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Radiomics Analysis for Clinical Decision Support in Nuclear Medicine

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Radiomics – the high-throughput computation of quantitative image features extracted from medical imaging modalities- can be used to aid clinical decision support systems in order to build diagnostic, prognostic, and predictive models, which could ultimately improve personalized management based on individual characteristics. Various tools for radiomic features extraction are available, and the field gained a substantial scientific momentum for standardization and validation. Radiomics analysis of molecular imaging is expected to provide more comprehensive description of tissues than that of currently used parameters. We here review the workflow of radiomics, the challenges the field currently faces, and its potential for inclusion in clinical decision support systems to maximize disease characterization, and to improve clinical decision-making. We also present guidelines for standardization and implementation of radiomics in order to facilitate its transition to clinical use.

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Recent advancements in both medical imaging and artificial intelligence (AI) are shaping a unique opportunity for developing tools that maximize the extraction of information from medical images to produce actionable insights. Prognostic models based on historical patient data have been applied in the various medical fields with varying degrees of success.[1,2] In the last few decades predictive, prognostic, and diagnostic machine learning algorithms trained on imaging data have been developed for a diverse number of diseases.[3-5] Since the information extracted from radiological images (termed imaging features) is able to reflect the individual phenotype of both patient and disease simultaneously; such models have the potential to improve quality of healthcare by informing clinical decision support systems, and thus facilitating personalized medicine. Personalized medicine entails tailoring treatment to the individual characteristics of the patient and the disease, rather than using a one-size-fits-all approach commonly used in clinical practice.[6]

The combination of sufficient data with the appropriate AI methods has fueled the rapid advancements in disease prognosis and diagnosis.[7,8] More recently, the high-throughput extraction of crafted quantitative imaging features from large numbers of radiographic images, termed radiomics, has produced clinically relevant predictive, prognostic, and diagnostic

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models.[3,9,10] Radiomics is based on the hypothesis that quantitative imaging data provides additional information on tissue phenotype, disease biology, and surrounding microenvironment.[3,11] Advantages of the radiomics approach include: the noninvasive nature of most imaging modalities; information can be collected on the phenotype of the disease site, on healthy tissue, and on the surrounding microenvironment,[3] unlike biopsies, multiple large volumes of tissue can be analyzed differentially; predictive, prognostic, and diagnostic models can be built using otherwise unused historical imaging data (retrospective studies); it can be performed in a way that is both distinct and complementary to other relevant data sources, such as clinical parameters and genotype.[9,12-14]

In this review, we examine molecular imaging techniques, including their limitations, as well as radiopharmaceutical tracers. We proceed to describe radiomics, its workflow and limitations from image acquisition to model building, the existing guidelines and recommendations for standardization, the potential applications of radiomics specific to nuclear medicine, and examples of published available applications. Finally, we reflect upon future applications of radiomics in nuclear imaging.

Molecular Imaging

Dedicated imaging approaches employing computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission tomography (SPECT), or hybrid imaging modalities like PET/CT, SPECT/CT, or even PET/MRI are a cornerstone in the diagnosis and management of various medical conditions, including malignancies.[15,16] In contrast to anatomy-based imaging (eg, CT scans), nuclear imaging techniques such as PET or SPECT visualize biologic and molecular characteristics, often by means of radiopharmaceuticals that target specific structures, receptors, or pathways.[17]

Radiopharmaceutical Tracers

Of the multitude of radiopharmaceutical tracers in existence, only a few have been implemented in routine clinical practice,[18-20] with fluorodeoxyglucose (FDG) the most widely applied tracer.[21] In oncology, tumor-specific tracers like PSMA or somatostatin receptor ligands also play an important role in clinical routine.[22,23] A focus toward imaging the different hallmarks of cancer[24] is apparent in the tracers developed in recent years such as markers for proliferation,[25] perfusion,[26,27] and hypoxia[28-30] using PET radiopharmaceuticals. With regards to SPECT imaging, a few new approaches have reached application in humans, as standard routine radiopharmaceuticals such as ^{99m}Tc-labeled phosphonates are still widely used.[31,32] For tumors with low avidity for ^{18}FDG, other compounds have been proposed, with both diagnostic and theragnostic applications (eg, ^{89}Zr-labeled monoclonal antibodies in metastatic breast cancer, PSMA ligands in prostate cancer,[33,34] ^{18}F-choline in prostate cancer or hepatocellular carcinoma).[35] ^{68}Gallium radiolabeled somatostatin analogues have been shown to improve image quality in neuroendocrine tumors in comparison to the commercially available ^{111}In-octreotide SPECT tracer, with a significant clinical impact on the intended management.[36,37]

Treatment strategies based on immuno-PET, the tracking and quantification of monoclonal antibody targets with PET, could be tailored to each individual patient, hence limiting the costs for patients that would not display response to treatment (eg, HER2neu).[38,39]

The high accuracy of such new molecular imaging agents raises numerous questions that must be studied in clinical trials to establish how the agents may be used to affect clinical outcomes favorably. For this reason, correlation of the predictive and prognostic features to the diagnostic findings is one of the main focuses of current AI research.

