

Artificial Intelligence in *Cancer*

Artif Intell Cancer 2020 June 28; 1(1): 1-38



A**I****C**

Artificial Intelligence in Cancer

Contents**Bimonthly Volume 1 Number 1 June 28, 2020****EDITORIAL**

- 1 Artificial intelligence and omics in cancer
Coulouarn C

EVIDENCE REVIEW

- 8 Management of cancer patients during the COVID-19 pandemic: A comprehensive review
Cassell III AK, Cassell LT, Bague AH

MINIREVIEWS

- 19 Application of artificial intelligence in clinical non-small cell lung cancer
Liu Y

ORIGINAL ARTICLE**Basic Study**

- 31 Impact of blurs on machine-learning aided digital pathology image analysis
Ogura M, Kiyuna T, Yoshida H

ABOUT COVER

Editor-in-Chief of *Artificial Intelligence in Cancer*, Dr. Cedric Coulouarn has a long-standing expertise and track record in liver cancer with focus on TGF-beta signaling, non-coding RNA and functional genomics, including a 5-year experience at the National Cancer Institute. He currently heads a team at Inserm in France focused on studying the role of TGF-beta signaling in liver carcinogenesis. He is an active member of the French and European associations for the Study of the Liver (AFEF and EASL), International Liver Cancer Association, European Network for the Study of Cholangiocarcinoma. Dr. Coulouarn is also acting as a referee in scientific committees for evaluation of French and international Grants. He is teaching at University Paris-Diderot and University of Rennes 1, France.

AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Cancer (AIC, Artif Intell Cancer)* is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIC mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Electronic Editor: *Ji-Hong Lin*, Production Department Director: *Xiang Li*, Editorial Office Director: *Jin-Lai Wang*.

NAME OF JOURNAL

Artificial Intelligence in Cancer

ISSN

ISSN 2644-3228 (online)

LAUNCH DATE

June 28, 2020

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Mujib Ullah, Cedric Coulouarn

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2644-3228/editorialboard.htm>

PUBLICATION DATE

June 28, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

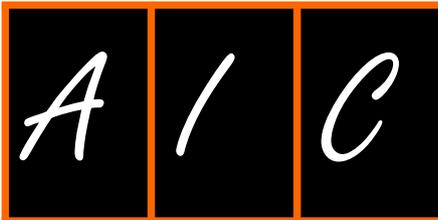
<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Application of artificial intelligence in clinical non-small cell lung cancer

Yong Liu

ORCID number: Yong Liu 0000-0002-4048-5837.

Author contributions: Liu Y performed the writing of the paper.

Conflict-of-interest statement: The author declares no conflicts-of-interest related to this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: May 14, 2020

Peer-review started: May 14, 2020

First decision: June 8, 2020

Revised: June 17, 2020

Accepted: June 19, 2020

Article in press: June 19, 2020

Published online: June 28, 2020

Yong Liu, Department of Thoracic Surgery, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430011, Hubei Province, China

Corresponding author: Yong Liu, MD, PhD, Surgical Oncologist, Department of Thoracic Surgery, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, No. 26, Shengli Street, Wuhan 430011, Hubei Province, China. liuyong7575@163.com

Abstract

Lung cancer is the most common cause of cancer death in the world. Early diagnosis, screening and precise individualized treatment can significantly reduce the death rate of lung cancer. Artificial intelligence (AI) has been shown to be able to help clinicians make more accurate judgments and decisions in many ways. It has been involved in the screening of lung cancer, the judgment of benign and malignant degree of pulmonary nodules, the classification of histological cancer, the differentiation of histological subtypes, the identification of genomics, the judgment of the effectiveness of treatment and even the prognosis. AI has shown that it can be an excellent assistant for clinicians. This paper reviews the application of AI in the field of non-small cell lung cancer and describes the relevant progress. Although most of the studies to evaluate the clinical application of AI in non-small cell lung cancer have not been repeatable and generalizable, the research results highlight the efforts to promote the clinical application of AI technology and influence the future treatment direction.

Key words: Artificial intelligence; Machine learning; Non-small cell lung cancer; Diagnosis; Prognosis; Therapy

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Artificial intelligence has been shown to help clinicians make more accurate judgments and decisions in non-small cell lung cancer screening and preliminary evaluation of lung nodules, histological differentiation and diagnosis, genomic identification, decision-making of therapy, prognosis of overall survival, metastasis or recurrence. Electronic medical records could be used as a source of artificial intelligence

P-Reviewer: Sorrentino R
S-Editor: Wang JL
L-Editor: Filipodia
E-Editor: Liu JH



to help clinicians. This manuscript reviews the state of art artificial intelligence applications in clinical non-small cell lung cancer for those who will be interested in this field.

Citation: Liu Y. Application of artificial intelligence in clinical non-small cell lung cancer. *Artif Intell Cancer* 2020; 1(1): 19-30

URL: <https://www.wjgnet.com/2644-3228/full/v1/i1/19.htm>

DOI: <https://dx.doi.org/10.35713/aic.v1.i1.19>

INTRODUCTION

The global tumor statistics report released in 2018 shows that lung cancer is the malignant tumor with the highest morbidity and mortality in the world. The incidence of lung cancer accounts for 11.6% of the incidence of all tumors, and the mortality rate accounts for 18.4% of the deaths of all tumors^[1]. Due to the late onset of clinical symptoms and limited screening procedures, a large number of patients are diagnosed as advanced^[2]. Histologically, about 85% of new lung cancer cases are classified as non-small cell lung cancer (NSCLC), 10% are small cell lung cancer, and 5% are other variants^[3]. Most NSCLC can be divided into three categories: squamous cell carcinoma, adenocarcinoma and large cell carcinoma^[4]. Patients need the most accurate personalized treatment from doctors. Therefore, doctors need to obtain genomics, proteomics, immunohistochemistry and imaging data, in addition to histological, clinical and demographic information in order to develop precise treatment plans for patients. There are many factors, such as high cost of testing and treatment discontinuity, which will limit the timely access to data. This has aroused people's interest in developing artificial intelligence.

Artificial intelligence (AI) is an important product of the rapid development of computer technology. It has a profound impact on the development of human society and the progress of science and technology through communication and cooperation with multidisciplinary and multifield, especially the organic combination with medicine, which is one of the most promising fields. John McCarthy first proposed the concept of AI: To develop machine software with human thinking mode, so that computers can think like humans^[5]. Machine learning (ML) is a method to realize AI, which belongs to a subfield of AI. It analyzes and interprets data through machine algorithms, learns from it, and then makes decisions or predictions about something. Therefore, unlike manually writing software routines to complete specific tasks with a specific set of instructions, machines use a large number of data and algorithms to "train", which give machines the ability to learn how to perform tasks. ML comes directly from the idea of the early artificial intelligence crowd. For many years, algorithm methods include decision tree learning, inductive logic programming, clustering, reinforcement learning and Bayesian network, etc. These algorithms allow information to be classified, predicted and segmented to provide insights that are difficult to obtain by the human eye or cognitive system.

