TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(2):32-9
DOI: 10.4274/tmsj.galenos.2024.2024-5-1

REVIEW

REVOLUTIONIZING LUNG CANCER CARE: THE MULTIFACETED APPROACH OF ARTIFICIAL INTELLIGENCE, LIQUID BIOPSIES, AND CIRCULATING TUMOR DNA IN SCREENING, DIAGNOSIS, AND PROGNOSIS

Ahmet Arda Ünal, Yiğit Yazarkan, Gamze Sönmez, Ateş Kutay Tenekeci

Hacettepe University School of Medicine, Ankara, TÜRKİYE

ABSTRACT

Screening for lung cancer has been seeing new developments, with a focus on emerging technologies and the integration of artificial intelligence. While low-dose computed tomography shows promise in reducing mortality rates, challenges, especially regarding screening guidelines and radiation exposure, have been known for a long time. Additionally, discrepancies in screening methods across countries have been challenging the necessity of standardized protocols and cost-effective approaches. Liquid biopsy, particularly circulating tumor DNA analysis, presents a promising non-invasive method for early lung cancer detection and monitoring. Recent studies highlight its potential in detecting genetic mutations, predicting treatment responses, and monitoring minimal residual disease. However, standardization and clinical validation are crucial for widespread adoption. Integration of artificial intelligence into lung cancer screening holds significant promise for enhancing accuracy and workflow efficiency, reducing the burden on radiologists. Successful implementation necessitates validation, regulatory approval, and ethical considerations. Collaborative efforts among clinicians, data scientists, engineers, and policymakers are crucial for translating research into practice, ultimately maximizing the impact of artificial intelligence on patient outcomes. Continued research, validation, and collaboration are imperative for realizing the full potential of these advancements and addressing challenges in clinical implementation.

Keywords: Artifical intelligence, circulating tumor DNA, early detection, liquid biopsy, lung cancer

INTRODUCTION

Lung cancer is a serious health condition affecting millions worldwide, challenging both medical professionals and patients alike. As one of the most prevalent and deadly cancers globally, it warrants a thorough examination to understand its complexities, advancements in treatment, and the evolving landscape of hope for those affected (1). Each day, around 340 individuals succumb to lung cancer, a staggering figure nearly 2.5 times higher than the fatalities from colorectal cancer, the second-leading cause of cancer-related deaths (1). According to Cancer Statistics, in 2024, approximately 81% of the 125,070 lung cancer deaths will be directly attributed to cigarette smoking, with an additional 3,500 deaths linked to second-hand smoke exposure (1, 2). While smoking is recognized as a significant risk factor for the development of lung cancer, the incidence of lung cancer in individuals who have never smoked remains steady or is on the rise (3). There are some other risk factors such as marijuana use, asbestos exposure, and electronic cigarettes (4, 5). The connection between marijuana use and lung cancer is uncertain because of contradictory findings, while the association with electronic cigarettes remains unclear, partly due to the influence of prior or concurrent cigarette use and the absence of long-term data (4). Asbestos exposure combines synergistically with tobacco use, leading to higher rates of lung cancer compared to either risk factor alone (5). Additional risk factors include exposure to radon, hormonal factors, and infectious factors (5). Chronic obstructive pulmonary disease

Address for Correspondence: Ahmet Arda Ünal, Hacettepe University Faculty of Medicine, Ankara, TÜRKİYE
e-mail: ahmetunal18@hacettepe.edu.tr
ORCID iD of the authors: AAÜ: 0000-0001-7156-344X; YY: 0009-0000-8989-5207; GS: 0009-0001-3488-0283; AKT: 0009-0007-6224-945X
Received: 06.05.2024 Accepted: 27.06.2024

Cite this article as: Ünal AA, Yazarkan Y, Sönmez G et al. Revolutionizing lung cancer care: the multifaceted approach of artificial intelligence, liquid biopsies, and circulating tumor DNA in screening, diagnosis, and prognosis. Turk Med Stud J. 2024;11(2):32-9.

and a positive family history are also linked to lung cancer, as well as the tobacco exposure (5).

The biological mechanisms driving lung cancer are intricate, and the tumors exhibit significant variability, making their development still not fully comprehended (6). Recent advancements in understanding pathways, detection technologies for actionable genetic abnormalities, and the development of new medications have enabled physicians to customize treatment options. In lung adenocarcinoma, several significant pathways that can be targeted have been recognized, including epidermal growth factor receptor (EGFR), phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin, RAS-mitogen-activated protein kinases, and neurotrophic tropomyosin-receptor kinase/ROS1, anaplastic lymphoma kinase, mesenchymal-epithelial transition factor, human epidermal growth factor receptor 2 (HER2) pathways (7, 8) (Figure 1). Numerous medications targeting these pathways have been created and have demonstrated clinical advantages (9). However, despite the disease control provided by targeted therapy in non-small cell lung cancer (NSCLC), tumors inevitably develop resistance to drugs (9). Understanding the mechanisms of resistance and creating combination therapies are crucial for enhancing treatment outcomes (9). Despite challenges, in recent years, the use of immune-checkpoint inhibitors, primarily monoclonal antibodies that hinder the inhibitory immune checkpoints cytotoxic T-lymphocyte associated protein 4 (CTLA4) and programmed cell death protein 1 (PD-1), along with its ligand programmed cell death protein ligand 1 (PD-L1), have transformed the approach to treating advanced-stage NSCLC (7). These treatments offer long-lasting disease management for specific patients, whether utilized independently or in conjunction with other therapies, reshaping the treatment landscape (7).

