Review Article

Artificial intelligence applications in personalizing lung cancer management: state of the art and future perspectives

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Abstract: Lung cancer is still a leading cause of cancer-related deaths worldwide. Vital to ameliorating patient survival rates are early detection, precise evaluation, and personalized treatments. Recent years have witnessed a profound transformation in the field, marked by intricate diagnostic processes and intricate therapeutic protocols that integrate diverse omics domains, heralding a paradigm shift towards personalized and preventive healthcare. This dynamic landscape has embraced the incorporation of advanced machine learning and deep learning techniques, particularly artificial intelligence (AI), into the realm of precision medicine. These groundbreaking innovations create fertile ground for the development of AI-based models adept at extracting valuable insights to inform clinical decisions, with the potential to quantitatively interpret patient data and impact overall patient outcomes significantly. In this comprehensive narrative review, a synthesis of various studies is presented, with a specific focus on three core areas aimed at providing clinicians with a practical understanding of AI-based technologies' potential applications in the diagnosis and management of non-small cell lung cancer (NSCLC). The emphasis is placed on methods for diagnosing malignancy in lung lesions, approaches to predicting histology and other pathological characteristics, and methods for predicting NSCLC gene mutations. The review culminates in a discussion of current trends and future perspectives within the domain of AI-based models, all directed toward enhancing patient care and outcomes in NSCLC. Furthermore, the review underscores the synthesis of diverse studies, accentuating AI applications in NSCLC diagnosis and management. It concludes with a forward-looking discussion on current trends and future perspectives, highlighting the LANTERN Study as a pioneering force set to elevate patient care and outcomes to unprecedented levels.

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Keywords: Non-small cell lung cancer (NSCLC); artificial intelligence (AI); prediction model radiomics

Submitted Feb 14, 2024. Accepted for publication Jul 19, 2024. Published online Oct 30, 2024.
doi: 10.21037/jtd-24-244
View this article at: https://dx.doi.org/10.21037/jtd-24-244

Introduction

Lung cancer is still a leading cause of cancer-related deaths worldwide. The late stage of diagnosis and the heterogeneity of imaging features and histopathology pose significant challenges for clinicians, in particular, to choose the best treatment option. Non-small cell lung cancer (NSCLC) is the most prevalent subtype of lung cancer; the mainstay of therapy is surgery, chemotherapy, radiation, immunotherapy, or molecularly targeted therapy. Although there has been considerable progress in lung cancer therapy, the overall survival rate continues to be low, and individualized approaches are necessary to enhance patient outcomes (1). It is widely believed by the scientific community that progress in lung cancer therapy depends on the creation of cutting-edge methods that recognize the heterogeneity of the disease enabling personalized treatments for individual patients. In recent years, artificial intelligence (AI) has arisen as a valuable resource in oncology, particularly in the field of image detection and evaluation. The term AI refers to the use of computational technologies to emulate human-like intelligent behavior and analytical reasoning. John McCarthy initially defined AI in 1956 as the science and engineering of constructing intelligent machinery. AI is a field within computer science that includes a series of algorithms able to analyze large-scale big data to execute complex functions, emulating human intellect (2).

Machine learning (ML) is a subset of AI that formulates algorithms primarily dependent on prior, predefined data without direct programming. Deep learning (DL) is a sub-discipline of ML (*Figure 1*) rooted in a neural network framework modeled after the human brain (*Figure 2*); DL algorithms do not have to specify features in advance, allowing them to autonomously discover features by exploring the data independently. This data-driven mode makes it more insightful and useful. Today, convolutional neural networks (CNNs) are the most widely used type of DL architecture in the domain of medical image analysis (3).

These methodologies are used in imaging in the field of radiomics, where accumulating evidence demonstrates that this can be utilized for quantitative assessment of tumors for activities such as disease characterization or predicting outcomes. The potential of these approaches is huge, and it has been revealed in helping clinical experts to uncover cancer characteristics that fail to be appreciated by naked eyes (4), significantly surpassing the human operator and all earlier related technologies in image recognition and analysis. In this context, radiomics is a nascent and rapidly progressing discipline that merges insights from radiology, oncology, and informatics, highlighting the convergence of medicine and engineering (5). Growing evidence suggests that radiomics can be utilized for quantitative analysis of tumors for activities such as disease characterization or outcome prediction, marking a significant research trajectory in medical applications (6).

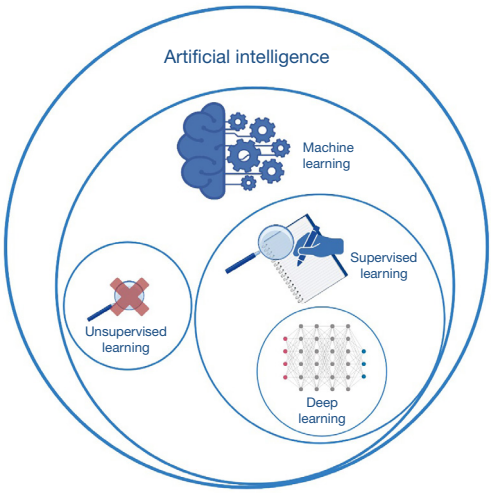

Figure 1 Implementation of deep learning as a form of supervised learning within the subset of machine learning methods in artificial intelligence (created with BioRender.com).

