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REVIEW ARTICLE

Advances in Radiomics to Assess Immunotherapy Associated with Efficacy and Adverse Events for Non-small Cell Lung Cancer

Haoyu An[1,*], Zhiheng Qiu[2], Yukun Zhou[3,a]

[1]*Faculty of Medicine, The Chinese University of Hong Kong, Ma Liu Shui, Hong Kong*
[2]*School of Data Science, City University of Macau, Macao, China*
[3]*China Pharmaceutical University, Jiangning, Nanjing, Jiangsu, China*
[a]*Email: 2020192123@stu.cpu.edu.cn*

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ABSTRACT

Radiomics enables high-throughput extraction of information from images, including features not easily visible or quantifiable to the clinician, and analyzes them to yield visual quantitative parameters. Immunotherapy, an emerging treatment for lung cancer, has significantly altered the traditional treatment paradigm due to its exceptional therapeutic effects. However, the absence of objective and precise tools for evaluating efficacy and adverse events hampers the comprehensive scientific assessment of immunotherapy's benefits and risks. Despite being in its nascent stages, numerous studies have demonstrated the utility of radiomics in early diagnosis, prognosis prediction, and guidance for personalized lung cancer treatment. This review summarizes the progress of radiomics in evaluating the efficacy and adverse effects of immunotherapy for non-small cell lung cancer, aiming to maximize its efficacy and minimize its risks, and discusses its clinical significance, future goals, and challenges.

1. INTRODUCTION

As per the Global Cancer Statistics 2020, lung cancer, with an estimated 2.2 million new cases and 1.8 million deaths, was the second most common cancer diagnosed and the leading cause of cancer mortality [1]. The high incidence and mortality rates of lung cancer thus contribute to a great disease burden. The two primary types of lung cancer are non-small cell lung cancer (NSCLC, 85%) and small cell lung cancer (SCLC, 15%) [2]. Traditional treatment modalities for NSCLC include surgery, chemotherapy, targeted therapy, and radiotherapy [3]. Recently, immune checkpoint inhibitors (ICIs), particularly anti-programmed cell death receptor-1 (PD-1)/programmed death ligand 1 (PD-L1) antibodies, have revolutionized advanced NSCLC treatment due to their significant impact on improving patient prognosis [4,5]. In the KEYNOTE-024 trial (NCT02142738), 305 advanced NSCLC patients were assigned to either the PD-1 inhibitor Pembrolizumab group or the chemotherapy group for treatment. The Pembrolizumab group had a significantly longer median progression-free survival (PFS) than the chemotherapy group (10.3 months vs 6.0 months) [6]. In the phase III PACIFIC trial (NCT02125461), 476 patients treated with the PD-L1 inhibitor Duvalumab had a median PFS of 16.8 months, compared to 5.6 months in the placebo group of 237 patients [7]. Based on these findings, the U.S. Food and Drug Administration (FDA) has approved ICIs, including Pembrolizumab and Duvalumab, for the treatment of advanced NSCLC.

The primary biomarkers for predicting the efficacy of NSCLC ICIs include PD-1/PD-L1, tumour mutation burden (TMB), and microsatellite instability (MSI)/mismatch repair (MMR) [8]. International mainstream guidelines suggest that stage IV NSCLC patients with driver gene-negative can benefit from single-agent immunotherapy when the PD-L1 TPS is ≥50% (Class IA evidence). The latest NCCN NSCLC guideline identifies TMB as a biomarker to guide NSCLC treatment with ICIs [9]. Additionally, microsatellite instability-high (MSI-H) is the first FDA-approved screening marker for pan-tumour ICIs. However, numerous challenges persist, including lengthy testing periods, high costs, inconsistent standards, low success rates, undefined thresholds, and even controversy over blood and tissue samples. Moreover, with an incidence of less than 5% in lung cancer, MSI-H could potentially serve as a predictor of immunotherapy efficacy [10]. The most common immune-related adverse events (irAEs) in NSCLC patients primarily affect the skin, colon, endocrine organs, liver, and lungs [11].

*Corresponding author. Email: 1155199943@link.cuhk.edu.hk

Biomarkers such as CD177, CEACAM1, immunoglobulin genes, baseline levels of interleukin-6, and sCTLA-4 can predict the occurrence of cellular toxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor-associated irAEs in melanoma. However, only a few biomarkers are available for predicting irAEs in NSCLC patients, and even fewer for predicting PD-1/PD-L1 inhibitor-associated irAEs.

