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Advances in the Application of Deep Learning in Prognostic Models for Non-Small Cell Lung Cancer

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Abstract

Non-small cell lung cancer (NSCLC) is one of the cancers with the highest incidence and mortality rates worldwide. Accurate prognostic models can guide clinical treatment plans. With the continuous upgrading of computer technology, deep learning, as a breakthrough technology in artificial intelligence, has shown good performance and great potential in the application of NSCLC prognostic models. Research on the application of deep learning in the prediction of NSCLC survival and recurrence, therapeutic efficacy, distant metastasis, and complications has made certain progress and is showing a trend of multi-omics and multi-modal integration. However, there are still some deficiencies. In the future, in-depth exploration should be carried out, model validation should be strengthened, and clinical practical problems should be solved.

Keywords

Deep Learning, Non-Small Cell Lung Cancer, Prognostic Model

1. Background

According to statistics, one sixth of the global population dies from lung diseases every year [1]. With the increasing severity of air pollution, smoking, and population aging, the incidence and mortality rates of lung diseases are rising year by year, becoming a global concern [2]. The conventional diagnostic methods include bacterial culture/non-culture methods, imaging examinations, pathological tissue analysis, antigen detection, serological detection, PCR detection, etc. These methods have limitations in terms of sensitivity, specificity, and time delay. Therefore, there is an urgent need to develop simple and rapid diagnostic procedures for the early diagnosis of lung diseases. Non-small cell lung cancer (NSCLC) is the main cause of lung cancer-related deaths. The survival risk stratification of NSCLC patients can help doctors formulate individualized treatment plans, plan follow-up plans, and prolong the survival period of patients. Artificial intelligence can identify key information from a large amount of medical information and help patients with prognosis. Currently, tumor lymph node metastasis (TNM) staging is the main method for survival risk stratification and an important indicator for doctors to judge the survival risk of patients. However, TNM staging requires pathological detection, which may pose an infection risk to patients. To solve this problem, lung cancer is the leading cause of cancer deaths worldwide and the most common type of new cancer [3], among which non-small cell lung cancer (NSCLC) accounts for 80% to 85% of lung cancer cases [4]. Deep learning technology has shown great potential in disease diagnosis, prognosis assessment, and treatment sensitivity prediction [5]-[7]. Previous studies have demonstrated that deep learning can predict lymph node metastasis in thyroid cancer [8], breast cancer [9], and gastric cancer [10]. Applying deep learning methods to the survival risk stratification of NSCLC not only reduces the burden on doctors and patients but also has the potential to achieve hierarchical diagnosis and treatment. The model research in this paper helps doctors clarify the corresponding survival risk and clinical staging, comprehensively assess the overall condition of patients, and assist doctors in comparing and weighing multiple methods for comprehensive treatment, which may prolong the survival period of patients. Using deep learning technology to solve the problem of survival risk stratification for patients is of great significance.

2. Introduction to the Application of Deep Learning in Biomedical

Field The rapid development of large-scale high-throughput biotechnologies such as genomics, medical imaging, electronic health records, and mobile health has led to an explosive growth of complex, multi-dimensional data related to human health and diseases [11]. Large-scale datasets of genes, transcriptomes, proteins, metabolites, cells, tissues, patients, and populations have provided unprecedented opportunities for data-driven translational biomedicine [12]. However, the scale, noise, heterogeneity, incompleteness, and complexity of large-scale biomedical data pose significant challenges to traditional computational methods [13]. Therefore, new computational methods are needed to address these issues and fully exploit the potential of these large-scale biomedical data. In recent years, advanced technologies such as artificial intelligence, machine learning, and deep learning have demonstrated strong capabilities in handling large-scale data, bringing new solutions to biomedical research. Artificial intelligence, in a broad sense, refers to the technology that enables machines to possess intelligence, including but not limited to machine learning. Machine learning, as an important branch of artificial intelligence, improves the performance of computer systems through relevant algorithms based on experience. Deep learning is a branch of machine learning that mainly uses artificial neural networks (ANN) as learning models. These three concepts form an inclusive relationship, not a parallel or opposing one. The cutting-edge artificial intelligence technology of deep learning has taken the lead in extracting meaningful patterns and relationships from large and complex datasets [14]. Deep learning involves artificial neural networks with multiple layers, and these hierarchical structures enable direct learning of hierarchical feature representations from raw data [15]. Traditional machine learning usually relies on a large amount of human effort for feature extraction (such as encoding or manual screening) to train models [16]. In contrast, deep learning automatically performs feature extraction through its consecutive neural network layers [17], with each layer transforming the input into a higher-level and more abstract representation, thereby enabling the modeling of extremely complex functions [18]. After training, deep neural networks (DNNs) can quickly process new inputs for prediction through nonlinear transformations in the hierarchy, and their flexible structure is suitable for customization in various biomedical applications such as images, sequences, graphs, and text [19]. In most cases, deep learning reduces the need for manual feature engineering, allowing models to directly learn complex representations from raw data. In summary, advanced technologies such as artificial intelligence, machine learning, and deep learning have introduced revolutionary changes to biomedical data analysis. By leveraging these technologies, we can deeply understand and effectively utilize the potential of large-scale biomedical data, thereby bringing more opportunities and improvement solutions to translational biomedical research and medical services.

