Review Article

Recent advancements in lung cancer research: a narrative review

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Background and Objective: Lung cancer remains the leading cause of cancer-related mortality worldwide, with a 5-year survival rate ranging from 10% to 20%. The majority of cases are categorized as non-small cell lung cancer (NSCLC) (80%) and small cell lung cancer (SCLC) (20%), with NSCLC being the more prevalent type. Tobacco use, particularly cigarette smoking, is a significant contributor to over 80% of lung cancer cases. Early diagnosis is challenging due to limitations in screening methods, resulting in many cases being identified only in advanced stages. Moreover, current treatment options often exhibit low efficacy, partly due to an inadequate understanding of the disease's pathogenesis. This narrative review aims to summarize recent discoveries and advancements in lung cancer research, focusing on improvements in diagnosis, treatment, and understanding of the disease.

Methods: A comprehensive literature review was performed utilizing the PubMed Central database to identify recent studies relevant to lung cancer. This review synthesizes findings from various research articles to provide a cohesive summary of advancements in the field.

Key Content and Findings: In the past decade, notable progress has been achieved in lung cancer research, particularly concerning diagnostics and treatment strategies. Novel therapeutic approaches, including immunotherapy and genomic-targeted therapies, have demonstrated promising results. Understanding the tumor microenvironment (TME) and the role of T lymphocytes has become crucial for developing effective treatments. Additionally, advancements in immune checkpoint inhibitors (ICIs) have shown potential in enhancing patient outcomes. Improvements in tumor detection technologies are also anticipated to facilitate earlier diagnosis, ultimately contributing to better survival rates.

Conclusions: Significant strides have been made in lung cancer research over the last ten years, particularly in diagnostics and treatment methodologies. Future research should prioritize exploring the TME, the function of T lymphocytes, and the efficacy of ICIs while continuing to innovate in tumor detection technologies. Such efforts are essential for enhancing treatment outcomes and improving the overall quality of life for lung cancer patients.

Keywords: Lung cancer; treatment; screening; early detection; tumor microenvironment (TME)

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Introduction

Lung cancer continues to be the foremost cause of cancer-related mortality worldwide, with projections estimating a 67% increase in incidence by 2040 (1). The grave nature of the disease is further underscored by its low 5-year survival rate of 10-20% (2). Early-stage lung cancer (stage I) can have survival rates exceeding 60–70% with appropriate surgical intervention (3). Furthermore, specific subtypes such as non-small cell lung cancer (NSCLC) can benefit from targeted therapies, which have shown improved survival outcomes, with some patients experiencing prolonged remission (4). Recent studies indicate that patients with driver mutations like EGFR or ALK can achieve 5-year survival rates over 70% with targeted therapies (5). Therefore, a more nuanced understanding of lung cancer survival rates is essential for patients and clinicians alike.

NSCLC and small cell lung cancer (SCLC) are two primary types of lung cancer that differ significantly in terms of histology, clinical behavior, and treatment approach. NSCLC, comprising approximately 85% of lung cancer cases, includes subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma; it is generally characterized by slower progression and a higher likelihood of localized disease at diagnosis. In contrast, SCLC accounts for about 15% of cases and is marked by rapid growth, early metastasis, and strong association with smoking, necessitating aggressive systemic chemotherapy and radiation therapy (6,7) Additionally, SCLC arises from neuroendocrine cells and is more likely to produce paraneoplastic syndromes, while NSCLC treatment often involves surgical resection and targeted therapies based on specific molecular alterations (8).

While numerous risk factors are associated with lung cancer, smoking remains the predominant cause, accounting for over 85% of cases globally (9). Additional risk factors include passive smoking, occupational hazards, air pollution, pre-existing chronic lung diseases, and hereditary cancer syndromes, all of which can exacerbate lung cancer progression (10).

Aging populations contribute significantly to lung cancer mortality, with estimates suggesting that demographic changes could account for approximately 0.38 million lung cancer deaths globally (11). According to Fan *et al.* (12) lung cancer deaths increased by 0.97 million from 1990 to 2019, reflecting a 91.8% rise over 29 years. Despite a slight decline in age-standardized mortality rates, the absolute number of deaths continues to grow due to population dynamics. This emphasizes the need for targeted strategies tailored to each region's demographic and epidemiological context.