Deep learning is a technology to realize ML. There are two key aspects in the description of advanced definition of deep learning: (1) A model composed of multilayer or multistage nonlinear information processing; and (2) A supervised or unsupervised learning method for feature representation at a higher and more abstract level^[6]. There are many kinds of network learning models for deep learning, such as convolutional neural networks (CNN), recurrent neural networks, bi-directional long-term and short-term memory cyclic neural networks, multilayer neural networks, etc. Among them, the CNN is one of the representative algorithms of deep learning, which is a kind of feed forward neural networks with deep structure and convolution calculation. It consists of a series of layers. Each layer performs specific operations, such as convolution, pooling, loss calculation, etc. Each middle layer receives the output of the previous layer as its input and finally extracts the high-level abstraction through the fully connected layer. In the process of back propagation in the training stage, the weights of neural connection and kernel are optimized continuously. A CNN has the ability of representation learning, which can classify input information according to its hierarchical structure. Therefore, it is also called "translation invariant artificial neural network (ANN)".

There are two main methods of data processing in ML: Supervised learning and

unsupervised learning. Supervised learning specifically refers to the use of labeled data learning process to assist, so as to achieve learning objectives. The advantage is that the generalization ability of the machine itself can be given full play, and problems such as classification and regression can be effectively solved. Unsupervised learning does not need to be marked, and it explores the similarity between instances according to specific indicators and methods or the value relationship among features. The algorithms commonly used in unsupervised learning are as follows: Deep confidence network, automatic encoder, *etc.* The most important research problems of unsupervised learning include clustering, correlation analysis and dimension reduction. Other learning methods include reinforcement learning, which optimizes the model to get the best decision by giving different feedback to different choices in the iterative process, semisupervised learning that mixes supervised and unsupervised learning and transfer learning with models as an experiential training.

AI can improve patients' treatment results, ameliorate patients' treatment process and even mend medical management^[7]. In view of the increasing application of AI in lung cancer treatment (Figure 1), this paper will review the AI applications being developed for NSCLC detection and treatment as well as the challenges facing clinical adaptability.

APPLICATION OF AI IN SCREENING AND PRELIMINARY EVALUATION OF NSCLC

Pulmonary nodules are the early signs of lung cancer, which are of great significance for the diagnosis of early lung cancer. Early detection, early diagnosis and early treatment can improve the survival rate and prolong the survival time of patients. The national lung screening test showed that low-dose computed tomography (LDCT) screening was associated with a significant 20% reduction in overall mortality among current and previous high-risk smokers^[8]. While conducting LDCT screening to detect patients with early-stage lung cancer, the number of health checkups, disease screenings and follow-up examinations is increasing. As a result, the workload of radiologists has multiplied. The increasing workload aggravates the fatigue of doctors, affects the quality of reading images and the accuracy of diagnosis results. The emergence of AI is just like a drop of sweet dew in a long drought for radiologists. AI can carry out self-learning and self-evolution under semi-supervision. At the same time as improving the accuracy of diagnosis, the time for doctors to read the images is greatly shortened, which solves the clinical needs well^[9].

Most uncertain lung nodules were discovered by accident^[10]. Every year, more than 1.5 million Americans are diagnosed with accidental detection of lung nodules^[11]. Most of these nodules are benign granuloma and about 12% may be malignant^[12]. Another potential hazard of lung cancer screening is the over diagnosis of slow-growing, inactive cancers. If left untreated, these cancers may not pose a threat. Therefore, over diagnosis must be identified and significantly reduced. Identifying the nature of pulmonary nodules by AI can effectively reduce the clinical work pressure as well as the long-term follow-up workload and ameliorate the psychological pressure of pulmonary nodule owners. In the field of cancer imaging, AI has found tremendous utility in three main clinical tasks: Detection, characterization and monitoring. In current clinical practice, imaging methods used to assess the presence of lung cancer include chest X-ray, computed tomography (CT) and positron emission tomography/computed tomography (PET/CT).

Chest X-ray is one of the most commonly used methods. The covering of the chest ribs on the lung field often affects the radiologists' reading of the film and increases the missed diagnosis rate of the lung nodule shadow. von Berg *et al*^[13] used a dual energy subtraction technology based on ANN to reduce the bone density shadow in the X-ray film, expose the lung nodule covered by the bone structure and improve the sensitivity and specificity of the radiologist in the diagnosis of lung nodules. Nam *et al*^[14] recently developed an algorithm for detecting malignant pulmonary nodules on chest X-ray films based on deep learning and compared its performance with that of physicians, half of whom were radiologists. They used 43292 cases of chest X-ray data. The ratio of normal to pathological changes was 3.67. Using external validation data sets, they found that the area under the curve (AUC) of the developed algorithm was higher than 17 of the 18 doctors. When all doctors used this algorithm as the second reader, they found the improvement of nodule detection.

For lung cancer screening, the sensitivity and specificity of LDCT are much higher than that of general chest X-ray^[15]. More than 200 thin-layer images can be

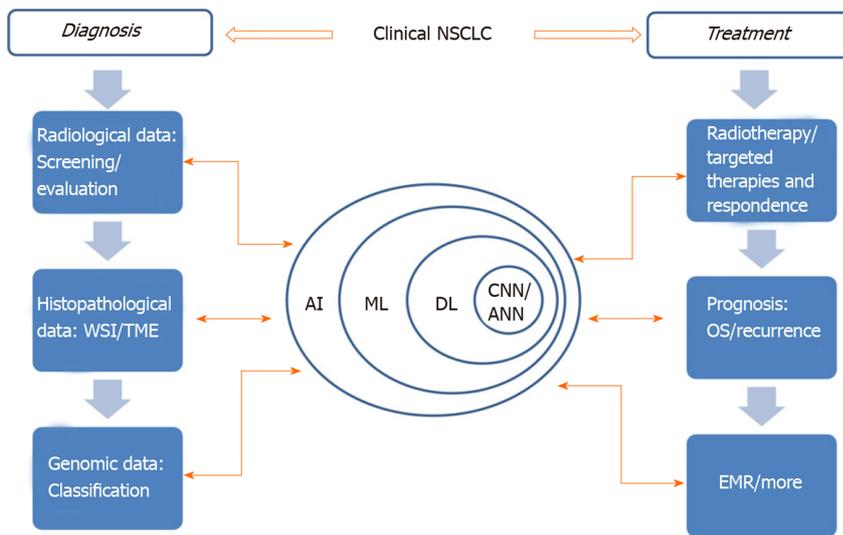


Figure 1 The application of artificial intelligence involved in clinical non-small cell lung cancer. Learning process and application of AI in different fields are indicated by those two-way arrows. AI: Artificial intelligence; ANN: Artificial neural network; CNN: Convolutional neural networks; DL: Deep learning; EMR: Electronic medical record; ML: Machine learning; NSCLC: Non-small cell lung cancer; OS: Overall survival time; TME: Tumor microenvironment; WSI: Whole slide image.

reconstructed after high-resolution CT scanning or spiral CT scanning, which results in excessive reading of radiologists. Pulmonary nodules < 3 mm are more time-consuming and laborious. This has caused a considerable workload for radiologists in the traditional mode. Pulmonary nodule AI detection software is most sensitive to pulmonary nodules of 3-6 mm followed by nodules above 6 mm. Nodules of 3-6 mm are the most easily missed diagnosis by human vision^[16]. After the application of AI, the daily working time can be halved without changing the inspection amount, and there will be no missed diagnosis due to excessive fatigue^[17,18]. Detection refers to the positioning of objects of interest in X-rays or CTs and is collectively referred to as computer-aided detection^[19]. In the early 2000s, methods of computer-aided detection for automatically detecting lung nodules on CT were based on traditional ML methods, such as support vector machines^[20]. Computer-aided detection is used as an assistant in LDCT screening to find missed cancers and to detect brain metastases on MRI to improve radiological interpretation time while maintaining high detection sensitivity^[21]. The computer-aided detection x system has been used for the diagnosis of pulmonary nodules by thin-layer CT^[22].

