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Research Article

Radiomics Approaches to Assess Tumours Anti-PD-1 or Anti-PD-L1 Immunotherapy: Imaging Biomarkers, New Development and Challenges

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ABSTRACT

Although immunotherapy has changed the management of various tumors and obtained unexpected responses, lots of cancer patients failed in this new treatment. Thus, identifying predictive biomarkers to select patients who benefit from immune checkpoint blockades therapy is crucial. Computational medical imaging (called as radiomics), which is a rapidly evolving discipline, having the advantage of non-invasive ,the ability to further describe the phenotype of the tumor and evaluate its microenvironment. This review is focused on the progress of computational imaging analysis and radiomics-based biomarkers for evaluating efficacy of anti-PD-1/PD-L1 immunotherapy, and predicting immune-related side effects.

Keywords: Radiomics; Computational medical imaging; Immunotherapy; Oncology

INTRODUCTION

The immune checkpoint: programmed death 1 (PD-1)/ programmed death ligand-1 (PD-L1) signaling pathway plays a key role in tumor escape immune response from the host.1 PD-1 and PD-L1 pathway blockade therapy has achieved durable antineoplastic responses and long-term remission in a wide range of cancer patients [1-3]. Although unprecedented results are observed, the immune therapy is failed in a lot of cancer patients.[4] Therefore, finding predictive biomarkers to select patients who would benefit from immune therapy is crucial to prevent them from treatment failure, high economic loss and severe immunotoxicity. Currently, tumor immunohistochemical staining is the preferred method to detect the expression of PD-L1. However, its clinical application is not satisfactory, and there are some clinical practice problems that have not been solved. For example, NSCLC benefit patients, the expression of PD-L1 can range from 1% to 100%. Even the patients with negative PD-L1 staining, about 20% to 25% of them respond to treatment. [5] The expression of PD-L1 is not equal to immune therapy treatment effective because the variability and spatial intratumoral heterogeneity of tumor. It is necessary to obtain the information of tumor immune microenvironment at the same time.

During immunotherapy, response became a new challenging issue in oncology practice.Immune-related side effects included symptomatic pseudoprogression (PsPD), delayed response, hyper-progressive disease(HPD), immune-related pneumonitis and so on. Immune-related side effects, interfere with the evaluation of clinical outcomes, and even endanger the lives of patients. [6] Recently, new criteria for evaluating response to immunotherapy immune in solid tumors (iRECIST) were accepted. However recent reports [7,8] suggested that the iRECIST criteria failed to distinguish true progression from pseudoprogression in some patients. More precise assessment methods are urgently needed for evaluating the efficacy of immunotherapy.

Recent studies [9,10] have suggested molecular imaging of the immune checkpoint receptor PD-1 and its ligand PD-L1 as a strategy to guide anti-PD-1 or anti-PD-L1 targeted immune checkpoint therapy. Although these radiolabeled antibodies have advantages as imaging agents (i.e. naturally high avidity, ease of production andantigen specificity , etc.), several disadvantages have also been noted, including long circulation times, nonspecific uptake, and high background signal, resulting in more than 24-hour intervals between the injection of tracers and visualization of target molecules. These results need more preclinical studies support further investigations of these agents for clinical use.

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Computational medical imaging, called as radiomics, which is non-invasive and allows evaluation tumor and its microenvironment, has been a supplement to the biopsy. The final goal of radiomics is to identify imaging biomarkers as decision support tools for clinical practice. Then clinicians will be promoted a better understanding of cancer biology to assess changes and treatment sequences during disease progression. Radiomics-based biomarkers become a research hotspot for predicting anti-PD-1/PD-L1 treatment effective.

RADIOMICS AS A NOVEL TOOL TO QUANTITATITIVELY ANALYSE TUMOR IMAGING

Computational medical imaging (radiomics) is a promising and rapidly growing discipline.19 Using conventional analysis of standard imaging examinations, such as magnetic resonance imaging (MRI),computerized tomography (CT)and positron emission tomography (PET), which relies on visual interpretation based on simple features - such as tumor size, total shape, contrast or signal intensity, radiomics approach computerized these imaging exams and translated them into complex quantitative data. These high-dimensional data allow for a more in-depth description and analysis of the tumor's phenotype. The basic assumption is that data from these exams could reflect the structure of the tissue, as well as their cellular and molecular composition.

