PET-based Radiomics Analysis for Predicting Prognosis and Differentiation Treatment-Related Changes in Glioma: A Systematic Review

Mahsa Shakeri (MSc)[1,2], Azadeh Amraee (PhD)[3], Seyyed Mohammad Hosseini (MSc)[1,2], Leili Darvish (PhD)[4,5], Forough Farkhondeh (MSc)[6], Ahmad Mostaar (PhD)[7], Hossein Ghadiri (PhD)[1,2]*

[1]Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]Research Center for Molecular and Cellular Imaging (RCMCI), Advanced Medical Technologies and Equipment Institute (AMTEI), Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Medical Physics, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
[4]Mother and Child Welfare Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[5]Department of Radiology, Faculty of ParaMedicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[6]Medical Physics Department, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[7]Department of Medical Physics and Biomedical Engineering, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Corresponding author:
Hossein Ghadiri
Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
E-mail:
h-ghadiri@tums.ac.ir

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ABSTRACT

Background: The assessment of treatment-induced changes in glioma and the evaluation of glioma prognosis are crucial components of effective treatment management. Radiomics models based on Positron Emission Tomography (PET) imaging can provide critical insights into therapeutic response monitoring.

Objective: This systematic review aimed to evaluate the performance of PET-based radiomics models in distinguishing treatment-related changes and predicting the prognosis of glioma.

Material and Methods: In this systematic review, the articles were searched from the Web of Science databases, MEDLINE, PubMed, and EMBASE. The search terms were "amino acid PET", "PET", "glioblastoma", "glioma", "positron emission tomography", "machine learning", "deep learning", "radiomics", "artificial intelligence", "AI", "prognosis", "outcome", "post treatment changes", "treatment-related changes", "progression", "true progression" "pseudo-progression", and "necrosis". The titles, abstracts, and full text of the recognized citations were reviewed by two independent reviewers and then the selected articles were abstracted by two independent reviewers based on a standard grid. PRISMA checklist was applied to assess the overall quality of evidence for each outcome.

Results: The PET-based radiomics models outperform conventional PET parameter models, such as maximum tumor-to-brain ratios and mean tumor-to-brain ratios in distinguishing post-treatment changes and predicting glioma prognosis. The model integrating radiomics features and the conventional PET parameters achieved superior diagnostic performance compared to radiomics and conventional parameter models solely in differentiation treatment related changes.

Conclusion: PET based radiomics models demonstrate enhanced capability in differentiating tumor recurrence from treatment-related changes. The implementation of these models can facilitate personalized treatment plans and increase the patient's overall survival or quality of life.

Keywords

PET; Radiomics; Glioma; Treatment Related Changes; Prognosis

Introduction

Glioma is a heterogeneous group of primary brain tumors, with considerable chemical and histological heterogeneity, posing significant challenges to their treatment and management.

Gliomas accounted for 26.3%, of all primary Central Nervous System (CNS) tumors and approximately 80% of malignant brain tumors [1, 2].

Glioma treatment typically employs a multimodal approach, aiming to remove or reduce tumor size while effectively managing associated symptoms [3-6]. Tumor surgery is often the first step to preserving brain function while removing the tumor completely. Due to the aggressive behavior, postoperative external beam radiation, concurrent Temozolomide (TMZ) chemotherapy, and additional adjuvant temozolomide were administered after surgery to target remaining tumor cells and lower the chance of recurrence [7, 8]. The use of these combination therapies has been associated with improved median survival rates for glioma patients [9]. Despite the postoperative care, the median Overall Survival (OS) for these patients is just fifteen months [10]. Gliomas present notable challenges in clinical management due to their diverse histological and molecular characteristics. One of the critical issues in glioma treatment is the accurate differentiation between post treatment or treatment-related changes, including Pseudoprogression (PSP), Radio-necrosis (RN), and true glioma progression, including progression/recurrence because each requires distinct therapeutic interventions with a significant effect on patient prognosis and outcomes. Moreover, monitoring tumor progression is essential in these patients after treatment, as it helps determine the next steps in their care. Confirming whether a tumor is recurring or progressing informs surgeons and patients about the best treatment strategy [11, 12].

Previous studies have indicated the importance of imaging modalities including Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) in accurately characterizing glioma progression, pre and post treatment management [13-18]. Advanced imaging techniques, such as amino acid PET including O-(2-[18F] fluoroethyl)-L-tyrosine (18F-FET), 18F-fluorodeoxyglucose (18F-FDG), 11C-methionine (11C-MET), 3,4-dihydroxy-6-[18F]-fluoro-l-phenylalanine (18F-DOPA), and 11C-choline (11C-CHO) [10, 19-21] and cerebral blood volume (CBV) evaluation with perfusion-weighted MRI, and Magnetic Resonance Spectroscopy (MRS), suggest deeper analysis of tumor characteristics and microenvironment than conventional MRI. Several studies represented superior performance for amino acid PET, such as MET PET (accuracy of 89.6%) [19], DOPA (accuracy of 82%) [22], and FET (accuracy ranging between 81% and 99%) [23, 24] for distinguishing glioma post treatment recurrence/progression and provide complementary and comparable information to the MRI as a gold standard. They represented that amino acid PET can be an essential tool for distinguishing tumor progression/recurrence from PSP, and radiation necrosis [10].

In recent years, radiomics, Artificial Intelligence (AI), Deep Learning (DL), and Machine Learning (ML) have enhanced research on glioma patients [12, 13, 15, 17, 25-29]. Accordingly, PET imaging and advancements in radiomics analysis hold promise in providing quantitative and qualitative insights into glioma behavior and helping in distinct diagnosis, distinguishing recurrence from treatment-associated modifications, and treatment strategizing [15].