Materials and methods

This narrative review is based on a selective literature search carried out in PubMed and Cochrane Library databases from origin to December 2022, with the aim of

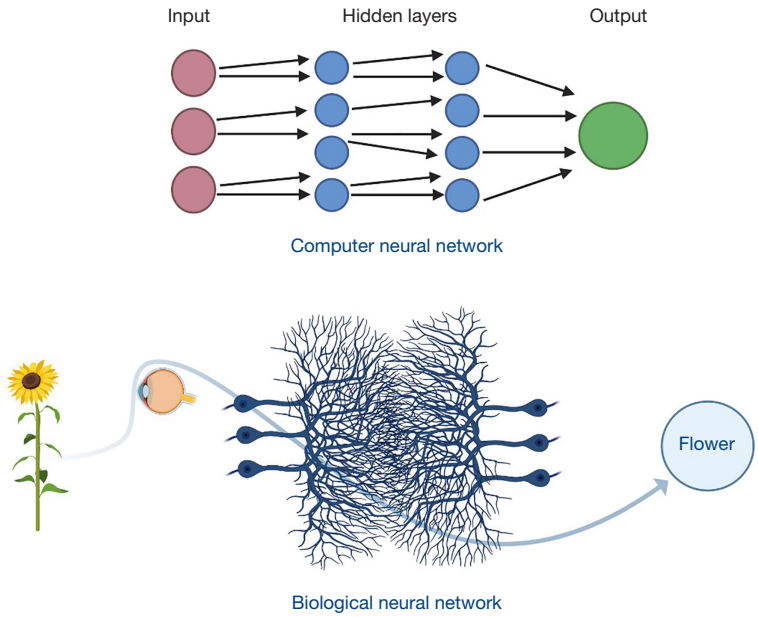

Figure 2 Analogous parallels between artificial neural networks and biological neural networks. Hidden layers in artificial neural networks can be compared to brain interneurons (created with BioRender.com).

finding relevant studies using combinations of the following search terms: "Artificial Intelligence (AI), Radiomics, Deep Learning (DL), Machine Learning (ML), lung cancer, lung malignancy, lung nodules, Non-Small Cell Lung Cancer (NSCLC)". The search strings on PubMed and Cochrane Library were ("AI and Lung nodules"), ("Lung cancer and Artificial Intelligence"), and ("NSCLC and AI"). Text (Free Full texts), Article type (All except Books and Documents), (Humans [Filter]), and (English [Filter]) without any limits on the publication year. These publications were then selected by two distinct authors (F.L. and G.G.). The inclusion/exclusion criteria were reported herein:

(I) Inclusion criteria were (i) english-language; (ii) article types were: clinical trials, randomized controlled trials, case-control studies, prospective or retrospective cohort studies, review and meta-analyses.

(II) Exclusion criteria: (i) article not written in English; and (ii) the following kind of articles: books, documents, editorial comments, abstracts, case reports, guidelines, or consensus statements.

Two authors (F.L. and G.G.) independently reviewed the full texts of the identified papers. A third author (M.C.) resolved emerging discrepancies. The selected articles were then examined in full, processed, and summarized to align with the objectives of the review. Finally, the chosen papers were read by all authors and discussed to draw reliable conclusions.

AI and the solitary pulmonary nodule

DL and computer-aided detection (CAD) for distinguishing between benign and malignant tumors

DL solutions are currently leading the field in pulmonary nodule detection. DL algorithms have demonstrated similar or superior performance to medical professionals in various healthcare environments. Their applications include detecting pulmonary nodules in chest radiographs or computed tomography (CT) scans, improving candidate identification for r lung cancer screening (LCS) and forecasting the malignancy of pulmonary nodules (7). Radiologists face hurdles in detecting lung cancer from chest radiographs due to limited contrast resolution. This constraint can obscure lesions that overlap with anatomical structures, leading to higher rates of false-negative diagnoses (8). Lesion size, shape, and location are all independent factors in detection error and can lead to missing lesions during the interpretation of chest radiographs (9). CAD software was developed in the 1970s to increase the accuracy of chest radiography for nodule detection (10). The use of computer algorithms in CAD

Table 1 AI applications in pulmonary nodule detection and classification

Study	Method used	Number of images/patients	Results
Kakeda, 2004 (10)	Traditional CADe and CADx systems in chest radiography for nodule detection and diagnosis	45 lung cancer patients and 45 healthy patients	Improved efficacy in nodule detection in chest radiographs
Roos, 2010 (13)	DL system for consistently classifying nodule types in CT scans, determining the management strategy for LCS participants	20 patients with clinical suspicion of pulmonary nodules	Suggested the use of DL systems to help in consistently classifying nodule types in CT scans for LCS
van Ginneken, 2010 (14)	Automated Nodule Detection 2009 (ANODE09) study: Web-based framework evaluating nodule detection algorithms from LCS CT scans	55 anonymized CT scans	Limitations: uniform dataset from one center, same scanner, and protocol
Armato, 2011 (15)	Lung Nodule Analysis 2016 (LUNA16) trial: used 888 scans with 1,186 nodules from LIDC and IDRI for instruction and assessment. Reference values based on annotations from four radiologists	888 scans with 1,186 nodules	Best algorithm achieved sensitivity of 97.2% with 1 false positive per scan on average, continues to be used as a benchmark for AI algorithms
Christe, 2013 (16)	Combining human observer with CAD system resulted in higher sensitivity for detecting lung nodules compared to combining two different CAD systems	900 nodules	Improved sensitivity for lung nodule detection when combining human observer with CAD system
Ciompi, 2017 (17)	AI algorithm to classify pulmonary nodules into various types using a dataset of 943 subjects with 1,805 nodules from the Multicenter Italian Lung Detection (MILD) trial	943 subjects with 1,805 nodules	Performance of the system was within inter-observer variability of four experienced human readers, demonstrating effectiveness in classifying nodules similarly to an independent human expert

AI, artificial intelligence; CADe, computer-aided detection; CADx, computer-aided diagnosis; DL, deep learning; CT, computed tomography; LCS, lung cancer screening; LIDC, lung image database consortium; IDRI, image database resource initiative; CAD, computer assisted detection.

systems can aid in identifying various medical conditions. This includes the use of computer-aided detection systems (CADe) to help detect irregularities or lesions in medical images, and computer-aided diagnosis systems (CADx) to assist in the analysis and diagnosis of medical images. Such systems have the potential to improve the accuracy and speed of medical diagnosis, particularly in situations where human evaluation may be limited or prone to errors. CAD systems can aid in the detection of chest CT pulmonary nodules by initially screening a large number of chest CT images and highlighting suspicious lesions. This can help radiologists to make secondary discrimination, decrease their workload, and improve screening efficiency. Traditional CADe systems usually consist of two main stages: (I) selection of candidate nodules and (II) removal of false positive nodules (FPN) while preserving true positive nodules (TPN) (11). By enhancing these steps, more cases of lung cancer that may have been missed during routine chest imaging can be identified. This could lead to improved survival rates (12).

