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Artificial intelligence, machine learning, and radiomics in lung cancer classification

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ABSTRACT

Lung cancer is a highly heterogeneous disease that presents significant challenges in accurate diagnosis and classification due to its diverse histological and molecular characteristics. Traditional diagnostic methods, while valuable, are often limited by invasiveness, subjectivity, and an inability to fully capture tumor complexity. Recent advancements in artificial intelligence (AI), machine learning, and radiomics have transformed the field, offering enhanced precision, efficiency, and objectivity in lung cancer classification. These technologies enable detailed analyses of imaging data, histopathological findings, and molecular profiles, facilitating improved subtype identification, outcome prediction, and personalized treatment strategies. Cytopathology remains a cornerstone of lung cancer diagnostics, particularly for small biopsies and cytological samples, which are often the only materials available in advanced stages. The integration of AI-driven methods into cytopathology and radiomics workflows has shown substantial potential to overcome the limitations of traditional approaches, reduce interobserver variability, and accelerate the diagnostic process. This review underscores the transformative role of AI and radiomics in lung cancer management, highlighting their synergy in advancing precision oncology. As ongoing research continues to refine these methodologies, the future of lung cancer care is poised for significant advancements, offering improved diagnostic accuracy, personalized therapies, and better patient outcomes.

Keywords: Lung cancer, heterogeneity, cytopathology, artificial intelligence

Stem cells implicated in the development of lung carcinoma are primarily derived from four key proliferative cell types within the airways: basal cells, Clara cells, Type II pneumocytes, and neuroendocrine cells associated with the Amine Precursor Uptake and Decarboxylation (APUD) system. Furthermore, it has been proposed that lung tumors may originate not only from these proliferative cells but also from an undifferentiated progenitor or stem cell that acts as a precursor [1, 2]. These undifferentiated cells are thought to be distinct from basal or reserve cells. Evidence suggests that such cells are absent in the normal adult respiratory epithelium and may only emerge following damage to proliferative cells [1].

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While hyperplastic, metaplastic, and dysplastic epithelial anomalies, including carcinoma in situ, are now well-characterized morphologically, the precise histogenetic pathways underlying lung carcinoma remain uncertain [3]. Tumorigenesis is an evolutionary process, driven by ongoing genetic mutations and selective pressures in a Darwinian manner [4, 5]. As hyperproliferation occurs during tumor progression, increased genetic instability fosters the development of a diverse population of cancer cells, referred to as clonal subpopulations (Fig. 1) [5, 6]. As hyperproliferation occurs during tumor progression, increased genetic instability facilitates the emergence of a heterogeneous population of cancer cells, referred to as clonal subpopulations (Fig. 1) [5, 7]. The first, the monoclonal (linear) model, proposes that tumor evolution occurs in a sequential and orderly manner. Mutations in oncogenes and tumor suppressor genes drive successive rounds of clonal expansion, with each new mutation leading to the dominance of a single, more advanced clone [8]. This model envisions tumor progression as a straightforward linear process.

In contrast, the multiclonal model presents a more complex and dynamic framework. While all tumor cells originate from a single initiated cell, tumor evolution involves the coexistence of genetically diverse clones [9, 10]. Over time, the population sizes of these clones may fluctuate - some expanding, others remaining stable, and some becoming extinct. This ongoing interplay creates a “messy” evolutionary pathway, where tumors at advanced stages may eventually be dominated by a single clone. In both models, the intensity of color represents the degree of tumor progression, while different colors symbolize distinct clones [5].

The microenvironment within tumors is inherently heterogeneous. Variations in factors such as vascular density, the infiltration of normal cells, and the composition of the extracellular matrix contribute to this complexity. This heterogeneity may explain the emergence of diverse phenotypes among tumor cells, influenced by their specific local environments. Importantly, this intra-tumor heterogeneity extends beyond individual cell phenotypes to encompass a range of phenotypic features, including gene expression (e.g., surface mark-

