Precision Medicine in Lung Cancer Theranostics: Paving the Way from Traditional Technology to Advance Era

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Abstract

Precision medicine for lung cancer theranostics is an advanced model combining prevention, diagnosis, and treatment for individual or specific population diseases to match individual patient differences. It involves collection and integration of genome, transcriptome, proteome, and metabolome features of lung cancer patients, combined with clinical characteristics. Subsequently, large data and artificial intelligence (AI) analysis have emerged to identify the most suitable therapeutic targets and personal treatment strategies for treatment of patients with lung cancer. We review the development and challenges associated with diagnosis and therapy of lung cancer from traditional technology, including immunotherapy prediction markers, liquid biopsy, surgery, and tumor immune microenvironment and patient-derived xenograft models, to AI in the era of precision medicine. AI has improved precision medicine and the predictive ability and accuracy of patient outcomes. Finally, we discuss some opportunities and challenges for lung cancer theranostics. Precision medicine in lung cancer can help us find the optimum treatment dose and time for a specific patient, which can advance the development of lung cancer therapeutics.

Keywords

artificial intelligence, precision medicine, lung cancer, immunotherapy, theranostic, tumor microenvironment

Introduction

Lung cancer is the most common tumor in the world,[1,2] and its morbidity and mortality rank first among all types of malignant tumors.[3] According to statistics, the number of new cases of lung cancer accounts for 12.9% of all tumor types every year. In 2015, Obama proposed a "precision medical plan," aimed at promoting individualized genomics research. China also developed a precision medicine[4,5] plan combined with fields such as protein and metabolomics studies to provide individualized diagnosis and treatment plans for patients,[6] to develop immunotherapy prediction markers, liquid biopsy, surgery, and tumor immune microenvironment markers, symbol models, and use artificial intelligence research to provide more accurate diagnosis and treatment for lung cancer.[7,8] To implement the concept of precision medicine, combined with various biomarkers such as gene mutations, proteins, RNA, and metabolites, AI analysis methods that combine accurate surgical resection and coordination of surgical treatment are important platforms to achieve satisfactory curative effects in lung cancer theranostics. AI technology has been successfully applied to the segmentation and recognition of tumor cells from tumor pathological images and can also accurately quantify immunohistochemical staining results. Deep learning technology can also be used to identify the expression of PD-L1 in lung cancer tissues, and the results are objective and repeatable without errors

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associated with human operators. In addition, it can also identify lymphocytes, tumor cells, and stroma in slices and display the spatial distribution of various cells through three-dimensional reconstruction, which is also a potential factor for judging the efficacy of immunotherapy.[9,10] In this review, the diagnosis and treatment of lung cancer and the progress of AI applications in precision medicine will be described.

Several previous studies have focused on radiotherapy,[11,12] immunotherapy,[13] and nanomedicine[14,15] treatments for lung cancer and used AI to mine predictive markers in the medical field.[16,17] This allows the precise prediction of cancer progression. Figure.1 summarizes the development of precision medicine from traditional technology to AI applications for lung cancer theranostics. This review summarizes the traditional technological developments in lung cancer theranostics and AI applications in the era of precision medicine.

The General Concept of Precision Medicine for Lung Cancer Theranostics

Precision medicine is a novel model for the prevention, diagnosis, and treatment of diseases of individuals or specific groups which considers the individual differences of patients. Precision medicine for lung cancer specifically refers to the collection and integration of the genome, transcriptome, and proteome of patient groups; metabolic, genetic, and molecular biology characteristics; and the clinical characteristics, vital signs, imaging findings, pathological types, and the lifestyle and living environment using big data analysis to identify the most suitable therapeutic target and treatment and to achieve precise treatment for lung cancer.[18]

The completion of the Human Genome Project[19] and the output of massive molecular biological data such as the proteome, transcriptome, and metabolome are the cornerstones for the realization of precision medicine. The development of advanced detection technology, represented by next-generation sequencing technology and big data analysis, is the driving force for the development of precision medicine for proteomics. Some scientists believe that gene mutations and targeted therapy are types of precision medicines which are different from traditional treatment methods. Numerous breakthroughs have been made in targeted therapies for lung cancer.[20-22]

Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation[22,23] and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase. Targeted therapy for the EML4-ALK fusion gene significantly improves the efficacy of middle and advanced lung cancer.[24-26] However, the proportion of NSCLC' driver genes which are known, is still less than 50%. The improvement in survival of patients with targeted therapies is far from what is expected to be a near-cure for lung cancer.