The use of low-dose computed tomography (LDCT) scans in LCS has led to a significant increase in the volume of images that radiologists must analyze, which can be a challenging and time-consuming task. Furthermore, the elevated frequency of false positives is an additional concern, as it may lead to superfluous diagnostic evaluations and invasive medical procedures for patients who are not afflicted with lung cancer. These issues highlight the need for more efficient and accurate methods of analyzing LDCT scans for LCS. As known, the low dose CT scan differs in quality to CT scan performed for staging, and for this reason, images acquired with this instrument are lower in quality. This is one of the main reasons for which it is hard to give a definitive definition only on the basis of the images. As shown in *Table 1*, a comparison among studies collecting the use of CAD or DL has been made. AI using CAD or DL methods has been implemented to decrease radiologist errors and increase the detection rate of pulmonary nodules. However, before employing DL techniques, the CAD system realized only poor detection performance (sensitivity of 70% or lower) for lung nodules and a markedly high false positive rate, which was

inadequate for clinical application (13).

The Automated Nodule Detection 2009 (ANODE09) study was the pioneering web-based framework for assessing nodule detection algorithms from LCS CT scans (14). The primary limitations of this study were the dataset size and the uniformity; all the images were acquired from a single center, using the same scanner and protocol. To address these limitations, the Lung Nodule Analysis 2016 (LUNA16) trial was established using 888 scans with 1,186 nodules from the Lung Image Database Consortium (LIDC) and Image Database Resource Initiative (IDRI) for training and established (15).

To guarantee robustness, the reference values for each scan were based on annotations from four radiologists. The best algorithm achieved a sensitivity of 97.2%, with an average of one false positive per scan. As a result, it continues to be used as a benchmark for more recent AI algorithms (18).

Christe *et al.* demonstrated that combining a human observer with any CAD system resulted in higher sensitivity for detecting lung nodules compared to combining two different CAD systems (16). Ciompi *et al.* developed an AI algorithm to categorize pulmonary nodules into solid, part-solid, non-solid, perifissural, calcified, and speculated employing a dataset of 943 subjects with 1,805 nodules from the Multicenter Italian Lung Detection (MILD) trial (17). They showed that the system's accuracy was comparable to the inter-observer variability of four experienced human readers, thereby confirming the effectiveness of the system at classifying nodules equivalently to an independent human expert. Radiologists have introduced the concept of "nodule type" in interpreting CT scans, where they must differentiate between various types of opacities based on their appearance and, more importantly, their likelihood of being malignant. In this context, the range of variability reached by the proposed system makes it the first suitable system for automatic analysis of CT scans in LCS. This study indicated that a DL system could assist in reliably categorizing nodule types, which influences the management strategy for LCS participants. According to the National Institute of Health and Care Excellence, for individuals undergoing a chest CT scan as part of targeted LCS, AI-derived CAD software technologies have the potential to be economically beneficial. Therefore, although there is not yet sufficient evidence to endorse the software as standard practice, centers may implement it as part of targeted LCS. Proof needs to be generated to ensure the potential advantages of using the software are achieved in practice and to facilitate comparisons of the various technologies (19).

Malignancy prediction

The existing management strategies for indeterminate pulmonary nodules rely on qualitative or quantitative estimates of the malignancy risk of these nodules. The prominent examples include Lung-RADS by the American College of Radiology, guidelines by the Fleischner Society, and the British Thoracic Society (20). Lung-RADS® is a quality control mechanism that aims to standardize the reporting and management recommendations for LCS CT. It is designed to minimize confusion in the interpretation of LCS CT results and to streamline outcome monitoring. A comprehensive atlas and lexicon will be established to facilitate this process. The atlas will feature a medical audit and outcome monitoring process, while the lexicon of LCS CT terminology and reporting format will standardize the language used in reports. Many experiences in literature are now reporting the role of AI in LCS (see *Table 2*).

The Brock model, also known as the Pan-Canadian Early Detection of Lung Cancer or PanCan model, was developed in 2013 to estimate the risk of malignancy in pulmonary nodules (25). The model includes various predictors such as patient demographics, nodule size, type, and morphology. The Brock model is currently integrated into the British Thoracic Society nodule management guidelines (26,27) and is recommended in the Lung-RADS version 1.1. Although the Brock model has demonstrated that radiologists can more precisely evaluate the malignancy risk of a nodule, there is no consensus when radiologists are requested to identify the signs of malignancy (28). In 2020, Baldwin *et al.* conducted a validation study on lung nodules measuring 5–15 mm, which were identified unexpectedly at three hospitals in the UK. In this study, the lung cancer prediction convolutional neural network (LCP-CNN) was evaluated against the Brock University model, recommended in UK guidelines, and it was found that AI enhances risk prediction (21).

