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AI in *Pulmonary Oncology* Opportunities, Risks, and Future Directions

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Abstract

Artificial intelligence has the potential to revolutionize pulmonary oncology through improved diagnostic accuracy, personalized treatment strategies, and enhanced prognostic capabilities for lung cancer patients. Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer accounting for approximately 85% of all cases. AI-based medical image analysis enables detection and characterization of early-stage lung cancer through radiomic analysis of computed tomography images. Artificial intelligence can integrate multi-omics approaches including genomics, transcriptomics, proteomics, and immunogenomics to advance precision oncology for lung cancer. However, several significant obstacles prevent widespread clinical adoption, including limited standardized AI training in medicine, insufficient external validation of models, and safety and ethical concerns regarding algorithmic transparency and data privacy. This paper critically evaluates the evolving role of AI technology in pulmonary oncology, examining current applications in diagnostic imaging, radiomics, genomics, transcriptomics, immuno-oncology, liquid biopsy, and pediatric oncology. We also discuss technical challenges including data quality, model interpretability, and validation requirements, and propose future directions emphasizing multicenter collaboration and explainable AI frameworks.

Keywords: Artificial Intelligence, Lung Cancer, Pulmonary Oncology, Diagnostic Imaging, Radiomics, Transcriptomics, Immuno-oncology, Liquid Biopsy, Precision Medicine.

1. Introduction

Artificial intelligence encompasses both machine learning and deep learning approaches that enable computers to perform tasks requiring human intelligence. In healthcare, AI continuously develops to assist clinicians in providing improved patient care through analysis of vast data volumes and prediction of clinical trajectories based on historical data [1]. The number of publications on AI in pulmonary medicine increased fivefold from 2015 compared to 2010-2014, reflecting growing research interest. In pulmonary oncology specifically, AI applications include computer vision for lung nodule detection and malignancy risk assessment, molecular signature analysis for tumor characterization, and prediction models for treatment response and survival outcomes [2]. Deep learning, particularly convolutional

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neural networks, has demonstrated particular promise in analyzing chest imaging to identify lung cancers at early, potentially curable stages [3]. The integration of AI into pulmonary oncology faces distinct challenges. Unlike general pulmonary medicine, oncology applications require integration of multimodal data including imaging, pathology, genomics, and clinical history. Additionally, the pediatric population with lung tumors presents unique considerations due to developmental differences and distinct clinical characteristics compared to adults [4]. Federated learning approaches, which apply algorithms to decentralized databases without centralizing patient data, offer potential solutions for developing robust models while preserving privacy [5].This current AI applications in pulmonary oncology, including medical imaging, radiomics, genomics, transcriptomics, immuno-oncology, liquid biopsy, and pediatric applications, while critically evaluating technical challenges and future directions for clinical implementation.

2. Role of Artificial Intelligence in Medical Imaging for Lung Cancer

Medical imaging employs diverse techniques to visualize the structure and function of the human body in health and disease. In the context of pulmonary oncology, AI applications refer to a computer's capacity to recognize, assess, and process thoracic images reliably, accurately, and efficiently [6]. The integration of AI with medical imaging holds potential to transform lung cancer care through improved detection, characterization, and treatment monitoring [7]. Human limitations in visual perception and cognition contribute to diagnostic errors in thoracic radiology. Disease prevalence, patient characteristics, reader variability, false positives, and false negatives constrain the utility of medical imaging for lung cancer screening and diagnosis [8]. Computer-aided diagnostic tools have demonstrated potential to reduce human error, particularly given increasing imaging volumes and limited radiologist availability [9].

The radiologist's primary responsibility remains image interpretation, requiring integration of multiple data points for clinical decision-making. Physical and mental fatigue impair accurate interpretation, and subspecialty variability in expertise affects diagnostic consistency [10]. Therefore, AI applications in thoracic oncology primarily aim to support and enhance human performance throughout the diagnostic process, including image analysis, segmentation, classification, and reconstruction [11]. AI can assist in distinguishing benign from malignant pulmonary nodules and predicting surgical or treatment outcomes at early stages [12]. Image segmentation partitions images into meaningful regions for rapid identification of relevant structures. Correct segmentation ensures accurate diagnosis by highlighting abnormalities. Classification assigns images to diagnostic categories based on extracted features. When machine learning and deep learning are combined, AI can achieve performance comparable to human experts [13]. CNN classifiers have

proven valuable for pulmonary nodule characterization and malignancy risk assessment.

