Radiomics in radiotherapy: Applications and future challenges

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Abstract
Radiomics has the potential to personalize patient treatment by using medical images that are already being acquired in clinical practice. Recently, with the development of computational and imaging technology, radiotherapy has brought unlimited opportunities driven by radiomics in individual cancer treatment and precision medicine care. This article reviews the advances in the application of radiomics in lung cancer, head and neck cancer, and other cancer sites. Additionally, we comment on the future challenges of radiomic research.

KEYWORDS
application and future challenges, radiomics, radiotherapy

1 | INTRODUCTION TO RADIOMICS

1.1 | What is radiomics?
Radiomics utilizes many, sometimes thousands, of automated feature extraction algorithms to transform region of interest imaging data into first-order or higher-order feature data.1,2 Furthermore, it improves the accuracy of clinical diagnosis, and has prognostic and predictive value by mining and analyzing the underlying relationship between the levels of the clinical data.3,4

1.2 | Why is radiomics a good choice to personalize patient treatment?
Radiomics rather than other -omics studies, which are advancing the development of radiation physics or cancer therapy, are now being utilized.5 There are three main aspects to the development of radiomics in radiology and oncology research:

1. There is an urgent clinical need.
   - Lack of more effective clinical methods to decode tumor heterogeneity.

2. Accurate computing technology as a guarantee.
   - Use of deep learning, machine learning, and artificial intelligence is on the rise.

   It is widely known that individual differences in tumors, as a result of tumor heterogeneity, are the key to the lack of effective treatment.6,7 Clinically, there is a great heterogeneity of tumors, and clinicians need clear decision-making information to support decisions about the treatment.8 Tumor heterogeneity is mainly manifested in morphology, gene expression, metabolism, proliferation, metastasis, and response to treatment.9 This might be the reason the same tumor type and treatment strategy results in a good prognosis in some patients, whereas similar patients have a recurrence or metastasis. The key concept behind radiomics is that the image contains more information than visual perception information. This hidden information can be extracted using complex algorithms to probe tumor heterogeneity.

2 | APPLICATION OF RADIOMICS IN RADIOThERAPY
As one of the three main means of tumor treatment, radiotherapy makes a major contribution to the cure rate of tumors. Radiotherapy has brought unlimited opportunities in cancer treatment, there is an
emerging and urgent need for personalized radiation therapy strategy that should be delivered. Radiomics is widely studied in the radiotherapy of lung cancer, and head and neck cancer. Here, we mainly introduce radiomics from these two aspects, and briefly explain the application in radiotherapy of other tumors.

2.1 | Radiomics in lung cancer

For locally advanced lung adenocarcinoma, radiomic features describing tumor phenotype were used as biomarkers for radiotherapy prognosis and had a strong correlation with distant metastasis. Radiation injury is one of the complications of radiotherapy. It was found that the difference in radiomic features increases with the accumulation of treatment dose, which could predict the incidence of radiation pneumonitis in patients with radiotherapy. Another study came to a similar conclusion, they found significant feature changes extracted from daily computed tomography (CT) as the treatment progressed. A rapid decrease in the mean CT number within gross tumor volume was associated with a higher survival rate. Also, part of the feature changes was found to be dose-related, which could be used to predict the clinical outcome according to the daily changes of CT. Patients with recurrent lung cancer after stereotactic body radiotherapy are often accompanied by ground-glass artifacts. Radiomics technology can detect local recurrence 2–5 months after stereotactic body radiotherapy, which is before that of a professional radiologist. Recently, a multicentric study reported that a prediction model incorporating positron emission tomography and CT radiomic features can accurately predict local recurrence with a sensitivity of 100% and a specificity of 96%. In patients with non-small cell lung cancer, radiotherapy can affect radiomic features, which can be used as a predictor of tumor clinical response at the end of radiotherapy, known as delta-radiomics (Δradiomics). Radiotherapy combined with the changes of Δradiomics (before and after radiotherapy) can better predict the overall survival and distant metastasis. Lung cancer radiomic studies mainly focus on the diagnosis, description of tumor biological characteristics, and prognosis. These studies provide additional information for the precise treatment of lung cancer by more fully mining the value behind the imaging.

2.2 | Radiomics in head and neck cancer

The morbidity and mortality of human papilloma virus (HPV)-positive oropharyngeal squamous cell carcinoma were higher than those of HPV-negative oropharyngeal squamous cell carcinoma. One study showed that CT imaging features can distinguish between HPV positive and HPV negative oropharyngeal squamous cell carcinoma and can be used to select appropriate treatment strategy. In head and neck cancer, such as oropharyngeal head and neck squamous cell carcinoma and non-oropharyngeal head and neck squamous cell carcinoma, different cell sublines have different radiosensitivity factors and different resistance to radiation. Radiomics can also identify sublines (subregions) of radioresistant cells in the tumor, so that individual therapeutic protocols can be developed to selectively increase the dose of radiation to these sublines of cells. In a 2014 study, Aerts et al. showed that a radiomic signature composed of four features models can provide prognostic information about intratumoral heterogeneity and can be used to predict survival, pathological grading, and gene expression typing. In addition to these studies, in head and neck cancer radiotherapy, the parotid gland usually receives a higher dose of radiation. Thus, its anatomical structure and radiomic features will change. The volume, mean intensity, fractal dimension, and entropy of the parotid gland decreased significantly at different time points during radiotherapy, which can be used to monitor the treatment response. For patients with glioblastoma, surgery and postoperative radiotherapy are often used. In these patients, radiotherapy with a uniform dose is usually associated with early recurrence. Rathore et al. used a support-vector machine, a machine learning algorithm, to grade the risk of peritumoral recurrence by extracting the radiomic features from the peritumoral region after surgery. These data gave a dose escalation regimen based on the recurrence probability score of the peritumoral region.

