Review Article

Transforming Lung Cancer Management with AI and Biomarkers: From Early Detection to Targeted Therapies

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Abstract: Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) representing the primary histological subtypes. Approximately 85% of cases are classified as NSCLC, whereas SCLC is characterized by its aggressive clinical course and poor prognosis. Major risk factors for SCLC include smoking, environmental exposures, and genetic predispositions. Early detection is critical; low-dose computed tomography (LDCT) has demonstrated a significant reduction in lung cancer–specific mortality. The use of biomarkers, such as microRNAs (miRNAs), has enhanced diagnostic accuracy by improving risk stratification and distinguishing malignant from benign pulmonary nodules. Artificial intelligence (AI)-driven imaging technologies have revolutionized lung cancer screening by increasing diagnostic precision and operational efficiency. Advances in molecular characterization, including identification of mutations and gene fusions involving EGFR, KRAS, ALK, and NTRK, have facilitated the development of personalized therapeutic strategies. In particular, immunotherapies and targeted agents, such as TRK inhibitors, have demonstrated promising efficacy in NSCLC. Nevertheless, significant challenges remain, including therapy resistance, healthcare disparities, and limited accessibility to screening programs. Emerging technologies, such as liquid biopsies and deep learning–enhanced imaging, continue to drive improvements in early detection and treatment paradigms. Future research should prioritize the integration of AI, novel therapeutics, and precision medicine approaches to optimize lung cancer management. By advancing early diagnostic capabilities, expanding personalized interventions, and addressing disparities in access to care, meaningful progress can be achieved in reducing lung cancer mortality.

Keywords: Lung cancer; Non-small cell lung cancer (NSCLC); Small cell lung cancer (SCLC); Low-dose computed tomography (LDCT); MicroRNAs (miRNAs); Artificial intelligence (AI).

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Introduction

Lung cancer remains the leading cause of cancer-related mortality among both men and women in the United States and is the foremost cause of cancer-attributed deaths globally among men, and the second among women [1-2]. The high incidence and mortality rates of lung cancer underscore the urgent need for early diagnosis and effective therapeutic strategies. In recent years, pathogenic germline variants—previously termed mutations—have been identified as significant contributors to an increased predisposition to lung cancer in certain individuals [3]. This genetic susceptibility, combined with environmental exposures such as tobacco smoke, occupational hazards, and

air pollutants, makes early detection particularly crucial in high-risk groups [4]. Importantly, lung cancer demonstrates notable sex-based disparities. A higher incidence among non-smoking women compared to non-smoking men suggests distinct biological and molecular characteristics, necessitating sex-specific clinical approaches [5]. Lung cancer commonly manifests as epithelial-derived carcinomas and can aggressively invade local tissues or metastasize if left untreated [6]. It is also the most frequently observed second primary malignancy, arising independently from prior cancers [7]. Histologically, lung cancer is broadly classified into two principal subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), each with distinct molecular profiles, clinical behaviors, and treatment responses [8].

Despite advancements, lung cancer still accounts for approximately 2 million new cases and 1.8 million deaths globally per year [9]. Current treatment modalities—including surgery, chemotherapy, radiation, and targeted therapies—are evolving rapidly, driven by growing insights into the molecular underpinnings of lung cancer [10]. Moreover, the discovery of microRNAs (miRNAs) as diagnostic and prognostic biomarkers has opened new avenues for non-invasive screening and personalized medicine. Parallel efforts have focused on developing robust screening methods such as low-dose computed tomography (LDCT) and DNA methylation-based diagnostics, aiming to improve early detection rates. In recent years, artificial intelligence (AI) has emerged as a transformative tool in lung cancer care, improving the detection, classification, and monitoring of disease through advanced image analysis and risk prediction algorithms [11]. These developments reflect a broader shift toward precision oncology, integrating computational and molecular approaches to guide tailored interventions.

This review will comprehensively discuss: the biological and clinical distinctions between SCLC and NSCLC; advances in screening and diagnostic methodologies; AI-powered imaging analysis; the role of pharmacological agents and miRNA biomarkers in disease management. Through this synthesis, we aim to highlight how integrative strategies can improve outcomes and reshape the future of lung cancer management.

