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A COMPREHENSIVE REVIEW OF INTEGRATING AI AND MEDICAL IMAGING IN LUNG CANCER DIAGNOSIS

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Abstract

Lung cancer, a leading cause of global malignancy-related deaths, poses challenges due to late-stage diagnoses and diverse features in imaging and histopathology. Traditional approaches relying on clinical trials and expert opinions lead to time-consuming processes. Integrating artificial intelligence (AI) addresses these challenges, employing data-driven algorithms for prediction and classification. As AI subclasses, machine learning (ML) and deep learning offer sophisticated models that overcome historical computational obstacles. AI is crucial in lung cancer detection, spanning screening to diagnosis, especially in asymptomatic cases. Challenges in lung cancer screening underscore the need for accurate methods. AI improves the accuracy of low-dose computed tomography (LDCT) for lung cancer detection, with computer-aided diagnosis systems and AI-based programs enhancing radiologists' sensitivity and reducing false-negative rates. The narrative review explores AI applications in lung cancer detection, focusing on its role in the clinical workflow. The article introduces a deep-learning framework for chest radiography analysis, featuring a novel approach with a deep convolutional neural network (DCNN) algorithm-based software. The DCNN aids radiologists in detecting malignant pulmonary nodules, exhibiting improved sensitivity and reduced false-positive rates. While the study suggests potential clinical effectiveness, challenges in generalizability exist. In chest CT screening, AI algorithms match radiologists' performance levels. Collaborative approaches, such as concurrent reading and second-reader paradigms, show increased sensitivity and reduced interpretation time. Ongoing research and validation are emphasized for practical integration into routine clinical practice. Whole Slide Imaging (WSI) integration with AI and deep learning transforms cytopathology, enhancing pathologists' efficiency. The combination facilitates tumor cell recognition and segmentation and predicts gene mutations, envisioning AI assisting pathologists in routine tasks for personalized treatment decisions.

The future trajectory of AI in lung cancer focuses on overcoming challenges through federated learning and proposes "Medomics" for holistic insights. Despite promising results, real-world implementation faces barriers requiring infrastructure development. This comprehensive review provides insights into the evolving landscape of AI applications in lung cancer detection, showcasing advancements and highlighting avenues for future developments with the potential to revolutionize lung cancer diagnosis and treatment.

INTRODUCTION

Lung cancer, being a leading cause of malignancy-related deaths globally, poses significant challenges due to late-stage diagnoses and the heterogeneity of imaging and histopathological

features. [1] The intricate decision-making process for treatment options requires consideration of clinical staging, histopathology, and genomic features. Traditional approaches rely heavily on clinical trials and the expertise of doctors, leading to time-consuming processes for accurate diagnosis and treatment planning [2-4]. Integrating artificial intelligence (AI) into the field of lung cancer offers a promising solution to streamline and enhance the decision-making process. AI, a data-driven algorithm, utilizes existing data for prediction and classification. It comprises vital components, including the training dataset, pretreatment methods, algorithms for generating prediction models, and pre-trained models to expedite model building based on prior experience. Machine learning (ML) and deep learning are subclasses of AI, with deep learning incorporating multiple layers for feature selection and model fitting simultaneously [5-8]. Historically, the computational demands of developing multidimensional algorithms for image analysis have been a hindrance, requiring extensive time and resources. Advances in chip technology and software optimization have significantly increased computational power, enabling the development of more sophisticated prediction models. Traditional models, such as decision trees (DTs) and support vector machines (SVMs), have been complemented and surpassed by deep learning models like artificial neural networks (ANNs), convolutional networks (CNNs), recurrent neural networks (RCNNs), long-term and short-term memory (LSTM), and generative adversarial networks (GANs). In the 21st century, the integration of AI into human life, particularly in the medical field, has become prominent. The heterogeneity of lung cancer makes it an ideal candidate for AI applications, with numerous studies showcasing its effectiveness in lung nodule detection, histopathological diagnostics, disease risk stratification, drug development, and prognosis prediction. This narrative review explores the integration of AI and medical imaging for lung cancer detection, presenting AI models and their applications across the clinical workflow, encompassing screening and diagnosis [9-12].

There are challenges associated with detecting lung cancer in asymptomatic patients, and it emphasizes the significance of screening methods. Approximately 7% of lung cancer patients are asymptomatic, and over half of those undergoing lung cancer resection exhibit no symptoms [13]. Various screening methods, such as imaging, sputum cytology, blood tests, and breath tests, have been attempted. However, only imaging, specifically low-dose computed tomography (LDCT), has demonstrated the ability to diagnose lung cancer earlier and improve patient survival. [14] While chest X-rays (CXRs) are commonly used, LDCT has proven more effective in diagnosing lung cancer. The repetitive nature of the imaging workflow provides an opportunity for artificial intelligence (AI) to play a role, as extended reading can cause eye fatigue and potential errors in interpretation. Mistakes in reading CXR or LDCT images are common and can lead to malpractice lawsuits. Despite the expertise of radiologists, approximately 20% of lung nodules smaller than 3 cm are missed [15, 16]. Integrating computer-aided diagnosis systems or AI-based programs has improved the accuracy of pulmonary nodule detection on CXRs. The sensitivity of radiologists increases with the assistance of AI, leading to a reduction in false-negative rates and a significant impact on diagnosis in 6.7% of cases. In CT images, AI-based programs have demonstrated a sensitivity of more than 90% in detecting lung nodules. The ongoing integration of AI into lung cancer screening protocols is highlighted as a promising development. [17, 18]

Medical Imaging and Lung Cancer Detection

A deep-learning framework for the automatic analysis of Chest radiography images

Chest X-rays (CXR). Chest radiography remains the prevailing radiological method for lung cancer screening despite its acknowledged limitations compared to low-dose CT [19]. Chest X-rays (CXR) represent the most frequently utilized imaging modality in the medical field, thoroughly examining the patient's thorax with a radiation exposure of 0.1 mSv, equivalent to 10 days of natural background radiation. The development of computer-aided diagnosis (CAD) systems for CXR dates back to the 1960s [20], initially involving manual labeling of image features like shape, size, intensity, and texture before further analysis. In the digital era, computers can directly analyze images, with radio mics expanding the definition of image features by computing pixel-by-pixel and expressing the region of interest as a large matrix through mathematical techniques. Studies indicate that revisiting

baseline chest radiographs during follow-up examinations can reveal previously overlooked lung cancer nodules, with up to 90% being identified as the mass grows in size [21]. Various factors contribute to misdiagnoses, such as overlooking nodules, ignoring subtle densities, and experiencing the satisfaction of searching when another abnormality is detected [22–24]. Challenges in detecting lung nodules on chest radiographs arise from lesion characteristics, including size, density, and location [25–27].