Hybrid Imaging

While nuclear imaging techniques have the ability to visualize metabolic processes, the lack of precise anatomical localization, and line-of-sight attenuation information necessitates the pairing with an anatomical imaging technique, such as MRI or CT or rely on transmission methods. Though different imaging modalities can be performed sequentially, the difficulty in perfectly coregistering the molecular and anatomical images has led to the development of dedicated hybrid imaging hardware, such as PET/CT, SPECT/CT, and PET/MR[40] scanners.

Hybrid molecular-anatomical imaging provides information about the metabolic activity and anatomy of a given region that could otherwise be misleadingly interpreted on solely nuclear imaging, such as areas of variable physiologic uptake.[41] FDG-PET/CT has widespread clinical use in oncology due to its superior diagnostic value compared to anatomical or molecular imaging alone,[42] in addition to its ability to predict tumor response at a very early stage in the course of a treatment, even in the absence of anatomical changes.[43]

Limitations of Functional Imaging

A major limitation of functional imaging in oncology is the lack of specificity to malignancy. For instance, the uptake of the radiotracer FDG used in PET imaging can be increased due to various causes that range from normal physiology to malignancy.[44] A further limitation is the qualitative or semiquantitative assessment of scans, which are subject to inter- and intraobserver variability,[45,46] influencing the final diagnosis or management. Both lack of specificity and observer-induced variability are expected to be minimized with standardized radiomics workflows.

Radiomics Workflow

Image Acquisition and Tumor Segmentation

The radiomics workflow starts with the image acquisition, and attention needs to be given to the settings and protocol

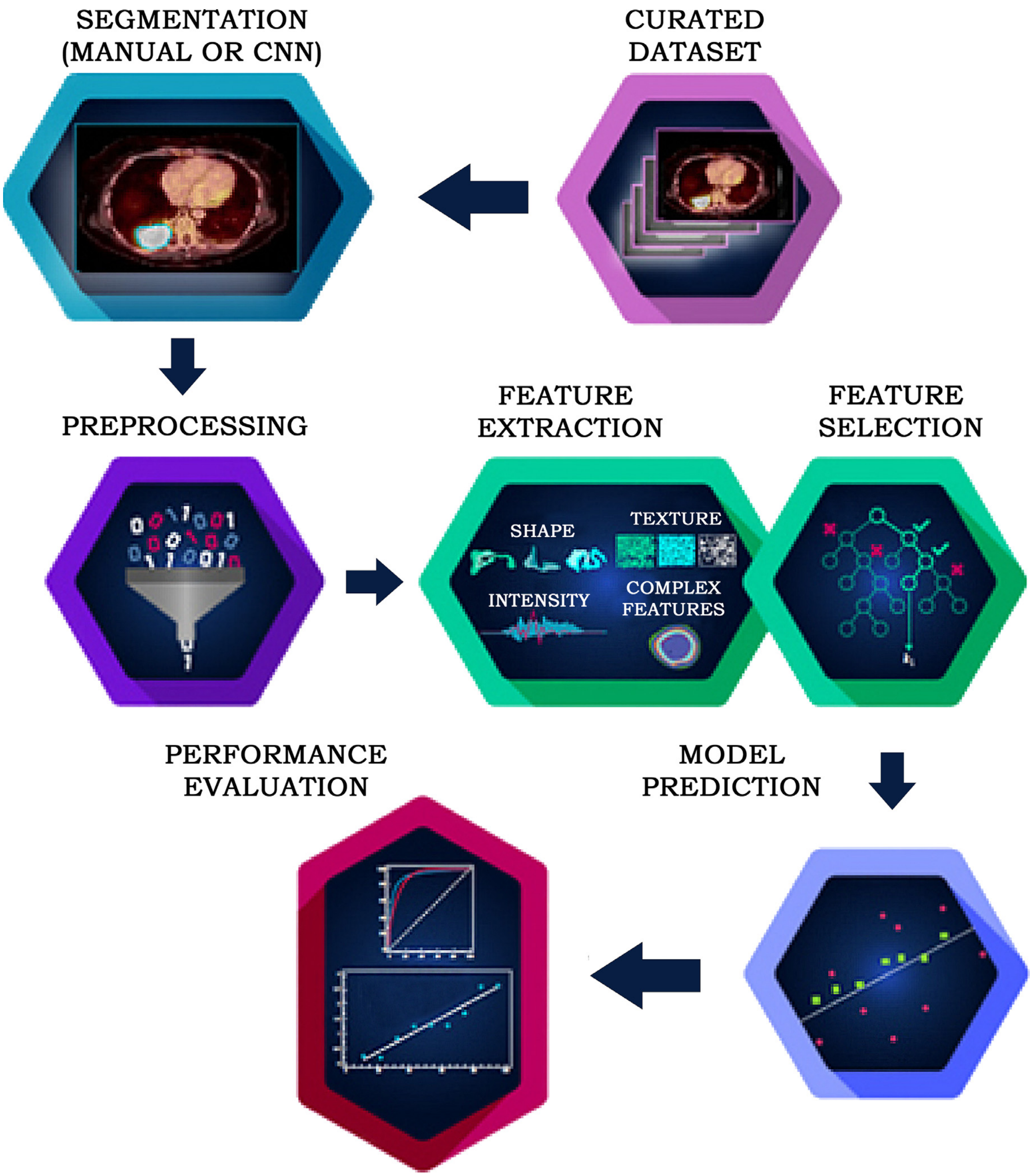

Figure 1 Graphic depiction of the radiomics workflow.

