

Systematic Review

[18F]FDG PET-Based Radiomics and Machine Learning for the Assessment of Gliomas and Glioblastomas: A Systematic Review

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Abstract: Background: Some evidence of the value of 18F-fluorodesoxyglucose ([18F]FDG) positron emission tomography (PET) imaging for the assessment of gliomas and glioblastomas (GBMs) is emerging. The aim of this systematic review was to assess the role of [18F]FDG PET-based radiomics and machine learning (ML) in the evaluation of these neoplasms. Methods: A wide literature search of the PubMed/MEDLINE, Scopus, and Cochrane Library databases was made to find relevant published articles on the role of [18F]FDG PET-based radiomics and ML for the assessment of gliomas and GBMs. Results: Eight studies were included in the systematic review. Signatures, including radiomics analysis and ML, generally demonstrated a possible diagnostic value to assess different characteristics of gliomas and GBMs, such as the methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter, the isocitrate dehydrogenase (IDH) genotype, alpha thalassemia/mental retardation X-linked (ATRX) mutation status, proliferative activity, differential diagnosis with solitary brain metastases or primary central nervous system lymphoma, and prognosis of these patients. Conclusion: Despite some intrinsic limitations of radiomics and ML affecting the studies included in the review, some initial insights on the promising role of these technologies for the assessment of gliomas and GBMs are emerging. Validation of these preliminary findings in multicentric studies is needed to translate radiomics and ML approaches in the clinical setting.

Keywords: PET; PET/CT; positron emission tomography; [18F]FDG; glioma; glioblastoma; machine learning; radiomics



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1. Introduction

Gliomas are the most prevalent primary neoplasms originating from the brain, and this group of tumors encompasses a wide range of different histological entities that can be classified according to their differentiation and grading. In this setting, the World Health Organization (WHO) classification suggests that an increased degree of atypia and mitotic activity are typical of advanced forms of gliomas, classified as grade IV and also named glioblastomas (GBMs) [1–3]. Gliomas account for 30% of all primary brain tumors and are

the cause of the vast majority of deaths related to primary brain tumors; in addition, the survival of the patients is strictly related to the grade of the neoplasm, with GBMs being characterized by the worst outcomes [4–7]. The initial management of gliomas usually consists of surgical resection with subsequent chemo- or radiotherapy [5,8,9].

Imaging plays a crucial role in the assessment of gliomas, in particular, with magnetic resonance imaging (MRI), which has the ability to provide useful structural information and can support the identification of aggressive forms [10–12]. Positron emission tomography (PET) imaging can also be used for the evaluation of these neoplasms, in particular, with the use of radiolabeled amino acid tracers [11]. In addition, other radiopharmaceuticals have also been used to evaluate them [13–15].

The most used tracer worldwide for performing PET imaging is 18F-fluorodesoxyglucose ([18F]FDG), as it reflects the glycolytic activity of the tissues analyzed in the scan [16]. Based on this ability, this radiopharmaceutical has proven its ability to evaluate a wide range of different pathological conditions, both neoplastic and benign [17–19]. Even though the high physiological uptake in the brain typical of [18F]FDG can potentially limit the usefulness of this tracer for the assessment of brain neoplasms, some studies in the past have demonstrated a possible diagnostic and prognostic role of imaging based on this tracer in gliomas, in particular, for high-grade forms or GBMs. Additionally, the ability to distinguish them from other tumoral forms affecting the central nervous system has been reported [11,15,20–27].

Radiomics, also called texture analysis, is a term that defines the extraction of specific quantitative features from PET and other images, and studies in this field have recently experienced an increase [28–30]. Similarly, machine learning (ML) focuses on the development of algorithms that can use different combinations of features to predict a specific target [31–34].

The aim of this review is therefore to provide an overview of the existing literature on the value of [18F]FDG PET-based radiomics and ML in the assessment of gliomas and GBMs.

2. Materials and Methods

This systematic review was performed according to the “Preferred Reporting Items for a Systematic Review and Meta-Analysis” (PRISMA 2020 statement), employed as a guide in its development. The complete PRISMA checklist can be found in the Supplementary Materials. The question behind the development of this review was: Can [18F]FDG PET-based radiomics be useful for the assessment of gliomas and GBMs? The study eligibility criteria were as follows: patients confirmed to have gliomas or GBMs who underwent [18F]FDG PET imaging and radiomics analyses based on this imaging modality.