Late-stage diagnoses significantly hinder prognosis. Early detection of lung cancer is crucial for improving outcomes, and low-dose chest computed tomography (CT) screening is currently the standard method (13). However, this technique has a high false-positive rate (14,15). Therefore, advancing lung cancer management requires innovative techniques across various dimensions. This review consolidates the latest developments in lung cancer research, encompassing detection, treatment, and immunological and genomic studies while identifying future research directions. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-979/rc).

Methods

A literature review focusing on studies published between 2010 and 2024 was conducted in the PubMed Central database to gather the latest research on lung cancer (*Table 1*).

Lung cancer detection

Lung cancer screening

Lung cancer is often diagnosed at advanced stages, characterized by local invasion, lymph node involvement, and distant metastasis, primarily due to the absence of early symptoms (16). This underscores the urgent need for more sophisticated screening methods to detect tumors before they progress to malignancy. The gold standard for evaluating the effectiveness of screening is the reduction of mortality rates (17). To maximize the benefits of lung cancer screening, it is essential to target individuals at the highest risk. However, participation bias in screening trials remains a significant challenge; those most at risk are often the least likely to engage in screening programs (18) (Hestbech *et al.*, 2011). Notably, studies such as the National Lung Screening Trial (NLST) and the UK Lung Cancer Pilot Screening Trial (UKLS) have illustrated decreased participation rates among current smokers, older adults, and individuals from lower socioeconomic backgrounds (19-21).

Chest radiography

Chest radiography remains the standard initial diagnostic method for lung cancer in primary care. Recent advancements in computer-aided diagnostic (CAD) technology and artificial intelligence (AI)-based software

Table 1 The search strategy summary

Items	Specification
Date of search	25 Jun 2024
Database	PubMed Central
Search terms used	"lung cancer", "non-small cell lung cancer (NSCLC)", "small cell lung cancer (SCLC)", "risk factors", "symptoms", "diagnosis", "treatment", "chemotherapy", "targeted therapy", "immunotherapy", "early detection", "prognosis", "biomarkers", "radiotherapy", "pathology", "genetics", "lung cancer screening", "smoking and lung cancer", "environmental factors", "clinical trials"
Timeframe	Mainly literature published from 2010 to 2024
Inclusion and exclusion criteria	Inclusion: (I) English-language articles; (II) original publications, including clinical trials, literature reviews, and review papers. Exclusion: non-English language article
Selection process	Studies were selected based on relevance to lung cancer; studies that found/theorized new discoveries or built upon earlier evidence with new trials/research

have improved the detection of actionable lung nodules on radiographs (13,22). Current guidelines from NICE recommend chest radiography for early examination in all patients, with the exception of those over 40 years old presenting with unexplained hemoptysis (23).

CT screening

Virtual bronchoscopy, a CT-based 3D imaging technique, allows for non-invasive assessment of the tracheobronchial tree, facilitating diagnosis of airway stenosis due to cancer (24). Enhanced recognition of lung nodules, especially centrally located ones, is achievable through CAD and AI systems (25,26). Definitive histological diagnosis in suspected lung cancer cases requires bronchoscopic or image-guided biopsy (27).

The introduction of photon-counting CT (PCCT) in 2021 marked a significant advancement in imaging technology. PCCT delivers ultra-high-resolution images and offers numerous benefits, including improved spatial resolution and reduced contrast material dosage (28,29). The system's ability to directly convert input photons into electrical signals enhances imaging quality while minimizing electronic noise. Furthermore, spectral imaging capabilities allow for quantifiable functional data collection, such as lung perfusion metrics (28). K-edge imaging, facilitated by PCCT and novel contrast agents, opens avenues for future imaging applications (30).

Over the past decade, the eligibility criteria for screening have evolved significantly, influenced by emerging research and public health recommendations. As of 2023, individuals aged 50 to 80 years are generally recommended for screening (31). Factors include a history of heavy smoking (a minimum of 20 pack-years). Both current smokers and former smokers who quit within the last 15 years are included in this group.

The last decade has seen changes in screening recommendations. Previously, guidelines primarily targeted older populations, specifically those aged 55 to 74 years. Recent updates have broadened the age range to those individuals as young as 50 years. Furthermore, new risk factors have been integrated into the guidelines, such as a family history of lung cancer, exposure to secondhand smoke, and occupational hazards. Another significant shift is the emphasis on shared decision-making, encouraging healthcare providers to discuss the potential benefits and harms of screening rather than issuing a blanket recommendation for all eligible individuals.