Machine learning techniques now feature in numerous medical image processing applications for thoracic oncology. AI classifiers for lung disease detection typically require large labeled datasets for training, though they may underperform when applied to data from different scanners or institutions. Biased classifiers show degraded performance when encountering data acquired under different conditions. AI and machine learning can reduce reader-dependent error rates by enabling standardized classification based on textural, anatomical, and physiological features. The interpretative error rate for missed lung malignancies ranges from 1.1% to 3%, with commission errors approximating 2% [14]. Recent research demonstrates significant inter-radiologist variability in quantifying CT attenuation coefficients of pulmonary lesions, affecting tumor node metastasis staging, prognosis prediction, and treatment planning. Deep learning represents the most advanced AI technology, capable of automatically identifying, categorizing, and quantifying imaging data without manual feature engineering [15].

3. AI in Lung Cancer Radiomic Features

Deep learning encompasses machine learning methods inspired by neural networks in the brain. Convolutional neural networks now dominate medical image processing, including thoracic oncology applications [16]. Neural network layers include convolution, pooling, activation, and fully connected operations. The convolutional kernels that process images extract deep radiomic features [17]. Deep radiomic features differ from traditional handcrafted radiomic features despite conceptual similarities. At shallow network levels, deep features detect texture, shape, and intensity characteristics comparable to handcrafted features. However, as network depth increases, additional abstract features learned from training data emerge, becoming increasingly difficult to interpret intuitively. This creates an opaque relationship between model inputs and outputs [18]. Deep radiomic features may complement handcrafted features when model interpretability is not paramount. Deep learning models can process complete images without requiring region-of-interest segmentation, preserving spatial information. Transfer learning enables application of pre-trained features and models to different imaging tasks [19].

3.1 Handcrafted versus Deep Radiomic Features

Handcrafted radiomic features are explicitly defined mathematical descriptors of tumor phenotype, including shape, intensity, and texture characteristics. These features are computed following segmentation and require careful feature selection to avoid redundancy. Deep radiomic features, by contrast, are automatically learned from data through hierarchical neural network architectures. While handcrafted features offer interpretability and reproducibility across platforms, deep

features often achieve superior predictive performance at the cost of transparency [20].

3.2 Functional Radiomic Features

Beyond structural imaging, functional modalities provide complementary information about tumor biology. 18F-fluorodeoxyglucose positron emission tomography reflects glucose metabolism and has been widely integrated with CT for lung cancer evaluation. PET-based radiomics alone can distinguish adenocarcinoma from squamous cell carcinoma, with one study of 210 adenocarcinoma and 186 squamous cell carcinoma patients demonstrating predictive capability, though external validation remains necessary [21]. PET/CT radiomics offers the advantage of combining functional and structural information. Studies have demonstrated efficacy in distinguishing pulmonary tuberculosis, lymphoma, and other benign lesions from lung cancer [22]. Additionally, PET/CT radiomics has shown promise for predicting EGFR mutation status, with one study of 248 lung cancer patients achieving an area under the curve of 0.87 when combining clinical and radiomic signatures [23].

4. AI in Lung Cancer Genomics and Transcriptomics

4.1 AI in Lung Cancer Genomics

The application of AI in lung cancer genomics encompasses analysis of gene mutations and variations, assessment of genomic instability, and study of epigenetic modifications. Deep learning models including convolutional neural networks and recurrent neural networks facilitate detailed analysis of large-scale genomic data, enabling precise identification and classification of specific genetic mutations like EGFR, KRAS, and ALK [24]. Machine learning algorithms further extend AI's capability by estimating mutation frequency and distribution across diverse populations, aiding personalized treatment plan formulation. AI excels in integrating multi-omics data for comprehensive understanding of genetic mutation impacts on disease progression and prognosis [25]. Predictive models utilizing machine learning analyze gene mutation data to forecast disease prognosis, treatment responses, and survival rates, assisting clinicians in decision-making processes [26]. Leading AI-based initiatives including Foundation Medicine, Tempus, and IBM Watson for Oncology exemplify the transformative potential of AI in enhancing precision of lung cancer diagnosis and treatment [27].