2.1. Search Strategy

The Scopus, Cochrane Library and PubMed/MEDLINE databases were used to perform a literature search to identify published articles evaluating the role of [18F]FDG PET-based radiomics and ML in the evaluation of gliomas and GBMs. The algorithm used for the research was: (“glioma” OR “glioblastoma”) AND (“radiomics” OR “texture” OR “textural” OR “machine learning”) AND (“PET” OR “positron emission tomography”).

The search for papers suitable for the inclusion in the review had no beginning date limit; this research was updated until 31 July 2024. Only articles in the English language were considered. Conference proceedings, preclinical studies, reviews, case series, and reports were not included in the review. The reference lists of the retrieved articles were also screened to find additional papers suitable for the inclusion in the review and to expand our search. Pre-registering of the present paper was not performed.

2.2. Study Selection

Two researchers (F.B. and F.D.) independently reviewed the titles and abstracts of the articles retrieved with the literature search according to the specified requirements for inclusion or exclusion and the literature search strategy. The same authors independently evaluated all the relevant studies to extract data from all the available sources, also including full text, tables, figures, and Supplemental Materials. In case of discrepancies between the two researchers, a consensus meeting was performed to solve them.

2.3. Quality Assessment

Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) evaluation was used to perform the quality assessment of these studies, including the risk of bias and applicability concerns [35]. The radiomics quality score was also used to evaluate the overall quality of the papers included in the review [36]. Quality assessment was performed independently by two reviewers, and a consensus meeting was again performed to solve any discrepancies among the reviewers.

2.4. Data Extraction

Two reviewers independently evaluated the retrieved studies to collect relevant information. For each study included in the review, data concerning the basic information of the study were collected. Furthermore, information about the type and numbers of PET tomographs used, the activity of the injected radiotracer, the setting of the study, the performance validation method, the type of ML or statistical technique used, and the main results reported in the study were also collected. The main findings of the retrieved articles included in this review are therefore reported in the Results section.

3. Results

3.1. Literature Search

The research algorithm allowed us to retrieve a total of 432 papers: 301 from the Scopus database, 10 from the Cochrane Library, and 121 from the PubMed/MEDLINE database. After a deduplication process, the literature search retrieved a total of 288 articles. Subsequently, 280 of them were excluded for further analysis after reviewing the titles and abstracts for different reasons: 200 because the reported findings were not within the field of interest or within the scope of this review, 26 were systematic reviews, and 54 because they were performed with tracers different from [18F]FDG. Therefore, 8 studies addressing the role of [18F]FDG PET-based radiomics and ML for the assessment of gliomas and GBMs were selected and retrieved in the full-text version [37–44]. No additional studies were found after analyzing the reference lists of these articles (Figure 1).

The quality assessment of the papers included in the review using QUADAS-2 evaluation did not, in general, underline a high risk of bias and applicability concerns in all the domains, with a little exception in the index test domain (Figure 2). In addition, the radiomics quality score was generally low for all the papers included in the study. One of them obtained a score of 14 (38.89%), 3 obtained scores of 13 (36.11%), 3 obtained scores of 12 (33.3%), and lastly, a single paper obtained a score of 11 (30.56%).