Regardless of growing interest in the use of radiomics and PET imaging for glioma characterization, a need for a systematic review to explore the application of PET-based radiomic models has remained for prognosis and post-treatment assessment in glioma. This study aimed to systematically investigate the capabilities of PET-based radiomics and AI models for the investigation of prognosis and differentiation post-treatment changes, including progression, recurrence, PSP, and radio-necrosis in glioma patients. The present study aimed to clarify the diagnostic and prognostic utility of these models and identify areas that need fur-

ther research and clinical application.

Material and Methods

Eligibility Criteria

The present study included cross-sectional, case-control, cohort, and studies assessing the relevance of PET-based AI models (radiomics, ML, and DL models) in assessing prognosis and differentiating glioma progression or recurrence from treatment-related changes. Case reports, case series, review articles, editorials, and commentary and abstracts of articles were excluded from the study. The study also excluded papers evaluating MRI-based AI models, studies assessing glioma segmentation and Isocitrate Dehydrogenase (IDH)-mutant with AI.

Search Strategy

In June 2024, the following databases were electronically searched from January 1st, 2005, to June 31st, 2024 including Web of Science databases, MEDLINE, PubMed, and EMBASE using a detailed search strategy with no language restriction. The search terms used were "amino acid PET", "PET", "glioblastoma", "glioma", "positron emission tomography", "machine learning", "deep learning", "radiomics", "artificial intelligence", "AI", "prognosis", "outcome", "post treatment changes", "treatment-related changes", "progression", "true progression" "pseudo-progression", and "necrosis". The study's methodology was derived from an initial review of related literature and a comprehensive internet search approach of systematic reviews of radiation therapy outcomes and PET based radiomics, ML, and DL models. The search strategy was reviewed and commented on by two independent medical librarians. In addition, the reference list of related papers included in the study was examined. Afterward, the results were hand-searched based on the titles and abstracts to exclude studies according to exclusion criteria.

Selection process

The titles and abstracts of the recognized citations were reviewed by two independent reviewers using a standardized screening guide. We retrieved the full text of all citations recognized as qualified by at least one reviewer. A standardized, pilot-tested format was then used by two reviewers to independently screen the full text for eligibility. Third reviewers were contacted to resolve disagreements.

Data abstraction

The selected articles were abstracted by two independent reviewers based on a standard grid comprising the following items: purpose of the study, comparison method, training, dataset, models, validation, test, Area Under Curve (AUC), sensitivity and specificity, accuracy, and conclusion. In addition, to assess the methodological quality of the involved studies, two reviewers used the Radiomic Quality Score (RQS) [30], a tool based on sixteen items that indicates the quality of radiomics study. Results of analyses restricted to PET based AI models were recorded for prognosis, post treatment changes, and radiotherapy outcomes in glioma patients. PRISMA checklist was used to evaluate the overall quality of evidence for each outcome.

Results

Study selection

A total of 1056 articles were found in the initial literature review. Title and abstract screening were done, and after that 112 studies were selected for full-text screening, of which 101 studies were excluded. Finally, 11 articles were included in the systematic review (Figure 1). Duplicate and conference data were the most common exclusions.

PET radiotracer

The majority of included studies (10 studies) (Table 1) focused on radiolabeled amino acid PET. Amino acid radiotracers, including

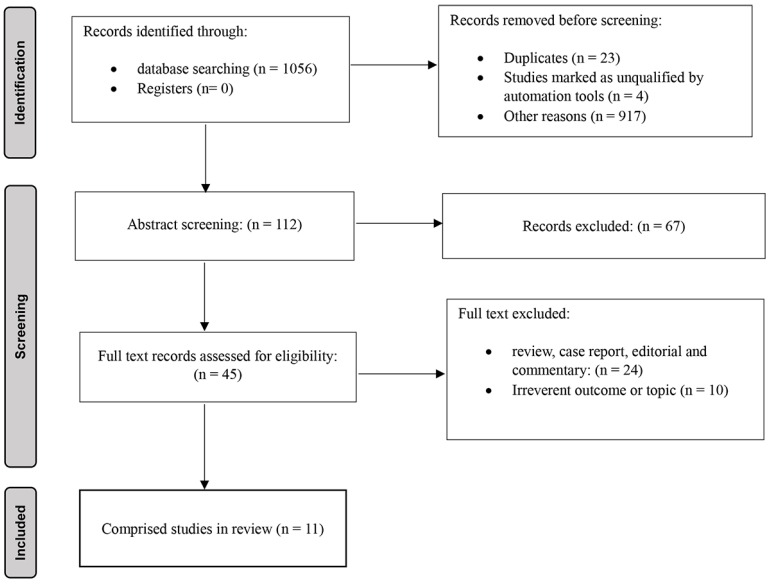

Figure 1: Database and register flow diagram for identifying studies

6 studies used O-(2-[18F] fluoroethyl)-L-tyrosine (FET) [31-37], 2 studies utilized L-3,4-dihydroxy-6-[18F]-fluoro-phenylalanine (18F-DOPA), and 2 studies used 11C-methionine (MET). In addition, one study used a nucleoside analog probe: 3'-deoxy-3'-18F-fluorothymidine (FLT) (Table 1).