In the field of oncology, radiomics has discovered application programs as a diagnostic tool, a predictive tool for predicting response(e.g., disease progression or recurrence). Being widely used in a variety of tumors, such as glioma, head and neck cancer, breast cancer,lung cancer, prostate cancer, rectal cancer, liver cancer.Take glioma for example, radiomics has successfully detected malignancies in screening MRI scans, provided a method for distinguishing between benign and malignant lesions, predicted the risk of recurrence after treatment, and provided a non-invasive method for assessing treatment response and aided to select patients who would benefit from treatment.

This method have several advantages:(1)Noninvasive; (2)Capable of evaluating the tumour and its microenvironmentcomprehensively , thus characterizing their spatial heterogeneity;(3)being easily repeat over time, having the potential to understand the changes in disease and history throughout treatment sequence.

PROCESS OF RADIOMIC ANALYSIS

The procedure of radiomic analysis can be divided into several different stages: (1) image acquisition and segmentation, (2) feature extraction and selection of the most characteristic features, (3) use selected features to construct classifiers to predict the outcome of interest, (4) evaluate model performance and statistical analysis. (Figure 1).

Image acquisition and segmentation

Computational medical imaging quantitative analysis and radiomics used to quantify the distribution of signal intensities of the volume interest can be applied to different and multiple imaging modalities. Determining the volume of interest is first and the key step in radiomic analysis. Several methods can be used to determine the area that needs to be analyzed. The gold standard for present radiomic analysis is manual identification by radiologists. However, the approach which try to average or aggregate different delineations and descriptions from multiple individual readers is potentially more cumbersome. The reconstructed image are imported into software, which allows a professional radiologist to place a border or assigned markers around the designated area of interest for each slice of the displayed image. The automatic segmentation method has high precision and repeatability. In the case of manual delineation is time consuming and prone to inter-observer variability, it has been shown that compared with semi-automatic or manual delineation method the automated approaches are fast and reduce inter-observer variability. But semi-automated segmentation methods is the most commonly used, and often performed by a radiologist for final check, also been used as a gold standard method. Especially when tumors are in more healthier structures, it is necessary to be manually re-corrected by an experienced radiologists to manually correct the outline of the computer.

Feature extraction and selection of most characteristic features

Different types of radiomic feature are introduced as below.

Semantic feature: These are features of the tumor that described by radiologist during analysis of the images. These features tend to be more adaptable to changes in the scanner and acquisition parameters, but are subject to subjective evaluation and interobserver variation. In case of lung cancer, some of thesecharacteristics include the location of pulmonary nodules, the presence of emphysema, glass opacity, effusion,etc. Then the imaging data need to be pre-processed to reduce the impact of different scanners to obtain images with different spatial resolutions (e.g. reading images through a Gauss filter), which may be useful for subsequent analysis.

Computational imaging characteristics: These characteristics usually divided into statistical features, shape and volumetric features. First-order statistical features which are related to the statistical moments within the volume of interest and are calculated from the voxel intensities of the image without considering spatial and architectural relations. These features include entropy, skewness, kurtosis, standard deviation, average, median,range asymmetry, and variance. Illustrating with examples, the standard deviation and variance reflect the difference of degree between gray levels and mean value in the histogram. And shape features include width, height, depth, circumference, area, eccentricity, compactness, radial distance, roughness, elongation equivalent diameter, and three-dimensional sphericity of the nodule. Volumetric features include margins, volume, minimum and maximum diameters. Other features include three-dimensional shape and edge sharpness.

Second-order features (Texture features): Second-order features are higher-order statistical indicators used to identify spatial and architectural relationships the intensities of voxels of interest area, and used to assess heterogeneous enhancement. And the calculation of which is mainly based on the matrix described by Haralick et al. For instances gray-level co-occurrence matrices (GLCM), gray-level run length matrix (GLRLM), gray-level size zone matrix (GLZLM) , neighborhood gray-leveldifferent matrix (NGLDM).

Wavelet features: These features provide a method for acquiring multi-scale qualities across multiple different frequencies and wavelengths. And these features include two attributes: Fourier transforms and Linear filter, as Gabor filter, which can be used for both pre-processing steps and collecting spatial or frequency characteristics. 59, 60 The collected features can be global (the value of the whole region of interest) or local (the value of each tumor region).

