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Radiomics and radiogenomics for precision radiotherapy

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ABSTRACT

Imaging plays an important role in the diagnosis and staging of cancer, as well as in radiation treatment planning and evaluation of therapeutic response. Recently, there has been significant interest in extracting quantitative information from clinical standard-of-care images, i.e. radiomics, in order to provide a more comprehensive characterization of image phenotypes of the tumor. A number of studies have demonstrated that a deeper radiomic analysis can reveal novel image features that could provide useful diagnostic, prognostic or predictive information, improving upon currently used imaging metrics such as tumor size and volume. Furthermore, these imaging-derived phenotypes can be linked with genomic data, i.e. radiogenomics, in order to understand their biological underpinnings or further improve the prediction accuracy of clinical outcomes. In this article, we will provide an overview of radiomics and radiogenomics, including their rationale, technical and clinical aspects. We will also present some examples of the current results and some emerging paradigms in radiomics and radiogenomics for clinical oncology, with a focus on potential applications in radiotherapy. Finally, we will highlight the challenges in the field and suggest possible future directions in radiomics to maximize its potential impact on precision radiotherapy.

Keywords: radiomics; radiogenomics; radiotherapy; imaging; biomarkers

INTRODUCTION

Imaging plays an important role in clinical oncology, including diagnosis, staging, radiation treatment planning, evaluation of therapeutic response, and subsequent follow-up and disease monitoring [1–4]. In current radiology practice, the interpretation of clinical images mainly relies on visual assessment of relatively few qualitative imaging metrics. While this approach has been undoubtedly valuable in the diagnostic setting, there is an unmet need for methods that allow more comprehensive disease characterization and reliable prediction or early assessment of treatment response and prognosis toward the goal of personalized or precision medicine.

Radiomics has recently emerged as a promising tool for discovering new imaging biomarkers, by high-throughput extraction of quantitative image features such as shape, histogram and texture that captures tumor heterogeneity [5–9]. Radiomics can be applied to any type of standard-of-care clinical images such as CT, MRI or PET, and used in a variety of clinical settings, including diagnosis, prediction of prognosis, and evaluation of treatment response. When combined with appropriate statistical or bioinformatics tools, models can be developed that will potentially improve prediction accuracy of clinical outcomes. A closely related field, radiogenomics, is concerned with the study of relations between radiomic features at the tissue scale and with underlying molecular features at the genomic, transcriptomic or proteomic level [10–17], which may allow identification of the underlying biological basis of imaging phenotypes.

The fields of radiomics and radiogenomics have experienced significant growth in the past few years. Many radiomic studies have identified novel imaging signatures that have demonstrated improved diagnostic, prognostic or predictive performance over currently used imaging metrics (such as tumor size) in various oncologic applications. In the following, we will provide an overview of their technical aspects and discuss some potential clinical applications with a focus on radiotherapy.

WORKFLOW OF RADIOMICS

Radiomics typically involves multiple serial steps, including image acquisition, tumor segmentation, feature extraction, predictive modeling, and model validation. Figure 1 shows a general workflow of radiomics. More details about each step are presented below.

Image acquisition

In current oncology practice, various imaging modalities such as CT, MRI and FDG-PET are used to provide direct visualization and evaluation of the underlying anatomical or physiological properties of each tumor in individual patients [18]. Clinical images are typically acquired with the goal of maximizing the contrast between normal and diseased tissues. There is often a lack of standardization of imaging protocols across institutions with different acquisition and reconstruction parameters, which may have a significant impact on the image features. For radiomic analysis, it is essential to standardize or harmonize the imaging data in multicenter validation studies. High performance computational tools such as GPU [19] may be leveraged to process the images in order to mitigate various artifacts for radiomics analysis.

Tumor segmentation

After the images are acquired, the next step for radiomics is segmentation of the region of interest—in most cases, the gross tumor. For patients treated with radiotherapy, their tumors have already been manually delineated by radiation oncologists, and are available from the treatment planning system. These preexisting contours can greatly facilitate retrospective radiomic analysis. However, there can be significant variations in tumor contours among different oncologists. To account for intra- and inter-rater variations, it is important to evaluate the robustness of image features and their effect on downstream analysis by perturbing the tumor contours or using multiple delineations. Alternatively, tumors can be contoured more consistently using semi-automated segmentation algorithms with minimal human inputs, such as seed points [20]. Using deep-learning techniques for substantially improved segmentation of normal and malignant structures is an active area of research [21–23]. In the near future, deep-learning–based auto-segmentation tools that are robust enough for routine radiomics applications should be available.

