Emerging Applications of Radiomics in Neurological Disorders: A Review

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Abstract

Radiomics has achieved significant momentum in radiology research and can reveal image information invisible to radiologists’ eyes. Radiomics first evolved for oncologic imaging. Oncologic applications (histopathology, tumor grading, gene mutation analysis, patient survival, and treatment response prediction) of radiomics are widespread. However, it is not limited to oncologic analysis, and any digital medical images can benefit from radiomics analysis. This article reviews the current literature on radiomics in non-oncologic, neurological disorders including ischemic strokes, hemorrhagic stroke, cerebral aneurysms, and demyelinating disorders.

Introduction And Background

While no new imaging modalities have been invented within the last few decades, technological advances in image acquisition and analysis have greatly improved the diagnostic utility of radiologic imaging. In recent times, the emergence of new segmentation software packages (e.g., neural networks) has led to the rise of quantitative image analysis in radiology [1]. A more sophisticated concept is converting digital medical images into mineable high-dimensional data, a process known as radiomics [2]. Traditionally, radiologists use a limited number of imaging features for diagnosis such as lesion size, density, lesion border, and enhancement. In contrast, radiomics can easily use many more quantitative features to predict and capture specific medical information. Radiomics relies on identifying potentially non-obvious imaging “features.” Here, “features” refers to the mathematical characteristics of the image.

Basics of radiomics

Radiomics is the high-throughput extraction of large amounts of quantifiable information from a region of interest (ROI) in digital medical images [3]. By converting medical images into hundreds or thousands of quantitative imaging features via data characterization algorithms, radiomics can extract information invisible to the human eye [4]. The extracted features can then be evaluated to make predictions, and the most predictive features are selected. Then, predictive models are built on top of these selected features to make predictive decisions regarding various medical conditions.

A radiomics pipeline starts with image processing. In image processing, different medical images from various centers and vendors are normalized and harmonized to neutralize the effect of different scanners and reconstruction techniques. After normalization of the images, the area of interest (lesions) is segmented. For segmentation, two-dimensional or three-dimensional images can be used; moreover, segmentation can be manual (done by an expert radiologist), semi-automated, or fully automated. The segmented area is then analyzed using a computational method, and hundreds and thousands of different quantitative features are extracted from the segmented regions. These quantitative features are essentially the mathematical relationship between different pixels and voxels of the segmented area. The most commonly used radiomics features are intensity (histogram) features, shape features, and texture features [5]. In addition, different types of filters (wavelet and Gaussian filters) can be applied to the images before feature extraction, which can multiply the number of extracted features many times. The extracted features are then used to train different machine learning models for different predictions such as tumor grade, histopathologic diagnosis, gene mutations, treatment response, patient survival, complications, and many more clinically relevant outcomes [6]. However, using hundreds and thousands of features to train the predictive learning models is not ideal. It is well-known that if a predictive model is trained with “too many” features, the subsequent trained model will work well on the training dataset but poorly in the real world (also referred to as overfitting in machine learning). To avoid this challenge, only the most predictive features must be utilized for model training, and the rest of them should be discarded. This act is referred to as “feature selection.” There are many different approaches to finding the most predictive features, and most
of them are mathematical-based platforms. In radiomics, one of the most commonly used feature selection techniques is the least absolute shrinkage and selection operator (LASSO) [6].

Different machine learning models (neural networks, random forest, decision trees, support vector machine [SVM], etc.) are then trained to utilize the selected features to predict one element of a specific clinical question. Each trained model is then tested either on a test dataset, or an external dataset, or via cross-validation. Performance of models is usually reported by accuracy, sensitivity, specificity, and area under the curve (AUC). AUC is a standard metric for performance measurement, especially implemented to test the performance of various machine learning approaches. AUC ranges from 0 to 1, with values closer to 1 suggesting a better predictive model. The most robust predictive model is then reported. It is very common to summate different models to create a higher-performing model (ensemble techniques) [7]. A flowchart depicting the various steps of the radiomics pipeline has been summarized in Figure 1.

**FIGURE 1: The radiomics pipeline.**

MRI: magnetic resonance imaging; CT: computed tomography; PET: positron emission tomography; SPECT: single-photon emission computed tomography; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder

**Review**

**Applications in neurological disorders**

The first applications of radiomics in imaging were in the field of oncology. This was also due to the support from various genomic projects and abundant biomolecular research data, which motivated researchers to devote their efforts to oncologic applications [8]. So far, the most common application of radiomics regarding oncologic imaging is the prediction of histopathology, tumor grading, genetic mutations, prediction of treatment response, the chance of recurrence, and patient survival. However, the application of radiomics is not limited to oncologic imaging and can essentially be extended to any clinical condition [5-7].

