Technical Challenges in the Clinical Application of Radiomics.

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review article

Technical Challenges in the Clinical Application of Radiomics

abstract

Radiomics is a quantitative approach to medical image analysis targeted at deciphering the morphologic and functional features of a lesion. Radiomic methods can be applied across various malignant conditions to identify tumor phenotype characteristics in the images that correlate with their likelihood of survival, as well as their association with the underlying biology. Identifying this set of characteristic features, called tumor signature, holds tremendous value in predicting the behavior and progression of cancer, which in turn has the potential to predict its response to various therapeutic options. We discuss the technical challenges encountered in the application of radiomics, in terms of methodology, workflow integration, and user experience, that need to be addressed to harness its true potential.

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INTRODUCTION

Radiomics can be defined as the extraction and analysis of large amounts of advanced quantitative imaging features (imaging biomarkers) with high throughput from medical images obtained through various modalities.[1] Tumor heterogeneity in terms of its microstructure and microenvironment has immense value in prognostication of the disease and in therapy planning and response assessment.[2] Therefore, radiomics can not only yield more actionable information from medical images but also help personalize medical care. Furthermore, it has the potential to play a significant role in drug development.[3]

REVIEW

A malignant disease may present similarly but have different outcomes. Biopsies are somewhat limited in the information they provide, because different parts of a malignant lesion may have different molecular characteristics, and tumor phenotype tends to change over time. Personalized medicine aims to better predict individual patients' outcomes and better select optimal treatments, based on improved serum, molecular, tissue, and imaging biomarkers.[4] Radiomics contributes by evaluating the imaging biomarkers that define the tumor signature, which directly informs its behavior and progression. This information guides the multispecialty oncology team to design a highly personalized therapeutic plan for a patient based on exactly how that particular patient's cancer is expected to respond.

The underlying mechanism is that of quantitative image analysis (QIA), defined as a process that involves using digital images to provide data and information, with computer technology that recognizes patterns, creates maps, and processes signals within images in a way the human eye cannot.[5] The main steps include capturing the image, storing the image (ie, compression), correcting imaging defects, enhancing the image, segmenting objects in the image, and measuring the image. The resultant units of information from QIA are called quantitative imaging biomarkers. A quantitative imaging biomarker can be defined as an objective characteristic derived from an in vivo image measured on a ratio or interval scale as an indicator of a normal biologic or pathogenic process or a response to a therapeutic intervention.[6]

Radiomics as a methodology can be incorporated with other analytic processes to study disease processes in a more holistic way, with a focus on deciphering the genotype-phenotype relationship. One such method is called radiotranscriptomics. Transcriptomics is the study of the transcriptome—the complete set of RNA transcripts that are produced by the genome—under specific circumstances or in a specific cell using high-throughput methods, such as microarray analysis. Comparison of transcriptomes allows the identification of genes that are differentially expressed in distinct cell populations or in response to different treatments. Radiotranscriptomics has been described as an approach to combine transcriptome information, including

gene expression and isoform variation, and quantitative image annotations.[7] Radiogenomics or imaging genomics refers to the study of the relationship between the imaging characteristics of a disease (ie, the imaging phenotype or radiophenotype) and its gene expression patterns, gene mutations, and other genome-related characteristics.[8]

Cancer lesions comprise many different cell types, but the concept of tumor heterogeneity is not fully understood. Presence of clonal variations, leading to clonal interference and mutualism, has been studied as a factor that determines the so-called personality traits of a cancer.[9] Radiomics has the ability to create a comprehensive picture of the microstructure and microenvironment of a tumor lesion. These techniques measure several hundreds of different features in the scan and use algorithms to construct data that assess the entire three-dimensional tumor phenotype. Texture analysis shows that some tumors are highly heterogeneous, likely made up of a variety of cell types with different molecular abnormalities. In general, the greater the degree of heterogeneity, the harder it is to treat the cancer and the more likely it is for the cancer to develop resistance to therapy.[10] Patients with heterogeneous tumors tend to have poorer chances of survival than those whose tumors have a more homogeneous architecture. In this regard, radiomics has been shown to outperform standard imaging techniques in the pathologic response assessment of cancers, such as non–small-cell lung cancer.[11]