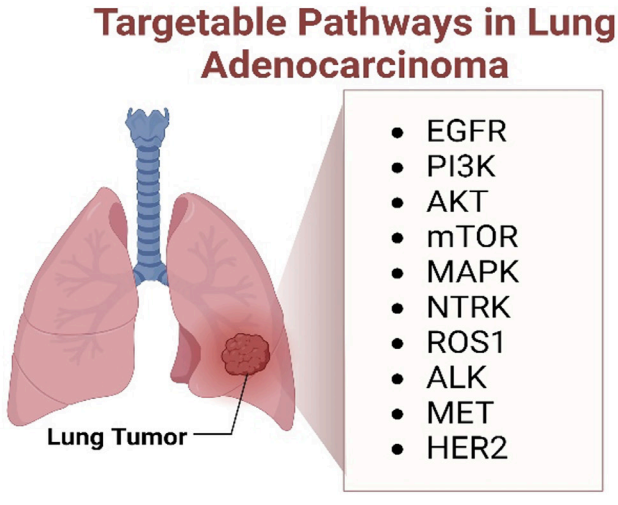

Figure 1: Targetable pathways in lung adenocarcinoma. Created with BioRender.com.
EGFR: Epidermal growth factor receptor, PI3K: Phosphatidylinositol 3-kinase, mTOR: Mammalian target of rapamycin, MAPK: RAS-mitogen-activated protein kinases, NTRK: Neurotrophic tropomyosin-receptor kinase, ALK: Anaplastic lymphoma kinase, MET: Mesenchymal-epithelial transition factor, HER2: Human epidermal growth factor receptor 2

In this review we aim to discuss the latest developments in the diagnosis of lung cancer, worldwide screening programs, and the role of artificial intelligence (AI).

Lung Cancer Screening in the World

Early detection through screening holds the promise of reducing lung cancer mortality by facilitating timely intervention, enabling curative treatments, and improving overall survival (OS) rates. Numerous research endeavors have delved into the significance of low-dose computed tomography (LDCT), with the most extensive being the National Lung Screening Trial (NLST) (10-14). In 2011, this trial revealed that there was a 20% reduction in lung cancer mortality (with a 95% confidence interval ranging from 6.8% to 26.7%) (10, 14). More recently, another randomized clinical trial, Nederlands Leuvens Screening Onderzoek (NELSON), concluded that there was a notable decrease in lung cancer mortality among individuals who received volume computed tomography (CT) screening compared to those who did not undergo any screening (11). A recent cohort study by Silvestri et al. (12) found that there was a notable shift towards detecting early-stage lung cancer, which was significant. However, adherence to lung cancer screening (LCS) was lacking, which likely influenced the lower-than-anticipated rate of cancer detection (12).

Screening for lung cancer is most beneficial when focused on individuals with a high risk of developing the disease, and there are various methods available to pinpoint these high-risk individuals. The NLST and NELSON studies employed straightforward criteria to identify individuals at high risk (10, 11). NLST targeted individuals aged 55-74 years who had smoked at least 30 pack-years and, if they quit, had done so within the last 15 years (10). NELSON focused on individuals aged 50-74 years who had a history of smoking more than 15 cigarettes per day for over 25 years or over 10 cigarettes per day for over 30 years, with recent quitters within the past 10 years also included (11).

In any screening program, it is crucial that the advantages outweigh the drawbacks. There are unique challenges specific to LDCT LCS, such as effectively stratifying the risk of potential participants, managing radiation exposure, and handling incidental findings. Moreover, for a screening program requiring extensive infrastructure, considerations of cost-effectiveness and workforce are crucial. While data on these matters exists within LCS trials, variations in methods and healthcare systems among studies make it challenging to directly apply results across different screening populations. The introduction of different guidelines aims to standardize the reporting and handling of findings from screenings, potentially lowering both harms and expenses (13).

Screening methods may differ in different countries (15). In Japan, systematic screening has been provided to all individuals within the specified target demographic (men and women aged 40-79 years) using chest X-rays and sputum cytology (16). Despite randomized controlled trials conducted in the United States of America and Europe indicating that chest radiography

is ineffective and that LDCT is effective in reducing mortality, Japan continues to advocate for X-rays and sputum cytology (16). LCS methods among countries and their advantages/disadvantages are shown in Table 1.

Current Methods in Lung Cancer Screening

In 2013, the United States Preventive Services Task Force (USPSTF), largely influenced by findings from the NLST, endorsed yearly LDCT screening for individuals aged 55 to 80 years with a minimum 30 pack-year smoking history, regardless of current smoking status or having quit within the previous 15 years (17). These guidelines were broadened following the more recent NELSON trial outcomes, which demonstrated reduced lung cancer mortality with LDCT in a population with a lower overall risk, as well as insights gleaned from sophisticated modeling studies (11). The current USPSTF recommendation for LCS now extends to adults aged 50 to 80 years with at least a 20 pack-year smoking history, including current smokers or those who quit within the past 15 years (18). In 2022, the Centers for Medicare and Medicaid Services assessed the evidence for Medicare coverage of LCS, adopting similar eligibility criteria, albeit with a slightly lower upper age limit of 77 years instead of 80 (19).

The current standards not only widen the scope of eligibility and accessibility for LCS compared to the 2013 guidelines but also demonstrate potential for improved health outcomes at the population level (2). Computational modeling indicates that annual screening of individuals meeting the revised USPSTF criteria could yield a 13.0% decrease in lung cancer mortality, preventing 503 lung cancer fatalities and accumulating 6918 additional life-years per 100,000 individuals aged 45 to 90 years over their screening lifespan (3). By contrast, adherence to the 2013 USPSTF recommendations was projected to achieve a 9.8% reduction in lung cancer mortality, averting 381 lung cancer-related deaths and accumulating 4882 extra life-years per 100,000 individuals in the same demographic (20, 21).