To overcome these challenges and enhance the efficacy of chest radiography, the studies introduce the concept of computer-aided detection (CAD) software. Previous studies, including one by Kakeda et al. in 2004, demonstrated the utility of CAD in analyzing radiographs with nodules, albeit with an average false-positive rate of 3.15 per image. The struggle to distinguish true-positive from falsepositive markings limited the improvement in the cancer-detection rate, as de Hoop et al. noted in 2010. Xu et al. (2011) reported that false positives generated by their CAD software were often identified as typical anatomical structures, making them easily dismissible by radiologists. Building on the premise of CAD, the paper introduces a novel approach utilizing a deep convolutional neural network (DCNN) algorithm-based software for detecting malignant pulmonary nodules on chest radiographs. The study involved the evaluation of frontal chest radiographs from four different centers by 12 readers with varying experience levels. The DCNN software demonstrated an overall sensitivity of 67.3% and a low false-positive rate of 0.2 per image. Radiologists exhibited a 5.2% improvement in average sensitivity when re-reviewing radiographs with the assistance of the DCNN software, with one center not showing an increase in sensitivity. The software-aided session successfully detected 15% of previously missed nodules, accompanied by a reduction in false positives per image. The study's findings suggest that the DCNN algorithm-based software can improve the clinical effectiveness of chest radiography in detecting malignant pulmonary nodules. However, the variations in sensitivity improvement among centers indicate potential challenges in generalizability. The reduction in false-positive marks per image is a notable improvement compared to previous CAD software studies [28-30].

The DCNN software not only facilitated the identification of missed nodules but also assisted in dismissing false positives. When considering sensitivity alone, the DCNN software exhibited a sensitivity (67%) comparable to other studies, such as IQQA-Chest Workstation and OnGuard version 5.2, which detected 76% and 78% of lung nodules, respectively. The study's standard of reference is that nodules detected by CT scan might have affected sensitivity, particularly for subtle or non-visible part-solid and ground-glass nodules. The DCNN software's performance alone resembled the average performance of radiologists, with variations among centers potentially linked to differences in difficulty levels. The stand-alone DCNN software demonstrated a significantly lower false-positive rate of 0.2 marks per image than previous studies. The DCNN-based algorithm showed false-positive rates ranging from 0.02 to 0.34 per image, contrasting the higher rates reported in most CAD software studies. This study differed in generalizability, conducting image selection and review with a uniform protocol across four centers on three continents, incorporating diverse nodule phenotypes and patient populations. However, the study had limitations, including the retrospective manual collection of radiographs, spectrum bias due to the exclusion of specific images, and a predetermined nodule size criterion. The study did not adjust for the ratio of abnormal to normal radiographs and lacked a time interval between stand-alone and software-aided sessions, potentially introducing recall bias. The absence of lateral radiographs and the study's selective inclusion criteria may impact external validity. This multicenter study suggests that a commercially available DCNNbased algorithm performed comparable to 12 radiologists in detecting malignant lung nodules on chest radiographs. The DCNN may contribute to reducing false-positive examinations for nodule detection, but further studies with a crossover design are warranted to validate these findings. [30-36] Furthermore, Radiomics, based on mathematical principles, assigns the computer the task of dealing with the various image qualities of CXR. For accurate radiomics data, image augmentation is crucial before nodule detection, involving procedures like pre-processing, lung segmentation [37-39], and rib suppression [40]. Malignancy/benign classification underwent further analysis using distinct algorithms. Decision tree-based algorithms were prevalent before 2011, but deep learning-based algorithms demonstrated their prowess in image analysis thereafter. CheXNet, a deep learning algorithm trained on Chest-Xray14, a vast CXR database, surpassed radiologist performance in detecting 14 pulmonary diseases, including lung nodules and masses, with AUROCs of 0.78 and 0.87, respectively [41]. Subsequent deep learning models improved sensitivity to 0.83 at a false-positive rate of 0.2 per CXR [42]. Presently, several FDA-approved software programs are available [43-45].

Artificial intelligence for detection and characterization of lung cancer CT screening Chest CT Screening

Artificial Intelligence (AI) broadly refers to computer systems that interpret and learn from data to accomplish specific tasks. Deep learning, a methodology enabling computers to learn highdimensional features from extensive data, has significantly advanced AI systems. The breakthrough occurred in 2012 when Krizhevsky et al. successfully implemented a convolutional neural network (CNN), surpassing existing algorithms in the ImageNet Large Scale Visual Recognition Challenge (ILSVRC). This method finds applications in various fields, including autonomous driving, natural language processing, big data analytics, and medical image interpretation. In medical image analysis, CNNs are the preferred methodology, demonstrating performance comparable to or exceeding human capabilities on numerous tasks. The exploration of algorithms for automatic detection and characterization of pulmonary nodules on CT scans began over two decades ago, with a notable surge in studies over the past decade. This escalation can be attributed to the widespread adoption of deep learning, the organization of challenges, the availability of public datasets, and the imminent implementation of lung cancer screening. [46-47]

They are ensured that the minimum quality level is imperative for both human and artificial intelligence (AI) diagnostic assessments of CT scans. In the context of screening, maintaining a low radiation dose is crucial. Historically, high-quality scans with an average effective dose of 1.5 mSv were achievable, particularly in lung cancer screening trials such as the NLST. Technological advancements since 2009 have introduced iterative reconstruction algorithms to clinical practice, offering a significant improvement over filtered back projection by iteratively refining reconstructed images to enhance overall image quality and reduce artifacts. The progress in iterative reconstruction has facilitated the implementation of ultra-low-dose CTs, approaching radiation doses comparable to X-rays for chest scans (approximately 0.5 mSv on average). Deep learning techniques have further contributed to optimizing radiation dose and reconstruction time in recent years. A pilot study demonstrated the visibility of all nodules >2 mm in standard low-dose CT scans replicated in ultralow-dose images. Additionally, an independent study reported higher sensitivity in ultra-low-dose CT with iterative reconstruction compared to low-dose CT with filtered back projection. These findings underscore the potential of integrating deep learning techniques to enhance radiation dose efficiency and image reconstruction in CT scans, offering promising avenues for improved screening outcomes [48-50].