Regional variations in eligibility criteria further illustrate the complexity of lung cancer screening. In the United States, the U.S. Preventive Services Task Force (USPSTF; https://www.uspreventiveservicestaskforce.org/uspstf/) recommends annual LDCT screening for individuals aged 50 to 80 years with a history of 20 pack-years of smoking. Conversely, European guidelines differ by country; while some have adopted similar criteria to the U.S., others, like the UK, have been slower to implement widespread screening programs, focusing instead on pilot initiatives. In Asia, particularly in Japan and South Korea, screening criteria may be adjusted to account for lower smoking rates and the higher prevalence of adenocarcinoma among non-smokers. Australia and New Zealand align their recommendations with those of the U.S. while also considering

a broader array of risk factors beyond smoking (32).

On the whole, the evolution of lung cancer screening eligibility reflects an increasing understanding of the disease and its associated risk factors. Although there is a trend toward more inclusive criteria, implementation varies widely across regions due to differences in health policies, smoking prevalence, and healthcare infrastructure. This underscores the necessity for tailored public health strategies in lung cancer screening globally.

Low-dose computed tomography (LDCT) screening

LDCT remains the primary method for lung cancer screening and staging (9). The effective radiation dose from LDCT is significantly lower, which is 22% than that of standard CT scans. Studies indicated that low dose CT was about 2 mSv while standard CT was 7 mSv for chest CT (33). While chest radiography is widely used, it has not been shown to reduce lung cancer mortality compared to LDCT (24). Recent trials focusing on at-risk populations have demonstrated LDCT's efficacy in diagnosing early-stage disease, although its impact on mortality rates has been less clear. While beneficial for early detection, LDCT faces significant limitations. The high false-positive rate, ranging from 23% to 51% in major trials, poses a substantial challenge for both patients and healthcare systems (34,35). The National Lung Screening Trial reported that 96.4% of positive results were ultimately false positives, leading to unnecessary follow-up procedures and psychological distress. Accurate assessment of nodule characteristics remains challenging, with inter-observer variability in measuring and characterizing lesions ranging from 15% to 30%, potentially resulting in inconsistent management decisions (36).

The landmark NLST randomized over 53,000 individuals at risk (ages 55–74 years with a smoking history) to receive either annual LDCT or chest X-ray screening. Results revealed a notable decrease in all-cause (6.7%) and lung cancer-specific mortality (20%) in the LDCT group (34). This trial also highlighted a decrease in late-stage diagnoses, prompting the USPSTF to recommend extending the upper age limit for LDCT screening to 80 years (37).

The increasing use of immune checkpoint inhibitors (ICIs) for early-stage and locally advanced lung cancer is significant, particularly as LDCT screening programs enhance early diagnosis in at-risk communities (38,39).

Magnetic resonance imaging (MRI)

Emerging evidence suggests that lung MRI could serve as a valuable screening tool, performing comparably to LDCT but with a lower false-positive rate and no exposure to radiation (40,41). MRI has demonstrated its ability to differentiate lung cancer from conditions such as severe fibrosis and obstructive pneumonia (41). Techniques like diffusion-weighted imaging (DWI) and short tau inversion recovery (STIR) turbo-spin echo sequences have shown high diagnostic performance in N-staging of NSCLC (42,43). Furthermore, contrast-enhanced MRI is beneficial for evaluating brain metastases in patients with clinical stage III lung cancer (44). Innovative MRI techniques, such as 3D dynamic contrast-enhanced perfusion sequences, also predict post-operative lung function in patients with concurrent chronic obstructive pulmonary disease (COPD) (40,45).

Histopathological examinations

Bronchoscopy

Bronchoscopy is important for the workup of lung cancer, facilitating the diagnosis and staging of pulmonary lesions through techniques including navigational bronchoscopy (46) and endobronchial ultrasound (EBUS) (47). Navigational bronchoscopy, utilizing technologies such as electromagnetic navigation and virtual bronchoscopic guidance, has significantly improved the diagnostic performance for peripheral lung nodules. Study (48) has shown that its accuracy can range from 68% to 77%, particularly for lesions located in challenging anatomical areas. EBUS, especially when employed for transbronchial needle aspiration, has become the gold standard for mediastinal staging, providing a diagnostic yield of approximately 85% for assessing lymph nodes and adjacent structures. This technique is particularly valuable in differentiating between malignant and benign conditions and enhancing the accuracy of lung cancer workups, allowing for more precise treatment planning (49). Recent guidelines recommend their use to optimize patient outcomes and minimize the need for more invasive procedures (50).