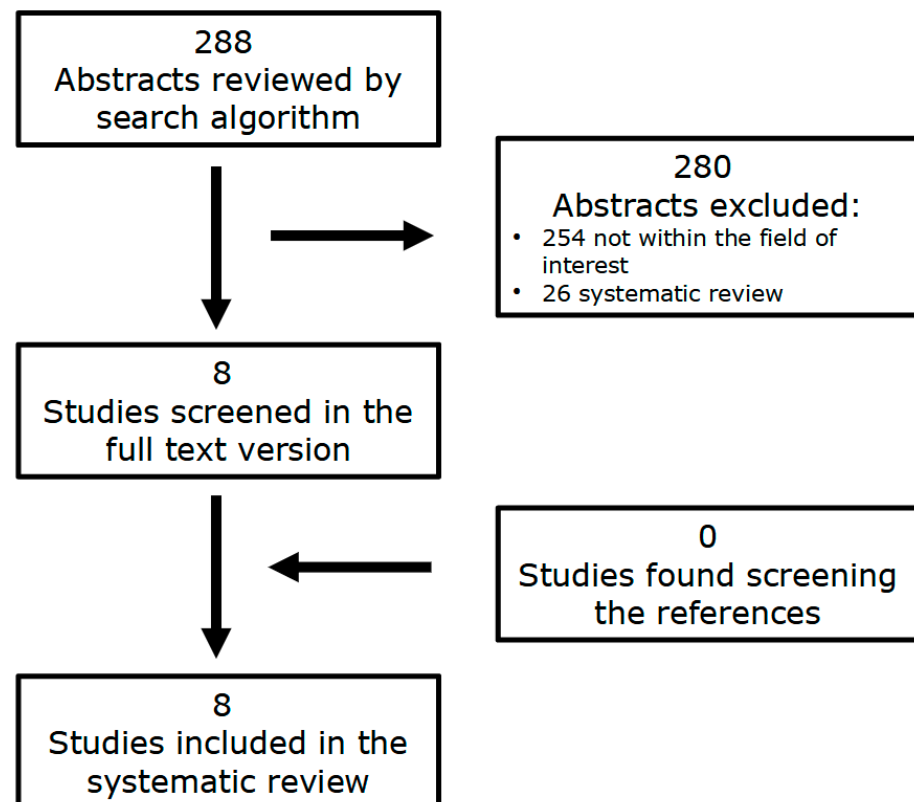


Figure 1. Flowchart of the research process for eligible studies evaluating the role of [18F]FDG PET-based radiomics and ML for the assessment of gliomas and GBMs.

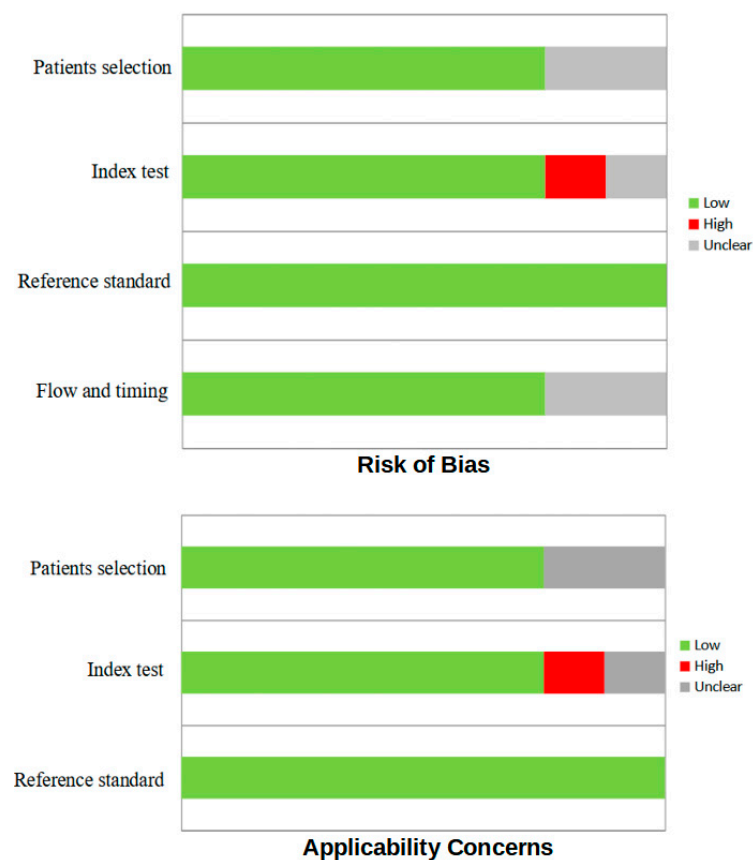


Figure 2. QUADAS-2 quality assessment results for risk of bias and applicability concerns for the studies included in the present review.