Therefore, for detailed understanding of the molecular mechanisms underlying lung cancer, more drive genes must be explored. At the same time, precision medicine concepts, such as gene mutation biomarkers and feature maps combined with surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy means the implementation of the appropriate
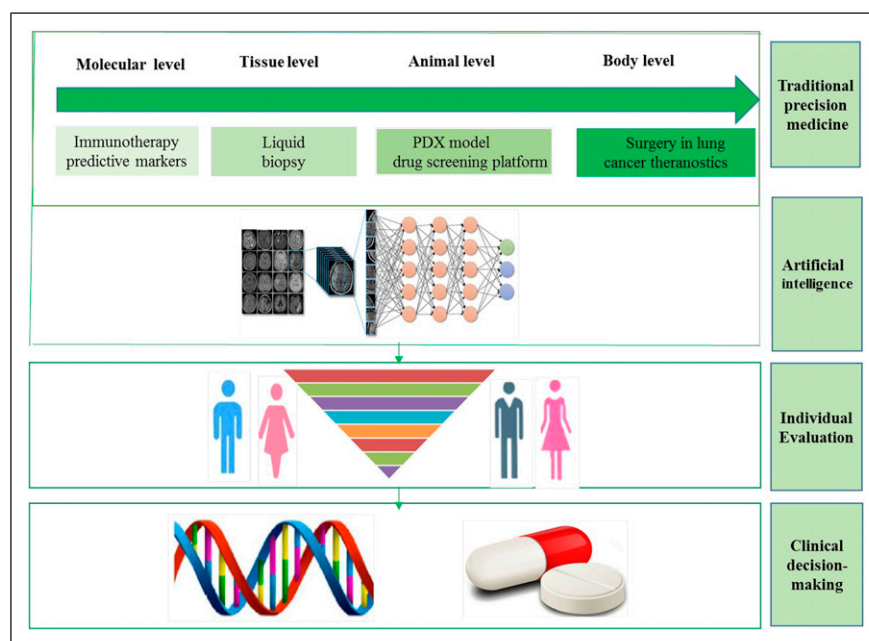

Figure 1. A schematic representation of precision medicine development from traditional technology to AI applications for lung cancer theranostics. After comprehensive analysis of precision medicine for lung cancer theranostics, decision-making for patients will become more specific to individual.

treatment at the right time, for individual patients, is the most suitable model precision current lung cancer medicine.[27,28]

Immunotherapy Predictive Markers at the Molecular Level

Tumor immune microenvironment checkpoint inhibitors, such as CTLA4, PD-1, and PD-L1 inhibitors, play a key role in tumor immunotherapy[29,30] in lung cancer. A variety of tumors such as malignant melanoma was observed to have good clinical effect, and the patients often can bring benefit for a long time, and had side effects than traditional cytotoxic chemotherapy drug. However, the introduction of various immunotherapy drugs also raises many questions regarding the choice of immunotherapy drugs and predictive markers for analyzing the efficacy of immunotherapy. The expression level of PD-L1 in tumor tissues is a relatively well-recognized predictive marker for immunotherapy currently, but it is undeniable that some PD-L1 negative patients can also benefit from immunotherapy, while some PD-L1-positive patients do not respond to immunotherapy.

At present, various antibodies are used to detect PD-L1.[31] More clinical trials should be designed to solve the problem of choosing the appropriate antibodies and the cut-off value setting of the expression rate of PD-L1.[32] $CD8^+$ cells in tumor-infiltrating immune cells have been considered to be related to efficacy in many studies, and CD8+ cells were observed in the effective immunotherapy group before treatment than in the non-responsive immunotherapy group. A recently study[33] revealed that PD–1+ tumor-associated macrophages (TAMs) may play an important role in a colorectal cancer animal model, the PD-1 was only being active in different adaptive immunity in mice and PD-1 inhibitors were found to enhance the ability of macrophage cells to suppress tumor growth.[34,35] Activation of indole amine 2, 3-dioxygenase (IDO) can inhibit the activity of T cells.[36] In malignant melanoma, the detection rate of IDO in the effective immunotherapy group was 37.5%, while that in the ineffective group was only 11.1%. However, whether IDO can be used as an independent predictor still requires further studies.[37-39] Bcl-2-interacting mediator of cell death (BIM) is an important factor associated with cell apoptosis.[40,41] Combining PD-1 with PD-L1 can activate downstream BIM to induce apoptosis of immune cells, and the detection of BIM +/PD-1 + CD8 T cells in peripheral blood provides a means of monitoring the non-invasive immune efficacy. Large PD-1 inhibitors in clinical trials, neutrophils and lymphocytes proportion, baseline lactate dehydrogenase, eosinophil count is associated with clinical outcomes; however, these indicators cannot be used to guide patient medication; immunotherapy is close to infiltrating cells in the tumor microenvironment. Furthermore, peripheral blood may not be able to represent tumor immune features of local *JAK1* and *JAK2* gene mutations[42] and the absence of beta 2-Cadrin mutations and damage T cell function can also lead to immune treatment resistance.[43,44]