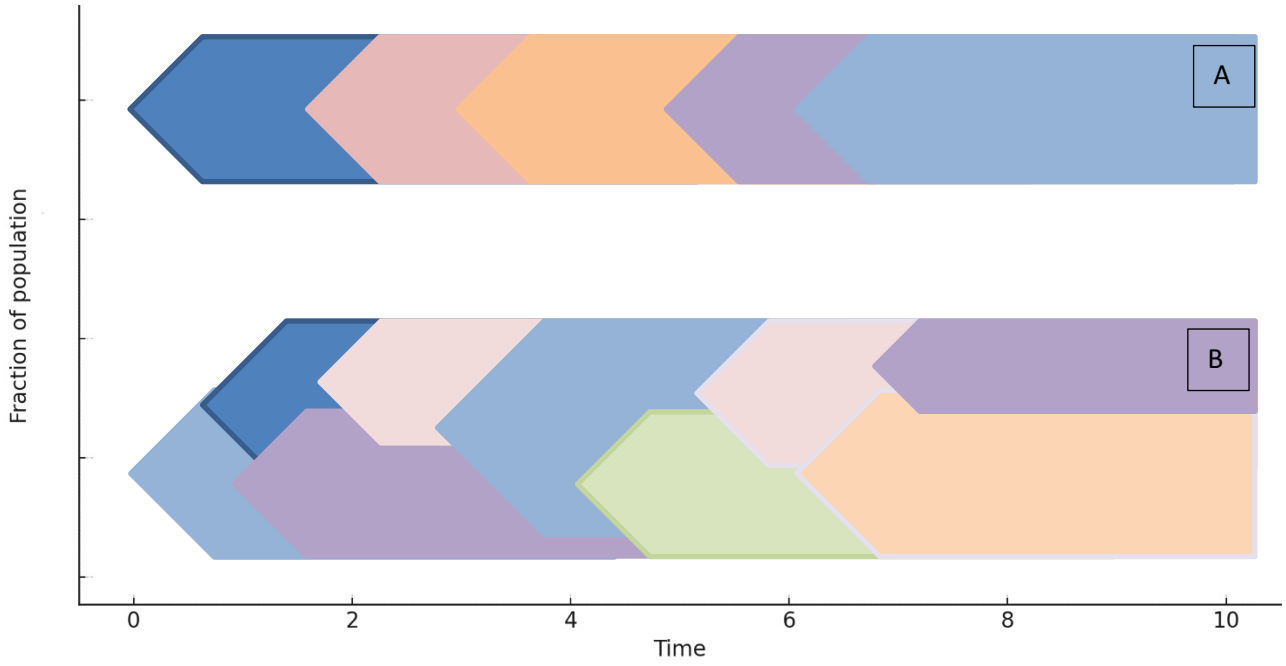

Fig. 1. Tumor evolution can be modeled as either a linear or a multiclonal process. The linear (monoclonal) model (A) depicts tumor progression as an orderly sequence of clonal expansions driven by successive mutations, with each new mutation producing a dominant, more advanced clone. In contrast, the multiclonal model (B) describes a more dynamic and complex process, where genetically diverse clones coexist, compete, and fluctuate in size, leading to a non-linear evolutionary pathway. While advanced tumors may eventually be dominated by a single clone, this occurs after significant periods of clonal diversity. Both models highlight the interplay between order and randomness in tumor progression (*Adapted with modifications from: Marusyk A, Polyak K. Tumor heterogeneity: Causes and consequences. Biochim Biophys Acta. 2010;1805(1):105-117. doi: 10.1016/j.bbcan.2009.11.002* [5]).

ers, growth factor and hormone receptors), metabolic activity, motility, angiogenesis, proliferation, immune response, and metastatic potential [5, 7, 9].

The interplay between genetic alterations and morphological phenotypes is well-documented in lung carcinoma. For example, in pleomorphic carcinomas with heterogeneous differentiation, molecular heterogeneity has been linked to Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) mutation status, alterations in gene copy number, and differences in protein expression and phosphorylation levels [9, 11]. Beyond pleomorphic carcinomas, lung carcinomas are characterized by significant histological heterogeneity. Different phenotypic patterns and levels of differentiation are often observed between microscopic fields and histological sections. Approximately 50% of tumors exhibit multiple major histological subtypes [11].

Lung carcinomas are typically classified based on their most differentiated component, while the degree of differentiation is assessed based on the least differentiated regions. This dual criterion complicates the classification of individual tumors [9, 12]. For instance, a predominantly undifferentiated tumor with squamous cell carcinoma (LUSC), or lung cancer subtypes such as adenocarcinoma (LUAD) features is commonly classified as poorly differentiated LUSC or LUAD [13, 14].

This pronounced phenotypic variability is particularly relevant in the analysis of small biopsies and cytological samples, which are often the only available diagnostic material at advanced stages of lung cancer [5, 12]. These small samples provide a limited representation of the tumor's histological and genetic diversity. Their ability to reflect the clonal composition and the quantitative distribution of different growth patterns and tumor subtypes is constrained by the sample's origin, size, and location [7].

