Review

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Artificial intelligence in clinical applications for lung cancer: diagnosis, treatment and prognosis

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Abstract: Artificial Intelligence (AI) is a branch of computer science that includes research in robotics, language recognition, image recognition, natural language processing, and expert systems. AI is poised to change medical practice, and oncology is not an exception to this trend. As the matter of fact, lung cancer has the highest morbidity and mortality worldwide. The leading cause is the complexity of associating early pulmonary nodules with neoplastic changes and numerous factors leading to strenuous treatment choice and poor prognosis. AI can effectively enhance the diagnostic efficiency of lung cancer while providing optimal treatment and evaluating prognosis, thereby reducing mortality. This review seeks to provide an overview of AI relevant to all the fields of lung cancer. We define the core concepts of AI and cover the basics of the functioning of natural language processing, image recognition, human-computer interaction and machine learning. We also discuss the most recent breakthroughs in AI technologies and their clinical application regarding diagnosis, treatment, and prognosis in lung cancer. Finally, we highlight the future challenges of AI in lung cancer and its impact on medical practice.

Keywords: artificial intelligence; diagnosis; lung cancer; prognosis; treatment.

Introduction

Lung cancer is one of the most common malignant tumors with the fastest increase in morbidity and mortality [1–3]. The survival of patients with lung cancer at 5 years after diagnosis is only 10–20% in most countries, because of the fact that most of the diagnosed lung cancers are in the middle and late stages of the disease and their treatment methods are limited [4, 5]. Lung cancer is clinically classified mainly according to histopathology, which can be divided into non-small cell lung cancer and small cell lung cancer. The majority of lung cancer is classified as non-small cell lung cancer, accounting for about 85–90%, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma and squamous adenocarcinoma [6]. The International Association for Lung Cancer Research (IASLC) stages lung cancer according to the criteria of tumor diameter, lymph node metastasis and distant metastasis, and divides lung cancer into I–IV stages [7], of which stage I–II is early stage and stage III–IV is advanced lung cancer. Most lung cancer usually tend to be diagnosed at an advanced stage and may be associated with poor prognosis. In addition, limitations of treatment selection and prognosis evaluation has also brought challenges to clinicians.

As yet, the diagnosis of lung cancer mainly relies on computed tomography (CT) and tissue biopsy. Whereas CT is easy to be misdiagnosed, and tissue biopsy is invasive. Meanwhile, the sensitivity and specificity of non-invasion biomarkers for lung cancer need to be improved [8]. Moreover, tumor location, pathological type, presence of metastases, and complications make diagnosis difficult, resulting in more than half of lung cancer patients having metastases at the time of diagnosis [9]. The common treatment of lung cancer is surgical resection and chemotherapy. Clinically, the treatment is mainly selected according to the histopathological classification. Small cell lung cancer is the most malignant, with a high recurrence rate of surgical resection, but is more sensitive to radiotherapy and

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chemotherapy. Non-small cell lung cancer accounts for about 85% of lung cancer, and there is a greater chance of surgical resection in the early stage of the disease [10]. However, with the current technical means, the surgical trauma is too large [11], and the targeting function of chemotherapeutic drugs is not ideal [12]. Furthermore, the diagnosis time of lung cancer, trauma of surgical treatment, drug resistance of chemotherapy drugs, metastasis and recurrence of the disease and other factors make the prognosis of patients difficult to evaluation [13]. In order to reduce the mortality of patients with lung cancer, accurate early diagnosis and timely treatment are highly significant [4].

