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Review Article

Advances And Prospect Of Artificial Intelligence In Theranostics Of Lung Cancer.

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Abstract

Lung cancer is the first cause of cancer death worldwide. How to realize precise theranostics and management of Lung cancer has huge clinical demand. In past decade, artificial intelligence (AI), especially machine learning (ML) and deep learning (DL) are broadly used in medicine. Herein we focus on reviewing the main advances of ML and DL in diagnosis, treatment and prognosis of lung cancer. Besides, we summarize AI's advantages, explore how AI assists theranostics of lung cancer by innovative AI algorithms, then we discussed the opportunities and challenges as well as the future directions in the clinical implementation of AI in lung cancer. Overall, AI integrated with multidisciplinary technology and data is a new development trend, its application in theranostics of lung cancer owns excellent clinical transformation value and prospect in near future.

Keywords : *Artificial intelligence; Deep learning; algorithms; Lung cancer; Theranostics.*

INTRODUCTION

Artificial intelligence (AI) is a new technical science that studies and develops theories, methods, technologies and application systems used to simulate, extend and expand human intelligence[1], It is an important driving force for the new round of scientific and technological revolution and industrial transformation. Its application exploration has become frontier hot spot since AI was proposed by mathematician john mccarthy in 1956 [2]. In the past decade, AI has been widely used in medicine[3], great advances have made in those directions such as nanoparticles-labeled tomography chip for biomarker detection[4], immunochromatographic assay and microfludic chip[5,6], medical biosensor for Healthcare System[7,8], cancer diagnosis and tumor nanomedicine[9-11], molecular image diagnosis[12], surgical interventions[13], drug discovery and overcoming multidrug-resistance[14], surgical skills training and assessment[15,16], hospital-wide big data analysis[17], and personalized therapy [18-20].

Machine learning is one kind of implementation pathway of AI, mainly study learning algorithms. Machine learning algorithms mainly include supervised learning, unsupervised learning, semi-supervised learning, reinforcement learning, deep learning, transfer learning, etc[21]. Deep learning (DL) is a new mean of machine learning, uses machines to treat various training data and to extract specific features by using backpropagation algorithms. DL mainly used multi-layered artificial neural networks to analyze data to establish DL models by using Convolutional Neural Network(CNN), Recurrent Neural Network(RNN), Deep Reinforcement Learning(DRL) and Generative Adversarial Network(GAN) [22]. DL models mainly adopt logic to treat data, recognize patterns, make conclusions, and make decisions[23]. In short, AI is based on the computer algorithm which is trained to realize the special functions including identifying and characterizing defined lesions. The computer algorithm is trained by exposing a large number of training elements using the previously described Machine Learning. Clinical decision support systems based on AI has made great advances[24].

Different types of AI computer systems are aimed to achieve different functions. Two main categories of AI systems are computer-aided detection (CADe) for lesion detection and

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computer-aided diagnosis (CADx) for optical biopsy and lesion characterization[25,26]. Other AI systems provide assisted treatments, such as lesion description for complete endoscopic resection[27], magnetically programmed diffractive robotics was developed[28], magnetically controlled wireless power supply capsule endoscopy with intelligent software was used for NIR imaging and treatment of gastrointestinal diseases[29].

AI owns three outstanding advantages. Firstly, AI can optimize and realize efficient and flexible nonlinear modeling for large data sets. Secondly, these models can provide explanations that make knowledge dissemination easier. Thirdly, the human brain performance can be influenced by fatigue, stress or limited experiences, AI can make up for the limited capabilities of humans, prevent human errors, provide machines some reliable autonomy, and enhance work productivity and efficiency. Therefore, in order to service the increasing patients, AI should be best choice to assist theranostics and management of patients.