(Fig. 1). To extract features in a stable and reproducible manner across multiple centers, a unified set of image acquisition protocols is desirable. Once data are collected and organized, the regions of interest (ROIs) are segmented on the images to be analyzed. The ROI defines the region from which radiomics features are to be extracted, and manual or semiautomatic segmentation by a qualified professional (eg, medical doctor) is currently the rate-limiting step in radiomics analysis.

Several software approaches are commercially available for medical imaging segmentation. As such, differences between observers as well as software might result in a significant difference in feature values. Interobserver variability[47] has been partially addressed in radiomics analyses by using features that do not vary significantly across observers. However, this approach might result in elimination of features that could contribute to the predictive/prognostic/diagnostic model. Recently, efforts to develop auto-segmentation solutions using deep learning methods have produced promising results.[48-50] Uptake of such methods in the radiomics workflow should result in more robust radiomics features, as observer variability will be mitigated and segmentation time will be significantly reduced compared to manual or semiautomatic segmentation.

Radiomics Features Extraction

A set of hand-crafted imaging features is calculated from the segmented ROI. These features include intensity, shape/

volume, and texture features, as well as higher order features such as radial gradient and filtered features.[3] Features describing intensity are calculated from histograms of the overall tumor intensity values (eg, mean, median, standard deviation, and skewness). Features describing shape/volume use the segmentation to describe characteristics such as sphericity and maximum diameter and are therefore especially subject to interobserver variability. Features describing tumor texture investigate relative positions of intensity values within the ROI, such as the quantification of the number of consecutive intensity values that occur in a certain direction. Texture feature values can dependent on image acquisition and reconstruction, as well as preprocessing methods such as voxel size resampling (necessary in case image resolution or spacing is different within datasets) or intensity discretization, which aggregates pixel intensities in the ROI into bins, either by having a fixed binwidth (eg, 25 Hounsfiled Units per bin) or by fixing the total number of bins.

With the exception of shape and volume, features can also be extracted from the images after filtering, with wavelet or Laplacian of Gaussian filters being the most commonly used, each with their own set of parameters. For these reasons, proper reporting of the preprocessing and feature extraction methods is critical for effective and reproducible radiomics studies. A detailed description of radiomics features can be found online on https://arxiv.org/abs/1612.07003.

As several toolboxes are available for radiomics feature extraction, some differences in feature names and the feature calculation formulas exist. A study[51] compared 649 PET features that were extracted using two different radiomics toolboxes based on the same features' definitions. Out of 649 features, only 80 features were found to have an interclass correlation coefficient >0.80.

As such, different implementations yield different radiomic feature values, and radiomics models rely on identical interpretation of the features to be applicable. Therefore, features calculated using different toolboxes could not be used to build or validate the same model. An initiative to standardize the radiomics features – the Image Biomarkers Standardization Initiative (IBSI) – has been initiated in an effort to standardize the extraction of image biomarkers (features) from medical imaging,[52] which is further described in the sections below.

Feature Selection

After performing extraction, the reduction of the number of features is the next important step in the radiomics workflow. Many of the extracted features do not correlate with the investigated outcome or may correlate highly with other radiomic or standard clinical features. These features do not provide new information and should therefore be excluded. Other features may exhibit either very low variance or may instead be highly chaotic across the cohort. In both cases, these features are likely to be limited in functionality, and should be excluded from analysis. After exclusion, the remaining informative features may still range in the hundreds, and therefore the risk of overfitting is nontrivial,[53] that is, the correlations between features and outcomes are likely to be spurious and contained solely to the cohort on which the model is trained. To analyze the models for overfitting, external validations are required to ensure proper characterization of model performance.[10]

Apart from statistical feature elimination, feature selection to ensure robust model development can be performed using various methods. One method is to test the stability and reproducibility of each feature. Reproducibility can be determined using test-retest analysis[54,55] on the same patient or phantom, as features should not change drastically when measured within a short time frame. Feature stability describes the similarity of features when measured on different scanners or different acquisition parameters,[56] and if stability is low, the feature is not useful when testing models on patients from other institutes. Other methods are also available, such as Recursive Feature Elimination[57] or LASSO[58] which can further reduce the number of features to more appropriate numbers, while some methods reduce the dimensionality of the feature space by aggregating correlated features such as Principle Component Analysis.[59] Selected features are then used to build so-called radiomics signatures.