The current landscape of AI algorithms for lung cancer detection on CT scans suggests that they may have reached a performance level comparable to that of radiologists, marking a significant advancement in the field. However, the need for further validation of these claims remains imperative. Previous studies primarily focused on individual performance assessments, needing an exploration of collaborative efforts between AI and radiologists. It is acknowledged that specific tasks pose varying difficulty levels for radiologists and AI algorithms, and collaboration might be advantageous. For example, sub-solid nodules, less contrasting with lung parenchyma, are often challenging for radiologists to detect. Conversely, AI might struggle with irregular nodules due to their rarity in training data.

Three paradigms for human-AI collaboration have been proposed: second reader, concurrent reader, and first reader. In the second reader scenario, the AI aids the radiologist after their initial assessment, allowing for a comprehensive review. Contemporary reading involves immediate access to AI results, influencing real-time image interpretation. The first reader paradigm confines radiologist assessment to AI-detected nodules, enhancing efficiency but potentially missing nodules overlooked by the AI. Several studies have explored the second reader paradigm, demonstrating increased nodule detection

sensitivity. Wormanns et al. [51] showed that a commercial AI system had similar sensitivity to radiologists individually but, as a second reader, exhibited higher sensitivity with an increased false positive rate. Subsequent studies confirmed these findings. In a concurrent reader scenario, a commercial AI system generating a second CT image with suppressed vessels and detected nodules demonstrated increased sensitivity, reduced specificity, and decreased interpretation time. Alternative screening workflow strategies have been explored, such as trained technicians supported by AI for prescreening, showing high sensitivity and specificity, making it a viable option for triaging scans for radiologists. The replacement of radiologists with technicians, supported by AI, offers a potential avenue for more cost-effective and feasible screening, particularly in regions facing a shortage of radiologists. While these collaborative approaches show promise, ongoing research and validation are crucial for their effective integration into routine clinical practice [52-60].

Task	Current state	Next steps
Detection, segmentation and classification	 Numerous publications presenting good performance; Commercial systems are available for clinical use as second or concurrent reader 	 Evaluate the performance of AI for pathologically proven cancers in solid nodules instead of suspicious nodules defined by a consensus of radiologists; Continue evaluation studies with novel deep learning-based AI systems in multi-center studies; Investigate workflows in which AI + trained technicians can triage screening CT scans to be sent for review by radiologists
Malignancy prediction	 Recent publications show performance better than or on par with radiologists; Results from Kaggle DSB 2017 demonstrate the potential of Al for malignancy prediction; No commercial systems available that provide a malignancy risk score 	 Evaluate the effect of an AI risk score on the performance of radiologists; initiate multi-center evaluation studies; Evaluate whether and how an AI risk score can be integrated into nodule follow-up guidelines

Table 1 Summary of the current state and next steps needed for detection and characterization of pulmonary nodules in lung cancer CT screening

Table 1 Summary of the current state and next steps needed for detecting and characterizing pulmonary nodules in lung cancer detection [61].

Table 1 provides an overview of the current status and future directions in identifying and characterizing pulmonary nodules in lung cancer CT screening. Existing literature indicates that advanced AI systems designed for detecting and characterizing lung nodules demonstrate performance levels comparable to those of seasoned radiologists. Numerous AI investigations introduce innovative frameworks for nodule detection in the lungs, with the reference standard established through the consensus of radiologists.

Recent research has indicated that artificial intelligence (AI) is rapidly approaching, if not already achieving, performance levels comparable to radiologists in various tasks essential for the current reporting frameworks in lung cancer screening. In its present state, AI algorithms support radiologists in interpreting CT scans for lung cancer screening. Future investigations should prioritize large-scale validation of innovative deep learning-based algorithms and explore new reading paradigms. If AI-assisted trained readers can efficiently triage regular scans, it could significantly enhance the cost-effectiveness of screening. The impact would be more pronounced if fully autonomous algorithms were allowed to perform triage independently by identifying potentially abnormal CT scans for radiologist review. However, ensuring independent algorithms' safe and responsible use requires more comprehensive implementation than scenarios where a trained reader is still involved [61].

Integrating Artificial Intelligence (AI), Deep Learning (DL), and Whole Slide Imaging in Lung Cancer Diagnosis

The introduction of Whole Slide Imaging (WSI) represents a significant milestone in the evolution of modern digital pathology. WSI relies on specialized slide scanners capable of converting glass slides into high-resolution digital images. Once stored on a server, pathologists can access these digital images on their computers or handheld devices. The approval of two vendors for WSI systems for primary diagnosis by the FDA in 2017 marked a pivotal moment, emphasizing the potential of digital pathology in healthcare [62, 63]. Drawing parallels with DICOM (Digital Imaging and

Communications in Medicine) in diagnostic radiology, efforts have been made to integrate WSI into PACS (Picture Archiving and Communication System) systems, facilitating the seamless adoption of digital pathology in hospitals and promoting information exchange [64,65]. This integration has paved the way for establishing digital pathology networks, enabling the sharing of expertise for consultations and making education accessible across geographical boundaries [66]. Each digital slide generated through WSI is characterized by its large size, potentially containing over 4 billion pixels and exceeding 15 GB when scanned at a resolution of 0.25 micrometers/pixel, equivalent to 40x magnification [67-69]. The massive data generated by WSI opens up new possibilities with recent advancements in Artificial Intelligence (AI) and Deep Learning (DL), particularly in image classification, segmentation, and transformation. This convergence of WSI and AI/DL creates a fertile ground for various applications in cytopathology, expanding the scope of digital pathology beyond traditional diagnostic practices.