3. Current Status of NSCLC Research Based on Deep Learning

In recent years, continuous development and utilization of deep learning in the biomedical field, as well as the increasing demand for molecular analysis of cancer, have led to the realization of the potential deep learning in cancer classification and biomarker status prediction. Methods based on deep learning have not only performed well in traditional medical image diagnosis [20] [21], but also in lung cancer [22] [23] prognosis models. Deep learning technology has achieved promising results in various medical image interpretation tasks, with potential to reach the level of human experts, such as detecting diabetic retinopathy in fundus photographs, classifying skin cancer in skin photographs, and detecting breast lymph node metastases in pathological images. Therefore, many studies have applied deep learning technology to the auxiliary diagnosis of NSCLC, with great potential in PET/ diagnosis. Hosny *et al.* [24] used 3D convolutional neural networks (CNN) to identify prognostic features in 114 NSCLC patients from 5 institutions before treatment, and then used transfer learning to achieve the same effect in surgical patients. The results showed that the CNN were significantly related to the survival risk of patients in both the radiotherapy and surgery datasets. Shreyesh *et al.* [25] compared three popular deep architectures: artificial neural networks, CNN, and recurrent neural networks, to predict the survival rates of lung cancer patients at different stages using the Surveillance, Epidemiology, End Results (SEER) cancer registry lung cancer dataset. When the patient's survival period was divided into "≤6 months", "0.52 years", and ">2 years", the root mean square error was 13.5%, while the traditional machine learning model had a root mean square of 14.87%. The deep learning model outperformed the traditional machine learning model in both classification and regression methods. Kim *et al.* [26] developed and validated a preoperative deep learning model based on CT to predict the disease-free survival rate of patients with clinical stage I lung adenocarcin. The dataset used for training, tuning, and internal validation consisted of patients with T1-4N0M0 adenocarcinoma resected 2009 to 2015, and the external validation dataset included patients with clinical T1-2aN0M0 (stage I adenocarcinoma resected in 2014. The results showed that the deep learning model had a C-index of 0.7 - 0.80 for internal validation and 0.71 - 0.78 for external validation, which was comparable to the clinical results (C-index 0.78 for internal validation and 0.74 for external validation). The deep learning model based on chest CT could accurately predict the disease-free period of patients with clinical stage I lung adenocarcinoma. Paul *et al.* [27] combined features learned from pre-trained deep learning networks withomics and traditional quantitative features, and used them in a decision tree classifier to predict the survival of adenocarcinoma patients. When using traditional quantitative features, decision tree classifier achieved a maximum accuracy of 77.5% (AUC: 0.712). When using deep features, the decision classifier achieved a maximum accuracy of 77.5% (AUC: 0.713). When the extracted deep learning features were combined with radiomics features, the accuracy reached 90% (AUC: 0.935). The deep learning features and radiomics features combined showed performance in survival prediction for adenocarcinoma patients. Some of the latest advances in deep learning in cancer research can be cited to further illustrate the widespread application and significant effectiveness of deep learning in the biomedical field, especially in cancer classification and prognosis prediction [28] [29].

