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Feature-based PET/MRI radiomics in patients with brain tumors

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Abstract

Radiomics allows the extraction of quantitative features from medical images such as CT, MRI, or PET, thereby providing additional, potentially relevant diagnostic information for clinical decision-making. Because the computation of these features is performed highly automated on medical images acquired during routine follow-up, radiomics offers this information at low cost. Further, the radiomics features can be used alone or combined with other clinical or histomolecular parameters to generate predictive or prognostic mathematical models. These models can then be applied for various important diagnostic indications in neuro-oncology, for example, to noninvasively predict relevant biomarkers in glioma patients, to differentiate between treatment-related changes and local brain tumor relapse, or to predict treatment response. In recent years, amino acid PET has become an important diagnostic tool in patients with brain tumors. Therefore, the number of studies in patients with brain tumors investigating the potential of PET radiomics or combined PET/MRI radiomics is steadily increasing. This review summarizes current research regarding feature-based PET as well as combined PET/MRI radiomics in neuro-oncology.

Key Points

- Radiomics allows extraction of quantitative imaging parameters from routine imaging data.
- PET and combined PET/MRI radiomics provide essential diagnostic information in neuro-oncology.

Machine learning is a widely used term that summarizes advanced statistical methods that can be used for the high-throughput extraction of quantitative features from medical images such as MRI or PET. These imaging features are usually beyond visual perception and not accessible through conventional visual image interpretation.[1] The conversion of medical images into data that can be combined with clinical data such as histomolecular findings or survival data subsequently to generate mathematical models is termed Radiomics.[1–3] These models can be used to estimate the prognosis or derive crucial biomarkers noninvasively. Importantly, radiomics allows the automated extraction of additional, potentially relevant information for clinical decision-making from imaging data at low cost, because these images are already acquired during routine

follow-up. Because imaging is particularly important in patients with brain tumors, the number of studies evaluating this method's benefit in neuro-oncology has been rapidly growing in recent years. Currently, the majority of studies applying radiomics are based on structural or advanced MRI techniques such as perfusion-weighted or diffusion-weighted imaging.

PET uses a variety of radiotracers and targets molecular and metabolic processes with a high specificity.[4,5] In addition to the structural information obtained from conventional MRI, PET imaging provides information about tumor metabolism. This additional information often enables an improved diagnosis and treatment management. Accordingly, the Response Assessment in Neuro-Oncology (RANO) Working Group and the European Association of Neuro-Oncology (EANO) recommend the use of PET imaging in patients with brain tumors in addition to MRI at all stages of the disease.[6,7]

A variety of radiotracers are available for patients with brain tumors such as 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) for assessment of glucose metabolism, [^{18}F]-3′-deoxy-3′-fluorothymidine (FLT) for evaluation of the proliferative activity of tumor cells, [^{18}F]-fluoromisonidazole (FMISO) for detection of hypoxia, and amino acid PET tracers such as [^{11}C]-methyl-L-methionine (MET), O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET), 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA), or [^{18}F]-fluciclovine (FACBC) targeting the overexpression of L-type amino acid transporter (LAT) system subtypes LAT1 and LAT2. In particular, the diagnostic value of amino acid PET tracers has been extensively validated over the past years in patients with brain tumors.[5–9] Consequently, the number of studies in patients with brain tumors investigating the potential of PET radiomics or combined PET/MRI radiomics based on radiolabeled amino acids is steadily increasing.

This review summarizes current research about feature-based PET as well as combined PET/MRI radiomics in neuro-oncology. The discussed studies and the key results are also summarized in Table 1.

PET/MRI Radiomics in Neuro-oncology

Determination of Tumor Proliferation in Gliomas

Knowledge about the proliferative activity of brain tumor tissue may be of value for the neuropathological differential diagnoses and the treatment management in patients with gliomas. For example, the proliferative activity of tumors can be assessed by immunohistochemistry using the marker Ki-67. Since to date the assessment of Ki-67 requires tissue samples, the noninvasive determination of the tumor proliferation is under investigation.