Artificial intelligence (AI) is a new field of study that develops theories, methods, technologies, and application systems to simulate, extend and expand human intelligence [14] (Figure 1). The technical system of AI can be summarized into four modules: natural language processing, image recognition, human-computer interaction and machine learning [15]. Natural language processing integrates linguistics, computer science, mathematics, other disciplines and mainly studies computer systems that can implement natural language communication, which includes information retrieval, information extraction, part of speech tagging, syntactic analysis, speech recognition, grammar parsing, language translation and so on [16]. Image processing technology includes image acquisition, image filtering and adjustment, feature extraction, amongst others. As compared to the traditional computer, the image processing technology in AI can effectively improve computing power and reduce chip computing energy consumption [16]. Human-computer interactive technology is the conversion of natural language processing and image recognition. It primarily includes computer graphics, interactive interface design, augmented reality, and so on [16]. Machine learning mostly incorporates supervised learning (classification and regression task) [17, 18], unsupervised learning, transfer learning, reinforcement learning, and integrated learning. Its representative algorithms encompass deep learning, artificial neural network, decision tree [19–22], enhancement algorithm, etc. Overall, the rule-based AI systems have achieved varying degrees of clinical value in lung cancer, including diagnosis [23, 24], treatment [25, 26] and prognosis [27, 28] (Figure 2) (Table 1). In this review article, we outline recent breakthroughs in AI technologies and their biomedical application in lung cancer (Supplementary Figure 1).

The role of artificial intelligence in lung cancer diagnosis

The function of artificial intelligence in lung cancer imaging

Lung cancer is a common malignant tumor with high clinical disability and fatality rates [5]. The most common imaging manifestations in the early stage of lung cancer is lung nodule, which increases the difficulty of manual film reading. CT [29] is often used in the clinical diagnosis of pulmonary nodules. Still, the CT images of pulmonary nodules are complex, and the accuracy of the results is closely related to radiologist's experience. Manual film reading often leads to missed diagnosis or misdiagnosis, thereby increasing the difficulty of early lung cancer diagnosis [8, 30, 31]. Therefore, the strategy of reducing observation error is substantial.

The value of AI recognition technology can perform multi-parameter cluster analysis and simplify the image, thus helping doctors screen for early lung cancer [8]. In recent years, it has been reported that the AI system can detect malignant pulmonary nodules based on chest CT images [32]. The model is designed by deep learning technology, and AI is applied to CT film analysis to assist doctors in improving lung cancer screening accuracy. More in-depth research shows that the AI system based on deep learning is applied to discriminate CT images to increase lung cancer screening and diagnosis efficiency [29]. For example, a core diagnostic component of the AI diagnostic system, which is supported and maintained by Diannei Technology Co. Ltd (Shanghai, China), is the 3D DenseSharp network [8, 33]. Based on the state-of-the-art multi-task learning deep neural network of 3DDenseNets [34], a single-queue data set is established, and the 3D DenseSharp network is developed to train and predict invasive labeling and lesion segmentation, which is more accurate than the clinical diagnosis of radiologists [33]. However, some studies have inferred that the diagnostic specificity of the AI diagnosis system is lower than that of radiologists because the blood vessels, bronchi, and lymph nodes of lung tissues can be misdiagnosed as pulmonary nodules by AI. However this defect can be compensated by precise segmentation. For example, Dobbins III first developed an automatic lung segmentation method and nodule detection technology, which achieved high accuracy of lung segmentation and correctly identified all nodules [33]. Xu

