Radiology: Imaging Cancer

REVIEW

Precision Digital Oncology: Emerging Role of Radiomics-based Biomarkers and Artificial Intelligence for Advanced Imaging and Characterization of Brain Tumors

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Advances in computerized image analysis and the use of artificial intelligence–based approaches for image-based analysis and construction of prediction algorithms represent a new era for noninvasive biomarker discovery. In recent literature, it has become apparent that radiologic images can serve as mineable databases that contain large amounts of quantitative features with potential clinical significance. Extraction and analysis of these quantitative features is commonly referred to as texture or radiomic analysis. Numerous studies have demonstrated applications for texture and radiomic characterization methods for assessing brain tumors to improve noninvasive predictions of tumor histologic characteristics, molecular profile, distinction of treatment-related changes, and prediction of patient survival. In this review, the current use and future potential of texture or radiomic-based approaches with machine learning for brain tumor image analysis and prediction algorithm construction will be discussed. This technology has the potential to advance the value of diagnostic imaging by extracting currently unused information on medical scans that enables more precise, personalized therapy; however, significant barriers must be overcome if this technology is to be successfully implemented on a wide scale for routine use in the clinical setting.

Supplemental material is available for this article.

Cross-sectional imaging techniques have a central role in the initial diagnosis and surveillance of brain tumors. CT and MRI are used for tumor identification, mapping, and determination of tumor extent and posttreatment surveillance as a routine part of standard of care. However, beyond the traditional, largely anatomic and qualitative-oriented role of imaging for the evaluation of brain tumors, there is increasing interest in more specific, noninvasive biomarkers that can be used for enhanced characterization of the tumor phenotype, prediction of response to therapy, prediction of survival, and distinction of treatment-induced changes or complications from tumor recurrence. Interest in discovering and developing better tumor biomarkers is partly fueled by the recognition of the increased complexity of these tumors, as evident in the incorporation of molecular and histologic features for defining many tumor entities in the 2016 World Health Organization Classification of Tumors of the Central Nervous System (1). There is also increasing complexity of different therapeutic regimens, including various systemic therapies, that are either in current use or under investigation, with interest in therapies targeting specific molecular pathways (2). These therapeutic advances hold the promise of more effective, personalized therapy for brain tumors. At the same time, they highlight the need for more precise biomarkers that enable earlier and optimal patient stratification and treatment selection. This represents both an opportunity and a challenge for medical imaging as it takes an even more central role in the decision-making process and optimal treatment selection in the future.

To meet these challenges, new MRI sequences that improve diagnostic performance have been developed. As a result, there has been significant progress in advanced imaging of brain tumors using a combination of standard sequences and more advanced MRI techniques, such as diffusion-weighted and tensor imaging, susceptibility-weighted imaging, perfusion and permeability imaging, and MR spectroscopy (3). There has also been progress in developing more standardized and reliable approaches for assessment of response to treatment, such as the use of the Response Assessment in Neuro-Oncology criteria (4,5). However, despite these advances, the imaging criteria currently used in routine clinical practice rely on qualitative assessment and relatively basic quantitative evaluation of the sequences performed, perhaps with the exception of some advanced techniques such as perfusion and permeability imaging, potentially ignoring or underusing large amounts of available quantitative data. To this end, there has been increasing interest in the use of advanced computerized image analysis approaches that enable objective, high-level quantitative evaluation of image features and pixel-level relationships for tumor characterization, commonly referred to as *texture* or *radiomic analysis* (Table 1). The interest in these types of analyses has been further

Abbreviations

AI = artificial intelligence, CNN = convolutional neural network, DL = deep learning, ML = machine learning

Summary

Radiomic-based approaches and artificial intelligence can be used to analyze medical images and construct prediction algorithms with the potential to advance medical imaging into a new era of noninvasive biomarkers and predictive analytics toward more personalized, precision medical diagnostics for the evaluation of brain tumors.

Key Points

- Radiologic images can serve as mineable databases containing quantitative features with potential clinical significance.
- Texture or radiomic analysis combined with machine learning can be used to extract image quantitative features and combine them with other clinical information to construct "intelligent" prediction algorithms that improve with algorithm use and "experience."
- Early studies suggest the potential for better characterization of brain tumors including prediction of tumor histologic characteristics, molecular characteristics, and patient survival.
- Wide-scale application of radiomic-based approaches in the clinical setting will require overcoming scientific, workflow automation, and regulatory approval barriers.

fueled by recent advances in artificial intelligence (AI), especially machine learning (ML), for image analysis and prediction algorithm development.

An increasingly large body of evidence suggests that radiomics and AI applications can leverage existing information on scans that are routinely obtained as part of a patient's workup, including information available on standard sequences and more advanced techniques, to enhance diagnostic evaluation of tumors and develop clinically useful noninvasive biomarkers for tumor characterization. These noninvasive applications will be discussed throughout this review with a focus on brain tumor imaging. An overview of texture and radiomic approaches for tumor analysis and the central role of ML in constructing prediction algorithms or classifiers will be discussed. The radiomic workflow and the use of "handcrafted" versus "deep" extracted features will be reviewed, followed by a general discussion of current applications for brain tumor analysis to demonstrate the potential of these approaches for tumor-specific biomarker development. The review will conclude with a discussion of the barriers and challenges for the adoption of this technology in the clinical setting and a brief discussion of potential next steps and early applications for deployment in the clinical setting.

Overview of Texture Analysis and Radiomics

Texture Analysis

There are variations in the use and definition of medical image texture analysis in the medical and computer science literature. Broadly defined, texture analysis refers to computerized analysis of pixel position and fine pixel density or intensity variations on an image, with extraction of mathematically derived quantitative parameters that reflect those variations (6–12) (Fig 1). Texture analysis provides a quantitative map of different pixel variations and their relationships on the image. The goal of texture analysis is to extract and analyze fine variations that are not observed or consistently incorporated into the diagnostic decision making on evaluation by the naked eye during routine qualitative image interpretation performed in clinical practice. Interest in texture analysis has emerged partly from early studies of human perception that demonstrated that despite its impressive performance, the human visual system may have difficulty in effortlessly discriminating certain textural characteristics, for example those related to higher-order statistical features of an object or image (8,13). Interest in the use of computer-assisted analytic methods for image analysis is also driven partly by the increasing amount and complexity of the available information on a patient's scan and electronic medical record.