Due to the simplicity of clinical implementation, size-based measurements such as the longest tumor diameter are widely used for staging and response assessment. However, size-based features and disease stages have limitations such as imprecise diagnosis. A preliminary work shows that AI can automatically quantify the radiographic characteristics of tumor phenotype, which has a significant prognosis for many types of cancer, including lung cancer^[23]. Liu *et al*^[24] combined a model of four semantic features (minor axis diameter, contour, concavity and texture) of quantitative scores. The accuracy of distinguishing malignant and benign nodules in lung cancer screening environment was 74.3%. In a separate study^[25], semantic features were identified from small lung nodules (less than 6 mm) to predict the incidence of lung cancer in the context of lung cancer screening. The AUC of the final model was 0.930 based on the total score of emphysema, vascular attachment, nodal location, border definition and concavity. Paul *et al*^[26] used a kind of pre-trained CNN after large-scale data training to detect lung cancer by extracting the features of CT images. They combined the extracted deep neural network features with the traditional quantitative features and obtained 90% accuracy (AUC: 0.935) by using the five best corrected linear unit features and five best traditional features extracted by vgg-f pre-trained CNN.

In recent years, the number of pure ground glass nodules (pGGN) has increased significantly. Judging its nature and making the treatment plan is very important. Qi *et al*^[27] retrospectively analyzed the clinical follow-up data of 573 CT scans belonging to 110 patients with pGGNs from January 2007 to October 2018. The Dr. Wise system based on CNN was used to segment the initial CT scan and all subsequent CT scans automatically. Then, the diameter, density, volume, mass, volume doubling time and mass doubling time of pGGNs were calculated. Kaplan-Meier analyses with the log-

rank test and Cox proportional hazards regression analysis were used to analyze the cumulative percentages of pGGN growth and identify risk factors for growth. It was found that persistent pGGNs showed a slow course. The 12-mo, 24.7-mo and 60.8-mo cumulative percentages of pGGN growth were 10%, 25.5% and 51.1%, respectively. Deep learning helps to clarify the natural history of pGGNs accurately. Those pGGNs with lobulated sign and larger initial diameter, volume and mass are more likely to grow up. Ardila *et al*^[28] trained a deep learning algorithm on the NLST dataset, which came from 14851 patients and 578 of those patients developed lung cancer the following year. They tested the model on the first test data set of 6716 patients, and the AUC reached 94.4%. A part of 507 patients was compared with six radiologists. When a single CT is analyzed, the performance of the model was the same or higher than that of all radiologists.

The diagnosis of simultaneous or metachronous multiple pulmonary nodules is a new challenge for clinicians. In a retrospective study^[29], a total of 53 patients with multiple pulmonary nodules, simultaneously or metachronously, were included. The coincidence rate of AI diagnosis and postoperative pathology to benign and malignant lesions was 88.8%. AI may represent a relevant diagnostic aid that can display more accurate and objective results when diagnosing multiple lung nodules. It may reduce the interpretation of results by displaying visual information directly to doctors and patients and the clinical status of multiple primary lung cancer patients. The time required and a reasonable follow-up and treatment plan may be more beneficial to the patient.

PET/CT using 18F-fluorodeoxyglucose (FDG) has been established as a great imaging method for the staging of patients with lung cancer^[30]. Schwyzer *et al*^[31] assessed whether machine learning would help detect lung cancer in FDG-PET imaging against the background of ultra-low-dose PET scans. The ANN was used to identify 3936 PET images, including images of lung tumors visible to the naked eye and image slices of patients without lung cancer. Based on clinical standard radiation dose PET images (PET 100%), 10% dose and 3.3% radiation dose (approximately 0.11 mSv), the diagnostic performance of the artificial neural network was evaluated. Their results indicated that even at very low effective radiation doses of 0.11 mSv, machine learning algorithms may contribute to fully automated lung cancer detection.

More and more new PET and single-photon emission computerized tomography tracers are used to explore various aspects of tumor biology, and hybrid multimodal imaging is increasingly used to provide multiparameter measurements. AI is needed to deal with the huge workload. According to reports^[32], texture and color analysis of human FDG-PET images can be used to judge heterogeneity within tumors, thereby distinguishing NSCLC subtypes. Using support vector machine algorithm to extract texture and color features from FDG-PET images to differentiate histopathological tumor subtypes (squamous cell carcinoma and adenocarcinoma), the area under the receiver operating characteristic curve was 0.89. The use of the least absolute shrinkage and selection operator method^[33] to derive radiographic descriptors of metastatic lymph nodes from FDG-PET images of patients with NSCLC has been found relate better with overall survival (OS) than the radiological data extracted from the primary tumor. Wang *et al*^[34] made a comparison of ML methods for classifying NSCLC mediastinal lymph node metastasis from PET/CT images. A CNN and four ML methods (random forest, support vector machine, adaptive boosting and artificial neural networks) were used to classify mediastinal lymph node metastases of NSCLC. PET/CT images of 1397 lymph nodes were collected from 168 patients and were evaluated by the five methods with corresponding pathology analysis results as gold standard. The accuracy of CNN is 86%, which is not significantly different from the best ML method that uses standard diagnostic features or a combination of diagnostic features and texture features. CNN is more accurate than ML methods that simply use texture features.

APPLICATION OF AI IN HISTOPATHOLOGY OF NSCLC

In the differential diagnosis of lung cancer, it is necessary to classify the types or subtypes accurately. Because the hematoxylin-eosin (HE) stained full-scale whole slide image (WSI) is usually at the megapixel level, the much smaller image blocks (about 300 × 300 pixels) extracted from it are often used as training input. For example, Wang *et al*^[35] trained a CNN model; each 300 × 300 pixel image block of lung adenocarcinoma WSIs stained by HE was classified as malignant or nonmalignant. The overall classification accuracy (malignant and nonmalignant) of the test set was 89.8%. This

method can detect tumor rapidly when the tumor area is very small, which will greatly help pathologists in future clinical diagnoses. In the study reported by Teramoto *et al*^[36], a deep CNN (DCNN) was developed for an automatic lung cancer classification scheme, which is a major deep learning technology. In the evaluation experiment, they used original database, including fine needle aspirate cytology images and HE stained WSIs and a graphics processing unit to train DCNN. First, the micro images were cropped and resampled to obtain the image with a resolution of 256×256 pixels. In order to prevent over fitting, the collected images were enhanced by rotation, flipping and filtering. The probability of three types of cancer was evaluated using the developed scheme, and its classification accuracy was evaluated using triple cross validation. In the results obtained, about 71% of the images were correctly classified, which is equivalent to the accuracy of cell technicians and pathologists.

The identification of early lung adenocarcinoma before operation, especially in the case of subcentimeter cancer, can provide important guidance for clinical decision making. Zhao *et al*^[37] developed a 3D deep learning system based on 3D CNN and multitask learning. The deep learning system had better classification performance than radiologists. In terms of three-level weighted average F1 score, the model reached 63.3%, while the four radiologists reached 55.6%, 56.6%, 54.3% and 51.0%, respectively.

With tumor microenvironment increasingly considered as an important factor affecting tumor progression and immunotherapy response, tumor microenvironment for lung cancer has been studied in depth. Saltz *et al*^[38] developed a CNN model to distinguish lymphocytes from necrotic or other tissues at the image spot level in multiple cancer types, including adenocarcinoma and small cell carcinoma of the lung. Then, by quantifying the spatial organization of lymphoid image plaques detected in WSIs, they reported the relationship between the distribution pattern, prognosis and lymphoid components of tumor infiltrated lymphocytes.