Biomarker examinations

Circulating tumor DNA (ctDNA)

Recent studies have highlighted the potential of ctDNA in NSCLC. A study identified mutations associated with NSCLC, achieving sensitivity and specificity rates of 85% and 96%, respectively (51). Notably, only 50% of early-stage NSCLC cases had detectable ctDNA, contrasting with late-stage cases where detection was universal. The human telomerase (*hTERT*) gene has been utilized to measure

circulating DNA levels, revealing significantly higher levels in NSCLC patients compared to matched controls (52,53).

Sputum analysis

In a study involving 187 high-risk patients exposed to asbestos, sputum cytology and LDCT revealed that 6 out of 18 lung cancer cases were detected through both methods (54). Additionally, sputum microRNA has shown promise as an early detection tool, with a panel of three miRNAs providing 72% sensitivity and 95% specificity for squamous cell carcinoma (55). Integrating sputum miRNA analysis with thoracic CT has demonstrated the capability to differentiate malignant neoplasms from solitary pulmonary nodules (56). Molecular and cytometric analyses of sputum have yielded specificities exceeding 90%, suggesting their potential as supplementary measures to enhance the accuracy of LDCT screening (17).

Lung cancer treatment

Lung cancer remains a significant health challenge, with standard treatments including radiotherapy, chemotherapy, and surgery. In recent years, targeted therapy and immunotherapy have emerged as promising modalities to enhance treatment efficacy.

Radiotherapy

Recent preclinical studies highlight the potential of combining radiotherapy with ICIs to improve patient outcomes. Evidence suggests that radiotherapy not only aids in local tumor control but also enhances systemic antitumor immune responses, a phenomenon known as the abscopal effect (57). For example, a case study demonstrated that radiation combined with anti-CTLA4 therapy led to improved outcomes in a patient with metastatic NSCLC (58). However, optimal treatment parameters such as timing, sequence, and dosage require further investigation.

Stereotactic body radiation therapy (SBRT) has shown promise in early-stage lung cancer, although tumor spread via air space (STAS) poses a challenge (59).

Chemotherapy

Chemotherapy faces challenges due to intrinsic and acquired resistance. Regulatory T cells (Tregs) in the lung cancer microenvironment contribute to this resilience, with studies indicating that chemoresistant mesenchymal cells exhibit lower E-cadherin levels (60). Tregs are linked to immunosuppressive chemoresistance, particularly in relation to Kras mutations and $CD8^+$ T-cell exhaustion (61).

Moreover, cancer-associated fibroblasts (CAFs) can influence chemotherapy responses. Research indicates that cisplatin may enhance AXL expression in CAFs, promoting the migration of AXL-expressing lung cancer cells (62). Patients with AXL^+ tumors and $GAS6^+$ stroma showed significantly lower 5-year disease-free survival rates, suggesting that targeting AXL or GAS6 could improve therapeutic outcomes (63).

Surgery

Surgical excision is a standard treatment for lung cancer; however, evidence suggests that surgical trauma may inadvertently stimulate tumor growth (64,65). The mechanisms remain unclear, but postoperative inflammatory responses may create immunosuppressive states (66,67). Zhao *et al.* demonstrated that surgical trauma upregulates CCL2, enhancing Treg recruitment and migration, thus complicating postoperative recovery (68).

In addition, recent studies have highlighted the effectiveness of sublobar resection in treating small peripheral lung tumors, particularly in early-stage lung cancer patients. When comparing sublobar procedures, such as wedge resection or segmentectomy, with lobectomy, a study (69) indicates that sublobar resection can yield similar survival outcomes in carefully selected patients (older individuals or those with comorbidities). The adoption of minimally invasive techniques, such as video-assisted thoracoscopic surgery (VATS), has been shown to enhance recovery and reduce complications (70). Long-term outcomes suggest that sublobar resection can provide adequate local control and overall survival, especially when combined with adjuvant therapies (70). Recent guidelines have begun to recommend sublobar resection for specific patient groups (71), and ongoing clinical trials are exploring its benefits in terms of quality of life and pulmonary function post-surgery (72). As a whole, sublobar resection is increasingly recognized as a viable treatment option for small peripheral lung tumors (73).

Combination therapy

Combining chemotherapy and radiotherapy may enhance the tumor microenvironment (TME) and improve ICI efficacy. Radiation and certain chemotherapeutics can induce immunogenic cell death, increasing antigen load

and MHC expression, leading to a greater influx of tumor-infiltrating lymphocytes (TILs) (74,75).