The main objective and rationale behind texture analysis of tumors is to provide a noninvasive quantitative map of tumor heterogeneity, which in turn is used to predict a molecular or clinical end point of interest (9–12). Interest in texture analysis is not new, and reports of potential applications date back to the early days of computerized image analysis (7,8,14). However, there has been a revival of interest in texture analysis applications in the past decade, fueled by the impressive advances in computational power, increasing interest in quantitative biomarkers, and a general trend toward digital health applications and more precise, personalized medicine.

There is not a uniform definition for texture analysis in the literature. In the medical and radiology literature, texture analysis has been used to refer to a range of quantitative features that include primary (or first-order) statistical features, secondary statistical features, and higher-order statistical features or more complex relationships that are derived from model-based and transform-based methods (9–12) (Table 1). However, texture has also been defined more narrowly as the second-order determinants of spatial interrelationships of pixel (or voxel) gray-level values or texture matrix–based features (15–17). For simplicity and clarity, the broader range of quantitative features that can be extracted—including the previously mentioned—will all be included under the umbrella of handcrafted radiomic features in this review. For the rest of this review, the term *radiomics* will be used to describe this process or articles performing this type of analysis. Table 1 provides a broad overview of handcrafted texture or radiomic features. A more detailed discussion of these features is beyond the scope of this article but can be found in a number of reviews or reference manuals on this topic (6–10,12,15,16).

Radiomics

The term *radiomics* was first introduced in the medical literature in 2012, defined as "high throughput extraction of quantitative imaging features with the intent of creating mineable databases from radiological images" (18,19). In a more recent review, the definition of radiomics was expanded to "high-throughput extraction of quantitative features that result in the conversion of images into mineable data and the subsequent analysis of these data for decision support" (15). So far, the majority of published radiomic studies have been based on analysis of CT, MRI, or PET scans, but there is no reason to restrict

Table 1: Summary of Handcrafted Quantitative Features

Feature Type	Description
Intensity-based statistical features, intensity histogram–based features, and intensity volume histogram–based features	Describe the distribution of gray levels and their relationship
Morphologic features	Describe the geometric characteristics of a region (area) or volume of interest
Local intensity features	Describe voxel intensities around a center voxel within a defined neighborhood*
Texture matrix–based features†	GLCM: describes how combinations of discretized gray levels of neighboring voxels are distributed along one of the image directions GLRLM: evaluates the distribution of discretized gray levels in terms of run lengths (defined as the length of a consecutive sequence of voxels with the same gray level along a fixed image direction) GLSZM: provides a count of the number of groups (or zones) of linked voxels GLDZM: provides a count of the number of groups (or zones) of linked voxels that share a specific discretized gray-level value and possess the same distance to the ROI edge NGTDM: the sum of gray-level differences of voxels with discretized gray level *i* and the average discretized gray level of neighboring voxels within a fixed Chebyshev distance NGLDM: tries to capture the coarseness of the overall texture

Note.—The above summary is modified based on the Image Biomarker Standardization Initiative (16). All of the above features can fall under the category of handcrafted radiomic features. Handcrafted (or hand-engineered) refers to the fact that these are all derived using clearly defined or explicit mathematical formulas designed by experts, often independently and prior to the experiment, in contradistinction to deep features extracted using deep learning approaches, such as convolutional neural networks, that are learned from data (see text). GLCM = gray-level co-occurrence matrix, GLDZM = gray-level distance zone matrix, GLRLM = gray-level run-length matrix, GLSZM = gray-level size zone matrix, NGLDM = neighboring gray-level dependence matrix, NGTDM = neighborhood gray-tone difference matrix, ROI = region of interest.

* Only voxels within the ROI are used as a center voxel, but the corresponding local neighborhood can extend outside the ROI.

† The term *texture analysis* is sometimes used to refer only to extraction of texture matrix–based features, whereas others use the term more broadly to include the broader range of extracted features, similar to handcrafted radiomic features.

radiomic analysis to these or any specific imaging modality. The exact definition and application of the term *radiomics* is likely to further expand with newly developed and increasingly sophisticated image analytic methods, an example of which will be discussed in the following sections when discussing the use of features extracted using deep learning (DL).

It is important to note that traditional radiomic feature extraction neither requires nor is based on AI, or more specifically ML. However, ML approaches such as convolutional neural networks (CNNs; a type of DL) can be used for direct image analysis and feature extraction (Table 1). Regardless of the method used for extracting radiomic features, ML is a powerful approach for developing algorithms based on extracted quantitative features to construct clinically useful prediction models or classifiers. It is worthwhile to distinguish the radiomics process from the traditional computer-aided diagnosis and detection systems. As discussed by Gillies et al (15), computer-aided diagnosis and detection systems are usually stand-alone systems designated by the Food and Drug Administration for use in either the detection or diagnosis of disease and are typically designed to deliver a single answer (eg, presence or absence of an abnormality). On the other hand, radiomics is a process designed to extract vast amounts of quantitative features from digital images that can be mined for hypothesis generation, testing, or both. These data can then be combined with other patient characteristics and clinically available information to develop decision support tools, and therefore some radiomics applications could be implemented as an extension of computer-aided diagnosis and detection.

When discussing radiomic features, one may make a distinction between semantic and agnostic features as the two broad categories of features that can be extracted using radiomics, as discussed by Gillies et al (15). Semantic features refer to characteristics or features commonly used in the radiology lexicon to describe a lesion of interest (ie, size, shape, and the presence of necrosis), which may be quantified for incorporation into radiomic models. The other broad category of features, agnostic features, can be characterized as mathematically extracted quantitative descriptors that are generally not part of radiologists' lexicons (15). Examples of agnostic features include the first-, second-, and higher-order statistical features that were discussed earlier. Many of the published texture and radiomics studies are based primarily on agnostic features, but there is no reason to impose any such limitation as the ultimate goal is to take advantage of all available clinically useful information. Having a component that includes or reflects semantic features also has a potential advantage in the sense that making any algorithm more "explainable" (20,21) may improve user acceptance as well as regulatory approval.