Several studies have focused on radiomics as a methodology applied in the field of oncology. These include multimodality diagnostic approaches using computed tomography, magnetic resonance imaging (MRI), and positron emission tomography (PET) where radiomic methodology was applied to extract imaging biomarkers to better understand the malignant disease processes, more accurately detect, stage, or restage the disease, and, more importantly, inform therapeutic management. Examples include models to improve the diagnostic accuracy of lung nodules,[12] develop insights for prediction of recurrence of hepatocellular carcinoma,[13] and predict response to or failure of radiation therapy in lung cancer.[14] These are efforts under way to improve the reliability and robustness of these techniques to increase physician confidence in their application as a decision support system.[12,15] Furthermore, approaches that combine radiomics with standard techniques have yielded promising results in earlier, more accurate detection[16] as well as therapy response prediction and assessment.[17]

Multiple collaborative efforts are under way to promote scientific discovery in the field of radiomics and imaging genomics. The most prominent on this front is the Radiologic Society of North America Quantitative Imaging Biomarker Alliance, which has played a key role in establishing platforms and standards to improve reliability and reproducibility of radiomic techniques. Given that this is an inherently multidisciplinary process requiring analysis of large data sets from various sources, collaborations among radiologists, medical physicists, pathologists, molecular geneticists, and computer and data scientists have become increasingly important in realizing real value in this field. Major data repositories, such as the Quantitative Imaging Biomarker Alliance data warehouse,[18] the Cancer Imaging Archive,[19] and the Cancer Genome Atlas,[20] have been established to promote such efforts. There are multiple steps in a typical radiomic technique (Fig 1), each with its own set of challenges. In this article, we discuss two main sets of challenges faced in the field of radiomics.

TECHNICAL CHALLENGES

As a novel image analysis technique, radiomics is purported to have significant clinical usefulness in the future; however, there are numerous challenges being encountered in terms of its architectural design and framework, logistic needs, and issues related to user experience and workflow.

Workflow Integration

Traditional picture archiving and communication system (PACS) platforms do not have the necessary capabilities to develop radiomic algorithms, nor do they have the ability to integrate the radiomic outputs into clinical workflows. Many actors (eg, clinician researchers, data scientists, algorithm developers) must be able to collaborate with one another and interact with multimodality data sets during the development of algorithms. Once developed, these outputs must seamlessly tie into the physician workflow, which requires deep integration into examination worklists, imaging viewers, and electronic medical record (EMR) systems. The PACSs and specialty radiomic systems available today lack the necessary integration points to advance the science and clinical practice. As PACSs and EMRs have adopted newer standards, including Health Level-7 (HL7) Fast Healthcare Interoperability Resources (FHIR) and DICOMweb, the ability to integrate with these systems has become easier, but functionality gaps remain for research, development, and clinical use.