The KEYNOTE-189 trial showed that pembrolizumab combined with chemotherapy improved overall survival and progression-free survival (PFS) in untreated advanced NSCLC patients, regardless of PDL1 expression (76) (similarly, the CheckMate 227 trial demonstrated superior PFS in patients treated with nivolumab and ipilimumab compared to chemotherapy) (77).

Ongoing clinical trials are exploring combinations of ICIs with vascular endothelial growth factor (VEGF) inhibitors, oncolytic viruses, and epigenetic modifiers, with promising early results (78,79).

Targeted therapy

Extensive genomic profiling of NSCLC has led to the identification of molecular subtypes that are oncogene-addicted and highly susceptible to targeted therapies (80). Notable discoveries include mutations in the epidermal growth factor receptor (EGFR), as well as fusions involving BRAF, EML4-anaplastic lymphoma kinase (ALK), and ROS1 receptor tyrosine kinase. Patients with metastatic disease have experienced significantly improved survival and response rates due to therapies targeting the tyrosine kinase domains of these driver oncogenes. However, these targeted therapies only benefit 15–20% of patients, and resistance mechanisms often develop, limiting their overall efficacy (81). Therefore, further molecular characterization of the tumor landscape is essential for developing innovative treatment strategies and identifying novel biomarkers that influence disease progression (82).

The target-rich environment of the TME in both primary and secondary lung cancers has greatly contributed to the development of new anticancer therapies. Various medications that target components of the TME, including immune checkpoints, aromatase, and vascular endothelial growth factor (VEGF), have already received clinical approval (74).

The TME may also have prognostic implications in lung carcinogenesis, particularly concerning stage-dependent immune cell infiltration (83). Specific TME states could serve as biomarkers for determining disease stage, type, clinical outcomes, and treatment responses (84).

Furthermore, therapeutic strategies targeting the TME have shown promising results in enhancing cancer treatment efficacy. For instance, a study (85) demonstrated that the combination of anti-programmed cell death protein 1 (PD-1) therapy with a TME-modulating agent, CX-5461, significantly improved tumor control in preclinical models of pancreatic cancer, leading to increased survival rates. Additionally, a clinical trial by (86) evaluated the use of TGF-β inhibitors in patients with advanced solid tumors, reporting a 30% objective response rate and notable reductions in fibrosis within the TME, which correlated with improved immune infiltration and activity. These interventions highlight the potential of targeting the TME to overcome therapeutic resistance and improve patient outcomes.

Research targeting the extracellular matrix (ECM) has shown that components like matrix metallopeptidase 14 (MMP14), hyaluronan, and lysyl oxidase may have therapeutic potential. In NSCLC, ECM density has been found to inhibit T cell infiltration into tumor beds (87). Therefore, targeting the ECM could enhance T cell access to tumors and improve antitumor efficacy (88).

Tumor-derived angiogenic factors are crucial for the formation of new blood vessels, facilitating the migration and proliferation of endothelial cells essential for tumor invasion and progression. Bevacizumab, an angiogenesis inhibitor, is one of several drugs approved or in clinical trials for NSCLC. However, the role of angiogenesis in lung carcinogenesis remains poorly understood (89). Notably, some NSCLC cases exhibit nonangiogenic growth patterns, challenging the traditional view that tumor growth relies solely on neoangiogenesis (90). These tumors often have a poorer prognosis and may utilize existing blood vessels rather than induce new ones. Thus, it is critical to enhance our understanding of tumor vasculature and angiogenic signaling in NSCLC (88).

In 2015, nivolumab, a PD-1 antibody targeting the PD-1/programmed death-ligand 1 (PD-L1) axis, became the first ICI approved for NSCLC. Since then, several additional ICIs have received approval, both as monotherapies and in combination with other treatments (88).

Currently, three antibodies targeting PD-1 and PD-L1 are authorized for second- or third-line treatment of metastatic NSCLC. Pembrolizumab has been shown to significantly improve overall survival (OS), PFS, and response rates compared to standard platinum-doublet chemotherapy (90). Consequently, pembrolizumab has emerged as a standard of care for this patient cohort.