In 2016, the Ministry of Health (MoH) in Türkiye organized an LCS workshop, highlighting the significance of community screening due to the epidemiological profile of lung cancer in the country (22). Despite consensus on the importance of screening, the feasibility of a nationwide program was questioned due to occupational and environmental exposures, as well as concerns about false-positive results and overdiagnosis, particularly in regions endemic to tuberculosis infection (23). Consequently, it was decided to initiate a regional pilot study in the Aegean region (23). As of now, Türkiye does not have an official LCS program in place for high-risk or former smokers (23).

Despite the documented clinical benefits of LDCT LCS recommended by the USPSTF, reports indicate significant underutilization (24). The lack of widespread adoption of LDCT screening since its inception stems from a multitude of factors. Following the release of the NLST and NELSON findings and subsequent guideline recommendations, LCS has remained

Table 1. Lung cancer screening methods among countries and their advantages/disadvantages (15).

Country	Screening method	Advantages	Disadvantages
Japan	X-ray to men and women aged 40-79 years	High participation to screening (50% of eligible population) Lower dose of radiation	Population's negative attitude towards radiation X-ray based screening needs confirmation with CT and this leads to both extra cost and radiation
United States of America	Low dose CT to 50-80 years of age with a 20 pack-year smoking history	High number of CT machines in the country Physicians are educated about screening	Low participation due to its cost (5% of eligible population) No discussion with GPs after the screening
China	Low dose CT to 50-74 years with a 20 pack-year smoking history who are current smokers or quit in the past 5 year	Low cost of CT in the country High awareness towards lung cancer in the country Free access to any hospital in the country	Low trust to doctors in the society High number of patients living in rural areas Low number of CT machines in the rural parts of the country.
South Korea	Low dose CT to current smokers aged 54-74 years with a 30 pack-year smoking history	Political support towards screening Low cost of the CT	Low participation of patients due to "lack of time" Physician awareness is low about screening
Canada	Low dose CT to 55-74 years of age who are currently or have previously smoked and have a 20 pack-year smoking history	Government support towards screening Low cost of CT High number of CT machines in the country	Lack of knowledge among citizens due to its newer implantation Lack of data about cost, participation rate etc.

CT: Computed tomography, LCS: Lung cancer screening, GP: General practitioner

a subject of contention among healthcare providers due to uncertainties surrounding its applicability, associated costs, benefits, and false positive rates (25).

Primary care providers' role in cancer screening, including assessing eligibility and making referrals, contributes to the low rate of LCS (26, 27). Challenges such as limited knowledge of LDCT screening and competing patient health concerns hinder referral rates, along with inconsistent recommendations from primary care societies (26, 27). Additional concerns surrounding LCS involve issues regarding insurance coverage and cost-effectiveness. LDCT has been determined to be cost-effective, as evidenced by seven separate analyses showing an effectiveness ratio of US $100,000 or less per quality-adjusted life years gained (28). Patients' psychosocial characteristics and attitudes towards cancer screenings also contribute significantly to underutilization. LCS presents unique challenges compared to established cancer screenings due to the perceived stigma surrounding it as a disease primarily caused by smoking, which can deter individuals from seeking screening (29). Therefore, considering these negative aspects and utilizing evidence-based data, the development of new screening methods could enhance the effectiveness of screening programs.

The Newest Methods in Lung Cancer Screening

Liquid Biopsy

Liquid biopsy is a recent technology in oncology, especially important in the treatment of lung cancer, the leading cause of cancer-related deaths globally (1). This new non-invasive approach analyzes circulating biomarkers in the blood, such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomes and microRNAs, providing vital information (30). This method allows us to understand tumor behavior, which can alter treatment strategies tailored to the individual characteristics of each cancer patient. The utilization of liquid biopsy in lung cancer is important, given the disease's typical late diagnosis and poor prognosis. With early detection of cancer through sensitive identification of ctDNA or other biomarkers, liquid biopsy has the potential to initiate early treatment, significantly improving patient survival rates. As liquid biopsy technology advances, it becomes increasingly precise, cost-effective, and integral to standard cancer care protocols. The capacity of liquid biopsy to detect a wide range of biomarkers, such as mutations, rearrangements, methylations, and changes in gene expression, provides an integrated view of the genetic landscape of cancer. These developments enhance lung cancer therapy, moving toward a more targeted, effective, and minimally invasive approach to managing one of the most challenging diseases in modern medicine (30).

Circulating Tumor DNA

With these new technologies, ctDNA via liquid biopsies represents a transformative approach that augments traditional cancer detection and monitoring methods. This non-invasive technique provides genomic profiling of tumors, which is necessary in the era of precision medicine (31). Utilizing ctDNA analysis shows promising data in several key areas: early detection of malignancy and minimal residual disease (MRD), assessing the dynamic genetic landscape of tumors in response to therapy, and predicting responses to immunotherapy (31). The ability of ctDNA testing to detect genetic mutations and alterations in blood samples allows oncologists to overcome the limitations of standard tissue biopsies. Moreover, liquid biopsies offer an integrated view of tumor heterogeneity and provide insights into tumor genetics' evolutionary pathways, thereby allowing for personalized treatment adjustments that have the potential to improve patient outcomes (31). With their promising applications, the sensitivity and specificity of ctDNA assays require standardization and clinical validation to realize their potential in routine clinical practice (31).