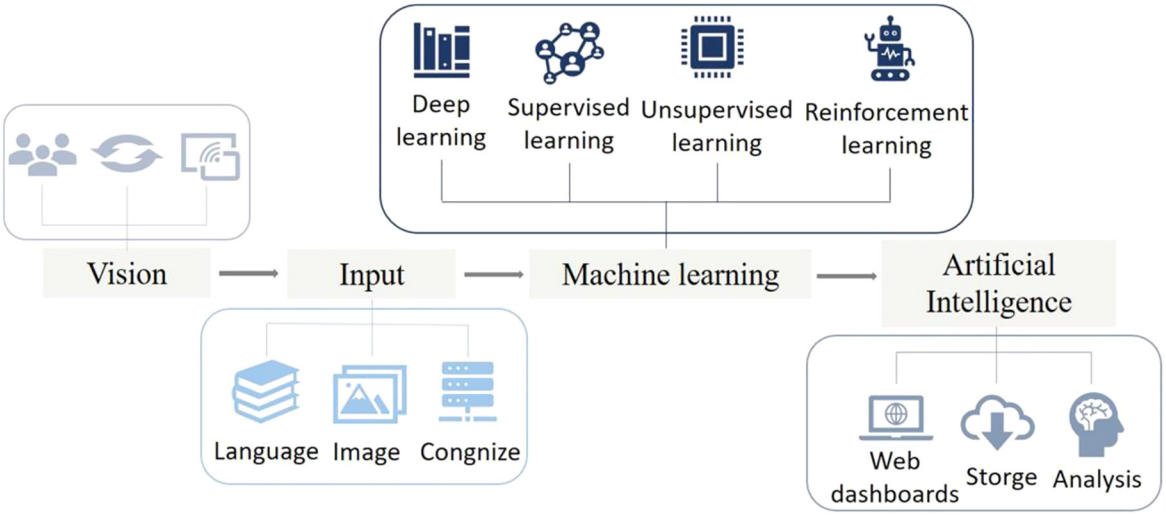


Figure 1: The classification of AI.

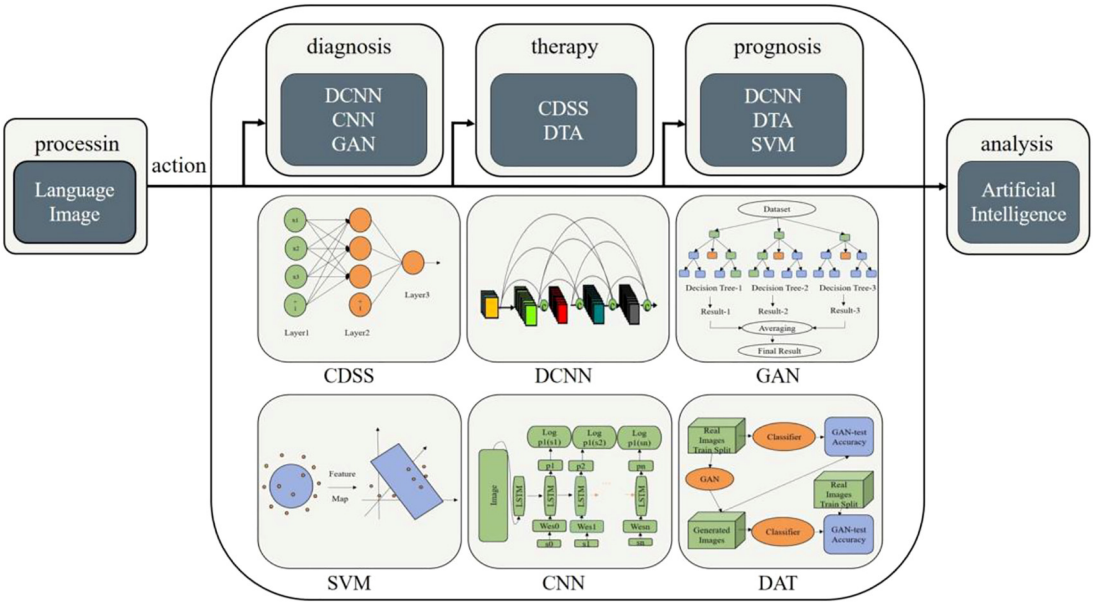


Figure 2: The function diagram of AI in diagnosis, treatment and prognosis of lung cancer.
CDSS, compressed data storage system; DCNN, deep convolutional network; DTA, decision tree analysis; SVM, support vector machine; CNN, convolutional network; GAN, generative adversarial networks.