Atezolizumab is the only PD-L1 antibody currently licensed for previously treated metastatic NSCLC. The OAK trial demonstrated improved survival with atezolizumab compared to docetaxel, regardless of PD-L1

expression levels on tumor or immune cells (91). Ongoing trials are evaluating the efficacy of other PD-L1 antibodies, including avelumab and durvalumab, in managing metastatic NSCLC. Durvalumab has also been assessed in patients with locally advanced, non-metastatic (stage III) inoperable NSCLC. In this trial, patients who completed standard treatment, including radiation and chemotherapy, were assigned to receive durvalumab or a placebo. Durvalumab significantly increased median PFS and improved time to recurrence or death, leading the FDA to designate it as a breakthrough therapy for this patient population (92).

Overall, ICI trials are transforming treatment for patients with locally advanced and metastatic NSCLC. Based on performance status, second-line immunotherapy is increasingly prescribed for patients who do not respond to first-line chemotherapy. While pembrolizumab has been approved as a first-line therapy for patients with advanced NSCLC whose tumors express PD-L1 in at least 50% of cancer cells, only 25–50% of NSCLC patients exhibit such expression, with fewer meeting the regulatory threshold (93). Investigating other combination therapy approaches is essential to achieve even better clinical outcomes.

Immunotherapy

Immunotherapy aims to counteract immunosuppressive mechanisms and enhance immune cell function (94). Long-term success rates remain limited, with complete response rates of only 5–15% in most solid tumors, and only 25–30% of melanoma patients and 15–20% of lung cancer patients maintaining durable responses beyond five years (95-97).

At the cellular level, both $CD8^+$ and $CD4^+$ T cells are crucial for effective antitumor immune responses, as demonstrated in KRAS-driven mouse models where PD-1 inhibition's therapeutic efficacy required both cell types (98). Beyond traditional $Foxp3^+$ Tregs, newly identified subpopulations such as $FOXA1^+$ Tregs are implicated in inhibiting antitumor immunity and increasing PD-L1 expression (99). Natural killer (NK) cells also play a vital role in tumor immunosurveillance, with CD96 acting as a negative regulator of NK cell function (100). In the pre-metastatic niche, CCL2 from hypoxic tumor cells recruits granulocytic myeloid cells that suppress NK cell functions (101), while IL-1R8 restricts NK cell maturation and effector functions (102).

The TME contains critical immune components, including tumor-infiltrating B lymphocytes and tertiary lymphoid structures (TLS), which correlate with improved prognosis in NSCLC patients (103). Patient-derived tumor-infiltrating B lymphocytes can present tumor antigens to $CD4^+$ TILs, with activated B cells linked to $IFN\gamma^+$ $CD4^+$ T cells and exhausted B cells associated with immunosuppressive Tregs (104).

Therapeutic approaches have evolved to target these mechanisms. Preclinical research has shown that dendritic cells (DCs) transduced with CCL21 can reduce tumor burden by enhancing immune cell infiltration into the TME (105). A phase I trial using intratumoral vaccination with CCL21-expressing DCs in advanced NSCLC demonstrated increased PD-L1 expression and improved $CD8^+$ T cell infiltration (106). Recent strategies have integrated DC enhancement with checkpoint inhibitors and standard therapies (107), though the immunosuppressive TME can limit DC vaccine effectiveness when used alone (88).

Novel therapeutic targets continue to emerge. The IL-1β-targeting antibody canakinumab has shown promise in reducing lung cancer incidence and mortality in atherosclerosis patients (108) and is under evaluation in phase III trials for NSCLC (78). Additionally, the complex role of Nrf2 in carcinogenesis, with both tumor-suppressive and pro-oncogenic properties, presents potential therapeutic opportunities (109,110).

Key areas for future discoveries in lung cancer management

TME

To better understand the TME and its complex signaling pathways, it is essential to overcome existing technological barriers. Emerging studies are investigating the intricate crosstalk between tumor and stroma in preclinical models (111). This has led to the development of CCCExplorer, a computational tool for analyzing cell-cell communication pathways from multicellular genomic datasets.

Recent advancements have enabled the exploration of TME transcriptomes in human lung tumors at the single-cell level (112). Technologies such as multiplexed immunohistochemical staining (113), multiparametric flow cytometry (114), cytometry by time of flight (CyTOF) (115), and single-cell sequencing (84) have further resolved TME features in clinical specimens. By quantifying specific cellular components in human tumors, researchers aim to predict clinical outcomes, identify biomarkers, and uncover therapeutic targets through regression-based deconvolution of bulk gene expression data (116). This method has the

potential to evolve into a clinical test, as it can detect cellular heterogeneity from small volumes of various clinical specimens without relying on predefined marker panels.