A recent study investigated the role of ctDNA as both a diagnostic and a prognostic tool in lung cancer (32). It included 211 individuals suspected of having lung cancer, with 192 ultimately participating (32). These participants, who had an average age of 63 years, provided blood samples before surgery (32). The results showed the test had a sensitivity of 75% and a specificity of 89%, revealing it has reasonable specificity but moderate sensitivity for diagnosing lung cancer (32). The test's positive predictive value was 98%, highlighting its power in the detection of cancer presence (32). However, its negative predictive value was only 35%, indicating a limitation in excluding cancer when no ctDNA is found (32). A meta-analysis from Qiu et al. (33) analyzed data from 27 studies involving 3110 participants, mainly from Asia, to assess the effectiveness of ctDNA in detecting EGFR mutations in NSCLC. The results showed that the ctDNA test has a sensitivity of 62% and a specificity of 95.9%. This supports ctDNA as a non-invasive alternative to tissue biopsy for guiding EGFR-Tyrosine kinase inhibitors therapy in NSCLC (33).

Minimal residual disease in NSCLC can be defined as micrometastases that remain after initial therapy (34). MRD may be the cause of a metastatic relapse at other locations. Although MRD monitoring and detection are frequently used in patients with hematological malignancies, they can be difficult to sample in patients with solid tumors because of the low concentrations of CTCs, or components released into the bloodstream by cancer cells (34). A meta-analysis evaluates the effectiveness of ctDNA for detecting MRD in lung cancer (35). The meta-analysis investigated ctDNA MRD detection methods, including tumor-informed and tumor-agnostic approaches, across different stages of lung cancer (35). Findings showed moderate sensitivity and high specificity for ctDNA MRD predicting lung cancer recurrence (35). A recent study by Chen et al. (36) explored the application of ctDNA to detect gene mutations in patients with early-stage NSCLC through targeted sequencing. Results showed that this non-invasive method is especially beneficial in early-stage NSCLC, where traditional biopsy techniques may fail (36). The research demonstrated that ctDNA screening has a sensitivity of 53.8% and a specificity of 47.3% (36).

Circulating tumor DNA can also be used to monitor the efficacy of immunotherapy for NSCLC (37). A study was designed with 28 patients who received PD-1 or PD-L1 inhibitors (37). Then, next-generation sequencing was used to measure changes in ctDNA, defined by a greater than 50% reduction in the mutant allele fraction from the baseline, confirmed by a subsequent measurement (37). Notably, ctDNA provided an early indication of treatment response, with a median time to initial response of 24.5 days compared to radiographic responses, which were 72.5 days, illustrating ctDNA's faster detection capacity (37). Furthermore, patients demonstrating a ctDNA response experienced significantly extended progression-free survival, with a hazard ratio of 0.29, and improved OS, with a hazard ratio of 0.17 (37).

DNA methylation alterations, together with other tumor-derived characteristics, are emerging as promising biomarkers for lung cancer (38, 39). A recent study focuses on developing and validating a ctDNA methylation-based assay to aid in the early detection and diagnosis of lung cancer (40). This case-control study has participants from various clinical centers, including patients with lung cancer, benign lung disease, and healthy individuals (40). A quantitative polymerase chain reaction assay, LunaCAM, was created in two models: LunaCAM-S for screening, prioritizing sensitivity, and LunaCAM-D for diagnostic aid, emphasizing specificity (40). The validation of these models involved profiling DNA methylation on 429 plasma samples, yielding significant markers capable of distinguishing lung cancer from benign diseases and healthy conditions with high accuracy (40). In one meta-analysis of the diagnostic performance of methylated ctDNA for lung cancer detection, data from 33 studies were analyzed to assess the effectiveness of methylated ctDNA as a diagnostic biomarker (41). The results revealed variability in sensitivity and specificity across different studies, with a summary sensitivity estimate of 46.9% and a summary specificity estimate of 92.9% (41). The diagnostic odds ratio was 11.5, indicating the diagnostic power of methylated ctDNA in distinguishing lung cancer cases from controls (41). The area under the hierarchical summary receiver operating characteristic curve was 0.81, demonstrating sufficient diagnostic ability (41).

Circulating tumor DNA detection tests also predict the survival outcomes of patients (42). Assaf et al. (43) used ctDNA to predict survival outcomes in patients with metastatic NSCLC. This phase 3 IMpower150 trial involves 466 patients and assesses ctDNA at five different time points using a machine learning model to predict OS (43). The model demonstrated the capability to stratify patients into high-risk and low-intermediate-risk groups based on ctDNA levels, with differences in median survival times (43). Patients identified as high-risk based on early ctDNA levels had a median OS of 7.1 months, compared to 22.3 months for those in low-intermediate-risk categories (43). ctDNA screening can also be used in disease monitoring, and it has shown promising results (44).

Artificial Intelligence

Artificial intelligence (AI) is becoming an important aspect in the field of lung cancer detection (45, 46). AI algorithms that have been trained on different datasets of medical images can both help radiologists and clinicians, easing their workload and improving patient care (45, 46). AI models can be used in various ways to detect lung cancer (45, 46).

Low-dose CT scans (LDCT) are critical for reducing mortality in lung cancer, however, repeated CT scans can have some radiation-associated risks (47, 48). Deep-learning reconstruction (DLR) offers a novel approach by extracting true information from low-quality images, improving image quality without trade-offs (47, 48). These models were used during the Coronavirus Disease of 2019 pandemic (49). Another model, ClariCT.AI (ClariPI), shows promising results in post-processing imaging, particularly for ultra-LDCT (50). DLR is becoming a reconstruction method for LDCTs, improving accuracy in measuring lung nodule sizes while reducing radiation exposure, especially for long-term follow-up patients (50).