Small cell lung cancer (SCLC)

Small cell lung cancer (SCLC) is an anaplastic form of lung cancer with a five-year survival rate of approximately 7%, predominantly associated with smoking [12]. It is characterized by rapid cellular proliferation, genomic instability, high vascularization, and early metastatic spread. At diagnosis, more than 50% of patients present with distant metastases, and extensive brain involvement may be attributed to the neurotropic tendencies of the disease [13]. According to data from the World Health Organization (WHO), approximately 2.21 million new cases of lung cancer were diagnosed globally in 2020, resulting in 1.8 million deaths [14]. Patients with SCLC commonly present with symptoms such as persistent cough, dyspnea, and hemoptysis. Imaging often reveals a centrally located lung mass with extensive mediastinal

lymph node involvement, and roughly two-thirds of patients are diagnosed with metastatic disease [15]. Recent research has enhanced the understanding of the immunologic microenvironment and molecular subtypes of SCLC, contributing to improved disease staging and classification. The approval of two programmed death-ligand 1 (PD-L1) inhibitors, in combination with chemotherapy, has introduced immunotherapy-based regimens for the first-line treatment of extensive-stage SCLC. Additionally, lurbinectedin, a novel alkylating agent that inhibits oncogenic transcription, has been approved as a second-line treatment option for metastatic SCLC [16]. The transformation of non-small cell lung cancer (NSCLC) into SCLC represents a significant mechanism of resistance to chemotherapy, immunotherapy, and targeted therapies [17]. Given its aggressive nature and poor prognosis, SCLC is classified by the National Cancer Institute (NCI) as a recalcitrant malignancy. Urgent research efforts are focused on elucidating mechanisms of therapeutic resistance and developing novel treatment strategies [18].

Non-small cell lung cancer (NSCLC)

Non-small cell lung cancer (NSCLC) is among the most frequently diagnosed cancer types globally. Its epidemiological patterns are influenced not only by tobacco use but also by environmental factors such as air quality [19]. Chronic obstructive pulmonary disease (COPD) is frequently identified as a comorbidity in individuals newly diagnosed with NSCLC [20]. NSCLC accounts for approximately 85% of all lung cancer cases and encompasses the histological subtypes of squamous cell carcinoma, adenocarcinoma, and large cell carcinoma [21]. In its early stages, NSCLC is often non-metastatic, making surgical intervention a viable and potentially curative option when detected early. However, the low rate of early-stage diagnosis limits the applicability of curative surgery for most patients, who are typically diagnosed at more advanced stages [22]. The majority of NSCLC cases are identified at a late stage, significantly restricting curative treatment opportunities. Therefore, it is critical for primary care physicians to adopt proactive screening strategies, even in the presence of non-specific symptoms, particularly among high-risk populations, to enhance survival outcomes [23]. The molecular landscape of NSCLC is characterized by alterations in several key oncogenic drivers, including mutations in BRAF, EGFR, and KRAS, as well as translocations involving the anaplastic lymphoma kinase (ALK) gene and upregulation of the mesenchymal-epithelial transition pathway [24]. Additionally, recent research has identified fusions involving the neurotrophic tropomyosin receptor kinase (NTRK) genes as promising therapeutic targets. In response, the U.S. Food and Drug Administration (FDA) has approved the first-generation tropomyosin receptor kinase (TRK) inhibitors entrectinib and larotrectinib for patients with solid tumors harboring NTRK fusions, including those with NSCLC [25].

Lung cancer screening methods

Much of the existing research on CT lung cancer screening emphasizes the importance of participant selection, particularly regarding age and