4.2 AI in Epigenetics

AI integration into lung cancer epigenetics research has advanced understanding of epigenetic alterations including DNA methylation, histone modifications, and non-coding RNA regulation. Machine learning and deep learning algorithms analyze extensive methylation datasets to identify specific methylation patterns associated with lung cancer, serving as biomarkers for early detection and classification [28]. For histone modifications, AI analyzes acetylation and methylation data to construct detailed modification maps elucidating their distribution and changes in lung cancer [29]. Non-

coding RNA regulation analysis benefits significantly from AI capabilities. Machine learning models predict miRNA target genes and assess their roles in lung cancer, identifying new therapeutic targets. Similarly, AI predicts expression patterns and potential functions of long non-coding RNAs, uncovering their regulatory effects and aiding novel therapeutic mechanism discovery [30].

4.3 AI in Lung Cancer Transcriptomics

Transcriptomics examines gene expression and transcription levels in lung cancer using high-throughput sequencing methods including RNA-Seq. This approach provides comprehensive information about gene expression in lung cancer tissues and cells, enhancing understanding of mRNA and other transcription products [31]. AI has substantially impacted lung cancer genomics, particularly in transcriptomic analysis.

4.3.1 Gene Expression Profiling

Gene expression profiles specify particular patterns of genes activated or suppressed in lung cancer cells compared to normal lung cells. AI excels in handling and analyzing massive, high-dimensional gene expression datasets, efficiently extracting valuable information from complex data [32]. Through machine learning algorithms including random forests, support vector machines, and deep learning, AI discerns key genetic features associated with lung cancer [33]. AI models based on gene expression profiles enhance disease classification and diagnosis accuracy by distinguishing between benign and malignant tumors and different lung cancer types [34]. Furthermore, AI predicts patient prognosis and treatment efficacy using gene expression data, aiding physicians in formulating personalized treatment plans [35].

4.3.2 AI in mRNA Modification for Lung Cancer

Investigation of mRNA modifications, particularly N6-methyladenosine (m6A), has advanced significantly through AI applications. mRNA methylation represents a crucial regulatory mechanism affecting transcript stability and translation efficiency. Machine learning models including support vector machines, random forests, and deep learning networks have proven effective in identifying m6A modification sites [36]. These technologies utilize high-throughput RNA-Seq data to elucidate how m6A influences mRNA half-life and degradation. AI has successfully characterized m6A roles in mRNA localization and translation efficiency through integrated transcriptomic and proteomic analyses. The association of m6A modifications with lung cancer prognosis and treatment response has improved biomarker development and therapeutic targeting [37].

4.3.3 AI in Single-Cell Transcriptomics

AI has transformed single-cell transcriptomics in lung cancer, providing unprecedented insights into tumor microenvironment heterogeneity, cancer stem cells, and treatment resistance mechanisms. Comprehensive gene expression analysis through single-cell RNA sequencing elucidates lung cancer pathogenesis and immune evasion

strategies [38]. Machine learning identifies cell-type-specific gene signatures, revealing cellular heterogeneity in lung tumors. Clustering algorithms identify distinct tumor cell populations and track proliferation trajectories, illuminating cancer cell development. Integration of single-cell RNA-seq with spatial transcriptomics enables investigation of ligand-receptor interactions and cellular spatial distribution within the tumor microenvironment [39].