The potential of radiomics for predicting the Ki-67 expression levels was investigated by Kong et al. using the tracer FDG.[10] More than 1500 radiomics features were extracted from unfiltered and filtered FDG PET scans from 123 patients with primary glioma using the open-source PyRadiomics package in python (https://github.com/Radiomics/pyradiomics).[11] Before model generation, the patient cohort was randomly assigned to a training cohort (n = 82), and a test cohort (n = 41). After feature selection using the Wilcoxon rank-sum test followed by multivariate logistic regression with least absolute shrinkage and selection operator (LASSO) regularization, 9 radiomics features were used for the final model constructed by a kernel-based support vector machine. The radiomics model achieved a moderate diagnostic accuracy for the prediction of the Ki-67 expression levels of 82% in the training cohort, and 73% in the test cohort.

Mitamura et al. used the nucleoside analog FLT for the evaluation of the proliferative activity in 37 patients with newly diagnosed gliomas.[12] Two conventional PET parameters and 5 textural features were extracted, and linear regression analysis was used to compare the parameters with the proliferative activity determined by the Ki-67 index. The textural features kurtosis (r = 0.49; P = .003), entropy (r = 0.73; P < .001), and uniformity (r = –0.62; P < .001) showed the highest correlation with the Ki-67 index, outperforming conventional parameters such as the mean tumor-to-brain ratio (r = 0.39; P = .02) or the metabolic tumor volume (r = 0.40; P = .02).

Differentiation of WHO Tumor Grades and the Prediction of Prognosis in Gliomas

Since the publication of the revised World Health Organization (WHO) Classification of Tumors of the Central Nervous System in 2016,[13] the glioma genotypes' characterization has become increasingly important. At present, for the determination of the genotype, the acquisition of tissue samples is indispensable.

Pyka et al. evaluated whether PET radiomics using the amino acid tracer FET may contribute to the classification of gliomas.[14] A large group of 113 patients with WHO grade III or IV gliomas was retrospectively analyzed. Mean and maximum tumor-to-brain ratios, as well as textural features, were obtained from FET PET. The value of these parameters for the differentiation between WHO grade III and IV gliomas was assessed by receiver operating characteristic (ROC) and discriminant function analyses. The combination of textural features and metabolic tumor volume resulted in the highest discriminatory power with an area under the ROC curve (AUC) of 0.83. Furthermore, textural features derived from FET PET correlated with the prognosis of the patients in terms of progression-free and overall survival.[14]

Papp et al. used the amino acid tracer MET for survival prediction in a group of 70 patients with newly diagnosed glioma.[15] Clinical patient data, histomolecular characteristics, and radiomics features were combined and resulted in a total number of 56 features for each patient. After relevant features were identified by feature selection, mathematical models for predicting overall survival of more than 36 months were generated. The model which combined patient characteristics, histomolecular, and radiomics features yielded the highest diagnostic accuracy based on the Monte Carlo cross-validation (AUC, 0.90) for survival prediction.

Another study by Muzi et al. used the hypoxia PET tracer FMISO to examine the potential of maximum or mean tracer uptake combined with radiomics features to

Table 1. Applications of Feature-based PET/MRI Radiomics in Patients with Brain Tumors