Model Building

Once feature selection is finalized, radiomics models can be built using a wide range of machine learning algorithms. Softwares such as R,[60] MATLAB,[61] and scikit-learn (Python)[62] include implementations for various modeling algorithms ranging from simple decision trees or logistic regressions to more complex random forests or Bayesian networks. The models can be optimized for specific performance metrics. For instance, a model can be optimized for maximal specificity, and a cut off for sensitivity. Medical reports on modeling, including radiomics, are mainly optimized for the area under the receiver operating characteristic curve (AUC).[12] The receiver operating characteristic curve (ROC) describes the relationship between sensitivity and specificity for a binary classification model, allowing optimization for different cutoffs[63] (eg, setting a high sensitivity while sacrificing specificity). Another tool to evaluate a model is the calibration plot,[13] which depicts the relation between the true class of samples and the model-predicted probabilities.

Choosing a suitable algorithm for model building is an active field of research. Recent efforts on automating the process of selecting the best algorithm for a given dataset have been reported.[64,65] This reflects the superiority of some algorithms based on the nature of the dataset and of the outcome.

Guidelines for the Standardization of Radiomics

Radiomics research has already shown great promise for supporting clinical decision-making.[10] However, the fact that radiomics-based strategies have not yet been translated to routine practice can be partly attributed to the low reproducibility potential of most current studies. The workflow for

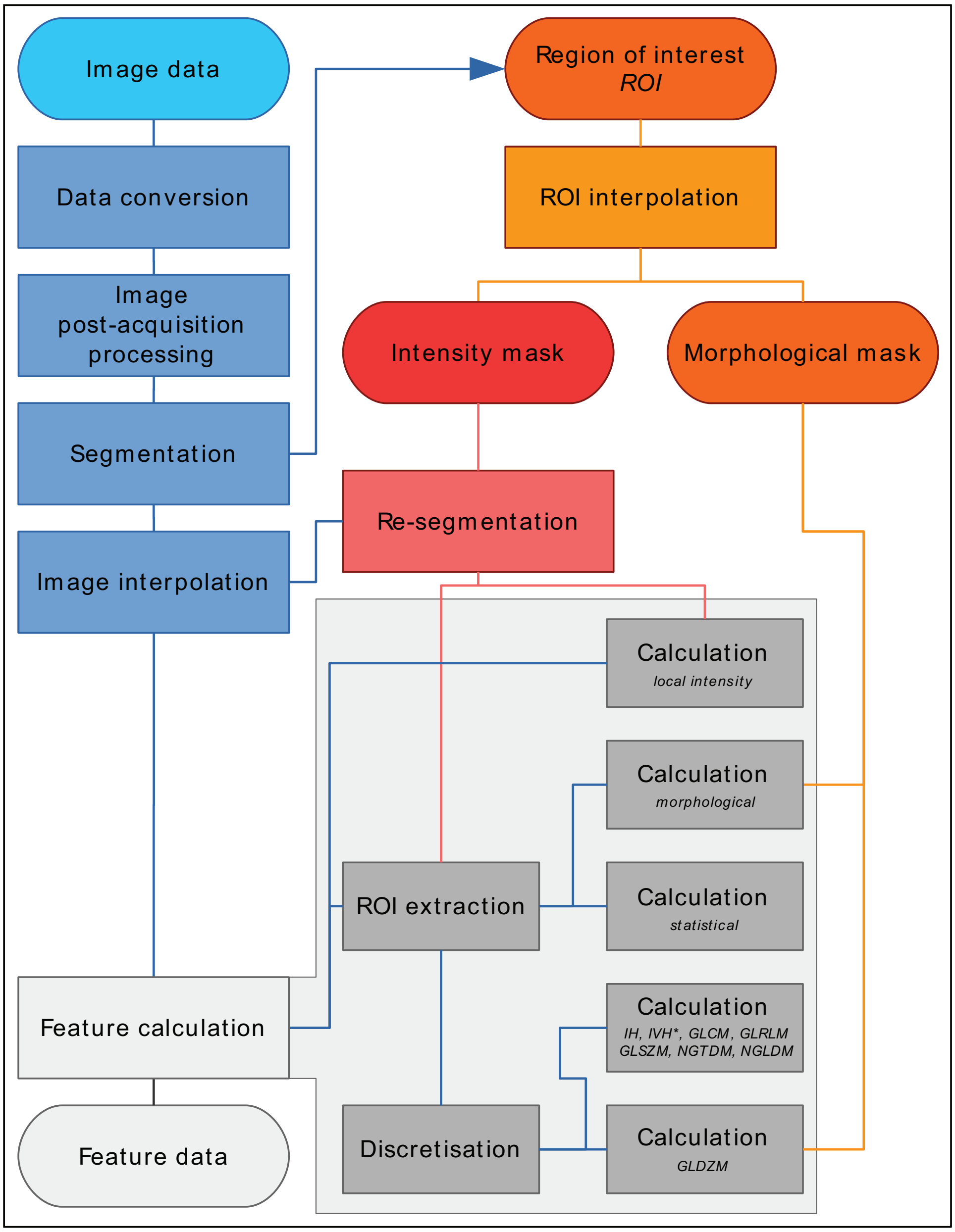

Figure 2 Radiomics computation workflow as defined by the IBSI.[52]

computing features is complex and involves many steps, often leading to incomplete reporting of methodological information (eg, texture matrix design choices and gray-level discretization methods). The study by Bogowicz et al[51] has shown that significant differences between features extracted using different radiomics toolboxes were associated with higher order radiomics features, while histogram-based features were the most reproducible. As a consequence, few radiomics studies in the current literature can be reproduced from start to end.

