engaging the patient's caregiver and family is needed to inform care discussions and planning. Active involvement of patient advocacy and research groups by healthcare systems, pharmaceutical companies, clinical trials, and legislators is critical to understanding how we can develop more patient-centric and less financially burdensome care.

## Conclusions

It is clear that individuals diagnosed with cancer are more vulnerable to the long-term effects of financial toxicity compared to the general population, and those with lung cancer appear to be at a particularly high risk (30, 32). Undoubtedly, this aspect of care is frequently overlooked due to other concerns such as treatment plans, imaging results, and complex symptom management. However, when patients are forced to make decisions to forego prescriptions, skip follow-up visits, or declare bankruptcy, the ability of the clinician to provide effective care is starkly limited and mortality rates rise. This not only affects patients receiving active treatment but likely impacts those in the survivorship phase as well, which may be a result of lost savings, increased unemployment, or lower wages leaving new challenges and worry in the place of cancer. Key areas of future focus include continued research and implementation of screening tools to identify those at risk, and effective utilization of multidisciplinary teams and care models to assess and develop individualized cost-conscious treatment methods. While this will help address clinician and institutional level approaches to combat this issue, a concerted effort must also be taken on a broader level to include insurance companies, pharmaceutical companies and medical governing bodies. With committed involvement of all stakeholders, the effects of financial toxicity can be limited while patient health and livelihood are enhanced.

## Author contributions

MB, CM, JZ, MH wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

Author MH declares the following: Ad board/Consulting fees: Regeneron.

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

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# Meeting an un-MET need: Targeting MET in non-small cell lung cancer

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The MET pathway can be activated by MET exon 14 skipping mutations, gene amplification, or overexpression. Mutations within this pathway carry a poor prognosis for patients with non-small cell lung cancer (NSCLC). MET exon 14 skipping mutations occur in 3-4% of patients with NSCLC, while MET amplifications are found in 1-6% of patients. The most effective method for detection of MET amplification is fluorescent *in situ* hybridization (FISH) and of MET exon 14 skipping mutations is RNA-based next generation sequencing (NGS). Immunohistochemistry (IHC) is an alternative method of diagnosis but is not as reliable. Early studies of MET tyrosine kinase inhibitors (TKIs) demonstrated limited clinical benefit. However, newer selective MET TKIs, such as capmatinib and tepotinib, have improved efficacy. Both drugs have an acceptable safety profile with the most common treatment-related adverse event being peripheral edema. One of the most frequent resistance mechanisms to EGFR inhibition with osimertinib is MET amplification. There is interest in combining EGFR inhibition plus MET inhibition in an attempt to target this resistance mechanism. Additional ways of targeting MET alterations are currently under investigation, including the bi-specific antibody amivantamab. Additional research is needed to further understand resistance mechanisms to MET inhibition. There is limited research into the efficacy of immune checkpoint inhibition for MET-altered NSCLC, though some data suggests decreased efficacy compared with wild-type patients and increased toxicity associated with the combination of immunotherapy and MET TKIs. Future directions for research will include combination clinical trials and understanding rational combinations for MET alterations.

KEYWORDS

**non-small cell lung cancer (NSCLC), MET exon 14, tyrosine kinase inhibitor, MET amplification, EGFR**

# Introduction

In the last decade, targeted cancer therapy has become a pillar in the management of non-small cell lung cancer (NSCLC). Genomic testing allows clinicians to identify oncogenic drivers that guide treatment decisions (1). The National Comprehensive Cancer Network (NCCN) guidelines recommend testing for a specific set of biomarkers in patients diagnosed with advanced or metastatic NSCLC. Commonly tested biomarkers include EGFR, BRAF, ERBB2, and KRAS mutations; ALK, ROS1, and RET rearrangements; NTRK 1/2/3 gene fusions; PD-L1 expression; and MET exon 14 skipping mutations and amplification (2). Results from this testing are used to determine eligibility for novel therapies, which can improve both survival and quality of life for patients (3, 4).

The mesenchymal-epithelial transition (MET) oncogene is a receptor tyrosine kinase primarily expressed in epithelial cells (5). MET signaling is involved in the proliferation, invasion, and survival of cells. Gain-of-function MET alterations have been seen in several types of cancer, including NSCLC (5–7). These alterations occur as a result of point mutations, insertions, or deletions and promote cell survival and angiogenesis *via* induction of VEGF. MET alterations include exon 14 skipping mutations, gene amplification, and protein overexpression (7). Each of these alterations have been detected in NSCLC. They are associated with a poor prognosis (7). MET exon 14 skipping mutations are more common in elderly patients over the age of 70, women, and non-smokers (8). MET amplification is often diagnosed in patients under the age of 65 with a smoking history (9, 10).

MET directed therapies have emerged in recent years as treatment options for patients with advanced NSCLC with MET exon 14 skipping mutations and amplification. These treatments include both tyrosine kinase inhibitors (TKIs) and antibodies, and can target MET and the MET ligand, hepatocyte growth factor (HGF) (11). The GEOMETRY Mono-1 and VISION trials demonstrated improved clinical benefit for MET TKIs and led to the FDA approval of capmatinib and tepotinib, respectively. This review outlines the biology and detection of common MET alterations, summarizes currently available treatment options for patients with MET alterations, and identifies future directions for the use of MET TKIs in NSCLC.

# MET alterations

## MET exon 14 skipping mutations

MET exon 14 skipping mutations can occur through point mutations or genomic deletions that lead to a loss of exon 14. This increases protein stability by preventing ubiquitin-mediated degradation resulting in enhanced MET signaling and potential for malignancy (12, 13). The mutation occurs in 3-4% of patients with NSCLC (11).

## MET amplification

MET amplification is a result of focal gene amplification which causes an increase in gene copy number (GCN). Approximately 1-6% of patients diagnosed with NSCLC have a MET amplification. In addition to its role in certain malignancies, it has also been identified as a mechanism of acquired resistance for EGFR TKIs (14).

## MET alteration detection methods

Fluorescent *in-situ* hybridization (FISH) from solid tissue biopsy is the gold standard for detection of MET amplification (14, 15). The MET/CEP7 ratio can distinguish between true focal amplification versus polysomy of chromosome 7, which does not alter oncogenicity. Most studies use a cutoff MET/CEP7 ratio of ≥ 2 (13, 14).

Next generation sequencing (NGS) is an alternative to FISH that is becoming increasingly more common for diagnosis of MET amplification and exon 14 skipping mutations. A caveat to NGS is that there is no standardized method of detection and some assays do not control for CEP7. Studies have shown a discrepancy between diagnosis of MET amplification using FISH versus NGS (9, 14, 16). Generally, a cutoff with GCN ≥10 is preferred as it corresponds to a high level of MET amplification. The higher cutoff has been shown to have greater concordance with FISH. FISH is superior to NGS for detection of moderate to low levels of MET amplification (9, 16, 17).

Immunohistochemistry (IHC) has been studied and used to detect MET overexpression. However, IHC is not a reliable predictor of MET alterations such as exon 14 skip mutations or amplification (18). In a small cohort study of 181 patients, use of IHC to diagnose MET alterations was compared to FISH and NGS. A total of 3 out of 181 patients were diagnosed with MET amplification, 2 *via* FISH and 1 *via* NGS. Two out of three of these same patients screened negative for MET amplification based on IHC results. In addition, 71 of 181 patients screened positive for a potential MET alteration based on MET IHC but only 1/71 had a confirmed MET amplification and 2/71 had a MET exon 14 skipping mutation (18). Similar findings were shown in a study evaluating MET overexpression by IHC in diagnosing MET alterations in lung sarcomatoid carcinomas compared to FISH. There was a 50% sensitivity for IHC, 83% specificity, and a positive predictive value of 21.4% (19).

MET exon 14 skipping mutations are best diagnosed using DNA-based or RNA-based NGS (20). It is posited that RNA-based sequencing may be superior to DNA due to the ability to detect a wide array of mutational variants that may not affect or alter a splice site. One study comparing DNA versus RNA-based NGS for detection of MET exon 14 alteration found that 11 of 856 (1.3%) samples were positive using DNA-based sampling. RNA testing detected alterations in 17 of 404 (4.2%) patients.

Furthermore, 286 samples were tested using both DNA and RNA-based sequencing. MET exon 14 alterations were detected in 10 samples *via* RNA testing. However, 6 of those samples were not detected using DNA (21). Additional studies have shown similar results demonstrating the superiority of an RNA-based approach to testing (22).

Liquid biopsy is an alternative diagnostic strategy to solid tumor biopsy that can identify MET alterations through NGS of circulating cell-free DNA (cfDNA) that is shed from solid tumors (23). In addition to diagnosing tumor-specific alterations to inform treatment decisions, liquid biopsy is also able to identify resistance mechanisms (15).

Regardless of the method used, detecting MET alterations can be difficult due to both the wide array of variants that can lead to altered MET expression and lack of a standardized approach to diagnosis.

## MET tyrosine kinase inhibitors

MET TKIs are sub-divided into three categories based on drug structure and the way in which the drug binds to MET. Type I MET TKIs are ATP-competitive inhibitors. Type I is further subdivided into type Ia and type Ib. Type Ia inhibitors bind to MET *via* the solvent front residue, G1163, and are known as non-selective MET TKIs as this residue is not specific to MET. Type Ib inhibitors function independent of this residue and selectively bind to MET alone. Due to their selectivity, type Ib MET TKIs have superior anti-tumor activity and a more tolerable safety profile. Type II MET TKIs are also ATP-competitive inhibitors but instead bind to the inactive form of MET. Type III MET TKIs bind allosterically outside of the ATP domain (24).

### Type 1a, non-selective MET TKIs

#### Crizotinib

Crizotinib not only exerts an inhibitory effect on MET, but also ALK, ROS, and RON. Crizotinib was originally approved for treatment of NSCLC with ALK or ROS1 rearrangements (25, 26). Additional studies of crizotinib have not been as promising for patients with MET alterations as they were for ALK or ROS1 rearrangements (27). The phase I trial, PROFILE 1001, first studied the role of crizotinib in treatment of advanced NSCLC patients with many genetic variants including MET alterations. Of the 69 patients enrolled with MET exon 14 skipping mutations, 65 were evaluable and there was an objective response rate (ORR) of 32% (95% CI 21-45) with median progression free survival (PFS) of 7.3 months (95% CI 5.4-9.1). Median duration of response (DOR) was 9.1 months (95% CI 6.4-12.7) (28). In addition, among 38 patients included in the study with MET amplification diagnosed by FISH, the high MET amplification group (MET to CEP7 ratio ≥ 4) had longer median PFS with crizotinib compared to patients with medium and low MET amplification (6.7 months vs 1.9 months vs 1.8 months) (29). Treatment-related adverse events (TRAEs) of any grade were common and seen in 94% of patients. The most common TRAE was peripheral edema in 51% of participants followed by GI symptoms and fatigue (28, 30). Twenty nine percent of patients experienced a TRAE of grade 3 or higher. The most common high-grade adverse events included elevated transaminases (4%) and dyspnea (4%) and one patient had treatment-related death due to interstitial lung disease (ILD) (28). PROFILE 1001 resulted in FDA breakthrough approval of crizotinib to treat MET alterations in NSCLC (Table 1).

The METROS study, a phase II trial, investigated the efficacy of crizotinib in patients with MET dysregulation including MET exon 14 skipping mutations and amplification. In the MET cohort, ORR was 27% (95% CI 11-47) with median PFS of only 4.4 months (95% CI 3.0-5.8) (31). Similar results were seen for NSCLC patients with MET alterations enrolled in the phase II AcSé trial (32). Several ongoing phase II trials including MATCH and MATRIX continue to study the potential role of crizotinib in treating MET-altered NSCLC (Table 2).

### Type 1b, selective MET TKIs

#### Capmatinib

Capmatinib was FDA-approved for treatment of NSCLC with MET exon 14 skipping mutations in 2020. This was based on data from the GEOMETRY Mono-1 study, a phase II clinical trial. The study enrolled 364 patients with confirmed MET exon 14 skipping mutations or MET amplification. Patients were further stratified based on prior treatment history. Among patients with MET exon 14 skipping mutations, 69 received prior therapy and had an ORR of 41% (95% CI 29-53) and median PFS of 5.4 months (95% CI 4.2-7.0). In contrast, 28 treatment-naïve patients had an ORR of 68% (95% CI 48-84) and median PFS of 12.4 months (95% CI 8.2-NE). The time to respond to capmatinib was rapid for both groups, as short as first tumor evaluation at 6 weeks. Results suggested an increased benefit in the treatment naïve population (13).

Patients with MET-amplified NSCLC had limited response to capmatinib. The trial closed early for futility in patients with MET amplification with GCN <10. While tumor response was seen for patients with GCN ≥ 10, this still did not meet the threshold for clinical relevance (ORR 29%, 95% CI 19-41, median PFS 4.1 months, 95% CI 2.9-4.8 in 69 previously treated patients; ORR 40%, 95% CI 16-68, median PFS 4.2 months, 95% CI 1.4-6.9 in 15 treatment-naïve patients) (13).

Capmatinib had an acceptable safety profile. TRAEs occurred in 88% of patients who received treatment, with peripheral edema seen in 50% of patients. Grade 3 or higher adverse events occurred in 67% of participants, and again

TABLE 1 Published Trials of Type I MET TKIs.

| Drug | Study, trial name | Population | Treatment | MET alteration | N | Objective response rate (ORR) | Progression free survival (PFS) |
|---|---|---|---|---|---|---|---|
| Crizotinib | NCT00585195, PROFILE-1001 | Advanced NSCLC with MET exon 14 skipping mutation or MET amplification | Crizotinib 250mg BID | MET exon 14 skipping | 65 | 32% | 7.3 months |
| | | | | Low amplification (MET/CEP7 ratio 1.8-2.2) | 3 | 33.3% | 1.8 months |
| | | | | Medium amplification (MET/CEP7 ratio 2.2-4) | 14 | 14.3% | 1.9 months |
| | | | | High amplification (MET/CEP7 ratio ≥4) | 21 | 38.1% | 6.7 months |
| | NCT02499614, METROS | Pretreated, advanced NSCLC with MET deregulation | Crizotinib 250mg BID | MET exon 14 skipping and MET amplification (MET/CEP7 ratio >2.2) | 26 | 27% | 4.4 months |
| | NCT02034981 | Advanced NSCLC with c-MET ≥ 6 copies or c-MET mutations (including exons 14 and 16-19) | Crizotinib 250mg BID | c-MET ≥ 6 copies | 25 | 16% | 3.2 months |
| | | | | c-MET-mutations | 28 | 10.7% | 2.2 months |
| Capmatinib | NCT02414139 GEOMETRY Mono-1 | NSCLC with MET exon 14 skipping mutation or MET amplification | Capmatinib 400mg BID | MET exon 14 skipping, treatment naïve | 28 | 68% | 12.4 months |
| | | | | MET exon 14 skipping, prior treatment | 69 | 41% | 5.4 months |
| | | | | MET amplification, GCN ≥ 10, treatment naïve | 69 | 29% | 4.1 months |
| | | | | MET amplification, GCN ≥10, prior treatment | 15 | 40% | 4.2 months |
| | | | | MET amplification, GCN 6-9, prior treatment | 42 | 12% | 2.7 months |
| | | | | MET amplification, GCN 4-5, prior treatment | 54 | 9% | 2.7 months |
| | | | | MET amplification, GCN <4, prior treatment | 30 | 7% | 3.6 months |
| Tepotinib | NCT02864992 VISION | NSCLC with MET exon 14 skipping mutation or MET amplification | Tepotinib 500mg qd | MET exon 14 skipping | 99 | 46% | 8.5 months |
| | | | | MET amplification (GCN ≥2.5) | 24 | 41.7% | 4.2 months |
| Savolitinib | NCT02897479 | Unresectable or metastatic pulmonary sarcomatoid carcinoma or NSCLC with MET exon 14 skipping mutation | Savolitinib 600mg if ≥ 50kg or 400mg if <50kg | MET exon 14 skipping | 61 | 49.2% | 6.9 months |

peripheral edema was the most common high-grade event. Serious TRAEs were seen in 13% of participants and 11% discontinued treatment as a result (13, 30, 33).

## Tepotinib

The phase II VISION trial led to FDA approval of tepotinib in 2021 as a second-line therapy for patients with MET exon skipping NSCLC. A total of 152 patients with MET exon 14 skipping mutations were enrolled in the study and received treatment. There was an ORR of 46% (95% CI 36-57) based on independent review, and median PFS was 8.5 months (95% CI 6.7-11). There was no significant difference in response for patients who had received prior lines of treatment from those who had not (34). Response time was considered rapid, and the majority of patients had a response within 6 weeks of treatment initiation.

TRAEs occurred in 89% of patients. Peripheral edema was the most common adverse effect, occurred in 63% of patients, lead to dose reduction in 16% of patients, dose interruption in 18%, and discontinuation in 5%. Twenty-eight percent of participants experienced a grade 3 or higher adverse event. The most common high-grade event (7%) was peripheral edema, followed by increased amylase and lipase. Serious TRAEs were reported in 15% of patients and 11% discontinued treatment (30, 34, 35).

A sub-group analysis of 23 patients with MET exon 14 skipping mutations and brain metastases demonstrated a robust treatment response with an ORR of 47.8% (95% CI 26.8-69.4) and median DOR of 9.5 months (95% CI 5.5-NE). There were 15 patients evaluated using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria, 12 received prior chemotherapy. 7 patients had measurable disease per RANO-BM and 8 had non-enhancing, non-target lesions. 9 had a partial response (PR), 3 with stable disease (SD), and 3 with progressive disease (PD) (36).

TABLE 2 Active Trials of Type I MET TKIs.

| Drug | Trial | Phase | Population | Treatment arms |
|---|---|---|---|---|
| Crizotinib | NCT02465060, MATCH | II | Advanced refractory NSCLC with MET amplification and MET exon 14 skipping mutation | Crizotinib PO BID |
| | NCT02664935, MATRIX II | II | NSCLC with ROS1 fusion, MET amplification, or MET exon 14 skipping mutation | Crizotinib PO BID |
| Capmatinib | NCT04427072, GeoMETry-III | III | Previously treated NSCLC with MET exon 14 skipping mutation | Capmatinib PO BID<br>Versus<br>Docetaxel IV q21d |
| | NCT04677595, GeoMETry-C | II | Advanced NSCLC with MET exon 14 skipping mutation | Capmatinib PO BID |
| | NCT04926831, Geometry-N | II | NSCLC with MET exon 14 skipping mutation or high MET amplification | Capmatinib PO BID |
| | NCT03693339 | II | NSCLC with MET exon 14 skipping mutation | Capmatinib PO BID |
| | NCT02276027 | II | NSCLC with c-MET gene alteration | Capmatinib PO BID |
| | NCT02323126 | II | c-MET positive NSCLC | Capmatinib PO BID and nivolumab q2w |
| | NCT02750215 | II | Advanced NSCLC with MET exon 14 skipping mutation who received prior MET inhibitor therapy | Capmatinib PO BID |
| Tepotinib | NCT04739358 | I/II | MET-driven NSCLC with at least 1 intracranial lesion | Tepotinib PO qd alone<br>Versus<br>Tepotinib qd and concurrent TKI of choice |
| Savolitinib | NCT02117167, SAFIR02_Lung | II | MET-altered NSCLC | Savolitinib PO qd<br>Versus<br>Pemetrexed IV q3w |
| | NCT04923945 | III | Locally advanced or metastatic NSCLC with MET exon 14 skipping mutations | Savolitinib PO qd |

The efficacy and safety of tepotinib in an elderly population over the age of 75 with MET exon 14-altered NSCLC was further investigated in an additional group of patients and was consistent with the findings from the VISION trial (ORR 39.7%, 95% CI 28-52.3; median PFS 8.6 months, 95% CI 6.9-12.4) (35). Peripheral edema was the most common adverse event and occurred in 51.4% of the elderly patient population. Thirty four percent of patients over 75 had grade 3 or higher TRAEs and 14.7% discontinued treatment (35).

Results from the VISION trial in patients with MET-amplified NSCLC were analyzed separately. MET amplification was defined as GCN ≥2.5. A total of 24 patients were enrolled in the study with an ORR of 41.7% (95% CI 22.1-63.4) and median PFS of 4.2 months (95% CI 1.4-NE). Sixteen patients reported TRAEs of any grade and 7 of those patients were grade 3 or higher. Peripheral edema was again the most common adverse event and was reported in 37.5% of patients (37) (Table 1).

### Savolitinib

Savolitinib was approved in China for conditional use in NSCLC with MET exon 14 skipping mutations following a multi-center phase II trial. The study enrolled 70 patients with confirmed MET exon 14 skipping mutations; 36% had pulmonary sarcomatoid carcinoma. There was an ORR of 49.2% (95% CI 31.1-55.3) in the tumor response evaluable set with a median PFS of 6.9 months and median OS of 14 months (38). Forty-six percent of patients experienced a high-grade TRAE and 24% were serious. Elevated liver enzymes and peripheral edema were the most common grade 3 or higher adverse events, and one patient died of tumor lysis syndrome which was attributed to savolitinib (38).

## Type II MET TKIs

### Cabozantinib

Cabozantinib is another non-selective MET TKI that targets VEGFR1-3, RET, TIE2, FLT-3, KIT, and MET. It is currently FDA-approved for treatment of medullary thyroid cancer, renal cell carcinoma, and hepatocellular carcinoma. In a phase II trial, patients with advanced NSCLC with wild-type EGFR were randomized to receive cabozantinib alone, erlotinib alone, or erlotinib with cabozantinib. The study showed improved PFS in the cabozantinib alone group (4.3 months, HR 0.39, 80% CI 0.27-0.55) and the cabozantinib and erlotinib combination cohort (4.7 months, HR 0.37, 80% CI 0.25-0.53) compared to erlotinib alone (1.8 months, 95% CI 1.7-2.2) (39).

While the study had promising results, the trial did not test for MET alterations and it is unclear what role cabozantinib can play in the treatment of patients with MET alterations. One small study of patients with stage IV lung adenocarcinoma with MET exon 14 skipping mutations randomly assigned 8 patients

to receive either crizotinib or cabozantinib. In the study only one patient ultimately received cabozantinib and had a complete response (CR) (40). More data is required to evaluate the efficacy of cabozantinib in MET-altered NSCLC. Results are awaited in the ongoing phase II trial, CABinMET (Supplemental Table 2) (41).

For information regarding additional Type II MET TKIs including merestinib, foretinib, and glesatinib and the Type III MET TKI, tivantinib, please see Supplemental Tables 1, 2.

## MET antibodies

In addition to MET TKIs, there are several antibodies targeting MET that have been studied or are in development for treatment of NSCLC. Amivantamab is a bispecific antibody targeting EGFR and MET. It was first presented in the phase I CRYSALIS study, which included a population of NSCLC patients with EGFR exon 20 insertion. There was an ORR of 40% (95% CI 29-51) and median PFS of 8.3 months (95% CI 6.5-10.9). The most common adverse events were rash and infusion reactions, and the most common severe adverse event was hypokalemia (5%) (42). Updated results from the CHRYSALIS study were recently presented at the 2022 ASCO meeting including preliminary data from 55 patients with MET exon 14 skipping mutations. Among 22 treatment-naïve patients there was an ORR of 50%. An ORR of 17% was seen in patients with prior treatment. To date, 11 of the 15 patients who responded to amivantamab remain on treatment. These results suggest that amivantamab has anti-tumor activity for both EGFR and MET-altered NSCLC (43).

Early data from the phase II CHRYSALIS-2 trial was also presented at the 2022 ASCO meeting in which amivantamab was given in combination with the EGFR TKI, lazertinib, for patients with NSCLC who progressed on platinum-based chemotherapy and osimertinib. There were 162 patients who received treatment with an ORR of 33% and clinical benefit rate of 57% with median DOR of 9.6 months (44). The ongoing phase III MARIPOSA and MARIPOSA-2 trials are investigating amivantamab and lazertinib as potential first line therapy in EGFR-mutant NSCLC.

Emibetuzumab is a humanized IgG4 monoclonal bivalent MET antibody designed to block MET signaling. It was studied in a phase II trial in combination with erlotinib for treatment of stage IV, EGFR-mutated NSCLC. The study showed no significant difference in PFS for patients treated with the combination of erlotinib and emibetuzumab compared to erlotinib alone. However, *post hoc* analysis revealed that for 24 patients with markedly high MET expression there was a significant improvement in median PFS of 15.3 months in the combination group (45).