Feature selection

Due to the high-dimensional effects of radiological variables,computational medical imaging currently includes about 50 to 500 spatial quantitative features and some studies even have as many as 5,000 features.The great number of features lead to "curse of dimensionality," an classic contention in the field of omics (genomics, proteomics, etc.), which leads to the possibility of obtaining false positive results. Multiple comparison adjustments (Bonferroni correction) and control error rates (Benjerni-Hochberg) are the commonly used methods to deal with this problem. Univariate and multivariate models were used to do feature selection. The common univariate algorithms such as Chi square test,Fisher exact test and Wilcoxon rank sum test,which can compare the correlation between the features and the selected outcome variable to determine the most predictive features. Multivariate models not only solves the problem of univariate analysis by measuring the feature correlations of the selected results, but also helps to resolve the associations between features. Multivariate models of radiometric analysis include minimum redundancy maximum relevance,joint mutual information, and variable importance on projection measure for principal component analysis (PCA-VIP) to realize selecting the top features.

Constructing a classifier

Supervised and unsupervised are two primarily different classification approaches. Combined with the selected top features, it has the function to predict the probability of an event or the outcome of interest.

Supervised classification models: This model based on a set of labels (first training sets), to evaluate the category of interest (second training sets). The two training sets should be independent. When independent queues are not available, the method of dividing the initial data set or cross-validation is usually used, but the interpretation of the results must be cautious. Support vector machines, random forest classifiers, linear discriminant analysis, quadratic discriminant analysis, are widely used in the field of computational medical imaging.

Unsupervised model: In some cases, the outcome labels are not clear. The unsupervised model first classifies the selected characteristics into different categories without using any predefined labels, the aim of which is to discover the hidden categories. The methods of partitioning data (clustering methods) include hierarchical-, Bayesian-, and partitioning-based approaches. Even with known outcome labels, unsupervised clustering also be used to evaluate the practicability of the selected functions. There is no uniform standard to construct model. These are the methods of partitioning data (clus-tering), and establishing association.

Evaluate Model Performance and Statistical Analysis

Evaluate model performance refers to the representation of data from multiple levels through advanced statistical learning methods organized in multiple levels. The level is not predefined by the user, but is obtained from the data of the algorithm, thereby imitating the functions of human neurons. Devariable selection can be achieved in an integrated way, based on raw data and identification features. In the context of supervised classification methods, as the performance of delta-radiomic features is usually achieved by a receiver operating curve multiplying the true positive rate by the false positive rate, and constantly changing the decision threshold. The results are reported as AUC, and the higher the AUC,the higher the classification performance. And other indicators for assessing performance include accuracy, reliability, sensitivity, specificity, and true and false predictive rates. In the methods of unsupervised classification, complex image features are produced directly from the raw data, like clustering, making evaluate performance more complicated . External validity measures include purity, normalized mutual information, Rand index, and F measure are used to assess cluster quality. Internal quality criteria metrics include high intra-cluster similarity and low inter-cluster similarity.

Radiomics can Personalise Immunotherapy

In this field, predictive biomarkers is primary need, peripheral blood provide biomarkers to predict and monitor patients' responses to treatment seems to be an ideal method. Alice O et al84 analyzed peripheral blood samples from advanced non–small cell lung cancer (NSCLC) patients, who received first or second treatment cycle of PD-1–targeted therapies. The PD-1 blockade effector-like phenotypic signature of CD8 cells (HLA-DR+ CD38+ Bcl-2lo) were detected increasing in~70% of patients. And a delayed or absent PD-1+ CD8 T-cell response had been observed in 70% of patients with disease progression, while 80% of patients with clinical benefit exhibited PD-1+ CD8 T-cell responses. The results showed that peripheral blood analysis could provide valuable insights for NSCLC patients who treated with PD-1–targeted therapies. analyzed peripheral blood samples from 20 stage IV melanoma patients before and after weeks of anti-PD-1 immunotherapy. The pre-treatment frequency of HLA-DR+CD14+ CD16−monocytes in patients was a strong predictor of progression-free and overall survival in

response to anti-PD-1 immunotherapy. These biomarkers improved clinical outcomes of anti-PD-1 immunotherapy.