Artificial intelligence used in this field is generally called Computer-aided Diagnostic (CAD) systems. The CAD system plays a critical role in LCS, particularly with the increasing use of LDCT for early detection (51). These systems rely on radiological images, typically collected from public databases like LIDC-IDRI, LUNA16, ELCAP, and ANODE09 (51). These public databases provide a diverse range of CT scans with lung nodules, facilitating the development and training of CAD algorithms. LIDC-IDRI, established by the National Cancer Institute, is a widely utilized database containing chest CT scans annotated by expert radiologists. LUNA16 is another publicly available dataset specifically designed for training deep learning algorithms for lung nodule detection. CAD systems help radiologists by reducing observational errors, providing a second opinion, and improving the diagnostic process (52, 53).

Convolutional neural networks (CNNs) are examples of CAD systems that were developed in a multidisciplinary fashion, demonstrating high sensitivity in nodule detection and aiding specialists in the diagnostic process (46). Chi et al. (54) developed a CNN-based system achieving a precision of 88%, a sensitivity of 89%, and a specificity of 96%. Nasrullah et al. (55) utilized CMixNet, achieving a sensitivity of 94% and a specificity of 91%, analyzing nodules for classification as benign or malignant. Other approaches, combining CNNs and data augmentation, achieved an accuracy of 95% (45, 46). Hybrid networks combining CNNs with novel three-dimentional (3D) frameworks like IR-UNet++ feature extraction techniques can achieve remarkable accuracy in the categorization of lung histopathology images (45, 46, 56). Cai et al. (57) employed MaskRCNN for nodule identification with a sensitivity of 88.70% and provided segmentation and 3D visualization capabilities. Manickavasagam et al. (58) developed a CNN with five convolutional layers that reached high accuracy, sensitivity, and specificity.

After nodule detection, lung nodule segmentation presents challenges due to its small size and proximity to edges or vessels (59). Various segmentation systems, like U-Net and fully CNN, are aiming to improve accuracy in that area (59). Different algorithms were being developed for segmenting a lung nodule (59). These models prioritize enhancing nodule boundaries, especially near blood vessels and the pleural tissue (59). Pezzano et al. (60) introduced a U-Net-based model with the Multiple Convolutional Layers module, improving boundary definition. Dong et al. (61) incorporated voxel and shape heterogeneity properties, capturing variations in gray voxel values effectively. Al-Shabi et al. (62) achieved outstanding results compared to other models, with an area under the curve of 95.62%. These models are making significant advancements in lung nodule segmentation, particularly in challenging cases. By recognizing these subtle patterns and abnormalities that may not be seen with the human eye, AI systems hold the potential to revolutionize LCS and diagnosis (46).

Virtual biopsy methods that use the spatial and temporal heterogeneity of the tissues surrounding the solid tumors are currently being developed. These virtual biopsy methods use deep learning methods to detect non-invasive radiomic signals or biological features related to clinical outcomes (63, 64). The main goal is to replace surgical biopsies and histopathologic analysis. Additionally, these techniques are advancing the development of a personalized medical system. At the Mayo Clinic in Rochester, Lee et al. (65) developed a machine-learning technique known as Computer-Aided Nodule Analysis and Risk Yield (CANARY). CANARY discovered nine distinct radiomic signals defining the lung cancer spectrum (65). CANARY as a virtual biopsy technique correlates directly with adenocarcinoma invasion (65). In their study, Lafata et al. (66) discovered that tumors exhibiting greater homogeneity and attenuation on CT imaging were associated with detectable ctDNA TP53 mutations and stable alterations in ctDNA content during the early stages of therapy.

These models are not only used for nodule detection and segmentation but also for clinical outcomes. AI models were being developed to interpret medical data, predict tumor metastasis, guide treatment decisions, and assess patient prognosis. These new models are also offering personalized medicine approaches to patients (45, 46). They are aiding clinicians in the management, diagnosis, and prediction of treatment outcomes. A model developed by Pérez-Morales et al. (67) estimated lung cancer patients' outcomes when the tumor was identified during screening by using radiomic properties from the intratumoral and peritumoral regions. Yu et al. (68) created a model to predict the mortality risk of patients after first-line treatment by using data from patients who had undergone surgery for stage I NSCLC. Cousin et al. (69) conducted a study aiming to identify a CT-based delta-radiomics signature for distinguishing individuals who are likely to benefit from PD-1/PD-L1 inhibitors in advanced or recurrent NSCLC.

Interdisciplinary research efforts combining radiomics, digital pathology, and machine learning hold promise for further advancements in lung cancer diagnosis and prognosis. AI applications for LCS are shown in Table 2.

The Road Ahead

Advancements in AI offer the potential to actualize harder tasks such as identifying image-based biomarkers and detecting lung nodules, which is another step towards personalized medicine. By enabling non-invasive and repeatable cancer detection, these innovations promise to enhance therapeutic management significantly.