cumulative lifetime smoking exposure, the primary risk factor for lung cancer [26]. Low-dose computed tomography (LDCT) has become a critical method for the early detection of lung cancer, offering a potential reduction in mortality rates associated with the disease [27]. LDCT provides sensitivity comparable to that of conventional CT scans but with lower radiation doses and faster scan times, enhancing patient safety and convenience [28]. The scheduling of low-dose spiral CT scans (LDCT) should be individualized based on the anticipated growth rate of pulmonary nodules in the target population [29]. The National Lung Screening Trial (NLST) and the Dutch-Belgian Lung Cancer Screening Trial (NELSON) provide robust evidence supporting the efficacy of CT lung cancer screening, demonstrating significant reductions in mortality. The data reveal mortality reductions ranging from 8% to 26% for men and 26% to 61% for women identified as high-risk individuals [30]. Additionally, risk data derived from CT scans can inform about concurrent conditions, such as coronary heart disease (CHD) and emphysema, offering further incentives for individuals to engage in screening [31]. Annual CT lung screening has been shown to detect early-stage lung cancer more effectively than chest radiography (CXR), contributing to a decrease in lung cancer mortality, particularly among high-risk individuals [32]**.**

Current guidelines emphasize the importance of offering smoking cessation services to participants in lung cancer screening programs. However, there is limited data on the optimal integration of these services for both high-risk and low-risk smokers within the context of CT lung cancer screening [33]. Lung cancer screening rates exhibit considerable variation based on sociodemographic factors, including race, ethnicity, gender, and socioeconomic status (SES). Furthermore, healthcare disparities hinder the participation of high-risk populations—especially minority and low-SES groups—in lung cancer screening programs [34]. The incorporation of biomarkers into lung cancer screening has shown promise in improving risk stratification, refining the identification of eligible populations, and distinguishing between benign and malignant nodules [35]. Some biomarkers are being investigated as potential stand-alone diagnostic tools for lung cancer. Advancements in bronchoscopy technologies, which allow for improved detection and sampling of early-stage lung tumors, are contributing to more accurate diagnoses [36].

Concerns about the cumulative radiation exposure associated with repeated LDCT screenings have led to the exploration of non-invasive, easily accessible, and cost-effective alternatives to supplement LDCT. Blood-based tests, particularly those targeting stable long noncoding RNAs (lncRNAs), hold promise for enhancing early diagnosis and improving the accuracy of LDCT screenings [37]. Liquid biopsy techniques, which detect circulating tumor DNA (ctDNA) in blood samples, are also emerging as a valuable tool in lung cancer screening. With advancements in molecular and sequencing technologies, ctDNA has the potential to identify genetic alterations, track resistance mutations, and guide clinical decision-making [38].

Lung Cancer Diagnostic Techniques

Early and accurate diagnosis of lung cancer remains a critical challenge in clinical oncology, as the disease often presents without symptoms until it has progressed to advanced stages. As a result, many patients are only diagnosed when symptoms such as persistent cough, chest pain, or unintended weight loss prompt clinical investigation. This delay underscores the urgent need for reliable, non-invasive screening tools, particularly for individuals at high risk. One promising avenue in early lung cancer detection is the use of DNA methylation biomarkers. Aberrant epigenetic modifications—such as global DNA hypomethylation and gene-specific promoter hypermethylation—are hallmarks of lung carcinogenesis and have been extensively investigated as diagnostic and prognostic indicators [39]. These biomarkers offer the potential for sensitive and specific detection of lung cancer from minimally invasive samples, including blood, sputum, and bronchial washings.

In response to the need for early detection strategies, the National Comprehensive Cancer Network (NCCN) recommended low-dose computed tomography (LDCT) in 2018 as the standard screening modality for individuals at elevated risk of developing lung cancer [40]. LDCT has demonstrated superior sensitivity in identifying pulmonary nodules compared to conventional radiography, leading to earlier diagnoses and improved survival rates in high-risk populations. Parallel to these clinical advancements, significant progress has been made in the application of deep learning-based imaging technologies to lung cancer diagnostics. These technologies enhance the detection, segmentation, and classification of pulmonary nodules, including the ability to distinguish neoplastic from non-neoplastic lesions. Deep learning models—particularly convolutional neural networks (CNNs)—have shown exceptional promise in automating image analysis with high accuracy and efficiency. Ongoing research is focused on the development of novel neural network architectures and loss functions to further improve model performance and robustness [41]. Taken together, these advances in both molecular diagnostics and AI-driven imaging represent a paradigm shift in the early detection and diagnosis of lung cancer, with the potential to significantly reduce mortality through timely intervention.