Onartuzumab is a recombinant humanized monoclonal monovalent antibody against MET. There have been several phase II and III clinical trials investigating the benefit of onartuzumab in combination with erlotinib and common chemotherapy regimens with no significant benefit in PFS or OS gained (46). Of note, while participants in these trials were tested for MET overexpression in their tumors, they were not tested for specific MET alterations such as MET exon 14 skipping mutations or amplification. Thus, it is possible that onartuzumab could have significant antitumor activity for patients with certain MET alterations, although this has not yet been studied.

More recently the antibody-drug conjugate (ADC), telisotuzumab vedotin, was developed. The ADC consists of a c-MET antibody linked to a microtubule inhibitor and was given FDA breakthrough therapy designation for EGFR wild-type NSCLC following initial data from the ongoing phase II LUMINOSITY trial. Tumors were tested for c-MET overexpression using IHC and subdivided into intermediate or high c-MET expression groups. Of the 136 patients who received treatment so far, there was an ORR of 52.2% in the c-MET high, EGFR wild-type group and 24.1% in the c-MET intermediate, EGFR wild-type group. Peripheral neuropathy, nausea, and low albumin levels were the most common TRAEs (47).

One other MET antibody under investigation is Sym015, which is made up of a mixture of 2 humanized antibodies (48).The antibodies bind non-overlapping epitopes on the SEMA-a domain of MET which promotes MET receptor internalization and degradation by preventing HGF from binding to MET (48). There is preliminary data on a phase II trial of Sym015 for treatment of NSCLC with MET amplification or exon 14 skipping mutation (48). Twenty patients were included in the expansion cohort with an ORR of 25% and disease control rate (DCR) of 80%. There was a response benefit for MET TKI naïve participants with an ORR of 50% and 100% DCR. Median PFS was 6.5 months for MET TKI naïve patients and 5.4 months for patients who received prior MET TKI therapy. The drug was considered safe with TRAE in 42.2% of patients, 13.3% of which were grade 3 or higher. The most common adverse events were fatigue and peripheral edema (48).

## Immunotherapy for patients with MET alterations

There is limited clinical benefit for use of immune checkpoint inhibitors (ICI) in patients with MET-altered NSCLC. Several studies have demonstrated modest efficacy (49, 50). This includes a multicenter, retrospective study in which 36 patients with MET alterations had an ORR of 16% to ICI therapy and median PFS of 3.4 months (95% CI 1.7-6.2) (50). Similar results were found in another study of 22 patients with MET exon 14 skipping NSCLC treated with ICI therapy (ORR 17%, 95% CI 6-36, median PFS 1.9 months, 95% CI 1.7-2.7) (49). There is no apparent correlation between biomarkers such as PD-L1 expression ($\geq$50%) or tumor mutational burden in predicting response to immunotherapy in this group of patients (49, 51).

Interestingly, one retrospective, multicenter study demonstrated an improved response to ICI therapy. Thirty patients with a MET mutation were evaluated and received either pembrolizumab or nivolumab. There was an ORR of 35.7% and median PFS of 4.9 months (95% CI 2.3-NE) (52). NCCN guidelines currently recommend single-agent targeted therapy for initial management of MET exon skipping NSCLC rather than chemotherapy or immunotherapy (2).

Genetic heterogeneity within MET-dysregulated NSCLC-including MET skipping mutation versus amplification, as well as co-occurring mutations, may affect response to immunotherapy. One study analyzed patients with NSCLC with MET exon 14 skipping mutations, MET amplification GCN≥10, and MET amplification GCN <10 for additional co-occurring mutations (53). Investigators found that there were more co-occurring mutations in MET-amplified tumors compared to the MET exon 14-mutated tumors, and that the type of co-mutation was dependent on the degree of MET amplification. The most common mutations were TP53, KRAS, and KEAP1. KRAS mutations were more common in MET-amplified tumors with GCN <10 while KEAP1 mutations were more frequent with GCN ≥10 (53). Patients with MET amplification with GCN ≥10 had worse median OS compared to GCN <10 (4 months vs 12 months, $p$=0.001) (53). While MET-amplified tumors with GCN ≥10 showed the worst OS of any cohort, treatment with immunotherapy after progression on first-line chemotherapy greatly improved OS compared to chemotherapy (36.0 months vs 4.0 months, $p$=0.004). A similar improvement in OS was seen with GCN <10 treated with ICI versus chemotherapy (19 months vs 8 months, $p$<0.0001). In contrast, OS was not statistically improved for patients with MET exon 14 skipping mutations (16 months ICI vs 10 months chemotherapy, $p$=0.147) (53). These findings suggest a difference in response to immunotherapy-based MET alteration subtype.

One reason immunotherapy may have limited efficacy in MET-altered NSCLC is through inhibition of stimulator of interferon gene (STING) signaling. The STING pathway promotes interferon (IFN) response and is integral in the recruitment of T-cells and NK-cells (54). A retrospective cohort study analyzed MET copy number and STING levels in patients previously diagnosed with NSCLC. Among 81 patients treated with anti-PD1 therapy following progression on first-line chemotherapy, those with the worst response to treatment were found to have high MET copy numbers and low IFNB. This suggested that MET amplification leads to impaired tumor immunogenicity and, therefore, reduces response to ICI (54).

The combination of a MET TKI with an ICI could potentially overcome resistance to immunotherapy. However, there is concern for increased toxicity with combination therapy. One phase II trial of NSCLC with high tumor PD-L1 expression (≥50%) randomized treatment-naïve patients 2:1 to receive combination pembrolizumab and capmatinib or pembrolizumab alone. The trial was terminated early due to toxicity concerns with combination therapy. At data cutoff, 51 patients were enrolled in the combination arm and 25 in the pembrolizumab-alone arm. Nineteen out of fifty-one patients (37.3%) in the combination arm discontinued treatment with 4 suspected deaths. Seven patients (28%) discontinued treatment in the single therapy arm (55). Further research is needed to determine the role of ICI therapy for treatment of patients with MET alterations both alone and in combination with targeted drugs.

## Acquired MET alterations in EGFR NSCLC

EGFR TKIs have been highly successful in the treatment of EGFR-mutant NSCLC. However, development of acquired resistance is common, and limits the long-term efficacy of this class of drugs. Approximately 60% of resistance to first generation EGFR TKIs is due to the T790M mutation which inhibits binding of TKIs to the ATP binding site of EGFR. Third generation EGFR TKIs such as osimertinib were subsequently developed to overcome common EGFR TKI resistance mechanisms such as the T790M mutation. MET amplification is another important mechanism of acquired resistance to EGFR TKIs that activates oncogenic signaling cascades downstream of EGFR through a bypass pathway (56–59). It occurs in approximately 30% of patients with progressive disease on EGFR TKIs (51). Importantly, MET amplification is one of the few known resistance mechanisms for third generation EGFR TKIs (58, 59).

Several trials have attempted to overcome resistance through combination therapy with MET TKIs. The INSIGHT study is a phase Ib/II trial that investigated the combination of tepotinib and gefitinib in patients with EGFR-mutant, T790M negative NSCLC with acquired resistance to EGFR TKI therapy compared to chemotherapy. While survival outcomes were similar overall for tepotinib and gefitinib compared to chemotherapy, sub-group analysis demonstrated a significant improvement in PFS and OS for patients with MET amplification treated with combination therapy (ORR 67% vs 43% median PFS 16.6 months vs 4.2 months, HR 0.13, 90% CI 0.04-0.43; median OS 37.3 months vs 13.1 months, HR 0.08, 90% CI 0.01-0.51) (60). A notably smaller survival benefit was shown for patients with high MET overexpression by IHC (ORR 68% vs 33%, median PFS 8.3 months vs 4.4 months, HR 0.35, 90% CI 0.17-0.74, OS 37.3 months vs 17.9 months, HR 0.33, 90 CI 0.14-0.76). This again suggests that the use of IHC to classify MET-altered NSCLC may inadequately identify the intended patient population which, in turn, impacts response to treatment. While overlapping toxicities with combination therapy is of concern, treatment was well tolerated in INSIGHT and the most common grade 3 or higher AEs were increased amylase (16%) and lipase (13%) (60).

Additional studies that utilized combination MET and EGFR TKIs to overcome MET-amplified EGFR TKI resistance include a phase Ib/II trial evaluating capmatinib and gefitinib and the phase Ib TATTON trial which included osimertinib in combination with savolitinib. Both showed similarly promising results to INSIGHT (Table 3) (61, 62). Continued studies of combination therapy to overcome MET-driven EGFR TKI resistance include the phase II SAVANNAH and ORCHARD trials of osimertinib and savolitinib in addition to INSIGHT2 with osimertinib and tepotinib (NCT03778229, NCT03944772, NCT03940703).

## Future directions

While MET TKIs have demonstrated clinical benefit and tolerable toxicity, the ability to diagnose and sequence MET alterations remains a challenge and there are currently no standardized methods to confirm MET alterations. In addition, as with all TKIs, duration of response can be limited by resistance. There are several proposed mechanisms of on-target and off-target resistance to MET TKIs. On-target mutations can affect drug-receptor binding and ATP inhibition (63, 64). Several mutations that confer resistance to type I MET TKIs include G1163R, which is associated with resistance only to crizotinib, D1228, and Y1230. Bypass pathways can also lead to off-target resistance *via* activation of oncogenic signaling cascades downstream from MET such as the MAPK and PI3K/AKT pathways. This can be mediated by mutations and amplifications in EGFR, KRAS, HER3, and BRAF (63, 64). Switching generations of MET TKIs may be feasible to overcome on-target resistance. One case report demonstrated the ability of cabozantinib to overcome a D1228 resistance mutation which was acquired during treatment with crizotinib. The patient presented had an initial PR at 6 weeks to cabozantinib but ultimately had PD after 4 months. Post-progression biopsy following treatment with cabozantinib did not detect the D1228 mutation (65). While these results are encouraging, the data thus far for type II and type III MET TKIs is not as promising as the selective MET inhibitors. Further understanding of resistance mechanisms and the role of combination therapy is needed.

There is an emerging role for combination therapy with MET and EGFR TKIs in EGFR-mutant NSCLC. Further research is needed to understand additional combination therapies in MET-altered NSCLC, including MET TKIs and ICIs. Several new agents targeting MET alterations are currently under investigation including the bi-specific antibody amivantamab. While not yet studied, such agents may be combined or used in place of MET TKIs to delay or prevent resistance.

## Conclusion

Treatment of NSCLC has significantly changed over the last decade with the rise of genetic testing and targeted cancer

TABLE 3 Trials of MET TKIs in Acquired EGFR Resistance.

| Study, trial name | Population | Treatment | MET alteration | N | Objective response rate (ORR) | Progression free survival (PFS) |
|---|---|---|---|---|---|---|
| NCT01982955, INSIGHT | EGFR-mutated NSCLC with MET overexpression or amplification with disease progression on EGFR TKI | Tepotinib 300mg or 500mg qd and Gefitinib 250mg qd Versus Standard chemotherapy | MET amplification | 19 | 67% vs 43% | 16.6 months vs 4.2 months |
| | | | MET overexpression | 34 | 68% vs 33% | 8.3 months vs 4.4 months |
| NCT02143466, TATTON | Advanced EGFR-mutated, MET-amplified NSCLC with disease progression on EGFR TKI | Savolitinib 300 or 600mg qd and Osimertinib 80mg qd | MET amplification | 138 | 48% | 7.6 months |
| NCT01610336 | EGFR-mutated, MET-dysregulated NSCLC with disease progression on EGFR TKI | Capmatinib 400mg BID and Gefitinib 250mg qd | Total | 100 | 29% | 5.5 months |
| | | | MET amplification, GCN ≥6 | 36 | 47% | 5.49 months |
| | | | MET overexpression | 78 | 32% | 5.45 months |
| NCT03778229, SAVANNAH | EGFR-mutated, MET+ NSCLC with progression on osimertinib | Savolitinib 300 or 600mg qd and Osimertinib 80mg qd | MET amplified or overexpressed | Active trial | Active trial | Active trial |
| NCT03944772, ORCHARD | EGFR-mutated, advanced NSCLC with progression on osimertinib | Savolitinib 300mg or 600mg qd and Osimertinib 80mg qd | None | Active trial | Active trial | Active trial |
| NCT03940703, INSIGHT 2 | EGFR-mutated, MET-amplified NSCLC with acquired resistance to osimertinib | Tepotinib 500mg qd and Osimertinib 80mg qd Versus Tepotinib 500mg qd alone | MET amplification | Active trial | Active trial | Active trial |

therapy. Activation of the MET pathway is an important oncogenic driver for many patients with NSCLC and has proven to be an effective target for therapy. The development of MET TKIs and, in particular, the selective MET TKIs tepotinib, capmatinib, and savolitinib, has altered the landscape of cancer treatment for an older population of patients who previously had limited treatment options outside of chemotherapy. The more recent emergence of MET antibodies including the bispecific antibody, amivantamab, is expanding upon available treatment options and is currently being studied as potential first-line therapy for EGFR-mutant NSCLC.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## Conflict of interest

CB reports the following disclosures: Advisory Board: AstraZeneca, BMS, Genentech, Jazz, JNJ, Novartis, Pfizer, Seattle Genetics, Takeda; Consulting Fee: Axiom Healthcare, Cardinal Health, Curio Science, CVS, OncLive. Targeted Oncology; Contracted Research: BMS; Speakers Bureau: Merck.

The remaining author declares 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.2022.1004198/full#supplementary-material

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# The sternum reconstruction: Present and future perspectives

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Sternectomy is a procedure mainly used for removing tumor masses infiltrating the sternum or treating infections. Moreover, the removal of the sternum involves the additional challenge of performing a functional reconstruction. Fortunately, various approaches have been proposed for improving the operation and outcome of reconstruction, including allograft transplantation, using novel materials, and developing innovative surgical approaches, which promise to enhance the quality of life for the patient. This review will highlight the surgical approaches to sternum reconstruction and the new perspectives in the current literature.

KEYWORDS

**sternum reconstruction, 3D printing, mesenchymal stem cells, sternum allograft, sternal tumors sternum, reconstruction, Prothesis, 3D materials**

## Introduction

Chest wall corrections are generally concerned with the resection of primary locally invasive chest wall malignancies or metastatic tumors (1, 2). The correct approach for the reconstruction depends on the size, location, and depth of the tumor, as well as the vitality of the surrounding tissues. The aim is to obtain clean surgical margins to afford the patients the longest time survival while avoiding recurrence. The majority of surgeons consider a defect bigger than 5 cm or including more than four ribs as a mandatory case for reconstruction due to the possibility of further complications related to the instability of the chest wall (2, 3). Moreover, certain defects, such as some apicoposterior defects, even of bigger dimensions, may not need reconstruction due to sufficient support provided by the shoulder or by the scapula (2, 3). The first goal of a chest wall reconstruction is to maintain the stability of the thorax, preserving the lung functions and protecting the intrathoracic organs, while minimizing the deformity which may

derive from the resection (4, 5). One of the most beneficial approaches in the last few decades is the discussion of each clinical case by a multidisciplinary team including thoracic surgeons, plastic surgeons, neurosurgeons, and radiation oncologists to provide the optimal setting and procedures tailored to the patient (4, 6, 7). The choice of the proper materials for the reconstruction is also necessary to obtain the optimal aesthetic effect and physical comfort (4, 6, 7).

One of the most challenging procedures for thoracic surgeons is the removal of the entire sternum for a tumor or infection infiltrating the bone (8, 9), which is quite frequent in tumors growing in the anterior part of the chest. The greater challenge is the reconstruction, which must guarantee the protection of the underlying visceral components, the space behind the sternum, and restoration of the stability of the chest wall and pulmonary function (9).

The capacity to maintain the stability of the chest wall has been extensively studied for its crucial role in preserving the dynamics of breathing (10, 11). Recently, computer simulations have helped guide reconstruction of the chest and prevent possible functional problems after surgery (12, 13). Reduction of thorax expansion may compromise the volume of the chest, with 20% loss of its normal capacity (6). The type of prosthesis is also critical because most of the patches are non-absorbable and synthetic and the patients are often young, with a long-life expectancy (10–14).

The prosthesis materials are designed to stretch uniformly, inducing a uniform tension at the extremities where they will be fixed (15–17). They are generally well tolerated if covered by viable tissue, although some reports described an infection rate between 10 and 25% for the use of synthetic meshes, which needed to be removed due to infection. Other interesting materials have been developed to avoid this problem, such as vinyl meshes, due to their flexible characteristics and biocompatibility, or the bovine pericardium prosthesis, which is completely biological and mitigates infection or contamination (18). Furthermore, the scientific community is trying to identify the best approaches to cover the chest, especially after sternum removal (11, 16). Currently, sternal reconstruction methods often employ a sandwich approach using a polymethyl methacrylate/polypropylene (PMM/PP) implant and a soft tissue flap (19, 20) (Figure 1). Another approach involves the use of a titanium rib-bridge system in addition to soft tissue flaps (21, 22) (Figure 1).

Long-term results related to PMM/PP hardware failure have found a solution using the rigid reconstruction of the sternum with a double-barrel free fibula flap plus titanium plates, with the soft tissues of the free flap as coverage (22, 23). This approach provides better stability due to the improved biomechanical design (23–25).

Moreover, sternectomy due to an infection after a cardiothoracic operation has an incidence between 1 and 4% (26); however, reconstruction of the bone provides long-term results, without significant morbidity, although several reports have emphasized the importance of coverage with a visceral component or muscles flaps (27–29). The most important step in sternal reconstruction is the setting of the anterior chest wall to avoid respiratory problems that may arise due to hypomobility of the chest wall (30). In recent decades, different techniques and materials have been used for sternal reconstruction, and currently (31), attention has been given to allograft sternum implantation for better aesthetic results and a more "natural" definition of the anterior chest, without immunosuppression.

## Sternum reconstruction for oncological reasons and infections

Primary malignant sternal tumors (PMSTs) are infrequent tumors, and most of them present at the stage of infiltration of the sternum and soft tissues (32, 33). Radical resection may be the most successful standard treatment, although the local aggressiveness of the tumor makes the surgical approach particularly complex and is associated with a high risk of recurrence (4, 32, 34).

Musculocutaneous flaps have been used to successfully cover extensive skin excisions (4, 28, 29, 35, 36). A representative demonstration of this method was shown in 2004 by Alain R. Chapelier et al., who reported 38 patients undergoing curative resection for PMST (37). The resections included the affected sternum, with partial or complete removal and *en bloc* asportation of the closed area. The sternal defects were reconstructed using a mesh for chest wall stability and the pectoralis major (PM) muscles with skin advancement or latissimus dorsi musculocutaneous flap to reconstruct the soft tissue cover.

The results are generally satisfactory, with low mortality. Furthermore, the stability of the chest can be supported by various prosthetic materials, such as two layers of Marlex mesh (MMM), as proposed by several authors (38–40), or a polytetrafluoroethylene (PTFE) patch (33) (Figure 1). Recently, another approach was introduced with methyl methacrylate bars to reduce the amount of prosthetic material, and thus, the risk of infection (7, 41). However, the PM is the most commonly used material for the correction of sternal defects, especially in men, but in women, skin closure or grafting of the donor site is commonly conducted (28, 29). In particular, musculocutaneous flaps guarantee the best aesthetic results and represents a well-vascularized soft tissue cover (28, 29).

Another less frequently used approach is momentum interposition, especially in patients undergoing resection of an irradiated sternum or recurrent tumors, such as sarcomas (42, 43). Although satisfactory results in high-grade tumors have not been reported, in patients with limited local recurrence or one metastasis, resection may be possible with good long-term

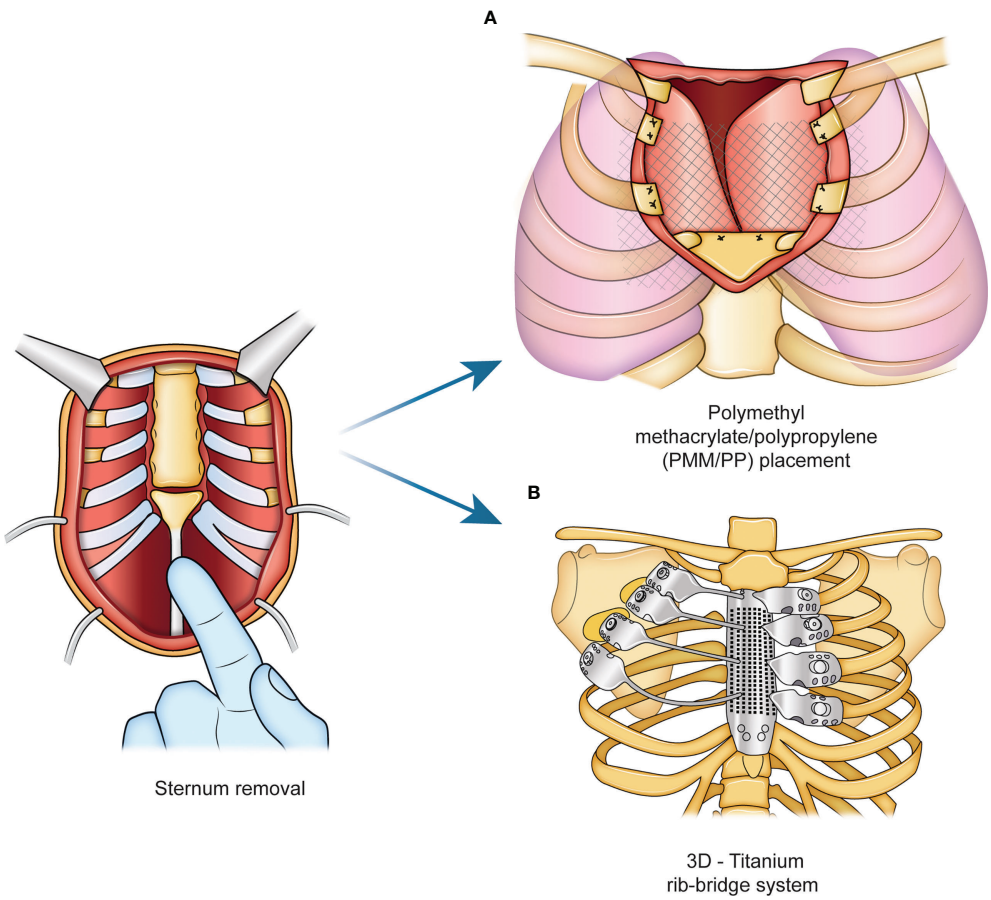


FIGURE 1
Standard procedure for sternal reconstruction. Current approaches for sternum reconstructive surgery rely on the use of a sandwich implant with a polymethyl methacrylate/polypropylene (PMM/PP) shown in panel **(A)**, and a titanium rib-bridge system, shown in panel **(B)**.

survival (5, 44–47). Nevertheless, in large sternal defects or patients with an irradiated sternum, reconstruction using musculocutaneous flaps is preferred because of the reduced risk of infection (24, 40, 46). Additionally, the use of methyl methacrylate mesh is recommended for reconstruction after complete sternectomy (48).

Secondary sternal tumors are infrequent and are associated with breast, thyroid, or kidney metastasis (49–51). They represent 15% of all sternal tumors and involve mainly the body of the sternum. Because they are infrequent, the scientific community has not reached a consensus regarding their treatment (50). Chemoradiotherapy and hormonal therapy are generally considered the gold standards of treatment (51, 52).

## Surgical techniques and prosthesis

The most common materials for sternum reconstruction are PTFE and MMM because they provide rigidity of the chest (11, 51). When PTFE is used for extensive anterior chest wall defects requiring rib resection up to the entire lateral aspect of the sternum, the reconstruction is based on a series of sternal punches passing through the sternum to accommodate the anchoring sutures of either the PTFE or the MMM (53).

### The methyl methacrylate mesh

Methyl methacrylate consists of a sandwich of two mesh layers to maintain the rigidity of the reconstruction. This product has been used since the 1980s and for several years it has been considered the best choice for the sternum and the entire or partial chest wall reconstruction (54). It is usually set by the thoracic surgeon with the first layer of polypropylene material fixed on the ribs, and the methyl methacrylate is generally used as a cover for the prosthesis, becoming an integral part of the chest support. This approach is particularly useful for massive chest wall demolitions, especially anteriorly

and laterally, to prevent chest deformity (55). On the other hand, the material characteristics of methyl methacrylate do not include fluid permeability, and this could be an unfavorable due to the risk of infection, pain, and rigidity of the thorax (55–57). The most frequent complications regarding the use of methacrylate (11) are fractures and infections, which have been described in 10–20% of patients, followed by the necessity to remove the prosthesis (11, 33). The scientific community and experts in the field agree that coverage with soft tissues is necessary to guarantee satisfactory long-term results (34, 58).