Taking inspiration from successes in the field of oncologic imaging, researchers have started to apply these techniques in non-oncologic diseases. The non-oncologic applications of radiomics in neurology are now emerging. The most common neurologic conditions (ischemic strokes, hemorrhagic stroke, cerebral aneurysms, and demyelinating disorders) are the most evaluated neurologic diseases by radiomics. In this paper, we review the most common applications of radiomics in the field of neurology. After a comprehensive search within the PubMed database, the related published studies in English were selected. After reviewing the articles, only studies with a complete radiomics pipeline (clear information about the patient population, segmentation techniques, radiomics software, number of total features, feature selection model, number of selected features, machine learning models, and model performance) were selected for this review. Applications regarding cerebral infarction and hemorrhage, cerebral aneurysms, and demyelinating disorders are included. Radiomic applications for neurodegenerative and psychiatric disorders are beyond the scope of this review.

**Ischemic stroke**

Stroke is the leading cause of disability and the fifth most common cause of death in the United States, with the majority (80%) of cases attributed to an ischemic etiology. Detection of ischemic stroke in the early
hemorrhage on traditional imaging remains a challenge at this time. Radiomics has been used for this task in patient management and decompressive craniotomy. Prediction of the early expansion of intraparenchymal hemorrhage on non-contrast head CT is crucial for approximately 40% at one month and 54% at one year after bleeding. Only 12-39% of patients with ICH can be treated appropriately because of severe edema and mass effect with an associated mortality of approximately 80% without treatment. At this time, there is no accurate technique to predict this catastrophic complication before the onset of mass effect (time of flight). The most predictive features were selected by LASSO and used to predict the symptomatic outcome of mechanical thrombectomy. In another study, internal carotid artery/M1 thromboses in 67 patients were analyzed using radiomics. A total of 326 features were extracted from thrombosis on both non-contrast CT and CT angiography (CTA). SVM, a machine learning approach, was used to predict recanalization with an AUC of 0.85 after IV alteplase treatment.[16]

**Identification of High-Risk Carotid Plaque**

It is well-known that not all carotid atherosclerotic plaques causing less than 50% stenosis are associated with an increased risk of brain infarction. Traditionally, the presence of intraplaque bleeding and lipid-rich necrotic core are considered indicators of unstable plaques. In one study, radiomics was used to extract multiple features from the carotid plaques on T1, T2, and magnetic resonance angiography (MRA) (time of flight). The most predictive features were selected by LASSO and used to predict the symptomatic atherosclerotic plaques in carotids. In the study, traditional techniques utilized by radiologists had an AUC of 0.80, while the radiomics approach achieved an AUC of 0.98 for this task.[17]

**Prediction of Malignant Middle Cerebral Artery Infarction**

Malignant middle cerebral artery (MCA) infarction is one of the most severe complications of cerebral infarction. It presents with rapid deterioration of neurologic status after large MCA infarction, mainly because of severe edema and mass effect with an associated mortality of approximately 80% without appropriate treatment. At this time, there is no accurate technique to predict this catastrophic complication in advance. In one study, radiomics was used on non-contrast brain CT scans within 24 hours after initial symptoms. The selected features could predict a malignant MCA infarction with an AUC of 0.91.[18]

**Intracranial hemorrhage**

Intracranial hemorrhage (ICH) is the second most common type of stroke, with a fatality rate of approximately 40% at one month and 54% at one year after bleeding. Only 12-39% of patients with ICH can achieve long-term functional independence.[19] The standard diagnostic technique for the detection of ICH is the non-contrast head CT. Differentiation between expansile versus non-expansile ICHs is crucial for patient management and decompressive craniotomy. Prediction of the early expansion of intraparenchymal hemorrhage on traditional imaging remains a challenge at this time. Radiomics has been used for this task.
radiomics analysis of aneurysms may help physicians design a better follow-up strategy and infer clinical features that are not visible to the radiologist's eyes.

