



Radiomics in cancer diagnosis, cancer staging, and prediction of response to treatment

In the same way that genomics describes the characterization of tumor phenotype using a wide and diverse array of genetic alterations (copy number, gene expression, methylation etc.), the term ‘radiomics’ refers to the characterization of tumor phenotypes based on a diverse array of image-derived, quantitative measurements (shape, morphology, intensity histogram, texture etc.). The image analysis tools used in radiomics build on those developed over the past decades for tasks such as computer-aided diagnosis of lung nodules and breast lesions. In radiomics these tools are applied to very large patient datasets to extract a multitude of image features, and statistical approaches are then used to analyze the data. Aside from mining aspects about tumor shape and size, more recent radiomics approaches aim to characterize the distribution of gray level intensities in the tumor region in two or three dimensions, through histogram or ‘texture’ analysis. Radiomic studies can be used to understand relationships between imaging characteristics of tumors, such as heterogeneity, and their genetic characteristics, phenotype, or expected treatment outcome. As with genetic analysis providing a glimpse of the multiple clones of tumor cells that comprise a tumor, radiomic analysis of tumor subvolumes or habitats within the tumor volume serves as an imaging metric of the heterogeneity of tumors.

In this volume, the reader can find papers describing the application of radiomic approaches to many different treatment sites, including glioblastoma, head and neck cancer, lung cancer, esophageal cancer, rectal cancer, and prostate cancer. They will also find many practical hints on how to embark on their own radiomic studies and to avoid some of the many potential pitfalls.

We start with a paper by Court *et al.*, describing computational resources for radiomics projects. This paper includes some practical tips on identifying an appropriate patient cohort, choosing a software (commercial and open-source) platform for segmentation, image feature extraction, and modeling/statistical analysis. Each of these steps in the radiomics pipeline must be carefully controlled, standardized, audited for quality control and robustness, and validated in independent datasets to ensure reliability and generalizability of results.

The next paper in this volume by Fave *et al.* outlines this challenge in detail, specifically describing the impact of quantization and smoothing on the correlation of image features with tumor volume, and how different pre-processing methods can impact the information content of the image features (giving better or worse prediction accuracy).

In the next paper, Lu and Chen provide a brief overview of some of the clinical uses (and limitations) of computed tomography (CT) and positron emission tomography (PET) imaging for tumor response assessment across a range of anatomic sites. They describe the routine use of change in standardized uptake values (SUVs) from sequential PET images during treatment to evaluate treatment response and even modify treatment adaptively. They also outline ways to stratify differential responders based on SUV values of tumor in comparison to the mediastinum and the liver. They also highlight studies where additions of PET/CT textural features improve the prognostic value of models based on SUV alone.

Subsequent papers in this volume illustrate uses of radiomics in specific cancers, with comprehensive descriptions of anatomic site-specific workflows and their associated technical challenges.

Wong *et al.* illustrate the diagnostic and therapeutic challenges posed by head and neck cancers that demonstrate high tumor heterogeneity and arise in a crucial but complex anatomical location in the body. They note that radiomic approaches have the potential to serve as prognostic and predictive biomarkers, with good correlations between these imaging biomarkers and known genetic drivers of treatment response. Lastly, they summarize some of the challenges with radiomic analysis and propose solutions to move the field forward.

Narang *et al.* describe the use of features extracted from magnetic resonance imaging (MRI) for glioblastoma. They review the many challenges encountered when using MRI images for radiomic studies. In particular, variability in image acquisition due to differences in scanners used and imaging protocols utilized, and segmentation of regions-of-interest can have a large impact on reliability and reproducibility of results obtained. As with other imaging techniques, assessing feature robustness is equally important for MRI radiomics. This paper outlines approaches to obtain generalizable radiomic signatures for outcome prediction and emphasizes the need for rigorous auditing and standardization of the image pre-processing pipeline

to minimize ‘drift’ in radiomic features due to systematic variabilities from acquisition and image-processing.

Scrivener *et al.* review the landscape of studies employing radiomics for diagnosis of lung cancer and prognostication of treatment outcomes for lung cancer using features extracted from CT and PET images. They address the added complexity of radiomic analysis posed by respiratory motion of the tumor during image acquisition and the role of three-dimensional versus four-dimensional image acquisition in deriving reproducible radiomic signatures. They provide clear guidelines for standardization of each step of the radiomic pipeline including image acquisition, tumor segmentation, feature extraction and model building and validation. They caution against overfitting of data that can occur easily and unknowingly when dealing with large numbers of potentially interrelated features extracted by algorithms and emphasize the need for built-in quality assurance and robustness assessment.

Van Rossum *et al.* describe the use of CT and PET images for radiomics studies of esophageal cancer. They stratify texture features into first-, second- and third-order statistics based on the complexity of information gathered from a single voxel, a pair of adjacent voxels or multiple adjacent voxels, respectively, and note that not all features are consistent and reproducible when baseline scans are obtained a few days apart. They also include a discussion on the influence of smoothing, quantization and segmentation of images on staging, prediction of response to treatment, and prediction of overall survival of patients.

Dinapoli *et al.* review the use of CT, MRI and PET in radiomic studies for rectal cancer. They describe studies where radiomic techniques predict treatment response in terms of overall survival and pathological complete response rates to neoadjuvant chemoradiation therapy or foretell the likelihood of metastatic involvement of pelvic lymph nodes and/or the liver. An important point made in their paper is the need for a reproducible workflow that will facilitate the wider use and validation of the findings of radiomic studies.

The last paper by Stoyanova *et al.* describes the use of multi-parametric MRI-based radiomic methods for diagnosis of prostate cancer and for discriminating between indolent and aggressive cancer foci within the prostate based on radiomic habitats to guide directed biopsies or risk-stratified treatment options. Furthermore, they describe the correlation between gene expression array analysis of directed biopsies of lesions in the prostate and quantitative multi-parametric MRI images. They demonstrate how non-invasive assessment of radiomic features on MRI images segregates patients into those with previously validated high-risk *vs.* low-risk transcriptomic signatures.

In summary, this volume provides the reader an introduction to the exciting potential of radiomics for a range of different problems, an overview of the state-of-the-art in radiomic literature across multiple anatomic sites and imaging modalities, as well as some practical guidance on developing their own radiomics studies.

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