Incorporating AI and DL into WSI not only enhances the efficiency of pathologists but also unlocks new avenues for automating complex tasks, such as image classification and segmentation. The combination of WSI and advanced AI techniques holds great promise for revolutionizing the field of cytopathology, potentially improving diagnostic accuracy and expediting pathology workflows. When detecting a lung nodule, obtaining information about its properties is crucial for effective clinical decision-making. The gold standard for determining these properties involves acquiring tissue samples through biopsy or surgery. While imaging features, as discussed earlier, offer insights into the characteristics of the nodule, histopathological features play a significant role in influencing subsequent treatment decisions. In the context of advancing digital technologies in radiology, the advent of whole slide imaging (WSI) has paved the way for digital histopathology. WSI involves capturing high-resolution images of pathology slides, enabling a comprehensive examination of tissue samples. With the digitization of WSI data, artificial intelligence (AI) applications can play a vital role in assisting pathologists with various tasks. This extends beyond traditional pathology practices and encompasses tumor cell recognition and segmentation functions.

Integrating AI into digital histopathology not only aids in automating routine tasks but also holds promise for enhancing the efficiency and accuracy of histopathological analysis. By leveraging AI algorithms, pathologists can streamline their workflow, leading to more precise identification and segmentation of tumor cells. This synergy between AI and digital histopathology exemplifies the ongoing digital transformation in healthcare, offering new avenues for improving diagnostic accuracy and patient care [68]. Coudray [69] showcases the potential of convolutional neural networks, particularly Google's inception v3, as a valuable tool in diagnosing lung cancer from histopathology slides. The neural network exhibited exceptional performance, almost unequivocally classifying typical versus tumor tissues with an AUC of ~0.99 and distinguishing between different lung cancer types with high accuracy (0.97 AUC). The sensitivity and specificity achieved by the model were comparable to those of a pathologist. Notably, the algorithm demonstrated its utility in cases where pathologists faced challenges, correctly classifying whole-slide images that had been misclassified by at least one of the pathologists. The model's high accuracy persisted despite various artifacts in the images related to sample preparation and preservation procedures. While the study's success is evident, further improvement is needed. The dataset used to train the deep neural network might not fully capture the diversity and heterogeneity pathologists observe in routine inspections, potentially lacking features such as necrosis, blood vessels, and inflammation. To enhance performance, additional slides containing these features would be crucial for retraining the network.

The study's application extends beyond simple classification, delving into predicting the mutational status of genes like EGFR, STK11, FAT1, SETBP1, KRAS, and TP53. The model demonstrated predictive capabilities for specific gene mutations, with STK11 mutations being predicted with the highest accuracy (~0.85 AUC). The ability to predict both cancer type and gene mutations quickly and inexpensively from histopathology images holds significant promise for advancing precision medicine. Integrating deep-learning convolutional neural networks into pathology practices is a valuable tool for assisting pathologists in classifying lung tissue whole-slide images. This assistance could be particularly beneficial in speeding up the diagnosis and classification during intraoperative

consultation, acting as an adjunct to telepathology. Looking ahead, the study envisions expanding the classification scope to include other types of less common lung cancers and histological subtypes. Additionally, the algorithm's extension to recognize a broader range of histologic features could provide a quantitative and spatial assessment, aiding pathologists in routine tasks and complex cases. The goal is to enable pathologists to focus on higher-level decisions, integrating histologic, molecular, and clinical information for personalized treatment decisions [70-71]. The future trajectory of AI applications in lung cancer is poised for significant developments, focusing on integration and practical applications. One key challenge addressed in the future outlook is the integration of small datasets to create large datasets for effective training. However, regulations on data sharing pose a substantial obstacle for researchers. A proposed solution is federated learning, which shares trained parameters instead of raw data. This approach involves training models separately at different hospitals, sending only the trained models to a central server, and then reporting the final model back to individual hospitals.

Furthermore, the future landscape of AI applications in lung cancer emphasizes the need for an integrated approach combining various aspects such as radiology, pathology, demographics, clinical data, and old and new technologies. Unlike previous research conducted in separate fields, this holistic integration is believed to reflect the reality of lung cancer better. The concept of multi-omics or "Medomics" is suggested, akin to the multidisciplinary teams in clinical lung cancer treatment. Integrating different domain knowledge and multidisciplinary collaboration is deemed valuable for future advancements [72-75]. Despite promising results in research and FDA approvals for some products, the translation of AI applications into real-world clinical workflows remains a challenge. Issues such as user interface design, data analysis speed, scalability of AI programs, internet bandwidth, and resource consumption pose barriers to practical implementation. The call for constructing more infrastructure is highlighted, indicating that further developments are needed before the widespread adoption of AI-assisted approaches in lung cancer diagnosis and treatment [76-80].

CONCLUSION

The article provides a comprehensive review of integrating artificial intelligence (AI) into lung cancer detection, from screening to diagnosis, focusing on medical imaging and histopathology. The application of AI in the context of lung cancer is particularly crucial due to the challenges associated with late-stage diagnoses and the diverse features present in imaging and histopathology.

Screening Challenges and AI in Lung Cancer Detection

The challenges associated with detecting lung cancer in asymptomatic patients are highlighted, emphasizing the importance of accurate screening methods. The review underscores the superiority of low-dose computed tomography (LDCT) over chest X-rays (CXR) for lung cancer detection. AI is positioned as a solution to enhance the accuracy of LDCT, reducing false-negative rates and improving radiologists' sensitivity. The introduction of computer-aided diagnosis systems and AI-based programs is showcased to alleviate the burden on radiologists and improve overall diagnostic accuracy.

Deep Learning Framework for Chest Radiography Analysis

The article introduces a deep-learning framework for chest radiography analysis, featuring a novel approach using a deep convolutional neural network (DCNN) algorithm-based software. The study evaluates the DCNN software's performance in detecting malignant pulmonary nodules in chest radiographs from four centers. The results suggest that the DCNN software can potentially improve the clinical effectiveness of chest radiography, exhibiting enhanced sensitivity and reduced false-positive rates. However, challenges in generalizability are acknowledged, indicating variations in sensitivity improvement among different centers.