2.3 | Radiomics in other tumors

For clinical outcome prediction of gastroesophageal junction adenocarcinoma treated by chemo/radiotherapy, the authors extracted the radiomic features from CT images of 146 patients before radiotherapy. The results showed that the imaging model can effectively divide patients into low-risk, medium-risk and high-risk overall survival groups. Another study used radiotherapy planning based on radiomics. First, a texture-based machine learning classifier was used to detect the tumor edge on magnetic resonance imaging, and then, the target volume and organs at risk were mapped from magnetic resonance imaging to CT by multimodal deformation registration. Finally, a treatment plan (including brachytherapy and external irradiation) was designed based on radiomics heterogeneity of lesions. Furthermore, fractal dimension features extracted from tumor subregions in locally advanced rectal cancer patients receiving neoadjuvant chemoradiotherapy, conformal radiotherapy, with a prescription dose of 55 Gy, were the most accurate predictors of pathological complete response. In addition, the emergence of volumetric intensity modulated arc therapy technology has reduced the occurrence of serious radiation liver injury. Cozzi et al. evaluated the clinical outcome of volumetric intensity modulated arc therapy in hepatocellular carcinoma radiotherapy. Their results showed that two features have good accuracy in the prediction of local control: the area under the curve of energy and Gray-level Non-Uniformity (GLNU), which were 0.6659 and 0.6396, respectively. For the prediction of overall survival, the area under the curve of the feature named compacity reached 0.8014. Another study quantitatively evaluated radiation-induced changes of internal obturator muscles after radiotherapy for prostate cancer. The authors found that the pattern of change in radiomic features varied with the irradiation dose. ΔIntensity and Δ95th percentile showed an upward trend with the dose, and the Gray-level Co-occurrence Matrix (ΔGLCM)-contrast showed a decreasing trend with the dose. It is an imaging level reflection of the physiological structure change.
3 | FUTURE CHALLENGES OF RADIOMICS IN RADIOTHERAPY

Since the concept of radiomics was proposed in 2012, the research using radiomics has been increasing year by year, and good research results have been achieved in various fields. However, with the deepening of the radiomic research, more and more limitations have been exposed, including the poor reproducibility of the research results and non-standard image acquisition protocols. These limitations make clinical conversion difficult. We present here a detailed summary of the limitations being faced in radiomics and ways to combat them.

3.1 | Images acquisition and reconstruction

The scanning equipment, parameters, and reconstruction methods in different medical centers are quite different, and these differences affect the stability of the radiomic features.31-33 Because of the lack of a uniform standard protocol for imaging and image acquisition, the quality of medical images of the same tumor lesions acquired by varied equipment are very different, which affects the features based on gray levels, such as histogram-based features, or texture-based features.34-35 The acquisition parameters of the imaging protocol must be strictly controlled; otherwise, the normalization, denoising, and other procedures should be applied to image pre-processing.

3.2 | Images segmentation

Region of interest segmentation mainly refers to tumor region segmentation, which is an important step in the radiomic workflow. In order to obtain reproducible image features, stable and accurate tumor delineation is very important. Manual segmentation is often considered the “gold standard,” but it is time-consuming and suffers from interobserver variability.36 Many studies have confirmed that automatic (or semi-automatic) segmentation can reduce uncertainty and improve efficiency, but the effect of tumor segmentation methods on the stability of features should not be ignored.37-38

3.3 | Features extraction

In radiomics, we are faced with a large number of features that result in the need to reduce the data dimensions, and improve the reproducibility and repeatability of parameters.39-40 Here, there is a flawed idea: more radiomic features are better. First, there is obvious repeatability between different radiomic feature categories, which not only increases the workload, but also requires a reduction in redundancy. Second, among different types of extraction methods, how to standardize the feature data in the process of reducing redundancy is also a challenge. Furthermore, there is “arbitrariness” because of a lack of uniform standards for reduction of redundancy.

There is also a lack of an effective “gold standard” or “reference standard” in feature extraction. For example, the “gold standard” for a series of clinical practices is listed in Table 1. With respect to radiomics, there are two issues that need to be addressed in future radiomics research. First, what are the valuable criteria for feature extraction? Second, what is the biological significance of these valuable features? So far, the answer has been elusive.

Images have a basic texture unit, also known as a texture primitive. The human body is made up of tissues and cells. What is the relationship between the smallest basic unit of radiomics and human tissue? There is no clear explanation or acceptable definition. In circumstances where the basic theory is not clear and the technical methods are not standardized, any “meaningful” research results obtained will have to be reconsidered.41 Only by clarifying the biological meaning and key influencing factors expressed by every radiomic feature can we promote the further development of radiomic studies.

3.4 | Modeling and analysis

Accurate and robust machine learning, deep learning algorithms, or statistical methods to establish classification or a prediction model are conducive to the transformation to clinical applications.42-43 However, using many features for classification and prediction from a limited sample not only takes a long time to calculate, but also might not be optimal. Most of the existing radiomic studies are limited to a single institution. Therefore, the conclusions suffer from a lack of external validation.

Radiomics studies must be repeatedly tested and refined by multicenter, large sample, and randomized controlled clinical trials in the future. This will enable them to guide clinical treatment accurately, reliably, and effectively.

4 | CONCLUSIONS

Radiomics has brought a rare opportunity for the development of radiotherapy. Artificial intelligence and big data can be used to greatly promote the development of individualized radiotherapy. Every process of radiomics is faced with challenges, but the challenges often coexist with the opportunities. The future is the era of artificial intelligence-precision medicine, and we have many clinical resources to utilize. There is still a long way to go to truly achieve a personalized, precise treatment of cancer.
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