Liquid Biopsy as a Non-invasive Approach

Tumors have heterogeneity; information from a single biopsy is not enough to provide information regarding other parts of the tumor, but tissue sampling of every tumor tissue in the body is almost impossible. Moreover, due to factors such as age, general conditions, and blood system obstacles, some patients are not suitable for biopsy, so the cancer diagnosis and testing technology has more superior development in this field. In 1869, Ashworth first proposed the concept of circulating tumor cells (CTCs).[45] In 1976, Novell et al defined CTCs as tumor cells derived from primary or metastatic tumors, separated from the basement membrane, which eventually enter the blood vessels through the stroma. At present, CTCs are found to exist in different forms in the peripheral circulation system as either single CTCs or aggregated tumor microemboli. Liquid biopsy detects CTCs in blood or urine, pleural effusion, circulating tumor DNA (ctDNAs), exosomes, etc. (carrying a variety of proteins, lipids, nucleic acids, etc.) to diagnose cancer.[46]

This non-invasive approach significantly reduces the risk of sampling compared to biopsy and is effective in prolonging patient survival. At present, liquid biopsy technology has been applied in China to monitor drug resistance and dynamically and longitudinally track tumor load and driver gene mutations, which can guide treatment at an early stage. However, although liquid biopsy is a convenient approach, tissue-based biopsy is still the gold standard; furthermore, sometimes relying solely on CT DNA may lead to misjudgment of efficacy. Such tumor tissue biopsy and CT DNA gene sequencing results in deviation caused by numerous reasons; the main source is that the samples may differ due to different tumor cell groups.[19] In addition, the sensitivity of different sequencing technology platforms, need standardization of clinical blood specimen sampling, storage, DNA extraction, and sequencing analysis process proposal to eliminate the deviation to the greatest extent.[47]

In addition to the CTCs and DNA, the tumor will release a small capsule of vesicular bodies, with a diameter of ~40–100 nm, which carry substances such as protein, DNA, and RNA,[48] and the miRNA secretion and its precursors of RNA is different, which may be related to RNA-induced compounds (RISC) combined with silence, Ago2 fail is a key component of RISC.[49] Exosome uptake by the recipient cells of exosomes may depend on various factors, including cell type, physiological state, and microenvironmental conditions.[50] Once exosomes are integrated into recipient cells, the contents of exosomes interact with their recipient cells, promote cell proliferation, transfer drug resistance, support induction of epithelial interstitial transformation, and enhance the migration ability of tumor cells. By extracting exosomes from the peripheral blood of patients and using high-throughput sequencing technology to analyze the nucleic acid expression profile in exosomes, prognosis of a certain population can be performed.