Intracranial aneurysm

Intracranial aneurysms are frequently found in patients undergoing brain imaging for unrelated indications such as stroke, multiple sclerosis, headache. These aneurysms can have an inherent risk of rupturing, resulting in life-threatening subarachnoid hemorrhages and even death. These are typically followed by serial MRA or CTA to assess for interval change in size. Aneurysms vary in size and morphology and have a variable risk of rupture depending on multiple factors that are invisible to radiologists' eyes. Radiomics may have an application in the prediction of the chances of future rupture of these aneurysms. In one study on 719 aneurysms, 12 morphologic features were extracted from three-dimensional-digital subtraction angiography (3D-DSA) angiogram. The LASSO regression demonstrated that "flatness" is the most crucial predictive feature for aneurysm stability. The subsequent model based on the radiomics morphology and clinical feature predicted the aneurysm stability with an AUC of 0.85 [30]. As is evident, only morphologic radiomics features (a subset of radiomics features) were used to predict aneurysm stability. There are no data about the other types of radiomics features (e.g., texture analysis). Not all studies are promising; in one study on 3D-DSA, the radiomics morphology features (extracted by Pyradiomic) were inferior to traditional morphology analysis (done by Matlab software) for predicting aneurysm stability [31]. In the future, radiomics analysis of aneurysms may help physicians design a better follow-up strategy and reduce the patients' radiation dose.
Demyelination

Inflammatory demyelinating disorders are a heterogeneous group of conditions characterized by acute or chronic inflammation involving the myelin, followed by reactive astrogliosis. There are different subtypes of demyelination such as multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), Marburg-type MS, concentric sclerosis of Baló, and acute disseminated encephalomyelitis [32].

Differeniating NMOSD and MS remains challenging in the clinic as well as on neuroimaging. Radiomics techniques have been implemented on T2-weighted sequences for this task. After extraction of 273 features, the LASSO-based logistic regression model selected 11 characteristic features with significant predictive capability. The final model based on these features and five clinical features (age, gender, antibodies to aquaporin-4, oligoclonal band, and spinal lesions) could differentiate NMOSD from MS with an AUC of 0.93 [33]. In another study, 485 radiomics features were extracted from spinal cord lesions. From the extracted features, nine were significantly different in MS and NMOSD. The final model, based on the nine extracted features, the size of the lesion, patients’ age, and expanded disability status scale, was able to differentiate multiple sclerosis from NMOSD with an AUC of 71.95 [34]. Radiomics has been used for the prediction of visual accuracy and outcomes in patients with optic neuritis. Seven radiomics features have been reported to be useful for predicting the patients’ visual accuracy and prognosis with the first episode of optic neuritis [35]. Estimating the age of removing plaques is also important in managing patients with demyelination and evaluating treatment response. Radiomics have been used for this task, and the features have been extracted from the T1, T2, fluid-attenuated inversion recovery, post-contrast T1, and quantitative susceptibility mapping sequences. The subsequent random forest models were able to estimate the age of the plaques with a median absolute error of 5.98 months [56].

Limitations

The common non-oncologic neurologic disorders studied by radiomics are summarized in Table 1. As shown in Table 1, the performance of radiomics analysis is promising in many different neurologic conditions. However, there are significant limitations as well as most of the publications are retrospective and based on small datasets from single medical centers. Moreover, there is significant heterogeneity in the radiomics pipeline design. There is no agreement regarding the radiomics software, the number of extracted features, the number of selected features, and the machine learning models. In addition, trained models are often not accessible to other researchers and many times not reproducible by other investigators. Such models end in publications and get cited, but unfortunately, have been unable to reach clinical implementation yet.