Feature extraction

Two types of radiomic features, semantic and agnostic, can be extracted from images to comprehensively characterize the tumor phenotypes. Semantic features are based on an existing radiology lexicon to qualitatively describe tumors, and can be derived from the existing guidelines for specific imaging reporting and the data system of the American College of Radiology. On the other hand, agnostic features are computational metrics with predefined mathematical formulations. There are various types of agnostic image features that describe tumor shape, intensity, and texture to capture intratumoral heterogeneity. The details of available agnostic features have been reviewed elsewhere [7, 24]. Many commonly used radiomic features have been integrated into open source software or commercial software platforms. Among these [25, 26], Deasy and colleagues have provided an open platform, known as CERR [27] (http://www.cerr.info/), to prototype algorithms for radiomic features specifically for radiotherapy research. On the commercial software side, we mention that companies such as Huiyihuiying, a Beijing-based company focusing on the use of radiomics and artificial intelligence for solving various clinical problems, afford a practically useful cloud-based platform for radiomics research (for more details or to set up a free research account, please visit the company's website: www.huiyihuiying.com).

Predictive modeling

Once the tumor phenotypes are decoded into minable feature vectors, algorithms from artificial intelligence or statistical learning can be applied to detect patterns that are associated with relevant clinical endpoints or biological/genomic traits. Regression or classification methods are selected based on the type of targeted variables, continuous values or class labels. In practice, due to the relatively large number of features compared with the small number of samples, feature selection is an essential step in mitigating the risk overfitting [28]. There are several approaches to achieving this. For instance, image features that show minimal changes to tumor contour variations and minimal redundancy or overlap with other features may be preferentially selected. In addition, various feature selection algorithms, stepwise forward/backward selection, and lasso among others, can be applied in order to identify the most informative ones to fit the prediction model. Cross validation is needed to minimize the potential selection bias. In addition to building predictive models with supervised learning algorithms, it is also feasible

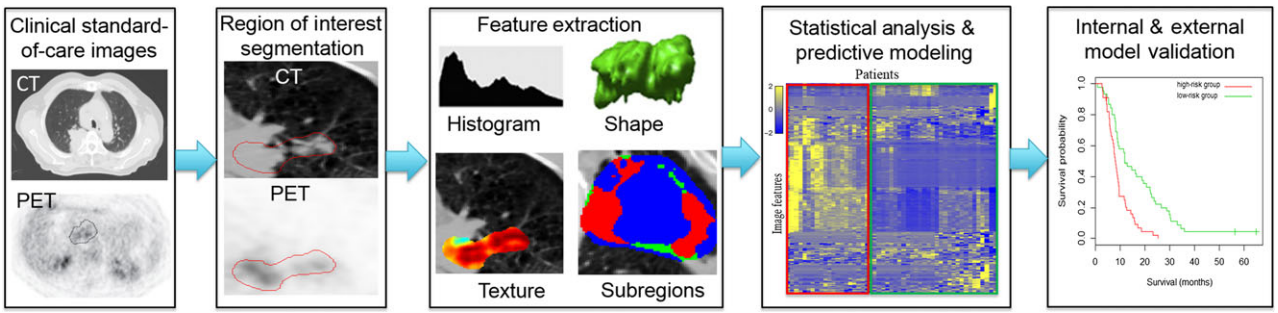

Fig. 1. Workflow of a typical radiomic study.

to apply exploratory unsupervised clustering algorithms to the radiomic features in order to discover novel classes of groups for a given disease [13, 14].

Model validation

Any radiomic signature should be validated on independent, preferably multiple external cohorts. While validation in a prospective clinical trial remains the gold standard and provides the highest level of evidence, there are several other more practical ways to demonstrate a model's validity and allow a quicker assessment of multiple competing models. Promising radiomic signatures can be tested with existing clinical trial data or retrospectively curated datasets. The key for validation is that training and testing should be entirely separate and no information leakage should occur between the two procedures [29]. In addition, it is also important to evaluate the relationship between the newly proposed radiomics signatures and known clinical and pathologic factors by combining them together in a multivariate model. Those radiomic signatures that provide independent prediction power are more likely to add clinical value for patient management.

Radiomics quality score and practical implementation

Recently, Lambin and colleagues have proposed the radiomics quality score (RQS) as evaluation criteria for radiomic studies [7]. The RQS contains sixteen key components that intend to minimize bias and enhance the usefulness of radiomics models. These recommendations cover the image acquisition protocol, image preprocessing, image feature extraction, and statistical modeling, which establish the reporting guidelines for future radiomic studies.