Traditional Handcrafted versus Deep Radiomics Features

There is an increasing use of CNNs for image analysis and tumor characterization. In the preceding sections, texture or radiomic features were described as including first-, second-, and higher-order statistical features as well as other complex features, including those based on more complex relationships derived using model-based and transform-based methods (6–12,15,16). Regardless of the variety of features that can be extracted and their complexity, these approaches share the characteristic that they are derived using clearly defined or explicit mathematical formulas designed by experts, often independent of or prior to the experiment. These features can be collectively referred to as "handcrafted" or "hand-engineered" features (Fig 2). In contradistinction to handcrafted features extracted using traditional radiomics, features extracted based on image analysis with DL approaches such as CNNs are not explicitly defined by an expert. Instead, they are learned from data through a learning algorithm, such as backpropagation. These may be referred to as deep (extracted) features and the process as "deep radiomics" (Fig 2).

Compared with DL, handcrafted features that include semantic features may be more limited in scope because they are based on a finite set of mathematically derived relations. Therefore, their predictive ability may be potentially inferior to DL in very large data sets. Handcrafted features, by definition, are explainable, which may be an advantage when compared with DL approaches. However, handcrafted features are prone to technical variations and noise, and they likely require image preprocessing and standardization to be generalizable and successfully applied on scans acquired using different techniques, scanners, or sites. Typically, handcrafted features work better on smaller data sets, which explains the preponderance of studies using this approach in the literature. DL is not constrained by a predetermined number or type of features and has the significant advantage of having the potential to "learn" any imaging feature(s) predictive of a given end point of interest. There is debate on whether the same extent of preprocessing would be needed for DL, and with sufficiently large and

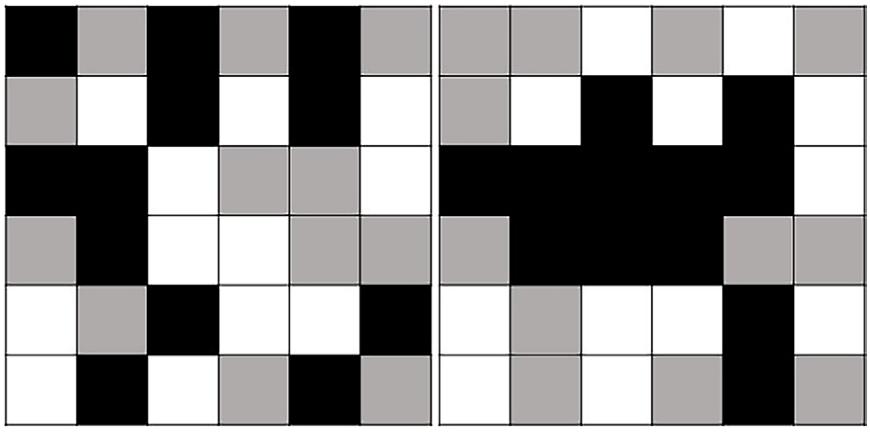

Figure 1: Texture or radiomic analysis for extraction of quantitative features reflecting higher-order pixel positions and relationships. Simplified diagram demonstrates two squares containing an identical number of white, gray, and black pixels. Using basic first-order statistical quantitative parameters, such as average or standard deviation, frequently used in traditional region of interest analysis, the boxes would have identical values, even though on visual inspection the patterns are clearly different. The objective of computerized image analysis approaches like texture or radiomic analysis is to extract quantitative parameters or features that capture the more complex, higher-order characteristics, such as those reflecting pixel positions and relationships.

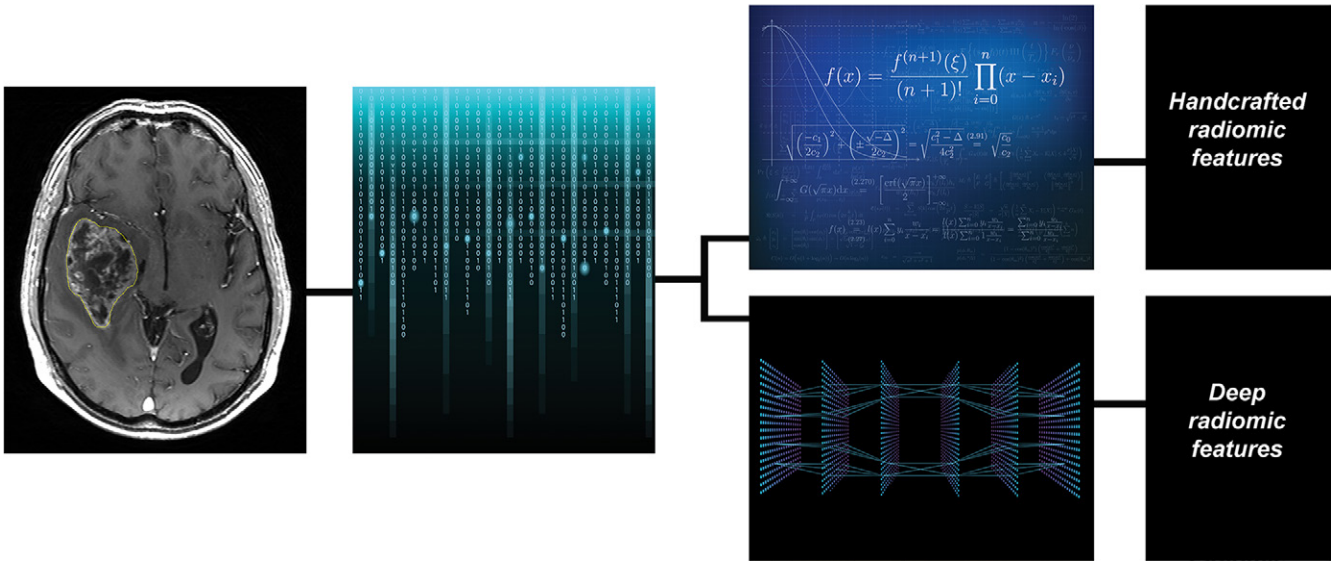

Figure 2: Texture or radiomic feature extraction: handcrafted feature versus deep features. During the process of texture or radiomic analysis, quantitative imaging features are extracted with the potential to serve as quantitative biomarkers that can be used to predict a clinical or molecular end point of interest. Broadly, traditional radiomic features may be defined as those derived using clearly defined or explicit mathematical formulas designed by experts, often independently and prior to the experiment, which may in turn be referred to as handcrafted or hand-engineered features. In contradistinction, features extracted based on image analysis with deep learning approaches, such as convolutional neural networks, are not clearly definable or derived using expert-designed explicit mathematical formulas. Instead, they are learned from data through a learning algorithm. These may be referred to as deep (extracted) features and the process as "deep radiomics."