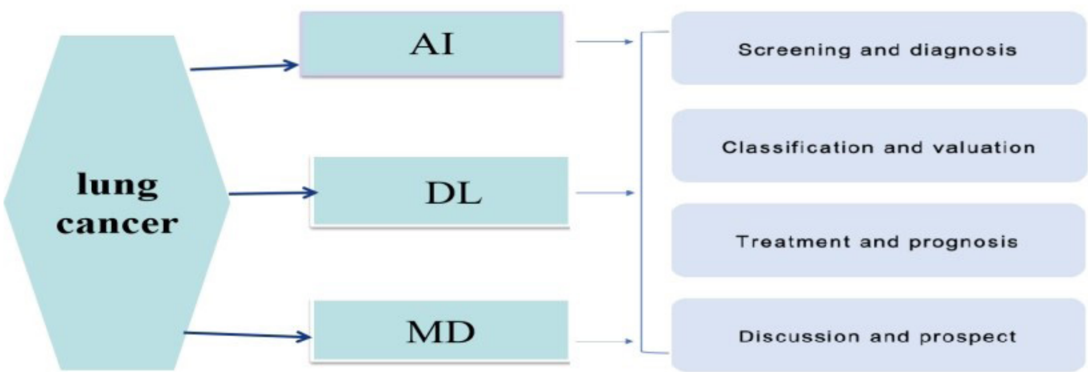
Medical and industrial cross integration is the indispensable way of innovation and development[30]. The concept of medical and industrial integration development is that: based on the cross integration of medicine and engineering, it continues to track hot areas such as molecular biology, genomics, artificial intelligence technology, big data, cloud computing, mobile healthcare, and the internet of things, using quantum computing, 5G/6G communication, block chain, nanotechnology, Internet of Things, AI, AR, VR, MR technologies, to achieve prevention and diagnosis of diseases, treatment and rehabilitation, drug research and development, Traditional Chinese Medicine technology innovation. In short, with clinical needs as the goal, nanotechnology etc as the tools, information processing as the method, multidisciplinary cross to break through the bottlenecks and challenges of disease diagnosis and treatment[31-37]. For example, integrated nano-oncology has made great progress[38]. Gold nanoprism-assisted human PD-L1 siRNA realized gene therapy and photothermal therapy on lung cancer[39]. The quantity of medical robots with embedded AI software have become more and more, and rapidly enter into clinical application[27,40].

Lung cancer is first commonest malignancy among men and the third commonest cancer in women worldwide[41]. The overall 5-year survival rate of lung cancer patients is approximately 20%, however varies markedly depending on cancer stage and molecular typing. Stage I lung cancer patient has a 5-year overall survival rate of greater than 75%, stage III lung cancer patient drops to 25% of 5-year survival rate [42]. Discovering early lung cancer is the only pathway for its cure.

Up to date, biomarker diagnosis, imaging diagnosis, cell and pathological diagnosis are the primary diagnostic techniques of lung cancer[43]. Imaging diagnosis includes nuclear magnetic resonance image(MRI), isotope image, ultrasound, positron emission tomography and Computer Tomography(PET/CT). X-ray chest radiography and CT are the two common anatomical imaging modalities that are regularly used to to recognize different lung diseases[44].

Herein we review the main advances of application of AI in diagnosis, treatment and prognosis of lung cancer. We outlook application prospect of AI in theranostics of lung cancer, and discuss about the opportunities and challenges brought by artificial intelligence (**Figure 1**).

Figure 1. Overview of application of AI in theranostics of lung cancer.



ADVANCES OF AI IN THERANOSTICS OF LUNG CANCER

It is well known that lung cancer is the first commonest cancer worldwide. How to realize precise theranostics of lung cancer owns great clinical demand. Up to date, as shown in **Figure 2**, CT-based imaging diagnosis is the primary tool to detect lung cancer at early stage[45], AI in lung cancer bright the chance to integrate computational power and clinical decision-making[46].