Lung cancer patients usually present with advanced, inoperable disease. Because the whole tumor specimen cannot be obtained, the size of the biopsy specimen obtained is usually very limited. It is difficult to distinguish squamous cell carcinoma and adenocarcinoma especially in poorly differentiated tumors because of their obscure histological features. ML in immunohistochemistry^[39] was applied to establish a comprehensive and automatic diagnosis strategy for NSCLC biopsy specimen subtypes, which successfully solved this problem. Koh *et al*^[40] described a comprehensive diagnostic strategy using a reliable and minimal immunohistochemistry team for histopathological subtype analysis of NSCLC biopsy specimens. The team used two ML methods: Decision tree and support vector machines to learn from 30 small NSCLC biopsies with fuzzy morphology. The decision tree model showed that the highest accuracy of the combination of two markers (such as p63 and CK5/6) was about 72% except for three other markers (*i.e.* TTF-1, Napsin A and P40).

Wang *et al*^[41] explored the correlation between the morphological features of the WSIs stained with HE and the NSCLC epidermal growth factor receptor (EGFR) mutation to achieve the purpose of predicting the risk of gene mutation. The results showed that the AUC of the EGFR mutation risk prediction model proposed in this paper can reach 72.4% on the test set, and the accuracy rate was 70.8%, suggesting a close relationship between morphological characteristics and EGFR mutations of NSCLC. Coudray *et al*^[42] trained a DCNN (inception V3) to accurately and automatically classify the WSIs obtained from The Cancer Genome Atlas. Its performance was comparable to that of the pathologist, and the average AUC was 0.97. They trained the network to predict the ten most common mutations in lung adenocarcinoma and found that six genes (*STK11*, *EGFR*, *FAT1*, *setbp1*, *KRAS* and *TP53*) could be predicted by pathological images. In the nonexperimental population, AUC was 0.733-0.856. It suggested that deep learning models could help pathologists detect cancer subtypes or gene mutations.

APPLICATION OF AI IN GENOMIC CLASSIFICATION OF NSCLC

Various molecular abnormalities affecting oncogenes and tumor suppressor genes have been reported in NSCLC. It is so important to identify potential lung cancer genome subtypes that a specific targeted therapy was proposed. For example, mutations in EGFR or anaplastic lymphoma kinase (ALK) receptors are significant in NSCLC because they provide molecular targets for customized treatment regimens.

The gene expression profile of NSCLC subtype has been established by

microarray^[43,44]. Microarray data used to identify NSCLC genetic subtypes can be used to train ML algorithms to better understand genomic pathways. Yamamoto *et al*^[45] screened 24 CT image traits performed in a training set of 59 patients, followed by random forest variable selection incorporating 24 CT traits plus six clinical-pathologic covariates to identify a radiomic predictor of ALK+ status. This predictor was then validated in an independent cohort ($n = 113$). Tests for accuracy and subset analyses were performed. It was found that ALK+ NSCLC had distinct characteristics at CT imaging that when combined with clinical covariate discriminated ALK+ from non-ALK tumors and could potentially identify patients with a shorter durable response to crizotinib.

With the commercialization of next generation sequencing technology and the improvement of the performance of these algorithms, clinicians will be able to better describe NSCLC based on genome data^[46]. Duan *et al*^[47] explored the application of the ANN model in the auxiliary diagnosis of lung cancer. They compared the effects of the back-propagation neural network with the Fisher discrimination model for lung cancer screening by combining the detection of four biomarkers, *p16*, *RASSF1A* and *FHIT* gene promoter methylation levels and the relative telomere length. The result of the back-propagation neural network AUC was higher than that of the Fisher discrimination analysis, which meant that the back-propagation neural network model for the prediction of lung cancer was better than Fisher discrimination analysis.

APPLICATION OF AI IN THERAPY OF NSCLC

Systemic treatment is needed in most stages of NSCLC; for example, those in stage II often need adjuvant radiotherapy and chemotherapy. The contour of organs at risk is an important but time-consuming part of radiotherapy treatment planning. Lustberg *et al*^[48] analyzed the CT scan data of 20 patients with stage I-III NSCLC and compared the user adjusted contour and manual contour based on atlas and deep learning contour. It was found that the median time of manual contour drawing was 20 minutes. When using atlas-based contour drawing, a total of 7.8 minutes was saved, while the deep learning contour drawing saved 10 minutes. It showed that it was a feasible strategy for users to adjust the contour generated by the software, which could reduce the contour time of organs at risk in lung radiotherapy. Compared with the existing programs, deep learning shows encouraging results.

At present, targeted therapies^[49] such as EGFR tyrosine kinase inhibitors, ALK inhibitors or angiogenesis inhibitors are used depending on the patients' molecular status. The prediction of targeted therapy response is mainly accomplished by biopsy to analyze the status of the targeted mutation. AI prediction models can complement this by identifying the imaging phenotypes associated with mutation status. Support for this approach comes from quantitative imaging studies of patients with NSCLC treated with gefitinib. The results^[50] showed that the mutation state of EGFR could be predicted by radiology. AI analysis of quantitative imaging data can also improve the assessment of response to targeted therapy. Bevacizumab (a monoclonal antibody against vascular endothelial growth factor)-treated NSCLC tumors had reduced FDG uptake and were found to have more patients responding to treatment (73% than 18%). In this study^[51], both PET and CT were independent of OS (PET, $P = 0.833$; CT, $P = 0.557$).

The level of PD-L1 expression detected by immunohistochemistry is a key biomarker to identify whether NSCLC patients respond to the treatment of PD-1/PD-L1. The quantification of PD-L1 expression currently includes a pathologist's visual estimate of the percentage of PD-L1 staining (tumor proportion score or TPS) in tumor cells. Kapil *et al*^[52] proposed a new deep learning solution that can automatically and objectively grade PD-L1 expression for the first time in advanced NSCLC biopsy. Using a semisupervised approach and a standard full supervised approach, they integrated manual annotation for training and visual tumor proportion scores for quantitative evaluation by multiple pathologists. It was believed to be the first proof of concept study that showed that deep learning could accurately and automatically estimate the PD-L1 expression level and PD-L1 status of small biopsy samples.

Researchers have studied the use of ML in predicting treatment failure or death. For example, Jochems *et al*^[53] studied ML methods for predicting early death in NSCLC patients after receiving therapeutic chemical radiation. Similarly, Zhou *et al*^[54] used ML to predict the failure of stereotactic body radiotherapy in early NSCLC patients. Both groups used ML methods to establish the prognosis model of early mortality or treatment failure, which could be used to inform patients of treatment plan and

optimize treatment. Kureshi *et al*^[55] studied the role of multiple factors in predicting tumor response to EGFR-TKI therapy (erlotinib or gefitinib) in patients with advanced NSCLC.

APPLICATION OF AI IN PROGNOSIS OF NSCLC

Accurate classification, clinical stage, molecular subtype and therapies of NSCLC are all important because prognosis is closely related to these factors. Hsia *et al*^[56] incorporated the clinical detection indicators and gene polymorphism detection results and predicted the prognosis of 75 lung cancer patients without indications of surgical treatment through the ANN model and made treatment plans accordingly. The actual average survival time of the patients was 12.44 ± 7.95 mo, while the ANN prediction result was 13.16 ± 1.77 mo with an accuracy of 86.2%. Zhu *et al*^[57] successfully used DCNN to directly predict the survival time of patients from lung cancer pathological images. Another lung cancer study^[58] showed that the prognosis of OS can be improved by adding genomic and radiological information to clinical models, thereby increasing the 95% confidence index from 0.65 (Noether $P = 0.001$) to 0.73 ($P = 2 \times 10^{-9}$), and the inclusion of radiation data led to a significant improvement in performance ($P = 0.01$).