Choi *et al.* developed a radiomic prediction model for the early detection of lung cancer from lung nodules with low-dose CT in 2018 (22). This model, based on two CT radiomic characteristics, achieved 84.6% accuracy, surpassing the one reported by Lung CT Screening Reporting and Data System (Lung-RADS). The general growth of a nodule on CT and growth not assessed from a single scan only appeared to be the most important

Table 2 The role of AI in lung cancer screening

Study	Number of images/ patients	Aim	Results	Comments
Armato, 2011 (15)	7,371	To identify all lung nodules in each CT scan	2,669 lesions marked as a nodule ≥3 mm by ≥1 radiologist	Reference database for CAD methods for lung nodule identification
Ciompi, 2017 (17)	1,805	To classify pulmonary nodules	Algorithm classifies nodules equivalently to an expert	System effectiveness corroborated, first for automatic CT analysis in lung cancer
Baldwin, 2020 (21)	1,397	To compare LCP-CNN with the Brock model	AUC for LCP-CNN: 89.6%, Brock model: 86.8% (P≤0.005)	AI improves risk prediction
Choi, 2018 (22)	72	To predict early detection of lung cancer	Prediction model accuracy: 84.6%, AUC: 0.89	Two-CT radiomic features achieve higher accuracy than Lung CT Screening Reporting and Data System (Lung-RADS®)
Ohno, 2020 (23)	290	To evaluate CADv with CNN for nodule measurement	AUC for CADv with CNN: 0.94, CADv without CNN: 0.69	CNN improves accuracy and nodule differentiation
Zhang, 2022 (24)	860	To compare detection rates between radiologists and AI	AI accuracy: 99.1% for solid nodules, 98.8% for non-solid	AI greatly increases detection sensitivity, outperforming radiologists

AI, artificial intelligence; CT, computed tomography; CAD, computer-aided diagnostic; LCP, lung cancer prediction; CNN, convolutional neural network; AUC, area under the curve; CADv, computer-aided detection of volume.

predictors of the malignant nature of the nodule. A CNN model was developed by Ardila *et al.* in 2019 to examine LDCT volumes to detect lung cancer. The model was able to accurately predict the risk of lung cancer over one and two years with an area under the curve (AUC) of 94.4% and 87.3%, respectively (29). The model had greater sensitivity and specificity for lung cancers compared to the human operators when only a single LDCT was available; similar diagnostic accuracy was observed when multiple LDCTs were available (14). Based on this evidence, a superior performance of the DL network methodology was claimed when compared to that of six independent radiologists when dealing with the assessment of malignancy (from one CT scan only).

Although these claims require extensive validation, AI algorithms may have achieved radiologist-level performance for detecting the malignant nature of a pulmonary nodule by CT. Nevertheless, these studies only evaluated individual performances and did not take into account any collaboration between human and machine (30).

Certain tasks that are more challenging for radiologists might be more manageable for the algorithm, and vice versa. For example, subsolid nodules are frequently overlooked by radiologists due to their lower contrast with lung tissue. Conversely, highly irregular nodules might not be identified by the AI because of their rarity in the training dataset (31,32). Regarding the capacity of a human reader to receive assistance from an AI system, two approaches have been outlined: second reader and concurrent reader. When employing computer-aided diagnosis (CAD) as a second reader, the radiologist initially reviews the study independently, submits it to the CAD system, and subsequently re-evaluates the study by concentrating on the CAD marks to finalize the results. Conversely, with CAD as a concurrent reader, the initial independent review by the radiologist is skipped; the study is processed by CAD and then presented to the radiologist, who either accepts or rejects the CAD marks and conducts a final search for any missed nodules (33). Silva *et al.* showed that CAD provides additional information to radiologists for detecting subsolid nodules in volumetric LDCT for LCS. However, CAD marks necessitate visual confirmation to correct false positives. Integrating CAD with visual reading results in optimal detection performance of subsolid nodules (32). For this reason, this setting would lead to the conclusion that humans and computers would likely work synergistically, leading to better performance in lung cancer diagnosis.

Deep learning-based automatic detection (DLAD) algorithms could precisely identify malignant pulmonary nodules on chest radiographs, occasionally outperforming physicians and improving physicians' performance when utilized as a "second reader". In 2018, Nam *et al.* developed

a DL algorithm by using 43,292 chest radiographs. DLAD demonstrated high specificity and successfully identified 100% of high conspicuity nodules, mostly large (>3 cm), nodules, and more nodules in overlap areas than four groups of physicians (8). They reported that the DL algorithm achieved a sensitivity of 71–91%, a specificity of 93–100%, and an AUC of 0.92–0.99, which were superior to the performance of most physicians involved in the study (8).

Compared with previously reported conventional image processing-based computer-aided diagnosis, DLAD exhibited a significantly reduced rate of false-positive findings and delivered high specificity while maintaining sensitivity, resulting in overall better detection performance than thoracic radiologists (34).

In 2020, Ohno *et al.* (23) analyzed the volumetric change and doubling time of pulmonary nodules of 170 patients with 290 nodules at chest CT, assisted by the CNN applied to computer-aided detection of volume (CADv) measurements. They indicated that the AUC of total volume change per day calculated by the CADv with CNN (AUC =0.94) was notably higher than CADv not using CNN (AUC =0.69), concluding that CNN is a useful tool for improving accuracy and nodule differentiation.

In 2022, Zhang *et al.* compared the performance of detecting lung nodules between Radiologist Observation and AI-assisted reading. For solid nodules, the accuracy and sensitivity of radiologists were 86.2% and 52.4%, respectively, much lower than 99.1% and 98.8% detected by AI. For partly solid nodules, the sensitivity of radiologists was 23.1%; much lower than the 100% achieved by AI. For non-solid nodules, the sensitivity of human observation was 25.2%, compared to 99.1% of AI. Therefore, AI-assisted reading greatly increased the detection sensitivity of part-solid and non-solid nodules by 74% compared with the radiologists' observation (24).