Figure 2. CT Imaging in lung cancer. Instruction of the imaging modalities used in lung cancer screening, diagnosis, radiation planning & delivery, and follow-up.
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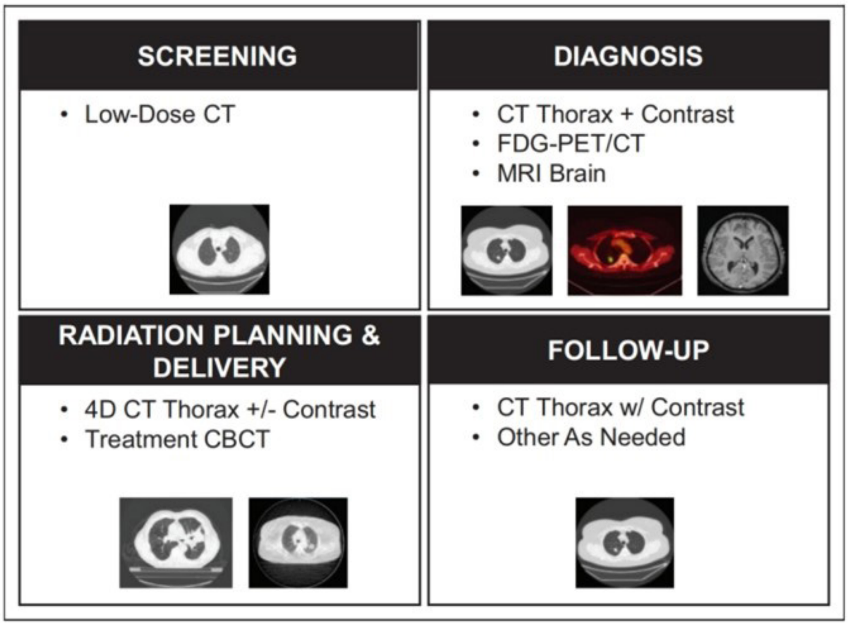

In the key National Lung Screening Trial (NLST) study, lung cancer screening with low-dose computed tomography (LDCT) showed a clear reduction in mortality[47]. Analogous results were also achieved in succeeding American and European studies[48,49]. Annual CT chest screening could reduce lung cancer mortality by at least 20% after 7 years compare with annual chest X-ray radiography[50].

While lung CT screening has the potential to dramatically reduce the number of lung cancer related deaths, the false positive rate of LDCT screening for lung cancer is reported to be as high as 96.4%[51], and the radiologists undertake high burden to make screening precise and efficient for large volumes of CT scans. On the one hand, it is very necessary to establish a new method that can effectively distinguish benign from malignant pulmonary nodules. At present, lot of scholars try to extract radiomic features of CT images of pulmonary nodules and establish theory models to realize the intelligent identification of benign and malignant pulmonary nodules[52-54]. On the other hand, there is an urgent requirement to seek an auxiliary mean, which can improve the diagnostic efficiency of lung cancer by integrating with CT imaging.

AI based on deep learning owns the ability of efficient self-optimization, which can enhance not only the recognition ability of pulmonary nodules with different properties as shown in **Figure 3**, but also helps to improve the diagnostic efficiency of early-stage lung cancer[55].

Figure 3. Categories of lung nodules in a CT scan; benign, primary malignant, and metastatic malignant (from left to right).
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AI systems for Lung Nodule Detection and Classification

Toğaçar et al. used three deep learning models such as LeNet, AlexNet and VGG-16 to detect lung cancer. In addition, the features obtained from the last fully connected layer of CNNs are used as input data for different machine learning models, including linear regression (LR), linear discriminant analysis (LDA), decision tree (DT), support vector machine (SVM), Nearest

Neighbor (NN) and softmax. The combination of the AlexNet model and NN classifier achieves effective classification precise rate of 98.74%[56]. Du et al. established a three-layer diagnosis system for lung cancer, in which three machine learning models such as decision tree C5.0, artificial neural network (ANN) and support vector machine (SVM) were involved[57]. Zheng et al. has achieved better performance not only for small nodules but also for large lesions based on this data set. This proves the effectiveness of the CAD system they developed for the detection of lung nodules[58]. Wang et al. developed an innovative CNN-based nodule-size-adaptive model for fast and precise candidate detection[59]. Pradhan et al. used a 3D Convolutional Neural Network (CNN) to identify lung cancer, they obtained training accuracy of 83.33%, testing accuracy of 100% and precision, recall, kappa-Score, and F-score of 1[60]. Xie et al. proposed a new automatic lung nodule detection framework with 2D Convolutional Neural Network (CNN) to assist the CT reading process[61]. Setio et al. established the LUNA16 architecture, an objective evaluation framework for automatic nodule detection algorithms using the largest publicly available chest CT scan reference database LIDC-IDRI data set[62]. Firmino et al. introduced a CAD system that contains two main components: 1) A computer-aided detection (CADe) module for detecting and segmenting suspicious lung nodules, 2) A computer-aided diagnosis (CADx) module, which realizes nodule level assessment and patient-level malignant tumor classification by analyzing suspicious lesions from CADe[63]. Sharma, et al. demonstrated and verified a new type of tuberculosis nodule detection system based on deep neural network[64]. Huang et al. proposed an Amalgamated - Convolutional Neural Network (A-CNN) and use it to screening pulmonary nodules[65].