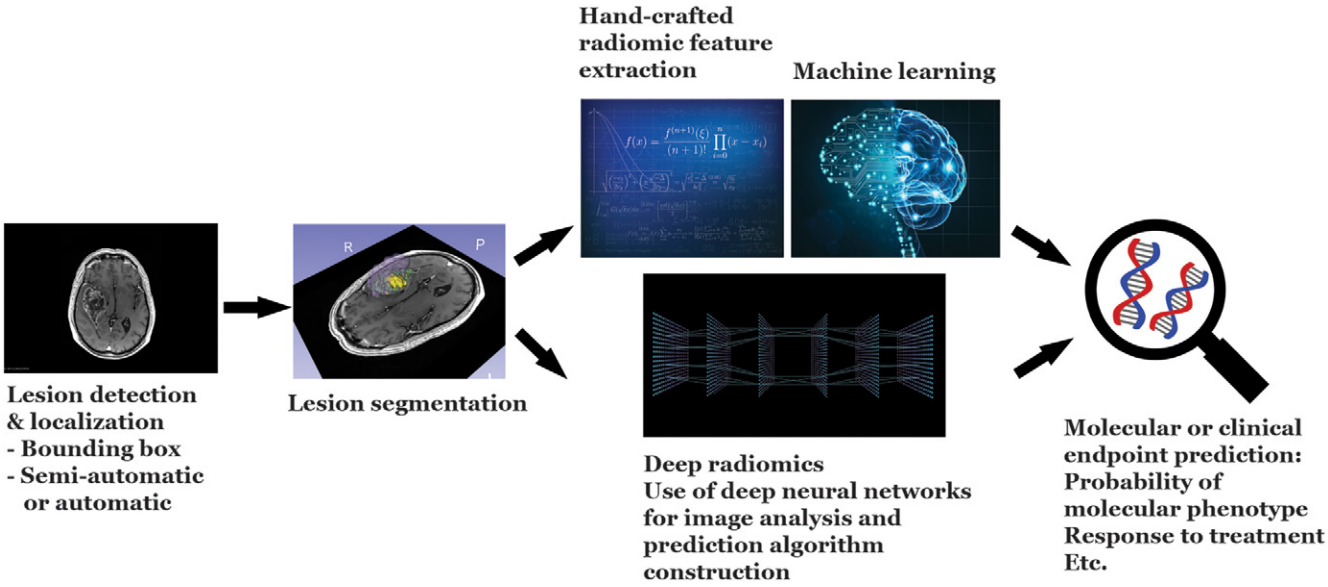

Figure 3: Overview of the radiomic workflow. The major steps in the radiomic workflow consist of lesion identification and localization, segmentation, feature extraction, and prediction model construction. In the short term, lesion detection and localization may be facilitated either by directing the algorithm using a bounding box approach by the radiologist or, alternatively, by the radiologist pointing at the lesion of interest using a cursor. However, in the long term, lesion identification may also be performed automatically by the algorithm. It should be noted that regardless of the degree of automation, these steps would be performed under the supervision of the expert radiologist, with the ability to make adjustments or modifications as needed.

varied data sets, image standardization may not be required for DL. It may even be argued that not only is standardization unnecessary, but it would have a negative impact by unduly removing information. However, these questions are unsettled at this time. In general, DL is more likely to have a poor or misleading performance on smaller data sets. Although many of the current texture or radiomic studies use handcrafted features for prediction, it is likely that deep radiomics will play an increasing role for this purpose. Early studies may report an advantage for either approach; however, at this time, there is insufficient evidence to conclude that deep radiomics will completely replace traditional radiomics or whether a combination of the two will yield the most robust biomarkers (22).

Prediction Model Construction and ML Classifiers

Radiomic features need to be incorporated into a prediction (classification) algorithm, which is called a "classifier," to be used for the determination of a molecular or clinical end point of interest. For example, analysis of a region of interest, such as a brain tumor, may yield hundreds or thousands of handcrafted radiomic features or deep radiomic features. There may also be nonradiomic features, such as clinical patient characteristics, biochemical results, or pathologic findings or molecular data obtained through biopsy that can be included as features in the classification model. Among the large number of features available, some will have variable associations (strong, weak, or insignificant) with the clinical end point of interest. Furthermore, among the different features, many may be redundant or highly correlated. Last, certain features may have a weak association with the outcome of interest when used in isolation but could increase in importance when used in combination with other features through interactions with those features. To predict a clinical end point of interest, an algorithm should be designed to analyze all the available features and optimize the set to the smallest number of characteristics that can accurately predict the outcome of interest.

Prediction algorithms or classifiers can be constructed using a purely classic statistical approach or ML. ML is particularly well suited for development of prediction algorithms with the potential for future translation into clinical decision support tools. One of the major advantages of ML over traditional software is that ML algorithms, as the name implies, can "learn" from experience and improve over time. There are many types of ML classification algorithms, and broadly, these can be divided into classic ML and DL (17,23–31). An example of DL that is widely used for medical image analysis is a type of artificial neural network called the CNN, as was discussed earlier.

When using handcrafted radiomic features, the feature extraction and prediction model construction steps are achieved in different steps (Fig 3). For example, features extracted from a lesion of interest are used as an input for a ML classifier for predicting an end point of interest. DL approaches, such as CNNs, can be used for direct image analysis and construction of a prediction model or classifier, combining the two steps and executing them using the same process. There is also a fundamental difference between classic ML and DL approaches. Generally, classic ML approaches are poorly suited to perform sophisticated image analysis, practically excluding them from the image analysis part of the radiomic process. However, the robust performance and complex architecture of DL makes DL-based approaches very attractive for image analysis and feature extraction applications. Although DL can be used both for image analysis and prediction algorithm reconstruction, it is not absolutely necessary, and one can combine DL and deep extracted features with other ML methods, including classic methods, for classification (32,33).