Patient-Derived Xenograft Model as a Drug Screening Platform

Establishment of a xenograft tumor model of patient origin can simulate in vivo the biological behavior of the tumor to a certain extent and provide reliable tumor growth indicators for clinical use. The fluorescence symbol model in a drug screening platform has been reported for *in vitro* drug screening, observation or drug therapy effect, to determine treatment for patients, and use the symbol detection model in individualized drug response, such as 3D tumor culture slide and fluorescence resonance energy transfer (FRET) symbol model. They simulate human drug response by culturing patient's tissue.[51] At present, the patient-derived xenograft (PDX) model can be established not only in tissue samples but also in enriching peripheral blood CTCs or malignant pleural effusion tumor cells. With the advanced biomedical technology, the PDX model can become the basis of developing *in vivo* models for predicting the efficacy and prognosis of lung cancer treatment modalities.[52] So far, considerable achievements have been made in targeted therapy and immunotherapy for lung cancer, but there are still a lot of mechanisms that remain unclear. The rapid development of precision medicine provides a convenient means and a large amount of information for the diagnosis and treatment of lung cancer, making it possible to formulate corresponding programs based on different driver gene mutation subclasses, as well as to predict the efficacy of immunotherapy through tumor mutation load, RNA sequencing, and other technologies.[53] Simultaneously, liquid biopsy technology can capture the tumor status in the body longitudinally and effectively monitor the efficacy of drugs. The integration of these indicators, formulating a standardized testing process, sequencing platform, and reducing monitoring costs is still a difficult problem. However, it can be predicted that individualized treatment modes guided by various biomarkers in the era of precision medicine will greatly improve the quality of life of patients.

The Role of Surgery in the Lung Cancer Theranostics

Accurate diagnosis is important for the implementation of precision medicine. Traditional imaging diagnosis and pathological diagnosis are unable to meet the needs of precision medicine. At present, accurate diagnosis of lung cancer should allow the detection of tumor-specific gene mutations and characteristic molecular markers of proteins, RNA, and metabolites, in addition to traditional diagnostic methods. These precise tests based on biological specimens should be reflected in every key point of patient diagnosis and treatment throughout the course of the disease. Sufficient and high-quality biological specimens can guarantee accurate diagnosis. CTCs contain circulating free DNA. Circulating cell-free DNA (cfDNA) has been developed rapidly,[54] and the concept of "liquid biopsy" has been introduced. However, owing to its low abundance and high requirements, it is still too early to be used in clinical practice. Puncture biopsies also

have the limitation of a high false-negative ratio and insufficient tumor tissue acquisition to complete some accurate tests.

With the development and wide application of minimally invasive technology, surgical biopsy will result in less trauma to patients.[55] Therefore, currently, surgical biopsy provides a strong guarantee of accurate diagnosis for some patients. Surgery is personalized based on cancer characteristics, including cancer expansion, from pre-invasive and local tumors to locally advanced, metastatic disease or residual disease after drug therapy, expected recurrence, and patient characteristics. Surgical management continues to evolve to provide the best tumor resection for each stage of NSCLC. Currently, surgery is still a valuable management tool for diagnosing and treating recurrence, as well as alleviating dyspnea and improving patient comfort in palliative care.

AI Application in Lung Cancer Theranostics

In recent years, the application of AI technology in the era of tumor precision therapy has further promoted personalized precision therapy for tumor patients.[56] AI technology can be applied to early screening of lung cancer in a normal population. At present, many AI technologies have been tentatively applied to the pathology and imaging diagnosis of lung cancer. Through AI technology, the accuracy and efficiency of lung cancer screening can be significantly improved. On the treatment side, AI technology can be used to determine how well a patient is responding to medication.

For example, the risk of recurrence, metastasis, and prognostic factors for lung cancer can be predicted. There have been many breakthroughs in related exploratory research worldwide, and all of them show good application prospects. There are three key steps in the application of AI technology in precision medicine. The first is the clinical data generated in the hospital. This is an important aspect that clinicians need to be involved in Ref. 57. By coming up with clinical scenarios and having high-quality data, we can use that data to train computers and build models that can be applied to the clinic. The second is the algorithm. Many computer languages/algorithms are open source and non-original algorithms that rely on existing models, so they encounter bottlenecks when applied in different scenarios.[58] We expect innovation from the engineering field to improve AI technology using original algorithms. The third is computing power, namely, the computing power of the AI. Many supercomputing centers in China are at the forefront of computing power in the world, which is our advantage. For example, in 2016, China hosted a high-performance computing (HPC) competition with its 93-petaflop Sunway TaihuLight supercomputer, and reached parity on the TOP500 list with the US.[59]

More cooperation is expected to yield more results. From the entire AI technology level, we see the advantages of the combination of medicine and industry. We have proposed clinical problems from a medical perspective, and with the cooperation of the engineering field, models with clinical application value can

be established through innovative calculation methods to carry out clinical verification. This work will further guide clinical practice and improve the basis for optimizing medical behavior, medical policies, and strategies.[60] We see that the development of precision medicine and the application of AI in oncology are closely related and complement each other. We believe that the application of intelligent oncology will play a significant role in promoting precision medicine in oncology.[61]