Despite these limitations, cytological diagnostics remain a vital tool in clinical practice. For example, touch imprints performed by thoracic surgeons have been shown to achieve sensitivity and specificity comparable to histological methods in lung cancer diagnostics [15].

PRECISION IN LUNG CARCINOMA CLASSIFICATION

Histological and Molecular Insights

Lung carcinomas display significant histological and molecular heterogeneity, necessitating precise classification for effective clinical management. Accurate diagnosis relies on histopathological analysis of tumor tissues, where classification is often guided by the most differentiated component and assessed using the least differentiated regions [11]. This dual criterion can complicate tumor categorization, particularly for adenocarcinomas and squamous cell carcinomas that exhibit mixed features. Research underscores the variability in patient outcomes and therapeutic responses across lung cancer subtypes, with each subtype exhibiting distinct genetic and phenotypic profiles [16]. For example, adenocarcinomas with micropapillary or solid growth patterns are strongly associated with aggressive behavior and poorer prognoses. Furthermore, LUAD histology serves as an independent predictor of lymph node metastasis, emphasizing the need for tailored therapeutic approaches [11, 17].

Recent advancements have introduced mathematical models that integrate immunohistochemistry and LUAD subtypes to predict lymph node metastasis more effectively [18, 19]. Molecular profiling, such as the evaluation of KRAS and Epidermal Growth Factor Receptor (EGFR) mutations, complements histological assessments and improves the classification of lung adenocarcinomas. In particular, cases with solid or micropapillary patterns have shown distinct molecular alterations that influence prognosis and guide therapeutic decisions. Comprehensive histopathological evaluations ensure accurate tumor classification, enabling personalized treatment strategies and improving patient outcomes [16, 20].

RADIOMICS AND AI INTEGRATION

Transforming Lung Cancer Diagnosis and Care

Radiomics, driven by advancements in Machine Learning, is revolutionizing lung cancer diagnosis and classification through the analysis of imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET). By extracting and analyzing high-dimensional imaging data, radiomics reveals critical connections between imaging features and tumor pathophysiology. Recent innovations, including the ProNet and iMRRN models, utilize deep learning to enhance the classification accuracy of LUAD, LUSC,

and small-cell lung cancer (SCLC), significantly improving diagnostic precision [21, 22].

One prominent application is PET-CT radiomics, which links FDG uptake patterns to aggressive tumor behaviors, facilitating subtype differentiation and enabling more accurate prognosis predictions. This non-invasive approach complements traditional histopathological analyses by providing detailed insights into tumor biology21. Despite the promising progress, challenges remain [23, 24].

Future developments in radiomics emphasize the integration of AI with molecular profiling to refine lung cancer subtyping further and enable truly personalized treatment strategies. By combining radiomic insights with genomic and immunologic data, researchers and clinicians can develop robust, patient-specific models for prognosis and therapy selection. As radiomics evolves, its potential to transform lung cancer care becomes increasingly evident, paving the way for more precise and effective clinical management [23, 24].

INTEGRATION OF AI WITH DIGITAL PATHOLOGY IN PERSONALIZED MEDICINE

The integration of AI and radiomics has significantly improved the speed and accuracy of lung cancer classification, enabling personalized medicine. Radiomics algorithms, validated using PET/CT and MRI, effectively distinguish NSCLC subtypes and support predictive models like CT-based nomograms for classifying SCLC and NSCLC [25, 26].

Digital pathology's telepathology capabilities allow pathologists in remote locations to access high-resolution images for second opinions or to collaborate with AI models trained on diverse datasets. Such implementations have been critical in studies where digital slides were shared across institutions to validate predictive AI models for cancer classification, ensuring consistency and reproducibility across clinical settings [26, 27].

However, challenges such as the high cost of scanners, technical issues with calibration, and the need for robust hardware infrastructure remain [6, 28]. Integration with laboratory information systems and collaboration between pathologists and AI developers are essential to overcome these barriers. For example, in one study, pathologists guided AI model training to improve tumor segmentation and subtype classification, demonstrating the importance of interdisciplinary efforts [26]. With a success rate of over 90% in rapid remote diagnosis, diagnostic and therapeutic decisions can be made in a timely manner based on findings from rapid remote online evaluations. A quality-assured rapid remote online evaluation process enables the assessment of both the quantitative and qualitative suitability of obtained cellular samples for further standard, immunocytochemical, and molecular pathological analyses. An interdisciplinary understanding of the clinical problem and morphological findings minimizes friction among disciplines and serves as an essential prerequisite for customized diagnostics [29-32].