To fully realize the benefits of AI in healthcare, there's a need for platforms that select various AI applications and integrate AI technology into medical systems. This integration is crucial for making AI a routine part of medical practice. There is also a need for future AI applications in LCS protocols to optimize the entire screening process (45, 46). This includes:

- Personalized risk assessment: Pre-screening AI applications will assess individual risk factors to optimize patient eligibility criteria.
- Low-dose imaging protocols: With deep learning-based algorithms, image selection will employ low-dose protocols to maintain high image quality while minimizing radiation exposure.
- Automated nodule detection: AI systems will automate the detection of lung nodules, reducing the workload on radiologists.
- Nodule characterization: Following detection, AI will aid in characterizing nodules as benign or malignant, optimizing resource utilization, and minimizing the likelihood of unnecessary biopsies or surgeries.

Table 2. Artificial intelligence applications for lung cancer screening

Function of the AI model	AI application
Reducing the radiation and true information extraction from the image	ClariCT.AI (ClariPI) (50)
Lung nodule detection (Computer-Aided Diagnostic Systems)	LIDC-IDRI (51, 52, 53)
	LUNA16 (51, 52, 53)
	ELCAP (51, 52, 53)
	ANODE09 (51, 52, 53)
Nodule detection and 3D visualization (Convolutional Neural Networks)	CMixNet (55)
	IR-UNet++ (45, 46, 56)
	MaskRCNN (57)
Nodule segmentation	UNet (59, 60)
	FCN (61, 62)
Virtual biopsy	CANARY (65)
Models designed for clinical outcomes	Perez-Morales et al. (67)
	Yu et al. (68)
	Cousin et al. (69)

FCN: Fully Convolutional Network

While the potential of AI in LCS is unlimited, several challenges be addressed to unearth its full benefits. Integration of AI algorithms into existing healthcare workflows requires careful validation, regulatory approval, and implementation strategies to ensure seamless adoption and compatibility with clinical practice. Also, the ethical and legal implications of AI in healthcare, including data privacy, transparency, and accountability, must demand careful consideration. Regulatory guidelines are essential to protect patient rights and ensure the responsible development of AI technologies in the medical field (46).

Collaboration between interdisciplinary teams of clinicians, data scientists, engineers, and policymakers is crucial to driving innovation into the real world. With partnerships between academia, industry, and healthcare institutions, AI's impact on LCS and beyond will be immense (70).

CONCLUSION

In summary, innovative technologies and analytical methods are transforming our approach to lung cancer management, offering new areas for early detection, personalized treatment, and improved patient outcomes. However, ongoing research and collaboration are crucial to maximizing the potential and addressing the potential risks of these groundbreaking advancements in clinical practice.

Ethics Committee Approval: *N/A*

Informed consent: N/A

Conflict of Interest: *One author of this article, Ateş Kutay Tenekeci, is a member of the editorial board of the Turkish Medical Student Journal. However, he did not take part in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.*

Author Contributions:

Concept: A.A.Ü., Design: A.A.Ü., Literature Search: A.A.Ü., Y.Y., G.S., A.K.T., Writing: A.A.Ü., Y.Y., G.S., A.K.T.,

Financial Disclosure: *The authors declared that this study received no financial support.*