All of the 8 papers included in the systematic review were based on a retrospective design [37–44]. The only tracer used in 7 papers [37–40,42–44] was [18F]FDG, while a single study used both [18F]FDG and [11C]methionine ([11C]MET) [41]. In addition, all the studies were performed using hybrid PET/computed tomography (CT) tomographs [37–44]. Three papers included only patients affected by GBMs [42,43,45], 2 articles included both gliomas and GBMs [38,41], 2 studies were performed with patients affected by low- and high-grade gliomas without specifying the number of GBM subjects [37,39] and lastly a single paper included, in its cohort, only glioma patients [44]. Information about the possible standardization of the PET acquisition and radiomics extraction was not present in all the studies; however, the voxel size, the resolution, and the acquisition setting were different between different studies. In addition, information about image preprocessing can be found in the Supplementary Materials; in general, the segmentation method was comparable among the different studies, since all of them used a manual segmentation. Noise reduction was not performed in any of the studies included in the review, while 3 of them (37.5%) used PET signal intensity standardization. Tables 1–3 briefly summarize the main results and the main characteristics of the studies included in the present review.

Table 1. Main characteristics of the papers included in the review.

First Author	N. Ref.	Year	Country	Study Design	N. Pts.	Neoplasm (Glioma or GBM)	Population Setting
Kong Z	[37]	2019	China	Retrospective	107	Low- and high-grade gliomas	Naive
Li L	[38]	2019	China	Retrospective	127	Glioma and GBM	Naive
Kong Z	[39]	2019	China	Retrospective	123	Low- and high-grade gliomas	Naive
Kong Z	[40]	2019	China	Retrospective	77	GBM	Naive
Wang K	[41]	2020	China	Retrospective	160	Glioma and GBM	Postoperative/ postRTT
Zhang L	[42]	2021	China	Retrospective	100	GBM	Naive
Cao X	[43]	2022	China	Retrospective	100	GBM	Naive
Zhang L	[44]	2023	China	Retrospective	102	Glioma	Naive

N.: number; Pts: patients; Ref.: reference; GBM: glioblastoma; RTT: radiotherapy.

Table 2. Main findings and results of the papers included in the review.

First Author	N. Ref.	Device	Number of Scanners	Mean Activity (MBq)	Setting	Software Used for Radiomics Analysis
Kong Z	[37]	PET/CT	1	5.55/kg	Assessing the MGMT promoter methylation status	PyRadiomics
Li L	[38]	PET/CT	1	5.55/kg	Predicting IDH genotype	PyRadiomics
Kong Z	[39]	PET/CT	1	5.55/kg	Assessing the proliferative activity	PyRadiomics
Kong Z	[40]	PET/CT	1	5.55/kg	Differentiating between lymphoma and glioblastoma	PyRadiomics
Wang K	[41]	PET/CT	1	3.7/kg for [18F]FDG, 555–740 for [11C]MET	Discriminating tumor recurrence from radiation necrosis	In-house built
Zhang L	[42]	PET/CT	1	370–555	Integrating MRI and PET/CT to improve the performance of differentiating glioblastoma from solitary brain metastases	In-house built

Table 2. Cont.

First Author	N. Ref.	Device	Number of Scanners	Mean Activity (MBq)	Setting	Software Used for Radiomics Analysis
Cao X	[43]	PET/CT	1	5.55/kg	Differentiating glioblastoma and solitary brain metastases with MRI and PET/CT	PyRadiomics
Zhang L	[44]	PET/CT	2	370–555	Predicting ATRX mutation status of IDH-mutant lower-grade gliomas	PyRadiomics

PET: positron emission computed tomography; CT: computed tomography; MBq: megabecquerel; kg: kilogram; ML: machine learning; AUC: area under the curve; IDH: isocitrate dehydrogenase; MGMT: O-6-methylguanine-DNA methyl transferase; ATRX: alpha-thalassemia/mental retardation X-linked; OS: overall survival; [18F]FDG: [18F]fluorodeoxyglucose, [11C]MET: [11C]methionine; LASSO: least absolute contraction and selection operator; ns: not specified; SVM: supporting vector machine; RF: random forest; LR: logistic regression; kNN: k-nearest neighbor; MRI: magnetic resonance imaging; SUV: standardized uptake value.

Table 3. Results and main findings of the studies considered for the review.