Radiomics, an emerging field in nuclear medicine and general medical imaging, lacks a rigorous definition. Generally, it refers to the non-invasive prediction of tumor behavior by extracting quantitative, reliable, and reproducible information from diagnostic images, particularly complex patterns difficult for human eyes to identify [12,13]. Unlike simple imaging, radiomic features correlate with genomic data and capture tumor phenotypic features, providing information about tumor heterogeneity to enhance survival prediction accuracy and facilitate patient stratification. Currently, the lack of objective and precise tools to evaluate the efficacy and adverse events of immunotherapy makes it challenging to accurately identify the optimal patients for immunotherapy. Therefore, the rapid development and improvement of radiomics is urgently needed to address these complex issues. This review summarizes the research progress of radiomics in assessing the efficacy and adverse events of immunotherapy for non-small cell lung cancer, aiming to promote the application of precision tumor immunotherapy.

2. ASSESSMENT OF EFFICACY

2.1. Relationship between Radiomics and Immunotherapy-Related Markers

Driver gene-negative lung cancer patients cannot benefit from targeted therapy, necessitating the exploration of new therapeutic strategies. Since the 1990s, the establishment of lung cancer immunotherapy, primarily based on immune checkpoint inhibitors (ICIs), has been gradual [14]. ICIs eliminate tumour cells by inhibiting immune checkpoints on their surface and reactivating the immune system's ability to recognize these cells. This process results in a sustained anti-tumour response and enhances patient survival rates. However, as immunotherapy is not suitable for all patients, there is an urgent need for biomarkers to evaluate treatment efficacy beforehand. Currently, biomarkers frequently used in clinical practice encompass PD-L1, TMB, and tumour infiltrating lymphocytes (TILs).

2.1.1. PD-1/PD-L1

Immunohistochemistry (IHC) and whole-genome sequencing serve as primary methods for PD-1 detection. However, tumour heterogeneity and sampling errors may undermine assay accuracy due to tissue sample limitations [15]. CT radiomics, showing promising potential for non-invasive evaluation of immunotherapy efficacy, has been employed to determine PD-1 expression status. Tian Q et al. developed a radiomic model and juxtaposed it with a clinical model to evaluate PD-1 expression efficacy in NSCLC [16]. The study encompassed 143 NSCLC patients (30 PD-1 positive and 113 negative), divided into a training set ($n = 101$) and a validation set ($n = 42$). Subsequently, a clinical model was formulated based on two factors—prealbumin and cysteine protease inhibitor C—closely associated with PD-1 expression. A radiomic model was constructed by extracting and filtering CT-based imaging features. Additionally, a CT nomogram was established by integrating clinical factors and radiomic features. The results indicated that radiomics could more accurately assess NSCLC PD-1 expression (AUC = 0.89 in the training set and AUC = 0.81 in the validation set). The radiomic nomogram (AUC = 0.92 in the training set and AUC = 0.86 in the validation set) demonstrated superior performance ($P < 0.05$). This study confirmed the high accuracy of CT radiomics and the radiomic nomogram in non-invasively evaluating PD-1 status, aiding in further estimation of immunotherapy effects. However, additional potential clinical factors, not limited to prealbumin and cysteine protease inhibitor C, should be meticulously considered. Furthermore, a larger validation set is required to verify the actual performance.