### PTFE

PTFE is another material frequently used for chest wall reconstruction (30). The material is flexible and easily conforms to the chest. The thickness of the mesh provides a permanent tight suture and good chest stability. Similar to MMM, PTFE is useful for large correction of the thorax, and it is recommended to cover it with viable tissue (11). The only difference compared to MMM is that, even if it becomes infected, immediate removal is not suggested, but rather, the scientific literature advises removing it after 6–8 weeks from infection, so the scar tissue can support the chest after the mesh removal (34, 59).

### Titanium plates

In the last few decades, new approaches and materials have been developed for prosthetic surgery, including thoracic surgery. The use of titanium is popular because it exhibits high strength, low weight, and intrinsic diamagnetic characteristics, which permits patients to continue using the magnetic resonance imaging diagnostic tool (60). The most important trait of titanium is its high biocompatibility. Different models have been used recently by surgeons, from the Borrelly steel staple-splint system to STRATOS bars, which are reportedly comfortable in regard to remodeling and fixing on the ribs (61, 62). The improved results are attributed to locking the bars in place using at least three screws to guarantee the stability of the chest in the area where the terminal part of the clean resected ribs margins needs to be fixed (61, 62). Several studies confirmed that the titanium bars may be more beneficial in cases of large thorax reconstruction, not only for guaranteeing the stability of the chest but also for preventing respiratory problems and infections (34). In particular, only a few complications have been observed, such as dislocations or ruptures of the bars, with an incidence frequency of around 0 to 11% of cases (63).

Moreover, titanium plates in association with acellular collagen matrixes or cryopreserved homografts may be an appropriate alternative in cases of re-operation or operation of a highly irradiated area (51, 53, 64). The titanium bars may be formed to the desired length and are anchored to the ribs to prevent fracture or dislocation, which occurred in only one patient who required plate replacement with acellular collagen matrix patching (64). The titanium plates are usually implanted at a 2:1 ratio, depending on the number of ribs resected (64). Moreover, if an acellular collagen matrix prosthesis is selected, a combination of titanium plates and an acellular collagen matrix patch can be used (65, 66). Another approach involves using titanium plates without an internal coverage material (7, 13, 22, 33, 38, 53).

However, the necessity to cover large reconstructions, often considered one of the main causes of high morbidity and mortality, led to the development of more innovative approaches. In particular, the versatility of materials has been considered a point of interest, and for this reason, the introduction of 3D-printed sternum prostheses has introduced a new paradigm of "chest wall reconstruction" (67, 68). A baseline high-resolution computed tomography scan is used to define a 3D model of the thorax and tumor mass using specific software (69). Through the use of powdered titanium and electron-beam melting technology, each layer is constructed and modeled as a personalized sternum to ensure optimal anchorage to the ribs and to ensure clean margins after surgical resection (59). Recently, several authors have reported customizing a titanium sternum model after resection with significant results (70).

Other interesting materials include carbon-fiber molds or alumina-ceramic models, which can be produced in a very short time, usually around 7 days, with very good aesthetic results (71). In particular, long-term results related to this new generation of materials showed that they remained very stable, even years after implantation (71, 72). For both the approaches, regarding the use of new materials and standards, a higher complication rate has been reported in patients with severe co-morbidities and older age (71–73). One equally important aspect is the cost of 3D-printed models, which depends on the size and thickness of the prosthesis. The use of traditional materials (i.e., a combination of titanium bars and mesh) is much cheaper (between 400 and 500 €) than the use of alumina prostheses, which usually cost around 10,000–15,000 € each (74).

## Allogenic sternal allografts and the future of regenerative medicine in sternum reconstruction

Cryopreserved allografts and homografts, recovered from cadaveric donors and stored at −80°, have also been considered as a possible solution to reconstruct the thorax after a large chest wall demolition, or in cases of severe local infection (75). These materials may be more useful than prosthetic materials since

they can be incorporated into native tissue along with the revascularization and cell populations (76). However, this approach is not widely used due to the challenges associated with identifying a donor in a short time period (77, 78). The sternochondral graft is usually derived from a tissue bank *via* an aseptic procedure, according to Italian rules (Figure 2). An antibiotic solution is added for 72 hours at 4°C, and cryopreservation at -80 °C is necessary to preserve the allograft from immunogenic alterations (77, 78). The sternum is then defrosted at 4–6 °C for 12 hours the day before surgery and is placed into a sterile bag. The graft is generally defrosted in a 0.9% NaCl solution with antibiotics (77, 78). The surgical procedure involves the removal of the sternum and associated subcutaneous or cutaneous tissues.

The most common approach to cover the allograft is using a PM muscle-flap reconstruction to ensure an ideal fit with the chest wall of the recipient (21, 28, 29, 40). Titanium bars are also fixed on the sternum to preserve the stability of the anterior chest. The PM muscle flaps are usually used, even in case of a good reconstruction, for an aesthetically favorable result (79).

Despite the availability of common materials used for sternum reconstruction, new regenerative approaches have been explored in recent decades (80). Scientists are trying to identify a strategy to promote tissue regeneration with bone remodeling using cell therapy specifically based on mesenchymal stem cells (MSCs), which appear to play a strategic role in bone healing, to implement sternal nonunion (81). In addition, MSCs have been considered for cartilage restoration after injury. Cartilage can self-repair in a complex structure with low metabolic capacity (82). Surgical approaches that involve the management of cartilage usually include microfractures and autologous osteochondral transplantation; however, there is currently a tendency to prefer those standards of care over the use of regenerative treatments. These treatments should be considered because they could replace surgical procedures that provide only short-term restoration in favor of a long-term regeneration (82, 83).

One of the main advantages of MSCs in the scope of cellular therapies is that MSCs, through a paracrine effect, exhibit anti-inflammatory activity, and thus, reduce fibrosis and anti-apoptotic activity while promoting cell proliferation (59). The optimal source of MSC retrieval is still debated since different tissues have been identified as potential sources of MSCs, such as bone marrow and adipose tissue (84, 85) (Figure 3). Bone

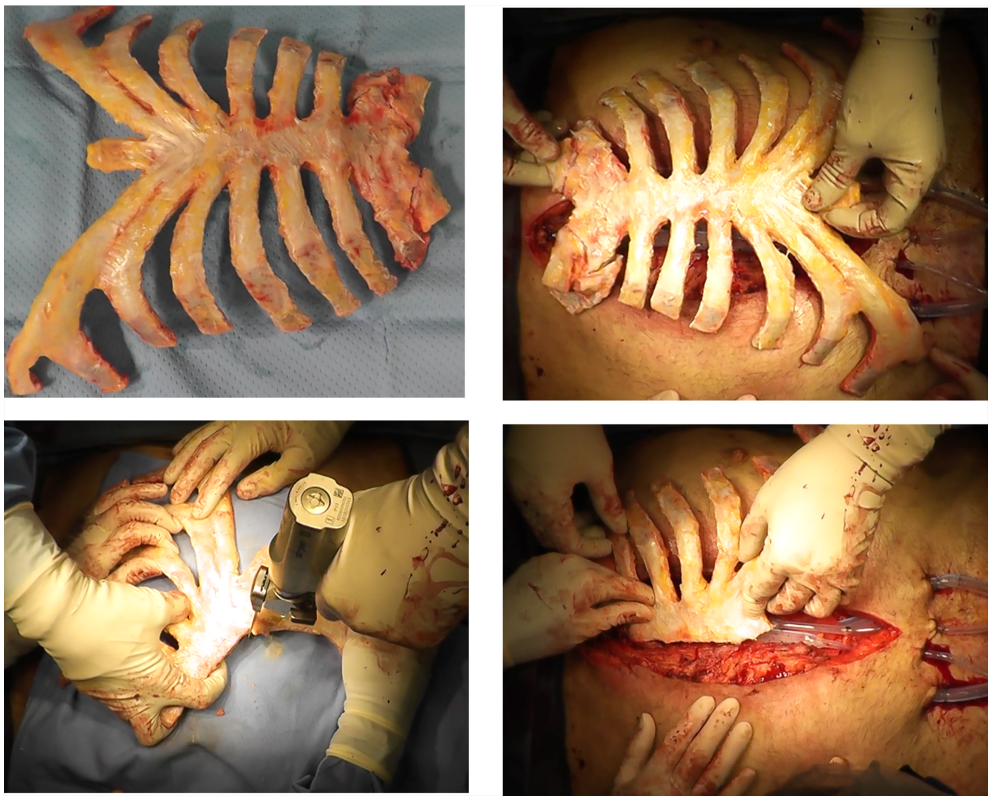

FIGURE 2
The sterno-chondral graft preparation. The sternum is usually derived from a tissue bank *via* an aseptic procedure.

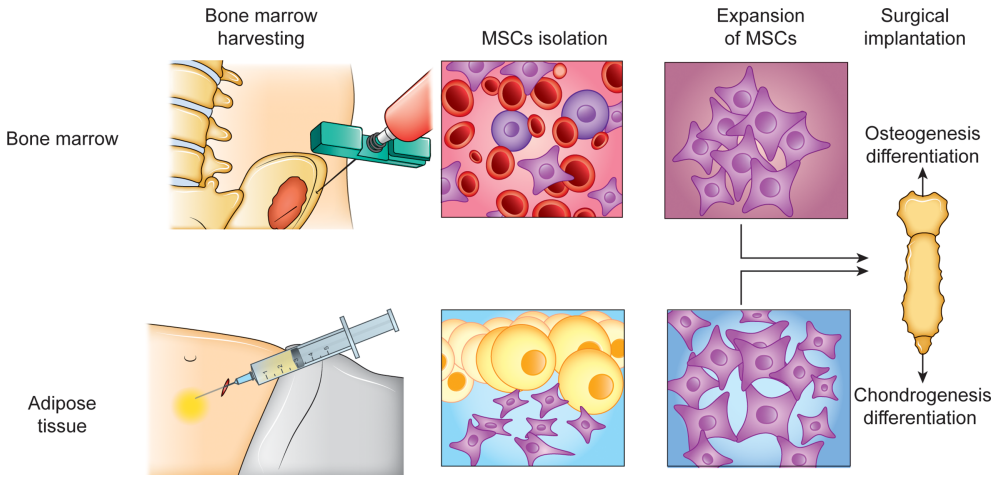


FIGURE 3
Regenerative approach for sternum reconstruction. Cell therapy approach specifically based on the transplant of MSCs for sterno-chondral reconstruction is a method for long term regeneration. Bone marrow (BM) and adipose tissue (AD) as sources for MSCs isolation, using their capacity to differentiate into both osteogenic and chondrogenic cells.

marrow mesenchymal stem cells (BMSCs) are the most widely used for musculoskeletal regeneration because they can differentiate into adipogenic, osteogenic, chondrogenic, and myogenic cells; however, adipose-derived mesenchymal stem cells (ADSCs) have shown greater genetic stability, proliferation capacity, and less senescence than BMSCs (85, 86) (Figure 3).

The new strategies in regenerative medicine involve more complex but tailored approaches in the field of bone and cartilage reconstruction. This is a new chapter in the field of tissue regeneration, although several limitations need to be clarified. In particular, numerous preclinical and clinical trials have confirmed that MSCs can differentiate into cartilage tissue under the influence of chondrogenic factors, facilitating their use for the repair of injured cartilage (87). Moreover, during the process of differentiation, MSCs can produce various extracellular matrices (ECMs) that are essential for the recovery of cartilage function (88). At the targeted repair areas, MSCs can release various cytokines, growth factors (GF), and chemokines, driving endogenous MSCs to enter lesion areas and creating an appropriate regenerative microenvironment while simultaneously aiding the regeneration of cartilage tissue (89). The combination of MSCs with exogenous biochemical or biomechanical stimuli, in addition to customized engineered scaffolds in MSC-based therapies, represents a significant advance in cartilage regeneration (89, 90).

Additionally, microfracture surgery is a commonly used technique for early-phase cartilage injury. In microfracture surgery, the surgeon drills several holes in the subchondral bone to discharge BMSCs, cytokines, and platelets from the marrow, which can stimulate the regeneration of cartilage (91, 92). Microfracture surgery is preferred by the majority of orthopedic surgeons for its simple single-stage technology and confined invasiveness (92). Furthermore, this approach was 90% successful in relieving pain postoperatively in cartilage lesions (93, 94). After performing microfracture surgery on full-thickness cartilage defects, histological evaluation of the early changes of the cartilage showed that the repair was induced by endochondral ossification in the depths of the microfracture punctures (95). Furthermore, endochondral ossification could activate osteoclasts and induce the reconstruction of cartilage, which regenerates earlier than subchondral bone. The Food and Drug Administration considers microfracture surgery to have a good prognosis in the treatment of small-sized cartilage injuries. Many types of research have shown that microfracture surgery can postpone cartilage degeneration, regardless of the lesion size (96, 97). However, some studies have reported that the post-surgical microenvironment of microfractures failed to induce the appropriate differentiation of BMSCs, leading to the formation of relatively unstable fibrous tissue rather than cartilage tissue (98).

Recently, in an attempt to identify an easy-to-handle cell substitute for MSCs, the stromal vascular fraction (SVF) was characterized for application in preclinical and clinical scenarios (95). The SVF includes not only ADSCs, but also a heterogeneous group of cells, such as progenitor cells, endothelial cells, fibroblasts, monocytes, macrophages, immune cells, muscle cells, pericytes, $CD34^+$ cells, GFs, adipocytes, and stromal components (99).

Like MSCs, the SVF is proangiogenic and immunomodulatory, and its cellular components can differentiate and proliferate, all of which make it suitable for tissue regeneration (97). The advantage of using SVF over expanded ADSCs becomes immediately apparent because the SVF, obtained *via* digestion with collagenase and centrifugation of autologous adipose tissue, can be easily harvested by the patient themself through liposuction. It therefore requires minimal handling and contains ADSCs in a density ranging from 0.06 to 4 CFU-f. Thus, the SVF could be injected directly into damaged tissue, reducing inflammation, promoting regeneration, and resulting in reduced healthcare costs and fewer hours of hospitalization (99–101). Indeed, SVF allows for a "one-step" surgical procedure whereby the SVF can be harvested and implanted in the same surgical session, without requiring *in vitro* expansion (101, 102). This procedure involves minimal cell manipulation and low culture-related risks, with no specific regulatory requirements for clinical translation, thus expediting surgery. The process, from surgical harvesting of adipose tissue to the production of the SVFs and their seeding on a scaffold, hydrogel, or their direct injection, takes a maximum of 4 hours (101, 102).

The first reported example of successful sternal reconstruction using adipose-derived SVF stem cells was reported in 2015 by Zain Khalpey et al., in addition to traditional techniques (103). They used a 3D-printed model for setting the sternum and SVF, with the injection of 300 million cells both locally and intravenously, deposited at the level of the healed area of the sternum (103). The initial results were almost complete pain reduction and sternum nonunion after 6 months. Future studies will be needed to clarify the use of autologous stem cells from the SVF in combination with commonly used surgical approaches (103).

Several protein drugs exploit the fact that bone regeneration can also occur by stimulating tissue repair using GFs, which can regulate MSCs to restore the damaged tissues (104). Small molecules, compared to macromolecules, exert a major effect as they are less immunogenic and have higher osteoinductive potential, in addition to reduced manufacturing costs and contamination risks (105). These benefits have motivated the increasing number of studies regarding these molecular drugs in the last decade. However, there are some limitations to their clinical application: first, they are small enough to also penetrate non-specific cells and trigger undesirable signaling cascades; second, they have non-specific adverse effects; and third, they require an effective delivery strategy, which remains an issue as it is necessary to develop an engineered scaffold that modulates the appropriate amount of the drug (106, 107). More sophisticated studies and examples of drug delivery systems are required to overcome this limitation and support the use of these small drugs in regenerative medicine (108).

## Discussion

In addition to defining new approaches and techniques to reconstruct the chest wall and sternum, there is a need for each surgeon and to consider the most appropriate clinical course, which depends greatly on the clinic and material availability. The scientific community is pushing more and more frequently to use bioabsorbable materials, and the newest approaches are represented by computed tomography with reconstructed 3D images and the production of a 3D printed bioscaffold (67, 68).

These innovations may support different prostheses, tailored not only for the enhancement of the resection but also to adapt it to each patient.

Metcalfe and Ferguson suggested that the skin layers may eventually be replaced with biomaterials or stem cells, although the current ability to regenerate tissue is still too limited for large-scale surgery (109).

In particular, one of the most interesting and studied approach is the use of scaffoldless of neocartilage made by native tissue using expanded chondrocytes and various exogenous stimuli. Strategies have been set for the integration, although several techniques have been developed (109–111). Specifically, these approaches are set on the hurdles of cartilage regeneration, with particular attention on the fibroblast growth factor 18 (FGF-18) which induces cartilage growth and reduces cartilage degeneration in osteoarthritis (112, 113). New recent technologies are able to induce juvenile chondrocytes generation with MSCs (114) and scaffolds now include biphasic, osteochondral designs that may immediately bear load (115).

The scaffoldless used also allow to the formation of constructs that can be immediately load-bearing upon implantation (36, 116). Another emerging approach is represented by the use of scaffolds with moieties, such as N-hydroxysuccinimide, that is able to bind collagen (117). The stimulation of the neocartilage by mechanical (28), anabolic (65), and, potentially, catabolic stimuli (65) may result in a synergistic interaction in cartilage formation. For FDA, new cartilage therapies should be resistant for long time. However, it is not well defined the calibration of the toughness and hardness, for the resistance to wear. In addition to mineralization, data on cartilage crosslinks in engineered or repair cartilages are not defined and described yet (118, 119). The next step of the use of new cartilage will be the durability test. However, though currently healing of cartilage defects continues to be elusive, given that emerging technologies are being validated clinically, the field is primed for an explosion of cartilage regeneration techniques that should excite those suffering from cartilage afflictions (118). Furthermore, while osteoarthritis is currently an intractable problem, exciting new discoveries bode well for the eventual healing of a problem that afflicts a quarter of our adult population. In conclusion, the

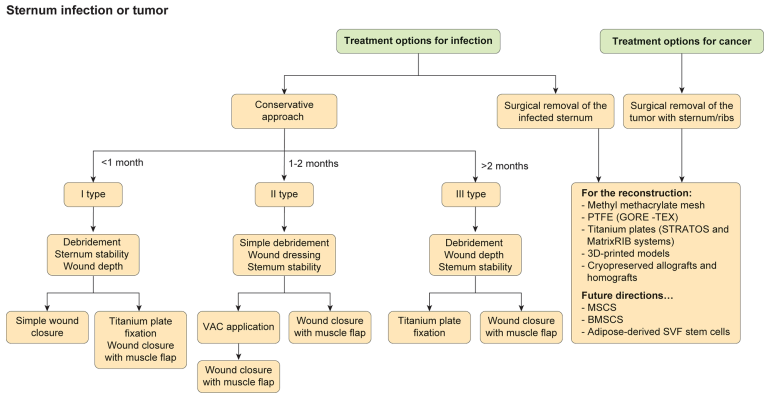


FIGURE 4
Treatments for sternal infections or tumor mass. The flowchart represents the different strategies in case of infection or cancer infiltrating the sternum.

most important aspect regarding chest wall defects is the severity of the lesion, including the condition, presence of infection, and presence or type of cancer. Additionally, the development and selection of appropriate biomaterials to reconstruct the thorax may improve the quality of life and long-term results. The choice to adopt one prosthesis instead of another one depends on the surgeon and specific clinic (Figure 4). Ultimately, a multidisciplinary team is necessary to assure more high-quality decisions.

## Author contributions

(I) Conception and design: BA and FS. (II) Administrative support: FS. (III) Provision of study materials or patients: BA and FS. (IV) Collection and assembly of data: BA and FS. (V) Data analysis and interpretation: BA and FS. (VI) Manuscript writing: BA, VM, LFZR; (VII) Revision end editing: MD, RS, FS. 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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# Lung adenocarcinoma concurrent with congenital pulmonary aplasia of the right upper lobe: A case report

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Lung adenocarcinoma, the most common subtype of lung cancer, has been always imposed serious threat to human health. Congenital pulmonary dysplasia (CPD) lacking typical clinical manifestations is a rare developmental anomaly. Pulmonary aplasia, the rarest subtype of CPD, may present with a variety of symptoms and is frequently associated with other abnormalities. This report describes an 81-year-old woman who presented with an irritant cough. Chest computed tomography (CT) and three-dimensional (3D) reconstruction revealed an irregular mass with a diameter of 5 cm in right lower lobe adjacent to the hilum. CT also indicated a rightward mediastinal shift and the complete absence of ipsilateral upper lobar tissue with bronchus ending in a terminal cecum, resulting in a diagnosis of pulmonary aplasia. The patient accepted lobectomy and lymph node dissection without complication, histopathologic examination combined HE staining with immunohistochemistry identified the tumor as adenocarcinoma. Three months after surgery, the patient was free of respiratory symptoms without chest pain. This report highlights the necessity of comprehensive evaluation for lung malignancy concurrent with CPD and the importance of identifying the diagnosis of pulmonary dysplasia.

KEYWORDS

**pulmonary aplasia, lung adenocarcinoma, CPD, lung abnormalities, 3D CT reconstruction**

## Introduction

Lung cancer is one of the most frequently diagnosed malignant tumors worldwide (1). In recent years, the incidence of lung adenocarcinoma (LUAD) has increased significantly, accounting for nearly 40% of all lung malignancies. In contrast, congenital pulmonary dysplasia (CPD), involving agenesis, aplasia, and hypoplasia, is

a rare developmental anomaly of the respiratory system with unclear aetiology (2). Unilateral pulmonary dysplasia of left lung has a higher incidence and a better prognosis than dysplasia of right lung and bilateral dysplasia, especially in preterm infants. Pulmonary aplasia, defined as an undeveloped bronchial primordium combined with a complete absence of lung tissues, is the least common subtype of CPD and is frequently associated with abnormal development of the cardiovascular system, gastrointestinal tract and other organs (3–5). The present report describes an elderly woman who was diagnosed of lung adenocarcinoma in right lower lobe concurrent with pulmonary aplasia of ipsilateral upper lobe, but without other developmental abnormalities.

## Case presentation

An 81-year-old Chinese woman, non-smoker, with irritant cough for 2 months was referred to the Department of Thoracic Surgery. She initially manifested dry cough without other respiratory symptoms including fever, chest pain, wheezing and hemoptysis. There was no history of hypertension, diabetes, carcinoma, and relevant familial diseases. On physical examination, breath sounds were slightly decreased in the right lower lobe without wet or dry rales, and abnormal cardiechema was not heard. Blood examination demonstrated that complete blood count, tumor markers, blood glucose and biochemical indicator were normal. Arterial blood gas analysis showed a pH of 7.47, a $PO_2$ of 74.1 mmHg, a $PCO_2$ of 41.5 mmHg, an $SO_2$ of 95.3% and an $HCO_3$ concentration of 30.5 mmol/L on room air. Electrocardiography showed sinus rhythm with an incomplete right bundle branch block. Pulmonary function tests revealed %VC of 77.9, %FVC of 81.7, %FEV1 of 64, FEV1% of 64.42 and %DLCO of 82.9.

Chest computed tomography (CT) and three-dimensional (3D) reconstruction demonstrated that the trachea and mediastinum were shifted toward right, accompanied with anterior herniation of the left lung crossing the midline. There were only two lobes in the right thoracic cavity, and the entire right upper lobe, including the lung parenchyma, pulmonary vessels and bronchial tree, was completely absent (Figure 1). In addition, 3D CT reconstruction and bronchoscopy confirmed that the bronchus of the right upper lobe was a terminal cecum, ruling out secondary obstruction due to bronchial stenosis or intrabronchial neoplasm (Figure 2). The volume of each lobe calculated by Turing platform of Huiying Medical Technology before surgery were 221 ml of right middle lobe, 1232 ml of right lower lobe, 834 ml of left upper lobe and 642 ml of left lower lobe. CT images also revealed an irregular mass of hyperdense with a diameter of 5 cm in right lower lobe adjacent to the hilum, surrounding the bronchus and arteries of lower lobe, as well as enlargement of subcarinal and lobar nodes. Bronchoscopy examination discovered a neoplasm in the right basal section, and the pathological type of biopsy was adenocarcinoma (Figures 3A-D). Bone scintigraphy, brain MRI and abdominal CT excluded tumor metastases. Echocardiography indicated mild regurgitation of mitral valves and a slight increase of pulmonary tension which were caused by aging of organs, with the normal location and structure of heart and great vessels, suggesting that the pulmonary aplasia of this patient was not combined with cardiovascular malformations.