To accelerate the translation of radiomics methods to the clinical environment, about 67 scientists from 25 institutions in eight countries have participated since September 2016 to the IBSI.[52] Figure 2 presents the standardized radiomics workflow defined by the IBSI.[52] The IBSI aims at standardizing both the computation of features and the image processing steps required before feature extraction. For this purpose, a simple digital phantom was designed and used in Phase 1 of the IBSI to standardize the computation of 172 features from 11 categories: 29 morphologic, 2 local intensity, 18 statistical, 23 intensity histogram, 5 intensity-volume histogram, 25 gray-level co-occurrence matrix, 16 gray-level run length matrix, 16 gray-level size zone matrix, 16 gray-level distance zone matrix, 5 neighborhood gray-tone difference matrix, and 17 neighborhood gray-level dependence matrix features. In Phase 2 of the IBSI, a set of CT images from a lung cancer patient was used to standardize radiomics image processing steps using five different combinations of parameters including volumetric approaches (2D vs 3D), image interpolation, resegmentation, and discretization methods. The initiative is now reaching completion and a consensus on image processing and computation of features has been reached over time.[66,67] However, more work is likely necessary to define and benchmark MRI and PET-specific image processing steps. Nonetheless, the standardized workflow of the IBSI (Fig. 1), along with benchmark values, could serve as a calibration tool for future radiomics investigations.

Overall, the use of standardized computation methods would greatly enhance the reproducibility potential of radiomics studies, and it may lead to standardized software solutions available to the community. It would also be desirable that the code of existing software be updated to conform to standards established by the IBSI. Furthermore, it is essential to rely on supplementary material (usually allowed in most journals) to provide exhaustive methodological details, including the comprehensive description of image acquisition protocols, sequence of operations, image postacquisition processing, tumor segmentation, image interpolation, image resegmentation and discretization, formulas for the calculation of features, and benchmark calibrations. Table 1 provides guidelines on feature computation details to be reported in radiomics studies as defined by the IBSI and Vallières et al.[68] Ultimately, we envision the use of dedicated ontologies to improve the interoperability of radiomics analyses via consistent tagging of features,

Table 1 Reporting Guidelines on the Computation of Radiomics Features (Adapted From Zwanenburg et al[52] and Vallières et al[68])

General	
Image acquisition	Acquisition protocols and scanner parameters: equipment vendor, reconstruction algorithms and filters, field of view and acquisition matrix dimensions, MRI sequence parameters, PET acquisition time and injected dose, CT x-ray energy (kVp), and exposure (mAs), etc.
Volumetric analysis	Imaging volumes are analyzed as separate images (2D) or as fully connected volumes (3D).
Workflow structure	Sequence of processing steps leading to the extraction of features.
Software	Software type and version of code used for the computation of features.
Image preprocessing	
Conversion	How data were converted from input images: eg, conversion of PET activity counts to SUV, calculation of ADC maps from raw DW-MRI signal, etc.
Processing	Image processing steps taken after image acquisition: eg, noise filtering, intensity nonuniformity correction in MRI, partial-volume effect corrections, etc.
ROI segmentation[*,†]	How regions of interests (ROIs) were delineated in the images: software and/or algorithms used, how many different persons and what expertise (specialty and experience), how a consensus was obtained if several persons carried out the segmentation, in automatic or semiautomatic mode, etc.
Interpolation	
Voxel dimensions	Original and interpolated voxel dimensions.
Image interpolation method	Method used to interpolate voxels values (eg, linear, cubic, spline, etc) as well as how original and interpolated grids were aligned.
Intensity rounding	Rounding procedures for noninteger interpolated gray levels (if applicable), eg, rounding of Hounsfield units in CT imaging following interpolation.
ROI interpolation method	Method used to interpolate ROI masks. Definition of how original and interpolated grids were aligned.
ROI partial volume	Minimum partial volume fraction required to include an interpolated ROI mask voxel in the interpolated ROI (if applicable): eg, a minimum partial volume fraction of 0.5 when using linear interpolation.
ROI resegmentation	
Inclusion/exclusion criteria	Criteria for inclusion and/or exclusion of voxels from the ROI intensity mask (if applicable), eg, the exclusion of voxels with Hounsfield units values outside a predefined range inside the ROI intensity mask in CT imaging.
Image discretization	
Discretization method	Method used for discretizing image intensities prior to feature extraction: eg, fixed bin number, fixed bin width, histogram equalization, etc.
Discretization parameters	Parameters used for image discretization: the number of bins, the bin width and minimal value of discretization range, etc.
Feature calculation	
Features set	Description and formulas of all calculated features.
Features parameters	Settings used for the calculation of features: voxel connectivity, with or without merging by slice, with or without merging directional texture matrices, etc.
Calibration	
Image processing steps	Specifying which image processing steps match the benchmarks of the IBSI.
Features calculation	Specifying which feature calculations match the benchmarks of the IBSI.