Collaborative Approaches in Chest CT Screening

In the context of chest CT screening, AI algorithms are reported to match or exceed the performance levels of radiologists. Collaborative approaches, such as second-reader paradigms, are explored to improve sensitivity and reduce interpretation time. The article emphasizes ongoing research and validation for effectively integrating these collaborative approaches into routine clinical practice. The potential role of AI-assisted trained readers in triaging regular scans is highlighted for improved cost-effectiveness in screening.

Integration of AI, Deep Learning, and Whole Slide Imaging in Cytopathology

Integrating Whole Slide Imaging (WSI) with AI and deep learning in cytopathology is discussed as a transformative development. WSI, coupled with AI applications, is seen as a tool to enhance the efficiency of pathologists, automating tasks such as image classification and segmentation. The synergy between AI and digital histopathology is portrayed as a means to streamline pathology workflows and improve diagnostic accuracy. The study showcases the success of convolutional neural networks in classifying lung tissue and predicting gene mutations, emphasizing the potential for advancing precision medicine.

Future Trajectory of AI in Lung Cancer

The review outlines the future trajectory of AI applications in lung cancer, emphasizing the challenges of small datasets and proposing federated learning as a solution. The concept of "Medomics," an integrated approach combining various aspects such as radiology, pathology, demographics, and clinical data, is introduced for future developments. Despite promising results, the article acknowledges the challenges in real-world implementation, pointing out issues such as user interface design, data analysis speed, scalability, internet bandwidth, and resource consumption. The call for infrastructure development signals the need for further advancements before the widespread adoption of AI-assisted approaches in lung cancer diagnosis and treatment.

This narrative review provides a comprehensive overview of the current state and future directions of AI applications in lung cancer detection. Integrating AI in medical imaging and histopathology is a promising solution to overcome challenges associated with late-stage diagnoses and the heterogeneity of lung cancer. The review highlights successful applications of AI in screening, chest radiography, chest CT, and cytopathology, showcasing advancements and suggesting avenues for future developments. However, the generalizability, data sharing, and real-world implementation challenges underscore the need for continued research and infrastructure development in AI-assisted lung cancer diagnosis and treatment.

In conclusion, the comprehensive review highlights the challenges posed by late-stage diagnoses and the heterogeneity of lung cancer, emphasizing the limitations of traditional approaches reliant on clinical trials and expert opinions. Integrating artificial intelligence (AI), particularly machine learning (ML) and deep learning, emerges as a transformative solution. AI addresses challenges in lung cancer detection, spanning screening to diagnosis, showcasing its potential in improving accuracy, reducing false-negative rates, and enhancing clinical workflows. The article delves into a deep-learning framework for chest radiography analysis, introducing a novel approach with a deep convolutional neural network (DCNN) algorithm-based software. The DCNN demonstrates effectiveness in detecting malignant pulmonary nodules, although challenges in generalizability are acknowledged. For chest CT screening, AI algorithms achieve performance levels comparable to radiologists, and collaborative approaches, such as concurrent reading and second-reader paradigms, exhibit increased sensitivity.

Integrating AI with Whole Slide Imaging (WSI) transforms cytopathology, enhancing pathologists' efficiency and facilitating tumor cell recognition, segmentation, and prediction of gene mutations. Despite promising results, challenges in real-world implementation are underscored, necessitating infrastructure development. Looking forward, the trajectory of AI in lung cancer emphasizes overcoming challenges through federated learning and proposes "Medomics" for holistic insights, integrating multidisciplinary aspects. While the review showcases advancements and potential, it

acknowledges barriers to real-world implementation, calling for ongoing research, validation, and infrastructure development for practical integration into routine clinical practice. The comprehensive insights in this review underscore the evolving landscape of AI applications in lung cancer detection, with the potential to revolutionize diagnosis and treatment [79-82].

References

- 1. Cancer. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer (accessed on 29 November 2023).
- 2. Migliore, M.; Palmucci, S.; Nardini, M.; Basile, A. Imaging patterns of early stage lung cancer for the thoracic surgeon. J. Thorac. Dis. 2020, 12, 3349–3356. [CrossRef] [PubMed]
- 3. Travis, W.D.; Brambilla, E.; Nicholson, A.G.; Yatabe, Y.; Austin, J.H.M.; Beasley, M.B.; Chirieac, L.R.; Dacic, S.; Duhig, E.; Flieder,
- D.B. et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J. Thorac. Oncol. 2015, 10, 1243–1260. [CrossRef]
- Nicholson, A.G.; Tsao, M.S.; Beasley, M.B.; Borczuk, A.C.; Brambilla, E.; Cooper, W.A.; Dacic, S.; Jain, D.; Kerr, K.M.; Lantuejoul, S.; et al. The 2021 WHO Classification of Lung Tumors: Impact of advances since 2015. J. Thorac. Oncol. 2021, 17, 362–387. [CrossRef]
- 6. Klang, E. Deep learning and medical imaging. J. Thorac. Dis. 2018, 10, 1325–1328. [CrossRef]
- 7. Lawson, C.E.; Marti, J.M.; Radivojevic, T.; Jonnalagadda, S.V.R.; Gentz, R.; Hillson, N.J.; Peisert, S.; Kim, J.; Simmons, B.A.; Petzold, C.J.; et al. Machine learning for metabolic engineering: A review. Metab. Eng. 2021, 63, 34–60. [CrossRef]
- 8. Leiserson, C.E.; Thompson, N.C.; Emer, J.S.; Kuszmaul, B.C.; Lampson, B.W.; Sanchez, D.; Schardl, T.B. There's plenty of room at the Top: What will drive computer performance after Moore's law? Science 2020, 368, eaam9744. [CrossRef]
- 9. Shalf, J. The future of computing beyond Moore's Law. Philos. Trans. A Math. Phys. Eng. Sci. 2020, 378, 20190061. [CrossRef]
- Somvanshi, M.; Chavan, P.; Tambade, S.; Shinde, S. A review of machine learning techniques using decision tree and support vector machine. In Proceedings of the 2016 International Conference on Computing Communication Control and Automation(ICCUBEA), Pune, India, 12–13 August 2016; pp. 1–7
- 11. Sesen, M.B.; Nicholson, A.E.; Banares-Alcantara, R.; Kadir, T.; Brady, M. Bayesian networks for clinical decision support in lung cancer care. PLoS ONE 2013, 8, e82349. [CrossRef]
- Gao, R.; Huo, Y.; Bao, S.; Tang, Y.; Antic, S.L.; Epstein, E.S.; Balar, A.B.; Deppen, S.; Paulson, A.B.; Sandler, K.L. Distanced LSTM: Time-distanced gates in long short-term memory models for lung cancer detection. In International Workshop on Machine Learning in Medical Imaging; Springer: New York, NY, USA, 2019; pp. 310–318.
- In, K.-H.; Kwon, Y.-S.; Oh, I.-J.; Kim, K.-S.; Jung, M.-H.; Lee, K.-H.; Kim, S.-Y.; Ryu, J.-S.; Lee, S.-Y.; Jeong, E.-T. Lung cancer patients who are asymptomatic at diagnosis show favorable prognosis: A Korean Lung Cancer Registry Study. Lung. Cancer 2009, 64, 232–237. [CrossRef]
- Quadrelli, S.; Lyons, G.; Colt, H.; Chimondeguy, D.; Buero, A. Clinical characteristics and prognosis of incidentally detected lung cancers. Int. J. Surg. Oncol. 2015, 2015, 287604. [CrossRef]
- 15. Melamed, M.R.; Flehinger, B.J.; Zaman, M.B.; Heelan, R.T.; Perchick, W.A.; Martini, N. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. Chest 1984, 86, 44–53. [CrossRef]
- Hocking,W.G.; Hu, P.; Oken, M.M.; Winslow, S.D.; Kvale, P.A.; Prorok, P.C.; Ragard, L.R.; Commins, J.; Lynch, D.A.; Andriole, G.L.; et al. Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. J. Natl. Cancer Inst. 2010, 102, 722–731. [CrossRef]
- 17. Chu, G.C.W.; Lazare, K.; Sullivan, F. Serum and blood based biomarkers for lung cancer screening: A systematic review. BMC Cancer 2018, 18, 181. [CrossRef]