[35] further used the deep learning model of time series scanning to significantly predict specific cancer outcomes (progression, distant metastasis, and local recurrence). With each additional follow-up scan of the convolution neural network (CNN) model (for example, 2-year overall survival: AUC=0.74, $p<0.05$), the model performance was enhanced to improve the prediction of clinical outcomes [35].

In addition, the value of AI in lung cancer imaging is not only limited to tumor detection but also can be used for lung cancer staging [36]. Lung cancer staging mainly depends on positron emission computed tomography (positron emission tomography [PET]/CT) and manual reading [9, 37, 38], both with low accuracy. The accuracy of tumor staging can be improved by using AI in PET images analysis. For example, tumor staging is performed using

Table 1: The different models of artificial intelligence in lung cancer.

Clinical applications	Technology of AI	References
Diagnosis		
Imaging	3D DenseSharp network, CNN	[29, 32–35, 39, 40]
Pathology	DCNN, GAN, CGAN, SVM	[43–50]
Laboratory indicators	Logistic regression, linear regression	[52–56]
Treatment		
Surgery	Cognitive computing system, CDSS	[66–71]
Drug selection	Machine learning, DTA	[75–77]
Prognosis	XGBoost, DCNN, DTA, SVM	[83–86]

CNN, convolutional network; DCNN, deep convolutional network; GAN, generative adversarial networks; SVM, support vector machine; CDSS, compressed data storage system; DTA, decision tree analysis; XGBoost, extreme gradient boosting.

18F-fluorodeoxyglucose (FDG-)-PET/CT)/CTAS through the CNN neural network [39, 40]. Firstly, a fixed threshold algorithm segmented the PET volume of interest to create a candidate region. Secondly, nine 120–3120 mm multi-plane reconstruction images were extracted from the anatomical environment of the three-dimensional location of 18F-FDG2 positive lesions in the patient space. The offsets of each 18F-FDGPET and CT relative to the segmentation center were 24, 12, 6, 3, 0, 23, 26, 212, and 224 mm, respectively. Finally, the coronal maximum intensity projection (MIP) of the whole body 18F-FDG-PET was reconstructed [39]. The contribution of 18F-FDG-PET, CT, MIP, and atlas information to classification lesions was evaluated. CNN uses the multiplanar reconstruction of PET and CT, the combination of 18F-FDG-PET-MIP and atlas, to predict the anatomical location of 18F-FDG lesions and determine if the lesions are potentially malignant tumors. This constitutes the standard for training all kinds of CNN and judges its classification and localization effect. The above studies show that the role of AI in lung cancer imaging analysis can improve the accuracy of lung cancer screening, shorten analysis time and improve the efficiency of clinicians [40].

The value of artificial intelligence in lung cancer pathology

At this moment in time, pathological biopsy is the gold standard for lung cancer diagnosis. However, due to multiply subtypes of lung cancer, it is difficult to accurately judge the pathological type by manual reading [41, 42]. AI analysis of abnormal structures in tissues or cells will significantly reduce false-negative rates, which can be more suitable for early detection and improve the accuracy of lung cancer classification.

The effects of artificial intelligence cytopathological diagnosis system in lung cancer diagnosis

Cytopathology is rapid and straightforward in lung cancer diagnosis, providing a strong basis for early diagnosis and treatment. However, there are still some limitations, such as a small number of samples, no organizational structures, high misdiagnosis rates of manual recognition, and so on. AI can solve this problem effectively. Teramoto [43] developed an automatic pathological classification model of lung cancer cells in microscopic images using a deep convolutional neural network (DCNN). The antagonistic network (generative adversarial networks, GAN) method is used automatically to generate cytological images, combined with actual and synthetic cytological images to improve the classification accuracy of DCNN. The results revealed that their overall classification accuracy of lung tissue cells was 85.3%, about 4.3% higher than previous studies not using GAN-generated images for pre-training. The above studies indicate that the AI cytopathological diagnosis system can classify lung cancer cells and effectively improve the efficiency of the cytopathological diagnosis of lung cancer.