PET Radiomics for differentiation post treatment changes from glioma progression

The results revealed that radiomics, ML, and DL models based on PET imaging demonstrate superior performance in differentiating post treatment changes in comparison to conventional PET parameters, such as maximum Tumor-to-Brain ratios (TBRmax), mean Tumor-to-Brain ratios (TBRmean), and Time to Peak (TTP) models in glioma patients [13, 32, 33, 37]. In addition, the model integrating radiomics features and the conventional PET parameters achieved superior diagnostic performance compared to radiomics and conventional parameter models solely (AUC of 0.85, 0.85, 0.78, sensitivity of 0.81, 0.73, 0.66, and specificity of 0.70, 0.80, 0.80, respectively) in distinguishing treatment-related changes from glioma progression [33]. The dynamic PET imaging dataset outperformed static imaging-based models, with the combined dynamic and static feature models. The AUC values for dynamic, combined static/dynamic, and static models were 0.805, 0.79, and 0.715, respectively, in a cohort of 85 patients [13]. The random forest model utilizing MET PET achieved highest performance in distinguishing recurrent brain tumor from radiation necrosis, with an AUC of 0.98 in 41 patients [38]. The FET PET radiomics models achieved an AUC of 0.93 for Linear Discriminant Analysis (LDA)-model [31], 0.85 for Logistic regression model [33], 0.74 [37], and 0.85 [35] for random forest in post treatment differentiation. The findings from the 18F-DOPA PET radiomics models demonstrated AUC values of 0.715 for static features and 0.805 for dynamic features when using the ElasticNet logistic regression model [13], For the XGBoost (XGB) model, the AUC values were 0.715 and 0.755 for static and dynamic datasets, respectively, while the random forest model achieved AUC values of 0.832 and 0.749 for static and dynamic datasets, respectively [13]. Table 2 showed the results of PET based radiomics models for dif-

ferentiation treatment related changes in glioma patients.

PET Radiomics for glioma survival stratification and prognosis

Generally, PET based DL and radiomics models represented higher performance than conventional models for predicting tumor proliferation, recurrence and survival of glioma patients (Table 2).

As compared to conventional clinical parameters alone, the combination of clinical parameters and radiomics using pretreatment dynamic FET PET data improved the prognostic

Table 1: Tumor and image characteristics of included studies

Author (year)	Number of Patients (Mean age and range (year))	Tumor Characteristics	Post or Pretreatment PET imaging	Fallow up	Imaging modality
Ahrari et al. [13] (2021)	85, 57 (21,80)	IDH-mutant anaplastic astrocytoma (8), IDH-wildtype anaplastic astrocytoma (12), IDH-mutant and 1p/19q anaplastic oligodendrogliomas (10), IDH-mutant glioblastomas (6), IDH-wildtype glioblastomas (49)	Post treatment PET imaging	6 months	18F-DOPA PET
Lohmann et al. [32] (2020)	34 ,57±12	IDH-wildtype glioblastoma (32), IDH-mutant glioblastoma (1), IDH-wildtype anaplastic astrocytoma (1)	Post treatment PET imaging	>2 months	18F-FET PET
Kebir et al. [31] (2020)	44, 51 (34–79)	Primary IDH-wildtype glioblastoma	Post treatment PET imaging	91.3 days	18F-FET PET
Muller et al. [33] (2022)	151, 52.3 (20.4–78.0)	Oligodendroglioma (17), IDH-mutant Astrocytoma (34), IDH-wildtype Astrocytoma (17), IDH-wildtype Glioblastoma (71), IDH-mutant Glioblastoma (11), Gliosarcoma (1)	-	>6 months	18F-FET PET
Hotta et al [38] (2019)	41, 55.5±13.2	Metastatic brain tumor (21), Glioma (20)	Post treatment PET imaging	>6 months	11C-MET PET
Paprottka et al. [35] (2021)	66, 55 (54.91±12.2)	Glioblastoma (51), Astrocytoma (9), Oligodendroglioma (13), Polycystic Astrocytoma (1)	Post treatment PET imaging	>12 months	18F-FET PET + DSC perfusion + APTw
Li et al. [36] (2023)	141, 59.3 (19.0–77.2)	IDH-wildtype glioblastoma	Pretreatment PET imaging	<12 months	18F-FET PET
Carles et al. [34] (2021)	32, 52 (30–77)	IDH-wildtype glioblastoma (14), IDH-mutant glioblastoma (10), Unknown glioblastoma (8)	Pre-rirradiation PET imaging	>3 months	18F-FET PET
Mitamura et al. [39] (2017)	37, 55.8 (8–84)	Diffuse astrocytoma (4), Anaplastic astrocytoma (9), Anaplastic oligodendrogliomas (2) Anaplastic ependymoma (1), Glioblastomas (21)	Pretreatment PET imaging	>12 months	18F-FLT PET
Shahzadi et al. [40] (2024)	132, 61 (24–77)	IDH-wildtype glioblastoma (119), IDH-mutant glioblastoma (8), Unknown glioblastoma (5)	Post operative and pre Chemoradiotherapy PET imaging	58 months	11C-MET PET + gadolinium-enhanced T1-w
Ahrari et al. [25] (2024)	18, 62 (45–69)	High-grade glioma	First PET imaging during treatment and the second PET imaging at the time of adjuvant temozolomide (TMZ) chemotherapy	> 1 year	18F-DOPA PET

DSC: Dynamic Susceptibility Contrast Imaging, APTw: Amide Proton Transfer-Weighted MRI Imaging, IDH-mutant: Isocitrate dehydrogenase, (18F-DOPA) PET: 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine Positron Emission Tomography, (18F-FET) PET: O-(2-[18F] fluoroethyl)-L-tyrosine Positron Emission Tomography, (11C-MET) PET: 11C-methionine Positron Emission Tomography, (18F-FLT) PET: nucleoside analog 3-deoxy-3′-18F-fluorothymidine Positron Emission Tomography

Table 2: The radiomics, machine learning, and deep learning models' characteristics and their performance of the including studies