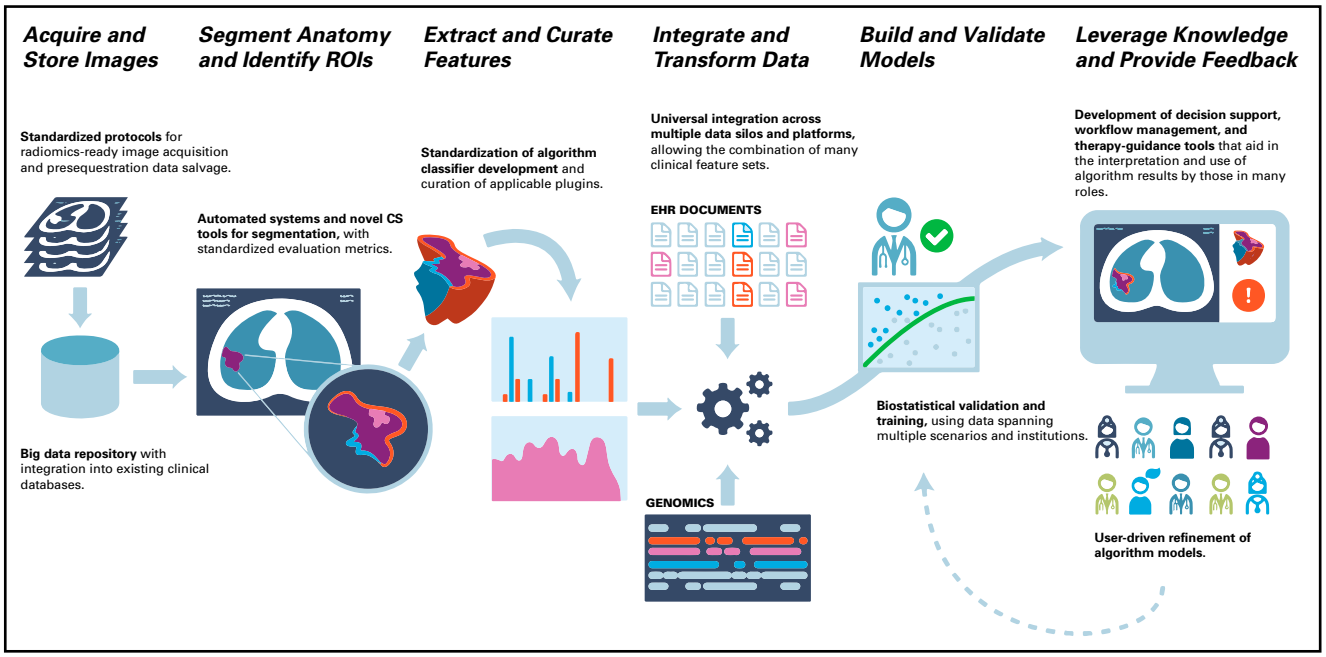

Fig 1. Typical radiomics workflow. The basic steps include image sequestration and preacquisition data salvage, data transfer and repository maintenance, image segmentation, feature extraction and classification, covariance matrices and data modeling, integration into clinical decision support systems, and biostatistic and outcome analysis. ROI, region of interest.

Imaging scans (or data) are designed to be extracted from standard-of-care images, leading to a large potential subject pool. Radiomic data are stored in a mineable form that can be used to build descriptive and predictive models, relating image features to phenotypes or gene-protein signatures. One challenge is the need to curate and store large sets of image volumes from a large number of clinical sites. The National Cancer Institute–supported Cancer Imaging Archive houses a large number of image collections and is used worldwide for cancer research and algorithm development. Cloud computing is a modern paradigm used to reduce the barrier to entry for cancer scientists to participate in challenges of rigorous validation of new algorithms.

Data Transfer, Management, and Deployment

Integration of radiomic data sets into clinical workflows is limited by the ability of existing systems and standards to accept nonstandard data sets. Attempting to map these new data sets to legacy (eg, DICOM, HL7) or emerging (HL7 FHIR) standards might provide a bridge solution but is more likely to be limiting in data resolution (amount of data stored) and utility (access to the user through existing software packages) to the end user. For instance, DICOM has a mechanism to store a sequence of items (array) in private tags. However, there is no guarantee that DICOM systems (eg, PACS, vendor neutral archive) will preserve private tags as data flows through those systems. Furthermore, these private tags are not queryable, essentially locking the data into the particular archive. Similarly, HL7 FHIR has extension models for nonstandard attributes of resources, but the lack of standardization in the emerging radiomic domains by definition makes data stored in these extensions proprietary.

The backbone of the radiomic infrastructure must support but not depend exclusively on existing health care standards. Standards like HL7 FHIR are the most promising, because they adopt newer Web architecture conventions and more easily support microservice architectures. The goal of microservice architecture is to compose applications from small special-purpose services, enhancing the overall flexibility and extensibility of solutions. That is, these architectures promote an open ecosystem where data are fluid and there are no restrictions on use. This is important because the way in which the data will be used is evolving, and there will be more data generated than used in any one application. A feature extractor might calculate thousands of features, but a prognostic algorithm might only use a handful.

Typically, standards have an opinion of how the data are going to be used, such as DICOM, where the standard describes means of data exchange. The DICOM QUERY supports a finite set of search criteria mostly modeled around the patient, study, series, and instance (or image) attributes. The DICOM QUERY has evolved over time to support interchange of data between DICOM archives; it was not designed to support big data analytic use cases. Furthermore, DICOM archives tend to have

internal data models, which reflect the DICOM standard for various performance and maintainability purposes. The implicit opinion of the standard is that the user wants to exchange data in a reliable way. Decoupling the storage format and pushing standards to the edge of the system increase flexibly and allow for the selection of technologies at the core that are less opinionated NoSQL databases. A distinction should be made between a feature repository and a clinical workflow system that consumes (or generates) features. The feature repository must contain gold-standard features accessible to all workflow applications.