This synergy between AI and digital pathology not only streamlines diagnostics but also supports personalized treatment strategies by linking histological and molecular data to therapeutic responses. As technology evolves, this integration holds immense potential to transform cancer care, making it more accurate, accessible, and tailored to individual patient needs.

ADVANCING PRECISION MEDICINE

The Future of Digital Pathology and AI Integration

The future of digital pathology and AI integration lies in advancing precision medicine through enhanced diagnostic accuracy, efficiency, and accessibility. Emerging techniques, such as self-supervised learning, enable the extraction of histomorphological patterns from whole-slide images (WSIs) without the need for manual annotations, providing insights into tumor heterogeneity and clinical outcomes [26]. AI-powered radiomics models, validated using PET/CT and MRI data, are increasingly being used to predict lung cancer subtypes and assess treatment responses [27, 33].

Digital pathology is also expected to expand its role in telemedicine, enabling real-time consultations and collaborative diagnostics across the globe. These advancements will depend on robust infrastructure, seamless integration with laboratory information systems, and standardization of workflows to ensure reproducibility and reliability [6, 28]. Furthermore, combining AI-driven pathology insights with genomic and transcriptomic data will open new avenues for personalized treatment strategies, bridging the gap between molecular profiling and clinical application [26].

As these technologies evolve, their integration into clinical workflows will redefine diagnostic paradigms, offering scalable, cost-effective, and patient-centric solutions in oncology and beyond.

With ongoing research, lung cancer management is on the cusp of transformative advancements. The integration of molecular profiling with digital pathology and AI is paving the way for unprecedented accuracy in therapeutic decision-making. These innovations bring the potential for enhanced patient outcomes and signify a shift toward precision oncology, where treatment is tailored to the unique biological characteristics of each individual's cancer [26, 33].

UNDERSTANDING THE LIMITATIONS OF AI AND MACHINE LEARNING IN LUNG CANCER DIAGNOSIS

Artificial intelligence and machine learning are often praised for their potential to revolutionise healthcare, and lung cancer diagnosis is no exception. However, the reality on the ground is more nuanced [34]. Many AI models are trained on limited datasets—often from a single hospital or demographic—which means they might not perform reliably when faced with patients from different backgrounds [35]. I've seen examples where a model works impressively in the lab, only to fall short in a real hospital setting.

Another concern that comes up frequently in clinical discussions is the "black box" nature of these systems. While deep learning algorithms can achieve high accuracy, they rarely offer explanations that make sense to medical professionals [35, 36]. And in medicine, if you can't explain a diagnosis, it's hard to trust it—let alone act on it.

There's also the question of bias. If a dataset underrepresents certain groups - say, women, minorities, or rare cancer subtypes - the resulting model might be less accurate for those patients. That's not just a technical issue; it's a real-world risk [35, 36].

So what's the way forward? First, we need larger, more diverse datasets, ideally pooled from different regions and healthcare systems. But that's not enough. We also need tools that can explain their reasoning, at least at a level that doctors can understand. And perhaps most importantly, clinicians must be properly trained—not just in how to use these systems, but in when not to trust them [35, 17].

AI can and should be a partner in cancer care—but it has to earn that role through transparency, reliability, and collaboration with the people who treat patients every day.

CONCLUSION

The integration of AI, Machine Learning, and radiomics into lung cancer classification represents a paradigm shift in oncology. These technologies not only address the limitations of traditional methods but also provide a more objective, efficient, and precise framework for diagnosis. By leveraging the vast potential of AI and radiomics, clinicians can reduce subjectivity, accelerate the diagnostic process, and implement personalized treatment strategies tailored to each patient's unique tumor profile. As ongoing research continues to refine these approaches, the future of lung cancer management appears poised for significant advancements, offering hope for improved patient outcomes and a new era in precision oncology.

Ethical Statement

Ethical approval is not required for this study. There are no human or animal elements in the study. This review was carried out by a brief literature screening. Informed consent has not been collected specifically for the patient samples included in this study.

Data Availability Statement

The corresponding author can provide the data supporting the study's conclusions upon reasonable request.

Authors' Contribution

Study Conception: HE, LW, AHU; Study Design: HE, LW; Supervision: HE, LW; Funding: HE, LW; Materials: HE, LW; Data Collection and/or Processing: HE, LW; Statistical Analysis and/or Data Interpretation: HE, LW; Literature Review: HE, LW; Manuscript Preparation: HE, LW, AHU, AFŞ, FST; and Critical Review: HE, LW.

Conflict of interest

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