[*] In order to reduce interobserver variability, automatic and semiautomatic methods are favored.

[†] In multimodal applications (eg, PET/CT, PET/MRI, etc) ROI definition may involve the propagation of contours between modalities via coregistration. In that case, the technical details of the registration should also be provided.

image processing parameters, and filters. For example, the Radiomics Ontology (www.bioportal.bioontology.org/ontologies/RO) could provide a standardized means of reporting radiomics data and methods and would more concisely summarize the implementation details of a given radiomics workflow.

Finally, some guiding principles already exist to help radiomics scientists further implement the responsible research paradigm into their current practice. A concise set of principles for better scientific data management and stewardship – the "FAIR guiding principles"[69] – has been defined, stating that all research objects should be findable, accessible, interoperable, and reusable. Implementation of the FAIR principles within the radiomics field can facilitate its faster clinical translation. In terms of the construction of radiomics-based prediction models via multivariable analysis, there are two basic requirements. First, methodological details and clinical information must be clearly reported or described to facilitate reproducibility and comparison with other studies and meta-analyses. Second, models must be tested in sufficiently large patient datasets distinct from teaching (training and validation) sets to statistically demonstrate their efficacy over conventional models (eg, existing biomarkers, tumor volume, cancer stage, etc). To allow for optimal reproducibility potential and further independent testing, all data, final models, and programming code related to a given study needs to be made available to the community.

Table 2 Quality Factors in Radiomics Studies (Adapted From Lambin et al[10] and Vallières et al[68])

Imaging	
Standardized imaging protocols	Imaging acquisition protocols are well described and ideally similar across patients. Alternatively, methodological steps are taken toward standardizing them.
Imaging quality assurance	Methodological steps are taken to only incorporate acquired images of sufficient quality.
Calibration	Computation of radiomics features and image processing steps match the benchmarks of the IBSI.
Experimental setup	
Multi-institutional/external datasets	Model construction and/or performance evaluation is carried out using cohorts from different institutions, ideally from different parts of the world.
Registration of prospective study	Prospective studies provide the highest level of evidence supporting the clinical validity and usefulness of radiomics models.
Feature selection	
Feature robustness	The robustness of features against segmentation variations and varying imaging settings (eg, noise fluctuations, interscanner differences, etc.) is evaluated. Unreliable features are discarded.
Feature complementarity	The intercorrelation of features is evaluated. Redundant features are discarded.
Model assessment	
False discovery corrections	Correction for multiple testing comparisons (eg, Bonferroni or Benjamini- Hochberg) is applied in univariate analysis.
Estimation of model performance	The teaching dataset is separated into training and validation set(s) to estimate optimal model parameters. Example methods include bootstrapping, cross-validation, random subsampling, etc.
Independent testing	A testing set distinct from the teaching set is used to evaluate the performance of complete models (ie, without retraining and without adaptation of cut-off values). The evaluation of the performance is unbiased and not used to optimize model parameters.
Performance results consistency	Model performance obtained in the training, validation, and testing sets is reported. Consistency checks of performance measures across the different sets are performed.
Comparison to conventional metrics	Performance of radiomics-based models is compared against conventional metrics such as tumor volume and clinical variables (eg, staging) in order to evaluate the added value of radiomics (eg, by assessing the significance of AUC increase calculated with the DeLong test).
Multivariable analysis with non- radiomics variables	Multivariable analysis integrates variables other than radiomics features (eg, clinical information, demographic data, panomics, etc).
Clinical implications	
Biological correlate	Assessment of the relationship between macroscopic tumor phenotype(s) described with radiomics and the underlying microscopic tumor biology.
Potential clinical application	The study discusses the current and potential application(s) of proposed radiomics-based models in the clinical setting.
Material availability	
Open data	Imaging data, tumor ROI, and clinical information are made available.
Open code	All software code related to computation of features, statistical analysis, and machine learning, and allowing to exactly reproduce results, is open source. This code package is ideally shared in the form of easy-to-run organized scripts pointing to other relevant pieces of code, along with useful sets of instructions.
Open models	Complete models are available, including model parameters and cut-off values.

Table 2 provides guidelines that can help to evaluate the quality of radiomics studies.[10,68] More guidelines on reproducible prognostic/diagnostic modeling can also be found in the TRIPOD statement.[70]

Radiomics in Nuclear Medicine

Nuclear imaging for assessment of diseases such as cancer and other nonmalignant disorders is increasingly being used to explore disease phenotype and to support individualized clinical decision-making on the path to personalized medicine.[20,71]

In FDG-PET scans, the standardized uptake value (SUV) is the main semiquantitative element that is routinely used in PET images, which is computed from a single voxel within the lesion (SUV_{max}) or from a segmented ROI that represent the higher metabolic activity in the tumor (SUV_{peak}).[72,73] However, these values are not sufficient to reflect the heterogeneity of FDG uptake and metabolism inside the lesion.[74-77] Initiatives to calibrate and standardize image acquisition and analysis protocols (eg, “resEArch-4Life” project – EARL[78]) have been implemented at accredited centers worldwide. Furthermore, criteria have been stipulated to assess solid tumor and lymphoma PET-response to therapy.[79-81]

Other quantitative parameters used in PET imaging include total lesion glycolysis (TLG) and metabolic tumor volume (MTV). These parameters are volume-based parameters, where MTV reflects the total tumor volume with metabolic activity above a certain threshold, while TLG measures the metabolic activity of a tumor. MTV and TLG have been reported to be more predictive of survival and response to therapy than SUV measurements. This suggests that quantitative imaging features decode more information about a tumor, supporting the main hypothesis upon which radiomics analysis is based.