The significance of artificial intelligence histopathological diagnosis system in lung cancer diagnosis

Histopathological examination is one of the main methods for pathologists to evaluate lung tumor subtypes. However, the accuracy of manual reading needs to be improved via the use of AI in the histopathological diagnosis system. For example, Yu [44] used 2,186 full-scan images from lung adenocarcinoma and squamous cell carcinoma patients from the Cancer Genome Map (the cancer genome atlas, TCGA) and 294 images from the Stanford tissue Microarray (tissue microarray, TMA) database. The results demonstrated that the classifier can effectively distinguish malignant tumors from adjacent healthy tissues (AUC=0.81) and distinguish lung adenocarcinoma from squamous cell carcinoma (AUC>0.75). Furthermore, Coudray [45] trained a deep convolution neural network for all slice images obtained from cancer genome maps, which can accurately and automatically classify lung tissue pathological images into adenocarcinoma, squamous cell carcinoma, and normal lung tissue. On the other hand, it was proved that AI could be used in lung cancer typing as well as for

detecting mutant genes in lung cancer. Coudray speculated that some gene mutations would change the arrangement of lung cancer cells in the section image; they predicted the 10 most common mutant genes in adenocarcinoma by training neural networks. It was observed that six of them (STK11, EGFR, FAT1, SETBP1, KRAS, TP53) could be predicted by pathological images, with an accuracy of 73.3–85.6%. In addition, a conditional generation antagonistic network (CGAN) was used to segment the nuclei of cancerous epithelial tissues, and effective histopathological features were designed to describe lung tumors so as to improve the accuracy of *EGFR* gene mutation risk prediction by using a support vector machine (SVM) classifier [46–48]. The above studies imply that AI can help pathologists quickly judge the type of lung cancer and predict the prognosis of patients through the analysis of digital pathological sections. As a result, the diagnostic efficiency of lung cancer can be significantly improved as well as reducing the frequency of misdiagnosis and missed diagnosis. In particular, deep learning can be used to establish a hematoxylin-eosin (HE) staining model to segment and classify cell karyotypes and tissue structure, so as to visualize the tumor microenvironment (TME) [49]. Based on the characteristics of TME, it can be used to establish a prognosis prediction model for lung cancer [50].

The AI pathological diagnosis system in lung cancer not only improves the work efficiency of pathologists but also has satisfactory stability and effectively reduces the rate of missed diagnosis and misdiagnosis. However, at this stage, the progress of pathological diagnosis using AI is still in the phase of laboratory research and not really applicable in clinical practice. Its limitations are as follows: 1. Data quality issues: At present, specimen processing, slice staining, and image labeling have not yet formed a standardized process. Therefore, the amount of data for AI training is insufficient, affecting the reliability of diagnosis. 2. Data integration problems: a large amount of data and insufficient effective data make the records for AI training missing or invalid.

The role of artificial intelligence in screening laboratory indicators relevant to lung cancer diagnosis