Additionally, cytotoxic agents can be delivered intratumorally into endobronchial tumors via bronchoscopy, allowing for the treatment of NSCLC and the identification of metastases in mediastinal lymph nodes (117). Recent phase I–III clinical trials have explored drug delivery systems for targeted therapy and immunotherapy, opening new avenues for personalized care (118). Nanomedicine also holds significant promise for enhancing lung cancer treatment.

Pre-metastatic niche targeting

The pathways driving the formation of a pre-metastatic microenvironment present potential therapeutic targets for preventing and treating metastases. The ALOX5 inhibitor Zileuton, typically used for asthma, has been shown to reduce lung metastasis in preclinical models by decreasing neutrophil leukotriene synthesis, without altering neutrophil levels (119). Similarly, Sivelestat, a small molecule inhibitor targeting neutrophil proteases, demonstrated efficacy in reducing lung metastases (120). While these findings support targeting neutrophils' pro-metastatic roles, caution is warranted as neutrophils can also exhibit anti-metastatic effects (121).

Preclinical studies have highlighted the effectiveness of lysyl oxidase-neutralizing antibodies (122), with human antibody development currently underway. Research has also proposed targeting CXC chemokine receptor 2 (CXCR2) to mitigate granulocyte recruitment mediated by platelets (123) and blocking C-C motif ligand 2 (CCL2)-CC-chemokine receptor 2 (CCR2) signaling to reduce monocyte mobilization and metastasis (124). However, blocking CCL2 can paradoxically increase monocyte release and enhance angiogenesis, potentially worsening outcomes (125). Exploring the potential of metastatic suppressive habitats, such as a TSP1-inducing peptide from prosaposin, may offer novel strategies (126).

Immunological research

Numerous studies have highlighted the connection between immunological dysfunction and lung cancer progression. T lymphocytes play a central role in cellular immunotherapy and are critical to tumorigenesis (127). Understanding T lymphocyte immunology could lead to novel treatments for lung cancer patients who do not respond to traditional therapies or have advanced disease (16).

Research has established the significant role of T regulatory lymphocytes (Tregs) in lung cancer, with higher Treg levels correlating with poor treatment responses (128). Tregs undermine antitumor immunity, allowing tumor evasion and maintaining tolerance to self-antigens (129). Elevated Treg levels in metastatic tumors have been shown to predict survival rates and recurrence (130).

In mouse models, Tregs partially inhibit $CD8^+$ T cell antitumor activity. Depleting Tregs in lung adenocarcinoma models enhances $CD8^+$ T cell recruitment and boosts granzyme expression, leading to increased tumor cell death (131). The immunosuppressive marker Foxp3, predominantly expressed in Tregs, has been linked to tumor cells secreting cytokines that promote Foxp3 expression (132). Additionally, IL-15 from SCLC tumor cells contributes to Treg development and enhances their immunosuppressive properties (133).

Research by Haruna *et al.* (134) indicates that increased $CCR8^+$ Treg infiltration correlates with poorer clinical outcomes in lung cancer. $CCR8^+$ Tregs demonstrate enhanced immunosuppressive characteristics compared to their $CCR8^-$ counterparts, suggesting a potential avenue for therapeutic intervention.

Genomic research

Molecular testing is crucial for identifying genetic mutations and biomarkers in lung cancer. Approximately 30% of KRAS-mutated lung adenocarcinomas exhibit loss-of-function mutations in the tumor suppressor LKB1 (STK11), affecting various cellular processes, including metabolism and metastasis (135). Recent studies have linked oncogenic driver mutations in KRAS, p53, and EGFR with distinct immune phenotypes in both murine and human lung adenocarcinomas (136).

Radiomics

AI is pivotal in the evolving fields of radiogenomics and radiomics, which hold great promise for enhancing risk classification and diagnostics (137). Radiomics allows for the extraction of information from medical images—such as CT, MRI, and PET—to improve understanding of tumor heterogeneity (138).

Tang *et al.* (139) introduced a clinical probability-weighted radiomics model to predict NSCLC prognosis,

integrating radiomic features with clinical factors. This model demonstrated strong performance, achieving an area under the curve (AUC) of 0.949, indicating its potential for personalized treatment decisions.

Real-time intravital optical imaging is also being utilized in preclinical models to observe dynamic cellular interactions during tumor growth, particularly between immune cells and disseminated cancer cells (140). Recent advancements, such as vacuum-stabilized imaging windows, have mitigated challenges in imaging the lungs during respiration (140,141).