Some radiomic features extracted from PET scans have been reported to be stable and reproducible (using the same extraction toolbox).[82] Furthermore, some features were found to be of prognostic value for different clinical outcomes, and different malignancies.[14,51,83,84] The potential application of these techniques will certainly have an impact on clinical decision-making, and treating patients according to their individual characteristics.[9,10]

Unmet clinical needs that may be addressed by radiomics in nuclear medicine imaging include detailed characterization of tumor metabolism, for example, in the context of diseases such as neuro-endocrine tumors or prostate cancer. Moreover, use of radiomics features in modeling will potentially improve the specificity of PET imaging applications,[85,86] which will ultimately improve patients stratification and personalized management. Correction for photon attenuation of the PET data using CT improves the quantitative accuracy of the signal collection, which should allow better characterization of the lesion under study.[87,88] This is expected to improve the ability of radiomics features to correlate with clinical outcomes. Moreover, it is hypothesized[89] that radiomics features extracted from different imaging modalities contain complementary information; another advantage for hybrid imaging.

Examples of Radiomics Applications in Nuclear Medicine

Integration of radiomic features extracted from PET with SUV has been used to provide a better interpretation in clinical practice than using SUV alone,[90] and several studies have already reported on the application of radiomics on PET images to predict clinical outcomes.[83,91-98]

Jia Wu et al[83] investigated the ability of ^{18}FDG-PET radiomic features to stratify patients into high- and low-risk groups for distant metastasis in early stage lung cancer. The authors reported a C-index of 0.71 for a predictive model containing two PET radiomic features. Adding these features to histologic subtypes has further improved the predictions, with a C-index of 0.8. The authors generated evidence for the ability of PET radiomics in aiding patients' stratification, which could easily be translated to clinics, following extensive validation.

Oh et al[91] reported on the association between FDG-PET radiomics features and response to chemotherapy, as well as survival in patients with oropharyngeal carcinoma. Authors concluded that textural FDG-PET features were predictive of both response to treatment and survival following chemotherapy.

Another study investigated the association between FDG-PET/CT radiomic features and prognosis in patients with advanced oropharyngeal squamous cell carcinoma.[92] Authors reported that a textural radiomics feature (uniformity) is an independent prognostic factor.

Chen et al[93] also studied the association of FDG-PET radiomic features with gene expression, and response to radiotherapy. The authors reported a significant association between radiomic features and patients' outcomes.

Cook et al[94] have correlated tumor textural features of FDG-PET using radiomic analysis with response to chemoradiotherapy, and survival following treatment in 53 patients non–small cell lung cancer (NSCLC). In this study, primary tumor texture was measured by coarseness, contrast, busyness, and complexity and response was assessed by CT Response Evaluation Criteria in Solid Tumors (RECIST) at 12 weeks.

The authors found that RECIST responders showed lower coarseness (mean, 0.012 vs 0.027; $P = 0.004$) and higher contrast (mean, 0.11 vs 0.044; $P = 0.002$) and busyness (mean 0.76 vs 0.37; $P = 0.027$) comparing with nonresponders. Neither complexity nor any of the SUV parameters predicted RECIST response. In addition, overall survival (OS), progression-free survival (PFS), and local PFS were lower in patients with high primary tumor coarseness (median, 21.1 mo vs not reached, $P = 0.003$; 12.6 vs 25.8 mo, $P = 0.002$; and 12.9 vs 20.5 mo, $P = 0.016$, respectively). Thus, tumor coarseness proved to be an independent predictor of OS on multivariable analysis. However, neither contrast, busyness, complexity, nor any of the SUV parameters showed significant associations with the survival parameters.

They concluded that in NSCLC, baseline FDG-PET scan uptake presenting abnormal texture as measured by coarseness, contrast, and busyness is associated with nonresponse to chemoradiotherapy by RECIST and with poorer prognosis.

In another study, Dong et al[95] investigated the role of delta radiomics – the observation of radiomics features across two or more time points – in predicting response to treatment in 58 NSCLC patients who underwent radio-chemotherapy. Primary tumor FDG uptake heterogeneity was measured by global and local scale textural features extracted from SUV histogram analysis (coefficient of variation, skewness, kurtosis, AUC of the cumulative SUV histogram) and normalized gray-level co-occurrence matrix (contrast, dissimilarity, entropy, and homogeneity). The authors found that significantly higher pretreatment coefficient of variation, contrast and MTV in responders comparing to nonresponders. In addition, the results of this study showed that early change of tumor textural analysis serves as a response predictor with higher sensitivity (73.2%-92.1%) and specificity (80.0%-83.6%) than baseline parameters. Furthermore, significantly higher OS and PFS were reported in patients with higher changes in contrast and AUC-cumulative SUV histogram. However, only change in contrast was found to be an independent prognostic factor of PFS and OS. The authors concluded that metabolic tumor heterogeneity change during radio-chemotherapy can predicting treatment response and OS in patients with locally advanced NSCLC.