Nasrullah et al. used two deep three-dimensional (3D) customized mixed link network (CMixNet) architectures for lung nodule detection and classification, respectively. Nodule detection were performed through faster R-CNN based on efficiently learned features from CMixNet and U-Net like encoder-decoder architecture. Classification of the nodules was performed through a gradient boosting machine (GBM) on the learned features from the designed 3D CMix Net structure. Better results were obtained compared to the existing methods[66]. Jung et al. used a three-dimensional deep convolutional neural network (3D DCNN) with shortcut connections and a 3D DCNN with dense connections for lung nodule classification. They used an ensemble method that aggregates the results of multiple trained models to boost performance[67].

Figure 4. (A) CNN detection of pulmonary nodules. (B) Two different types of ensemble methods. The general ensemble method (left) and checkpoint ensemble method (right) . (C) The flowchart of the three deep learning models.
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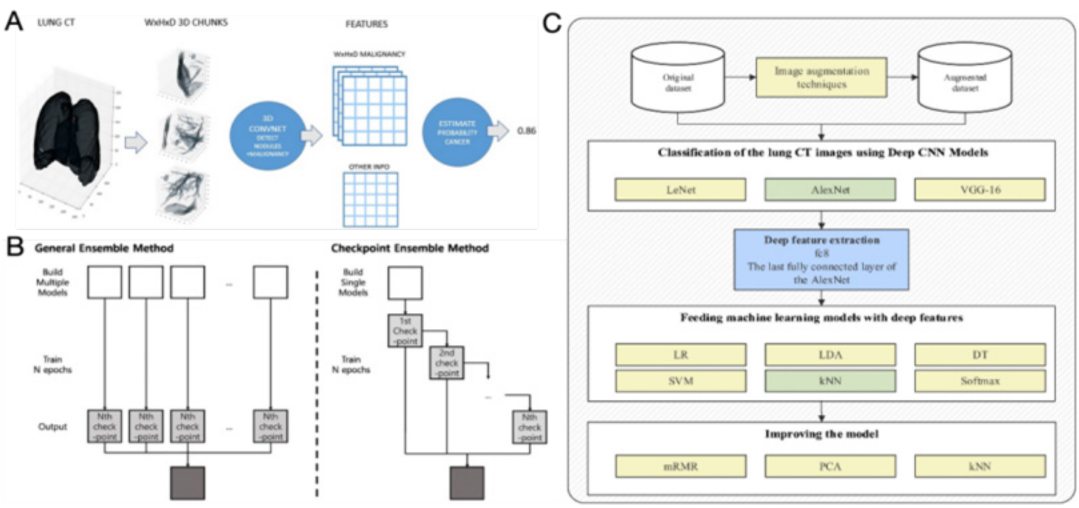

AI systems for lung Cancer Classification and TNM Staging

Lung cancer were classified into two major categories such as small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). SCLC constitutes approximately 15%, NSCLC constitutes approximately 85% of lung cancers. The pulmonary adenocarcinoma (ADC) and pulmonary squamous cell carcinoma (SqCC) are two most common entities in the NSCLC category, which constitutes approximately 90% of all NSCLC[68].

Kriegsmann et al. confirmed that convolutional neuronal networks (CNNs) could classify the most common lung cancers into subtypes including pulmonary adenocarcinoma (ADC), pulmonary squamous cell carcinoma (SqCC), and small-cell lung cancer (SCLC)[69]. Coudray et al. developed a deep convolutional neural network (inception v3) based on whole-slide images obtained from the cancer genome atlas to realize accurately and automatically classifying them into LUAD, LUSC or normal lung tissue[70].