Author (year)	Aim of study	Models [Methods for model evaluation]	Parameters Metrics	Feature Extraction and Model implementation Software	Type of Extracted features	Image modality	Outcome
Ahrari et al. [13] (2021)	Diagnosing treatment-related changes from high-grade glioma progression using DOPA PET static and dynamic radiomics	XGBoost (XGB), Random Forest, Elastic-Net logistic regression [5-folds CV]	Accuracy, AUC, F1, Precision, Balanced Accuracy	Pyradiomics (Nov 2021), scikit-learn Python package (Nov 2021), XGBoost Python package (Nov 2021)	94 radiomic features including statistical, histogram-based, texture and intensity features	18F-DOPA PET (static and dynamic DOPA PET)	The AUC values of LR model for dynamic, static, and combining of static/dynamic features were 0.805, 0.715 and 0.79, respectively. The dynamic dataset led to better findings than the static model (P<0.001). RF AUC value was 0.749 and XGB AUC was 0.715 for static datasets, and dynamic features had AUC of 0.832 and 0.755 (P<0.001 for the dynamic and static models' comparisons). RF and XGB models combining static and dynamic datasets and represented respective AUC of 0.834 and 0.804 for each model (both superior to static models, P<0.001). Best radiomics models represented a little better performance than the reference tumor-to-background (TBR) model (AUCs of 0.834 and 0.792, respectively, P< 0.001).
Lohmann et al. [32] (2020)	Differentiating PSP from early tumor progression using FET PET radiomics	Random Forest [7-folds CV, adjusted rand index (ARI)]	Sensitivity, Specificity, PPV, NPV, FNR, FPR, Accuracy, F1, MCC, AUC	Pyradiomics (version 3.0), Python package.	107 features including first order, shape, texture features GLCM, GLRLM, GLSZM, NGLDM, GLDM	18F-FET PET (static FET PET)	The FET PET radiomics model properly identified all PSP patients with 70% accuracy in the test dataset (AUC, 0.74; specificity of 40%; sensitivity of 100%; P=0.017). TBRmax was the best parameter for FET PET and showed sensitivity of 81%; and negative predictive value of 80%.
Kebir et al. [31] (2020)	Analysis of dynamic and static FET-PET models for detecting PSP of TP in IDH-wildtype GBM	Linear Discriminant Analysis (LDA)- classifier [3-folds stratified CV]	AUC, Sensitivity, Specificity	Python (version 3.7.1), R (version 3.5.3)	TBRmax, TBRmean,TTP	18F-FET PET (dynamic FET PET)	In the TP group in comparison to the PSP group TBRmax and TBRmean were higher significantly (P=0.033 and P=0.014, respectively). TTP's classification performance was the poorest, with an AUC of 55%. For the accurate detection of PSP, the AUC values for TBRmax and TBRmean were 0.68 and 0.74, respectively. The AUC (0.93) for the LDA-based approach was significantly greater than the TBRmax AUC. The AUC of classification increased to 93% (95% CI, 78–100%; sensitivity) by applying LDA model.
Muller at al. [33] (2022)	Static clinical FET PET using radioomics can distinguish treatment-related changes from tumor progression in gliomas	Logistic regression models [NA]	AUC, Sensitivity, Specificity	RadiomiX toolbox (Oncoradiomics, Liège, Belgium) in Matlab, R (version 4.0.5, R Studio, Inc., Boston, MA, USA).	TBRmax, TBRmean, 221 features including first order statistics, shape, GLCM, GLRLM, GLSZM, and features	18F-FET PET (dynamic PET)	In the test dataset, the logistic regression model based on the TBRmean and TBRmax produced an AUC value of 0.78, sensitivity of 0.66, and specificity of 0.80. In the test dataset, the model that was exclusively based on radiomics features produced an AUC value of 0.85, sensitivity 0.73, and specificity of 0.80. The greatest diagnostic performance was achieved by the model that combined the parameters of standard FET PET with two radiomics characteristics, yielding an AUC value of 0.85, sensitivity value of 0.81, and specificity value of 0.70.

Author (year)	Aim of study	Models [Methods for model evaluation]	Parameters Metrics	Feature Extraction and Model implementation Software	Type of Extracted features	Image modality	Outcome
Hotta et al. [38] (2019)	Distinguishing a recurrent brain tumor from radiation necrosis by using 11C-MET radiomics models	Random forest [10-folds CV]	AUC, Gini Index	R package	42 PET features including metabolic tumor volume, conventional SUVmax, texture features	11C-MET PET	MET PET radiomics model and tumor-to-normal cortex (T/N) ratio investigation showed AUC values of 0.98 and 0.73, sensitivity values of 90.1% and 60.6%, and specificity values of 93.9% and 72.7%, respectively. The most relevant feature for distinguishing recurrence from radiation necrosis was gray level co-occurrence matrix (GLCM) dissimilarity.
Paprottka et al. [35] (2021	FET-PET, MRI, APTw, and DSC perfusion data used to distinguish tumor progression from treatment-related changes in gliomas	Random Forest classifier [3-folds CV]	AUC, accuracy, sensitivity, specificity	MATLAB (MathWorks, Natick, MA, USA), scikit-learn implementation	5th, 25th, 50th, 75th, and 95th percentile intensity, Shannon Entropy, interquartile Range, Volumes of hot-spot areas	18F-FET PET + DSC perfusion +APTw	The Random Forest classifier trained with FET-PET, DSC-derived cerebral-blood-volume (CBV) intensity maps and APTw, resulted AUC value of 0.85, accuracy value of 0.86, sensitivity value of 0.91, and specificity value of 0.71 for the recognition progressive disease (PD) from treatment-related changes. Random Forest represented significantly higher performance (P=0.03) compared to MRI with an accuracy value of 0.82 sensitivity value of 0.95, specificity value of 0.41, and FET-PET with accuracy value of 0.81, sensitivity value of 0.81, specificity value of 0.82.
Li et al [36] (2023)	Analysis of static and dynamic FET PET features in newly diagnosed IDH-wildtype GBM in order to stratify survival	Linear Regression [5-folds CV]	AUC, accuracy, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV)	Pyradiomics (version 3.0.1), Python (version 3.8.5) using scikitlearn package (version 0.24.1)	First-order, shape, and texture features, which were extracted from TBR (79 features) and TTP images (94 features)	18F-FET PET (static and dynamic PET)	A clinical-radiomic model in comparison to clinical parameters and dynamic radiomic features resulted in the highest level of predictability of short-term survival with an AUC value of 0.74, sensitivity value 0.667 and specificity value 0.70 in the independent testing cohort.
Carles et al [34] (2021)	Identifying recurrence GBM (rGBM) patients after re-irradiation using prognostic model based FET PET radiomics features (RF)	Binary logistic regression [imbalance-adjusted bootstrap resampling]	AUC, Correlation, Kaplan–Meier curve performance	In-house software based on MATLAB® (The MathWorks Inc., Natick, MA).	135 features included SUV-Histogram group, Geometry, texture features: GLCM, GLRLM, GLSZM, NGTDM	18F-FET PET	In terms of time-to-progression prediction, Small-Zone-Low-Gray-Level-Emphasis (SZLGE) showed the best results (P=0.001). Results represented moderate recurrence location (RL) predictions with an AUC: 0.66 and sensitivity: 0.78 for the TTP-radiomics-signature and 0.63 and 0.79 for SZLGE, respectively. The results demonstrated the effectiveness of FET-PET radiomics for prognostic assessment and selecting rGBM-patients benefiting from re-irradiation.