2.1.2. TMB

Balard et al. demonstrated that TMB outperformed PD-L1 in predicting the efficacy of ICIs. However, the widespread adoption of TMB assay was hindered by the invasive nature of biopsy and the high cost associated with whole exome sequencing (WES) [17]. Wang et al. developed a support vector machine-based fusion-positive tumor prediction model to determine TMB status in early-stage lung adenocarcinoma (LUAD) [18]. They included 61 pulmonary nodules (PNs) from 51 LUAD patients with postoperative diagnoses, which were divided into a training cohort (41 PNs) and a test cohort (20 PNs). 718 quantitative three-dimensional radiological features were extracted from the segmented volume of each PNs and 78 clinical and pathological features were obtained from the medical record. In the training and test sets, the AUC values for predicting TMB status using radiomic features were 0.707 and 0.606, respectively. However, the combination of radiomics with clinical information showed improved prediction performance, achieving AUC values of 0.775 and 0.671, respectively. This demonstrates the feasibility and effectiveness of using radiomics to predict TMB. Guan et al. retrieved CT images of 37 lung cancer patients from The Cancer Imaging Database (TCIA), extracted radiomic features using medical image processing software (3D Slicer), and subsequently identified 9 imaging features associated with TMB using LASSO regression [19]. Lastly, a prediction model for TMB was developed using logistic regression, considering 3 imaging features. Interestingly, the AUC of the CT model reached 0.882, suggesting that the model based on CT radiomic features was highly effective in predicting the TMB status of squamous lung cancer. In conclusion, TMB prediction models based on CT radiomic features demonstrate strong performance, particularly in predicting the TMB status of squamous lung cancer at present. By comparing the model development process, it becomes evident that standardizing image processing, such as utilizing professional medical image processing software, as well as ensuring the rationality of radiomic feature selection, including the application of appropriate regression methods, both contribute significantly to enhancing prediction accuracy.

2.1.3. TILs

The killing effect of tumour-infiltrating lymphocytes (TILs) on tumour cells in the tumour microenvironment remains controversial in terms of its relationship with patient prognosis. Currently, radiomics can partially predict the infiltration of TILs. Khorrami et al. divided 139 NSCLC patients from two institutions into a training group ($n = 50$) and two independent validation groups ($n = 62$, $n = 27$) [20]. The researchers used

machine learning to compare the differences ("delta") in the radiomic texture (DelRADx) of the tumour nodes before and after 2–3 cycles of ICIs treatment. DelRADx demonstrated excellent performance in predicting the efficacy of immunotherapy, achieving AUC values of 0.88, 0.85, and 0.81 in the training and validation sets, respectively. Additionally, this research discovered a strong association between concurrently measured radiological risk scores (DRS) and overall survival (OS) (HR [95% CI] = 1.64 [1.22, 2.21]; P = 0.0011). It is worth noting that the radiomic features surrounding the tumour exhibited an association with the density of TILs observed in diagnostic biopsy samples. The research successfully demonstrated the accuracy of radiomic prediction in determining the level of TILs infiltration. However, the ability of TILs infiltration level to identify the immunotherapy response in NSCLC patients remains uncertain and requires further investigation.

2.2. Predicting Immunotherapy Efficacy Based On Radiomics

Radiomics, through the use of data representation algorithms, can potentially identify disease characteristics that are challenging to discern and evaluate visually by extracting quantitative features from medical imagery. Based on imaging data from concluded clinical studies, radiomic biomarkers present promising development prospects in the field of immunotherapy.

Trebeschi and colleagues conducted a retrospective analysis of contrast-enhanced CT scans from 123 advanced NSCLC patients, encompassing 572 primary and metastatic lesions, prior to immunotherapy. They discovered that lesions responsive to immunotherapy typically exhibited radiomic features with more heterogeneous morphological contours, including inhomogeneous density patterns and compact borders [21]. To evaluate the predictive power of radiomics for immunotherapy efficacy, they employed machine learning to develop a single radiomic biomarker. The biomarker demonstrated excellent performance in NSCLC cases with lung metastases (AUC = 0.83, $P < 0.001$) and lymph node metastases (AUC = 0.78, $P < 0.001$). Furthermore, the radiomic biomarker showed good performance in primary tumours (AUC = 0.79, P = 0.05), liver (AUC = 0.75, P = 0.13), and adrenal gland lesions (AUC = 0.70, P = 0.18), although it did not reach statistical significance due to the limited sample size. This study illustrated that even a single radiomic biomarker can facilitate the prediction of a patient's response to immunotherapy.