Wang *et al*^[59] proposed a computational histomorphometric image classifier using nuclear direction, texture, shape and tumor structure to predict the recurrence of early NSCLC diseases from digital HE tissue microarray slides. The results showed that the combination of these four features could predict the early recurrence of NSCLC, but it had nothing to do with clinical parameters such as gender, cancer stage and histological subtype. Yu *et al*^[60] reported that Zernike shape characteristics of the nucleus could predict the recurrence of NSCLC adenocarcinoma and stage I squamous cell carcinoma.

In an article published in 2018, Saltz *et al*^[38] described the use of CNN combined with pathologist's feedback to automatically detect the spatial tissue of tumor infiltrating lymphocytes (TIL) in the tissue slide image of The Cancer Genome Atlas and found that this feature predicted the prognosis of 13 different cancer subtypes. In a related study, Corredor *et al*^[61] showed the spatial arrangement of TIL clusters in early NSCLC, which was found by calculating the adjacent TILs and the prognosis of cancer cell nuclear recurrence risk compared with TIL density alone. The accuracy of the model in predicting recurrence was 82% and 75%, respectively, which proved to be an independent prognostic factor.

Blanc-Durand *et al*^[62] trained a CNN in 189 NSCLC patients who received PET/CT examination. The subcutaneous adipose tissue, visceral adipose tissue and muscle weight were automatically segmented from the low-dose CT images. After a quintuple cross validation of a subset of 35 patients, body surface area was standardized as the anthropometric index extracted by deep learning. Cox risk regression analysis showed that body surface area normalized visceral adipose tissue/subcutaneous adipose tissue ratio was an independent predictor of progression free survival and OS in NSCLC patients.

Another study^[63] evaluated the ability of CT radiomic features in patients with lung adenocarcinoma to predict distant metastasis. The phenotype of the primary tumor was quantified with 635 radiomic features in the pre-treatment CT scan. Univariate and multivariate analyses were performed using the consistency index to evaluate the efficacy of radiotherapy. Thirty-five radiomic features were used as prognostic indicators for distant metastasis (consistency index > 0.60 , FDR $< 5\%$) and 12 prognostic indicators. Notably, tumor volume was only a moderate prognostic indicator for distant metastasis in the discovery cohort (consistency index = 0.55, $P = 2.77 \times 10^{-3}$). This study suggested that radiomic features that capture the details of the tumor phenotype can be used as prognostic biomarkers for clinical factors such as distant metastasis.

APPLICATION IN ELECTRONIC MEDICAL RECORDS OF NSCLC

Electronic medical records (EMR) can be used in clinical diagnosis and treatment, medical insurance and scientific research. EMR is rich in information that can provide evidence of clinical diagnosis, treatment and data source of clinical research phenotype. In Wang *et al*^[64]'s study, multiobjective ensemble deep learning, a dynamic integrated deep learning and adaptive model selection method based on

multiobjective optimization, was developed. The information extracted from EMRs through analysis can better predict the treatment results than other conventional methods. According to accurate prognosis prediction, we can stratify the risk of treatment failure of lung cancer patients after radiotherapy. This method can help to design personalized treatment and follow-up plan and improve the survival rate of lung cancer patients after radiotherapy.

FUTURE CHALLENGES

It is one of the key directions of medical research in the information age to build a big database by collecting and integrating various biomics, clinical detection indicators and nonbiological environmental background data of patients. Effective analysis and interpretation of these data will be the top priority, and the integration and analysis of the existing massive information is precisely the biggest advantage of AI.

At present, the investment in AI in lung cancer and the entire medical field is huge, but there is still a certain distance from the actual clinical application. The lack of a high-quality standardized lung cancer clinical database is an important factor restricting AI's use in lung cancer research. The deficiency of research sample size causes most prediction or diagnostic studies to not fully simulate the actual clinical environment, limiting the value of clinical applications. Studies^[65] have pointed out that the current use of AI in the medical field, such as inadequacy of correct methods and evaluation criteria in ANN and the credibility of the results is questionable. In addition, in terms of social regulations, lack of common technical regulations on medical responsibility issues and information security issues exists.

In the future, major medical centers should take the lead to establish a multicenter standardized lung cancer clinical database as a world-class database in line with epidemiology and to develop an AI system that meets the clinical environment. Diagnosis, treatment and optimization of medical resources have positive significance. On the other hand, active promotion of AI-related system regulations, technical specification, audit systems to provide institutional support and corresponding constraints for the development of AI are needed. AI has promising prospects for lung cancer research in the future, but it is still full of challenges.

According to the accuracy stated, which is around 90%, misjudgment may happen in 10% of cases, which reflects a pitfall of AI. Therefore, in clinical work, AI must be placed in a subordinate position. It should exist as an assistant to clinicians and provide auxiliary information under the supervision of doctors to avoid mistakes as much as possible.

CONCLUSION

AI has become an indispensable method to solve complex problems in modern life. In this review, I introduced various attempts and applications of AI in clinical work of NSCLC patients. According to a large number of imaging, histology, genomics, EMR system and other data, doctors can accurately diagnose and treat NSCLC patients. It has been shown that AI is gradually becoming a powerful assistant for doctors. Oncologists, radiologists and surgeons should continue to integrate AI into the clinical treatment of NSCLC in order to provide more patients with accurate and personalized therapy. Over time, both patients and doctors will benefit from the combination of AI and clinical practice.

REFERENCES

- 1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- 2 **Molina JR**, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc* 2008; **83**: 584-594 [PMID: 18452692 DOI: 10.4065/83.5.584]
- 3 **Travis WD**, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol* 2013; **31**: 992-1001 [PMID: 23401443 DOI: 10.1200/JCO.2012.46.9270]
- 4 **Ganeshan B**, Panayiotou E, Burnand K, Dizdarevic S, Miles K. Tumour heterogeneity in non-small cell