AI repeatedly demonstrated itself as a promising innovation for the malignancy prediction of lung nodules. Almost all the studies concluded that incorporating AI into standard radiological diagnostic pipelines will foster enhanced patient care through earlier and more accurate detection of the disease, thereby paving the way toward better outcomes (35). Promising studies are now evaluating the role of AI in the determination of lung nodules malignancy. For example, the DOLCE study is a prospective, observational multicenter study to assess the clinical utility of an AI-assisted CT-based lung cancer prediction tool (LCP) for managing incidental solid and part solid pulmonary nodule *vs.* standard care (36). Another interesting study is the DART study (also collecting data through the Lung Health Check program) that has the aim of developing new ways of using computer technology (AI) to improve lung health care (37).

AI for predicting histology and other pathological features

Lung cancer is a complex and heterogeneous disease that can be categorized into two main histological types: NSCLC and small cell lung cancer (SCLC). NSCLC represents approximately 85% of all lung cancer cases, while SCLC represents the remaining 15%. NSCLC can be further classified into three subtypes based on the histological features: adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma. ADC is the most common subtype of NSCLC, accounting for about 40% of all cases, followed by SCC, which represents around 30% of NSCLC cases. Large cell carcinoma is a less common subtype, accounting for approximately 10–15% of NSCLC cases. Each subtype of NSCLC has distinct molecular and genetic characteristics, which may affect the response to treatment and prognosis of the disease. Therefore, accurate subtyping of NSCLC is crucial for personalized treatment decisions and clinical management. Lung biopsy remains up until now the cornerstone for diagnosis of lung cancer, obtained either by image-guided transthoracic needle biopsy or transbronchial by bronchoscopic techniques. Although the histopathologic analysis by experienced pathologists remains the gold standard for diagnosing NSCLC histologic subtypes, it is occasionally challenging to accurately differentiate poorly differentiated ADC and SCC due to similar morphologic characteristics (38) thus requiring confirmatory immunohistochemistry (IHC). Furthermore, it is time-consuming and difficult for a pathologist to analyze highly intricate pathologic images through morphological assessment of tissue sections. In contrast, highly sensitive and automatic AI requires limited human intervention to classify lung cancer histological types/subtypes by analyzing radiological images (CT/PET) and digital histopathological slides using DL algorithms especially CNN (39) to assist (not replace) the pathologists in the decision-making process, making more precise diagnosis of NSCLC (39). Therefore, several studies investigated the various AI models for classifying the histology of NSCLC based on digital histopathological slides and gene profiles, comparing with the performance level of experienced pathologists. Recent studies using AI in pathology aimed to (I) forecast routine diagnostic

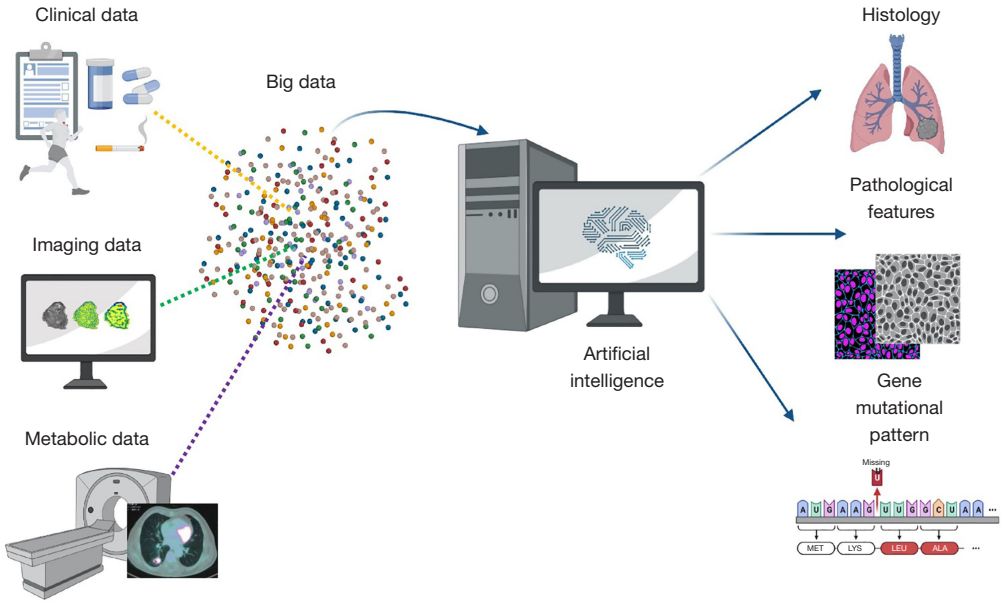

Figure 3 Integrated use of big data (imaging, clinical and metabolic data) through artificial intelligence for predictive purposes at histological, pathological and genetic state.

characteristics (e.g., disease *vs.* normal tissue, determine tumor grade, and differentiate cancer types) and (II) uncover new insights into disease (e.g., predict gene mutation status, disease recurrence, and outcome) (40). These algorithms can significantly aid pathologists in determining the ratio and distribution of histologic subtypes/patterns in a specimen, which is currently a tedious process (41).