The Multidisciplinary team including thoracic surgery, anesthesiology, respirology, oncology and radiology, reached a consensus on the treatment of neoadjuvant chemotherapy or operation. The patient refused adjuvant treatment before operation and requested radical surgery of lung cancer. She underwent lobectomy of right lower lobe and lymph node dissection under general anesthesia. A tumor measured 4.5×4×3.5 cm in size was located near the bronchial stump of right lower lobe. The cut surface showed a solid tumor with greyish white color. Immunohistochemical staining of tumor indicated that NapsinA, TTF-1, CK7 were positive expression and CgA, Syn, CD56 were negative expression (Figures 3E, F). Lymph node involvement was as follows: Group 2 lymph nodes (0/1), Group 4 lymph nodes(0/1), Group 7 lymph nodes (2/3), “Group 9 lymph nodes” (0/1), “Group 10 lymph nodes” (2/3), “Group 11 lymph nodes” (1/1) and “Group 12 lymph nodes” (2/2). The combination of HE and immunohistochemical studies lead to a diagnosis of right lung adenocarcinoma (pT2N2M0), which was consistent with preoperative pathological type and staging. Postoperative chest CT and 3D reconstruction indicated more pronounced mediastinal shift toward right and adequate recruitment of the right middle lobe (Figure 4). The volume of each lobe by Turing platform after surgery were 406 ml of right middle lobe, 888 ml of left upper lobe and 762 ml of left lower lobe. The volume of each lobe after operation was significantly increased compared with that before operation. The patient felt well after surgery without complications and refused genetic testing of tumor, targeted therapy, chemotherapy. At follow-up 3 months after discharge by telephone, the patient reported no chest pain or irritant cough.

## Discussion

To our knowledge, this is the first report of lung cancer concurrent with congenital pulmonary aplasia. Lung cancer is the most common type of malignancy and the leading cause of cancer-related deaths around the world, with more than 2 million new diagnosed and 1.6 million died per year (6). About 85% of lung cancer is non-small cell lung cancer (NSCLC), and the incidence of lung adenocarcinoma (LUAD) is increasing year by year (7). Despite the availability of more individualized treatments, including surgery, chemoradiotherapy, and molecular targeted drugs, the prognosis of NSCLC remained poor, with 5-year overall survival rate at 17.7% (8).

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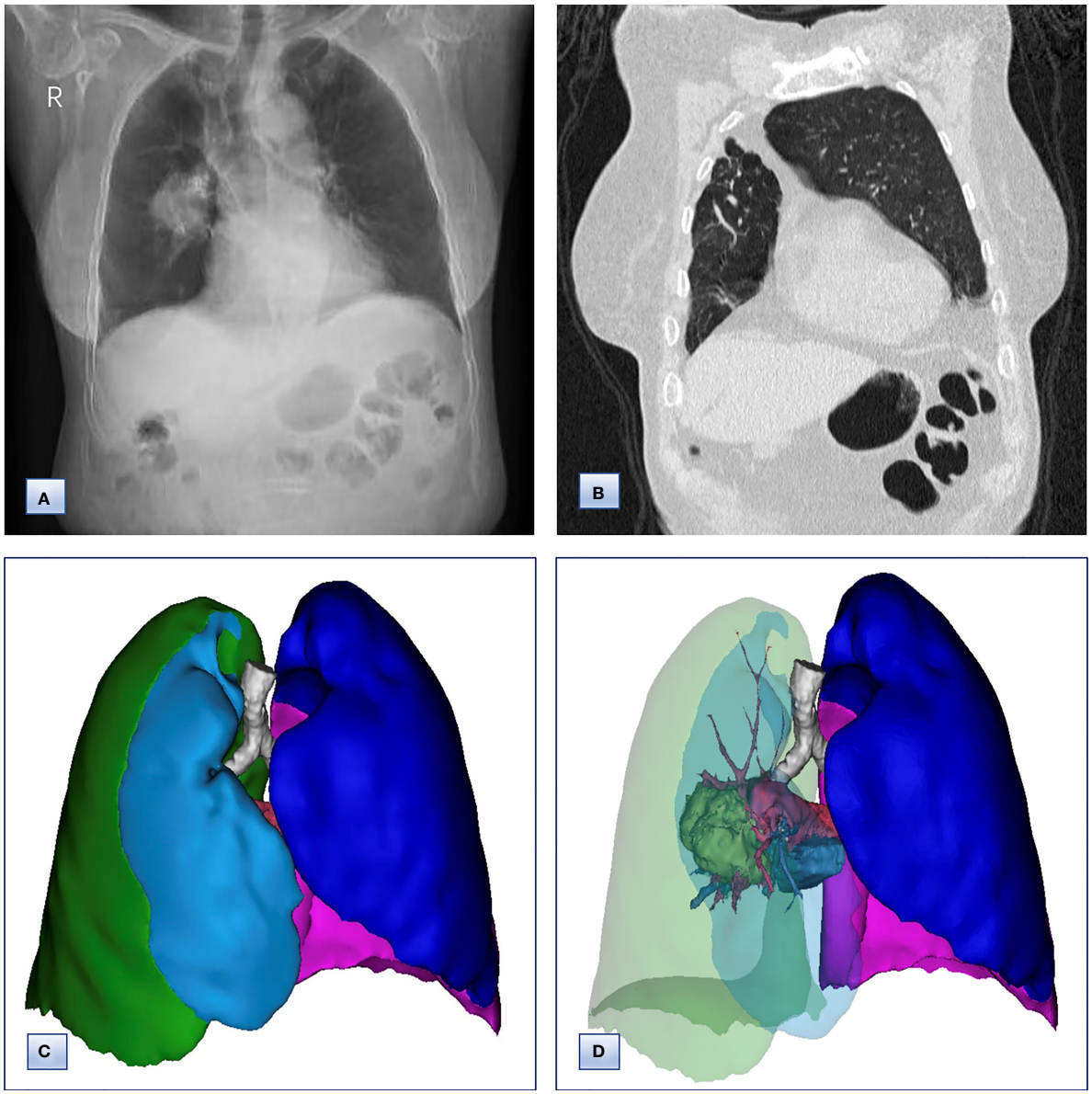


FIGURE 1
Chest radiographs, computed tomography and 3D CT reconstruction before surgery. **(A)** Chest radiographs, revealing that the trachea and mediastinum were shifted to the right. **(B)** Coronal chest CT images, indicating the absence of a horizontal fissure anterior to the aorta, with anterior herniation of the left lung crossing the midline. **(C, D)** 3D reconstruction of CT images, showing **(C)** only two lobes of the right lung and **(D)** complete absence of lung tissue from the right upper lobe, including the lung parenchyma, pulmonary vessels and bronchial tree.

In contrast, pulmonary developmental arrest is an exceedingly uncommon congenital defect, with a prevalence of approximately 1–2 per 200,000 births (9). Congenital pulmonary dysplasia has been classified into three subtypes: agenesis (the complete absence of lung tissue), aplasia (a main bronchus ending in a terminal cecum) and hypoplasia (a bronchus with rudimentary pulmonary tissue). Because of their similar radiography appearance, pulmonary agenesis, aplasia, and hypoplasia have been termed "lung agenesis-hypoplasia complex", which can be present in an entire lung, a lobe or a segment (10).

About 10-20% of newly diagnosed lung cancer patients had a clinical stage of IIIA/N2 before operation. Although the therapeutic strategies for stage IIIA/N2 NSCLC patients are controversial, numerous research have verified that surgery provided longer survival compared with chemotherapy or chemoradiotherapy, especially for patients with lymph nodes smaller than 3 cm (11). Common postoperative complications of

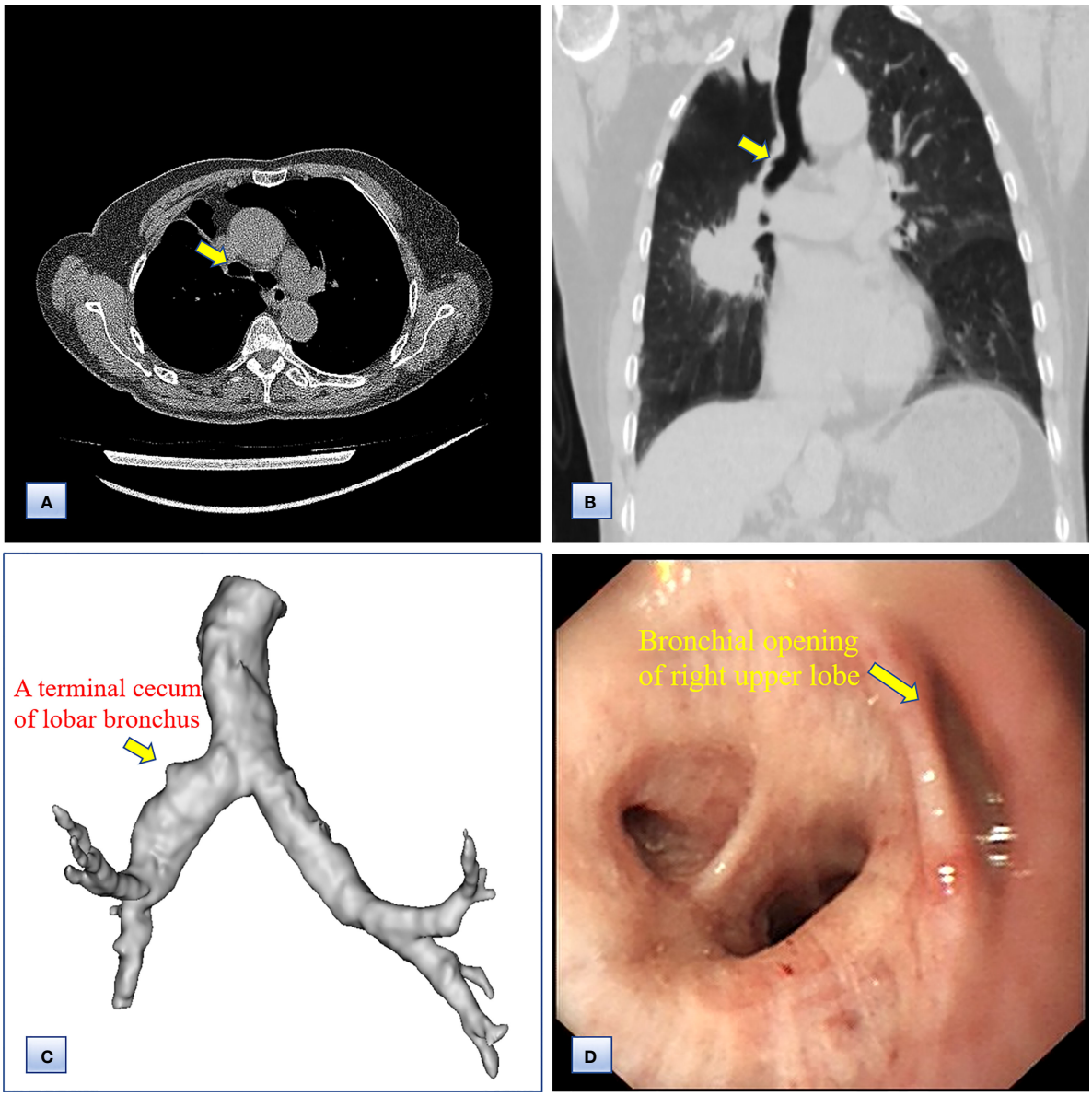


FIGURE 2
Computed tomography and bronchoscopy examination of the bronchi before surgery. **(A, B)** Axial **(A)** and coronal **(B)** chest CT images, showing the bronchus of the right upper lobe as a bud. **(C)** 3D CT reconstruction, indicating that the bronchus of the right upper lobe was a terminal cecum, and that the bronchial tree had not formed at the distal end. **(D)** Bronchoscopy examination, confirming the undeveloped bronchial primordium and ruling out a secondary obstruction.

lobectomy included pulmonary embolus, respiratory failure, bronchopleural fistula, hemothorax, pneumothorax and pneumonia. The patient underwent radical surgery for lung cancer without any postoperative complications, and refused chemotherapy and targeted therapy after surgery.

Pulmonary aplasia, characterized by a rudimentary bronchus without lung tissue, is the least common subtype. However, pulmonary aplasia and agenesis, which are considered as an entity, are usually congenital and resulting in a similar anomaly due to the complete absence of lung (12). The pathogenesis of pulmonary dysplasia is still unclear. Its onset, between the fourth and fifth week of gestation, may be caused by a duplication of the distal upper arm of chromosome 2, de-regulating calcium signal-related proteins and mitochondrial bioenergetic dysfunction (13–16). Patients with pulmonary aplasia were frequently unilateral, with pulmonary dysplasia of left lung being of higher incidence and lower mortality.

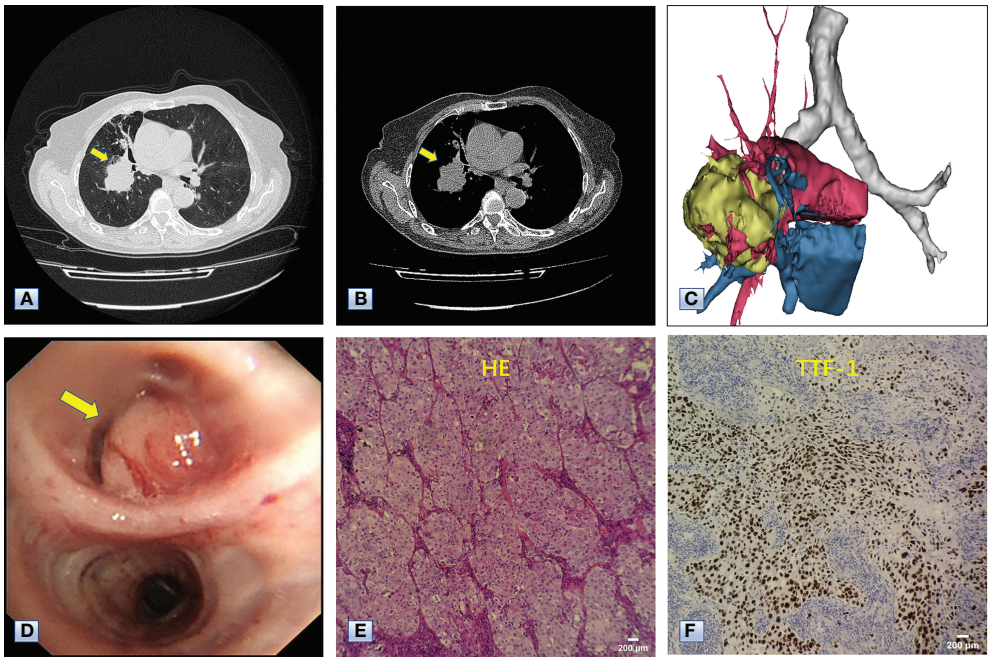


FIGURE 3
Chest CT, bronchoscopy and pathologic examination of the mass in the right lower lobe. **(A, B)** Axial images of chest CT, revealing a mass approximately 5 cm in diameter in the right lower lobe adjacent to the hilum (arrows). **(C)** 3D reconstruction revealing that the mass was adjacent to the hilum and invaded the surrounding vessels, indicating the mass was a malignancy. **(D)** Bronchoscopy results, showing a neoplasm (arrow) in the bronchus of the right basal segment. **(E)** Hematoxylin-eosin staining showing the complete absence of normal alveolar structure, replaced by growing cancer cells with enlarged nuclei and cloudy cytoplasm. **(F)** Immunohistochemical staining with antibodies to TTF-1, indicating that the tumor cells positively expressed TTF-1. The combined results of HE staining and immunohistochemistry indicated that the mass in the right lower lobe was an adenocarcinoma.

Most patients with congenital pulmonary aplasia were diagnosed in infancy or childhood, with few remaining asymptomatic into adulthood. About 50% of patients with unilateral lung dysplasia died within 5 years of birth, whereas bilateral pulmonary dysplasia was life-threatening. Furthermore, neonates with irreversible pulmonary underdevelopment may require long-term cardiopulmonary support (17). The clinical manifestations of pulmonary aplasia including cough, exercise intolerance, recurrent respiratory infections, wheezing and dyspnea were various depending on the number of alveoli. Bronchitis was the most frequent symptom in patients with pulmonary aplasia for the bronchial cecum serving as a source of infections (18). In addition, few patients remaining asymptomatic until adulthood were incidentally diagnosed by imaging examination, possibly due to the developmental defect of less lung tissue without cardiovascular abnormalities.

The diagnosis of pulmonary aplasia which is extremely challenging due to the lack of specific symptoms and signs requires a suspicious medical history, careful physical examination, and comprehensive auxiliary examinations. Physical examination may detect an asymmetrical chest with tracheal deviation and abnormal breath sounds (19). Chest radiographs, CT scan, magnetic resonance imaging (MRI), bronchoscopy and bronchography are critical diagnostic approaches, with 3D CT reconstruction being the most important. Chest radiographs of pulmonary aplasia usually revealed diminished radiolucency and the shift of mediastinum, while CT images can distinguish the absence of lung tissue from atelectasis (20, 21). CT examination of the patient indicated a mediastinal shift toward right, the complete absence of right upper lobe and anterior herniation of left lung, coexisting with an irregular mass in right lower lobe adjacent to the hilus. Moreover, 3D CT reconstruction and bronchoscopy ascertained the bronchus of the right upper lobe as a blind pouch, a indicative of congenital undeveloped bronchial primordium, and ruled out secondary atelectasis caused by tumors, tuberculosis, infection and swollen lymph nodes.

Because patients with unilateral pulmonary aplasia have a significant amount of normal lung tissue, the occurrence and severity of associated malformations may become the most important factor affecting prognosis. Multiple developmental abnormalities have been reported in patients with pulmonary dysplasia, including coarctation of the aorta, esophageal atresia, pulmonary artery atresia, lung herniation, ventricular septal defect

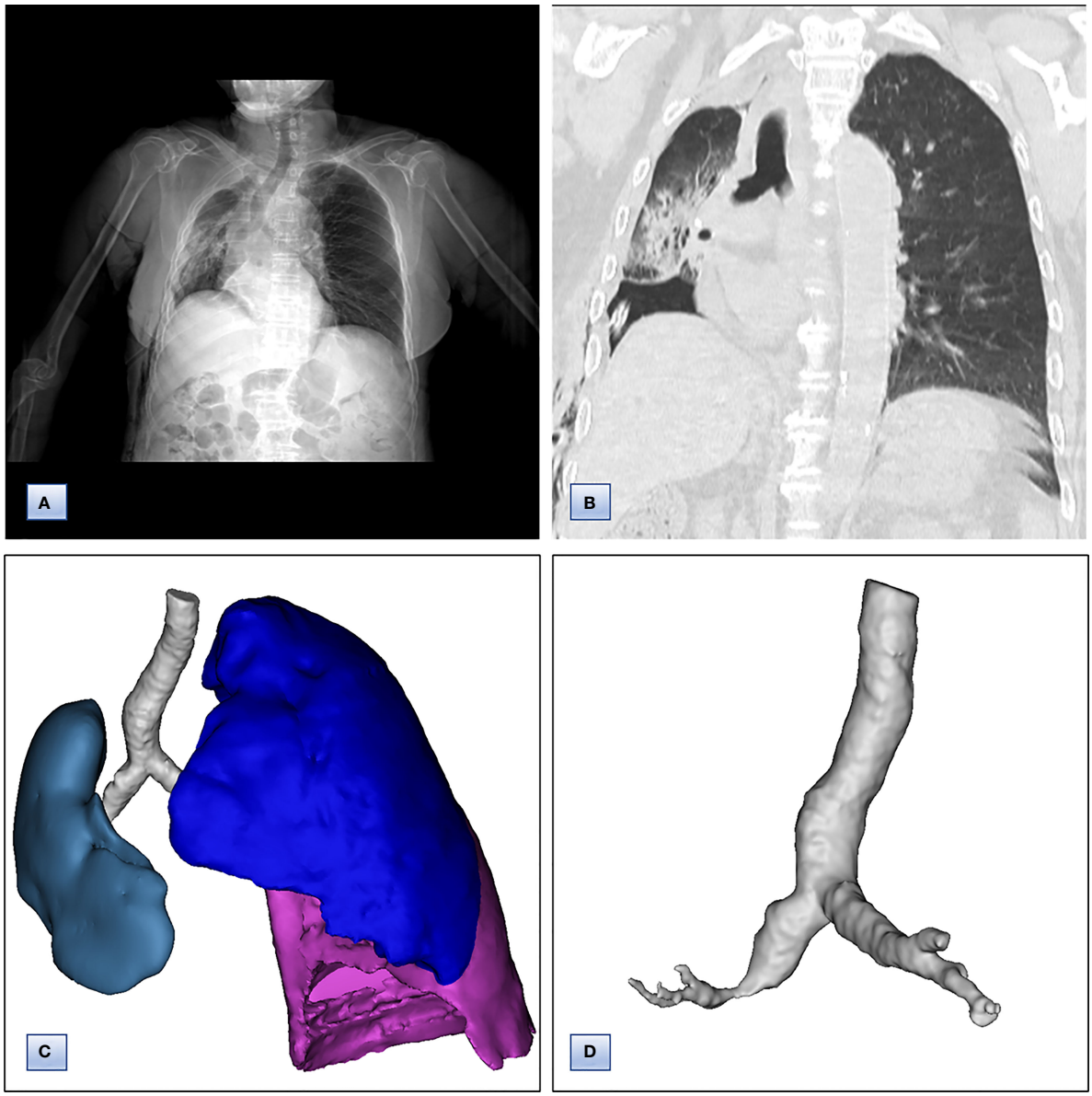


FIGURE 4
Chest computed tomography and7 3D CT reconstruction after surgery. **(A)** Chest CT, revealing that the trachea and mediastinum were more obviously shifted to right than that before surgery. **(B)** Coronal chest CT images, indicating adequate recruitment of the right middle lobe. **(C, D)** 3D reconstruction of CT images, showing **(C)** only middle lobe in right thoracic cavity and **(D)** unobstructed bronchus of right middle lobe.

and tetralogy of Fallot (3, 21–23). Ultrasonography excluded the abnormalities of heart, aorta, main pulmonary artery and abdominal organs. Current consensus is that prophylactic surgery is not required in asymptomatic patients with pulmonary dysplasia. The patient underwent a lobectomy due to the tumor in right lower lobe instead of pulmonary dysplasia in right upper lobe. Pathological examination of HE staining and immunohistochemistry revealed that the tumor was adenocarcinoma with regional lymph node metastasis. Activating mutations in epidermal growth factor receptor (EGFR) have been found in approximately 50-60% of Asian female patient, and this non-smoking female patient refused genetic testing of the tumor. Eight previous reports about patients with right pulmonary aplasia have been published (Table 1), whereas, to our knowledge, pulmonary aplasia of one lobe concurrent with ipsilateral lung cancer has not been reported previously.

In summary, this report described an elderly woman with adenocarcinoma in right lower lobe concurrent with pulmonary aplasia of ipsilateral upper lobe, and emphasized the characteristic changes of CT images and bronchoscopy.

TABLE 1 Summary of right pulmonary aplasia of the scalp.

| No. | Authors, year | Age, Gender | Onset age | Location | Symptom | Surgery | Combined with lung cancer | Other abnormalities | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | D Ryland et al. (1) | 3m, N/A | 1m | Right whole lung | Tachypnoea | No | No | The presence of 13 ribs | Death |
| 2 | T B Buxi et al. (2) | 4d, M | 24 hours after birth | Right whole lung | Respiratory distress | Yes | No | None | Death |
| 3 | Thomas Nowotny et al. (3) | 4m, M | 2m | Right whole lung | An airway infection | Yes | No | None | Clinically stable |
| 4 | Peter Lee et al. (4) | 10m, M | From birth | Right whole lung | Respiratory distress | Yes | No | Patent ductus arteriosus and bronchopulmonary sequestration | Favourable |
| 5 | Se Hwan Kwon et al. (5) | N/A, F | Incidental | Right whole lung | Asymptomatic | No | No | None | Favourable |
| 6 | Arshad et al. (6) | 20y, F | 17y | Right whole lung | Dyspnea on exertion | No | No | MRKH syndrome | Favourable |
| 7 | Augusto et al. (7) | 5y, F | Incidental | Right whole lung | Asymptomatic | Yes | No | Right diaphragmatic hernia | Favourable |
| 8 | Pandey NN et al. (8) | 7m, N/A | From birth | Right whole lung | Respiratory distress and feeding difficulties | No | No | Diaphragmatic hernia and tetralogy of Fallot | Favourable |
| 9 | Present case | | | | | | Yes | | |

MRKH, Mayer-Rokitansky- Küster-Hauser; M, male; F, female; m, months; N/A, not available.