Study	No. of Patients Total (Training/Test)	Indication	PET Tracer	No. of Features		Feature Selection Method	Classification Method	Performance (Training/Test)
				Initial	Final			
Kong et al.[10] (2019)	**123** (82/41)	Evaluation of proliferative activity in gliomas	FDG	1561[a]	9	Logistic regression with LASSO regularization	SVM	0.88/0.76 (AUC)
Mitamura et al.[12] (2017)	**37** (37/0)	Evaluation of proliferative activity in gliomas	FLT	7[b]	1	n.a.	Linear regression	Textural features correlated with Ki-67
Pyka et al.[14] (2015)	**113** (113/0)	Determination of WHO grades in gliomas	FET	8[b]	3	Discriminant function analysis	Discriminant function analysis	0.83/n.a. (AUC)
		Prediction of survival in gliomas	FET	8[b]	1	Multivariate Cox regression	Multivariate Cox regression	Radiomics features correlated with PFS and OS ($P < .05$)
Papp et al.[15] (2018)	**70** (70/0)	Prediction of survival in gliomas	MET	56[b]	56	Hierarchical ML-based approach	Genetic algorithms	0.90/n.a. (AUC) (OS > 36 months)
Muzi et al.[16] (2020)	**72** (72/0)	Prediction of survival in gliomas	FMISO	97[c]	10	Pearson correlation and forward stepwise selection	Multivariate Cox regression	Concordance index, 0.774 ($P < .05$)
Li et al.[18] (2019)	**127** (84/43)	Prediction of survival in gliomas	FDG	1561[a]	11	Elastic net	Multivariable logistic regression	Model correlated with OS ($P < .05$)
		Prediction of IDH genotype in gliomas	FDG	1561[a]	11	Elastic net	Multivariable logistic regression	0.91/0.90 (AUC)
Lohmann et al.[23] (2018)	**84** (84/0)	Prediction of IDH genotype in gliomas	FET	39[d]	2	Fisher score	Logistic regression	80%/n.a. (accuracy)
Haubold et al.[25] (2020)	**42** (42/0)	Prediction of IDH genotype in gliomas	FET (+MRI)	19 284[a]	64*	Randomized logistic regression	Random forest	0.88/n.a. (AUC)
		Prediction of 1p/19q co-deletion in gliomas	FET (+MRI)	19 284[a]	32*	LCSI	Random forest	0.98/n.a. (AUC)
		Assessment of ATRX mutation in gliomas	FET (+MRI)	19 284[a]	8*	Randomized logistic regression	Random Forest	0.85/n.a. (AUC)
		Prediction of MGMT promoter methylation status in gliomas	FET (+MRI)	19 284[a]	16*	Randomized logistic regression	SVM	0.76/n.a. (AUC)
Yu et al.[26] (2019)	**57** (57/0)	Prediction of MGMT promoter methylation status in gliomas	MET	13[b]	1	n.a.	n.a.	Kurtosis and skewness higher in patients with methylated MGMT promoter
Kong et al.[27] (2019)	**107** (71/36)	Prediction of MGMT promoter methylation status in gliomas	FDG	1561[a]	5	Logistic regression with LASSO regularization	SVM	0.94/0.86 (AUC)
Wang et al.[31] (2019)	**160** (112/48)	Differentiation of radiation necrosis from tumor recurrence in gliomas	FDG, MET (+MRI)	912[b]	15	LASSO regression	Logistic regression	0.99/0.91 (AUC)

Table 1. Continued

Study	No. of Patients Total (Training/Test)	Indication	PET Tracer	No. of Features		Feature Selection Method	Classification Method	Performance (Training/Test)
				Initial	Final			
Hotta et al.[32] (2019)	**41** (41/0)	Differentiation of radiation necrosis from tumor recurrence in gliomas and BM	MET	42[d]	42	Gini index	Random forest	0.98/n.a. (AUC)
Lohmann et al.[33] (2018)	**62** (62/0)	Differentiation of TRC from local tumor relapse in BM	FET (+MRI)	42[d]	5	Wilcoxon rank sum	Logistic regression	0.86/n.a. (AUC)

ATRX, alpha thalassemia/mental retardation syndrome X-linked; AUC, area under the receiver operating characteristic curve; BM, brain metastases; FDG, 2-[^{18}F]-fluoro-2-deoxy-D-glucose; FET, O-(2-[^{18}F]fluoroethyl)-L-tyrosine; FLT, [^{18}F]-3′-deoxy-3′-fluorothymidine; FMISO, [^{18}F]-fluoromisonidazole; IDH, isocitrate dehydrogenase; LASSO, least absolute shrinkage and selection operator; LCSI, linear combination of Shannon information terms; MET, [^{11}C]-methyl-L-methionine; MGMT, O^6-methylguanine-DNA-methyltransferase; ML, machine learning; n.a., not available; SVM, support vector machine; TRC, treatment-related changes.
[a]Feature extraction using PyRadiomics[23]; [b]Feature extraction using in-house software; [c]Feature extraction using the Medical Imaging Analysis toolkit in R[17]; [d]Feature extraction using LIFEx[24].
*No PET features used in the final model.

prognosticate the overall survival.[16] In a group of 72 patients with 69 glioblastomas, 86 radiomics features were extracted from FMISO PET using the Medical Image Analysis toolkit implemented in R.[17] For model generation, clinical and standard PET parameters were added to the radiomics features. After feature selection, the additional prognostic benefit of radiomics features was assessed and led to an increase of the concordance indices from 72% to 77%.

The tracer FDG was also evaluated for the prediction of prognosis in 127 glioma patients.[18] Before evaluation, the patient cohort was randomly subdivided into a training cohort (n = 84), and a test cohort (n = 43). Radiomics features were calculated using PyRadiomics.[11] A total of 1561 features were extracted from unfiltered (99 features) and filtered images (1462 features). After feature selection, the best performing model generated by multivariable logistic regression consisted of 11 radiomics features and 2 clinical features and stratified patients according to overall survival differences. Again, the combination of radiomics features with clinical parameters yielded the best diagnostic performance for predicting prognosis.