Author (year)	Aim of study	Models [Methods for model evaluation]	Parameters Metrics	Feature Extraction and Model implementation Software	Type of Extracted features	Image modality	Outcome
Mitamura et al [39] (2017)	Comparing FLT uptake heterogeneity using textural features with conventional PET parameters in newly diagnosed gliomas and examining correlations between the results and proliferative activity	Linear regression, Cox regression [NA]	AUC, Correlation, Kaplan–Meier curve performance	In-house software in C environment (gcc 4.9.3). SPSS (version 22)	First-order features: the standard deviation of the gray-level histogram distribution, skewness, kurtosis, entropy, uniformity, tumor-to-contralateral normal brain tissue (T/N) ratio, MTV	18F-FLT PET	The significant correlations between tumor-to-contralateral normal brain tissue T/N ratio and Ki-67 index (P=0.02) and metabolic tumor volume with Ki-67 index (P=0.02) were obtained. The results indicated skewness and kurtosis were associated with OS (P=0.03 and 0.02, respectively). Patients with skewness values less than 0.65 survived 1462 days on average, compared to 917 days for those with values greater than 0.65 (P=0.02). Mean survival was 1616 days for patients with kurtosis values less than 6.16, in comparison to 882 days for those with values greater than 6.16 (P=0.006).
Shahzadi et al [40] (2024)	Predicting time-to-recurrence and overall survival in GBM using 3D convolutional neural networks with MET PET and gadolinium-enhanced T1w	Cox regression, random survival forest, and XGBoost_ linear model 3D-CNN models: 3D-VGGNet, 3D-ResNet, and 3D-DenseNet [5-folds stratified CV]	AUC, C-index	MIRP Python toolkit (version 1.1.3), R (version 4.0.3), Python (version 3.7.0), Keras (v2.3.1), TensorFlow (v2.1.0)	327 features from PET 209 features from T1cw-MRI, Local intensity features, Intensity-based statistical features, Intensity-volume, histogram, Intensity histogram, GLCM, GLRLM, GLSZM, NGTDM, Grey level distance zone, Neighborhood grey level, Log transformed features	11C-MET PET+ gadolinium-enhanced T1-w	In the test group the MET PET 3D-DenseNet model indicated the best performance for residual tumor detection. For T1c-w MRI, the logistic regression model with conventional radiomics features had the best performance (AUC: MET-PET 0.95, T1c-w MRI 0.78). For the prognosis of TTR and OS, the MET-PET 3D-DenseNet model combined with age and MGMT status performed best (Concordance-Index: TTR 0.68, OS 0.65). Conventional and deep learning-based radiomics can detect residual tumors on MET PET more accurately than on T1c-w MRI.
Ahrari et al [25] (2024)	Evaluating a model based on DOPA PET radiomics variation over time in high grade glioma for forecasting progression-free survival	Random forest, Logistic regression, Xgboost linear model, Cox regression, 3D-CNN models including 3D-ResNet, and 3D-DenseNet, 3D-VGGNet [4-folds CV with 25 repetitions, 7-folds CV]	AUC, C-index	In-house software for fractures extraction, Python (version 3.8) using the scikit-survival	9 conventional features such as TBRmax, TBRmean, and tumor-to-striatum, MTV, region-based dynamic TTP, and the slope of the linear regression for the data obtained between the 10th and 30th min, 199 radiomics features (static TBR radiomics (94features), dynamic TTP (94 radiomics features) and 11 morphological features)	18F-DOPA PET (static and dynamic PET)	The highest prediction performance of progression-free survival was obtained with the SVM model in combination with recursive feature elimination (RFE) for delta-absolute radiomics (ΔAR: C-index = 0.783) and with C-index feature selection for delta-relative radiomics (ΔRR: C-index = 0.740). This performance was consistent when informative features were transferred from a 35-patient group, resulting in a C-index of 0.751 (0.716–0.784, P=0.06). GLCM Information Correlation 2 feature from dynamic TTP parametric images appeared as the most important radiomics feature in both models.