In addition to early detection, appropriate staging and grading of tumors or lesions are also very necessary in order to formulate appropriate cancer treatment strategies[71]. The tumor-lymph node-metastasis (TNM) staging system is one of the popular cancer staging methods[72].

Moitra et al. developed a simple and fast CNN model integrated with Recurrent Neural Network (RNN) to realize automatic AJCC staging of NSCLC. The developed CNN-RNN model is obviously superior to other machine learning algorithms under consideration[73]. Moitra et al. established a 1D CNN model to realize automatic staging and histopathological grading of non-small cell lung cancer[74].

AI Systems for EGFR mutation screening of Lung Cancer

Lung cancers were mainly classified into two types such as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The gene mutations in epidermal growth factor receptor (EGFR) tyrosine kinase domain such as exon 19 E746-A750 deletion and exon 21 L858R point mutation are the commonest mutation points. EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, can treat effectively lung cancer patients with gene mutation of EGFR[75]. How to identify quickly gene mutation of EGFR owns great clinical requirement. 1575 radiomics features were extracted from PET images of 75 lung cancer patients with EGFR mutation based on contrast agents such as 18F-MPG and 18F-FDG. The Mann-Whitney U test was used for single factor analysis, the Least Absolute Shrinkage and Selection Operator (Lasso) Regression was used for feature screening, then the radiomics classification models were established by using support vector machines and ten-fold cross-validation, and were used to identify EGFR mutation in primary lung cancers and metastasis lung cancers(**Figure 5,6**), accuracy based on 18F-MPG PET images are respectively 90% for primary lung cancers, and 89.66% for metastasis lung cancers, accuracy based on 18F-FDG PET images are respectively 76% for primary lung cancers and 82.75% for metastasis lung cancers. The area under the curves (AUC) based on ^{18}F-MPG PET images are respectively 0.94877 for primary lung cancers, and 0.91775 for metastasis lung cancers, AUC based on ^{18}F-FDG PET images are respectively 0.87374 for primary lung cancers, and 0.82251 for metastasis lung cancers. In short, both 18F-MPG PET images and 18F-FDG PET images combined with established AI classification models can identify EGFR mutation, then direct clinical doctors to select matched target drug to treat lung cancer patients[**Table 1**].The established AI model for screening EGFR mutation based on PET imaging of patients with lung cancer own clinical translational prospects[76].

Figure 5. Experimental flowchart.
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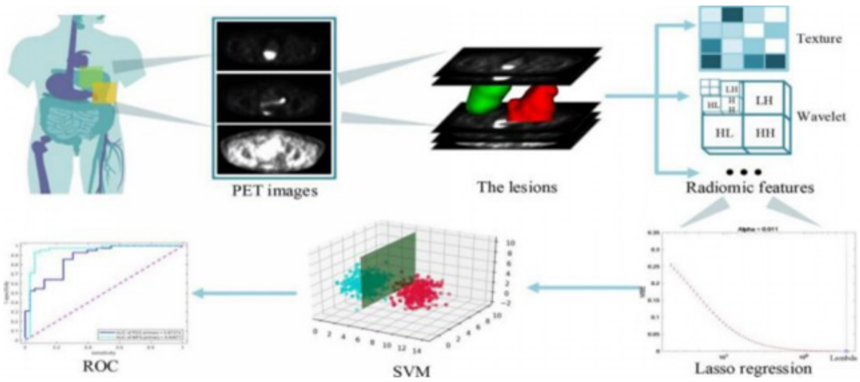

Figure 6. Patients classification: (A) 18F-MPG PET images; (B)18F-FDG PET images
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A