- lung carcinoma assessed by CT texture analysis: a potential marker of survival. *Eur Radiol* 2012; **22**: 796-802 [PMID: 22086561 DOI: 10.1007/s00330-011-2319-8]
- 5 **Hamet P**, Tremblay J. Artificial intelligence in medicine. *Metabolism* 2017; **69S**: S36-S40 [PMID: 28126242 DOI: 10.1016/j.metabol.2017.01.011]
- 6 **Sui J**, Liu M, Lee JH, Zhang J, Calhoun V. Deep learning methods and applications in neuroimaging. *J Neurosci Methods* 2020; **339**: 108718 [PMID: 32272117 DOI: 10.1016/j.jneumeth.2020.108718]
- 7 **Kononenko I**. Machine learning for medical diagnosis: history, state of the art and perspective. *Artif Intell Med* 2001; **23**: 89-109 [PMID: 11470218 DOI: 10.1016/s0933-3657(01)00077-x]
- 8 **National Lung Screening Trial Research Team**, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; **365**: 395-409 [PMID: 21714641 DOI: 10.1056/NEJMoa1102873]
- 9 **Ciampi F**, Chung K, van Riel SJ, Setio AAA, Gerke PK, Jacobs C, Scholten ET, Schaefer-Prokop C, Wille MMW, Marchianò A, Pastorino U, Prokop M, van Ginneken B. Towards automatic pulmonary nodule management in lung cancer screening with deep learning. *Sci Rep* 2017; **7**: 46479 [PMID: 28422152 DOI: 10.1038/srep46479]
- 10 **Scholtz JE**, Lu MT, Hedgire S, Meyersohn NM, Oliveira GR, Prabhakar AM, Gupta R, Kalra MK, Shepard JO, Hoffmann U, Ghoshhajra BB. Incidental pulmonary nodules in emergent coronary CT angiography for suspected acute coronary syndrome: Impact of revised 2017 Fleischner Society Guidelines. *J Cardiovasc Comput Tomogr* 2018; **12**: 28-33 [PMID: 29195841 DOI: 10.1016/j.jcct.2017.11.005]
- 11 **Gould MK**, Tang T, Liu IL, Lee J, Zheng C, Danforth KN, Kosco AE, Di Fiore JL, Suh DE. Recent Trends in the Identification of Incidental Pulmonary Nodules. *Am J Respir Crit Care Med* 2015; **192**: 1208-1214 [PMID: 26214244 DOI: 10.1164/rccm.201505-0990OC]
- 12 **Furman AM**, Dit Yafawi JZ, Soubani AO. An update on the evaluation and management of small pulmonary nodules. *Future Oncol* 2013; **9**: 855-865 [PMID: 23718306 DOI: 10.2217/fon.13.17]
- 13 **von Berg J**, Young S, Carolus H, Wolz R, Saalbach A, Hidalgo A, Giménez A, Franquet T. A novel bone suppression method that improves lung nodule detection: Suppressing dedicated bone shadows in radiographs while preserving the remaining signal. *Int J Comput Assist Radiol Surg* 2016; **11**: 641-655 [PMID: 26337439 DOI: 10.1007/s11548-015-1278-y]
- 14 **Nam JG**, Park S, Hwang EJ, Lee JH, Jin KN, Lim KY, Vu TH, Sohn JH, Hwang S, Goo JM, Park CM. Development and Validation of Deep Learning-based Automatic Detection Algorithm for Malignant Pulmonary Nodules on Chest Radiographs. *Radiology* 2019; **290**: 218-228 [PMID: 30251934 DOI: 10.1148/radiol.2018180237]
- 15 **Horeweg N**, Nackaerts K, Oudkerk M, de Koning HJ. Low-dose computed tomography screening for lung cancer: results of the first screening round. *J Comp Eff Res* 2013; **2**: 433-436 [PMID: 24236740 DOI: 10.2217/cer.13.57]
- 16 **Liang M**, Tang W, Xu DM, Jirapatnakul AC, Reeves AP, Henschke CI, Yankelevitz D. Low-Dose CT Screening for Lung Cancer: Computer-aided Detection of Missed Lung Cancers. *Radiology* 2016; **281**: 279-288 [PMID: 27019363 DOI: 10.1148/radiol.2016150063]
- 17 **Jha S**, Topol EJ. Adapting to Artificial Intelligence: Radiologists and Pathologists as Information Specialists. *JAMA* 2016; **316**: 2353-2354 [PMID: 27898975 DOI: 10.1001/jama.2016.17438]
- 18 **Kermany DS**, Goldbaum M, Cai W, Valentim CCS, Liang H, Baxter SL, McKeown A, Yang G, Wu X, Yan F, Dong J, Prasadha MK, Pei J, Ting MYL, Zhu J, Li C, Hewett S, Dong J, Ziyar I, Shi A, Zhang R, Zheng L, Hou R, Shi W, Fu X, Duan Y, Huu VAN, Wen C, Zhang ED, Zhang CL, Li O, Wang X, Singer MA, Sun X, Xu J, Tafreshi A, Lewis MA, Xia H, Zhang K. Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. *Cell* 2018; **172**: 1122-1131.e9 [PMID: 29474911 DOI: 10.1016/j.cell.2018.02.010]
- 19 **Castellino RA**. Computer aided detection (CAD): an overview. *Cancer Imaging* 2005; **5**: 17-19 [PMID: 16154813 DOI: 10.1102/1470-7330.2005.0018]
- 20 **Chassagnon G**, Vakalopoulou M, Paragios N, Revel MP. Artificial intelligence applications for thoracic imaging. *Eur J Radiol* 2020; **123**: 108774 [PMID: 31841881 DOI: 10.1016/j.ejrad.2019.108774]
- 21 **Ambrosini RD**, Wang P, O'Dell WG. Computer-aided detection of metastatic brain tumors using automated three-dimensional template matching. *J Magn Reson Imaging* 2010; **31**: 85-93 [PMID: 20027576 DOI: 10.1002/jmri.22009]
- 22 **Chan HP**, Hadjiiski L, Zhou C, Sahiner B. Computer-aided diagnosis of lung cancer and pulmonary embolism in computed tomography-a review. *Acad Radiol* 2008; **15**: 535-555 [PMID: 18423310 DOI: 10.1016/j.acra.2008.01.014]
- 23 **Parmar C**, Grossmann P, Bussink J, Lambin P, Aerts HJWL. Machine Learning methods for Quantitative Radiomic Biomarkers. *Sci Rep* 2015; **5**: 13087 [PMID: 26278466 DOI: 10.1038/srep13087]
- 24 **Liu Y**, Balagurunathan Y, Atwater T, Antic S, Li Q, Walker RC, Smith GT, Massion PP, Schabath MB, Gillies RJ. Radiological Image Traits Predictive of Cancer Status in Pulmonary Nodules. *Clin Cancer Res* 2017; **23**: 1442-1449 [PMID: 27663588 DOI: 10.1158/1078-0432.CCR-15-3102]
- 25 **Liu Y**, Wang H, Li Q, McGettigan MJ, Balagurunathan Y, Garcia AL, Thompson ZJ, Heine JJ, Ye Z, Gillies RJ, Schabath MB. Radiologic Features of Small Pulmonary Nodules and Lung Cancer Risk in the National Lung Screening Trial: A Nested Case-Control Study. *Radiology* 2018; **286**: 298-306 [PMID: 28837413 DOI: 10.1148/radiol.2017161458]
- 26 **Paul R**, Hawkins SH, Balagurunathan Y, Schabath MB, Gillies RJ, Hall LO, Goldgof DB. Deep Feature Transfer Learning in Combination with Traditional Features Predicts Survival Among Patients with Lung Adenocarcinoma. *Tomography* 2016; **2**: 388-395 [PMID: 28066809 DOI: 10.18383/j.tom.2016.00211]
- 27 **Qi LL**, Wu BT, Tang W, Zhou LN, Huang Y, Zhao SJ, Liu L, Li M, Zhang L, Feng SC, Hou DH, Zhou Z, Li XL, Wang YZ, Wu N, Wang JW. Long-term follow-up of persistent pulmonary pure ground-glass nodules with deep learning-assisted nodule segmentation. *Eur Radiol* 2020; **30**: 744-755 [PMID: 31485837 DOI: 10.1007/s00330-019-06344-z]
- 28 **Ardila D**, Kiraly AP, Bharadwaj S, Choi B, Reicher JJ, Peng L, Tse D, Etemadi M, Ye W, Corrado G,