Yang and colleagues integrated radiomics, laboratory data, and baseline clinical data to construct a multi-omics deep learning model. This model, based on the Simple Temporal Attention (SimTA) module, aimed to predict the efficacy of anti-PD-1/PD-L1 monotherapy in patients with advanced NSCLC [22]. Cross-validation revealed that the prediction model effectively discriminated between responders and non-responders, with an AUC of 0.80 (95% CI: 0.74–0.86). It was evident that the progression-free survival (PFS) and overall survival (OS) of the low-risk group were significantly longer than those of the high-risk group. Similarly, Yang and colleagues amalgamated radiomic features from CT images with clinicopathological features to construct a radiomic nomogram model, aiming to predict the long-term clinical benefits of immune checkpoint inhibitors (ICIs). The results indicated that the AUC for the training and validation cohorts was 0.848 and 0.795, respectively, while the PFS for these cohorts was 0.749 and 0.791, respectively [23]. In conclusion, the radiomic nomogram model, which combines radiomics and clinicopathological features, holds promise as a noninvasive biomarker for predicting immunotherapy efficacy. This has significant implications for guiding individualized treatment in advanced NSCLC.

Numerous studies have established a close relationship between the status of intratumoural and peritumoural immune infiltration and the efficacy of immunotherapy [24–26]. Presently, three distinct immune phenotypes are accurately delineated: immune-inflamed, immune-excluded, and immune-desert. Immune-inflamed tumours, characterized by dense and functional infiltration of CD8+ cells, tend to respond to immunotherapy. Sun and colleagues developed a predictive model that integrates contrast-enhanced CT images with RNA-seq genomic data, incorporating five radiomic features closely associated with CD8+ T cells. Conversely, immune-excluded and immune-desert tumours exhibit less responsiveness to immunotherapy, attributable to the absence of immune effector cell infiltration or the enrichment of immunosuppressive cells. The predictive model demonstrated a robust capability to forecast the gene expression profile of CD8+ T cells in the TCGA validation set, achieving an AUC value of 0.67 (95% CI: 0.57–0.77; P = 0.0019) [27]. The estimation of CD8 T cell counts using this radiomic signature undeniably offers a novel approach for predicting clinical outcomes in patients undergoing immunotherapy.

3. ASSESSMENT OF IMMUNE RELATED ADVERSE EVENTS

Immune-related adverse events (irAEs) are defined as adverse drug reactions of varying severity, caused by immune dysregulation, excluding non-specific infusion reactions observed in a series of immunotherapy clinical trials. Specifically, the immune mechanisms underlying irAEs encompass enhanced T-cell activity against antigens in tumours and normal tissues, increased levels of pre-existing autoantibodies, elevated inflammatory cytokine levels, and an amplified complement-mediated inflammatory response [28]. A comprehensive meta-analysis reported the incidence of irAEs to be approximately 83% for CTLA-4 inhibitors, 72% for PD-1 inhibitors, and 60% for PD-L1 inhibitors [29]. At present, specific irAEs are monitored clinically using conventional laboratory markers, including routine chemistry, myostatin clearance, thyroid function tests, and serum cortisol/adrenocorticotropic hormone levels [30]. To enhance the safety of immunotherapy for lung cancer, the development of additional radiomic biomarkers for the diagnosis and prediction of irAEs is underway.

3.1. Diagnosis and Prediction of ICIs-Associated Pneumonia

Off-target effects, resulting from immune system overactivation, can impact various organ systems and tissues [31]. Typically, the most common immune-related adverse events (irAEs) are dermal, gastrointestinal, and endocrine toxicities, while neurological, cardiac, and pulmonary toxicities are deemed potentially lethal.

Colen et al. developed a predictive model for immune-checkpoint inhibitor (ICI)-associated pneumonia by extracting radiomic features from chest CT scans. The model correctly identified two out of 32 patients treated with ICIs who

developed ICI-associated pneumonia [32]. Despite the limited size of the training sample, this model could be beneficial in stratifying patients at risk of developing pulmonary toxicity, thereby allowing timely adjustment of therapies to enhance the safety of ICIs. In a similar vein, Tohidinezhad et al. constructed a predictive model by extracting the most predictive radiomic features from pneumonia-associated CT images and implementing a 75-mm spherical region of interest. This model accurately diagnosed 10 out of 12 cases [33]. These findings suggest that radiomic biomarkers, when applied to CT imaging, could aid clinicians in accurately identifying and diagnosing ICI-associated pneumonia.