REFERENCES

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12-49. [Crossref]
2. Islami F, Goding Sauer A, Miller KD et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68(1):31-54. [Crossref]
3. LoPiccolo J, Gusev A, Christiani DC et al. Lung cancer in patients who have never smoked - an emerging disease. Nat Rev Clin. Oncol 2024;21(2):121-46. [Crossref]
4. de Groot PM, Wu CC, Carter BW et al. The epidemiology of lung cancer. Transl Lung Cancer Res. 2018;7(3):220-33. [Crossref]
5. Pallis AG, Syrigos KN. Lung cancer in never smokers: disease characteristics and risk factors. Crit Rev Oncol Hematol. 2013;88(3):494-503. [Crossref]
6. Sinjab A, Rahal Z, Kadara H. Cell-by-cell: unlocking lung cancer pathogenesis. Cancers (Basel). 2022;14(14):3424. [Crossref]
7. Fresno Vara JA, Casado E, de Castro J et al. PI3K/Akt signalling pathway and cancer. Cancer Treat Rev. 2004;30(2):193-204. [Crossref]
8. Fumarola C, Bonelli MA, Petronini PG et al. Targeting PI3K/AKT/mTOR pathway in non-small cell lung cancer. Biochem Pharmacol. 2014;90(3):197-207. [Crossref]
9. Yuan M, Huang LL, Chen JH et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther. 2019;4:61. [Crossref]
10. National Lung Screening Trial Research Team; Aberle DR, Adams AM et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. [Crossref]
11. de Koning HJ, van der Aalst CM, de Jong PA et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020;382(6):503-13. [Crossref]
12. Silvestri GA, Goldman L, Tanner NT et al. Outcomes from more than 1 million people screened for lung cancer with low-dose CT imaging. Chest. 2023;164(1):241-51. [Crossref]
13. Dickson JL, Horst C, Nair A et al. Hesitancy around low-dose CT screening for lung cancer. Ann Oncol. 2022;33(1):34-41. [Crossref]
14. Adams SJ, Stone E, Baldwin DR et al. Lung cancer screening. Lancet. 2023;401(10374):390-408. [Crossref]
15. Poon C, Wilsdon T, Sarwar I et al. Why is the screening rate in lung cancer still low? A seven-country analysis of the factors affecting adoption. Front Public Health. 2023;11:1264342. [Crossref]
16. Horinouchi H, Kusumoto M, Yatabe Y et al. Lung cancer in Japan. J Thorac Oncol. 2022;17(3):353-61. http://doi.org/10.1016/j.jtho.2021.11.020 [Crossref]
17. Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160(5):330-8. [Crossref]
18. US Preventive Services Task Force; Krist AH, Davidson KW et al. Screening for lung cancer: US Preventive Services Task Force recommendation statement. JAMA. 2021;325(10):962-70. [Crossref]
19. National Coverage Analysis. Screening for lung cancer with low dose computed tomography. 2015 February 5. Available from: [Crossref]
20. Oken MM, Hocking WG, Kvale PA et al. Screening by chest radiograph and lung cancer mortality: the prostate, lung, colorectal, and ovarian (PLCO) randomized trial. JAMA. 2011;306(17):1865-73. [Crossref]
21. Meza R, Jeon J, Toumazis I et al. Evaluation of the benefits and harms of lung cancer screening with low-dose computed tomography: modeling study for the US preventive services task force. JAMA. 2021;325(10):988-97. [Crossref]
22. Turkey cancer control programme. 1st ed. Ankara Republic of Turkey Ministry of Health Turkey Public Health Institution Cancer Control Department; 2016. [Crossref]
23. Cangır AK, Yumuk PF, Sak SD et al. Lung cancer in Turkey. J Thorac Oncol. 2022;17(10):1158-70. [Crossref]
24. Sorscher S. Inadequate uptake of USPSTF-recommended low dose CT lung cancer screening. J Prim Care Community Health. 2024,15:21501319241235011. [Crossref]
25. De Koning H, Van Der Aalst C, Ten Haaf K et al. PL02.05 effects of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population-based trial. J Thorac Oncol. 2018;13(Suppl 10):185. [Crossref]
26. Triplette M, Kross EK, Mann BA et al. An assessment of primary care and pulmonary provider perspectives on lung cancer screening. Ann Am Thorac Soc. 2018;15(1):69-75. [Crossref]
27. Pham D, Bhandari S, Pinkston C et al. Lung cancer screening registry reveals low-dose CT screening remains heavily underutilized. Clin Lung Cancer. 2020;21(3):206-11. [Crossref]
28. Puggina A, Broumas A, Ricciardi W et al. Cost-effectiveness of screening for lung cancer with low-dose computed tomography: a systematic literature review. Eur J Public Health. 2016;26(1):168-75. [Crossref]
29. Quaife SL, Marlow LAV, McEwen A et al. Attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities: informing screening communication. Health Expect. 2017;20(4):563-73. [Crossref]
30. Revelo AE, Martin A, Velasquez R et al. Liquid biopsy for lung cancers: an update on recent developments. Ann Transl Med. 2019;7(15):349. [Crossref]
31. Gobbini E, Swalduz A, Levra MG et al. Implementing ctDNA Analysis in the clinic: challenges and opportunities in non-small cell lung cancer. Cancers (Basel). 2020;12(11):3112. [Crossref]
32. Leung M, Freidin MB, Freydina DV et al. Blood-based circulating tumor DNA mutations as a diagnostic and prognostic biomarker for lung cancer. Cancer. 2020;126(8):1804-9. [Crossref]