- Naidich DP, Shetty S. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nat Med* 2019; **25**: 954-961 [PMID: 31110349 DOI: [10.1038/s41591-019-0447-x](https://doi.org/10.1038/s41591-019-0447-x)]
- 29 **Li X**, Hu B, Li H, You B. Application of artificial intelligence in the diagnosis of multiple primary lung cancer. *Thorac Cancer* 2019; **10**: 2168-2174 [PMID: 31529684 DOI: [10.1111/1759-7714.13185](https://doi.org/10.1111/1759-7714.13185)]
- 30 **Lardinois D**, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, von Schulthess GK, Steinert HC. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003; **348**: 2500-2507 [PMID: 12815135 DOI: [10.1056/NEJMoa022136](https://doi.org/10.1056/NEJMoa022136)]
- 31 **Schwyzler M**, Ferraro DA, Muehlethaler UJ, Curioni-Fontecedro A, Huellner MW, von Schulthess GK, Kaufmann PA, Burger IA, Messerli M. Automated detection of lung cancer at ultralow dose PET/CT by deep neural networks - Initial results. *Lung Cancer* 2018; **126**: 170-173 [PMID: 30527183 DOI: [10.1016/j.lungcan.2018.11.001](https://doi.org/10.1016/j.lungcan.2018.11.001)]
- 32 **Ma Y**, Feng W, Wu Z, Liu M, Zhang F, Liang Z, Cui C, Huang J, Li X, Guo X. Intra-tumoural heterogeneity characterization through texture and colour analysis for differentiation of non-small cell lung carcinoma subtypes. *Phys Med Biol* 2018; **63**: 165018 [PMID: 30051884 DOI: [10.1088/1361-6560/aad648](https://doi.org/10.1088/1361-6560/aad648)]
- 33 **Carvalho S**, Leijenaar RTH, Troost EGC, van Timmeren JE, Oberije C, van Elmpt W, de Geus-Oei LF, Bussink J, Lambin P. 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET)-Radiomics of metastatic lymph nodes and primary tumor in non-small cell lung cancer (NSCLC) - A prospective externally validated study. *PLoS One* 2018; **13**: e0192859 [PMID: 29494598 DOI: [10.1371/journal.pone.0192859](https://doi.org/10.1371/journal.pone.0192859)]
- 34 **Wang H**, Zhou Z, Li Y, Chen Z, Lu P, Wang W, Liu W, Yu L. Comparison of machine learning methods for classifying mediastinal lymph node metastasis of non-small cell lung cancer from ¹⁸F-FDG PET/CT images. *EJNMMI Res* 2017; **7**: 11 [PMID: 28130689 DOI: [10.1186/s13550-017-0260-9](https://doi.org/10.1186/s13550-017-0260-9)]
- 35 **Wang S**, Chen A, Yang L, Cai L, Xie Y, Fujimoto J, Gazdar A, Xiao G. Comprehensive analysis of lung cancer pathology images to discover tumor shape and boundary features that predict survival outcome. *Sci Rep* 2018; **8**: 10393 [PMID: 29991684 DOI: [10.1038/s41598-018-27707-4](https://doi.org/10.1038/s41598-018-27707-4)]
- 36 **Teramoto A**, Tsukamoto T, Kiriya Y, Fujita H. Automated Classification of Lung Cancer Types from Cytological Images Using Deep Convolutional Neural Networks. *Biomed Res Int* 2017; **2017**: 4067832 [PMID: 28884120 DOI: [10.1155/2017/4067832](https://doi.org/10.1155/2017/4067832)]
- 37 **Zhao W**, Yang J, Sun Y, Li C, Wu W, Jin L, Yang Z, Ni B, Gao P, Wang P, Hua Y, Li M. 3D Deep Learning from CT Scans Predicts Tumor Invasiveness of Subcentimeter Pulmonary Adenocarcinomas. *Cancer Res* 2018; **78**: 6881-6889 [PMID: 30279243 DOI: [10.1158/0008-5472.CAN-18-0696](https://doi.org/10.1158/0008-5472.CAN-18-0696)]
- 38 **Saltz J**, Gupta R, Hou L, Kurc T, Singh P, Nguyen V, Samaras D, Shroyer KR, Zhao T, Batiste R, Van Arnam J; Cancer Genome Atlas Research Network, Shmulevich I, Rao AUK, Lazar AJ, Sharma A, Thorsson V. Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images. *Cell Rep* 2018; **23**: 181-193.e7 [PMID: 29617659 DOI: [10.1016/j.celrep.2018.03.086](https://doi.org/10.1016/j.celrep.2018.03.086)]
- 39 **Shulimzon TR**. Endomicroscopy, Not "Optical Biopsy" (Yet). *Am J Respir Crit Care Med* 2017; **195**: 962 [PMID: 28362205 DOI: [10.1164/rccm.201608-1616LE](https://doi.org/10.1164/rccm.201608-1616LE)]
- 40 **Koh J**, Go H, Kim MY, Jeon YK, Chung JH, Chung DH. A comprehensive immunohistochemistry algorithm for the histological subtyping of small biopsies obtained from non-small cell lung cancers. *Histopathology* 2014; **65**: 868-878 [PMID: 25130792 DOI: [10.1111/his.12507](https://doi.org/10.1111/his.12507)]
- 41 **Wang Q**, Shen Q, Zhang Z, Cai C, Lu H, Zhou X, Xu J. [Prediction of gene mutation in lung cancer based on deep learning and histomorphology analysis]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* 2020; **37**: 10-18 [PMID: 32096372 DOI: [10.7507/1001-5515.201904018](https://doi.org/10.7507/1001-5515.201904018)]
- 42 **Coudray N**, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, Moreira AL, 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 [PMID: 30224757 DOI: [10.1038/s41591-018-0177-5](https://doi.org/10.1038/s41591-018-0177-5)]
- 43 **Ohashi K**, Sequist LV, Arcila ME, Moran T, Chmielecki J, Lin YL, Pan Y, Wang L, de Stanchina E, Shien K, Aoe K, Toyooka S, Kiura K, Fernandez-Cuesta L, Fidias P, Yang JC, Miller VA, Riely GJ, Kris MG, Engelman JA, Vnencak-Jones CL, Dias-Santagata D, Ladanyi M, Pao W. Lung cancers with acquired resistance to EGFR inhibitors occasionally harbor BRAF gene mutations but lack mutations in KRAS, NRAS, or MEK1. *Proc Natl Acad Sci USA* 2012; **109**: E2127-E2133 [PMID: 22773810 DOI: [10.1073/pnas.1203530109](https://doi.org/10.1073/pnas.1203530109)]
- 44 **Kikuchi T**, Daigo Y, Katagiri T, Tsunoda T, Okada K, Kakiuchi S, Zembutsu H, Furukawa Y, Kawamura M, Kobayashi K, Imai K, Nakamura Y. Expression profiles of non-small cell lung cancers on cDNA microarrays: identification of genes for prediction of lymph-node metastasis and sensitivity to anti-cancer drugs. *Oncogene* 2003; **22**: 2192-2205 [PMID: 12687021 DOI: [10.1038/sj.onc.1206288](https://doi.org/10.1038/sj.onc.1206288)]
- 45 **Yamamoto S**, Korn RL, Oklu R, Migdal C, Gotway MB, Weiss GJ, Iafate AJ, Kim DW, Kuo MD. ALK molecular phenotype in non-small cell lung cancer: CT radiogenomic characterization. *Radiology* 2014; **272**: 568-576 [PMID: 24885982 DOI: [10.1148/radiol.14140789](https://doi.org/10.1148/radiol.14140789)]
- 46 **Podolsky MD**, Barchuk AA, Kuznetsov VI, Gusarova NF, Gaidukov VS, Tarakanov SA. Evaluation of Machine Learning Algorithm Utilization for Lung Cancer Classification Based on Gene Expression Levels. *Asian Pac J Cancer Prev* 2016; **17**: 835-838 [PMID: 26925688 DOI: [10.7314/apjcp.2016.17.2.835](https://doi.org/10.7314/apjcp.2016.17.2.835)]
- 47 **Duan X**, Yang Y, Tan S, Wang S, Feng X, Cui L, Feng F, Yu S, Wang W, Wu Y. Application of artificial neural network model combined with four biomarkers in auxiliary diagnosis of lung cancer. *Med Biol Eng Comput* 2017; **55**: 1239-1248 [PMID: 27766520 DOI: [10.1007/s11517-016-1585-7](https://doi.org/10.1007/s11517-016-1585-7)]
- 48 **Lustberg T**, van Soest J, Gooding M, Peressutti D, Aljabar P, van der Stoep J, van Elmpt W, Dekker A. Clinical evaluation of atlas and deep learning based automatic contouring for lung cancer. *Radiother Oncol* 2018; **126**: 312-317 [PMID: 29208513 DOI: [10.1016/j.radonc.2017.11.012](https://doi.org/10.1016/j.radonc.2017.11.012)]
- 49 **Ellis PM**, Al-Saleh K. Multitargeted anti-angiogenic agents and NSCLC: clinical update and future directions. *Crit Rev Oncol Hematol* 2012; **84**: 47-58 [PMID: 22405734 DOI: [10.1016/j.critrevonc.2012.02.004](https://doi.org/10.1016/j.critrevonc.2012.02.004)]
- 50 **Aerts HJ**, Grossmann P, Tan Y, Oxnard GR, Rizvi N, Schwartz LH, Zhao B. Defining a Radiomic