4. Application of Deep Learning in Prognostic Models of Non-Small Cell Lung Cancer

In recent, deep learning has rapidly developed in the research of assisting precise diagnosis and treatment of lung cancer due to its powerful information processing capability. The research hotspots mainly focus lung cancer diagnosis, prediction of gene phenotype and gene mutation, and prognosis assessment. In terms of prognosis assessment, researchers generally focus on survival and recurrence, treatment efficacy distant metastasis, and complications. This article briefly introduces the research progress and existing problems of deep learning in the application of NSCLC prognostic models from above perspectives [30].

4.1. Prediction of Survival and Recurrence

In recent years, with the widespread adoption of new treatment strategies, the 2-

year relative survival of lung cancer patients has increased [31], but the 5-year relative survival rate is still only about 23% [32]. Although early and treatment can improve the survival rate of lung cancer patients, according to previous studies [33], the recurrence rate of lung cancer after surgical resection of malignant remains between 30% and 60%. Therefore, predicting survival and recurrence remains the mainstream of cancer prognostic models.

4.2. Prediction of Efficacy

In the evaluation of treatment effectiveness, the Response Evaluation Criteria in Solid Tumours (RECIST) [34] is still the most used standard for NSCLC, especially in clinical trials of new treatment methods or new drugs. Li *et al.* [35] included 289 patients squamous cell carcinoma (SCC) who had received immunotherapy, and used neural networks to screen various clinical variables to establish predictive models with disease control rate (R) and objective response rate (ORR) as outcome indicators. The results showed that the AUC of the internal validation of the DCR model was 0.952, and the AUC of the external validation was 0.949. The AUC of the internal validation of the ORR was 0.8030, and the AUC of the external validation was 0.704. Another team [36] also a model based on clinical variables using neural networks to predict the efficacy of immunotherapy in LUAD patients. In the training set, the AUC of the model predicting ORR and DCR was 0.901 and 0.857, respectively; in the test set, the AUC was 0.817 and 0.824, respectively.

4.3. Prediction of Distant Metastasis

Distant metastasis is a major specific in the late stage of lung cancer, with lung cancer prone to metastasize to the liver, brain, bones, and adrenal glands, and deaths related to cancer metastasis account for 90% of all lung cancer deaths [37]. Predicting the likelihood of tumor-specific metastasis and stratifying patients by can enable targeted interventions for high-risk lung cancer patients. Previously, scholars [38] [39] used traditional machine learning methods to predict distant metastasis inCLC based on imaging features, but the predictive power was generally limited. Subsequently, scholars have also tried to improve the prediction results using deep learning methods. Tau *et al.* [40] included 264 NSCLC patients with PET/CT and followed up for at least 6 months, using a DenseNet machine learning architecture to build a binary classification model to predict the M0/M1 classification before and after treatment. The average accuracy for predicting the M classification treatment was 0.82 ± 0.04, but for predicting the M classification at the end of treatment, the average accuracy was still low, only 0.63 ± 0.05. Xu *et al.* [41] used a time series model, including 268 stage III NSC patients who received radical chemoradiotherapy, using chest CT images before treatment and at 1, 3, and 6 months after treatment, and a model using CNN and recurrent neural network transfer learning to predict patient outcomes, which could predict survival well (AUC = 0.74), but the performance predicting distant metastasis was still low (AUC = 0.657). The performance of predicting distant metastasis based on radiomics using deep learning was, which may be related to the limitations of the imaging site, position, and resolution, providing limited information that cannot fully represent the overall state of the human body predict systemic metastasis. Numerous studies [42] [43] have shown that the biological characteristics of tumor cells—such as proliferation, invasion, metastasis, immune escape, and angiogenesis—are regulated by the tumor microenvironment (TME) and changes in gene expression. Consequently, researchers are very interested in genomics-based analysis. Baradei *et al.* [44] utilized a convolutional variational autoencoder to extract features from RNA sequencing, microRNA sequencing, and DNA methylation data from 19 LUAD patients. They built a deep learning model based on three heterogeneous data layers to distinguish the metastatic state, achieving an accuracy of 3.83% ± 0.44% and an AUC of 0.91. Liu *et al.* [45] further explored 70,640 methylation sites from 461 LUAD samples and 248 miRNAs from 513 samples, through LASSO and survival analysis, finally identified 22 genes that play a key role in the immune regulation mechanism of LUAD, and used these 2 genes to build a deep learning model based on an encoder architecture to predict distant metastasis, with AUC and area under the precision-recall curve (AR) reaching 0.92 and 0.89, respectively, and outperforming common methods in bioinformatics such as DNN, multil perceptron, random forest, and decision tree [46]. This confirmed the potential of deep learning in predicting distant metastasis in lung cancer through genomics, and also suggested that facing the same prognostic event, collecting information from different perspectives, and using multi-omics and multi-modal integration methods might achieve higher accuracy.