| Reference number | Target | Imaging | Number of patients | Extracted features | Selected features | Software for feature selection | AI model | Findings | Limitations |
|------------------|--------|---------|--------------------|-------------------|------------------|-------------------------------|----------|----------|-------------|
| 1                | Detection of hyperacute infarction on non-contrast CT | NCCT | 139 | 10 | 6 | Run-length matrix | SVM, DT, AdaBoost | AUC of 0.62 for the detection of hyperacute infarcts. No difference between two and eight hours from symptom onset. The performance of the classifiers did not depend on the size of the infarction. | No external validation group and the study considered the contralateral hemisphere as normal. |
| 2                | Prediction of successful thrombolysis by radiomics analysis of thrombus | NCCT | 169 patients | retrospective training: 47 patients | 1,405 | Univariate feature selection | SVM | AUC of 0.58 to predict the successful first passage. AUC of 0.76 to predict the number of passages required for successful recanalization. | Single-center study, the target was radiologic recanalization and not patients' prognostic manual segmentation. |
| 3                | Prediction of recanalization after IV alteplase treatment from radiomics analysis of thrombus | NCCT and CTA | 67 | 326 | 38 | Linear discriminative analysis | SVM | AUC of 0.85 for prediction of recanalization after IV alteplase treatment using a combination of radiomics features of NCCT and CTA. The performance of radiomics was superior to traditional analysis of thrombus (thrombus length, thrombus volume, etc.). | Small dataset. The results were reported by cross-validation and there was no external validation cohort; manual segmentation. |
| 4                | Detection of high-risk carotid atherosclerosis | Dynamic contrast-enhanced | 162 | 788 | 33 | ITK-SNAP | LASSO | AUC of 0.689 in the training cohort and 0.886 in the test cohort for detection of high-risk plaques. Radiomics model and radiomics+ traditional model were better than traditional (human-based) model alone. | Small dataset; no external validation. Manual segmentation. Radiomics analysis was based on single axial (2D) images of the largest plaque area, and 3D analysis was not performed. |
| 5                | Prediction of malignant acute middle cerebral artery | CTA | Train: 87 Test: 38 | 286 | 8 | Artificial intelligence | LASSO | AUC of 0.91 on real group to predict malignant infarcts. | Retrospective. No clinical data were used. No external validation. |
| Indication                                      | Dataset | n    | k   | Method                | Regression | Feature Selection   | Validation | p-value | Dataset Details |
|------------------------------------------------|---------|------|-----|-----------------------|------------|---------------------|------------|---------|-----------------|
| Prediction of the hematoma expansion           | NCCT    | 167  | 4   | MatLab                | Pearson correlation | 23 different ML models | Single-center retrospective study | 0.726%   | Radiomics were included. Retrospective study. No external validation. Manual segmentation. |
| Prediction of the hematoma expansion           | NCCT    | 313  | 58  | Artificial intelligence Kit | Multivariate logistic regression | Addition of radiomics to clinical factors significantly improved the prediction of hematoma expansion | Single-center retrospective study |          | Only small hematomas <10 ccs were included. No external validation dataset. |
| Prediction of the hematoma expansion           | NCCT    | 386  | 4   | Artificial intelligence Kit | Multivariate logistic regression | AUC of 0.85 in external validation. (This number appears maximal because it was tested on an external dataset of another medical center) | Retrospective study |          |                   |
| Differentiation between neoplastic and non-neoplastic hematomas | NCCT     | 77   | 100 | Pyradiomics            | Gini impurity measures, Random forest | Radiomics and machine learning yielded equal or superior performance in comparison to radiologists | Small dataset. Single-center retrospective study |          |                   |
| Prediction of aneurysm rupture                 | CTA     | 122  | 107 | 89                    | Pyradiomics              | The radiomics model was better than the traditional (morphologic) model. The combination was better than each model individually | Small dataset. Retrospective single-center study. No clinical data were built to build the models. Aneurysms were followed for only 2 years |          |                   |
| Prediction of aneurysm rupture                 | 3D DSA  | 420  | 12  | 4                    | Pyradiomics | AUC of 0.85 in predict aneurysm rupture. No difference between the different models | Retrospective single-center study. Only aneurysm between 4 to 8 mm included. Most of the aneurysms ruptured |          |                   |
| Prediction of aneurysm rupture                 | 3D DSA  | 383  | 13  | 13                   | Pyradiomics | NA                  | Retrospective single-center study |          |                   |
| Differentiation between MS and NMOSD          | T2 (3 T) | 273  | 11  | Not mentioned         | LASSO               | Multivariate analysis | Only T2 sequences. Optic nerves were not evaluated. Only 2D images were used | Retrospective single-center study |          |                   |
| Differentiation between MS and NMOSD          | T2 (3 T) | 485  | 9   | Not mentioned         | LASSO               | Multivariate logistic regression analysis | Only T2 images of the cord were used. Cross-sectional study and no follow-up was performed. Single-center study |          |                   |
| Prediction of optic neuritis                   | STIR and T1 fat-sat-C | 25   | 91  | 7                    | Pyradiomics | Multivariate logistic regression | Radiomics may predict the visual outcome in optic neuritis | Small dataset |          |                   |
TABLE 1: Non-oncologic radiomics applications in neurology disorders.

| Reference | Application |
|-----------|-------------|
| [1] | estimation of the age of demyelination plaques with FLAIR, T1+C, QSM, and RIA R package. |

Conclusions

Radiomics is an emerging research field in radiology based on the extraction of image information beyond obvious visible information. Although oncologic imaging is the most widely studied field, preliminary results regarding the applications of radiomics in non-oncologic neurological disorders are promising. Based on our current knowledge, radiomics solutions have been used for infant brain detection on non-contrast brain CT, characterization of neoplastic versus non-neoplastic cerebral hemorrhages on CT, prediction of cerebral aneurysmal rupture on CTA, and characterization of demyelination lesions on MRI with acceptable performance. However, this field is still in its infancy and many challenges must be resolved before widespread clinical application. The main challenges are the lack of a uniform approach in radiomics pipeline design, small datasets, lack of external validation datasets, and the inability of investigators to reproduce published work in diverse research and clinical environments. Further randomized controlled studies are needed before widespread clinical applications of radiomics in neurological disorders.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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