For a typical radiomics study, image acquisition and tumor segmentation are operated by experienced imaging technologists and radiologists, and are often the bottleneck and most time-consuming parts. By contrast, feature extraction, predictive model construction and validation can be automated and therefore are done in a much more time-efficient manner.

CURRENT STATUS AND RESULTS OF RADIOMICS IN RADIOTHERAPY

There has been tremendous growth in radiomics research in the past few years [5–8, 30–36]. Given the very large number of studies, it is not possible to provide an exhaustive list of articles in a single review. Below we highlight a few studies that may be potentially relevant for improving patient management in radiotherapy. Aerts and colleagues proposed a radiomics signature for predicting overall survival in lung cancer patients treated with radiotherapy [37]. They extracted over 400 quantitative features from CT images to describe tumor intensity, shape and texture. Based on these features, they constructed a radiomic signature that captured intratumor heterogeneity, which was shown to be prognostic in several independent validation cohorts, including one head-and-neck cohort. In another study by the same group, radiomics analysis was used to investigate the association of MRI features with survival and progression in glioblastoma [38]. The radiomic signature showed significant stratification of patient prognosis, which was stronger compared with clinical or traditional imaging metrics. Moreover, these findings were independently validated in a multicenter clinical trial cohort.

Wu *et al.* investigated quantitative radiomic features of FDG-PET and CT for predicting distant metastasis in early-stage non–small cell lung cancer (NSCLC) after stereotactic ablative radiotherapy (SABR) [39]. Based on image features characterizing tumor morphology and intratumoral metabolic heterogeneity, a radiomic signature was built that significantly improved the prognostic value compared with conventional imaging metrics. Moreover, combining imaging and histologic information yielded further improvement in prediction of distant metastasis. In another study, Cui *et al.* performed the first investigation to study the FDG-PET radiomic features for predicting overall survival in 139 locally advanced pancreatic cancer patients treated with SABR [40]. The proposed radiomic signature showed significant association with survival after independent validation and, importantly, remained an independent predictor of survival after adjusting for known clinicopathological risk factors.

Van Rossum *et al.* investigated whether subjective and quantitative assessment of baseline and post-chemoradiation FDG-PET can improve the prediction of pathologic complete response to preoperative chemoradiotherapy in esophageal cancer beyond the clinical predictors [41]. Though statistical incremental values were observed for the proposed radiomic signatures, there was only limited discriminatory improvement beyond the clinical predictors. In an ongoing study, they are investigating whether adding diffusion-weighted MRI radiomic features could improve potential predictive power. El Naqa and colleagues studied FDG-PET/CT radiomics and combined them with clinical information to assess the risk of locoregional recurrences and distant metastases in head-and-neck cancer [42]. The prognostic value of constructed prediction models was confirmed in an external cohort. The radiomic model may have the potential to allow for personalization of chemoradiation treatments for head-and-neck cancer patients.

EMERGING PARADIGMS OF RADIOMICS FOR PRECISION RADIOTHERAPY

Intratumoral partitioning for characterizing spatial heterogeneity

Up to this point, the vast majority of radiomic studies have been focused on analysis of the primary tumor. While texture features provide a measure of intratumor heterogeneity to a certain extent, this characterization is not complete. Because their calculation is applied to the entire tumor as a whole, this approach implicitly assumes that the tumor is heterogeneous but well mixed, and neglects the regional variations within a tumor that have been previously demonstrated. To address this issue, the concept of habitat imaging was proposed to capture imaging heterogeneity more explicitly at a regional level [8, 43].

Cao and colleagues proposed a clustering-based algorithm for identifying the significant subvolumes in primary tumors from dynamic contrast-enhanced (DCE) MRI in head and neck cancer [44]. They showed that large, poorly perfused subvolumes of the primary tumor at baseline and persisting during the early course of chemoradiotherapy can potentially predict local or regional failure, which could potentially stratify patients for local dose

intensification. Gatenby and colleagues proposed cascading T1 post-gadolinium MRI with T2-weighted fluid-attenuated inversion recovery sequences in order to divide the whole tumor into multiple regional habitats with distinct contrast enhancement and edema/cellularity [45]. A preliminary study of 32 TCGA glioblastoma multiforme patients showed that the distribution of MRI-based habitats was significantly correlated with survival. Wu *et al.* [46] developed a robust tumor-partitioning method by a two-stage clustering procedure, and identified three spatially distinct and phenotypically consistent subregions in lung tumors. One subregion, associated with the most metabolically active, metabolically heterogeneous, and solid component of the tumor, was defined as the 'high-risk' subregion. The volume of high-risk intratumoral subregion predicted distant metastasis and overall survival in patients with NSCLC treated with radiation therapy.