- Montani, F.; Marzi, M.J.; Dezi, F.; Dama, E.; Carletti, R.M.; Bonizzi, G.; Bertolotti, R.; Bellomi, M.; Rampinelli, C.; Maisonneuve, P.; et al. miR-Test: A blood test for lung cancer early detection. J. Natl. Cancer Inst. 2015, 107, djv063. [CrossRef]
- 20. Lodwick, G.S.; Keats, T.E.; Dorst, J.P. The Coding of Roentgen Images for Computer Analysis as Applied to Lung Cancer. Radiology1963, 81, 185–200. [CrossRef]
- 21. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lungcancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365(5):395–409.
- 22. White CS, Salis AI, Meyer CA. Missed lung cancer on chest radiography and computed tomography: imaging and medicolegal issues. J Thorac Imaging 1999;14(1):63–68.
- 23. Fardanesh M, White C. Missed lung cancer on chest radiography and computed tomography. Semin Ultrasound CT MR 2012;33(4):280–287.
- 24. Samuel S, Kundel HL, Nodine CF, Toto LC. Mechanism of satisfaction of search: eye position recordings in the reading of chest radiographs. Radiology 1995;194(3):895–902.
- 25. Del Ciello A, Franchi P, Contegiacomo A, Cicchetti G, Bonomo L, Larici AR. Missed lung cancer: when, where, and why? Diagn Interv Radiol 2017;23(2):118–126.
- 26. Kundel HL. Predictive value and threshold detectability of lung tumors. Radiology 1981;139(1):25–29.
- 27. Drayer JA, Vittitoe NF, Vargas-Voracek R, Baydush AH, Ravin CE, Floyd CE Jr. Characteristics of regions suspicious for pulmonary nodules at chest radiography. Acad Radiol 1998;5(9):613–619.
- 28. Austin JH, Romney BM, Goldsmith LS. Missed bronchogenic carcinoma: radiographic findings in 27 patients with a potentially resectable lesion evident in retrospect. Radiology 1992;182(1):115–122.
- 29. Kakeda S, Moriya J, Sato H, et al. Improved detection of lung nodules on chest radiographs using a commercial computer-aided diagnosis system. AJR Am J Roentgenol 2004;182(2):505–510.
- 30. de Hoop B, De Boo DW, Gietema HA, et al. Computer-aided detection of lung cancer on chest radiographs: effect on observer performance. Radiology 2010;257(2):532–540.
- 31. Novak RD, Novak NJ, Gilkeson R, Mansoori B, Aandal GE. A comparison of computer-aided detection (CAD) effectiveness in pulmonary nodule iden tification using different methods of bone suppression in chest radiographs J Digit Imaging 2013;26(4):651–656.
- 32. van Beek EJR, Mullan B, Thompson B. Evaluation of a real-time interactive pulmonary nodule analysis system on chest digital radiographic images: a prospective study. Acad Radiol 2008;15(5):571–575.
- 33. De Boo DW, Uffmann M, Weber M, et al. Computer-aided detection of small pulmonary nodules in chest radiographs: an observer study. Acad Radiol 2011;18(12):1507–1514.
- 34. White CS, Flukinger T, Jeudy J, Chen JJ. Use of a computer-aided detec tion system to detect missed lung cancer at chest radiography. Radiology 2009;252(1):273–281.
- 35. Dellios N, Teichgraeber U, Chelaru R, Malich A, Papageorgiou IE. Computer aided Detection Fidelity of Pulmonary Nodules in Chest Radiograph. J Clin Imaging Sci 2017;7:8.
- 36. Park SH, Han K. Methodologic Guide for Evaluating Clinical Performance and Effect of Artificial Intelligence Technology for Medical Diagnosis and Prediction. Radiology 2018;286(3):800–809.
- Mostafavi, M. and Shabani, M. (2024) Leveraging Nanotechnology for Addressing COVID-19: Revealing Antiviral Approaches and Hurdles. World Journal of Nano Science and Engineering, 14, 1-14. doi: 10.4236/wjnse.2024.141001
- 38. Mehrnaz Mostafavi, Mahsa Alizadeh, Mahtab Shaabani, Hamed Asadi, Metallic nanomaterials in cancer theranostics: A review of Iron oxide and Gold-based nanomaterials (2021) SDRP Journal of Nanotechnology & Material Science 3(1) doi:https://doi.org/10.25177/JNMS.3.1.RA.10736
- 39. Jaeger, S.; Candemir, S.; Antani, S.; Wang, Y.X.; Lu, P.X.; Thoma, G. Two public chest X-ray datasets for computer-aided screening of pulmonary diseases. Quant. Imaging Med. Surg. 2014, 4, 475–477. [CrossRef] [PubMed]