Asymptomatic patients with pulmonary aplasia of one lobe do not require surgical treatment, and can tolerate lobectomy, which plays a vital role in the comprehensive evaluation of lung cancer concurrent with pulmonary dysplasia.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Huai'an Hospital of Xuzhou Medical 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

All authors made a significant contribution to this report. BM and C-XuW drafted the manuscript. X-HZ revised the 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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# Efficacy and safety of brigatinib in *ALK*-positive non-small cell lung cancer treatment: A systematic review and meta-analysis

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**Background:** Brigatinib is a central nervous system-active second-generation anaplastic lymphoma kinase (ALK) inhibitor that targets a broad range of *ALK* rearrangements in patients with non-small cell lung cancer (NSCLC). The current study aimed to analyze the pooled effects and adverse events of brigatinib in patients with *ALK*-positive NSCLC.

**Methods:** The pooled estimates and 95% confidence intervals (CI) were calculated with DerSimonian-Laird method and the random effect model.

**Results:** The pooled objective response rate (ORR) and disease control rate (DCR) of brigatinib were 64% (95% CI 45%-83%) and 88% (95% CI 80%-96%), respectively. The pooled mPFS was 10.52 months (95% CI 7.66-13.37). In the subgroup analyses by treatment line, the highest mPFS was reached in first-line treatment (24.00 months, 95% CI 18.40-43.20), followed by post-crizotinib second-line treatment (mPFS=16.26 months, 95% CI 12.87-19.65), and second-line with any prior ALK tyrosine kinase inhibitors (mPFS=12.96 months, 95% CI 11.14-14.78). Among patients with any baseline brain metastases, the pooled intracranial ORR (iORR) was estimated as 54% (95% CI 35%-73%) for any treatment line, and 60% (95% CI 39%-81%) for first-line treatment. Intracranial PFS (iPFS) reached 19.26 months (95% CI 14.82-23.70) in patients with any baseline brain metastases. Creatine phosphokinase (CPK) increased (44%, 95% CI 26%-63%), diarrhea (37%, 95% CI 27%-48%), and nausea (28%, 95% CI 17%-39%) of any grade were the most common adverse events.

**Conclusion:** Brigatinib is effective in the treatment of patients with *ALK*-positive NSCLC, particularly showing robust intracranial PFS. Brigatinib used as first-line treatment yielded superior PFS compared with brigatinib used as other treatment lines. These results suggested a benefit of using brigatinib earlier in the patient's management. All adverse events are manageable, with CPK increased and gastrointestinal reactions found to be the most common types.

**Systematic Review Registration:** https://inplasy.com/inplasy-2022-3-0142/, identifier (INPLASY202230141).

KEYWORDS

non-small cell lung cancer, ALK-positive, brigatinib, efficacy, adverse events

# 1 Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80-85% of lung cancer cases, which are the most common fatal malignancy and leading cause of cancer mortality worldwide (1). Unfortunately, the prognosis of NSCLC remains poor, with estimated 5-year survival rate of 16%, and more than 50% of patients have advanced disease at diagnosis. For patients with advanced NSCLC, platinum-based chemotherapy is the standard treatment. For these patients, objective response rate (ORR) was approximately 30%; however, the therapeutic effect generally lasts only 4-5 months (2–4). Fortunately, with the increasing understanding of the pathogenesis of NSCLC in the past decades, the prognosis of patients has been improved substantially by using newly developed targeted drugs (5, 6). Anaplastic lymphoma kinase (ALK) gene rearrangement accounts for approximately 3-5% of advanced NSCLC (7). Advanced NSCLC harboring an *ALK* rearrangement (*ALK*-positive NSCLC) can be effectively treated with small-molecule tyrosine kinase inhibitors (TKIs) that target ALK, which have shown stunning efficacy and favorable safety profile in this subgroup of patients (8).

Crizotinib was the first ALK-TKI approved for *ALK*-positive NSCLC by the U.S. Food and Drug Administration (FDA). In first-line treatment, crizotinib achieved ORR from 61 to 74% with a median progression-free survival (PFS) of 8–11 months (9–11). However, almost all patients with *ALK*-positive NSCLC treated with crizotinib eventually develop resistance, leading to disease progression, including the development of central nervous system (CNS) metastases (12–14). Several next-generation ALK-TKIs have been developed including second-generation TKIs such as ceritinib, alectinib, and brigatinib (15–17). These next-generation ALK-TKIs have been proved to be more potent and CNS–penetrant compared to crizotinib and can retain variable activity against different crizotinib-resistant *ALK* mutations (18, 19).

Brigatinib is a new second-generation ALK inhibitor that was developed to overcome resistance to crizotinib. In a multi-center phase II study, brigatinib showed strong effectiveness among patients with crizotinib-refractory *ALK*-positive NSCLC. Among 222 patients receiving one of two dosing regimens of brigatinib (90 mg once daily versus 180 mg once daily with a 7-day lead-in at 90 mg), the confirmed ORRs were reported to be 45% and 54%, with a median PFS of 9.2 months and 16.7 months, respectively (20). Based on findings reported in this phase II study, the U.S. FDA granted accelerated approval to brigatinib in patients with locally advanced or metastatic *ALK*-positive NSCLC who have progressed on or are intolerant to crizotinib in April 2017. Further in May 2020, U.S. FDA also issued full approval for brigatinib for front line treatment. Since first approval of brigatinib, studies have been conducted in clinical and real-world settings that evaluated efficacy and safety of brigatinib in different countries. However, substantial differences have been observed in regard to clinical outcomes, which might be partly attributed to small sample size, variances in patient characteristics and study settings. For example, the ORRs ranged from 0.40 to 0.97 in two recent clinical studies (21, 22). Hence, it is of utmost importance to calculate the pooled effect of brigatinib in order to clarify its efficacy.

In the current study, we conducted a systematic review and meta-analysis to investigate the efficacy and adverse events of brigatinib among patients with *ALK*-positive NSCLC in both clinical and real-world settings. The findings of this study shall enlighten further scientific research and clinical applications.

# 2 Methods

## 2.1 Search strategy

We identified eligible studies through a comprehensive search of PubMed (Medline), EMBASE (Excerpta Medica Database), Cochrane Library and Web of Science up to August 2021. Keyword search terms were ('brigatinib') and ('non-small cell lung cancer' or 'NSCLC'). We have also inspected the reference list of the retrieved studies in case we would miss relevant studies which met our inclusion criteria. Additionally, in order to obtain the latest information, conference abstracts that were presented in the 57th Annual Meeting (Virtual) of the American Society of Clinical Oncology (ASCO) June 4–8, 2021, and European Society for Medical Oncology (ESMO) Congress September 16-21, 2021 were also screened.

## 2.2 Selection criteria

Eligible studies were selected based on prespecified PICOS criteria. P (participants): *ALK*-positive NSCLC; I (intervention): oral brigatinib therapy; C (control): none; O (outcomes): ORR, disease control rate (DCR), PFS, intracranial ORR (iORR), intracranial PFS (iPFS), or adverse events (AEs); S (study designs): phase I, II or III clinical study, prospective cohort study, retrospective cohort study, or real-world evidence study. Articles dealing with mechanism research, pharmacology research, other non-efficacy research, or those not in English were excluded. We did not exclude studies involving patients pretreated with prior ALK inhibitors, nor did we exclude studies involving patients receiving chemotherapy. Where there were duplicate studies, articles published earlier or those that provided more detailed information or with longer follow-up time were selected (Figure 1). Two independent reviewers screened the articles according to the criteria to determine eligibility, and a third researcher resolved the differences if any.

## 2.3 Data extraction and analysis

This study conducted data analysis according to the PRISMA Statement (23). The following information was extracted in a predesigned form: first author, publication year, study design, population, age, male percentage, sample size, country, follow-up time, brigatinib medication, brain metastases at diagnosis, previous use of ALK-TKI prior to brigatinib, ORR, DCR, PFS, iORR, iPFS, and AEs. One researcher was responsible to extract the data independently, whereas another reviewed the data to ensure accuracy.

## 2.4 Statistical methods

To evaluate the therapeutic effect of brigatinib in patients with *ALK*-positive NSCLC, we analyzed the best responses. The estimated odds ratio/percentage/months and 95% confidence interval (95% CI) of the ORR, DCR, PFS, iORR, and iPFS were extracted. In cases when multiple sets of data were provided in a study, we extracted only the best response data using standard dosage treatment (180 mg qd with 7-day 90 mg lead-in).

The toxicities and AEs reported in each study were classified and merged. Only the incidence of 10 common AEs was analyzed and reported. Stata 14 was used for data merger analysis and heterogeneity tests. Heterogeneity among the studies was assessed by the Cochran Q test and the $I^2$ statistics. For the Q statistic, $P < 0.10$ was considered statistically significant for heterogeneity. For the $I^2$ statistic, which indicates the percentage of the observed between-study variability due to heterogeneity rather than chance, the following ranges were used: no heterogeneity ($I^2 = 0\%–25\%$), low heterogeneity ($I^2 = 25\%–50\%$), moderate heterogeneity ($I^2 = 50\%–75\%$), and high heterogeneity ($I^2 = 75\%–100\%$). DerSimonian-Laird method and the random effect model were used to calculate pooled effect size and draw forest plots. For studies with moderate or higher heterogeneity ($I^2 \geq 50\%$, $P<0.10$), we also conducted meta-regression to analyze the sources of heterogeneity in the studies. Finally, sensitivity analysis was also conducted in order to explore the impact of excluding an individual study on the pooled results. Two-tailed $P$ value < 0.05 was defined as with statistical significance for all tests, except for heterogeneity test between studies.

The protocol of this study has been registered in INPLASY (ID: INPLASY202230142).

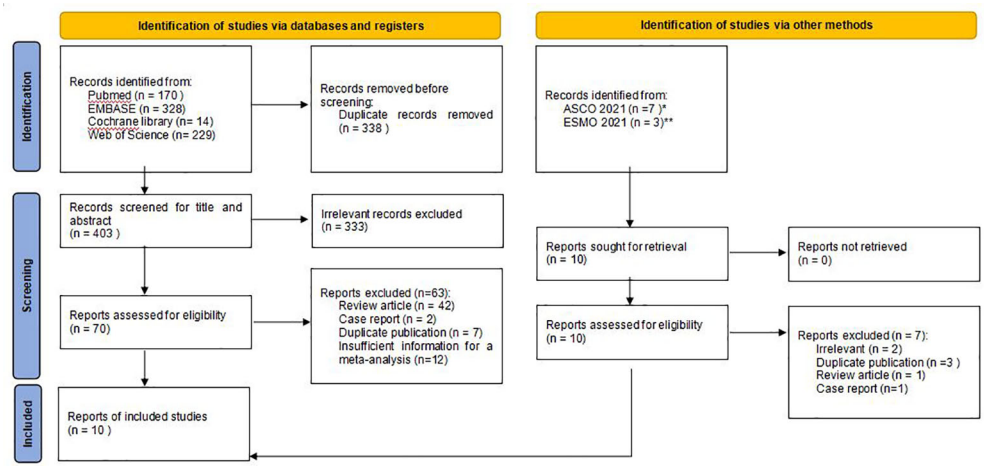


FIGURE 1
Flow chart of study selection. ASCO*: American Society of Clinical Oncology; ESMO**: European Society for Medical Oncology.

## 2.5 Quality assessment

As only single-arm cohort studies were included in the final analysis, CASP-Cohort-Study-Checklist was used for quality assessment (24). The CASP-Cohort List, a quality assessment tool, was proposed by the Oxford Evidence-based Medical Center in 2004 for cohort studies. The tool consists of 12 questions and 3 sections which were used to evaluate each study.

## 2.6 Assessment of publication bias

Stata 14 with meta-regression was used to analyze the sources of heterogeneity. Publication bias was inspected by a Deeks funnel plot. In addition, Begg's and Egger's test was also conducted to testify the funnel plot asymmetry.

# 3 Results

## 3.1 Eligible studies

We retrieved 741 articles from 4 databases in the initial search. After reading the title and abstract, excluding duplicate and irrelevant articles, we selected 70 articles for further review. After manual reading of the full text, 62 papers were excluded due to the following reasons: review article (n=42), case report (n=2), duplicate publication (n=6), or insufficient information for a meta-analysis (n=12). In addition, 3 conference abstracts with most updated results (ALTA, BrigALK2, J-ALTA) were also included after searching and reading from abstracts presented in ASCO 2021 (n=2), and ESMO Congress 2021 (n=1) (22, 25, 26). Finally, 10 articles with 942 patients were included in this meta-analysis (Figure 1) (21, 22, 25–33).

## 3.2 Study characteristics and quality evaluation

Baseline features of each included study are shown in Table 1. The final analysis included 10 studies that consisted of a total sample size of 942, including six randomized clinical trial studies and four retrospective real-world evidence studies. The 10 studies were first published in 2018 and most recently in 2021. The sample size ranged from 20 to 301, covering Asia, Europe, the Americas, and other regions. The median age ranged between 43-61 years. Male patients accounted for 41% to 60%, and 17% to 82% of the included subjects had brain metastases at baseline. Only two studies used brigatinib as first-line treatment. The details about treatment lines and number of participants for each study are also presented in Supplemental Table 1.

The result of literature quality assessment is shown in Appendix 1. Detection bias was moderate as only 5 studies (50%) used an independent review committee (IRC) to assess disease progression or treatment response.

## 3.3 Meta-synthesis of results

Six studies reported results of ORR. The ORR in the combination group was 64% (95% CI, 45%-83%), but large heterogeneity of the overall ORR was observed, which was statistically significant ($I^2$ = 94.2%, P<0.001) (Figure 2A). It is worth mentioning that brigatinib was used as first-line treatment in two studies with a total of 169 patients (22, 27). The subgroup analysis indicated a higher ORR of 86% (95% CI, 63%-108%) among patients who received brigatinib as first-line treatment (Supplemental Figure 1).

The DCR was presented in four eligible studies, containing 35 patients treated with brigatinib as first-line drug, and 182 patients treated with brigatinib as second-line or higher line drug. The pooled DCR was estimated as 0.88 (95% CI, 0.80-0.96) (Figure 2B). Chi-square test and $I^2$ statistic demonstrated the statistical heterogeneity ($I^2$ = 62.2%, $P$=0.047), indicating moderate heterogeneity in the overall DCR.

Nine included studies reported PFS. It should be mentioned that these nine studies did not completely overlap with the six studies included in the analysis for ORR. The reason was that some of the six studies provided both ORR and PFS, whereas others only provided ORR or PFS. The pooled PFS was 10.52 months (95% CI, 7.66-13.37) (Figure 3A). Cochran's Q and $I^2$ statistics showed moderate level of heterogeneity with statistical significance ($I^2$ = 86.6%, $P$<0.001). Subgroup analyses based on different treatment lines were also performed for PFS (Figure 3B). Only one study (n=137) used brigatinib as first-line treatment, providing a median PFS of 24.00 months (95% CI, 18.40-43.20). Two studies (n=119) investigated efficacy for brigatinib as second-line medication post crizotinib (PFS=16.26 months, 95% CI, 12.87-19.65). Two other studies (n=65) were conducted among NSCLC patients using brigatinib as second-line treatment after use of any prior TKI (PFS=12.96 months, 95% CI 11.14-14.78).

The iORR was presented in four eligible studies, including 78 patients with any baseline brain metastases or measurable CNS metastases. The effects of brigatinib treatment on iORR are shown in Figure 4. Estimations of individual iORR ranged from 25% to 66%, which resulted in a summary iORR of 54% (95% CI: 35%-73%). Moderate heterogeneity was detected ($I^2$ = 56.6%, $P$=0.075) and a random effect model was selected to summarize effect size. Subgroup analysis was also conducted to evaluate the iORR efficacy of brigatinib when used as first-line treatment. Analysis of two studies with a total of 52 patients indicated a higher iORR of 60% (95% CI, 39%-81%) among patients who received brigatinib as first-line treatment (Supplemental Figure 2).

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TABLE 1 Characteristics of the 10 included studies.

| Study | Study design | Population | Age (years) | Male % | Sample size | Country | Follow-up (months) | Brigatinib dose | Brain metastases at diagnosis | ALK-TKI before brigatinib |
|---|---|---|---|---|---|---|---|---|---|---|
| Camidge 2018 (32) | Single-arm, open-label, multicenter study; phase II, open-label, multicenter study | PhI/II (Phase 1/2 trial (NCT01449461). Age ≥ 18 years, adequate organ and hematologic function, and one or more measurable lesions. | 53 (30-73) | 52% | 50 | USA and Spain | 24.9 (0.2-47.6) | 90-240 mg/day | 100% | ALK-TKI naive or pretreated |
| Lin 2018 (28) | Multicenter retrospective study | Patients were identified at three participating institutions. All patients had advanced NSCLC with an *ALK* rearrangement. Patients had to have received alectinib with progression of disease before receiving brigatinib. | 55 (22-76) | 41% | 22 | USA | – | NA | 18 (82%) | ALK-TKI pretreated: 1: 5 (23%); 2: 15 (59%); 3: 4 (18%); |
| Heredia 2020 (31) | Retrospective observational study | Patients ≥18 years of age with a pathologically confirmed diagnosis of locally advanced or metastatic disease (stage IIIB–IV) NSCLC, *ALK* positive and progression after at least one prior ALK-TKI therapy or treatment discontinuation due to intolerable toxicity. | 53.43 (27–73) | 56.5% | 46 | America | 9.3 (0.26–28.39) | 180 mg qd with 7-day 90 mg lead-in | 25 (54.3%) | ALK-TKI pretreated |
| Descourt 2021 (26) | Retrospective multicentric study (BrigALK2) | Inclusion criteria were: at least 18 years old; advanced NSCLC; *ALK* positive NSCLC; previous treatment with at least one ALK inhibitor including crizotinib. | 60 ± 12.7 | 40.4% | 183 | France | 40.5 (38.4-42.4) | 180 mg qd with 7-day 90 mg lead-in | 131 (71.1%) | ALK-TKI pretreated |
| Camidge 2021 (27) | Phase III, open-label, randomized study (ALTA-1L) | Adults with locally advanced/metastatic NSCLC and ≥ 1 measurable lesion who had not received prior *ALK*-targeted therapy. Asymptomatic or stable CNS metastases were permitted. | 58 (27-86) | 50% | 137 | 20 countries | 40.4 (0-52.4) | 180 mg qd with 7-day 90 mg lead-in | 47 (34.1%) | ALK-TKI naive |
| Nishio 2021 (29) | Single-arm, multicenter, open-label study (J-ALTA) | Eligible patients (≥20 years of age) confirmed stage IIIB, stage IIIC, or stage IV NSCLC with documented *ALK* rearrangement. | 53 (23–82) | 47% | 47 | Japan | 12.4 | 180 mg qd with 7-day 90 mg lead-in | 8 (17.0%) | ALK-TKI pretreated |
| Stinchcombe 2021 (21) | Single arm phase 2 trial (NCT02706626) | Patients were required to have advanced *ALK* + NSCLC, progression | 55 (32-71) | 60% | 20 | USA | 22 (0.89-30.5) | 180 mg qd with a 7-day | 11 (55%) | ALK-TKI pretreated |

*(Continued)*

TABLE 1 Continued

| Study | Study design | Population | Age (years) | Male % | Sample size | Country | Follow-up (months) | Brigatinib dose | Brain metastases at diagnosis | ALK-TKI before brigatinib |
|---|---|---|---|---|---|---|---|---|---|---|
| | | on a next generation ALK TKI, ECOG performance status of 0-2, adequate organ function, and measurable disease. There was no restriction on the number of prior therapies. | | | | | | lead-in at 90 mg | | |
| Popat 2021 (30) | Retrospective chart review (UVEA-Brig) | Adults with *ALK*-positive mNSCLC, including those with brain lesions, resistant to or intolerant of ≥1 prior ALK inhibitor and ECOG performance status ≤3 were eligible. | 53 (29–80) | 43% | 104 | Austria, France, Germany, Ireland, Italy, Spain, Norway, Switzerland, UK | 16.5 | 89.4% received standard dose | 66 (63%) | ALK-TKI pretreated |
| Gettinger 2021 (25) | Single -arm, open-label, multicenter study (Phase I/II); phase II, open-label, multicenter study (ALTA) | Phase I/II (NCT01449461) was a single arm trial with nine sites in the United States and Spain, and ALTA (NCT02094573) was a randomized phase II trial with 71 sites in 18 countries. In both trials, eligibility stipulated age ≥ 18 years, adequate organ and hematologic function, and one or more measurable lesions. | Phase I/II 54 (29,83) Arm A 51 (18,82) Arm B 57 (20,81) | Phase I/II: 51%; ALTA: Arm A 45%; Arm B 42 | Phase I/II: 79; ALTA: Arm A: 112; Arm B: 110 | 20 countries | Phase I/II 27.7 (0.2,88.3); ALTA: Arm A 19.6 (0.1,62.8); Arm B 28.3 (0.1, 66.8) | 180 mg qd with a 7-day lead-in at 90 mg | Phase I/II study: 63%; ALTA: 67% (arm B) | ALK-TKI naive or pretreated |
| Kondo 2021 (22) | Phase 2, single-arm, open-label, multicenter study (J-ALTA) | Adults (aged ≥20 y), stage IIIB/IIIC/IV *ALK* + NSCLC. TKI-naive. | 61 (29,82) | 47% | 32 | Japan | 14.2 (3,19) | NA | 7 (22%) | ALK-TKI naive |

NA, Not Available.

Three studies reported iPFS among a total of 167 patients with any baseline brain metastases. The effects of brigatinib treatment on iPFS are shown in Figure 5. Median iPFS ranged from 14.60 months to 24.00 months. The pooled iPFS was 19.26 months (95% CI: 14.82-23.70). No heterogeneity was detected based on testing for included studies ($I^2$ = 0.0%, $P$=0.419).

## 3.3.1 Sensitivity analysis

Sensitivity analysis was conducted for studies that showed moderate or high heterogeneity. Results are shown in Supplemental Figure 3. Results showed that the study by Kondo et al. has the greatest impact on summary results of ORR (Supplemental Figure 3A). After excluding the study by Kondo et al., the summary ORR was 0.57 (95% CI 0.41-0.73) (data not shown). All 95% CI of ORR in the sensitivity analysis ranged between 0.36-0.88.

For sensitivity analysis of DCR, the study by Kondo et al. also showed the greatest impact on pooled effect size (Supplemental Figure 3B). After excluding the study by Kondo et al., the summary DCR was 0.83 (95% CI 0.78-0.90) (data not shown). The range of 95% CI in sensitivity analysis was 0.77-1.00.

## 3.3.2 Source of heterogeneity

First, we performed a meta-regression analysis of the ORR. Sample size was used as a covariate to perform single factor

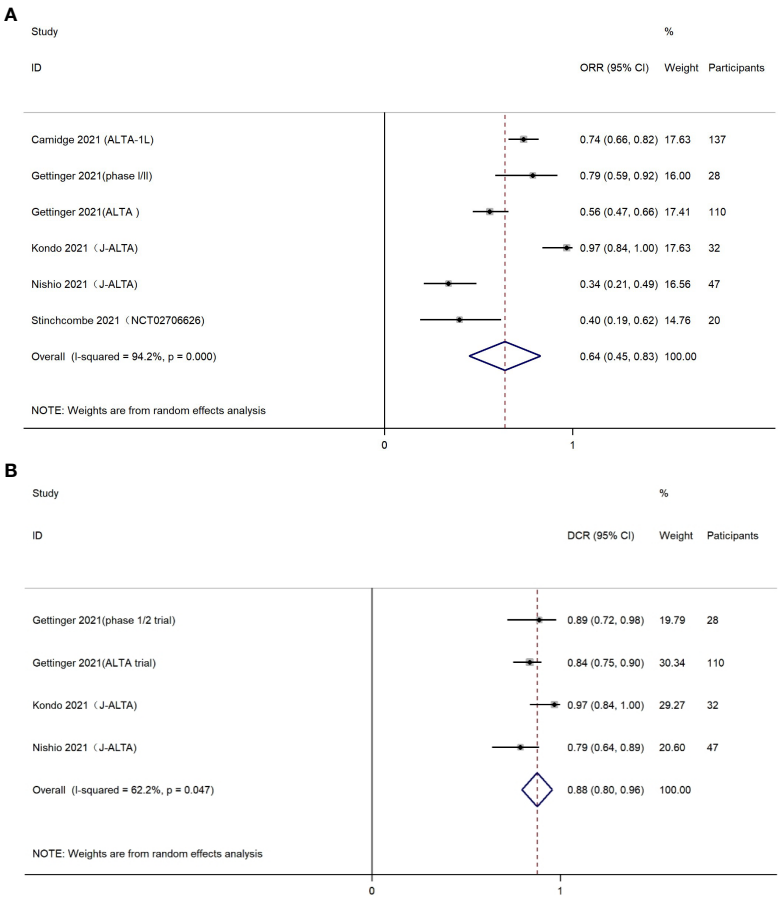


FIGURE 2
**(A)** Forest plot of objective response rate (ORR); **(B)** Forest plot of disease control rate (DCR).

meta-regression analysis (*P*=0.925) (Supplemental Figure 4A). Sample size did not contribute to heterogeneity. Subsequently, we also used brain metastases at baseline as a single covariate to conduct univariate meta-regression analysis. Baseline brain metastases had no significant effect on heterogeneity either (*P*=0.890) (Supplemental Figure 4B).