Data set	EGFR wild type	EGFR-activating mutation
75	33	42

Training set	EGFR wild type	EGFR-activating mutation
50	22	28

Test set	EGFR wild type	EGFR-activating mutation
25	11	14

B

Data set	EGFR wild type	EGFR-activating mutation
43	21	22

Training set	EGFR wild type	EGFR-activating mutation
29	14	15

Test set	EGFR wild type	EGFR-activating mutation
14	7	7

Table 1. Performances of the model.
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Training set	**Accuracy**	**Precision**	**Sensitivity**	**Specificity**	**F1**
^{18}F-MPG					
Primary foci	0.9	0.96	0.8571	0.9545	0.9057
Metastasis	0.8966	0.875	0.9333	0.8571	0.9032
^{18}F-FDG					
Primary foci	0.76	0.8333	0.7143	0.8182	0.7692
Metastasis	0.8275	0.7778	0.9333	0.7143	0.8485
Validation set	**Accuracy**	**Precision**	**Sensitivity**	**Specificity**	**F1**
^{18}F-MPG					
Primary foci	0.92	0.9286	0.9286	0.9091	0.9286
Metastasis	0.9285	1	0.8571	1	0.9230
^{18}F-FDG					
Primary foci	0.76	0.8333	0.7143	0.8182	0.7692
Metastasis	0.7857	0.75	0.8571	0.7143	0.8

AI Systems for Lung Cancer surgery therapy

Robotic-assisted pulmonary lobectomy is suitable for patients being able to tolerate conventional lobectomy. Robotic lobectomy owns those advantages such as decreased rates of blood loss, blood transfusion, air leak, chest tube duration, length of stay, and mortality. Especially the use of artificial intelligence (AI) and machine learning (ML) can help in surgical decision-making by improving the recognition of minute and complex anatomical structures. All these advancements have led to faster recovery and fewer complications in Surgical patients [27,77,78].

The use of robotic assistance for complex pulmonary resections such as segmentectomy and sleeve lobectomy has steadily increased in recent years. Robotic surgery is well-suited for complex pulmonary operation given its specific advantages related to superior optics and precise tissue manipulation and dissection[79,80]. Diego, et al. developed robotic-assisted complex pulmonary surgery with a specific focus on right upper sleeve lobectomy for lung cancer[81,82]. Liu, et al. developed puncture surgical robot for lung nodule biopsy. MRI and CT image of patient with lung nodule was obtained, established multimode molecular imaging data, established two models for image segmentation, Double-well NET I and Double-well Net II, which are based on the potts model, double -well potential, network approximation theory and operator-splitting methods. DN-I provides a data-driven way to learn the region force functional, and to enhance segmentation performance. The Double-well Nets introduce an innovative approach that leverages mathematical foundations to enhance segmentation performance. Under the directing of image models, puncture surgical robot realizes a needle precisely reach the lesion site, extract diseased tissue, reduce the occurrence of complications, ensure fast recovery of lesion site[83].

With future advancements such as AI-driven automation, nanorobots, microscopic incision surgeries, semi-automated telerobotic systems, and the impact of 5G connectivity on remote surgery, robotic-assisted pulmonary lobectomy will achieve great advances to improve precision and accuracy, own obvious advantages[84].

AI Systems for Lung Cancer prognosis

Predicting survival rates helps providers to ensure the best treatment plan (involving life quality and medical expenses of patients). Accurately predicting the survival rate of lung cancer patients is one very difficult work. Due to the increasing complexity of lung cancer, many time and biological characteristics, and differences in patient populations, it remains a challenge [85]. The application of AI in clinical decision-making such as especially predicting survival rates of lung cancer patients will improve healthcare operations.

Xu et al. evaluated deep learning networks for predicting clinical results by analyzing time-series CT images of locally advanced NSCLC patients[86]. Histological subtype prediction is one main mission in grading NSCLC tumors. Moitra et al. developed a more accurate deep learning model by integrating convolutional and bidirectional cycle neural networks to achieve histological subtype prediction, the model can be used in the automated prognosis analysis of patients with non-small cell lung cancer (NSCLC)[87].