The Common Terminology Criteria for Adverse Events (CTCAE) classifies immune-related adverse events (irAEs) into grades 1 through 5 based on severity. If severe irAEs (irSAEs) of grade 3 or higher occur, the administration of immune-checkpoint inhibitors (ICIs) should be permanently halted. Consequently, there is an urgent need to develop biomarkers that can predict irSAEs, which could significantly reduce the mortality rate associated with immunotherapy. Mu et al. conducted a retrospective study involving 146 advanced non-small cell lung cancer (NSCLC) patients, generating a radiographic score (RS) from radiomic features extracted from baseline PET, CT, and PET/CT fusion images [34]. They developed a nomogram model that combined the RS with the type and dosing schedule of ICIs to predict irSAEs in patients with advanced NSCLC. The model demonstrated significant predictive value, with area under the curve (AUC) values of 0.92 and 0.88 for the training and prospective validation cohorts, respectively. This underscores the substantial value of PET/CT images in predicting irSAEs.

3.2. Diagnosis and Prediction of General irAEs

The use of radiologic methods to detect immune-checkpoint inhibitor (ICI)-related toxicity is gaining clinical consensus, despite the lack of reported specific radiomic features of immune-related adverse events (irAEs). A recent study identified a correlation between general irAEs (primary and secondary adverse events) detected via 18F-FDG PET/CT and the efficacy of immunotherapy for certain cancers. This finding could illuminate the potential of radiomics in predicting other types of irAEs in non-small cell lung cancer (NSCLC) patients. Nobashi et al. found that the onset of ICI-related thyroiditis, detected through early 18F-FDG-PET/CT, was associated with clinical improvement in patients with renal cell carcinoma, malignant melanoma, and lymphoma at a 12-month follow-up [35]. In a similar study, Sachpekidis et al. conducted 18F-FDG-PET/CT on 16 metastatic melanoma patients undergoing ibritumomab treatment. They found that seven patients developed at least one type of irAE, most commonly colitis and arthritis. Notably, these seven patients had significantly longer progression-free survival (PFS) than those without irAEs ($P = 0.036$) [36]. These findings suggest that certain irAEs may be linked to the efficacy of immunotherapy in NSCLC patients. Further exploration of these irAEs using advanced radiomic methods could provide valuable insights.

4. DISCUSSION

Radiomics, a current research focal point, has demonstrated potential in non-invasively evaluating certain adverse events and the efficacy of immunotherapy treatments in lung cancer patients by predicting the status of related markers. Based on existing research and forward-thinking, we foresee three primary medical applications.

1. Early Detection and Diagnosis: By integrating radiomics with artificial intelligence and machine learning algorithms, we can potentially enhance early disease detection and diagnosis, such as cancer, by identifying subtle tissue changes that may be imperceptible to the human eye.
2. Personalized Medicine: Radiomics can contribute to the development of personalized treatment plans by offering detailed insights into tumor heterogeneity without invasive procedures.
3. Treatment Response and Prognosis: Radiomics can be utilized to predict patient outcomes and monitor treatment responses, aiding in treatment plan adjustments and enhancing patient outcomes.

However, we also recognize several challenges and future research directions.

1. Standardization: There is a pressing need for standardization in the extraction and analysis of radiomic features to ensure result reproducibility and comparability.
2. Integration with Other Omics: Merging radiomics with other omics data, such as genomics, proteomics, and metabolomics, can offer a more holistic understanding of diseases.
3. Clinical Validation: More clinical studies are required to validate the practical utility of radiomics.
4. Improving Algorithms: The development of advanced algorithms is necessary to enhance the accuracy and stability of models for feature extraction and analysis.
5. Data Sharing and Collaboration: Promoting data sharing and collaboration can aid in the development of more robust and generalizable radiomic models.

5. CONCLUSION

This review highlights recent advancements in radiomics for evaluating the efficacy and adverse effects of immunotherapy in non-small cell lung cancer. However, several limitations persist. These include the absence of multicentre prospective radiomic studies to guide clinical practice, due to a lack of standardized imaging research methods. Furthermore, the stability and accuracy of radiomic features are influenced by factors such as image reconstruction algorithms, preprocessing methods, transmission protocols, inter-observer variation, and feature extraction algorithms. Currently, radiomics is in a phase of ongoing development and represents a future trend in precision oncology diagnosis and treatment technology. Addressing these challenges is crucial for achieving clinical transformation. Consequently, further research is required to resolve the issues discussed and to validate these findings.

DECLARATIONS

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contribution

HA contributed in conceptualization, methodology and supervision. ZQ contributed in literature search and organization. All authors contributed in writing – review & editing the manuscript and commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

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