PSP: Pseudoprogression, TP: True Progression, TTP: Time To Peak, TBR: Tumor To Brain Ratios, TBRmean: mean Tumor-To-Brain Ratios, TBRmax: maximum Tumor-To-Brain Ratios, TTP: Time-To-Peak, TTR: Time To Recurrence, MTV: Metabolic Tumor Volume, SUV: Standard Uptake Value, 18F-DOPA PET: 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine Positron Emission Tomography, (11C-MET) PET: 11C-methionine Positron Emission Tomography, (18F-FLT) PET: nucleoside analog 3′-deoxy-3′-18F-fluorothymidine Positron Emission Tomography, MRI: Magnetic Resonance Imaging, ATPw: Amide Proton Transfer-Weighted, DSC: Dynamic Susceptibility Contrast MRI, CV: Cross Validation, AUC: Area Under The ROC Curve, PPV: Positive Predictive Values, NPV: Negative Predictive Value, FNR: False Negative Rate, FPR: False Positive Rate, MCC: Matthews Correlation Coefficient, GLCM: Gray Level Co-Occurrence Matrix, GLRLM: Gray Level Run Length Matrix, GLDM: Gray Level Dependence Matrix, GLSZM: Gray-Level Size Zone Matrix, NGTDM: Neighboring Gray Tone Difference Matrix, OS: Overall Survival, RF: Random Forest, LR: Logistic Regression, LDA: Linear Discriminant Analysis, 3D-CNN: 3-Dimensional Convolutional Neural Network, 3D-VGGNet: 3-Dimensional Vision Geometrical Group Network, SVM: Support Vector Machine, LDA: Linear Discriminant Analysis, MIRP: Medical Image Radiomics Processor

accuracy for short-term survival assessment of patients with newly diagnosed IDH-wildtype glioblastoma [36]. The FET-PET demonstrated potential in predicting recurrence in glioblastoma (GBM) patients undergoing re-irradiation, with an AUC and sensitivity of 0.66 and 0.78, respectively [34]. In addition, the 3D-DenseNet model based on postoperative 11C-MET PET demonstrated strong performance in identifying residual tumors, achieving an AUC of 0.95. In terms of time to recurrence (TTR) and OS prognosis, the 3D-DenseNet model based on MET PET, which incorporated age and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status achieved the best performance, with concordance indices of 0.68 for TTR and 0.65 for OS [40]. In addition, 18F-DOPA delta radiomics, using Recursive Feature Elimination (RFE) and Support Vector Machine (SVM) represented high performance in predicting progression-free survival in rare high-grade glioma, with a concordance index of 0.751 (95% CI: 0.716–0.784, *P*-value=0.06) [25].

Discussion

The present study is a systematic review on relevant clinical topics and challenges of glioma prognosis and distinguish treatment related changes, including progression, PSP, and RN using PET based radiomics models. This review summarizes the key findings and discusses their implications for practice. Such a review is essential for advancing personalized medicine in the care of glioma patients and ultimately improving patients' treatment outcomes and quality of life.

In the course of glioma treatment, progression or recurrence, PSP, and RN are all potential outcomes [41]. Approximately 60% of patients with low-grade gliomas experience tumor recurrence within five years [42, 43], while around 40% of grade III gliomas and 90% of grade IV gliomas progress within two years [42, 44]. Recurrence in glioma, particularly in high-grade forms, such as glioblastoma, remains a significant challenge in neuro-oncology. Gliomas, characterized by diffuse infiltration of adjacent brain tissue, frequently recur despite aggressive treatment approaches, including surgery, radiation, and chemotherapy. Recurrence is typically localized to the primary tumor site, few centimeters around the tumor bed and the resection site, although multifocal or distant recurrences can also occur [45, 46]. Even with the addition of temozolomide to GBM radiation therapy, the most common site of initial recurrence remains local failure [4, 45, 47-49]. The mechanisms driving glioma recurrence are complex and multifactorial, involving intrinsic and adaptive tumor cell resistance, tumor heterogeneity, and immune evasion [50, 51].

Abbasi et al. represented that PSP happened in 36% of (95% confidence range, 33–40%) high-grade glioma patients and can occur in up to 20% of individuals following routine temozolomide chemoradiotherapy [52]. Through PSP, inflammation, edema, endothelial damage, abnormal capillary permeability, Blood Brain Barrier (BBB) disruption and oligodendroglia injury can cause a new or increased contrast enhanced lesion after chemoradiation (mostly during six months after treatment) [2, 18, 41]. The chance of developing diseases is raised within three months to years after the therapy and occurs mostly in MGMT-methylated tumors treated with TMZ [2, 41, 53].

Furthermore, among patients with malignant gliomas, RN is a severe radiotherapy-induced local tissue response. In most cases, it occurs within three to twelve months of radiation therapy, but it can occur years later as well [53]. RN is characterized by endothelial damage, severe neurotoxicity, the release of tumor necrosis factor-alpha (TNF-), damage to the BBB, glial damage, and deteriorating of edema that causes the emergence of new regions displaying abnormal improvement simulating true progression and recurrence [2, 53]. Several pathological criteria classified RN from other glioma-post treatment circumstances,

including histological examination, gliosis, edema, hyalinization, endothelial thickening, thrombosis, vessel occlusion, and fibrinoid deposition [2, 54]. The majority of radiation necrosis occurs in regions that receive the highest radiation dose, typically near the tumor site and within the resected tumor surgical cavity [54]. On traditional MRI, it can be difficult to distinguish RN from tumor progression, as contrast-enhancing masses on T1-weighted contrast-enhanced imaging are often similar to those seen in tumor recurrence [2, 55].

Radiotracers play a crucial role in diagnosing and treating gliomas. Traditional MRI is extremely difficult to use in routine clinical care or clinical trials to determine whether a tumor has responded, especially in pre-contrast T1-weighted images [56]. In order to manage brain tumors, Response Assessment in Neuro-Oncology group (RANO) recommended radiolabeled amino acid PET [57]. Among the various tracers in PET imaging for glioma, 18F-FET, 11C-MET, 18F-DOPA, and 11C-CHO are particularly notable, due to their ability to highlight various aspects of tumor biology and metabolism [13, 17, 58, 59].