As a general rule, a traditional radiomic approach with classic ML may perform better with smaller data sets because DL typically requires larger data sets for algorithm training and development (17). Early studies suggest that there may be an advantage to combining the two approaches, but this requires further investigation. Whether assessments of very large data sets with DL approaches will completely replace the traditional radiomic approach, or if the two will be combined for an optimal biomarker and classifier development, is not a settled question and will have to be determined in future investigations. A detailed discussion of different ML methods is beyond the scope of this article but can be found in various publications and review articles on the topic (17,23–31).

Summary of the Radiomic Workflow

The major steps in the radiomic workflow are illustrated in Figure 3 and include lesion identification and localization, segmentation, feature extraction, and prediction model construction. Additional complexities and consideration related to various steps in the workflow are discussed in Table 2. Familiarity with the radiomic flow is important both for understanding the process as well as the multiple levels of complexity involved and challenges that must be overcome for eventual translation into a clinical decision support tool. As should be evident based on the earlier discussion, DL can in theory be used to perform every major step in the radiomic workflow, including localization and segmentation of a tumor (34,35), extraction of deep features, and construction of a prediction algorithm or classifier. It is therefore likely that DL will play an important role in radiomic-based clinical decision support tools of the future. However, one should not write off other approaches such as those based on traditional computer vision or combination of classic ML with DL for certain processes. On the basis of early studies, there may be a need or at least an advantage of combining different approaches (22). Whether with sufficiently large data sets the DL can completely replace the other components will have to be determined in future investigations.

Radiomic Models for Tumor Evaluation

Brain tumor evaluation applications consist of a mixture of traditional texture or radiomic studies using handcrafted features as well as the use of DL for tumor evaluation. Because MRI is the advanced imaging modality most commonly used for tumor evaluation, the majority of the radiomic studies performed for brain tumor evaluation use MRI, so this section will focus on radiomics applications based on MRI scans. However, some studies also show potential for application of radiomics to brain CT scans (36) or other modalities (37) for brain tumor evaluation. Although many of the studies are based solely on radiomic features, it is important to note that when planning investigation and development of clinical decision support tools, analysis should not be limited to radiomic features alone. On the contrary, all available information should be used, including clinical, biopsy, and molecular data, when available (34,38) for prediction model construction as part of a patient care pathway. There is also an important secondary consideration of ensuring that radiomic features have additional value and are not simply surrogates or redundant features to more basic parameters such as tumor size or other routinely obtained information. Studies are beginning to incorporate and demonstrate the additive value of radiomics (38) to more routinely obtained image-based or clinical parameters.

Histologic Classification and Grading of Tumors

Despite the exquisite anatomic detail and functional information provided using advanced MRI techniques, distinction of tumor type or grades is not always possible using current approaches for image interpretation. Radiomic approaches have the potential to further enhance noninvasive tumor characterization by enabling histopathologic classification or grading (Table 3 and Table E1 [supplement]). Preliminary studies have shown that tumor radiomic features may be used to distinguish different tumor types, such as primary brain tumors from metastases (39–41), primary central nervous system lymphoma (41–44), or other tumor types (41). Radiomic analysis has also been reported to help the distinction of glioblastoma from pilocytic astrocytoma (45), distinction of different histologic types of craniopharyngiomas (46), discrimination of meningioma subtypes (47), or distinction of nonfunctioning pituitary adenomas subtypes (48). Radiomic analysis combined with basic clinical information can also help in distinguishing different types of brain metastasis, and for certain metastasis types, the performance has been reported to be superior to expert radiologist evaluation (49). Some studies also suggest that radiomic features can be used for predicting tumor grade, such as distinguishing different grade gliomas (50–58). Radiomic analysis may also be used to estimate tumor proliferation indexes such as Ki67 (57) or for the differentiation of infiltrating tumor from vasogenic edema (59).

Classification of Molecular Characteristics of Tumors

Incorporation of molecular characteristics of tumors into diagnostic and treatment algorithms is key for optimal tumor therapy, explaining the incorporation of certain tumor molecular features into the most recent World Health Organization tumor classification. It is therefore no surprise that developing noninvasive biomarkers for predicting tumor molecular characteristics is an area of great interest and active investigation. Multiple investigations have demonstrated the potential of radiomic approaches for prediction of tumor molecular phenotype (Table 3 and Table E1 [supplement]). These include determination of isocitrate dehydrogenase 1 mutation status in gliomas (34,60–66), determination of nondeleted versus co-deleted 1p/19q status (62,64,67,68), prediction of O(6)-methylguanine-DNA methyltransferase promoter methylation status (69), isocitrate dehydrogenase 1/2-mutant with a telomerase reverse transcriptase promoter mutation (61), or prediction of p53 status or other molecular characteristics (70,71) in gliomas. One study also used radiomics for prediction of mutations in *BRAF* and catenin β-1 in craniopharyngiomas (46).

Table 2: Overview of Major Considerations for the Lesion Identification and Segmentation Steps in the Radiomic Workflow