33. Qiu M, Wang J, Xu Y et al. Circulating tumor DNA is effective for the detection of EGFR mutation in non-small cell lung cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2015;24(1):206-12. [Crossref]
34. Frisone D, Friedlaender A, Addeo A. The role and impact of minimal residual disease in NSCLC. Curr Oncol Rep. 2021;23(12):136. [Crossref]
35. Zhong R, Gao R, Fu W et al. Accuracy of minimal residual disease detection by circulating tumor DNA profiling in lung cancer: a meta-analysis. BMC Med. 2023;21(1):180. [Crossref]
36. Chen KZ, Lou F, Yang F et al. Circulating tumor DNA detection in early-stage non-small cell lung cancer patients by targeted sequencing. Sci Rep. 2016;6:31985. [Crossref]
37. Goldberg SB, Narayan A, Kole AJ et al. Early assessment of lung cancer immunotherapy response via circulating tumor DNA. Clin Cancer Res. 2018;24(8):1872-80. [Crossref]
38. Mathios D, Johansen JS, Cristiano S et al. Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nat Commun. 2021;12(1):5060. [Crossref]
39. Cristiano S, Leal A, Phallen J et al. Genome-wide cell-free DNA fragmentation in patients with cancer. Nature. 2019;570(7761):385-9. [Crossref]
40. Wang Z, Xie K, Zhu G et al. Early detection and stratification of lung cancer aided by a cost-effective assay targeting circulating tumor DNA (ctDNA) methylation. Respir Res. 2023;24(1):163. [Crossref]
41. Jee J, Lebow ES, Yeh R et al. Overall survival with circulating tumor DNA-guided therapy in advanced non-small-cell lung cancer. Nat Med. 2022;28(11):2353-63. [Crossref]
42. Borg M, Wen SWC, Andersen RF et al. Methylated circulating tumor DNA in blood as a tool for diagnosing lung cancer: a systematic review and meta-analysis. Cancers (Basel). 2023;15(15):3959. [Crossref]
43. Assaf ZJF, Zou W, Fine AD et al. A longitudinal circulating tumor DNA-based model associated with survival in metastatic non-small-cell lung cancer. Nat Med. 2023;29(4):859-68. [Crossref]
44. Jung HA, Ku BM, Kim YJ et al. Longitudinal monitoring of circulating tumor DNA from plasma in patients with curative resected stages I to IIIA EGFR-mutant non-small cell lung cancer. J Thorac Oncol. 2023;18(9):1199-208. [Crossref]
45. Davri A, Birbas E, Kanavos T et al. Deep learning for lung cancer diagnosis, prognosis and prediction using histological and cytological images: a systematic review. Cancers (Basel). 2023;15(15):3981. [Crossref]
46. Cellina M, Cacioppa LM, Cè M et al. Artificial intelligence in lung cancer screening: the future is now. Cancers (Basel). 2023;15(17):4344. [Crossref]
47. Kang E, Min J, Ye JC. A deep convolutional neural network using directional wavelets for low-dose X-ray CT reconstruction. Med Phys. 2017;44(10):360-75. [Crossref]
48. Zhang D, Mu C, Zhang X et al. Image quality comparison of lower extremity CTA between CT routine reconstruction algorithms and deep learning reconstruction. BMC Med Imaging. 2023;23(1):33. [Crossref]
49. Borghesi A, Sverzellati N, Polverosi R et al. Impact of the COVID-19 pandemic on the selection of chest imaging modalities and reporting systems: a survey of Italian radiologists. Radiol Med. 2021;126(10):1258-72. [Crossref]
50. Nam JG, Ahn C, Choi H et al. Image quality of ultralow-dose chest CT using deep learning techniques: potential superiority of vendor-agnostic post-processing over vendor-specific techniques. Eur Radiol. 2021;31(7):5139-47. http://doi.org/10.1007/s00330-020-07537-7 Erratum in: Eur Radiol. 2021;31(8):6410. [Crossref]
51. Ziyad SR, Radha V, Vayyapuri T. Overview of computer aided detection and computer aided diagnosis systems for lung nodule detection in computed tomography. Curr Med Imaging Rev. 2020;16(1):16-26. [Crossref]
52. Li R, Xiao C, Huang Y et al. Deep learning applications in computed tomography images for pulmonary nodule detection and diagnosis: a review. Diagnostics (Basel). 2022;12(2):298. [Crossref]
53. Gu Y, Chi J, Liu J et al. A survey of computer-aided diagnosis of lung nodules from CT scans using deep learning. Comput Biol Med. 2021;137:104806. [Crossref]
54. Chi J, Zhang S, Yu X et al. A novel pulmonary nodule detection model based on multi-step cascaded networks. Sensors (Basel). 2020;20(15):4301. [Crossref]
55. Nasrullah N, Sang J, Alam MS et al. Automated lung nodule detection and classification using deep learning combined with multiple strategies. Sensors (Basel). 2019;19(17):3722. [Crossref]
56. DiPalma J, Suriawinata AA, Tafe LJ et al. Resolution-based distillation for efficient histology image classification. Artif Intell Med. 2021;119:102136. [Crossref]
57. Cai, L, Long T, Dai Y et al. Mask R-CNN-Based detection and segmentation for pulmonary nodule 3D visualization diagnosis. IEEE Access 2020;8:44400-9. [Crossref]
58. Manickavasagam R, Selvan S, Selvan M. CAD system for lung nodule detection using deep learning with CNN. Med Biol Eng Comput. 2022;60(1):221-8. [Crossref]
59. Huang X, Sun W, Tseng TB et al. Fast and fully-automated detection and segmentation of pulmonary nodules in thoracic CT scans using deep convolutional neural networks. Comput Med Imaging Graph. 2019;74:25-36. [Crossref]
60. Pezzano G, Ribas Ripoll V, Radeva P. CoLe-CNN: Context-learning convolutional neural network with adaptive loss function for lung nodule segmentation. Comput Methods Programs Biomed. 2021;198:105792. [Crossref]
61. Dong X, Xu S, Liu Y et al. Multi-view secondary input collaborative deep learning for lung nodule 3D segmentation. Cancer Imaging. 2020;20(1):53. [Crossref]
62. Al-Shabi M, Lan BL, Chan WY et al. Lung nodule classification using deep local-global networks. Int J Comput Assist Radiol Surg. 2019;14(10):1815-9. [Crossref]
63. Li Y, Liu J, Yang X et al. Radiomic and quantitative-semantic models of low-dose computed tomography for predicting the poorly differentiated invasive non-mucinous pulmonary adenocarcinoma. Radiol Med. 2023;128(2):191-202. [Crossref]
64. Scapicchio C, Gabelloni M, Barucci A, et al. A deep look into radiomics. Radiol Med. 2021;126(10):1296-311. [Crossref]
65. Lee J, Bartholmai B, Peikert T et al. Evaluation of computer-aided nodule assessment and risk yield (CANARY) in Korean patients for prediction of invasiveness of ground-glass opacity nodule. PLoS One. 2021;16(6):e0253204. [Crossref]
66. Lafata KJ, Corradetti MN, Gao J et al. Radiogenomic analysis of locally advanced lung cancer based on CT imaging and intratreatment changes in cell-free DNA. Radiol Imaging Cancer. 2021;3(4):e200157. [Crossref]
67. Pérez-Morales J, Tunali I, Stringfield O et al. Peritumoral and intratumoral radiomic features predict survival outcomes among patients diagnosed in lung cancer screening. Sci Rep. 2020;10(1):10528. [Crossref]
68. Yu W, Tang C, Hobbs BP et al. Development and validation of a predictive radiomics model for clinical outcomes in stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2018;102(4):1090-7. [Crossref]
69. Cousin F, Louis T, Dheur S et al. Radiomics and delta-radiomics signatures to predict response and survival in patients with non-small-cell lung cancer treated with immune checkpoint inhibitors. Cancers (Basel). 2023;15(7):1968. [Crossref]
70. Sardanelli F, Colarieti A. Open issues for education in radiological research: data integrity, study reproducibility, peer-review, levels of evidence, and cross-fertilization with data scientists. Radiol Med. 2023;128(2):133-5. [Crossref]