Wu et al. established a convolutional neural network (CNN) framework called Deep LRHE to predict the risk of lung cancer recurrence by analyzing the histopathological images of lung cancer patients [88]. Afshar et al. investigated the function of 3D CNNs to quantify radiographic tumor characteristics and predict overall survival possibility[89]. Wang et al. developed a deep convolutional neural network(CNN) model to identify automatically the tumor area of advanced lung cancer from H&E pathology images as shown in **Figure 7**. They found that many characteristics of tumor shape are significantly related to tumor prognosis. So they established one prognostic risk prediction model for lung cancer[90]. Tau et al. proposed a deep machine learning model integrated with a convolutional neural network (CNN) to predict the potential of newly diagnosed non–small cell lung cancer (NSCLC) to metastasize to lymph nodes or distant sites[91]. Chamberlin et al. used AI to detect automatically lung nodules and coronary calcium in the course of low-dose CT scans, and realized lung cancer screening. The result is that the system has good accuracy and prognostic value[92].

Figure 7. (A) Use two data sets and other comparison models to describe the workflow based on deep learning. (B) Flow chart of analysis process that Wang et al. developed to automatically identify the tumor area of lung ADC from H&E pathology images.
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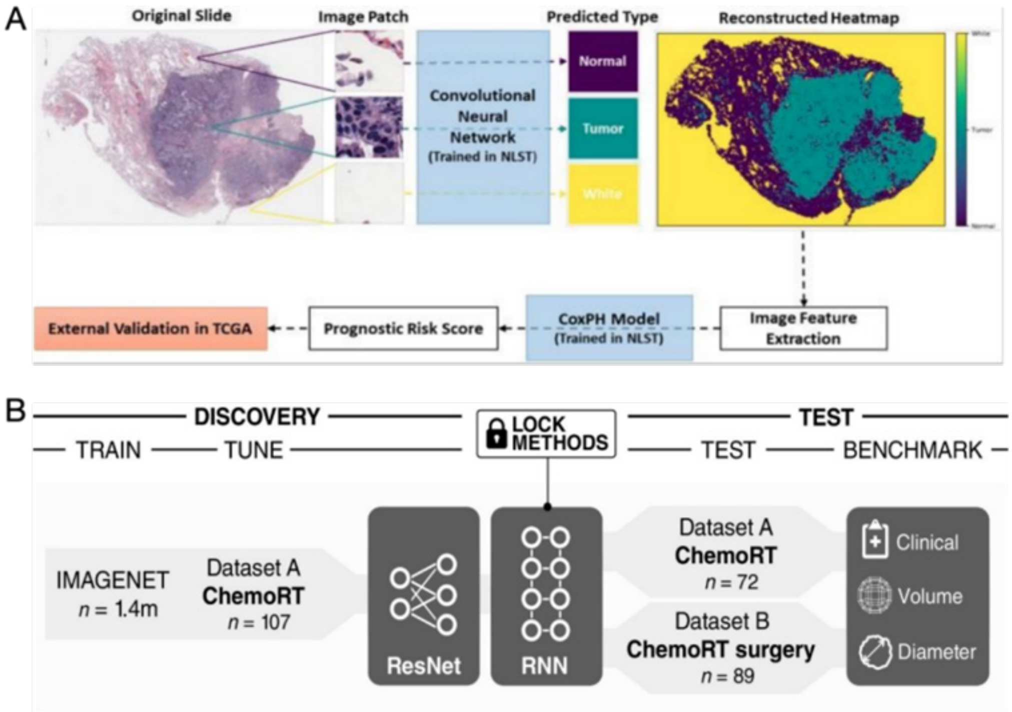

DISCUSS OPPORTUNITIES AND CHALLENGES AND FUTURE DIRECTION

Artificial intelligence (AI) have realized to handle successfully complex nonlinear relationships, fault tolerance, parallel distributed processing and learning[93]. AI display unique advantages such as self-adaptation, simultaneous operation of quantitative and qualitative knowledge and validating model results from some clinical studies in multiple fields[94]. AI also exhibit multipurpose in the filed of clinical medicine[95]. AI not only can make full use of the various aspects data of clinical diversity, but also can help to address some problems such as current lack objectivity and universality in expert systems[96,97]. Especially DL techniques improve our ability to interpret imaging data[98, 99]. Those AI results can enhance sensitivity of data analysis and ensure much fewer false positives than radiologists. However, they also exist the risk of overfitting the training data, and cause a brittle degraded performance in certain settings[100].