- Response Phenotype: A Pilot Study using targeted therapy in NSCLC. *Sci Rep* 2016; **6**: 33860 [PMID: 27645803 DOI: 10.1038/srep33860]
- 51 **de Jong EE**, van Elmpt W, Leijenaar RT, Hoekstra OS, Groen HJ, Smit EF, Boellaard R, van der Noort V, Troost EG, Lambin P, Dingemans AC. [18F]FDG PET/CT-based response assessment of stage IV non-small cell lung cancer treated with paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches. *Eur J Nucl Med Mol Imaging* 2017; **44**: 8-16 [PMID: 27600280 DOI: 10.1007/s00259-016-3498-y]
- 52 **Kapil A**, Meier A, Zuraw A, Steele KE, Rebelatto MC, Schmidt G, Brieu N. Deep Semi Supervised Generative Learning for Automated Tumor Proportion Scoring on NSCLC Tissue Needle Biopsies. *Sci Rep* 2018; **8**: 17343 [PMID: 30478349 DOI: 10.1038/s41598-018-35501-5]
- 53 **Jochems A**, El-Naqa I, Kessler M, Mayo CS, Jolly S, Matuszak M, Faivre-Finn C, Price G, Holloway L, Vinod S, Field M, Barakat MS, Thwaites D, de Ruyscher D, Dekker A, Lambin P. A prediction model for early death in non-small cell lung cancer patients following curative-intent chemoradiotherapy. *Acta Oncol* 2018; **57**: 226-230 [PMID: 29034756 DOI: 10.1080/0284186X.2017.1385842]
- 54 **Zhou Z**, Folkert M, Cannon N, Iyengar P, Westover K, Zhang Y, Choy H, Timmerman R, Yan J, Xie XJ, Jiang S, Wang J. Predicting distant failure in early stage NSCLC treated with SBRT using clinical parameters. *Radiother Oncol* 2016; **119**: 501-504 [PMID: 27156652 DOI: 10.1016/j.radonc.2016.04.029]
- 55 **Kureshi N**, Abidi SS, Blouin C. A Predictive Model for Personalized Therapeutic Interventions in Non-small Cell Lung Cancer. *IEEE J Biomed Health Inform* 2016; **20**: 424-431 [PMID: 25494516 DOI: 10.1109/JBHI.2014.2377517]
- 56 **Hsia TC**, Chiang HC, Chiang D, Hang LW, Tsai FJ, Chen WC. Prediction of survival in surgical unresectable lung cancer by artificial neural networks including genetic polymorphisms and clinical parameters. *J Clin Lab Anal* 2003; **17**: 229-234 [PMID: 14614746 DOI: 10.1002/jcla.10102]
- 57 **Zhu X**, Yao J, Huang J, editors. Deep convolutional neural network for survival analysis with pathological images. 2016 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2016 Dec 15-18; Shenzhen, China. IEEE, 2017: 544-547 [DOI: 10.1109/BIBM.2016.7822579]
- 58 **Grossmann P**, Stringfield O, El-Hachem N, Bui MM, Rios Velazquez E, Parmar C, Leijenaar RT, Haibe-Kains B, Lambin P, Gillies RJ, Aerts HJ. Defining the biological basis of radiomic phenotypes in lung cancer. *Elife* 2017; **6** [PMID: 28731408 DOI: 10.7554/eLife.23421]
- 59 **Wang X**, Janowczyk A, Zhou Y, Thawani R, Fu P, Schalper K, Velcheti V, Madabhushi A. Prediction of recurrence in early stage non-small cell lung cancer using computer extracted nuclear features from digital H&E images. *Sci Rep* 2017; **7**: 13543 [PMID: 29051570 DOI: 10.1038/s41598-017-13773-7]
- 60 **Yu KH**, Zhang C, Berry GJ, Altman RB, Ré C, Rubin DL, Snyder M. Predicting non-small cell lung cancer prognosis by fully automated microscopic pathology image features. *Nat Commun* 2016; **7**: 12474 [PMID: 27527408 DOI: 10.1038/ncomms12474]
- 61 **Corredor G**, Wang X, Zhou Y, Lu C, Fu P, Syrigos K, Rimm DL, Yang M, Romero E, Schalper KA, Velcheti V, Madabhushi A. Spatial Architecture and Arrangement of Tumor-Infiltrating Lymphocytes for Predicting Likelihood of Recurrence in Early-Stage Non-Small Cell Lung Cancer. *Clin Cancer Res* 2019; **25**: 1526-1534 [PMID: 30201760 DOI: 10.1158/1078-0432.CCR-18-2013]
- 62 **Blanc-Durand P**, Campedel L, Mule S, Jegou S, Luciani A, Pigneur F, Itti E. Prognostic value of anthropometric measures extracted from whole-body CT using deep learning in patients with non-small-cell lung cancer. *Eur Radiol* 2020; **30**: 3528-3537 [PMID: 32055950 DOI: 10.1007/s00330-019-06630-w]
- 63 **Coroller TP**, Grossmann P, Hou Y, Rios Velazquez E, Leijenaar RT, Hermann G, Lambin P, Haibe-Kains B, Mak RH, Aerts HJ. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiother Oncol* 2015; **114**: 345-350 [PMID: 25746350 DOI: 10.1016/j.radonc.2015.02.015]
- 64 **Wang R**, Weng Y, Zhou Z, Chen L, Hao H, Wang J. Multi-objective ensemble deep learning using electronic health records to predict outcomes after lung cancer radiotherapy. *Phys Med Biol* 2019; **64**: 245005 [PMID: 31698346 DOI: 10.1088/1361-6560/ab555e]
- 65 **Bertolaccini L**, Solli P, Pardolesi A, Pasini A. An overview of the use of artificial neural networks in lung cancer research. *J Thorac Dis* 2017; **9**: 924-931 [PMID: 28523139 DOI: 10.21037/jtd.2017.03.157]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