Besides tissue biomarker analysis, liquid biopsies have grown increasingly widespread. Liquid biopsy involves the examination of any tumor-derived product in the bloodstream or serum. Unlike tissue-based biopsies, which evaluate the spatial diversity of the tumor based on the sample site, liquid biopsies can capture temporal heterogeneity by collecting specimens from the bloodstream at various times, potentially revealing the progression of the disease. This technique is useful in various contexts. In early-stage disease, plasma next-generation sequencing (NGS) with comprehensive panels can offer high sensitivity and specificity, aiding in distinguishing benign from malignant nodules, guiding neoadjuvant therapy, and directing adjuvant therapy for patients undergoing surgical resection (42). Circulating miRNA serves as a potential clinical marker for detecting tumors and monitoring the progression of tumorigenesis through liquid biopsy (43). Zhang *et al.* (43,44) presented a novel computational approach for identifying significant circulating miRNAs that may be applied to early screening, diagnosis, and constant monitoring of lung cancer progression. Specifically, they used synthetic minority oversampling (SMOTE), a technique to assist AI in scenarios where the minority class is underrepresented, risking the overshadowing of its key features by the dominant class. Combined with random forests, this approach was used to detect lung cancer via circulating microRNA (miRNA), attaining an AUC of 0.99. Notably, this study employed a case-control design with samples not limited to early-stage disease, likely inflating performance results. Nonetheless, further exploration into AI/ML for liquid biopsy analysis is essential, as human assessment of such complex, high-dimensional data is impractical. AI is crucial for improving the sensitivity and specificity of liquid biopsies, ultimately benefiting patients through less invasive and earlier cancer detection.

AI models using radiological images for histology classification

Radiologists and oncologists may face challenges in accurately determining the histology of NSCLC tumors due to limited access to invasive techniques for tumor sampling during biopsies. Nevertheless, non-invasive approaches, including the utilization of medical image biomarkers and ML, have the potential to function as effective substitutes for predicting NSCLC histology (*Figure 3*). In 2020,

Table 3 Advances in predicting NSCLC histology using non-invasive approaches and machine learning

Study	Method used	Number of images/patients	Results
Pang, 2020 (44)	DL model on CT images	2,219 CT images	Overall accuracy: 87%, sensitivity: SCLC 90%, ADC 86%, SCC 92%
Moitra, 2020 (45)	DL model on CT scans	285,411 CT images of 211 NSCLC patients	Overall accuracy: 96.3%; AUC: 98.5%; validation accuracy: 94.4%
Guo, 2021 (46)	3D DL and radiomics on non-contrast CT images	920 patients	Overall accuracy: 75% (AUC 79–84%)

NSCLC, non-small-cell lung cancer; DL, deep learning; CT, computed tomography; SCLC, small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; AUC, area under the curve.

Pang *et al.* (44) proposed a DL model to classify SCLC, ADC, and SCC from 2,219 CT images. They found that the DL model was enough powerful to achieve an overall accuracy of 87% and a sensitivity of 90%, 86%, and 92% in classifying SCLC, ADC, and SCC, respectively. Similarly, in the same year, Moitra and Mandal (45) evaluated a DL model on CT scans belonging to 211 NSCLC patients (285,411 CT images). Their study included not only ADC and SCC but also a third non-specified NSCLC histological subtype. Their model reached an overall accuracy of 96.3% and an AUC of 98.5%. While dropout layers were used during training to minimize overfitting by setting some features to zero, all features were considered during the validation process. This artificially enhanced the model's accuracy, which reached 94.4%. They concluded that their model would be useful in the automated prognosis of NSCLC, and it would help radiologists and oncologists in the decision-making process.

Recently in 2021, Guo *et al.* (46) developed a 3D DL and Radiomics methodology to differentiate lung cancer histological types/subtypes (SCLC, ADC, and SCC) from non-contrast CT images, encompassing 920 patients. Results indicated that the DL models can distinguish SCLC, ADC, and SCC with an overall accuracy of 75% (AUC 79–84%) (see *Table 3*).

AI models using histopathological slide images for histology classification

In 2018, Khosravi (47) and his colleagues from Weill Cornell Medicine collected 12,139 IHC-stained whole-slide images as well as H&E-stained histopathology images from the Stanford Tissue Microarray Database (TMAD) and The Cancer Genome Atlas (TCGA). They trained all CNNs using the chosen images to distinguish between the two histological subtypes [ADC and SCC]. The results showed that complex CNNs could successfully distinguish ADC and SCC across heterogeneous tissue of the tumor slides with no error. Histologic intertumoral heterogeneity in ADCs is described in two terms: frequent (>80%) minor heterogeneity resulting from various growth patterns, such as lepidic, acinar, papillary, micropapillary, and solid in mixed adenocarcinomas (mADCs), and unusual major heterogeneity as seen in the adenosquamous lung carcinomas (AdSqLCs) (38). These tumor growth patterns impact clinical prognosis, as micropapillary and solid patterns are linked to a poorer prognosis (48). Additionally, it is occasionally challenging to distinguish the predominant and minor histologic subtypes; therefore, AI algorithms are applied in different studies to accurately classify ADC growth patterns. In 2019, Wei *et al.* (49) showed that AI can be used to aid pathologists in classifying the five growth patterns with 90% accuracy thus achieving a pathologist-level performance and ultimately contributing to more accurate grading of lung ADC (see *Table 4*). Moreover, this study compared CNN models and pathologists with diverse experience backgrounds, the CNN model accomplished slightly improved performance and was superior to inexperienced pathologists.

"Radio-genomics": AI models for predicting gene mutation in lung cancer

Somatic mutation profiling in oncology has revolutionized clinical practice. The discovery of driver mutations in NSCLC is a prime example. Molecular testing of advanced-stage lung ADC is now the standard of care and a key component of the diagnostic process. For lung ADC, all patients with advanced stages should be tested for epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) rearrangements, and PD-L1 levels to determine their potential response to EGFR, ALK, or ROS1 inhibitors, or

Table 4 AI applications in classifying histologic subtypes and growth patterns in lung ADC

Study	Method used	Number of images	Results
Khosravi, 2018 (47)	CNNs trained on IHC-stained and H&E-stained whole-slide images from Stanford TMAD and TCGA to discriminate ADC and SCC	12,139 whole-slide images	The successful distinction between ADC and SCC with no error. Histologic heterogeneity in ADCs: frequent minor heterogeneity (>80%) in mADCs and major heterogeneity in AdSqLCs
Wei, 2019 (49)	AI used to classify five growth patterns in ADC with 90% accuracy. Compared CNN models and pathologists with varying experience levels	143 whole-slide images	Achieved pathologist-level performance, superior to inexperienced pathologists in distinguishing growth patterns