Prediction of Molecular Markers in Gliomas

As mentioned previously, molecular markers are an essential part of the revised WHO classification of brain tumors of 2016. The clinically most relevant biomarkers are mutations of the isocitrate dehydrogenase (IDH) genotype or the loss of heterozygosity of the 1p/19q chromosome arms, but determination necessitates tissue samples.[19–21] Although not part of the current WHO classification of brain tumors, the O^6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status is also clinically relevant as it allows to predict the response to alkylating chemotherapy in glioma patients.[22] Reliable methods for a noninvasive determination of molecular markers would, therefore, be of high clinical relevance. Accordingly, several studies have addressed the value of PET radiogenomics for prognosticating these molecular markers.

Li et al. evaluated the potential of FDG PET radiomics for the assessment of the IDH genotype in 127 patients with gliomas. The final model combined 11 radiomics features and 2 clinical features and achieved high diagnostic accuracy for IDH genotype prediction in the training cohort (AUC, 0.91) and the test cohort (AUC, 0.90).

Besides FDG, also amino acid PET radiomics was investigated for the noninvasive prediction of the IDH genotype. Lohmann et al. performed a radiomics analysis based on the amino acid PET tracer FET for the prediction of the IDH genotype in 84 glioma patients.[23] In total, 39 features were calculated using the software LIFEx (https://lifexsoft.org).[24] After feature selection using the Fisher score, a 2-parameter logistic regression model achieved the highest diagnostic accuracy of 80% after 10-fold cross-validation. A subgroup analysis of patients investigated on a high-resolution dedicated BrainPET scanner revealed an increased diagnostic accuracy of 86% after 10-fold cross-validation. The model's better performance in the subgroup of patients examined on the BrainPET scanner is likely due to its higher spatial resolution and sensitivity.

Several studies investigated the potential of PET radiogenomics for the diagnosis of other molecular markers. Haubold et al. used FET PET/MRI radiomics to predict the IDH genotype, the 1p/19q codeletion, the MGMT promoter methylation status, and the alpha thalassemia/mental retardation syndrome X-linked (ATRX) genotype in 42 glioma patients.[25] A total of 19 284 features were extracted from unfiltered and filtered images using PyRadiomics.[11] After feature selection, the models were generated using linear support vector machines and random forest classifier. The best performing models predicted the MGMT status, the ATRX mutation, the IDH genotype, and the 1p/19q codeletion with a relatively high accuracy (AUC range, 0.76–0.98). It should be noted that all final radiomics signatures included only radiomics features extracted from MRI. Limitations of this study, however, are the small number of patients in combination with the large number of features, and the fact that PET features were not integrated into the final models. As suggested by the authors, this topic should be further investigated with a higher number of patients.

Radiomics features extracted from MET PET images were used byYu et al. to predict the MGMT promoter methylation status.[26] MET uptake values, and histogram and texture features were computed in a group of 75 glioma patients. Because only individual features were compared for classification, neither feature selection nor model generation was performed. The authors only reported that the histogram features skewness and kurtosis had significantly higher values in patients with methylated MGMT promoter.

Besides amino acid PET tracers, FDG was also used for radiomics-based prediction of the MGMT promoter methylation status. Kong et al. calculated 1561 radiomics features from FDG PET scans of 107 patients with newly diagnosed glioma.[27] The patient cohort was randomly assigned to a training cohort ($n = 71$), and a test cohort ($n = 36$). The most relevant features were selected by the sequential application of the Wilcoxon rank-sum test and logistic regression with LASSO regularization. The final model included 5 features, and the final support vector machine classifier model achieved an AUC of 0.94 in the training and 0.86 in the test dataset.

Differentiation of Brain Tumor Relapse from Treatment-Related Changes

In patients with brain cancer, the early differentiation between tumor relapse and treatment-related changes such as pseudoprogression or radiation necrosis is of utmost clinical importance.[5,28–30] Because conventional MRI alone cannot reliably differentiate between treatment-related changes and tumor recurrence, several studies have investigated the potential value of PET/MRI radiomics for this clinically challenging task.