In recent years, the detection technology of tumor markers of lung cancer has developed rapidly from a single carcinoembryonic antigen to the joint detection of five tumor markers [47, 51–53]. However the detection of tumor markers for lung cancer diagnosis is unreliable, and for this reason, the specificity and sensitivity need to be improved [52]. The combination of other laboratory indicators is expected to enhance the diagnostic efficiency of lung cancer. Still, the complex data is challenging to identify, resulting in extremely low utilization of laboratory test results [53]. The emergence of the AI system can solve this problem. Zhang [54] established a predictive model of PLC by logistic regression analysis, including specific tumor markers of PLC (CYFRA21-1, SCC-Ag, NSE, CEA), non-specific tumor markers (CA19-9, CA125, CA15-3), laboratory indexes such as LDH, tissue polypeptide antigen (TPA), tissue polypeptide specific antigen (TPS), NaspinA and clinical indexes such as sex, age, smoking and drinking. The results reported that the AUC and Youden indexes of the PLC predictive model were the superior compared to the simple combined detection strategy of tumor markers. While keeping the sensitivity basically unchanged, the specificity and true positive rate were greatly improved. In addition, studies exhibited that the lung cancer diagnostic model established by using ROC curve using human epidermis secreting protein 4 (HE4), apolipoprotein A2 (ApoA2), sarcosine (TTR), and secreting vascular cell adhesion molecule-1 (sVCAM-1) combined with carcinogenic antigen CEA can significantly improve the sensitivity and specificity of lung cancer diagnosis (AUC value of 0.988, with a sensitivity of 93.33% and specificity of 92.00%) [55]. Moreover, Bian used linear regression to analyze the role of plasma fibrinogen FBG and tumor markers in the lung cancer diagnosis. As expected, results showed that the combination of FBG, squamous cell carcinoma antigen SCC, carbohydrate antigen 125 (CA125), and neuron-specific enolase (NES) could improve the diagnostic specificity of lung cancer [56]. The above studies imply that the use of AI in the early diagnosis of lung cancer can improve the accuracy of lung cancer screening.

The status of artificial intelligence in the treatment of lung cancer

Currently, lung cancer treatment mainly includes surgical resection, radiotherapy, and drug treatment, but choosing the best treatment to improve the survival rate remains the most significant challenges [4]. According to the staging, tumor location, histological and genetic changes, there are various treatment strategies, and the best treatment can be selected. However, the workload of manual data analysis is substantial and associated with low accuracy [57, 58]. On the other hand, AI can model intelligent processing through computer systems [59–61]; doctors can quickly

identify critical information in patients' medical records, provide relevant evidence and optimize treatment options.

The function of artificial intelligence in lung cancer surgery

Surgical options for lung cancer include wedge resection, segmental resection, lobectomy and pneumonectomy [62, 63]. The 5-year survival rate after surgical treatment hovered around 50% [64, 65]. And most tumor patients have unresectable tumor lesions and underlying severe diseases (hypertension, heart disease, diabetes, etc.), resulting in poor quality of life after surgery. How to choose the best operation method is a problem that needs to be solved for now. At present, studies have shown that AI can improve the ability of surgical risk prediction so as to choose the best surgical method [66, 67]. For example, IBM Watson for Oncology (WFO), as a cognitive computing system, uses AI data analysis and image conversion capabilities to help doctors quickly identify key information in patients' medical records, display relevant evidence, and explore treatment options [68]. As a result, WFO treatment decision is highly consistent with the oncology committee (multi-disciplinary team, MDT). Furthermore, the AI-based compressed data storage system (Compressed Data Storage System, CDSS) can assist clinicians in choosing the mode of surgery, especially in the stage of metastatic lung cancer, where a relatively simple treatment scheme can be used to achieve the best treatment [69]. However, with the popularity of WFO, some clinicians conclude that WFO is unsuitable for cancer treatment options [70]. Furthermore, WFO data are biased due to differences in medical guidelines, ethnicity, and drug choices. Therefore, the use of AI in surgery needs to be further explored and improved. In addition, AI not only can be used to select the best surgical method, but also can improve the parameters of the operating room: control lighting or temperature, reduce wear and tear, thus achieving more interventions in a shorter time [71].

The function of artificial intelligence in drug selection for lung cancer treatment

Drug therapy for lung cancer includes chemotherapy, targeted therapy, and immunotherapy. In personalized medicine, how to choose the best therapeutic drugs remains to be solved [72]. The classification and staging of lung cancer and the extremely complex interaction between the immune system, tumor cells, and tumor microenvironment can interfere with tumor therapy [73, 74]. In order to select the best therapeutic drugs, Luo [75] proposed an integrated learning collaborative filtering method in machine learning, which, on the one hand, shortens the decision-making process of selecting the best compounds to achieve personalized lung cancer drug treatment. On the other hand, it identifies targets and drug candidates to promote personalized drugs [75, 76]. Through the machine learning method of baseline covariates, QUANIC uses unique, large-scale, multimodal and longitudinal data collected during the pioneer clinical studies to develop and verify mechanical and dynamic models of response and resistance to immunosuppression at immune checkpoints to achieve personalized immunotherapy for lung cancer [77]. The above studies show that AI assists in the selection of therapeutic drugs for lung cancer through machine learning to achieve personalized treatment.