Consideration	Description
Lesion identification and segmentation	Algorithm would detect a lesion automatically or by use of a bounding box, cursor, or interactive workstation
Tumor segmentation	2D versus 3D: • 2D approaches typically analyze the largest or central slice • 3D approaches typically analyze segmented volumes over multiple image slices covering the entire tumor • 2D models are not necessarily inferior to 3D models in terms of predictive performance, at least based on small studies (102)* Multisequence segmentation and feature extraction: • Although many of the current investigations using MRI radiomic analysis rely on one sequence (eg, postcontrast T1-weighted images), the optimal combination of sequences for prediction remains to be established • Future radiomic applications should ideally include the capability for multisequence analysis and feature extraction • The above will raise a number of technical challenges that will have to be overcome, including image registration for analysis Ground truth and manual versus automatic segmentation: • Manual segmentation by experts in the field is often treated as ground truth • A lesion's contours may not always be clearly defined due to known intrareader and interreader variations† • Manual segmentation is time-consuming and not practical for routine clinical implementation • Information extracted from the area immediately adjacent to a tumor may also have predictive value • Automatic or semiautomatic lesion segmentation could be considered to increase consistency and reproducibility
Application of normalization or standardization postprocessing algorithms	• Even with standardized techniques, some degree of technical variation in scan acquisition parameters, quality, or simply model- or vendor-related variations are inevitable • Handcrafted radiomic features are technique dependent (12,16,104–109), and reproducible application will likely require some degree of image "normalization" • The use of image normalization for deep learning applications is more controversial‡
Examples of postprocessing steps	• Image quality enhancement (smoothing, denoising, artifact reduction, etc) is ideally performed in the projection space, and although not necessarily specific for radiomics, it could impact extracted features • Registration (site dependent and variable need but commonly used in different brain imaging applications in which information from more than one sequence may have to be integrated) • Skull stripping • Intensity normalization • Interpolation to isotropic voxel spacing to make data sets comparable and extracted features reproducible; two approaches include downsampling or upsampling, each with unique advantages and disadvantages • Discretization of image intensities within an ROI or volume of interest

Note.—For the foreseeable future, key steps should proceed in a supervised manner, meaning that the expert radiologist should have the ability to make modifications to each step when warranted. The most important indicator of the utility of an algorithm as a biomarker would be judged based on the reliability for predicting the outcome of interest (eg, response to treatment, clinical outcome, etc) regardless of the intermediary steps used, as long as the algorithm yields reliable and reproducible results. DL = deep learning, ROI = region of interest, 3D = three-dimensional, 2D = two-dimensional.

* One reason that 2D models may not be inferior to 3D models is the concept of tumor habitats or subregions within the tumor volume that have distinct composition in terms of cellularity, blood flow, necrosis, and so forth. Consequently, features extracted from small subregions of the whole tumor volume may have unique predictive value. Early studies also suggest that a combination of the approaches may yield the best results (103).

† Multiple manual segmentations could be performed but again are impractical and would furthermore have the additional caveat of difficult-to-determine boundaries and variations. With sufficiently large data sets, DL evaluation of the entire image may be the ultimate solution.

‡ This may not be necessary for deep radiomics using DL because DL is robust at evaluating different levels of complexity and incorporating them into the algorithms, assuming that there is sufficient data and exposure of the algorithm to represent the breadth of variations encountered. However, there are counterarguments to this and these will have to be addressed in future investigations.

Table 3: Broad Summary of Investigated Radiomic Applications for Brain Tumor Evaluation

Prediction Phenotype	Specific Characteristics Predicted	References
Tumor histologic classification or differentiation of different tumor types (eg, glioma grades, GBM vs brain mets, met subtypes, etc)	• Differentiating glioma grade (I–IV, low vs high grade), Ki-67 labeling index • Classification/differentiation of GBM and brain metastasis or metastasis subtypes • Classification/differentiation of GBM, metastases, meningioma, PCNSL • GBM vs PCNSL • Prediction of type of brain mets (breast, SCLC, NSCLC, GI, and melanoma) • Pilocytic astrocytoma vs GBM • Meningioma subtype prediction (meningiothelial, fibrous, transitional) • Prediction of nonfunctioning pituitary adenoma subtypes (null cell adenomas from other nonfunctioning pituitary adenomas)	33, 39, 40, 41, 42, 43, 44, 45, 47, 48, 49, 51, 53, 54, 55, 56, 57, 58, 64
Tumor response or distinction of tumor recurrence from treatment response	• GBM: differentiate pseudoprogression from true progression • Primary or metastasis: differentiate radiation necrosis from recurrent brain tumor • Metastasis: response to stereotactic radiosurgery • Brain metastasis after SRS: true progression vs radionecrosis	36, 72, 73, 74, 75
Molecular end point prediction	• GBM IDH1 mutation status • GBM 1p/19q status • GBM TERT promoter mutation • GBM MGMT promoter methylation status • GBM Global DNA methylation subgroups and hallmark copy number variations • GBM molecular subtype (classic, mesenchymal, proneural, and neural) • Glioma p53 status • Craniopharyngioma: *BRAF* and CTNNB1 mutations	34, 46, 57, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 94
Prediction of survival (gliomas)	• Progression-free and/or overall survival	18, 32, 33, 37, 38, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 110
Other	• Pituitary adenomas: prediction of cavernous sinus invasion • Gliomas and metastases: differentiate vasogenic edema from nonenhancing tumor	59, 88

Note.—Please see Table E1 (supplement) for a more detailed list and description of specific studies. Some studies evaluate more than one category and therefore may be counted more than once in the table. CTNNB1 = catenin β-1, GBM = glioblastoma, GI = gastrointestinal, IDH1 = isocitrate dehydrogenase 1, mets = metastases, MGMT promoter = O(6)-methylguanine-DNA methyltransferase promoter, NSCLC = non–small cell lung cancer, PCNSL = primary central nervous system lymphoma, SCLC = small cell lung cancer, SRS = stereotactic radiosurgery, TERT = telomerase reverse transcriptase.

Posttreatment Change, Survival, and Other Studies of Interest

Distinguishing treatment-related changes in tumors continues to represent a challenge, even with the use of advanced MRI techniques. Preliminary studies suggest that radiomic analysis may be useful for distinction of progression or recurrence of primary or metastatic brain tumors from radiation necrosis and pseudoprogression (72–75). Multiple studies also suggest that radiomics can be used to predict patient survival (32,33,37,70,76–87). Radiomics has also shown potential for predicting the response of brain metastases to stereotactic radiosurgery (36). For pituitary adenomas, at least one study suggests that MRI-based radiomic features may be useful for predicting cavernous sinus invasion (88). As discussed earlier, the goal of these studies is to improve patient care by enabling more accurate diagnosis or optimizing treatment planning. Therefore, beyond prediction of probability for a specific molecular phenotype, the most promising and exciting application of these biomarkers is the establishment of a reliable and reproducible association with treatment response and outcomes. These associations may then enable better prediction of tumor response to different treatment, enabling earlier institution of the optimal therapy, with significant potential positive impact on patient care. Beyond prediction alone, quantitative and ML-based approaches also have the potential to optimize radiation therapy plans, potentially reducing toxicity to healthy tissues (89). Image-derived parameters may also be used to estimate tumor proliferation indexes such as Ki67, which potentially could be used to guide stereotactic biopsy (90).