5. AI in Lung Cancer Immuno-Oncology

5.1 AI in Studying Immune Evasion

The application of AI in studying immune escape mechanisms in lung cancer has yielded significant advancements, bringing nuanced understanding of complex tumor-immune interactions. Immunophenotyping analysis utilizing deep learning and machine learning techniques analyzes fluorescence-activated cell sorting data, allowing precise identification and classification of various immune cell subtypes and elucidating their roles in immune escape [40]. AI also enables analysis of T-cell receptor and B-cell receptor repertoires. Machine learning models decode complex clonal dynamics associated with immune escape by analyzing rearrangement sequences of TCRs and BCRs. Additionally, single-cell immunogenomics supported by AI algorithms enables granular investigation of functional states and interactions of heterogeneous immune cells within the tumor microenvironment [41].

5.2 AI in Immune-Related Gene Mutations

AI's ability to process vast genomic data has proven indispensable in identifying mutations pertinent to immune response, such as those in PD-L1, CTLA-4, and HLA genes. By decoding these genetic variations, AI aids in elucidating interactions between tumors and the immune system, thereby facilitating design of personalized treatment plans [42]. AI significantly enhances prediction of responses to immunotherapy. By scrutinizing immune-related genetic information, AI models forecast potential reactions to immunotherapy agents like PD-1/PD-L1 inhibitors. This predictive capability enables clinicians to tailor immunotherapy regimens more accurately, optimizing therapeutic efficacy and reducing likelihood of adverse reactions [43].

5.3 AI in Tumor Mutation Burden

AI has emerged as a transformative tool in estimation and prediction of tumor mutation burden in lung cancer. Utilizing comprehensive whole-genome sequencing data or specific gene panel data, AI powered by advanced deep learning and machine learning algorithms can meticulously analyze extensive genomic information, enabling precise estimation of TMB, which is crucial for understanding tumor profile [44]. TMB serves as a significant biomarker for determining immunotherapy efficacy. High TMB levels often correlate with better responses to immuno-oncology agents. By leveraging AI to integrate TMB data with other clinical parameters,

healthcare professionals can develop more personalized treatment plans, thereby enhancing therapeutic outcomes [45].

5.4 AI in Neoantigen Discovery

AI models excel in predicting likelihood of mutant proteins being processed into peptide fragments recognizable as neoantigens by the immune system. Tools such as DeepNovo and PepFormer aid in this endeavor. Additionally, AI algorithms critically evaluate stability of these peptides within biological environments, ensuring their viability as neoantigens [46]. Binding affinity of mutated peptides to major histocompatibility complex molecules is a crucial determinant of neoantigen effectiveness, with machine learning models like NetMHCpan and MHCflurry being instrumental in this prediction. AI also models the complex process of neoantigen generation and MHC presentation, filtering out the most promising candidates [47].

5.5 AI in Immune Microenvironment Analysis

AI algorithms demonstrate remarkable efficacy in single-cell RNA sequencing analysis, enabling identification and classification of various immune cell types within the tumor microenvironment, such as T cells, B cells, and natural killer cells. Machine learning techniques facilitate lineage tracing, revealing developmental and differentiation pathways of immune cells [48]. AI aids in functional gene expression analysis, evaluating immune cell states including activation, inhibition, and exhaustion, and constructing interaction networks between immune cells and tumor or stromal cells. AI technologies also excel at characterizing immunosuppressive microenvironments by identifying factors like regulatory T cells and myeloid-derived suppressor cells, and their impact on immune responses [49].

6. AI in Liquid Biopsy for Lung Cancer

6.1 AI for Early Detection and Screening

The application and research of AI in non-invasive liquid biopsy for lung cancer have seen remarkable advancements, especially in detection of circulating tumor DNA from blood samples. AI algorithms coupled with high-sensitivity techniques like digital polymerase chain reaction and next-generation sequencing can accurately identify lung cancer-specific mutations and molecular markers from large datasets, distinguishing early-stage lung cancer patients from healthy individuals [50].