Tumor partitioning can be combined with radiomic or texture analysis to allow more detailed and refined image phenotyping. Wu *et al.* [47]. showed that early change in texture features for the intratumoral subregion (associated with fast contrast-agent washout at DCE MRI) predicted pathological complete response to neoadjuvant chemotherapy in breast cancer. Cui *et al.* [48]. performed radiomic analysis on tumor subregions and defined 120 multiregional image features on MRI in glioblastoma. A five-feature radiomic signature was identified and independently validated in an external cohort as predicting overall survival, and it outperformed whole-tumor measurements. Stoyanova and colleagues investigated the association between MRI radiomic features and prostate cancer gene expression profiles from MRI-guided biopsy tissues [49]. They extracted radiomic features for the identified habitats on MRI/3D-ultrasound fusion and found strong associations between radiomic features and gene expression profiles.

Taken together, these studies support the need for tumor partitioning to identify aggressive intratumoral subregions, and this is applicable to many types of solid tumors that demonstrate intratumor heterogeneity at imaging. This may have significant implications for clinical oncology by identifying important tumor regions for biopsy. In addition, this is particularly relevant for radiotherapy treatment planning and adaptation, because high-risk tumor subregions associated with the aggressive disease can then be targeted with a radiation boost to potentially improve local control and patient survival.

Radiogenomics: integrating imaging with genomics

An emerging field that is closely related to radiomics is radiogenomics, which integrates imaging and genomic data with the goal of gaining biological interpretation or improving patient stratification for precision medicine [10–15, 50–54]. There are two major types of radiogenomic association studies. One approach that most radiogenomic studies so far have adopted is to find imaging correlates or surrogates of a specific genotype or molecular phenotype of the tumor. For instance, CT semantic and radiomic image features have been found to be associated with EGFR mutations in lung cancer [55, 56]; MRI radiomic features have been correlated with intrinsic molecular subtypes or existing genomic assays in breast cancer [57–59]. Radiogenomics can also be used create association maps between molecular features and a specific imaging phenotype so as to reveal its biological underpinnings. For example, tumors with a higher maximum standardized uptake value from FDG-PET have been demonstrated to be associated with the epithelial–mesenchymal transition in non–small cell lung cancer [60]. In another recent radiogenomic study, heterogeneous enhancing patterns of tumor-adjacent parenchyma from perfusion MRI were associated with the tumor necrosis signaling pathway and poor survival in breast cancer [15].

Another interesting area of investigation is classification of tumors into subtypes based on imaging phenotypes rather than molecular features. Recently, Wu *et al.* [14]. discovered and independently validated three breast cancer imaging subtypes, which were characterized as having homogeneous intratumoral enhancement, minimal parenchymal enhancement, or prominent parenchymal enhancement. In a large multicohort study of over 1 000 patients, each of the imaging subtypes was associated with distinct prognoses and dysregulated molecular pathways, and they were shown to be complementary to known intrinsic molecular subtypes.

Finally, one important direction that is particularly relevant for precision medicine is to leverage the complementary power of imaging and molecular data, and integrate them into a unifying model to further improve the prediction accuracy of clinical outcomes. Cottereau *et al.* [61]. showed that the combination of molecular profile and metabolic tumor volume at FDG-PET imaging improved patient stratification for progression-free and overall survival in diffuse large B-cell lymphoma. Grossmann *et al.* [62]. combined gene expression and CT radiomic signatures to enhance the accuracy of survival prediction in lung cancer. Cui *et al.* [63] showed that integrating MGMT methylation status and volume of the high-risk subregion at multiparametric MRI improved survival stratification in glioblastoma. These studies provide the initial evidence that image-based biomarkers can provide additional information beyond molecular analysis alone, and integrating both will provide more accurate assessment of individual tumors.

CHALLENGES IN RADIOMICS INVESTIGATIONS

Given the growing interest in the field, it is important to highlight some technical and practical challenges associated with radiomics and its ultimate clinical translation. These challenges include: standardization of image acquisition protocols and feature extraction, ensuring robustness and reproducibility of radiomic signatures in order to maximize the translational potential, and integration of large multicenter cohorts by cultivating the culture of data sharing.