The preceding sections have provided examples of potential applications of radiomics and ML for brain tumor evaluation. In the future, radiomic features can potentially be incorporated into staging systems and used to provide predictions for key tumor characteristics of interest in the radiology report (Fig 4).

Radiomics, Pathology, and Molecular Profiling

When discussing the potential for radiomic prediction of certain molecular features of tumors, it is worthwhile to step back and evaluate the broader potential implications and limitations of this approach. Even if proven to be reliable, in the absence of tumor-specific contrast agents, radiomic predictions will be based on associations of tumor macroscopic or microscopic image features with the molecular features and not direct con-

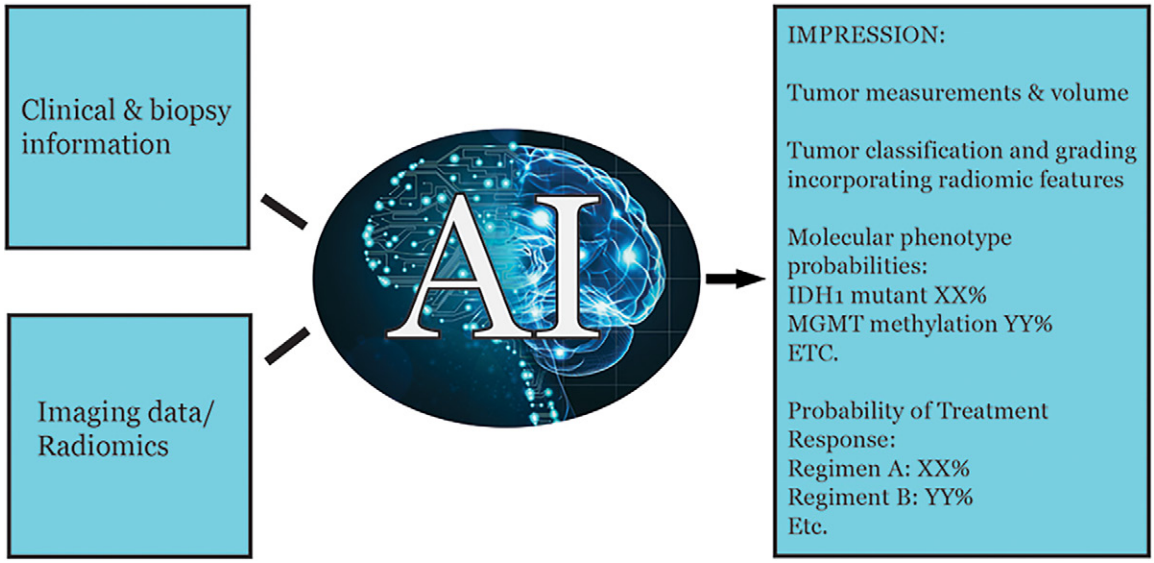

Figure 4: Potential example of a future radiology report incorporating radiomic features and machine learning for predictive modeling. One could even envision a preliminary draft of the report being generated automatically based on automated image analysis combined with natural language processing, which can then be modified by the expert radiologist as required. IDH1 = isocitrate dehydrogenase 1, MGMT = O(6)-methylguanine-DNA methyltransferase.

firmatory tests of the presence of a given mutation. Therefore, one should not take away from this review that radiomics will replace pathologic assessment and molecular profiling. However, radiomics has the potential to expand the frontiers of image-based noninvasive biomarkers further into the molecular realm. After all, even basic semantic image features have shown that imaging characteristics have an association with certain tumor phenotypes. It is also worth noting that just like imaging, AI will expand the frontiers of pathologic assessment, including in the semiautomated or automated analysis of pathologic slides and the use of ML approaches for incorporation of vast amounts of molecular data.

Notwithstanding the inherent indirect or statistical basis of radiomic approaches, there is true potential for radiomics and AI technology. This is because many treatment algorithms are far from perfect, some to the point of trial and error approach, especially for more advanced disease or disease that is unresponsive to standard, first-line therapy. As such, a good noninvasive predictive algorithm, even if not perfect, has significant potential for a clinical benefit in optimizing patient therapy. Furthermore, although radiomic markers cannot be expected to match molecular profiling in terms of accuracy or depth of detailed information provided, they do have the advantage of enabling whole-tumor analysis, in contradistinction to the sampling biases that are inherent in biopsy specimens due to tumor heterogeneity. By performing whole-tumor analysis, ML approaches can extract information from different tumor parts and surrounding regions, which may in turn be used to predict outcomes of interest or guide biopsy (50,90–92). Certain molecular analyses may also not be practical or cost-effective for routine clinical implementation, and radiomic-based approaches have the potential to fill that gap. Importantly, radiomics is based on studies already obtained as part of routine patient care, representing an additional added value without added inconvenience to the patient or new cost beyond that of the analytic platform. Although radiomics will not replace pathology or sophisticated molecular profiling, there is potential to reduce biopsies in select circumstances.

Radiomics and Advanced Imaging Techniques

Although many applications of radiomics so far are applied to conventional anatomic images, radiomics and ML can also be applied to advanced imaging techniques including, but not limited to, diffusion-weighted and tensor imaging, perfusion imaging, perfusion and permeability imaging, MR spectroscopy, and functional MRI (52,73,93–98) (Table 3, Table E1 [supplement]). The fusion of radiomics and advanced imaging techniques has the potential to enhance the use of information extracted from advanced imaging techniques in the same way that radiomics and ML can be used to extract additional information with predictive value from standard anatomic images. Indeed, overcoming the practical barriers in the radiomic workflow could by extension result in more workflow-friendly implementation and enhanced use of advanced imaging techniques.