There are two models of feature extraction: on demand and static. Each has its own benefits. Feature extraction is presumably computationally intensive because of both the amount of imaging data being processed as well as the time to retrieve imaging data from the archives. Caching of features statically at a point in time, such as when the patient is scanned, has a performance benefit for consumers but may have significant overhead in data storage for the information technology management team. Caching thousands of features for millions of examinations that might never get used may be unnecessary. Additionally, feature extraction techniques may evolve over time, making older features obsolete. As radiomic systems are being designed, it is fair to assume some subset of statically captured features will be cached within the individual workflow systems, and a vast majority of potentially useful features will be captured on demand as determined by the use case.

User Experience and Machine Intelligence in Health Care: Implications for Radiomics

Systems that correctly predict user behavior, classify complex data, suggest appropriate paths forward, or perform other similar tasks have now permeated the consumer space. Health care has so far lagged in its acceptance of machine intelligence.[21,22] However, the advent of radiomics is in step with a growing recognition of the diagnostic and workflow-transforming power of intelligent algorithms. The large amounts of data created by radiomics (genetic and pixel data) will require machine-learning algorithms to classify and validate pathology and imaging associations. It is therefore a valuable vehicle to explore the design challenges and opportunities faced when trying to encourage widespread clinical acceptance and adoption of these technologies.

Particularly in the United States, the legal implications of accountability have resulted in a culture where physicians tend to take comfort in having control of each step of care and are reluctant to relinquish that control to a machine, regardless of the reported accuracy of the technology.[21] This environment has frequently led to machine intelligence being relegated upstream and downstream from the core clinical interpretation, toward workflow optimization and quality control, or, alternatively, reserved for situations where there are not enough medical experts to diagnose patients at high volumes.

This is a valid approach; introducing algorithms in lower-risk environments allows data scientists and clinicians time to train and validate their classification models and feature sets atop live production data. However, this approach fails to consider the use patterns, data needs, attitudes, and other experience factors that are unique to the diagnostic setting. That is, successfully integrating an intelligent algorithm behind the scenes in an administrative or retrospective capacity does not guarantee that the algorithm and its knowledge will be usable when brought to the forefront of interpretation (ie, for use in clinical decision support).[21]

To better position radiomics to affect cancer detection, prognosis, and precision therapeutic planning, software designers and developers must gain a nuanced understanding of how clinicians interact with machine-learning and other intelligent systems and build the scaffolding necessary to bring clinical experts from a place of apprehension to one of trust. As a starting point, one can leverage common heuristics collected from other attempts to introduce machine intelligence into workflows.

Perception. Perception can refer to two aspects of design: a user's comprehension of and attitude toward information (ie, trust, confusion, disgust, mobilization) and the ability of a user to notice a change or distinguishing characteristic within data. The two are interrelated, and failing to consider the second can negatively affect the first. This heuristic has particular application in radiomics, given the heavy emphasis on visualizing the segmentation of anatomic regions and highlighting tumor heterogeneity. One must decide which components of the image analysis to reveal to an end user—whether to show a two- or three-dimensional image or simply a table or report of results. If images are involved, monitor calibration, color choice, artifact proximity, and size are only a few of the factors that can have an impact on perception.[23,25] User researchers can work with

clinicians to ascertain whether they are correctly interpreting the results of algorithms as well as identify their subjective response to the quality and usability of the data.

Provenance. Communication is a critical component of workflows, and most clinicians have a well-defined sense of their information network, even if they cannot articulate it. Knowing the source—whether person or machine, or which person or machine—often greatly affects whether information is trusted in decision making.[15,17,18] Often, users express hesitance in accepting the results of algorithms, because they do not understand how the analysis was performed or which raw data were analyzed to arrive at the presented conclusion. Ways to address this include pairing radiomic algorithm assessments with other trusted sources (eg, notes from the patient record, genomic reports) or providing access under the hood to the raw data that were used to develop the analysis.[24]

Agency. Although somewhat counterintuitive at first, a strong factor in encouraging adoption of new technologies is ensuring that the user feels empowered to inform, adjust, or reject the experience, particularly if those technologies seem to be making or heavily influencing decisions.[24] If a radiomic system suggests a certain treatment, the clinician should not feel concerned that informed disagreement will have negative personal consequences. Likewise, if an algorithm presents several diagnosis options, the user should be permitted to dismiss or promote one or more of the options, informing the model of his or her personal interpretation of the situation. Users also need to feel confident that their actions have the intended impact on the behavior of the algorithm, either immediately or over time. This is tied to perception. We must devise means of monitoring algorithms longitudinally and introduce important checks and balances into the human-machine dialogue.