Wang et al. used FDG PET, MET PET, and structural MRI images from 160 glioma patients for the development of a model to reliably diagnose tumor recurrence.[31] Before further processing, the patient cohort was divided into a training cohort ($n = 112$) and a test cohort ($n = 48$). The LASSO regression model was used for feature selection, and the model for predicting tumor recurrence was built using multivariable logistic regression analysis. The best performing model comprised 15 features from all 3 imaging modalities and had an AUC of 0.91 in the test dataset.

Hotta et al. used MET PET radiomics for distinguishing recurrent brain tumor from radiation necrosis in 41 patients with 44 brain tumors (gliomas, $n = 23$; metastatic brain tumors, $n = 21$).[32] Forty-two features were extracted, and the Gini index was used for the assessment of the most important features for classification. The random forest classifier was used for model generation, and the performance was evaluated by 10-fold cross-validation and achieved an AUC of 0.98 for the differentiation of recurrent brain tumor from radiation necrosis.

Lohmann et al. evaluated the potential of a combined analysis of FET PET and MRI radiomics for distinguishing brain metastases recurrence from treatment-related changes in a group of 52 patients.[33] Diagnoses were determined histologically in 19 patients or clinicoradiologically in the remaining 33 patients. Forty-two textural features were extracted from filtered and unfiltered MRI images as well as from FET PET, resulting in 168 radiomics features for each patient. After feature selection using the Wilcoxon rank-sum test, the best performing generalized linear model using logistic regression was generated by applying the Akaike information criterion. The highest diagnostic accuracy was achieved by a 5-parameter model combining features extracted from FET PET and MRI with an accuracy of 89%. Consequently, the combined evaluation of PET and MRI radiomics yields more diagnostic information than either modality alone.

Conclusions

Feature-based PET and PET/MRI radiomics offers great potential to contribute to an improved diagnosis and treatment management in neuro-oncology. Nevertheless, a few obstacles should be overcome before this method can be successfully integrated into clinical routine. Studies in neuro-oncology using PET and PET/MRI radiomics should pay more attention to the importance of the independent evaluation of the developed model in a test dataset that was not part of the model generation. Furthermore, for a successful translation of radiomics into clinical routine, model validation in large-scale cross-institutional datasets is of eminent significance. This obstacle could be overcome by multicenter cooperation and large-scale data sets from phase II or III clinical trials.

The reproducibility and transferability of the developed models and the underlying radiomics features should also be improved. These parameters often depend on many different factors, such as the image quality and the pre- and postprocessing steps. To overcome these shortcomings, Traverso et al. identified radiomics features from large-scale datasets that were reproducible.[34] For example, first-order features, that is, features extracted from the image histogram, were more reproducible than shape features or textural features. These efforts are of significant importance toward an improved standardization of radiomics and result comparability. Additionally, the

Image Biomarker Standardization Initiative (IBSI) provides benchmark datasets for workflow standardization between different research groups and radiomics feature nomenclature, definitions, and reporting guidelines.[35] The frequently used open-source radiomics packages PyRadiomics[11] and LIFEx[24] are in line with these guidelines. Besides the importance of adhering to the IBSI guidelines, future studies should particularly investigate features that have already been shown to be of value in other studies to identify a common set of particularly useful parameters for MRI or PET radiomics in neuro-oncology.

The interpretability of the extracted features is another factor that may hamper the widespread clinical use of the extracted features and generated models because they are mostly perceived abstractly. To improve the interpretability of feature-based radiomics, various methods, such as graph-based approaches, have been developed.[36] On the other hand, initial studies impressively show that a successful implementation of radiomics into clinical routine is feasible.[37] These studies should serve as motivation to overcome the described limitations. Importantly, future research has to address the question how much added value to radiomics does PET provide over the routinely acquired MRI, particularly if radiomics approaches continue to improve for both imaging modalities. Similarly, further studies should additionally investigate the synergistic potential of MRI and PET radiomics to improve the diagnostic accuracy.

In summary, feature-based PET/MRI radiomics has demonstrated its potential in the field of neuro-oncology. Of note, radiomics should not be solely considered as a stand-alone method but rather as an additional source of diagnostic information that can be automatically extracted from routinely acquired imaging data, thereby allowing an additional data evaluation at low cost. Furthermore, feature-based PET radiomics, combined with other imaging modalities such as MRI and clinical and histomolecular parameters, has a great potential to contribute significantly to improved diagnosis and treatment of patients with brain tumors.

Keywords

artificial intelligence | brain metastases | glioma | hybrid imaging | machine learning

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