Circulating tumor cells (CTCs)

CTCs are cancer cells that have shed from the primary tumor into the bloodstream and are considered significant biomarkers for monitoring disease progression and therapeutic responses. The ability to detect and analyze CTCs offers a minimally invasive method to gain insights into the molecular characteristics of tumors in real-time. Recent research has highlighted the pivotal role of CTCs in lung cancer management, demonstrating their potential in predicting patient outcomes and guiding treatment decisions (142). For instance, studies have shown that the presence and quantity of CTCs correlate with disease stage, metastatic spread, and overall survival rates in lung cancer patients (143). These findings underscore the importance of CTCs in personalized medicine, enabling tailored therapeutic strategies and improving clinical outcomes.

Future challenges and areas of focus

Lung cancer remains a challenging disease due to early detection difficulties and treatment obstacles. While screening may benefit early detection, some patients have comorbidities that complicate surgical options. New methods, such as stereotactic ablative body radiation (SABR), show promise for stage I lung cancer patients who are not surgical candidates (144).

The optimal frequency of CT scans for patients remains uncertain. Routine CT scans are necessary, given that new malignancies are often detected at each screening interval. However, repeated radiation exposure poses an oncogenic risk (17). High false-positive rates and late-stage malignancies emerging between screenings are significant limitations of LDCT. Further testing is needed to reduce false positives and address the LDCT blind spot for aggressive tumors.

Historically, sputum analysis has been explored for early detection, but initial results were disappointing. However, advancements in molecular biology have renewed interest in this technique, though clear advantages remain to be established (17).

Access to MRI is limited for lung cancer patients, restricting its use except in specific cases, such as brain staging or lung apex involvement. There are still significant knowledge gaps in lung cancer carcinogenesis that hinder the development of new treatments. For example, the roles of NK cell subsets in lung carcinogenesis are still not fully understood (89).

Further characterization of myeloid-derived suppressor cells (MDSCs), including polymorphonuclear (PMN-MDSCs) and monocytic (M-MDSCs) subsets, is essential. These cells suppress T cell activity and cytokine production (145). Understanding the distinct molecular characteristics of PMN-MDSCs and M-MDSCs could inform therapeutic strategies.

The potential of $LOX1^+$ cells as prognostic biomarkers in NSCLC merits investigation, especially given their increase in NSCLC patients. Studies suggest that stress-induced pathways can transform normal neutrophils into immunosuppressive $LOX1^+$ PMN-MDSCs (146). Targeting this pathway may have therapeutic implications.

Another area for exploration is the prognostic relevance of tumor-associated macrophages (TAMs) in NSCLC (147). The heterogeneity of macrophage phenotypes challenges the simplistic M1–M2 classification (148). TAMs represent a significant portion of the immune infiltrate in NSCLC and exhibit plasticity, leading to diverse phenotypic expressions influenced by the surrounding microenvironment (149).

Despite advances in immunotherapy, many NSCLC patients do not respond to ICIs or develop resistance after initial responses, necessitating deeper investigations into tumor escape mechanisms and the identification of biomarkers for immunotherapy responsiveness (90).

Immune checkpoint drugs can inadvertently trigger host immune responses. Research indicates that immune checkpoint antibodies conjugated to matrix-binding peptides show improved retention in tumor extracellular matrices, leading to effective antitumor responses with minimal side effects (150).

Recent studies have identified LKB1 mutations as a common genetic driver of primary resistance to PD1 inhibitors in KRAS-mutant lung adenocarcinomas (151). A better understanding of immune responses and evasion mechanisms will enhance the development of durable

immunotherapy regimens (152). Preoperative trials, where samples are collected before, during, and after surgery, may provide valuable insights into immune response dynamics (86). For instance, a recent trial of preoperative anti-PD1 treatment in early-stage operable patients showed a strong pathological response in 45% of participants (153).

Conclusions

Diagnosing lung cancer in its early stages remains challenging due to limitations in screening and diagnostic technologies. Ongoing research aims to combat this globally prevalent disease, emphasizing the importance of screening high-risk populations for early detection and timely treatment. Overcoming technological barriers is crucial for identifying predictive and diagnostic biomarkers and therapeutic targets. Continued advancements in understanding the TME and tumor immunology hold the potential to enhance lung cancer patient prognosis significantly.

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