4.4. Complication Prediction

The probability of complications after treatment for NSCLC patients is inconsistent. If complications are predicted early along with related factors, patients can be stratified by risk and guided for later intervention and care. Cancer patients have a higher risk of death from disease (CVD) than the general population [47]. Chao *et al.* [48] developed a deep learning CVD risk prediction model trained on 30,28 lung low-dose CT data from the National Lung Cancer Screening Trial. The model achieved an AUC of 0.871 on a separate test set of 2085 subjects and identified patients at high risk of CVD death (AUC = 0.768). Radiation pneumonitis (radiation pneumonitis, RP) is one of the major adverse reactions of chest radiotherapy. Liang *et al.* [49] used a 3D CNN to build a dose distribution-based RP prediction model. The model achieved an AUC of 0.842 and showed that the regions strongly associated with ≥2 grade and <2 grade RP cases were the dose area of the contralateral lung and the high dose area of the ipsilateral lung, respectively. Cui *et al.* [50] developed a model based on an actual deep learning neural network architecture that combines PET/CT, cytokines, and miRNA to predict the risk of radiation pneumonitis (RP) after radiotherapy in NSCLC patients. The results showed that the combined deep learning model had better predictive performance than the traditional model (C-index: 0.660 vs. 0.613). Cancer pain is very common in lung cancer, especially in the late stage. Bang *et al.* [51] used the Matthews correlation coefficient to study the performance of deep learning models in predicting the worsening of cancer pain in hospitalized lung cancer patients with different input lengths and time bins. The final model was based on long short-term memory best and achieved optimal performance with an input length of 120 hours and a time interval of 12 hours (AUC = 0.80), indicating that using deep learning for advanced cancer pain management can potentially improve patients' daily lives.

5. Summary and Outlook

In summary, deep learning is increasingly being used in various prognostic models for CLC and has shown its advantages in automatic image segmentation, feature extraction and screening, and processing of diverse data. Currently, the application of deep learning in NSC prognostic models mainly focuses on clinical and radiomic features, but its potential in genomics and pathology is also gradually being explored, with a trend towards multi-omics and multi-modalities. However, there are still some limitations and challenges in the current deep learning-based NSCLC prognostic models. Deep learning has shown great potential in various biomedical fields such as genomics, transcriptomics, proteomics, drug discovery, and disease biology, and has made progress. Compared to traditional machine learning methods, deep learning is more advanced in feature extraction, noise resistance, generalization, and multifunctionality. With the availability of large biomedical datasets and advancements in model architectures, deep learning has become a mainstream technology, widely applied in tasks such as predicting protein structures, gene regulation, drug-target, and disease outcomes. However, challenges such as model explainability and integration of multi-modal data need to be addressed to facilitate its widespread use in clinical applications. In the future, while it is important to cautiously consider the limitations of models, deep learning will continue to offer new insights through the analysis of large biomedical datasets, potentially revolutionizing the field of biomedicine. Ongoing advancements in network design and training methods will further unlock the potential of deep learning, thereby contributing to improvements in human health. The explainability of deep learning models remains a challenge, as does the integration of multi-modal data. Addressing these issues and incorporating biological knowledge will accelerate the translation of deep learning technology into clinical practice. Currently, deep learning is gaining new insights from large biomedical datasets and is transforming the field of biomedical research and translation. Continuous advancements in network architecture, explainability, and methodologies will further unlock the potential of deep learning to advance human health.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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