The results demonstrated the higher performance (higher AUC, sensitivity and specificity) of radiomics, ML, and DL models over conventional PET parameters-based models in distinguishing glioma treatment related changes [13, 31, 33]. This enhanced performance may be attributed to the ability of radiomics analysis to extract a diverse set of quantitative features from medical images, including texture, shape, and intensity characteristics. These comprehensive features can capture subtle changes in tissue characteristics that might not be apparent through traditional visual inspection or even conventional PET metrics including Standard Uptake Value (SUV) or TBR. These additional features can provide a more precise understanding of the tumor microenvironment and response to therapy, leading to improved diagnostic accuracy [13, 60].

In addition, radiomics models use advanced mathematical algorithms to analyze the complex relationships within the extracted features. These algorithms can recognize patterns and correlations that are difficult for human observers to perceive [33, 60]. Furthermore, advanced techniques, such as principal component analysis, recursive feature elimination, and logistic regression are applied in radiomics models to achieve higher predictive values and better distinguish treatment-related changes from tumor progression or recurrence [60].

FET, as a tyrosine analog, which is absorbed into the glioma cells via the L-type amino acid transporter, is used to monitor the amino acid transport capacity of brain tumors, related to tumor proliferation. The high sensitivity and specificity of FET PET in distinguishing glioma recurrence have been confirmed by several studies [61, 62]. Sensitivity typically ranges from 70% to 90%, indicating the percentage of actual glioma recurrences correctly identified by the test/model [62]. In evaluating model performance, sensitivity refers to the True Positive Rate (TPR), which estimates the proportion of real positive cases that the model correctly identifies (i.e., accurate detection of glioma recurrence). The specificity of a model refers to its ability to correctly identify actual negative cases (i.e., accurate detection of non-recurrence). High values for both sensitivity and specificity indicate that FET PET performs exceptionally well in accurately detecting recurrences and excluding non-recurrences in patients with gliomas [62]. A high sensitivity is essential for minimizing false negatives, which could lead to missed diagnoses of recurrences. Meanwhile, FET PET has a specificity of 60% to 90%, indicating a higher proportion of true negative results. This is a measure of the percentage of glioma cases that are correctly identified as negative by the test or model. High specificity helps reduce false positives and thus avoids unnecessary invasive procedures or treatments [34-36].

Results showed high sensitivity and specificity in detecting glioma recurrence and making it a valuable tool for monitoring therapeutic response and diagnosing disease progression [21, 62-65]. FET is the most widely used clinical and available tracer, and these results demonstrate its usefulness in detecting glioma recurrence accurately and precisely. This could explain why most of the studies reviewed used FET-PET models [23, 31, 32, 34-36]. Paprottka et al. concluded that the random forest model, combining FET PET data with advanced MRI imaging techniques, assesses disease progression with a sensitivity of 91% and a specificity of 70% [35]. Kebir et al. also developed a linear discriminant model by using FET PET image radiomics information, achieving excellent detection of pseudoprogrossion in IDH-Wildtype glioblastoma with an AUC of 0.93 in comparison to conventional PET parameters model TBRmax and TBRmean with AUC 0.68 and 0.74, respectively [31].

Another amino acid radiotracer is [11C] MET, which is actively transported into glioma cells. Tumor amino acid uptake by MET reflects tumor cell proliferation and angiogenesis. MET PET imaging has proven useful in detecting glioma recurrence and guiding treatment decisions, showing the highest sensitivity (90%) and specificity (87%) among the available radiopharmaceuticals, demonstrated superior diagnostic power for recurrence detecting. As it displays an impressive 90% sensitivity, it can detect even the smallest signs of recurrence, preventing missed diagnoses and ensuring nearly all cases are identified. Furthermore, its exceptional specificity of 87% allows for the confident exclusion of non-recurrence cases, thereby enhancing diagnostic reliability. These remarkable attributes solidify MET's position as a leading radiopharmaceutical for the precise evaluation of glioma recurrence [66, 67]. A group of researchers demonstrated the high performance of a radiomic approach using a random forest classifier to distinguish recurrent tumors from RN with MET. Their results showed an area under the curve (AUC) of 0.98, along with a sensitivity of 0.90 and a specificity of 0.939 [38]. Random forest is an ensemble learning algorithm that generates multiple decision trees during the training phase and determines the final classification based on the majority vote derived from the predictions of individual trees [68]. L. Breiman developed the random forest model in 2001, and it has since become highly successful in both classification and regression tasks due to its robustness and ability to handle complex datasets [69]. Multiple decision trees are combined to make predictions by averaging in settings where the number of variables exceeds the number of observations [69, 70]. It can also be adapted to a variety of ad hoc learning tasks and returns variable importance measures, which help identify the most influential features in the model's predictions [70]. Its advantage over other models lies in its capability to effectively handle complex datasets, deliver high predictive accuracy, and incorporate an inherent mechanism for evaluating feature importance. stems from its ability to handle complex datasets, provide high accuracy, and provide built-in feature importance evaluation [69, 71].

DOPA serves as a precursor to dopamine and norepinephrine, neurotransmitters implicated in pain modulation and stress response. Its accumulation in glioma cells, indicates the presence of functional dopamine transporters, which are often overexpressed in high grade glioma including glioblastoma. Studies have indicated that DOPA PET can effectively differentiates glioma recurrence from treatment-related changes, and providing valuable information for patient management [10]. Recent studies reported that DOPA PET exhibits higher sensitivity and comparable specificity to FET PET in detecting glioma recurrence [10, 61, 72]. Notably, only two studies reported higher sensitivity with FET PET compared to DOPA PET. It is important to mention that the current evidence supporting comparative

evaluation of these two imaging methods for assessing glioma recurrence is of very low quality. Therefore, further research is necessary to obtain more definitive and clinically meaningful results [10, 61, 72]. The selection of a specific radiotracer for PET imaging in glioma is determined by the particular tumor biological characteristics to be evaluated, including functional aspects of proliferation such as amino acid transport and glucose metabolism to neurotransmitter synthesis. Each radiotracer provides distinct insights into the pathophysiology of glioma, thereby assisting in diagnosis, staging, and monitoring of tumor progression and treatment response [73, 74].