The role of artificial intelligence in the prognosis of lung cancer

To date, the 5-year survival rate of patients with lung cancer is only 18%, and various factors influence their prognosis. Studies have shown that age, tumor size, race, sex, histological type, grade, T stage, N stage, surgery, chemotherapy, liver metastasis, and radiotherapy are related to the prognosis [69, 78–82], but the ability to judge the prognosis based on a single test item is limited. Therefore, a predictive model of lung cancer combined with AI must be established to improve the prognostic judgment [83]. According to related studies, AI can stage lung cancer by deep learning combined with PET and other imaging analyses to accurately predict the long-term survival efficiency of stage I lung adenocarcinoma (log-rank test 0.0023) and squamous cell carcinoma (log-rank test 0.023) [39]. Meanwhile, as an optimized distributed gradient enhancement library in deep learning, eXtreme Gradient Boosting (XGBoost) [83] sorts the importance of features based on the decision tree model. Finally, it includes essential variables in our model construction. After 19 functions were ranked and selected according to the functional importance using the XGBoost classifier, there were 17 characteristic variables left, which provided technical support for the prognostic analysis of lung cancer. For example, Huang et al. used this algorithm to build an XGBoost model to predict the 1-year mortality of lung cancer complicated with myeloma [83]. Through most prognostic factors, the model provides individualized drug

treatment for patients with bone metastasis of lung cancer to improve the survival rate of patients. With the development of AI, the ITEN (impact of treatment evolution in non-small cell lung cancer) model is further developed by using the neural network in deep learning, which can improve the survival benefit by changing the treatment model [84]. The overall survival rates predicted by the ITEN model and Nadler [85] were higher in patients with chemotherapy or targeted therapy than those predicted by the ITEN model. Moreover, the overall survival rate predicted by ITEN model is very consistent with the survival estimate reported by Itchins [86], which can accurately predict the survival efficiency of patients with non-small cell lung cancer. Overall, there is always a good correlation between the survival rate estimated by the ITEN model and the published data. The model is a reliable tool for predicting the impact of new treatments for non-small cell lung cancer on cost and survival [85].

Conclusions

With the breakthrough and application of key technologies such as neural networks and deep learning algorithms, the potential of AI application in the medical and health industry has been continuously excavated. AI plays a vital role in disease diagnosis and monitoring, efficacy evaluation, survival prediction, drug trials, and health management [87, 88]. Indeed, AI models of lung cancer have the characteristics of objectivity, high efficiency, multiplicity, and repeatability. This will undoubtedly relieve the burden of clinicians, reduce misdiagnosis caused by fatigue, and may change the current medical model. A growing number of AI models are being applied to monitor various data, including electronic health record data, imaging modalities, histopathology and molecular biomarkers, to improve the accuracy of disease risk prediction, detection and prediction of treatment response. However, AI is still in its infancy and has limitations in lung cancer application [89]. For example, AI is mainly based on public databases such as the Lung Image Database Consortium (LIDC-IDRI) to determine its validity, but it leads to a certain sampling bias [90]. The vast majority of medical AI products only detect a single disease [91]. Therefore, the identification and distinction of the disease is another challenge for the development of AI. Despite the promise of these early findings, future research is still needed to standardize AI data, and to improve both the generalizability and interpretability of results [92]. AI combined with radiography, genomics, pathology, electronic health records, and other data streams gathered into a powerful comprehensive diagnosis system and combined with 5G may be of great therapeutic value in lung cancer.

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