- 40.Nguyen, H.C.; Le, T.T.; Pham, H.; Nguyen, H.Q. VinDr-RibCXR: A Benchmark Dataset for Automatic Segmentation and Labeling of Individual Ribs on Chest X-rays. arXiv 2021, arXiv:2107.01327.
- Rajpurkar, P.; Irvin, J.; Zhu, K.; Yang, B.; Mehta, H.; Duan, T.; Ding, D.; Bagul, A.; Langlotz, C.; Shpanskaya, K. Chexnet: Radiologist-level pneumonia detection on chest x-rays with deep learning. arXiv 2017, arXiv:1711.05225.
- 42. Kim, Y.-G.; Cho, Y.;Wu, C.-J.; Park, S.; Jung, K.-H.; Seo, J.B.; Lee, H.J.; Hwang, H.J.; Lee, S.M.; Kim, N. Short-term reproducibility of pulmonary nodule and mass detection in chest radiographs: Comparison among radiologists and four different computer-aided detections with convolutional neural net. Sci. Rep. 2019, 9, 18738. [CrossRef] [PubMed]
- 43. Tam, M.; Dyer, T.; Dissez, G.; Morgan, T.N.; Hughes, M.; Illes, J.; Rasalingham, R.; Rasalingham, S. Augmenting lung cancer diagnosis on chest radiographs: Positioning artificial intelligence to improve radiologist performance. Clin. Radiol. 2021, 76, 607–614. [CrossRef] [PubMed]
- 44. Kim, J.H.; Han, S.G.; Cho, A.; Shin, H.J.; Baek, S.-E. Effect of deep learning-based assistive technology use on chest radiograph interpretation by emergency department physicians: A prospective interventional simulation- based study. BMC Med. Inform. Decis. Mak. 2021, 21, 311. [CrossRef]
- 45. Van Ginneken, B.; Armato, S.G., III; de Hoop, B.; van Amelsvoort-van de Vorst, S.; Duindam, T.; Niemeijer, M.; Murphy, K.; Schilham, A.; Retico, A.; Fantacci, M.E. Comparing and combining algorithms for computer- aided detection of pulmonary nodules in computed tomography scans: The ANODE09 study. Med. Image Anal. 2010, 14, 707–722. [CrossRef]
- 46. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. Commun ACM 2017;60:84-90. [Crossref]
- 47. Litjens G, Kooi T, Bejnordi BE, et al. A survey on deep learning in medical image analysis. Med Image Anal 2017;42:60-88. [Crossref] [PubMed]
- 48. Willemink MJ, Noël PB. The evolution of image reconstruction for CT-from filtered back projection to artificial intelligence. Eur Radiol 2019;29:2185-95. [Crossref] [PubMed]
- 49. Paks M, Leong P, Einsiedel P, et al. Ultralow dose CT for follow-up of solid pulmonary nodules: A pilot single-center study using Bland-Altman analysis. Medicine (Baltimore) 2018;97:e12019 [Crossref] [PubMed]
- Sui X, Meinel FG, Song W, et al. Detection and size measurements of pulmonary nodules in ultralow-dose CT with iterative reconstruction compared to low dose CT. Eur J Radiol 2016;85:564-70. [Crossref] [PubMed]
- 51. Jacobs C, van Rikxoort EM, Murphy K, et al. Computer-aided detection of pulmonary nodules: a comparative study using the public LIDC/IDRI database. Eur Radiol 2016;26:2139-47. [Crossref] [PubMed]
- 52. Silva M, Schaefer-Prokop CM, Jacobs C, et al. Detection of Subsolid Nodules in Lung Cancer Screening: Complementary Sensitivity of Visual Reading and Computer-Aided Diagnosis. Invest Radiol 2018;53:441-9. [Crossref] [PubMed]
- 53. Roos JE, Paik D, Olsen D, et al. Computer-aided detection (CAD) of lung nodules in CT scans: radiologist performance and reading time with incremental CAD assistance. Eur Radiol 2010;20:549-57. [Crossref] [PubMed]
- 54. Liang M, Tang W, Xu DM, et al. Low-Dose CT Screening for Lung Cancer: Computer-aided Detection of Missed Lung Cancers. Radiology 2016;281:279-88. [Crossref] [PubMed]
- 55. Teague SD, Trilikis G, Dharaiya E. Lung nodule computer-aided detection as a second reader: influence on radiology residents. J Comput Assist Tomogr 2010;34:35-9. [Crossref] [PubMed]
- 56. White CS, Pugatch R, Koonce T, et al. Lung nodule CAD software as a second reader: a multicenter study. Acad Radiol 2008;15:326-33. [Crossref] [PubMed]
- 57. Zhao Y, de Bock GH, Vliegenthart R, et al. Performance of computer-aided detection of pulmonary nodules in low-dose CT: comparison with double reading by nodule volume. Eur Radiol 2012;22:2076-84. [Crossref] [PubMed]