Lovinfosse et al[96] investigated the prognostic ability of textural features for OS, disease-free survival (DFS), and disease-specific survival for predicting the outcome of the patients with lung cancer treated by stereotactic body radiation therapy (SBRT). The authors reported that from the clinical variables age was the only predictor of outcome with significant association with DFS. However, among all clinical and imaging parameters, only dissimilarity was significantly associated with disease-specific survival and DFS in multivariate analysis.

In a similar study conducted by Takeda et al[97] also aimed at investigating potential application of texture analysis on predicting local recurrence in patients with Stage I lung cancer treated with SBRT. Three semiquantitative metabolic parameters, including SUVmax, MTV and TLG, and 4 texture parameters, including entropy and dissimilarity (derived from a co-occurrence matrix) and high-intensity large-area emphasis and zone percentage (derived from a size-zone matrix) were analyzed in this study. In univariate analysis, only high-intensity large-area emphasis was a significant predictor for LC. Histology, dose fractionation, and SUVmax were associated with PFS, and histology and dose fractionation was associated with OS. The authors concluded that texture parameters derived from FDG-PET/CT were reproducible and potentially beneficial for predicting LC in Stage I lung cancer patients treated with SBRT.

Yip et al[98] compared the differences in textural features values between 3D and 4D PET scans. Authors concluded that some textural features that are blurred by respiration movements can be better evaluated with 4D PET scans, and therefore may improve the results regarding prediction of the outcomes.

Although the above-reported studies show promise for acceptable predictions of clinical outcomes without the need for invasive procedures, the field has some obstacles to overcome.[9] As mentioned before, several techniques and reconstruction protocols are currently being used across centers, which may result in significant interinstitutional feature variations, similar to the known technical issues which cause significant changes in SUV values.[72,89,99-101]

Initiatives, such as EARL, are solid steps toward unified measurement units for PET images, which will certainly improve the robustness and reproducibility of radiomics features. ComBat (combine batches) is another method of handling interscanner variations.[102] It calculates confounding scanner effect and adjusts features values accordingly, thus harmonizing features values across different centers. A number of studies reported successful application of ComBat to harmonize data from different centers/settings.[103-105]

Further Challenges of Radiomics

Although radiomics has the potential to aid clinical decision-making, the development and interpretation of radiomics models need to be carefully performed. The momentum gained in the field led to the publication of underpowered radiomic studies that lack generalizability of the signatures developed.[89] Welsh et al[106] investigated exhaustively the reproducibility of the signature produced in the largest radiomics study conducted by Aerts et al,[3] using a different radiomics platform. Authors reported that the performance of the developed radiomics signature was equivalent to that of tumor volume, and three of the four radiomics features used to develop the signature were highly correlated with tumor volume. It was concluded that the use of different radiomics platforms may not necessarily reproduce exact results. The authors have also proposed "safeguards" for radiomics analysis, including the use of open-source radiomics platforms, comparison of model features' accuracy to gold-standard or applied clinical biomarkers/factors, exhaustive analysis of feature dependencies and correlations, image quality insurance and preprocessing, and inclusion of clinicians in the segmentation process of gross tumor volumes for clinical use.[106]

A Look Into the Future

Both fields, nuclear imaging and machine learning/radiomics, are growing and advancing rapidly. As mentioned before, several new tracers that target specific pathways/characteristics of tumors have been introduced. Also, the development of dynamic PET scans, for example, ^{18}FMISO[107] and ^{18}FMT,[108] which capture the dynamic status of the lesion can provide a better understanding of a lesion's biology. Concurrent advancement in radiomics analysis and its application on different imaging modalities will certainly accommodate the dynamic nature of such scans and decode more information about disease characteristics.

The consistent use of a scoring system (radiomics quality score), which has been proposed by Lambin et al,[10] as well as the "safeguards" proposed by Welch et al,[106] is expected to improve the quality of radiomics studies and ease its translation to clinical application. The radiomics quality score contains 16 different items presented as a checklist that try to summarize the quality of the radiomics workflow and of the reporting.

As evidenced, the potential application of quantitative imaging analysis in medicine is attracting scientists and clinicians alike and current efforts set the base for clinical trials and ultimately the application of radiomics models in clinical settings to improve personalized patient management. Practical steps to standardize various processes in the radiomics pipeline are gaining more momentum, which are needed before radiomics analysis perform efficiently and as expected. Furthermore, validation of radiomics models on external data remains crucial for ensuring robustness of models developed, ultimately aiming at maximizing the information extraction from molecular imaging and optimizing personalized management.

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