The Circulating Cell-free Genome Atlas study by GRAIL used a multi-cancer early detection test utilizing cfDNA and AI, reporting overall sensitivity of 51.5% (range 14.5-92.2%) in detecting cancers, with sensitivity directly proportional to disease stage. The study employed targeted methylation-based sequencing of cfDNA using a machine learning classifier to differentiate tumor-derived signals from non-tumor sources, achieving 99% specificity [51]. Recent advancements have significantly improved early NSCLC detection. Mathios and colleagues utilized cfDNA fragmentome analysis with machine learning to

achieve 75% sensitivity for Stage I-II NSCLC and 95% specificity, offering a novel approach to distinguish tumor-derived signals from non-tumor cfDNA [52]. Similarly, combining ctDNA with protein biomarkers increased sensitivity to 86.4% for early-stage NSCLC, highlighting the potential of multi-analyte approaches (53).

6.2 AI for Genotyping and Treatment Selection

In the realm of personalized treatment plans, AI systems leveraging deep learning and extensive datasets process and analyze large volumes of genetic data to pinpoint mutations and biomarkers associated with lung cancer. By predicting response of specific genetic profiles to targeted therapies, AI helps devise highly customized treatment protocols [54]. Data from the ENSURE, AURA phase 2 extension, and AURA 2 studies led to FDA approval of the Cobas EGFR Mutation Test v2 to detect specific mutations (exon 19 deletion or exon 21 L858R substitution) in patients' blood with NSCLC to determine candidates for treatment with erlotinib, as well as in patients with T790M mutations who would benefit from osimertinib [55].

6.3 AI for Monitoring Treatment Response and Resistance

In terms of monitoring treatment efficacy, ctDNA levels are dynamically measured throughout the treatment process to immediately assess tumor burden and response to therapy. AI models can predict treatment outcomes and potential resistance, providing real-time insights [56]. Patients who progress on osimertinib should always be checked for EGFR-C797S and other rare genetic alterations including BRAF-V600, KRAS, HER2, and MET. ctDNA represents an extremely useful, least invasive intervention with quick turnaround time, allowing targeting of additional alterations [57].

6.4 AI for Minimal Residual Disease Detection

The pursuit to identify early relapse post curative treatment in any malignancy is a matter of high regard. Current practices involve relying on clinical, radiological, and plasma-based tumor markers to identify early relapse in NSCLC patients treated with curative intent. The use of ctDNA in detecting minimal residual disease among NSCLC patients treated with curative intent at various post-treatment time points is forthcoming [58]. Chaudhuri and colleagues first observed ctDNA levels in unresectable NSCLC patients varying from Stages I-III, reporting that 17 out of 32 patients with detectable ctDNA within 4 months of completed treatment had lower freedom from progression and disease-specific survival than those with undetectable ctDNA. The study utilized Cancer Personalized Profiling by deep sequencing (CAPP-Seq), a targeted next-generation sequencing approach focusing on recurrent NSCLC mutations to achieve high sensitivity down to 0.002% mutant allele fraction [59].

Gale and colleagues validated ctDNA in 88 early-stage NSCLC patients post-treatment, achieving 90% sensitivity and 95% specificity for MRD detection, predicting relapse 4.8 months before radiographic recurrence. The LUNGCA-

1 study further confirmed ctDNA's utility, finding that persistent ctDNA at 3-7 days post-surgery predicted relapse with 92% sensitivity and a 6.1-month lead time in 330 patients [60].

7. Technical Challenges and Solutions

AI holds substantial potential to improve lung cancer detection, therapy, and prognosis. However, realizing this potential requires addressing significant challenges related to data quantity and quality, model interpretability, statistical validation, and ethics [1]. Data quantity and quality represent fundamental concerns. Medical data contains noise, missing values, and human error, all potentially impacting AI model performance. Creating large-scale, high-quality annotated datasets remains difficult, limiting model effectiveness and reliability [8]. Data variability compounds this problem, as imaging equipment and healthcare practices differ across institutions without standardization [10]. Integration of multiple data types including genomics, clinical information, and imaging requires advanced multimodal analysis capabilities [11].