Standardization

Currently, there is no universal image acquisition protocol for any imaging modality in clinical practice. The retrospectively acquired images are often heterogeneous, with a wide range of image acquisition and reconstruction protocols across different centers and among scanner manufacturers, which can significantly hamper quantitative radiomic analysis. To overcome this issue, there have been

several efforts to standardize the imaging protocol by the quantitative imaging biomarkers alliance (QIBA) [64] and the quantitative imaging network (QIN) [65], among others. In a retrospective analysis, several strategies have been proposed for harmonizing imaging scans such that they are comparable across multiple cohorts. A common strategy is to derive the underlying physiological measures from the functional imaging. For instance, the perfusion maps can be computed from DCE MRI based on pharmacokinetic modeling [66]. Another practical strategy is to gauge the imaging values with the value of the selected normal tissue region of interest as a baseline. For instance, on an individual basis, the average interquantile values of the background parenchyma can be used to normalize breast MRI scans [14]. In addition, the phantom study can be adopted to investigate the interscan and inter-vendor variability of the imaging-derived features [67, 68], which can provide useful insights into the uncertainties of quantitative imaging analysis.

Reproducibility

Prior to clinical translation of any putative biomarkers, the most critical step is rigorous validation in a prospective multicenter trial [1]. For radiomics, there can be many causes that render the radiomic analysis and results invalid, including poor experimental design, model overfitting, and unadjusted biases or confounding factors, among others. The meaning of reproducibility is 2-fold. First, it is essential to assure the predictive accuracy during radiomic signature construction. A rational radiomic design should include proper imaging standardization, a robustness test of radiomic features regarding segmentation variabilities, as well as rigorous model training and testing. Second, each radiomic analysis step should be well documented, and original codes and data should be easily accessible, allowing other investigators to replicate the results.

Data sharing

One of the biggest challenges in radiomics, and more generally in big data research [69], is the curation of image and relevant metadata across multiple centers [65, 69, 70]. It is important to match imaging with detailed clinicopathological and treatment information, as well as relevant clinical outcomes. There has been some progress toward data sharing under the initiative of the cancer imaging archive, where image and clinical data for various tumor sites are curated and shared publicly (http://www.cancerimagingarchive.net/). These cohorts are from single-institution or multicenter trails, which should greatly facilitate the discovery and validation of radiomic models. Nonetheless, compared with the abundant public gene expression data, the available imaging data are much less, and continuing efforts should be spent curating high-quality imaging datasets. Beyond technical challenges, there are also administrative and regulatory barriers that need to be overcome in order to make large-scale data sharing feasible in the future [69]. A cloud-based platform such as the one provided by Huiyihuiying Inc. may prove to be useful in facilitating data sharing and multi-institutional collaborative research.

CONCLUSION AND FUTURE OUTLOOK

Radiomics and radiogenomics have shown great promise for the discovery of new candidate imaging markers; such markers have demonstrated potential diagnostic and prognostic value in a variety of cancer types. Despite the enthusiasm and excitement around this, it should be noted that many radiomic and radiogenomic studies so far have been of hypothesis-generating nature, and rigorous validation in independent cohorts has been lacking. Another caveat is that existing biologic knowledge about a certain disease is not taken into account in many studies. To be of practical value, any new candidate imaging biomarkers should be complementary to known clinical and pathologic factors, i.e. adding value. One critical and yet currently an underexplored area of investigation is how radiomics can be applied to serial imaging scans to better evaluate therapeutic response, given the increasing availability of treatment regimens. Initial studies on simple delta-radiomics are encouraging, but the optimum approach to characterizing longitudinal change is yet to be defined. Moving forward, advanced machine-learning techniques, notably deep convolutional neural networks, are expected to be increasingly used to identify useful image features automatically, rather than defining them manually (personal communication from Ibragimov B, Toesca D, Chang D et al.). In order for this approach to work, a sufficiently large dataset will be required for training a reliable model, highlighting the need for curation of high-quality datasets and data sharing. Ultimately, prospective validation in multicenter clinical trials will be required to demonstrate the clinical validity and utility of newly identified imaging markers and truly establish the value of radiomics and radiogenomics in precision radiotherapy.

CONFLICT OF INTEREST

LX serves as the principal investigator of a master research agreement (MRA) with Varian Medical Systems. He also serves as the Chief Scientific Advisor of Huiyihuiying Medical Technology (Beijing) Co., Ltd.

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