We also performed meta-regression analysis for both DCR and PFS. However, both sample size and baseline brain metastases were not contributors to heterogeneity for these two outcome effects (Supplemental Figures 5, 6). Because of incomplete data collection of study factors, it is difficult to identify the sources of heterogeneity.

## 3.4 Assessment of AEs

A total of 7 studies provided data on AEs, which reported 54 AEs. Because different studies may have different descriptions of the same AEs and the classification of AEs is different, we reclassified 11 AEs, which were mentioned in at least five studies (Table 2). The Forest plot is shown in Figure 6, in which AEs were shown based on the following five groups: 1) gastrointestinal function abnormal; 2) general disorders; 3) investigation; 4) skin and subcutaneous tissue disorder; and 5) vascular disorders. Creatine phosphokinase (CPK) increased, diarrhea, and nausea were the three most common AEs and occurred in 44% (95% CI 26-63%), 37% (95% CI 27-48%) and 28% (95% CI 17-39%) of patients, respectively.

## 3.5 Assessment of publication bias

Funnel plot of DCR and PFS showed asymmetry, while ORR, iORR, iPFS did not show asymmetry (Supplemental Figure 7). Statistical tests for funnel plot asymmetry, both Begg's test and Egger's test, did not detect statistically significant asymmetry for all effect size evaluated, except iPFS (*P*=0.022) (Supplemental Table 2).

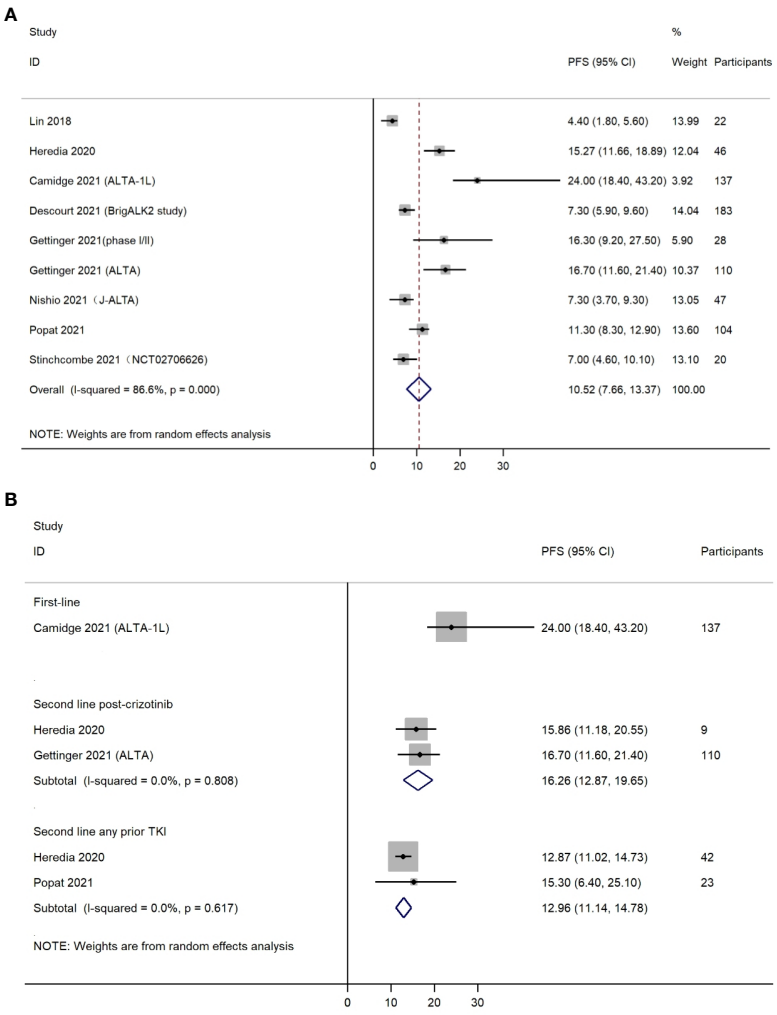


FIGURE 3
**(A)** Forest plot of overall progression free survival (PFS); **(B)** Forest plot of progression free survival (PFS) by treatment lines.

# 4 Discussion

## 4.1 Summary of the findings

The current meta-analysis included 10 articles consisting of 6 clinical trials and 4 real-world evidence studies. Data from 942 patients were analyzed. The ORR and DCR of patients with *ALK*-positive NSCLC were 0.64 (95% CI 0.45-0.83) and 0.88 (95% CI 0.80-0.96), respectively, and the PFS was 10.52 months (95% CI 7.66-13.37). In subgroup analyses by treatment line, brigatinib used as first-line treatment showed the longest median PFS (24.00 months, 95% CI 18.40-43.20). For intracranial efficacy, the pooled iORR was 0.54 (95% CI 0.35-0.73), while iPFS reached 19.26 months (95% CI 14.82-23.70). CPK increased, diarrhea, and nausea were the most common AEs of any grade. These results indicate that brigatinib is effective in the treatment of patients with *ALK*-positive NSCLC, particularly showing robust intracranial PFS. Brigatinib used as first-line treatment yielded superior PFS compared with brigatinib used as other treatment lines. All adverse events are manageable, with gastrointestinal reactions and CPK increased found to be the most common types.

## 4.2 Comparisons with other ALK inhibitors

In the last decade, the treatment of advanced NSCLC has shifted into determining molecular subtypes of the disease based on oncogenic drivers, which has led to the introduction of several newly approved biological agents (33). Numerous systematic review and meta-analysis studies have estimated the

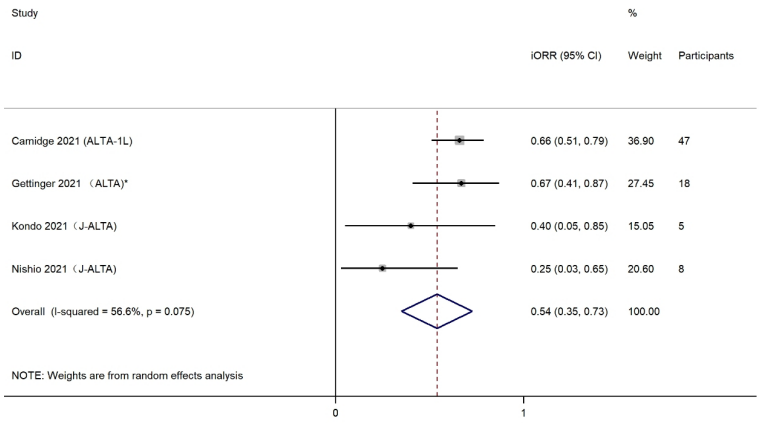


FIGURE 4
Forest plot of intracranial objective response rate (iORR).

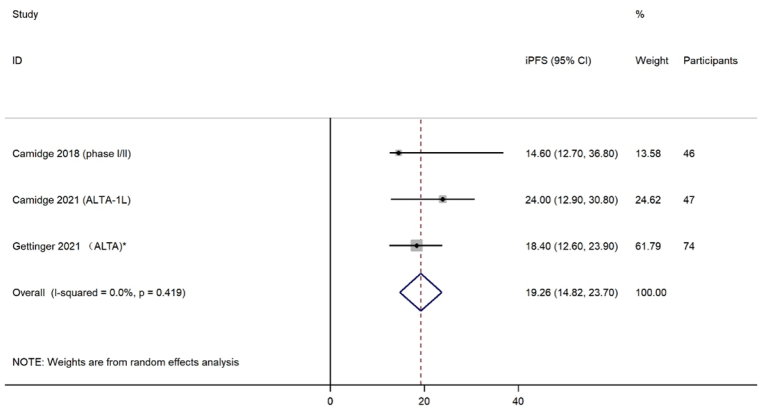


FIGURE 5
Forest plot of intracranial progression free survival (iPFS).

TABLE 2 Summary of toxicity.

| Toxicity | Classification | Incidence | 95% CI | Studies included |
|---|---|---|---|---|
| Diarrhea | Gastrointestinal function abnormal | 0.37 | 0.27-0.48 | 7 |
| Nausea | Gastrointestinal function abnormal | 0.28 | 0.17-0.39 | 7 |
| Vomiting | Gastrointestinal function abnormal | 0.16 | 0.12-0.21 | 6 |
| Constipation | Gastrointestinal function abnormal | 0.11 | 0.03-0.19 | 5 |
| Fatigue | General disorders | 0.23 | 0.16-0.31 | 5 |
| CPK increased | Investigations | 0.44 | 0.26-0.63 | 7 |
| AST increased | Investigations | 0.24 | 0.6-0.32 | 5 |
| Increased amylase | Investigations | 0.21 | 0.15-0.26 | 7 |
| Increased lipase | Investigations | 0.22 | 0.16-0.29 | 7 |
| Rash | Skin and subcutaneous tissue disorders | 0.12 | 0.05-0.19 | 5 |
| Hypertension | Vascular disorders | 0.27 | 0.12-0.41 | 6 |

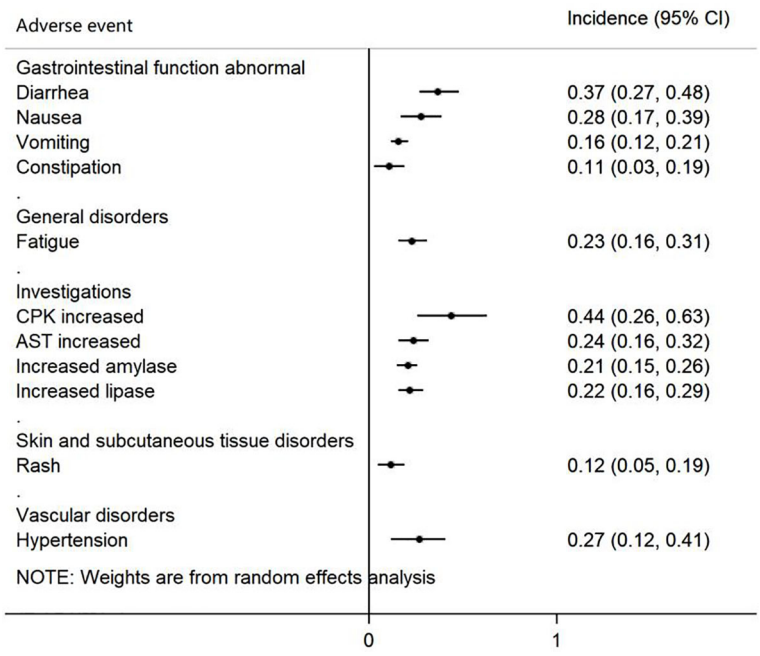


FIGURE 6
Forest plot of adverse events (AEs).

efficacy of other second generation ALK inhibitors such as alectinib and ceritinib. However, studies on brigatinib are scarce. A network meta-analysis study presented in the 2020 World Conference on Lung Cancer (WCLC 2020, Singapore) compared the efficacy of brigatinib with other approved ALK inhibitors or chemotherapy in patients with locally advanced or metastatic ALK inhibitor-naïve *ALK*-positive NSCLC (34). Five global RCTs (ALEX, ALTA-1L, ASCEND-4, PROFILE 1007, PROFILE 1014) evaluating 4 ALK inhibitors (alectinib, brigatinib, ceritinib, crizotinib) as first-line treatment in *ALK*+ NSCLC were included in the final analysis (34). This study found that 1L brigatinib had superior effects on IRC-assessed PFS compared to crizotinib (HR=0.49, 95% CI 0.35-0.68), and ceritinib (HR=0.42, 95% CI 0.26-0.67), while no significant differences were observed between brigatinib and alectinib (34). These results were in line with a more recent network meta-analysis study by Chuang et al., who updated the efficacy comparisons based on the most recent results of phase II-III clinical trials (CROWN, ALTA-1L, ALEX, J-ALEX, ALESIA, eXalt3). In this study, Chuang and his colleagues confirmed the superiority of brigatinib over crizotinib in terms of PFS (HR=0.49, 95% CI 0.35-0.69). Specifically, brigatinib showed stronger efficacy in patients with baseline brain metastasis (HR=0.25, 95% CI 0.14-0.44) compared to crizotinib, and the KM-estimated 4-year OS rate was 71% (53%-83%) with brigatinib (35). It is worth mentioning that the ALTA-1L study also confirmed that brigatinib could exhibit superior efficacy compared with crizotinib regardless of *EML4-ALK* variant and *TP53* mutation (27). Although low- (300 mg twice daily) and high-dose (600 mg twice daily) of alectinib showed lower HR than brigatinib in pairwise comparisons for PFS, no significant differences were observed (35). Moreover, Chuang et al. found that lorlatinib had a noticeable benefit over brigatinib in both overall PFS (HR=0.57, 95% CI 0.34-0.95) and non-brain metastases-PFS (HR=0.49, 95% CI 0.27-0.91) (35). However, ORR did not differ between brigatinib and lorlatinib. A recent French cohort study, LORLATU, investigated the efficacy and safety of lorlatinib after the failure of at least one ALK-TKI in *ALK*-positive NSCLC (36). The use of lorlatinib in this setting yielded an ORR of 49% and a median PFS of 9.9 months. Findings from this study confirm the position of lorlatinib as an effective rescue treatment after resistance to first- and second-generation ALK-TKIs, and the optimal sequencing of ALK-TKIs still remains to be further analyzed.

Of note, data on median OS are often unavailable in current studies. Our current study included the final results of the ALTA-1L trial, with approximately 15 months of additional follow-up since the second interim analysis (median follow-up=40 months for brigatinib) (27). However, OS was still maturing at final analysis (30% event rate) and indicated similar OS in the brigatinib and crizotinib arms (HR=0.81, 95% CI, 0.53-1.22). It is worth mentioning that, in this largest RCT comparing the efficacy of brigatinib and crizotinib, a cross-over design has been assigned. A total of 65 patients in the

crizotinib arm crossed over to brigatinib after BIRC-assessed progression (after 10-day washout from crizotinib). The 3-year OS was 71% (95% CI, 62%-78%) in the brigatinib arm, and 68% (95% CI, 59%-75%) in the crizotinib arm without adjustment for patients who crossed over from crizotinib to brigatinib (HR=0.81, 95% CI, 0.53-1.22, log-rank $p$=0.331). Further updated outcome reports of RCTs need to be followed to determine the effect of each ALK-TKI on OS, as this may revise decisions with regard to the choice of first-line ALK-TKIs.

CNS metastasis is a major concern in lung cancer. CNS metastases are present at diagnosis in ~30% of patients with *ALK*-positive NSCLC (37). First-generation crizotinib is limited in its ability to penetrate CNS and hence in most cases the disease progression site is CNS, particularly when baseline brain metastases are present [19]. A second-generation ALK-TKI such as brigatinib appears to be preferable to crizotinib for the treatment of brain metastases due to its high intracranial efficacy. The intracranial ORR was believed to be influenced by the ability to penetrate the blood-brain barrier (BBB) (38). Newly developed ALK-TKIs with improved BBB penetration such as alectinib, ceritinib, brigatinib, or lorlatinib have demonstrated significant intracranial activity that should contribute to improved overall survival. The presence of the dimethylphosphine oxide (DMPO) group in brigatinib was hypothesized to contribute to its high CNS efficacy (39). Our current study also demonstrated robust intracranial efficacy of brigatinib in treating patients with any baseline brain metastases or measurable CNS metastases (iORR=54%, median iPFS=19.26 months). In the ALTA-1L trial, the risk of intracranial progression was reduced by 56% in all patients (HR = 0.44) and by 71% in patients with any brain metastases at baseline (HR=0.29) with brigatinib compared with crizotinib (27). Brigatinib also showed superior intracranial OS versus crizotinib in patients with baseline brain metastases (HR=0.42, log-rank $P$ =0.02), suggesting a survival benefit in patients with brain metastases receiving brigatinib as the first ALK-TKI treatment (27). In addition, a recent meta-analysis also compared the intracranial response of second generation of ALK inhibitors with crizotinib (40). Indicators of response in CNS were superior for alectinib and brigatinib compared with those of crizotinib. Odds of achieving intracranial response was significantly higher with these two drugs (OR=5.87, 95% CI, 3.49-9.87; $P$< 0.00001) (40). Chuang et al. also confirmed that brigatinib exerted better efficacy for PFS than crizotinib, especially among patients with baseline brain metastasis (35). In addition, brigatinib seems to show superiority in intracranial efficacy over other second-generation ALK-inhibitors. However, the network meta-analysis did not detect any significant differences in PFS between brigatinib and alectinib or lorlatinib among patients with baseline brain metastases.

Like other ALK-TKIs, patients with asymptomatic or stable CNS metastases were permitted in clinical trials. The role of brigatinib in the treatment of symptomatic CNS metastases is still not very clear. A single arm phase II study of brigatinib alone for patients with symptomatic or asymptomatic brain metastases in *ALK*-positive NSCLC is still ongoing (NCT04634110) (41). Furthermore, a case report addressed brigatinib efficacy in leptomeningeal response showing that two patients with *ALK*-positive NSCLC with leptomeningeal carcinomatosis who progressed during heavy pretreatment with crizotinib and ceritinib subsequently experienced prolonged benefit with brigatinib (42). Disclosure of these trial results might enlighten future use of brigatinib in treating patients with brain metastases.

## 4.3 Comparisons with chemotherapy

Since most patients with NSCLC have advanced disease at diagnosis, chemotherapy is the mainstay of management. In clinical practice, platinum-based regimens are the most widely used in the treatment of advanced NSCLC. It is reported that the PFS with platinum-based chemotherapy is approximately 2.1–6.9 months among advanced NSCLC patients (43). A randomized prospective study showed that patients with *ALK*-rearranged NSCLC who received chemotherapy only had a median PFS of 8.1 months and the iORR was only 27.3% (44). A recent meta-analysis confirmed that brigatinib significantly prolonged PFS in ALK inhibitor-naïve patients compared with chemotherapy (PFS for brigatinib: 24.00 months (18.40-43.20); PFS for chemotherapy: 8.1 months (5.8-11.1); HR=0.23, 95% CI 0.16-0.34) (34).

## 4.4 Safety

Although brigatinib has a good clinical therapeutic effect, its use is still limited owing to AEs. The most common AEs associated with brigatinib treatment in the current study are CPK increased, diarrhea, and nausea. A recent study has reported high incidence of any grade of CPK increased (81%) (22). It is notable that only 24% of patients had grade ≥3 CPK increased, and no cases of clinically diagnosed rhabdomyolysis were reported (27). The incidence of grade ≥3 AEs was generally low (<5%) (22, 25, 28, 29, 31), although recent ALTA-1L final results showed moderate incidence of increased CPK (26%) and lipase (15%) (27). Low to moderate rates of brigatinib discontinuation (13%, 18/136) and dose reduction (44%, 60/136) due to AEs (27), the more reliable indicators of meaningful toxicity, showed that the safety profile of brigatinib has been consistent (45).

## 4.5 Strengths and limitations

Our study has several notable limitations. First, the current meta-analysis included both clinical trials and real-world evidence studies. The variances in study design, and most

importantly, the variances in baseline characteristics of study participants, might provide skewed results. For example, the definitions of PFS varied between clinical trial and real-world study. Second, the studies included had a short follow-up period, with the longest being 40.5 months and shortest being 9.3 months. Therefore, overall survival could not be investigated. Third, the current study contains a relatively small sample size, and therefore a subgroup analysis by treatment line was not feasible for each efficacy outcome. A further study with larger sample size is warranted for the disclosure of all efficacy outcome comparisons by treatment line. Fourth, brigatinib was used in different treatment lines in the included studies. Large variance of outcome efficacy was therefore reported and subgroup analysis by treatment line was not always possible. Finally, although an *in vitro* study has indicated that brigatinib is associated with a wide spectrum of *ALK* resistance mutations (19), sparse clinical reports can be found to elucidate the potential associations. More evidence is awaited to be depicted in future clinical and meta-analysis studies.

## 5 Conclusion

To summarize, brigatinib is effective in the treatment of patients with *ALK*-positive NSCLC, and it particularly yielded substantial intracranial responses and iPFS in patients with baseline brain metastases. Brigatinib used as first-line treatment yielded superior PFS compared with brigatinib used as other treatment lines. All adverse events are manageable, with gastrointestinal reactions and CPK increased found to be the most common types.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization. Requests to access these datasets should be directed to xingpuyuan@163.com.

## Author contributions

(I) Conceptualization: PX. and JL. (II) Methodology: XH, XZ, and JL. (III) Formal analysis: PX. (IV) Investigation: PX, XZ, and JL. (V) Data extraction: PX, XH, and XZ. (VI) Writing – Original Draft Preparation: PX and JL. (VII) Writing– Review & Editing: PX, XH, XZ and JL. (VIII) Funding Acquisition: JL. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

Dr. Junling Li has received speaker honorarium for serving on advisory board of Takeda (China) International Trading Co., Ltd.

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## Supplementary material

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# Malignant pleural effusion: Updates in diagnosis, management and current challenges

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Malignant pleural effusion (MPE) is a common condition which often causes significant symptoms to patients and costs to healthcare systems. Over the past decade, the management of MPE has progressed enormously with large scale, randomised trials answering key questions regarding optimal diagnostic strategies and effective management strategies. Despite a number of management options, including talc pleurodesis, indwelling pleural catheters and combinations of the two, treatment for MPE remains symptom directed and centered around drainage strategy. The future goals for providing improved care for patients lies in changing the treatment paradigm from a generic pathway to personalised care, based on probability of malignancy type and survival. This article reviews the current evidence base, new discoveries and future directions in the diagnosis and management of MPE.

KEYWORDS

**pleural, oncology, malignant pleural effusion (MPE), thoracoscopy (pleuroscopy), indwelling pleural catheter (IPC)**

## Introduction

Malignant pleural effusion (MPE) is the build-up of fluid between the lung and the chest wall as a result of cancer cells in the pleura. MPE is a common complication of cancer, with an incidence of 50 000 per year in the UK (1) and occurs in up to 15% of people with cancer. MPE can be associated with any type of cancer, both primary pleural malignancy (mesothelioma) and the result of secondary spread from other sites including

lung, breast and ovarian (2). The effects upon patients living with MPE are profound, including significant breathlessness, fatigue and impact on daily activity (3). Furthermore, MPE is typically associated with poor prognosis and a median survival of 3-12 months (4). Recent data has indicated that the impact of MPE on healthcare is substantial, with the estimated annual national cost in the USA surpassing $1.5 billion and hospital readmissions leading to costs of $236 million annually (5). Over the past decade, the management of MPE has progressed significantly with an ever increasing number of high quality randomised trials to guide best practice (6–9). Despite the improving evidence base, a number of challenges persist in this vulnerable patient population including optimising time to diagnosis and definitive fluid control. The issue of survival in MPE is of great importance as it informs patient and physician decision making regarding management strategies. The importance of accurate survival scores is amplified in this cohort of patients, in whom balancing the short survival time with volume of hospital contact for fluid management is paramount. Nonetheless, prognostication has been amongst the more challenging aspects of MPE management, due to significant heterogeneity in both underlying malignancy and performance status of patients.

This article reviews the recent advances and standards of care in the management of MPE, while addressing the challenges and key areas requiring further targeted studies over the coming years to optimise the care of patients suffering with MPE.