AI technology is widely used in lung cancer. For example, for the screening of lung cancer nodules, optimized AI software has an advantage over imaging doctors in judging the results of the images. An experienced radiologist may need 10 to 20 minutes to make a relatively accurate diagnosis from a set of CT data,[62] while an AI model may only require 10 seconds. AI technology can reflect its advantages in the following cases to help doctors improve efficiency.[63] First, in remote areas or areas with relatively less developed medical resources, AI can improve the accuracy of diagnosis.[64] Second, in large hospitals, artificial intelligence technology can improve the speed of film reading, greatly improving the diagnostic efficiency of imaging doctors and reducing human error.[65] In terms of the therapeutic effect, it is difficult to judge the image information related to the treatment by artificial methods, but it is possible to extract imaging features and find rules through AI to judge the therapeutic effect.

In addition, in the field of surgery, AI[66] is also widely used, such as the application of da Vinci robot to efficiently perform fine surgery and minimally invasive surgery.[67] The application of tumor AI technology is also reflected in nursing, rehabilitation, and other aspects, and virtual reality technology is of great help for better rehabilitation[66] and decision-making of future treatment plans.[68]

Challenges and Opportunities

The development of intelligent oncology has just begun. At present, the main factor restricting the development of AI technology is the quality of clinical data. For example, the standardized diagnosis, treatment degree and follow-up rate of diseases are relatively low, leading to a bias in these data and insufficient application value. However, in general, intelligent oncology in China lags behind the world in terms of overall concept and development progress.[60]

At present, various medical-related committees, including oncology, are vigorously promoting standardized treatments. Standardized diagnosis and treatment will help us collect high-quality clinical data, which will more effectively promote the application of AI technology in medicine, especially oncology.[69]

The research progress in AI technology for early screening, pathological diagnosis, prognosis assessment, surgical navigation, and immunotherapy of lung cancer will surely bring new opportunities for the diagnosis and treatment of lung cancer. At present, an increasing number of pulmonary nodules have been found during the examination. Although most pulmonary nodules are benign, there are still a high proportion of early lung cancers. Pulmonary nodules with a diameter of >3 cm have a high possibility of malignant transformation; therefore, we should focus on the screening of pulmonary nodules. However, the workload for pulmonary nodule screening is large, and diagnosis can be easily missed; furthermore, after the detection of pulmonary nodules, physicians need to accurately distinguish between benign and malignant nodules to provide suggestions for next treatment.[70] Histopathological and cytopathological diagnosis is an indispensable link in the diagnosis and treatment of lung cancer. Some researchers plan to use AI technology to classify different types of lung cancer (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma) to improve the accuracy and stability of pathological diagnosis.[71]

According to large information of pathological sections, the prognosis of patients with lung cancer can be accurately determined. Teramoto et al[71] used 2186 paraffin-based full-scan images of lung adenocarcinoma and lung squamous cell carcinoma from The Cancer Genome Atlas (TCGA) and 294 images from the tissue microarray (TMA) database. The quantitative features of 9879 images were extracted, and the top features were selected using a machine learning algorithm. The results showed that these features could predict the survival time of patients with lung adenocarcinoma ($P < .003$) and lung squamous cell carcinoma ($P < .023$).[71]

In addition, the development of a new generation of information technologies,[68] such as 5G technology, is changing the medical model of human beings, making remote diagnosis and treatment more common. With 5G technology,[72,73] doctors can retrieve images faster and carry out remote consultations and surgeries.[74] It can make treatments more affordable and accessible for people who might not currently be able to receive them due to cost and health insurance.

Conclusion

Precision medicine in lung cancer theranostics from traditional technology to AI can help us find the optimum treatment for a specific patient at the optimal dose and time. It can pave the way to advance the development of lung cancer theranostics, which brings infinite possibilities for improving the efficacy of lung cancer management.

Abbreviations

AI	Artificial intelligence
CTC	Circulating tumor cells
FRET	Fluorescence resonance energy transfer
HPC	High-performance computing
NSCLC	Non-small cell lung cancer
PDX	Patient-derived xenograft
RISC	RNA-induced compounds

TAM   Tumor-associated macrophages
TCGA   The Cancer Genome Atlas.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest concerning the research.

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