However, blood-based biomarkers also have some clinical practice problems that might cause unreliablity. Radiomics, an emerging field, which is non-invasive and allows evaluation tumor and its microenvironment, has being imaging biomarkers as decision support tools for clinical practice. In recent years, there is evidence that parameters obtained by texture analysis of radiological images, could reflecting the underlying spatial variation and heterogeneity of some tumours. By the means of radiomic analysis of CT images, a large number of radiomic features has been found having prognostic power that can infer the possibility of tumor metastasis at different sites and predict clinical outcomes. developed an immune pathology-informed model utilizing radiomics features that was a prediction of overall survival rate of lung cancer patients undergoing surgery treatment. The model can distinguish the patients with low CT image intensity and high heterogeneity image features, who had the highest survival of all those patients and who also had low PD-L1 expression in their tumours and high CD3 cell infiltration. Chen RY et al investigated the relationship between PD-L1 expression and immunohistochemical (IHC) biomarkers or the FDG-PET related radiomics in head and neck cancer (HNCs) patients. Thestudy found that the percentages of p16 and Ki-67 staining, as well as several PET/CT-derived textural features could provide additional information to determine tumor PD-L1 expression in HNCs. developed an eight variables radiomic signature model for CD8 cells, using CT images and RNA sequencing data from patients participated in the MOSCATO trial. Then Sun and colleagues used data of patients from two different datasets, who have been divided into different tumour-immune phenotypes to validate the concordance of the radiomic signature with gene signature of CD8 cells.. The radiomics signature was proven to be associated with clinical outcomes of the patients who treated with anti-PD-1 or PD-L1 immunotherapy. Thus, these studyies have provided an exciting analysis of the potential role of radiomics for personalising immunotherapy. And the results of such promising retrospective radiomics analyses still need to be further evaluated in prospective clinical trials.

Radiomics can Evaluate Immune-Related Side Effects

Due to the role of checkpoint inhibitors is different from cytotoxicity and targeted therapy, the response to immunotherapy may also be atypical. Imaging related response are observed such as pseudoprogression, delayed response, hyper-progressive disease, which interfere with the evaluation of clinical outcomes. These response have mainly been reported in patients with melanoma who received anti-CLTA4 treatment, about 15% of patients experienced pseudoprogression. These phenomenas can be explained by the recruitment and infiltration of T cells accompanied with edema and necrosis. At the same time, immune activation time and the beginning of clinical activity is still unpredictable. Cases of hyperprogression have been reported in several tumors, which is defined as the acceleration of tumor growth dynamics. Recently, after adjusting several standards, new criteria for evaluation of response to immunotherapy immune response evaluation criteria in solid tumors (iRECIST) were proposed and accepted. In some cases, the standard might be insufficient in clinical applications. Radiomics might be useful approach and effective supplement in clinical decision for immunotherapy. And radiomics models to predict pseudoprogression and hyperprogression will become the hot trend of our research.

These immunotherapies have also led to the development of new toxicity characteristics, called as immune-related adverse events(irAEs). Although irAEs are less common, such as pneumonitis which is a potentially deadly irAE. developed a two-feature radiomic model to predict immunotherapy-induced pneumonitis. Colen and colleagues performed radiomic analyses using chest CT images of patients who did (N=2) and did not (N=30) develop immunotherapy-induced pneumonitis. These radiomic features were significantly different and the model was highly accurate of immunotherapy-induced pneumonitis (accuracy, 100%, p= 0.0033). This study suggests that radiomic features has the potential to predict development of some immune-related side effects. And the results still need to be further evaluated in more studies.

CONCLUSION

Radiomics have shown tremendous promise as a means in diagnosis and treatment of oncology, including predict response of radiation therapy, different chemotherapeutic modalities, and recent explorations in the field of immune checkpoint inhibition therapy. Compared with current RECIST-based guidelines, imaging technologies have show an advantage in monitoring treatment response. In this article, we briefly overviewed the process of radiomic analysis, including image acquisition, building a classifier, evaluating model performance and statistical analysis. Although the initial results are excited, we also note that the standardization of image acquisition still be the great challenge to realize accurate radiomic analysis. Only after successful validation in large-scale trials radiomics can be achieved standardized verification and communication. We hope that radiomics will be widely developed in current immunotherapy, especially in evaluating treatment response and predicting immune-related adverse events, which can provide better clinical decision.

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