## The current investigation and management of suspected malignant pleural effusion

The current investigation and management pathway for a new pleural effusion is described in Figure 1

The pathway begins with a symptomatic patient presenting to either primary or secondary care with breathlessness, and basic imaging (chest radiograph) demonstrating a unilateral pleural effusion. The priorities for the patient and clinicians are to 1) establish a diagnosis while also 2) providing relief of symptoms. The initial procedure involves aspiration of pleural

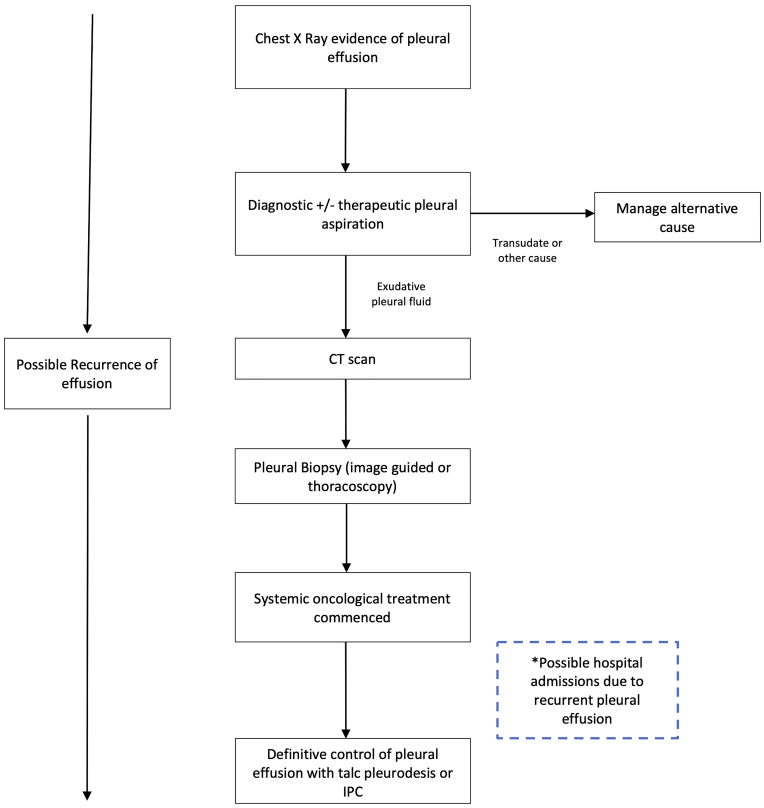


FIGURE 1
Current investigation and management pathway for diagnosis and management of malignant pleural effusion. Adapted from the British Thoracic Society Guidelines on management of pleural disease. CT, computed tomographic; IPC, Indwelling pleural catheter. Definitions: Transudate defined by pleural fluid with low protein and low lactate dehydrogenase (Light's criteria).

fluid with around 50mls sent for laboratory diagnostic analysis and assessment of cytology to establish a malignant diagnosis. In addition, a further 1-1.5 litres of fluid may be withdrawn to improve breathlessness.

Recent evidence suggests that the initial pleural aspiration may have limited utility in the diagnosis of MPE (10). The sensitivity of pleural fluid alone is low; even when malignant cells are detected, the sample may be insufficient to provide information to guide oncological treatment (10, 11) ('actionable histology'), and the fluid recurs in the majority of patients. Following this first procedure, the patient therefore requires further procedures to achieve a diagnosis (pleural biopsy), and a further 'definitive' pleural fluid control procedure. This is conducted using either chemical pleurodesis to seal the pleural space or indwelling pleural catheter insertion (IPC) to control breathlessness and prevent re-admission to hospital. The relative merits and risks of these methods are evaluated below.

# Updates in diagnostics

## Imaging

In parallel to patient symptoms, an early indicator of pleural malignancy is imaging of the thorax. The most commonly utilised imaging modalities to assess potential MPE are chest radiograph, ultrasound and contrast-enhanced CT. Chest radiographs remain of utility as they are readily accessed from primary care and are often represent the most rapidly available diagnostic tool. Possible findings to indicate MPE include asymmetrical pleural effusions in the presence of either pleural thickening or a large lung mass (12). More subtle and detailed diagnostics however require either ultrasound or CT, as standard PA chest radiographs require approximately 200mls of pleural fluid for interpretation (13).

### Ultrasound

Thoracic ultrasound (TUS) is now a significant part of the current standard of care for investigating MPE (14). TUS can detect smaller pleural effusions, alongside important predictors of malignant pleural disease causing pleural effusion such visceral and parietal pleural nodularity (15) as well as diaphragmatic nodules and thickening. The presence of pleural nodularity in conjunction with other features such as diaphragmatic nodularity or thickening on ultrasound has a positive predictive value for malignancy of between 83-100% (15, 16). Perhaps the most exciting paradigm shift for the use of ultrasound in MPE is it's use as a dual diagnostic and therapeutic tool in MPE. Thoracic ultrasound forms a standard of care to guide pleural interventions providing increased safety and effectiveness compared with blind needle insertion (17). Recent data suggests that ultrasound can help identify non expansile lung (NEL) during pleural aspiration, and thus guide which patients may benefit from specific treatments, such as pleurodesis versus indwelling pleural catheter (18). Although these studies require further validation, the impact could be significant due to the poor sensitivity (24%) of chest radiograph to identify NEL, thus allowing earlier personalisation of treatment in MPE. The most robust data for the use of ultrasound as a therapeutic tool arises from the SIMPLE trial showing that a 9 point ultrasound scan of the thorax following talc pleurodesis can confirm pleural adherence to guide chest drain removal and reduce hospital stay by one day, while reducing health care costs (19).

### Cross sectional imaging

Contrast CT imaging is an essential step in diagnosing MPE, providing a non-invasive modality to detect pleural features of malignancy such as circumferential pleural thickening, parietal pleural thickening > 1cm, and pleural nodules, with data suggesting these features carry a specificity of between 78-90% (20, 21). CT imaging is also required to assess for extra thoracic metastases and alternative sampling sites. CT is somewhat limited in cases where these features are absent, with a low negative predictive value for malignancy and thus further sampling of fluid or tissue is still required.

Some controversy exists around the utility of positron emission tomography (PET) in the diagnosis of pleural effusion caused by malignancy, with a modest reported specificity of 74%, and a sensitivity of 81% (22). Further confounders include the risk of false positives following talc pleurodesis or non-malignant inflammatory causes of pleural effusion. Thus PET scanning in the workup of MPE is not recommended routinely as part of international guidelines, however may have specific utility in providing biopsy targets for CT guided pleural biopsy where traditional investigations are precluded or have failed to secure a final tissue diagnosis (see below) (3, 23).

# Cytological vs. histological diagnosis – an evolving evidence base

## Pleural aspiration

For over a decade, international guidelines have advocated pleural aspiration as the first line investigation for suspected malignant pleural effusion. This typically involves withdrawal of sufficient pleural fluid for laboratory analysis and temporary relief of breathlessness. The diagnostic utility of pleural aspiration has, in recent studies, come into question. The diagnostic sensitivity of pleural fluid cytology is poor at only 37- 43% (11) of patients with proven MPE, and is worse with

certain cancers (6% in mesothelioma). Repeat pleural fluid sampling has also been shown to add little to overall diagnostic rates (11). Table 1 illustrates the rate of cytology positivity in specific cancer types. In addition, it is now clear that the finding of malignant cells in fluid alone is often insufficient to guide oncological treatment (24), with the increase in personalised oncological therapy requiring molecular markers to guide systemic therapy. As an example, in lung adenocarcinoma, current guidelines recommend assessment of multiple gene mutations prior to systemic treatment (25) with targeted treatment (such as immune modulating medication) offering the potential for favourable side effect profile and survival (26). In order to achieve this level of molecular marker analysis, tissue biopsy is often required, with fluid cytology likely to be insufficient. As a result, the case for a 'direct to biopsy' approach has been made (24) and future personalised strategies must target earlier biopsy when the cytological yield is most likely to be poor (for example in patients with a history of asbestos exposure and thus higher chance of mesothelioma).

The therapeutic aspect of pleural aspiration, typically removing 1-2L of fluid from the pleural space alleviates symptoms due to an improvement in diaphragm function, and relief of the pressure effect on the diaphragm, rather than improvement in lung function (27). In the absence of symptomatic relief from therapeutic pleural aspiration, other common causes of breathlessness should be considered including pulmonary embolus or pneumonia. Although pleural fluid is prone to reaccumulating following pleural aspiration, the procedure does have utility in guiding the best strategy for definitive fluid control (e.g. with indwelling pleural catheter, IPC or chemical pleurodesis), by helping to identify non expansile lung (NEL). NEL occurs when pleural aspiration is associated with a negative pleural pressure resulting in chest pain. In pleural malignancy, entrapped lung due to visceral pleural thickening or endobronchial tumour, prevents complete lung re-expansion following drainage. In these cases, pleural drainage causes excessive negative pleural pressures (<20cm H20) leading to adverse symptoms. Pleural manometry has been used to measure pleural pressures during pleural drainage, and thus predict NEL, although using manometry does not appear to reduce the risk of procedural pain (28). Early identification of NEL is essential in informing patient discussions regarding definitive pleural fluid control – in patient's whom the lung fully expands, viable options include chemical pleurodesis (which relies on pleural apposition) and IPC, whereas in those patients with NEL, IPC stands alone as the strategy of choice.

TABLE 1 Pleural Fluid cytological sensitivity by cancer type, adapted from Arnold et al. (11).

| | Pleural fluid sensitivity (%) |
|---|---|
| **All Cancer Types** | 46.4 (42.0-58.2) |
| **Mesothelioma** | 6.1 (2.8-11.2) |
| **Urological** | 11.8 (1.5-36.4) |
| **Haematological** | 40.0 (22.6-59.4) |
| **Lung** | 56.0 (48.1-63.7) |
| Adenocarcinoma | 82.0 (73.1-89.0) |
| Squamous | 14.3 (4.0-32.7) |
| Small Cell | 43.8 (19.8-70.1) |
| **Breast** | 70.7 (57.3-81.9) |
| **Ovarian** | 94.7 (82.2-99.4) |

(95% confidence interval).

## Pleural biopsy

As noted above, in suspected MPE, histological analysis of pleural tissue obtained *via* biopsy is typically required to guide oncological treatment. The most commonly used pleural biopsy techniques include: ultrasound guided or CT guided pleural biopsy using a cutting needle visualised under image guidance, or thoracoscopic pleural biopsies, done under direct visualisation of the pleural space using a fibreoptic camera.

CT guided pleural biopsies have a similar diagnostic yield, providing adequate tissue for diagnosis in over 87% of patients and actionable molecular marker information in a high proportion (29). Ultrasound guided biopsies result in similar diagnostic yield (over 90%) however carry significant advantages pertaining to the patient pathway and waiting times. Ultrasound guided biopsies are typically faster to undertake, can be conducted by physicians at the first meeting with the patient without requiring CT scanners, and do not expose patients to ionizing radiation (30). Ultrasound guided biopsies can be performed by either physicians or radiologists, and can be combined easily with therapeutic drainage procedures such as IPC. CT guided biopsies require radiologists to undertake and are generally not combined with definitive fluid drainage. A key caveat that clinicians must bear in mind in regards to image guided biopsy techniques, is that the quoted diagnostic figures reflect instances where there is pleural nodularity or thickening identifiable with the imaging technique (an adequate 'target'), and the diagnostic yield is likely to be significantly lower in the absence of this, in which case thoracoscopy should be performed. Recent data also indicates that the diagnostic sensitivity for molecular cancer markers is lower in image guided techniques than thoracoscopy (31).

Thoracoscopic biopsies are the preferred method of diagnosis for mesothelioma (3, 32), as larger tissue volumes are required and remain the overall gold standard diagnostic technique, with a diagnostic yield of 95% (33). Thoracoscopy facilitates direct visual inspection of the pleura and larger biopsies which are necessary to demonstrate fat or muscle invasion by tumour. Medical thoracoscopy can be performed

under local anaesthetic and be combined with IPC insertion as a day case procedure by pleural physicians. The surgical alternative, video assisted thoracoscopic surgery (VATS) has a similar diagnostic yield to medical thoracoscopy however, carries increased risk of postoperative pain and requires general anaesthesia with single lung ventilation (34). Despite this, in selected cases, VATS is the preferred option, namely in those with significant pleural adhesions or septations that would preclude medical thoracoscopy, as these can be treated at the time of intervention in the case of VATS. Both medical thoracoscopy and VATS provide the opportunity to undertake therapeutic definitive fluid control measures by instilling a chemical sclerosant into the pleural cavity at the time of the procedure (35).

## Updates in the management of malignant pleural effusion

Recurrent pleural effusion caused by malignancy is often a debilitating condition for patients, with adverse effects on activity levels and performance status (36). The effects of MPE can also impact patients' tolerance for systemic therapy resulting in a vicious cycle of pleural effusion build-up leading to lack of disease control measures such as missed systemic treatment. As such, patients and physicians are encouraged to openly discuss definitive management options for MPE, which despite great progress in recent years, remains palliative. The historical choice for prevention of pleural fluid recurrence has been chemical pleurodesis, with the greatest evidence base for graded talc as the agent of choice (37, 38). The chemical sclerosant precipitates a diffuse inflammatory reaction and fibrin deposition between parietal and visceral pleura, thus obliterating the pleural space and preventing fluid reaccumulation. The process typically requires an inpatient hospital stay for chest drain insertion and complete fluid drainage and is successful in approximately 70% of cases (6, 35). Although initially the success rate of pleurodesis was previously felt to be greater using talc poudrage at thoracoscopy, the TAPPS trial has shown pleurodesis failure rates at 90 days to be equivalent between poudrage and talc instillation *via* a chest tube (35).

IPCs are a silicone tube tunnelled under the subcutaneous tissue into the pleural space to allow ongoing drainage of pleural fluid in the patients home, by the patient themselves or a carer/nurse. IPCs carry some major advantages over talc pleurodesis, requiring only a day case procedure under local anaesthetic and providing equally effective management of MPE in patients with NEL. Over the past decade, IPCs have become the subject of a number of rigorous, high quality randomised clinical trials, with in depth evaluation of effectiveness in symptom control and cost effectiveness. Over this period these trials have not only seen a paradigm shift in the options offered to patients to manage MPE, but also the use of patient facing outcome measures (PROMS) as the primary outcome in the aforementioned clinical trials. These trials have shown that IPCs improve breathlessness and quality of life comparably to talc pleurodesis and reduce the length of hospitalisation by 2 days (6, 7). On this evidence alone, IPCs have become a viable option to patients with recurrent MPE, allowing a choice between IPC and talc according to patient preference. Whether IPCs should become a first line intervention *over* talc pleurodesis is however a more nuanced issue. IPC related complications occur in approximately 10-20% of patients, although the majority are minor and treatable, such as cellulitis, with true infection of the pleural space reported to be less than 5% (39, 40). In addition to this, the genuine impact of long term IPC drainage on both the patient and healthcare systems is significantly under-studied, as hospital admission days do not account for the limitations of requiring domiciliary drainage, often by a trained nurse. Even cost effectiveness studies do not clearly favour one intervention, with a *post hoc* analysis of the TIME-2 trial revealing that for patients with survival limited to <14 weeks, IPCs were more cost effective, however beyond this, talc pleurodesis was favourable (41).

Thus the choice between talc pleurodesis and IPC remains dependent on patient choice, resource availability and physician familiarity at the current juncture, although with the advent of combined treatments (see below), the balance of these factors may yet change. Spontaneous pleurodesis (autopleurodesis) has been reported with IPCs, and retrospective datasets have suggested the rate of autopleurodesis with IPCs to be 43-47% (37, 42), although in prospective studies suggest this is somewhat lower (24-27%) (9).

Figure 2 illustrates a suggested evidence based flowchart for the management of MPE, and the question future studies will seek to target is whether waiting times to definitive fluid control can be minimised or even delivered as part of a 'first intervention' for suspected MPE.

## Combination treatments

Recent large scale prospective studies have been undertaken to assess whether adjunctive treatments can improve the rate of pleurodesis with IPCs. The ASAP trial has shown that adopting an aggressive (daily) drainage strategy of IPCs over symptom guided drainage can almost double rates of autopleurodesis from 24% to 47% (9). The IPC PLUS randomised clinical trial showed that delivering talc as a sclerosing agent through an IPC can improve pleurodesis rates from 27% (standard care) to 51% at 70 days (8), showing promise for a combined treatment approach. It is essential to note however, that this outcome was in an enriched population wherein non expansile lung was excluded. This population is enriched as pleural apposition is required for successful pleurodesis, and typically not achieved in non expansile lung. If we compare this to the significantly higher rates of pleurodesis within the TAPPS trial *via* either talc

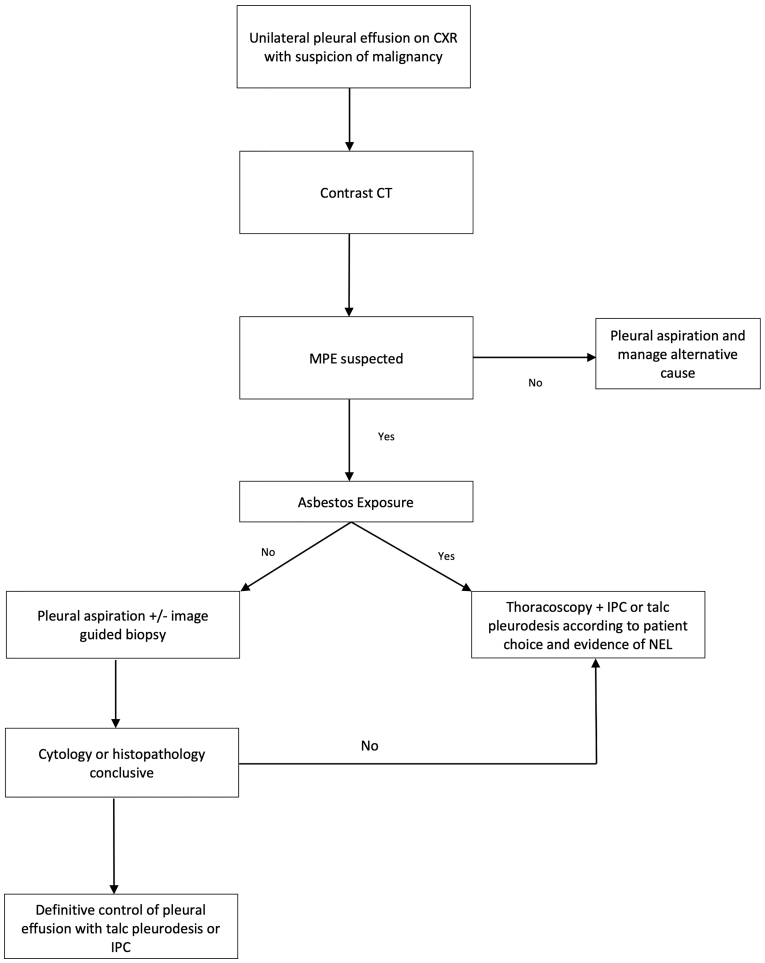


FIGURE 2
Authors suggested pathway for the investigation and management of suspected malignant pleural effusion based on current evidence. Diagnostic yield of tests noted: Pleural Aspiration 37-43% (11), Image guided pleural biopsy 84-93% (30), Thoracoscopy 95% (33). MPE, malignant pleural effusion; CT, computed tomography; IPC, indwelling pleural catheter; NEL, non expansile lung. Asbestos exposure determined by either imaging features such us pleural plaques or patient reporting. Asbestos exposure of importance due to increase in pre-test probability of mesothelioma.

poudrage or chest tube slurry (both with inpatient admission with no exclusion for NEL), it is clear that in cases where the patient's priority is in achieving pleurodesis as a 'one off intervention', the optimal method is *via* poudrage or slurry.

The final technique that has been explored to improve pleurodesis rates *via* IPC is the use of a silver nitrate coated catheter, designed to initiate inflammation in the pleural space and encourage pleurodesis. While this had some initially promising results in animal studies and early trials (43, 44), a recent randomised trial of 119 patients (SWIFT), showed no improvement in pleurodesis efficacy with these devices compared to standard IPCs (45). As a result, no further studies of the silver nitrate coated catheter are currently in progress.

Potentially exciting developments in the decision making between inpatient and IPC based pleurodesis are on the horizon. The first of these is with the awaited results of the recently completed OPTIMUM randomised clinical trial (46). This novel trial used a quality of life based primary outcome to evaluate IPC plus talc versus standard talc slurry. The evaluation of these two modalities with a patient facing outcome may move the field further towards a clearer answer in this discussion. The second large scale study addressing this issue is the TACTIC trial (ISRCTN11058680), which is currently in recruitment, assessing the pleurodesis success rate of thoracoscopy with talc and inpatient admission versus thoracoscopy with talc and IPC insertion to allow ambulation.

## Prognostication and outcome prediction: The future of MPE management?

To date, prognostication in MPE has been addressed by two prognostic scoring systems validated in MPE; the LENT and PROMISE scores. The LENT score was derived using 3 prospectively collected datasets and retrospectively derived. LENT assigns patients to a low, moderate or high risk of death (319, 130, 44 days median survival respectively) using pleural fluid LDH, ECOG score, blood neutrophil-to-lymphocyte ratio (NLR), and tumour type (47). In a validation cohort, the LENT score was found to perform significantly better than ECOG performance status alone in predicting survival.

The PROMISE study stratified patients into four survival categories at three months ranging from <25% to >75%. The score includes clinical parameters (ECOG performance score, previous chemotherapy and radiotherapy, cancer type) and biological variables (white blood cell count, C-reactive protein, haemoglobin and serum levels of tissue inhibitor of metalloproteinases-1, TIMP-1) (48). Despite their simplicity (with the exception of TIMP-1 in PROMISE which is not routinely measured in clinical practice) and external validation, there has been suggestion that alternative scoring systems are necessary to correct for regional demographics variation, for example in areas with high rates of EGFR adenocarcinoma mutations (49) and target specific tumour types. As such one recent study has sought to address this using disease specific models to allow more precision in survival prediction. The breast and lung effusion survival score (BLESS) was derived retrospectively from analysis of 562 patients, and validated in a separate cohort of 727 patients. Both the lung and breast models utilise variables of ECOG performance status, benign pleural fluid cytology, pleural fluid LDH and pleural fluid protein. The lung model adds history of surgery within 30 days and the presence of bilateral pleural effusions. The breast model adds NLR. The authors concluded that in lung and breast malignancy, the BLESS score outperformed LENT, adding another potential tool to the prognostication of MPE (50). It remains to be seen whether these scoring systems become widely utilised in clinical practice however, as no studies to date have demonstrated clinical impact on patient reported outcomes or the clinical pathway in MPE.

An area with great potential to progress the management of patients with MPE is that of more sophisticated biomarker prediction of clinical outcomes including fluid volume prediction and autopleurodesis. Other fields have successfully integrated biomarker driven care pathways (51) and this remains lacking in MPE and pleural medicine in general. Important data has been discovered as part of the PROMISE study which aimed to discover and validate pleural fluid biomarkers to predict outcomes. Despite the analysis of over 1200 proteins, only 4 showed significant association with survival – TIMP-1, VCAN, GSN and MIF. Of note however, none of these could predict pleurodesis success, which for patients may represent a more direct impact on choice of fluid management strategy.

In regards to predictors of fluid output and autopleurodesis, early data suggests that routine clinical laboratory tests are not helpful in predicting outcome (42). A recent study has identified Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor-B (TGF-B) and Basic Fibroblast Growth Factor (FGF2) as key players in auto-pleurodesis induced by IPC (52). However, this was a longitudinal study and further studies are needed to assess these findings. A blind exploratory study to screen for auto-pleurodesis regulators has not been performed, which is a necessary next step to objectively identify the underlying molecular mechanisms underpinning autopleurodesis.

### Novel directions

Of great interest is early translational work showing that cancer cell cultures' proliferation is promoted by seeding the cells in pleural fluid (53). This pro-growth property of pleural fluid opens up the possibility that pleural fluid may not be a bystander of malignant disease, requiring drainage only to provide palliation of symptoms, but may be an *active* promoter of cancer progression, thus emphasising the importance of achieving pleural fluid control early. Current strategies to do so are centred around mechanical methods of drainage and sealing the pleural space, however, in the coming years, significant efforts should be directed at more sophisticated biomarker analysis and validation and subsequent targeting of these with intrapleural immunological agents to 'turn the tap off'. If successful, such treatment strategies have the potential to bring about a true stepwise change in the management of MPE. However significant challenges exist in this regard, in particular the clinical heterogeneity of MPE depending on primary tumour (54) and the evidence from studies of intrapleural treatments for MPE to date which have yielded mixed results (55, 56).