AI also have to face some important challenges that must be resolved to ensure its practical application in theranostics of lung cancer[101]. Firstly, medical imaging data from the lungs can not be used as input data directly. Secondly, there is a more sad view to be put forward[102], which is referred to inherent uncertainties in medicine, and the possibility that the “black box” of neural networks/ML applications will reduce physician skills and transform rapidly some departments of healthcare in ways that appear to be practical and economic but with unintended negative consequences. Thirdly, there are several ethical and safety issues including using AI after obtaining patient consent and verifying who is responsible for the misdiagnosis or incorrect therapy[103]. Fourthly, AI cannot determine causal relationships. AI generated the predictions, doctors have to evaluate and interpret critically in clinically meaningful ways.

In the era of precision medicine, the predictability of artificial intelligence in cancer management has great promise in the near future[95]. However, the authors believe that AI cannot replace doctors completely, AI achieves the best performance, which is realized by using the way of human and machine collaboration. In near future, experts can study in depth the application of AI in the whole process of lung cancer management, for example, important main areas are early screening based on sensor for examining exhaled VOC biomarkers, pathology identification, risk assessment, therapy guidance and outcome prediction. Despite existing these various challenges[104], in the era of precision medicine, integrating Genomics, proteomics and metabolomics data with clinical information is very necessary for future clinical practice. Therefore, artificial intelligence have to integrate with multiple disciplines data in order to make a new breakthrough, it is a new development direction. In addition, it is very necessary to use large random events to test AI models.

Nanomaterials own unique nano-effects, for example, up conversion Nanoparticles, nano enzymes, gold nanoparticles based nanoprobes, which were used for targeted imaging and photodynamic or photothermal therapy of lung cancer[105,106,107]. AI technology has also integrated with nanotechnology, which was used for nanotheranostics of lung cancer, enhanced precise image localization of in vivo lung cancer, and directed local operation therapy. Medical and industrial cross owns unique advantages to solve key problem existed in diagnosis and therapy of lung cancer.

In 2022, USA Open AI company published Chat GPT, it blew up the novel world of artificial intelligence, it established large predictive models based on big data, brings new opportunities for precise theranostics of lung cancer[108,109]. However, application of AI in robotic-assisted pulmonary lobectomy still pose major challenges, which are the high cost of intelligence robotic systems, how to keep maintenance of robotic systems, how to keep the size of the robot systems, have to train surgeon to master how to use robots system to perform lung cancer surgery. To solve those challenges will bring innovative developing opportunities, which is also new developing direction for theranostics of lung cancer in near future.

CONCLUSION AND PROSPECTS

In recent ten years, AI technology has integrated with chromatographic chip, microfludic chip, biosensors and PET/CT, MRI imaging techniques, which were used for precise detection of lung cancer biomarkers and precise image localization of in vivo lung cancer, improved sensitivity and specificity of diagnosis, and realized automated diagnosis, staging, robotic-assisted treatment and prognosis of lung cancer with high efficiency.

Artificial intelligence (AI) and machine learning, especially deep learning and deep seek are increasingly applied in theranostics of lung cancer. This article provides an overview of the application of AI in theranostics of lung cancer. The development and validation of AI algorithms requires large volumes of well-structured data, and and the algorithms are capable of treating variable levels of data. It is very important that clinicians understand how AI can be applied in theranostics of lung cancer where diagnostic criteria overlap, how AI use to fit into everyday clinical practice, and how AI use to address issues of patient safety. AI owns a clear role in providing support for clinical doctors, but its relatively recent introduction means that confidence in its application still must be fully established. AI robot-assisted surgical operation also need clinical test and transform. AI will play a key role in aiding clinicians in the theranostics and management of lung cancer in the future, AI will bring the benefits for patients and doctors from its application in everyday clinical practice.

In conclusion, facing the requirement of clinical theranostics of lung cancer patients, AI integrating with multidisciplinary technology and data is a new development trend, application of AI in theranostics and and management of lung cancer owns excellent clinical transformation value and prospect in near future.

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Conflicts of interest

The authors declare no conflicts of interest.

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