Ahrari et al. employed dynamic radiomics models and static DOPA PET including random forest, ElasticNet logistic regression (LR), and XGBoost to differentiate high-grade glioma progression from treatment-related changes. Their results represented AUCs of 0.834 for the best radiomics model (i.e., random forest) which slightly outperformed the reference tumor-to-background (TBR) with an AUC of 0.792 (P<0.001). Additionally, their findings revealed a lower AUC of 0.79 for the LR model compared to the other models [13].

Interpreting these findings within the context of specific studies and clinical scenarios is essential, considering several factors including the imaging protocols, treatment effects, and patient population characteristics. It is important to recognize that imaging protocols can influence the reproducibility, robustness, and generalizability of radiomics features and models. When most data are derived from one or a few centers with specific protocols, the model may not generalize effectively to data acquired using different protocols. Therefore, standardization or harmonization of imaging protocols is essential to minimize these effects and improve the clinical utility of PET based radiomics [75]. In addition, glioma characteristics vary with age, as older patients often have more aggressive tumors and distinct genetic mutations (e.g., IDH mutations) [6]. Consequently, radiomics features derived from PET images may reflect these biological differences, affecting model performance across different age groups. Moreover, variations in follow-up duration and the timing of early or late changes in imaging biomarkers may lead to misinterpreted if follow-up timing is not standardized, resulting in biased or incomplete training data for the models.

Another key application of radiomics models is in predicting tumor prognosis and patient survival. By analyzing radiomic features extracted from PET scans, researchers may be able to predict tumor prognosis and patient survival rates [36]. For instance, specific texture patterns or intensity distributions may be associated with tumor aggressiveness, thereby influencing survival time. Carles et al. demonstrated that radiomics texture features derived from FET PET images were most effective in predicting time-to-progression (P=0.001) in glioblastoma. They suggested that FET-PET radiomics could play a valuable role in prognostic evaluation and in identifying glioblastoma patients who may benefit from re-irradiation [34].

Radiomic models can also support risk classification, helping recognize glioma patients at high risk of recurrence or poor response to standard treatments thereby informing personalized treatment strategies [25]. Shahzadi et al. demonstrated that a 3D-DenseNet model, based on MET-PET integrated with age and MGMT status, achieved the highest performance in predicting overall survival and time to recurrence in glioblastoma patients, with Concordance Indices of 0.65 for overall survival and 0.68 for time to recurrence [40].

The present study has several limitations. The small number of studies included and their heterogeneity particularly in terms of patient demographics, follow-up durations, glioma subtypes, and imaging protocols, may limit the generalizability of the findings. Consequently, further investigations involving additional models and PET radiotracers are

necessary to validate these results with greater accuracy. Moreover, selection bias may have influenced the studies, as patients unable to undergo surgery or chemoradiotherapy—often due to advanced-stage cancer or significant comorbidities—are frequently excluded. Additionally, confounding factors such as tumor grade, gender, race, and other comorbid conditions may affect treatment outcomes and radiomics model performance. Therefore, these variables should ideally be controlled in future analyses to improve the reliability of the findings.

Challenges and Future Directions

Although the potential benefits of PET based radiomic models in glioma management are significant, several challenges need to be addressed. The most important issue is the need for standardized protocols for image acquisition, feature extraction, and model development to ensure reproducibility in studies. Additionally, precise validation against clinical and pathological criteria for establishing the reliability and accuracy of these models, and integrating radiomic features with genomic, proteomic, and other clinical data can increase predictive power. Furthermore, overcoming barriers to clinical implementation, such as regulatory approval and integration into routine and standard clinical workflows, will be essential to realize the full potential of these models to personalized medicine in neuro-oncology, and paving the way for more effective therapeutic strategies [76].

Clinical Application

Integrating radiomics models with clinical protocols for managing glioma has the potential to revolutionize personalized care. Radiomics can extract high-dimensional imaging features from PET and other modalities, providing non-invasive biomarkers that complement conventional clinical factors. When incorporated into existing protocols, these models can help physicians as a diagnostic aid tool for tumor classification, guide treatment planning, and predict outcomes of glioma patients with greater precision before the treatment. Furthermore, radiomics-based models could assist in preoperative assessments, optimize radiotherapy dosing, and differentiate post-treatment changes from recurrence for each patient. However, successful integration requires rigorous validation, standardization of imaging protocols, and harmonization across clinical centers to ensure the models are reproducible, robust, and applicable in diverse healthcare settings.

Conclusion

This systematic review highlights the potential of PET-based radiomics as a promising approach for assessing post-treatment changes and predicting prognosis in glioma patients. The extraction and analysis of quantitative features from PET images, facilitated by machine learning (ML) and artificial intelligence (AI) models, demonstrate superior capability in distinguishing tumor progression or recurrence from treatment-related changes compared to conventional methods. Such advancements have great potential to enable personalized treatment strategies for improving overall survival and quality of life in glioma patients. Continued research and technological innovations are anticipated to overcome existing limitations, further enhancing the precision and clinical applicability of these tools for glioma management.

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Authors' Contribution

All authors contributed to the study's conception and design. The idea for the article was for M. Shakeri. The literature search was performed by M. Shakeri, H. Ghadiri and SM. Hosseini, studies selection was done by A. Amraee, and L. Darvish, data abstraction and

data analysis were performed by M. Shakeri, A. Amraee, F. Farkhondeh and A. Mostaar. The first draft of the manuscript was written by M. Shakeri and H. Ghadiri, and all authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

Ethical Approval

This systematic review is a part of our study. Approval was granted by the Ethics Committee of the Tehran University of Medical Sciences with approval number: IR.TUMS.MEDICINE.REC.1400.1080.

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Conflict of Interest

None

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