## Discussion

Over the last decade, great progress has been made in the treatment of MPE, with a formerly reactive and opportunistic approach moving to a robust evidence-based paradigm for both diagnostic and therapeutic options. Despite this, there remains key gaps in the evidence base. The true patient experience in MPE requires further assessment and the delivery of high yield diagnostics and definitive fluid control

should be evaluated to determine if patients can progress to systemic treatment and symptom control earlier than current international guidelines allow. Over the next decade, moving beyond drainage strategies to biomarker and immunological analysis of MPE formation and recurrence will be essential, and may even lead to targeted pharmacological treatment of malignant pleural effusion.

## Author contributions

DA was responsible for initial draft preparation and revision. All other authors were responsible for reviewing and approving the final manuscript. All authors are responsible for the overall content.

## 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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# Current status of and progress in the treatment of malignant pleural effusion of lung cancer

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Malignant pleural effusion (MPE) is a common complication in the late stage of malignant tumors. The appearance of MPE indicates that the primary tumor has spread to the pleura or progressed to an advanced stage. The survival time of the patients will be significantly shortened, with a median survival of only a few months. There are a variety of traditional treatments, and their advantages and disadvantages are relatively clear. There are still many problems that cannot be solved by traditional methods in clinical work. The most common one is intrapleural perfusion therapy with chemotherapy drugs, but it has a large side effect of chemotherapy. At present, with the development of medical technology, there are a variety of treatment methods, and many innovative, significant and valuable treatment methods have emerged, which also bring hope for the treatment of refractory and recurrent MPE patients. Several clinical trials had confirmed that drug-carrying microparticles has less adverse reactions and obvious curative effect. However, there is still a long way to go to completely control and cure MPE, and the organic combination of clinical work and scientific research results is needed to bring dawn to refractory MPE patients.

KEYWORDS

**malignant pleural effusion, lung cancer, angiogenesis, IPT, ATMPs-MTX**

## 1 Introduction

With advances in medical technology and in-depth research on the pathogenesis of malignant pleural effusion (MPE), innovative drugs and treatment strategies have been developed. MPE treatment has made many achievements. However, recalcitrant or recurrent MPE currently does not have effective treatment options. Therefore, the treatment of MPE is still a difficult clinical problem, and the current status and progress of MPE treatment are reviewed as follows.

Lung cancer accounts for 18.0% of all cancer deaths according to the latest 2020 Global Cancer Data Report from the World Health Organization's International Agency for Research on Cancer (IARC) (1). The data show that approximately 50% of malignant tumors can present with malignant pleural effusion (MPE). MPE is more common in lung cancer, breast cancer and lymphoma, with rates as high as 75%, and lung cancer has the

highest rate (2). MPE is one of the common complications of advanced malignant tumors, with a median survival of only 3-12 months (3–5).

Pleural fluid cytology is the easiest way to diagnose MPE and the gold standard for diagnosis. However, its sensitivity is limited in cases with few cancer cells, and the rate of positive detection (40%~87%) is relatively low (6); the rate of positive detection can be improved by testing pleural fluid samples multiple times or directly using pleural biopsy to detect cancer cells. For patients with clear primary tumors and asymptomatic MPE, no therapeutic intervention can be performed for the effusion itself (7–10). Once the amount of pleural effusion increases or if substantial pleural effusion is generated within a short period of time, it will cause symptoms such as cough, chest tightness, dyspnea and weakness, which will seriously affect the quality of life of patients. For MPE patients with obvious clinical symptoms, the primary aim of treatment is to relieve dyspnea, chest tightness and other symptoms (11, 12). The presence of MPE indicates that the primary tumor has spread to the pleura or has progressed to an advanced stage, and the survival of patients is significantly shortened. Once MPE is diagnosed in patients with tumors, it should be actively treated; otherwise, the accumulation of fluid will cause pulmonary atelectasis or recurrent lung infections and even threaten the life of the patient (13). With advances in medical technology and in-depth research on the pathogenesis of MPE, innovative drugs and treatment strategies have been developed. For example, the microparticles released by autologous tumor cells can be used to encapsulate chemotherapeutic drugs to achieve antitumor effects through two mechanisms: direct killing of tumor cells and activation of the autoimmune system (14, 15). However, recalcitrant or recurrent MPE does not currently have effective treatment options. Therefore, the treatment of MPE is still a difficult clinical problem, and the current status and progress of MPE treatment are reviewed as follows.

## 2 Routine clinical treatment modalities

Conventional clinical treatment mainly includes simple chest drainage, pleural fixation, thoracic thermal perfusion and intrathoracic drug infusion. Different treatment options have different indications and contraindications and different advantages and disadvantages, and clinicians usually conduct a comprehensive assessment to choose the most suitable treatment option for each patient.

### 2.1 Simple thoracentesis for fluid aspiration and tube placement for drainage

In patients with malignant tumors complicated with MPE, the tumor cells have spread or metastasized to the pleura at an advanced stage, and these patients have missed the opportunity for surgical treatment; in this case, internal palliative treatment is most commonly adopted in the clinic (16, 17). The primary task is to relieve respiratory distress and pain, and many clinicians will prioritize simple thoracentesis and aspiration or tube drainage. Thoracentesis alone can quickly relieve the symptoms of dyspnea, but it is a temporary treatment measure. The reason is that the intrathoracic pressure decreases significantly within a short period of time after fluid extraction, which in turn leads to fluid reunion, a faster increase in accumulated pleural fluid, and a higher recurrence rate (18). Repeated drainage of a large amount of pleural fluid can lead to hypoproteinemia, anemia, weakness, electrolyte disorders and other systemic symptoms (19, 20). In severe cases, circulatory collapse and death may occur. Therefore, simple chest puncture and drainage cannot solve the problem of recurrent massive pleural fluid in MPE and can actually accelerate the deterioration induced by the disease and lead to failure of primary tumor systemic treatment or poor efficacy.

### 2.2 Pleural fixation

Intrathoracic infusion of sclerosing agents, also known as pleural fixation, involves the use of sclerosing agents to chemically irritate and cause pleuritis, which causes adhesional atresia of the visceral and mural pleura and eventually leads to loss of the pleural space, causing a reduction in pleural fluid. The American Thoracic Society (ATS), in its latest edition of its MPE treatment guidelines issued in 2018 (7), recommends placement drainage or chemical pleural fixation as the preferred treatment option to relieve dyspnea in patients with symptomatic MPE without combined pulmonary atelectasis who have never been treated for MPE. The previous guidelines only recommended drainage as an option for patients with MPE combined with pulmonary atelectasis (10). The application of sclerosing agents under video-assisted thoracic surgery (VATS) is a common clinical method. And VATS talc poudrage is recommended for pleurodesis in patients with good performance status. The most commonly used drug in clinical pleural fixation is talcum powder (21–23). A randomized controlled trial has robustly demonstrated that there is no additional clinical effectiveness or cost-effectiveness benefit between talcum powder by thoracoscopy and talc slurry intercostal drainage for MPE patients (24). Therefore, talcum slurry and talcum powder have no difference in efficacy. It has the advantages of low cost and a high success rate compared with other sclerosing agents. The common side effects of talcum powder pleural fixation are fever and chest pain, which can be relieved in most patients but can cause serious adverse reactions in some patients, such as pulmonary edema, acute respiratory distress syndrome (ARDS), and acute respiratory failure (8, 25). In some cases, death can occur. Therefore, the application of talcum powder for pleural fixation for MPE has certain risks.

### 2.3 Thoracic thermal perfusion therapy

Thoracic thermal perfusion therapy takes advantage of the different tolerances of tumor cells and normal cells to different temperatures (26). Therefore, the key to successful thoracic thermal perfusion is to control the intrathoracic temperature, and conversely, if the temperature is not well controlled, the normal cells of the body will suffer much irreversible damage. Clinically, the intrathoracic temperature is usually maintained at approximately 43°C, which can damage and kill tumor cells without much interference with

and impact normal cell function (27). In addition, the increase in intrathoracic temperature caused by thoracic heat perfusion can significantly dilate blood vessels, promote the absorption of chemotherapeutic drugs, significantly increase the concentration of drugs in the thoracic cavity, and increase the ability of drugs to kill tumor cells. Therefore, compared with intratoracic perfusion treatment with chemotherapeutic drugs alone, intratoracic thermal perfusion combined with chemotherapeutic drugs shows more advantages (28–30). On the one hand, chemotherapeutic drugs can directly kill tumor cells, resulting in a reduction in pleural fluid production, and on the other hand, the increase in temperature can expand the pleural blood vessels and promote the absorption of chemotherapeutic drugs by tumor cells, which greatly improves the drug utilization rate and chemotherapeutic drug efficacy. Within 24 h after the end of perfusion, almost all patients showed profuse sweating, hot flashes, elevated body temperature and increased heart rate, which were relieved by symptomatic treatment. However, thoracic thermal perfusion chemotherapy is generally not recommended for patients with a very poor systemic condition or those who are unsuitable for thoracic thermal perfusion, such as patients with obvious liver and kidney failure, severe cardiovascular or cerebrovascular diseases, poor healing of anastomosis after surgery, and extensive adhesions in the thoracic cavity.

## 2.4 Intrapleural perfusion therapy

The most rapidly advancing and preferred treatment option is intrapleural perfusion therapy (IPT), which is the most widely used strategy in clinical practice due to its obvious efficacy, simplicity and lack of serious adverse effects and is suitable for most patients with MPE (31). It can prolong the survival time and improve the quality of life for most MPE patients. Currently, there are many kinds of drugs used for IPT treatment, including chemotherapeutic drugs, immunomodulators, and Chinese patent medicines. Many innovative drugs are in clinical trials or in the development stage, giving new hope to patients with recalcitrant or recurrent MPE.

### 2.4.1 Chemotherapy drugs

The chemotherapeutic drugs commonly used in clinical practice alongside thoracic infusion mainly include cisplatin, carboplatin, and bleomycin. Cisplatin, as a first-generation platinum drug, has strong antitumor activity and is thus more widely used in thoracic perfusion (32). Cisplatin can not only directly induce a local antitumor effect but also stimulate the pleura to cause pleurisy and pleural adhesions and cause chest occlusion; in addition, cisplatin can also be absorbed into blood circulation through the blood vessels on the pleura, which can inhibit primary foci and metastases and reduce pleural fluid in many ways (33). Moreover, this mode of drug delivery greatly improves the concentration of drugs in the chest cavity, reduces the toxic side effects caused by systemic chemotherapy, and is tolerated by most patients with mild adverse effects, making it the preferred treatment for MPE. Compared with the second-generation platinum drug carboplatin, the adverse effects of cisplatin mainly include gastrointestinal reactions and nephrotoxicity, with less bone marrow suppression. Typically, only a single chemotherapeutic agent is used clinically, but some investigators have combined multiple chemotherapeutic agents to enhance treatment efficacy by taking advantage of the synergistic effect of various drugs (34, 35). However, the toxic side effects of chemotherapeutic drugs, especially for many patients with advanced tumors who cannot tolerate them, for those who develop drug resistance after multiple doses, or for those with recalcitrant or recurrent MPE with poor response, can lead to the failure of local MPE treatment. Overall, chemotherapeutic agents administered *via* transthoracic infusion are effective, but resistance may occur after multiple doses, and there is limited overall efficacy and a high rate of pleural fluid recurrence.

### 2.4.2 Biological response modifiers

The main mechanism of action of biological response modifiers is to stimulate inflammation in the plasma membrane, causing fibrosis of mesothelial cells and adhesions to occlude the pleural space, leading to a decrease in pleural fluid production. The most commonly used clinical biological response modifier is the Nocardia rubra cell wall skeleton (N-CWS). On the one hand, it can inhibit tumor cells and enhance the activity of macrophages, T cells and natural killer (NK) cells (36, 37). On the other hand, it can induce interferon, lymphokine-activated killer cell and tumor necrosis factor production and anticancer effects. Therefore, N-CWS has good clinical efficacy in patients with lung cancer with MPE, can significantly improve the immune function and survival rate of patients, and has mild toxic side effects, so it is worthy of wide clinical application. However, it should be used with caution in patients with MPE who already have high fever and allergic reactions, as it may aggravate existing symptoms and cause deterioration of the patient's systemic condition.

# 3 Latest treatment advances

With the continuous development of tumor treatments and advances in antitumor drugs, the MPE treatment paradigm is being constantly modified, and an increasing number of new drugs and technologies are being applied in the clinic, such as antiangiogenic drugs, drug-carrying microparticles, and pleural bladder pumps. A large number of preliminary clinical studies have shown extraordinary efficacy and the ability to overcome some of the shortcomings of traditional treatment modalities and greatly reduce the toxic side effects caused by treatment, bringing new treatment strategies and modalities for MPE, especially for patients with MPE in whom existing treatments have been ineffective, for those with relapsed MPE, and for those who are resistant to traditional treatment methods. For patients with MPE who have relapsed or failed various treatments, indwelling pleural catheters are now clinically available.

## 3.1 Anti-angiogenic drugs

The generation, invasion and metastasis of malignant tumors and tumor angiogenesis are closely related (38). Therefore, inhibition of tumor neovascularization has become a new strategy for tumor therapy. The main antiangiogenic drugs are bevacizumab and recombinant human vascular endothelial growth factor (VEGF)

inhibitors, both of which can be administered by transthoracic perfusion. Both of these antiangiogenic drugs can be combined with platinum agents, and this combination is more effective than platinum agents or antiangiogenic drugs alone, producing greater increases in the inhibition of tumor cells and better reducing the formation of effusion.

### 3.1.1 Bevacizumab

VEGF is an important proangiogenic mediator, and VEGF/VEGFR-2 is an important signaling pathway for angiogenesis (39–44). The VEGF/VEGFR-2 axis mediates vascular endothelial cell proliferation and neovascularization (45), which leads to the production of pleural fluid (46). Bevacizumab, a human recombinant monoclonal antibody that mediates VEGF signaling, inhibits tumor angiogenesis, growth, and metastasis, reducing the generation and growth of blood vessels in the pleura and ultimately leading to a decrease in pleural fluid production. Tao et al. (47) retrospectively studied 21 patients with lung adenocarcinoma with MPE treated with bevacizumab combined with chemotherapy by intravenous infusion, and the MPE remission rate (RR) was 81.0%. The disease control rate (DCR) at 24 weeks was 89.5%, and 90.5% of patients experienced lung re-expansion after treatment. These results suggest that bevacizumab in combination with chemotherapy has significant efficacy and safety advantages for treating MPE in lung adenocarcinoma and is an option for patients with lung adenocarcinoma with MPE. The results of a study of patients with nonsquamous non-small-cell lung cancer with poorly controlled MPE after drainage tube placement or pleural fixation receiving bevacizumab in combination with chemotherapy showed a pleural effusion control rate (PECR, defined as the percentage of patients with no reaccumulation of MPE at 8 weeks) of 80%, pleural progression-free survival (PPFS) of 16.6 months, and overall survival (OS) of 19.6 months, and patients' quality of life significantly improved (48).

Many clinical studies (49–52) have also tried to explore the efficacy and safety of intrathoracic injection of bevacizumab combined with platinum-based drugs in the treatment of MPE, and the results of the studies have shown that intrathoracic injection of bevacizumab combined with platinum-based chemotherapeutic drugs showed increased overall efficacy (the difference is statistically significant, $P<0.05$) compared with administration of platinum-based drugs alone; the RR of the bevacizumab combined with cisplatin group can be as high as 83.33%, significantly higher than the 50.00% of the cisplatin group. In addition, intrapleural injection of bevacizumab reduced the level of VEGF in pleural fluid, with milder, tolerable toxic effects. Single-agent anti-vascular therapy is not ideal (53), and the combination of bevacizumab with platinum drugs in the treatment of MPE significantly increases the therapeutic effect compared with monotherapy. A meta-analysis (54) pooled data from 71 patients with non-small-cell lung cancer with MPE and, for the first time, evaluated the therapeutic effect of intrathoracic injection of different doses of bevacizumab in patients with non-small-cell lung cancer with MPE. The efficacy of low-dose bevacizumab was not inferior to that of high-dose bevacizumab, and the use of low-dose bevacizumab significantly reduced the incidence of adverse events and toxic side effects, suggesting that intrathoracic injection of low-dose bevacizumab can be a suitable treatment for patients with non-small-cell lung cancer with MPE. Currently, there are no uniform standards for the administration, dosing and duration of bevacizumab treatment in patients with MPE, and there are many controversies regarding which specific regimen should be used for the treatment of MPE. Some investigators (55) believe that bevacizumab is effective whether administered intravenously or by thoracic infusion, but the evidence for the use of bevacizumab in the treatment of MPE remains flawed due to study design biases and the small number of subjects.

### 3.1.2 Recombinant human VEGF inhibitors

Researchers have found that recombinant human VEGF inhibitors can downregulate the expression of VEGF and receptors (56), block VEGF and VEGFR tyrosine phosphorylation, and induce MMP expression (57). A recombinant human VEGF inhibitor was found to inhibit the production of blood vessels and lymphatic vessels in animal models (58). In 2015, Wei et al. (59) found that recombinant human VEGF inhibitors could only inhibit the production of effusion but not cause apoptosis or inhibit tumor growth. However, in recent years, investigators (60, 61) have concluded that recombinant human VEGF inhibitors can also inhibit tumor cell proliferation and induce tumor cell apoptosis. The combination of recombinant human VEGF inhibitors with platinum-based drugs exerts a synergistic effect, and combined administration is better than administration of platinum-based drugs alone (34). Combined administration can improve the quality of life of patients. On the one hand, platinum drugs can directly act on tumor cells and interfere with tumor cell DNA replication and transcription, thus inducing tumor cell necrosis. On the other hand, recombinant human VEGF inhibitors can promote the immune response, improve the local tumor microenvironment (62, 63), promote normalization of tumor vascular function (64), more effectively promote the delivery of platinum drugs to the tumor tissue (65, 66), and more effectively kill tumor cells. In a study evaluating the clinical efficacy and safety of a recombinant human VEGF inhibitor combined with chemotherapy for MPE in lung adenocarcinoma, the treatment group was given chemotherapy and recombinant human VEGF inhibitor *via* intrathecal administration, and the control group patients were given the same chemotherapy as the treatment group. The efficacy rates were 81.82% and 64.52% in the treatment and control groups, respectively (statistically significant difference, $P=0.027$). The MPE control rates (DCRs) were 93.94% and 79.03%, respectively (statistically significant difference, $P=0.013$). Dyspnea symptoms were significantly improved in the treatment group, and side effects were not significantly different between the two groups (67).

## 3.2 Drug-carrying microparticles

Normally, cellular microparticles in the human body are used to store, transport and digest cellular products and wastes and are important carriers for the transport of various substances (68). Researchers have used autologous tumor cell-derived microparticles (ATMPs) as novel individualized drug carriers (69–73). In other studies, ATMPs have been used as novel individualized drug carriers to deliver chemotherapeutic drugs to tumor cells in a targeted manner (74–76). These drugs can not only directly interfere with the

proliferation of tumor cells but also activate antitumor immunity (14, 77–79). In addition, ATMPs can be used to overcome the killing of normal cells by chemotherapeutic drugs and the resistance of tumor cells to chemotherapeutic drugs. The mechanism by which ATMPs encapsulating methotrexate (ATMPs-MTX) activate the neutrophil response as a treatment for MPE has been studied (80). ATMPs-MTX trigger neutrophil recruitment through activation of CXCL1 and CXCL2 released from macrophages (15, 81, 82). ATMPs also reverse drug resistance in cancer stem cells (CSCs). CSCs take up ATMPs-MTX better than do differentiated cancer cells, leading to CSC death (83). Guo et al. (84) demonstrated through mouse models and human experiments that ATMPs encapsulating chemotherapeutic drugs have almost no toxicity and have largely reduced toxic side effects compared with chemotherapeutic drugs in clinical applications. The ORR of 11 patients with advanced lung cancer with MPE treated with ATMPs-MTX was 90.91%, and the median survival time (MST) was 240 days, demonstrating excellent efficacy and only minor side effects. The low level of toxic side effects induced by ATMPs encapsulating chemotherapeutic drugs makes them a promising option for MPE treatment. Currently, many hospitals have used drug-carrying microparticles for MPE treatment. Although their efficacy and safety have been clinically validated, more subjects and clinical studies are needed to further evaluate their efficacy. There are still some concerns regarding the use of drug-carrying microparticles in oncology and MPE treatment. Primarily, the safety of microparticles needs to be determined; for example, ATMPs may contain oncogenic factors that may contribute to tumor progression (85).

## 3.3 Pleural bladder pump

Astoul et al. (86) performed an in-depth study of a peritoneal bladder pump for the treatment of ascites. The scholars first proposed and designed the pleural bladder pump for the treatment of MPE and named it the pleurapump system, whose specific mechanism is to drive the transfer of accumulated fluid from the pleural cavity to the bladder, from where it can drain from the body *via* the urinary system. The pump has pressure and position sensors on it to regulate the flow rate and drainage of the effusion and to monitor and record the amount of pleural fluid drained, which is very useful. Previous research on the peritoneal bladder pump (Alfapump system) has yielded some results (87, 88). These successes have inspired researchers to study pleural effusion. However, Astoul et al. conducted only 2 clinical trials, and both subjects experienced varying degrees of dyspnea after implantation of the pleural bladder pump. The investigators suspect that these outcomes may be related to pump dysfunction due to catheter obstruction (86). Studies of the pleurapump system for MPE treatment are still in the exploratory phase, and more subjects and clinical studies are needed to explore the efficacy and safety of this system in the future.

## 3.4 Indwelling pleural catheter

The currently recommended approaches for recurrent symptomatic MPE are indwelling pleural catheter (IPC) placement and pleural fixation, but IPC placement is significantly superior to repeat thoracentesis or tube placement for drainage and has been shown to be a powerful palliative treatment for patients with recurrent or treatment-resistant MPE. IPCs can be inserted and tunneled through the skin into the pleural cavity, allowing intermittent drainage and promoting pleural fixation. IPC placement is simple to perform and can usually be performed on an outpatient basis (89). IPCs are an effective means of controlling recurrent MPE, especially for patients with pulmonary atrophy and atelectasis who wish to have a shortened hospital stay (90). Thomas et al. (91) conducted a multicenter, randomized controlled clinical trial that included 144 patients with MPE. The researchers showed a reduction in the number of hospital days after IPC treatment compared with after talc pleural fixation, and there was no statistically significant difference in efficacy, in line with the findings of Davies, Ost et al. (92, 93) The results of the study were consistent. Data from a multicenter, randomized, open-label clinical trial suggest that IPCs are more effective in facilitating spontaneous pleural fixation and may improve quality of life (94). Significant improvement of dyspnea symptoms and fewer complications after IPC treatment were seen (95). Compared to talc pleural fixation, IPC placement has a very high safety profile (96): the incidence of pleural infection is <5% (patients usually respond to antibiotic therapy, and catheter removal is usually not necessary); prolonged, intermittent drainage of exudative pleural effusions or celiac disease may cause significant protein loss, leading to systemic malnutrition; and fibrin clots in the catheter lumen can lead to obstruction. In 2018, Bhatnagar et al. (97) studied the treatment of MPE by outpatient IPC placement combined with talcum powder and found that the odds of pleural fusion were significantly higher than those associated with IPC placement alone; in addition, serious adverse effects were rare and generally well tolerated by patients.

# 4 Summary and outlook

In summary, MPE is a common complication of advanced malignant tumors, and its appearance often indicates poor prognosis and short survival, which seriously affects patient quality of life. Furthermore, poorly controlled MPE can seriously affect the primary tumor systemic treatment plan, so MPE treatment is especially important in tumor treatment. At present, MPE is mainly treated medically, and intrathoracic infusion is the main strategy. With the continuous development of intrathoracic infusion drugs, many kinds of drugs are available, including chemotherapeutic drugs, immunomodulators, traditional Chinese medicines, antiangiogenic drugs and drug-carrying microparticles. MPE patients have benefited greatly from these novel therapies, which have shown good efficacy in clinical application, and clinical symptoms such as dyspnea and wheezing have been greatly improved. Currently, there are many means of MPE treatment, but there is no standard treatment protocol, especially for patients with recalcitrant or relapsed MPE, who suffer from limited overall treatment efficacy, which seriously affects the OS of patients. Therefore, although good results in the treatment of MPE have been achieved, especially *via* the use of highly beneficial antiangiogenic therapies and immunotherapies, the treatment of MPE, especially recalcitrant or relapsed MPE, is still a clinical challenge, and many issues remain to be solved in the future.

Therefore, it is important to explore the pathogenesis of MPE and combine treatment modalities and new therapeutic approaches to improve the quality of life and prolong the survival of MPE patients.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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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