AI, artificial intelligence; ADC, adenocarcinoma; CNNs, convolutional neural networks; IHC, immunohistochemistry; TMAD, Tissue Microarray Database; TCGA, The Cancer Genome Atlas; SCC, squamous cell carcinoma mADCs, mixed adenocarcinomas; AdSqLCs, adenosquamous lung carcinomas; CNN, convolutional neural network.

immunotherapy, respectively. Additionally, various other biomarkers, including BRAF, ERBB2, MET splice variants and amplifications, and rearranged during transfection (RET) rearrangements, are under clinical evaluation as indicators of response to targeted therapies (50).

In particular, the mutation of EGFR or ALK rearrangements were detected in 15% and 2% of NSCLC patients, respectively (51,52). Currently, the identification of these gene mutations necessitates invasive methods of tissue sampling either by image-guided or transbronchial needle biopsy (TBNB) from the primary tumor or its metastases. To overcome these invasive procedures, liquid biopsy and now AI approaches are trying to investigate/identify tumor mutations to avoid more aggressive procedures (and potentially to reduce the delay for treatment). The combination of medical imaging information derived from radiomics and tumor genomic data is frequently termed "radio-genomics" (53).

Coudray *et al.* (54) investigated 1,634 whole slide images (1,176 tumor tissue and 459 normal) using the CNN for distinguishing lung ADC, SCC, and normal lung tissue. The DL model demonstrated high performance (AUC =0.97) on par with pathologists. Beside diagnosing lung cancer, Radiomics has been extended to the prediction capability towards the genes' mutations; the authors have shown that the CNN model was capable of predicting the mutation of six genes (*EGFR*, *KRAS*, *FAT1*, *TP53*, *SETBP1*, and *STK11*) in lung ADC with (AUC =0.73–0.85) based on both frozen sections and HE stained formalin-fixed paraffin-embedded (FFPE) slides. The EGFR tyrosine kinase inhibitor (TKI) targeted therapy is the effective first-line treatment for NSCLC patients with EGFR mutations and offers longer progression-free survival (PFS) and improved quality of life (QoL) compared with chemotherapy. Therefore, many studies investigated the role of Radiomics in integrating CT images for predicting the EGFR mutation. Combining structural and functional imaging with clinical information and the outcome of liquid biopsy allows for the development of models that are most successful at predicting gene mutation. Zhang *et al.* (55) developed a more complex model using radiomics extracted from the CT images combined with clinical characteristics as (smoking history, sex, and histologic type), for potential discrimination of the *EGFR* mutation status and showed the ROC (AUC =0.86), which is greater compared to research using only the CT images with the ROC (AUC =0.77) (56).

On the contrary, only a few studies investigated other gene mutations (*ALK*, *KRAS*, *BRAF*, *ROS1*), and even fewer for the programmed-death-1 (PD-1)/programmed-death ligand (PD-L1) expression. Two Korean studies showed promising results, the first analyzed 172 patients with NSCLC from three hospitals in 2014 (57). They concluded that ALK+ NSCLC has unique features at CT imaging that, when integrated with clinical variables, discriminate ALK+ from non-ALK tumors; it could therefore identify patients with a response to crizotinib with a sensitivity of 83.3%, specificity of 77.9%, and accuracy of 78.8%. The second study, published in 2015 (58), analyzed 539 pathologically proven lung ADC for prediction of ALK, ROS1, or RET by using radiomics from the CT and PET images; it concluded that ALK/ROS1/RET fusion-positive lung ADC exhibits specific clinical and imaging characteristics, allowing effective differentiation of fusion-positive from fusion-negative lung ADC. PD-L1 expression level plays an important role in guiding immunotherapy for NSCLC patients according to the latest version of NCCN (Version 3.

Table 5 Radiogenomic approaches for predicting gene mutations in NSCLC

Study	Method used	Number of images/patients	Results
Coudray, 2018 (54)	CNN on whole slide images for distinguishing lung ADC, SCC, and normal lung tissue	1,634 whole slide images (1,176 tumor tissue and 459 normal)	High performance (AUC =0.97) comparable to pathologists. Prediction of six gene mutations (*EGFR*, *KRAS*, *FAT1*, *TP53*, *SETBP1*, *STK11*) in lung ADC (AUC =0.73–0.85)
Zhang, 2018 (55)	Radiomics model using CT images and clinical characteristics (smoking status, gender, histological subtype) for discriminating EGFR mutation status	180 NSCLC patients	ROC for combined model (AUC =0.86), higher than using CT images alone (ROC AUC =0.77) (56)
Yamamoto, 2014 (57)	Analysis using CT imaging and clinical variables for discriminating ALK^+ from non-ALK tumors	172 NSCLC patients	Sensitivity: 83.3%, specificity: 77.9%, accuracy: 78.8% for identifying patients with a response to crizotinib
Yoon, 2015 (58)	Analysis of lung ADC for predicting ALK, ROS1, or RET fusion using radiomics from CT and PET images	539 lung ADC samples	Good discrimination of fusion-positive from fusion-negative lung ADC based on clinical and imaging features
Jiang, 2020 (59)	Radiomics model based on PET/CT images of NSCLC patients for anticipating PD-L1 expression status	399 stage I–IV NSCLC patients	AUC =0.97 for anticipating PD-L1 expression. AUC =0.91 for predicting PD-L1 expression rates over 50%

NSCLC, non-small-cell lung cancer; CNN, convolutional neural network; ADC, adenocarcinoma; SCC, squamous cell carcinoma; AUC, area under the curve; EGFR, epidermal growth factor receptor; CT, computed tomography; ROC, receiver operating characteristic; ALK, anaplastic lymphoma kinase; RET, rearranged during transfection; PET, positron emission tomography; PD-L1, programmed-death ligand 1.