Pharmacological Approaches in Lung Cancer Management

The treatment landscape of lung cancer has evolved significantly over the past decade, with a shift from traditional cytotoxic chemotherapy to targeted and individualized pharmacological strategies. Therapeutic regimens now integrate chemotherapeutic agents, angiogenesis inhibitors, and kinase inhibitors based on the molecular profile of the tumor and the clinical characteristics of the patient. Cytotoxic agents, such as doxorubicin hydrochloride (Adriamycin) and docetaxel (Taxotere), continue to play a pivotal role in standard chemotherapy protocols. These drugs interfere with DNA replication or microtubule assembly, inducing apoptosis in rapidly dividing tumor cells. Despite their efficacy, these agents are often associated with

significant systemic toxicity and are typically reserved for advanced-stage or refractory cases (Table 1). A major advancement in lung cancer pharmacotherapy is the incorporation of anti-angiogenic agents such as bevacizumab (Avastin/Zirabev). These monoclonal antibodies inhibit the vascular endothelial growth factor (VEGF) signaling pathway, thereby suppressing tumor angiogenesis and improving progression-free survival in patients with non-small cell lung cancer (NSCLC). VEGF/VEGFR inhibitors have become standard adjuncts in combination regimens for advanced or metastatic disease.

Pemetrexed disodium (Alimta), an antifolate antimetabolite, is another widely used chemotherapeutic agent, particularly effective in non-squamous NSCLC. It is often co-administered with platinum-based drugs such as cisplatin, enhancing cytotoxicity through synergistic mechanisms. A more recent addition to targeted therapy options is selpercatinib, an oral RET kinase inhibitor that also exhibits VEGFR-inhibitory properties. It has shown efficacy in RET fusion-positive lung cancers and is administered orally twice daily, offering a more convenient and personalized treatment option. Table 1 provides a summary of key medications used in lung cancer treatment, detailing their dosage, route of administration, and therapeutic class. These agents exemplify the diverse pharmacological strategies currently employed in the management of lung cancer, highlighting the importance of molecular diagnostics in guiding therapeutic decision-making.

miRNA as biomarker for lung cancer

More than 70% of individuals diagnosed with lung cancer are identified at advanced stages, primarily due to the limitations of current early diagnostic techniques, which lack sufficient sensitivity and specificity. This underscores

Table 1. Medications used in lung cancer treatment, including dosage, route of administration, and therapeutic class.

Name of the medicine	Dosage	Class
Doxorubicin hydrochloride (Adriamycin)	60-75 mg/m² IV every 21 days**.**	Antibiotic
Avastin	15 mg/kg IV every 3 weeks.	VEGF/VEGFR inhibitors
Alimta (Pemetrexed Disodium)	ALIMTA 500 mg/m² IV Day 1 + Cisplatin 75 mg/m² IV (30 min post-ALIMTA) every 21 days.	Antineoplastics, Antimetabolites
Taxotere (Docetaxel)	75 mg/m^2 IV over 1 hr q3Weeks.	Antineoplastics, Antimicrotubular (Taxanes)
Zirabev (Bevacizumab)	15 mg/kg IV q3w with topotecan.	VEGF/VEGFR inhibitors
Selpercatinib	<50 kg: 120 mg PO BID ≥50 kg: 160 mg PO BID (Taking the medication orally twice a day)	RET Kinase Inhibitors, Antineoplastics, VEGFR inhibitors

the urgent need for reliable biomarkers to enable the early detection of tumors [42]. MicroRNAs (miRNAs) are small noncoding RNA molecules, typically 20 to 22 nucleotides in length, that play critical roles in various biological processes, including cell proliferation, apoptosis, inflammation, tumorigenesis, and angiogenesis [43]. Investigating miRNA expression patterns could not only lead to the development of advanced diagnostic, prognostic, and therapeutic strategies but also provide insights into the molecular pathways underlying the disease, potentially clarifying the variations in clinical treatment efficacy among patients [44].