The fields of user experience design and human-computer interaction are only beginning to engage the so-called black box of machine intelligence and its implications for product development.[26] However, radiomics is coming of age at a time when design professionals are growing increasingly aware of the need to develop meaningful heuristics, which means that clinical experts researching radiomics are exceptionally well positioned to collaborate with user experience and human-computer interaction to refine interaction patterns and data visualization techniques that work with subject matter experts, rather than replacing or obstructing them.

Methodologic Issues

Like any scientific methodology, radiomics will have to be robustly assessed and its outcomes rigorously evaluated for statistical validity to be accepted as a reliable and accurate technique for clinical use. Success of any radiomics-based clinical decision support system will depend on how it affects physician behavior. Here we describe some challenges being faced in the statistical validation of radiomics.

Sample size. Given the novelty of these methods and the challenges associated with their application, there have been a limited number of studies performed to validate the performance of radiomic algorithms. Generally, these were retrospective studies, with small sample sizes (50 to 150), yielding results with low statistical power and garnering low levels of confidence among physicians, who generally rely on major randomized studies to change practice behavior. Moreover, to apply neural-network or machine-learning algorithms, a large data set is required to build the underlying regression models.

Trial design. Challenges with using a bigger sample size for a radiomic study include access to patient data (for a retrospective study) or patient selection (for a prospective study). The latter will be difficult to design, given the issues with integration of radiomic application into the clinical workflow. There are issues with recall bias when it comes to a retrospective study, but designing a randomized controlled prospective trial for quantitative image analysis is prohibitively difficult; there are issues surrounding patient selection (determining robust inclusion and exclusion criteria given that radiomic algorithms require large data sets on which to work), challenges with blindfolding readers (unless a true fully automated radiomic application is running in the background, requiring no radiologist input), logistic challenges with data transfer (in a multicenter study), and, perhaps most importantly, challenges in assessing outcomes.

Outcome analysis. Measuring outcomes for a major study in this domain can be difficult. Although it is fairly straightforward to compare the performance of a machine with that of a radiologist, that may only be useful in assessing the performance of a CAD software. Besides, if a machine or application is more sensitive at detecting lesions, it may be predisposed to overcalls, significantly reducing specificity and warranting unnecessary clinical workup, health care dollar waste, and

patient anxiety. True outcome analysis looking at survival rates and/or metrics of quality of life will require long follow-up periods. Ultimately, the most important questions to ask is whether a machine system helps in early detection of cancer. Does it allow for early therapeutic intervention? Has it been shown to affect patient survival rates? One potential of application of radiomics could be better standardization of parameters used in treatment decisions across sites to make this larger data set–gathering easier.

Gold-standard issue. Another important consideration in designing research studies for radiomics is that of choosing the gold standard. The limitations of pathology as the gold standard are well known: sampling errors, no longitudinal correlation, and so on. In some cases, pathologic assessment is not warranted and therefore unavailable for comparison. Clinical follow-up in such cases becomes critical. The new set of imaging biomarkers that radiomics offers needs to be correlated with the serum or tissue biomarkers made available to us through digital pathology. A comparison needs to be made between these two kinds of biomarkers to assess their efficacy and impact in cancer prediction, assessment, stratification, and therapy planning.

Clinical interpretation of radiomics-based insights. The results of radiomics are not binary; they are complex and stratified. What does slightly increased risk of malignant progression mean in terms of guiding management? What does a slightly better response prediction to a certain treatment mean? Should it be administered? An important question that must be answered is whether the statistical confidence will be enough to stratify response to that information adequately. We feel that the results do not have to be binary to help. With new information on the likelihood of better response based on imaging parameters, could we provide this information to patients to help them make more appropriate personalized decisions? Gillies et al[1] also identify lack of standards as a challenge in terms of the guidelines for reporting and other aspects of radiomics. Furthermore, they mention that current cancer imaging modalities (PET/computed tomography, MRI, and potentially PET/MRI) have varied image reconstruction protocols, which poses yet another logistic and technical challenge to the application of radiomics in a way that yields reproducible results.[1]

In conclusion, radiomics as an applied technique has the potential to transform the practice of medical oncology and likely beyond. Although myriad technical challenges abound, there are opportunities for scientists, engineers, and clinicians to build information technology and biostatistical and informatic solutions to optimize radiomics for clinical use.

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