Scientific and Practical Barriers to Radiomic Applications

Thus far, a discussion of the many exciting potential applications of radiomics and AI has been provided. Notwithstanding the potential for this technology, it should be evident that significant barriers must be overcome before these applications can be implemented on a routine basis in clinical practice. Currently, image segmentation is often the rate-limiting step in the implementation of radiomic approaches and clinical deployment, at least in the foreseeable future until whole-image or scan analysis becomes possible on a routine basis using DL. Indeed, from a feasibility perspective, one may argue that segmentation would be the most achievable (Table 4). Deployment of

Table 4: Next Step in Radiomic Tumor Evaluation: Potential Pilot Deployments

Example	Advantages	Important Considerations
Automatic or semiautomatic segmentation and volumetric analysis	• Important rate-limiting step and a principal barrier for large-scale radiomic investigations for the foreseeable future* • Potentially the most straightforward achievable first step • Volumetric analysis an intermediary benefit and parameter that can be provided in the radiologic report for tumor evaluation • Bridge to radiomics	• Early iterations could be directed by the radiologist (bounding box, point to the lesion, interactive workstation) with automatic segmentation • Semisupervised: radiologist can modify contours • Later iterations could include automatic lesion detection (progressing to whole-image analysis)
Glioma grading	• Sufficient number of studies suggest the potential value of radiomics for distinction of low- from high-grade gliomas • From a standpoint of pilot deployment and testing in the clinical setting, this is one attractive first option	• More challenging than volumetrics but important actual application of radiomics • If the algorithm would significantly change management, any pilot deployment may have to be done "passively," that is, without affecting treatment planning beyond current standard imaging until appropriate prospective testing and validation has been performed
Distinguishing pseudoprogression from tumor progression and recurrence	• Currently a challenge and important for patient treatment • Successful implementation may clearly demonstrate value of radiomics in the clinical setting	

* In the long term, it may become possible to perform whole-image analysis for tumor evaluation.

a reliable and automated tumor-segmentation algorithm could also provide actual tumor volumes—an additional intermediary benefit—when assessing treatment response in both clinical and research contexts, which would provide supplemental information for assessing current disease response categories.

Some of the other barriers have already been alluded to and pertain to reproducibility and standardization of the radiomic process with appropriate quality controls ranging from image processing prior to feature extraction to the mechanics and approaches of the actual feature extraction and prediction algorithm construction (Fig 3, Table 2). The technical variations in radiomic studies were highlighted in a recent systematic review (99) and must be overcome if these approaches are to be reliably deployed and used in the clinical setting. To this end, various important initiatives are being undertaken, such as the "image biomarker standardization initiative" (16). One approach for improving reproducibility of radiomic studies for which there is emerging evidence is the use of DL or CNNs as an image standardization or normalization approach that may then improve the reproducibility of handcrafted radiomic approaches (100,101).

Another fundamental requirement for developing reliable and generalizable DL algorithms is the use of large data sets that are varied and representative of the different techniques and variations that may be encountered at the time of independent testing or deployment of the algorithm. A survey of studies performed thus far for brain tumor characterization shows that the patient numbers used in these studies are invariably small (Table E1 [supplement]). A majority of the studies evaluated fewer than 200 patients, with only a few studies evaluating between 200 and 500 or 500 and 1000 patients. Furthermore, the majority of studies are based out of a single institution. There is a need for large-scale, multi-institutional studies to advance the field. In this sense, multi-institutional collaborations and data sharing will be key in the development of reliable and generalizable algorithms. Thus, there is a need for platforms that enable seamless, secure data sharing, annotation, and algorithm development. These platforms are currently being developed by different vendors. Such collaborative platforms will accelerate algorithm development and translation from a protype to a potentially deployable clinical tool. Ideally, such platforms will be auditable, which could facilitate future regulatory approval.

Although scientific considerations are obviously paramount, one should not ignore the more practical barriers related to workflow as well as regulatory requirements. Without addressing these barriers, radiomics and AI are unlikely to ever realize their true potential. There is an ever-increasing demand on imaging services, and these demands are a challenge for the radiologists who have to interpret the studies as well as the health care system in terms of cost and sustainability. Making the radiomic process workflow friendly and seamless is essential if this technology is to be used routinely in clinical practice. In the bigger picture, some of the challenges of AI implementation may be much more basic and related to the robustness of basic information technology infrastructure within an organization or health system and the accessibility and connectivity of different components that unfortunately may frequently be in silos. These barriers must be broken down to enable seamless and optimal use of the information in a patient's medical chart and images for high-quality personalized care. For clinical implementation, the radiomic process needs to be automated and seamless. For example, image segmentation could be initiated by clicking on a region of interest,

and then an algorithm would work in the "background" with as little radiologist intervention as possible. There is sufficient evidence for pilot deployments of some of these approaches in the clinical setting, establishing their feasibility and, more directly, evaluating their potential value to patient care (Table 4).

It is also important to demonstrate that the radiomic applications have added value, both in terms of quality and timeliness of patient care as well as in cost savings. For example, potential benefits of using radiomic applications could include enabling earlier institution of the optimal treatment regimen, avoiding harmful and potentially toxic costly therapies that have a low likelihood of success, and potentially reducing certain noninvasive procedures and biopsies. These benefits will increase the likelihood that payors and decision makers will facilitate the implementation and adoption of this technology. Last, implementation of radiomics and AI into clinical practice presents unique challenges, especially for the AI component. The current approach for regulatory approval of computer-aided diagnosis and detection may not be suitable for AI algorithms that are designed to "learn" and change for optimal utility. There is a need for development of regulatory processes that are tailored for AI application, which may be achieved by implementation of validated regulatory pathways and precertification of companies proven to be able to develop and monitor algorithm performance reliably, with periodic updates for optimizing performance. All of these represent important challenges that need to be overcome in the coming years for this technology to realize its full potential.

Conclusion

In this article, radiomic analysis and the use of ML for prediction algorithm construction was reviewed. An increasingly large body of literature suggests that radiomic features are useful for characterization of brain tumors, including prediction of tumor histologic characteristics, certain molecular characteristics, and patient survival. There remain significant challenges and barriers to routine implementation of radiomic analysis in clinical practice. However, these challenges are not insurmountable, and radiomics, powered by AI, represents a new horizon in medical imaging and noninvasive diagnostic evaluation of brain tumors. Implementation of these technologies represents an opportunity to further advance the essential role of medical imaging in the care of patients with brain tumors by enabling more precise, personalized tumor characterization, which in turn will direct optimal and personalized therapy.

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