In lung cancer, circulating miRNAs act as either tumor suppressors or oncomirs, both of which are essential to the disease's pathophysiology. Research has shown that diagnostic panels incorporating multiple miRNAs are significantly more effective than those relying on single markers. Dysregulated expression of miRNA-21 and miRNA-141 has been validated as reliable biomarkers for the diagnosis and management of lung cancer [45]. In solid adenocarcinoma, elevated levels of miR-212-3p, miR-27a-3p, and miR-132-5p are commonly observed, while miR-205-5p serves as a marker for squamous cell carcinoma (SqCC) and non-squamous cell carcinoma (non-SqCC). In neuroendocrine tumors, such as small cell lung cancer (SCLC), ASCL1 is upregulated, and this upregulation strongly correlates with miR-375, miR-21-5p, and miR-34a [46]. Serum samples from SCLC patients and healthy donors exhibit distinct miRNA expression patterns, with SCLC patients showing significantly lower levels of miR-1 compared to healthy controls [47].

In lung cancer, increased expression of miR-17 and miR-19 influences the expression of key genes such as HIF1A, PTEN, BCL2L11, CDKN1A, and TSP1 (Table 2). This influence promotes tumor growth by inducing hypoxia, enhancing vascular permeability, stimulating cell proliferation, inhibiting apoptosis, and facilitating tumor cell migration [48]. Recent studies have identified miR-103a, miR-29a, and miR-486 as critical biomarkers for the early detection and prognosis of lung cancer, with promising potential for therapeutic applications [49]. In lung biopsy samples, miR-205 has been confirmed as specific for squamous cell carcinoma (SCC). In contrast, miR-411, miR-370, and miR-376a have been associated with poor post-resection survival outcomes in adenocarcinoma cases. A diagnostic assay known as "miRview Lung" has been developed, demonstrating an impressive accuracy of 94% in distinguishing between four major subtypes of lung cancer. This classification is based on the expression levels of eight specific miRNAs (miR-205, miR-21, miR-125a-5p, miR-29b, miR-106a, miR-129-3p, miR-7, and miR-375), underscoring the potential clinical significance of these biomarkers in histological classification [50].

AI-Powered Imaging Analysis for Lung Cancer Detection

The integration of artificial intelligence (AI) into lung cancer management has revolutionized diagnostic workflows, prognosis prediction, and treatment planning. Lung cancer, characterized by its heterogeneous presentation

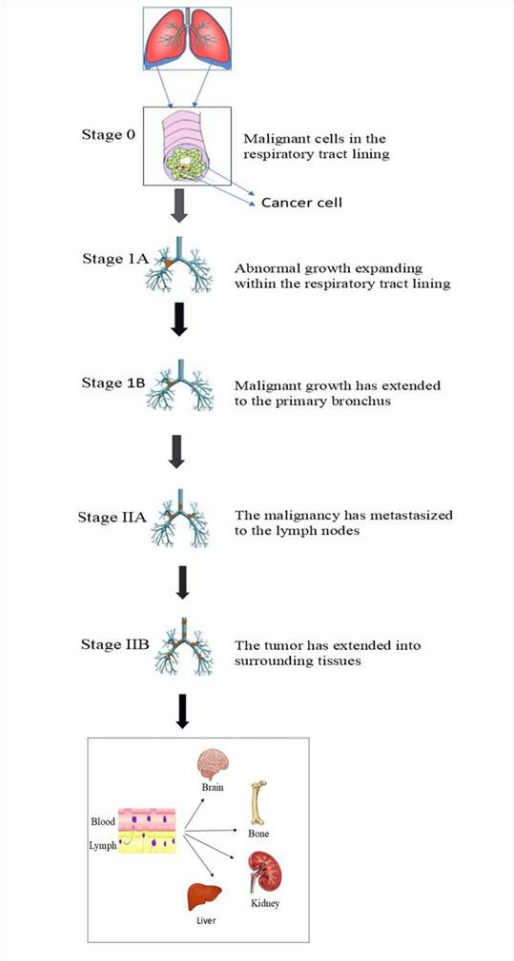

Figure 1. Progression of Lung Cancer through Different Stages. This diagram illustrates the sequential stages (stage 0 to Advanced Dissemination) of lung cancer development

Table 2. Roles of various microRNAs (miRNAs) in lung cancer, categorized by their involvement in early detection, diagnosis, tumor progression, prognosis, and biopsy-specific biomarkers.