Several approaches address these challenges. First, rigorous data cleaning according to standardized criteria reduces noise and corrects errors, improving data quality [14]. Multi-center collaboration with secure data sharing methods enables collection of larger, more diverse datasets while maintaining privacy and security [5]. Data augmentation techniques including image scaling, rotation, and shifting generate additional training examples. Ensuring consistent formatting and processing across all available data improves multimodal data integration[19]. Model interpretability presents particular challenges for deep learning models including CNNs. While CNNs excel at image recognition, the opacity of their decision-making processes limits clinical trust. Several techniques mitigate this limitation. Explainable AI methods including Gradient-weighted Class Activation Mapping generate heat maps visualizing model attention, helping clinicians understand which image regions influenced predictions. Attention mechanisms in CNNs analyzing CT images highlight potentially problematic areas. Local Interpretable Model-agnostic Explanations clarify predictions by showing which data aspects contributed to findings [15].

Shapley Additive Explanations (SHAP) offers a novel clarification approach based on game theory, enabling understanding of model function both locally and globally. SHAP is particularly valuable for medical images, where understanding how different image elements influence predictions is essential. SHAP's model independence and solid theoretical foundations make it well-suited for complex deep learning models in lung cancer detection, potentially increasing clinician confidence in AI diagnoses [20].

Rigorous statistical validation of AI models used in lung cancer research is essential for ensuring reliability and clinical utility. Stratified k-fold cross-validation maintains accurate representation of cancer stages and types,

providing high-quality performance estimates. Validation using independent datasets from different institutions tests model generalizability and reveals potential biases. Performance metrics beyond traditional measures should include precision-recall curves, area under the receiver operating characteristic curve, F1 scores, decision curve analysis, and calibration plots [7].

Ethical and privacy considerations surrounding patient data use present significant challenges. The European AI regulation establishes the first-ever legal framework on AI, addressing risks through four levels: unacceptable risk, high risk, limited risk, and minimal risk. Healthcare AI applications typically fall within limited or minimal risk categories [54]. The new Code of Ethics of the General Council of Medical Associations emphasizes that physicians must demand ethical and purposeful control of AI research based on transparency, reversibility, and traceability to guarantee patient safety. The risk of bias should not be attributed to AI itself; rather, input data may be biased, requiring human supervision to verify data and results [56].

Table 1: Technical Challenges and Solutions in AI for Lung Cancer

Challenge Category	Specific Problems	Potential Solutions
Data Quality	Noise, missing values, human error, small annotated datasets	Rigorous data cleaning, standardized criteria, multi-center collaboration, data augmentation
Data Heterogeneity	Variability across institutions, different imaging protocols	Consistent data formatting, transfer learning, domain adaptation techniques
Model Interpretability	Black-box nature of deep learning, limited clinical trust	Grad-CAM heatmaps, attention mechanisms, LIME, SHAP analysis
Statistical Validation	Overfitting, poor generalization, limited external testing	Stratified cross-validation, independent external datasets, appropriate performance metrics
Ethical Concerns	Data privacy, algorithmic bias, regulatory compliance	GDPR/HIPAA compliance, equity audits, transparent reporting, ethical guidelines

8. Conclusion

AI is significantly impacting pulmonary oncology through more rapid and accurate diagnosis, improved clinical outcomes, and enhanced ability to identify high-risk patients with greater precision and sensitivity. AI systems analyzing CT images and chest X-rays enable correct identification of pulmonary malignancies. Algorithms can automatically detect lung nodules, predict malignancy risk, and assist in treatment planning across multiple domains including radiomics, genomics, transcriptomics, immuno-oncology, and liquid biopsy. The implementation of AI raises legal and ethical issues, particularly in underdeveloped countries. Medical education should support and encourage students learning to use AI tools to address these challenges. Lung cancer diagnosis remains challenging, and AI models and approaches may improve diagnostic accuracy. These benefits could prove critical in situations where early detection and treatment are essential for reducing cancer-related morbidity and mortality.

Studies demonstrate that certain AI algorithms identify pulmonary malignancies with sensitivity and specificity comparable or superior to radiologists alone. Therefore, development of more sophisticated software and clinical trials with larger sample sizes is imperative to establish these tools as standard components of practice and guidelines. The growing body of scientific evidence supporting AI effectiveness will facilitate transition from

research tool in development to high-yield clinical instrument, ultimately improving patient outcomes.

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