2019). Jiang *et al.* in 2020 (59) developed a radiomics model based on PET/CT images of 399 stage I–IV NSCLC patients and concluded that radiomics may anticipate PD-L1 expression status in NSCLC relatively accurately with an AUC =0.97 and 0.91 predicting PD-L1 expression rates over 1% and over 50%, respectively (see *Table 5*).

Limitations of AI-based models

DLAD, although it has demonstrated encouraging outcomes in medical image analysis, faces some constraints because of the requirement for annotated data provided by radiologists, which could mirror the limitations of human perception and analytical judgment. The primary obstacle in applying deep CNNs to medical images is the image quality (60). Although AI models have demonstrated performance comparable to or surpassing that of humans, the intricacy of these models makes them challenging to decipher and comprehend how they arrive at their outcomes, which has resulted in the notion of AI models as "black boxes" (61). Another major concern is the applicability of these models to all patients, which could be resolved by creating continuous learning systems that employ cloud-based methods to enable the real-time delivery of clinical records and ongoing adjustment of the underlying training models. This would guarantee machine-independent consistency of the models (62).

In radiomics, the reproducibility of features is vital due to the variability in image acquisition, preprocessing, and segmentation. PET/CT scans provide extensive imaging data and parametric information but are prone to pitfalls and artifacts and are more costly and technically complex. The lack of a universal consensus on the optimal threshold for lung cancer radiomics is another challenge. Additionally, AI-based approaches require specialized skills, necessitating training for the next generation of radiologists and pathologists. Various AI algorithms have been created in NSCLC patient-focused studies, most of which are retrospective, single-center, with small training samples and lacking external validation, limiting their interpretability and generalizability. Moreover, a well-defined ethical and legal structure from stakeholders (healthcare providers, research organizations, patient advocacy groups, and government) is needed (63).

Conclusions

The application of AI to enhance the understanding and treatment of NSCLC is expanding but its introduction in clinical practice still faces obstacles. However, we may

Figure 4 LANTERN Study overview. The figure illustrates key phases of the LANTERN Study, from 'NSCLC Patients' through enrollment, and integrated data collection, to the creation of digital humanized avatars, culminating in practical implementation in the clinical setting. NSCLC, non-small-cell lung cancer; DHA, digital human avatar.

indeed bet that AI-based science will be ubiquitous and indispensable in lung cancer patients. This positive prevision relies on the fact that with the advent of omics sciences and precision medicine, the information obtained from the recalled omics technologies provides physicians with an enormous amount of data ("big data"). Only with the application of AI techniques, researchers and physicians will have the potential to deal with the complexity represented by the quantitative aspect of the big data-related features. For this reason, oncologists, radiologists and surgeons should persist in incorporating machine-learning tools into the clinical management of NSCLC and join the digital transformation that has already occurred in the business and technology sectors. Furthermore, future AI applications for precision medicine in NSCLC could combine radiomics and liquid biopsies into innovative companion diagnostics, offering valuable insights into tumor biology, disease progression, and treatment response in a minimally invasive and longitudinal manner (63).

In particular, as summarized in the present narrative and comprehensive review, there are several possible applications of AI in lung cancer management, with preliminary but very encouraging results:

(I) Computer-assisted diagnosis will facilitate the identification of early-stage disease, the detection of malignancy in lung lesions, as well as the prediction of histology and other pathological characteristics.

(II) Advanced AI methods will be useful to predict NSCLC gene mutations without performing a sample biopsy (thus reducing time and costs). Finally, physicians of the future will have powerful tools to predict response to treatments and the occurrence of a tumor recurrence, resulting in a real personalized strategy of care.

Future research perspectives

Several future perspectives have been suggested in the domain of precision medicine for lung cancer therapy; our Team has recently developed a multi-omics platform of research (LANTERN project) (64) that stands as a beacon of innovation, contributing valuable insights that align seamlessly with the evolving paradigm of personalized and preventive healthcare. As we navigate the complexities of lung cancer, the LANTERN project's multi-omics prospective research design, involving 600 NSCLC patients, presents an unparalleled opportunity to delve into the intricate interplay of genetic, molecular, and clinical factors. By carefully gathering radiomic, genomic, and metabolomic profiles, along with extensive medical and therapeutic information, the study aims to build digital humanized avatars that actively depict each patient's unique molecular and clinical landscape (*Figure 4*). This approach not only aims to enhance individualized therapeutic approaches but also has the potential to transform the future of cancer care by aiding the ongoing advancement propelled by sophisticated ML and AI methods. The LANTERN Study's commitment to ethical standards and compliance with regulations positions it as a pioneering effort that not only addresses current challenges in lung cancer care but also lays the foundation for future breakthroughs in precision oncology. As we reflect on the current trends and future perspectives in AI-based models, the LANTERN project emerges as a pivotal force in enhancing patient care and outcomes in NSCLC, paving the way for a new era in the battle against this challenging disease.

Acknowledgments

We thank Dr. Franziska Michaela Lohmeyer for her

precious support in English Editing.
Funding: None.

Footnote

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-244/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-244/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Lococo F, Ghaly G, Flamini S, Campanella A, Chiappetta M, Bria E, Vita E, Tortora G, Evangelista J, Sassorossi C, Congedo MT, Valentini V, Sala E, Cesario A, Margaritora S, Boldrini L, Mohammed A. Artificial intelligence applications in personalizing lung cancer management: state of the art and future perspectives. J Thorac Dis 2024;16(10):7096-7110. doi: 10.21037/jtd-24-244