Category	microRNAs (miRNAs) and their role
Early Detection	miR-103a, miR-29a, miR-486 as crucial biomarkers for early detection
Lung Cancer Diagnosis	miRNA-21, miRNA-141 as reliable biomarkers
Solid Adenocarcinoma	miR-212-3p, miR-27a-3p, miR-132-5p (higher expression)
Neuro endocrine tumours (SCLC)	ASCL1 upregulated, correlated with miR-375, miR-21-5p, miR-34a
SCLC Serum Expression	65 miRNAs upregulated, 13 downregulated; miR-1 significantly lower in SCLC
Tumour Growth & Progression	miR-17, miR-19 regulate HIF1A, PTEN, BCL2L11, CDKNA, and TSP1, fostering tumour growth
Post-Surgical Prognosis	miR-411, miR-370, miR-376a linked to low survival rates in adenocarcinomas
Biopsy-Specific Biomarkers	miR-205 verified as SCC-specific marker
Diagnostic Panel (miR view lung assay)	Uses miR-205, miR-21, miR-125a-5p, miR-29b, miR-106a, miR-129-3p, miR-7, miR-375 (94% accuracy)

Table 3: The clinical applications of artificial intelligence (AI) in lung cancer management, detailing the AI technologies used for various purposes

Clinical application	AI technology used
Lung Nodule Detection (CT, X-ray)	CNN, DCNN, 3D Dense Sharp network
Diagnosis & Classification	Deep learning, Machine learning
Prognosis Prediction	XG Boost, SVM, AI-based risk models
Treatment Planning	AI-driven segmentation, Cognitive computing
Personalized Medicine & Targeted Therapy	AI-enabled precision medicine, DTA

and high mortality rate, remains the leading cause of cancer-related deaths globally, largely due to delayed diagnosis and variable clinical manifestations [51]. AI offers a powerful solution to these challenges by efficiently managing complex datasets and automating repetitive, image-intensive tasks that are central to lung cancer evaluation [52]. One of the earliest and most impactful applications of AI in this domain is the automated detection of pulmonary nodules using computed tomography (CT) and chest radiographs. Advanced algorithms, such as convolutional neural networks (CNNs) and deep convolutional neural networks (DCNNs), have demonstrated diagnostic performance comparable to—and in some cases exceeding—that of experienced radiologists [53]. These tools not only accelerate image interpretation but also enhance sensitivity and specificity, thereby improving early detection rates. Beyond nodule detection,

AI is increasingly employed for disease classification, outcome prediction, and therapeutic decision-making. The clinical utility of AI in lung cancer is summarized in Table 3. The integration of machine learning and deep learning frameworks facilitates accurate tumor classification and staging. Prognostic models incorporating algorithms such as XGBoost, support vector machines (SVM), and ensemble learning techniques provide clinicians with individualized risk assessments. In treatment planning, AI-driven segmentation and cognitive computing support precise tumor delineation and radiotherapy planning. Furthermore, AI-enabled platforms contribute to the development of personalized therapeutic strategies through drug-target affinity (DTA) modeling and precision medicine approaches [54].

Conclusion

Lung cancer remains the leading cause of cancer-related deaths worldwide, highlighting the urgent need for advancements in diagnosis, treatment, and prevention strategies. The two primary subtypes, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), require distinct therapeutic approaches. Recent breakthroughs in molecular biology, imaging technologies, and artificial intelligence (AI) have significantly improved early detection, personalized treatment options, and our understanding of resistance

mechanisms. Screening methods like low-dose computed tomography (LDCT), along with biomarkers such as microRNAs, have shown promise in enhancing early diagnosis and patient outcomes. The integration of AI in imaging analysis has revolutionized lung cancer detection, increasing diagnostic accuracy and enabling more targeted, individualized treatment approaches. However, challenges remain, including the effective implementation of new therapies, overcoming healthcare access disparities, and addressing treatment resistance. Continued research into novel therapeutic targets, such as molecular docking studies and liquid biopsies, is critical for further progress in lung cancer management. Through collaborative efforts in precision medicine, early detection, and targeted therapies, there is hope for reducing the global burden of lung cancer and improving survival rates across diverse patient populations.

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