- 58. Lo SB, Freedman MT, Gillis LB, et al. JOURNAL CLUB: Computer-Aided Detection of Lung Nodules on CT With a Computerized Pulmonary Vessel Suppressed Function. AJR Am J Roentgenol 2018;210:480-8. [Crossref] [PubMed]
- 59. Ritchie AJ, Sanghera C, Jacobs C, et al. Computer Vision Tool and Technician as First Reader of Lung Cancer Screening CT Scans. J Thorac Oncol 2016;11:709-17. [Crossref] [PubMed]
- 60. Ghanavi J, Mostafavi M, Ghanavi Z, inventors. Method for the synthesis of metallic nano products. United States patent US 9,487,399. 2016 Nov 8.
- 61.Jalaledin G, Mehrnaz M, inventors. Method for producing rod-shaped and branched metallic nanostructures by polyol compounds. United States patent application US 12/870,792. 2011 Apr 21.
- 62. Evans, A.J.; Bauer, T.W.; Bui, M.M.; Cornish, T.C.; Duncan, H.; Glassy, E.F.; Hipp, J.; McGee, R.S.; Murphy, D.; Myers, C. US Food and Drug Administration approval of whole slide imaging for primary diagnosis: A key milestone is reached and new questions are raised. Arch. Pathol. Lab. Med. 2018, 142, 1383–1387. [CrossRef]
- 63. Abels, E.; Pantanowitz, L. Current state of the regulatory trajectory for whole slide imaging devices in the USA. J. Pathol. Inform. 2017, 8, 23. [CrossRef]
- 64. Niazi, M.K.K.; Parwani, A.V.; Gurcan, M.N. Digital pathology and artificial intelligence. Lancet Oncol. 2019, 20, e253–e261. [CrossRef]
- 65. DICOMWhole Slide Imaging (WSI). Available online: https://dicom.nema.org/Dicom/ DICOMWSI/ (accessed on 29 November 2021).
- 66. Sakamoto, T.; Furukawa, T.; Lami, K.; Pham, H.H.N.; Uegami,W.; Kuroda, K.; Kawai, M.; Sakanashi, H.; Cooper, L.A.D.; Bychkov, A. A narrative review of digital pathology and artificial intelligence: Focusing on lung cancer. Transl. Lung Cancer Res. 2020, 9, 2255. [CrossRef]
- 67. Giovagnoli, M.R.; Giansanti, D. Artificial Intelligence in Digital Pathology: What Is the Future? Part 1: From the Digital Slide Onwards. Healthc. Multidiscip. Digit. Publ. Inst. 2021, 9, 858. [CrossRef]
- 68. Šari'c, M.; Russo, M.; Stella, M.; Sikora, M. CNN-based method for lung cancer detection in whole slide histopathology images. In Proceedings of the 2019 4th International Conference on Smart and Sustainable Technologies (SpliTech), Split, Croatia, 18–21 June2019; pp. 1–4.
- 69.Coudray, N.; Ocampo, P.S.; Sakellaropoulos, T.; Narula, N.; Snuderl, M.; Fenyö, D.; Moreira, A.L.; Razavian, N.; Tsirigos, A. Classification and mutation prediction from non–small cell lung cancer histopathology images using deep learning. Nat. Med. 2018, 24, 1559–1567. [CrossRef]
- 70. Schaumberg, A. J., Rubin, M. A. & Fuchs, T. J. H&E-stainedwhole slide deep learning predicts spop mutation state in prostate cancer. Preprint at https:// doi.org/10.1101/064279 (2016).
- 71. Donovan, M. J. et al. A systems pathology model for predicting overall survival in patients with refractory, advanced non-small-cell lung cancer treated with gefitinib. Eur. J. Cancer 45, 1518–1526 (2009).
- 72. Jochems, A.; Deist, T.M.; Van Soest, J.; Eble, M.; Bulens, P.; Coucke, P.; Dries, W.; Lambin, P.; Dekker, A. Distributed learning: Developing a predictive model based on data from multiple hospitals without data leaving the hospital–a real life proof of concept. Radiother. Oncol. 2016, 121, 459–467. [CrossRef] [PubMed]
- 73. Jochems, A.; Deist, T.M.; El Naqa, I.; Kessler, M.; Mayo, C.; Reeves, J.; Jolly, S.; Matuszak, M.; Ten Haken, R.; van Soest, J. Developing and validating a survival prediction model for NSCLC patients through distributed learning across 3 countries. Int. J. Radiat. Oncol. Biol. Phys. 2017, 99, 344–352. [CrossRef]
- 74. Wang, D.D.; Zhou, W.; Yan, H.; Wong, M.; Lee, V. Personalized prediction of EGFR mutationinduced drug resistance in lung cancer. Sci. Rep. 2013, 3, 2855. [CrossRef]
- 75. Giang, T.-T.; Nguyen, T.-P.; Tran, D.-H. Stratifying patients using fast multiple kernel learning framework: Case studies of Alzheimer's disease and cancers. BMC Med. Inform. Decis. Mak. 2020, 20, 108. [CrossRef]
- 76. Gao, Y.; Zhou, R.; Lyu, Q. Multiomics and machine learning in lung cancer prognosis. J. Thorac. Dis. 2020, 12, 4531. [CrossRef]

- 77. Wissel, D.; Rowson, D.; Boeva, V. Hierarchical autoencoder-based integration improves performance in multi-omics cancer survival models through soft modality selection. bioRxiv 2022. [CrossRef]
- 78. Coory, M.; Gkolia, P.; Yang, I.A.; Bowman, R.V.; Fong, K.M. Systematic review of multidisciplinary teams in the management of lung cancer. Lung Cancer 2008, 60, 14–21. [CrossRef]
- 79. Denton, E.; Conron, M. Improving outcomes in lung cancer: The value of the multidisciplinary health care team. J. Multidiscip. Healthc. 2016, 9, 137–144. [CrossRef] [PubMed]
- 80. Wichmann, J.L.; Willemink, M.J.; De Cecco, C.N. Artificial Intelligence and Machine Learning in Radiology: Current State and Considerations for Routine Clinical Implementation. Investig. Radiol. 2020, 55, 619–627. [CrossRef] [PubMed]
- 81. Mostafavi, M., Ghanavi, J., Shaabani, M., Asadi, H., & Alizadeh, M. (2021). Application of semiconductor nanomaterials in cancer theranostics. J Nanomed Nanotechnol, 12, 563–564. https://www.walshmedicalmedia.com/open-access/application-of-semiconductornanomaterials-in-cancer-theranostics.pdf
- 82. Mostafavi M (2021) A Comparison of Virtual Colonoscopy Methods for Colon Cleansing. Colorec Cancer Vol: 7 No: 5.