First Author	N. Ref.	Performance Validation Methods	ML Models	Number of Features	Class Balancing	Omics	Main Findings
Kong Z	[37]	Train/test	SVM, LR	1561	50/50	PET	Five radiomics features displayed the best performance, with AUCs reaching 0.94 and 0.86 in the primary and validation cohorts, respectively, which outweigh the performances of clinical signature and fusion signature. In addition, the radiomics signature stratified the glioma patients into two risk groups with significantly different prognoses.
Li L	[38]	10 cross-fold	LR, OS	774	45/55	PET	The generated radiomic signature was significantly associated with IDH genotype and could achieve large AUC with the incorporation of age and type of tumor metabolism. The predicted results showed a significant difference in OS between high- and low-risk groups.
Kong Z	[39]	Train/test	SVM	1561	60/40	PET	Nine radiomics features were used to build a signature that achieved an AUC of 0.88 and 0.76 in the primary cohort and the validation cohort, respectively. The clinical signature and fusion signature had comparable performance in the primary cohort, but overfitted in the validation cohort. No significant prognostic impact was demonstrated.
Kong Z	[40]	5 cross-fold	One-node-decision-tree-classifier	107	70/30	PET	Different radiomics features were significantly different between lymphoma and glioblastoma. Features extracted from the SUV map demonstrated higher AUC than features from the further calibrated maps. Lymphoma has a higher SUV in most interval segments and is more mathematically heterogeneous.
Wang K	[41]	10 cross-fold	LASSO logistic regression	912	70/30	Multi imaging	The integrated model was significantly associated with postoperative tumor recurrence and was a good discriminator, with AUCs of 0.988 and 0.914 in the primary and validation cohorts, respectively.

Table 3. Cont.

First Author	N. Ref.	Performance Validation Methods	ML Models	Number of Features	Class Balancing	Omics	Main Findings
Zhang L	[42]	5 cross-fold	RF	4242	50/50	Multi imaging	The integrated diagnostic radiomics model using both DWI and 18F-FDG showed more efficient diagnostic performance than other single and mixed models.
Cao X	[43]	5 cross-fold	SVM, LR, kNN, RF, AdaBoost	1741	50/50	Multi imaging	The model set based on combined MRI and [18F]FDG PET/CT had the highest average AUC compared with isolated MRI or PET/CT signatures. Joint voting prediction showed better performance than individual prediction when all models agreed.
Zhang L	[44]	5 cross-fold	RF	5540	50/50	Multi imaging	The optimal multimodal model incorporated MRI and PET/CT images with AUCs in the training and test groups of 0.971 and 0.962, respectively. The clinical radiomics-integrated model, incorporating PET/CT, MRI, and clinical parameters, showed the best predictive effectiveness in the training and test groups (0.987 and 0.975, respectively).

PET: positron emission computed tomography; CT: computed tomography; MBq: megabecquerel; kg: kilogram; ML: machine learning; AUC: area under the curve; IDH: isocitrate dehydrogenase; MGMT: O-6-methylguanine-DNA methyl transferase; ATRX: alpha-thalassemia/mental retardation X-linked; OS: overall survival; [18F]FDG: [18F]fluorodeoxyglucose, [11C]MET: [11C]methionine; LASSO: least absolute contraction and selection operator; ns: not specified; SVM: supporting vector machine; RF: random forest; LR: logistic regression; kNN: k-nearest neighbor; MRI: magnetic resonance imaging; SUV: standardized uptake value.

3.2. Role of [18F]FDG PET-Based Radiomics and ML for the Assessment of Gliomas and GBMs

The role of [18F]FDG PET-based radiomics and derived ML techniques for the evaluation of different characteristics of gliomas and GBMs has been investigated by different studies. First, Kong et al. [37] included 107 glioma patients in their study, which aimed to build a radiomics signature for noninvasive measurement of the O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. They emphasized that gliomas with MGMT methylation tended to have a higher rate of cystic metabolic patterns and determined that the difference for this pattern between methylated and unmethylated neoplasms was statistically significant in the validation cohort but not in the primary cohort. The radiomics signature that was built performed the best when compared to clinical and fused (clinical and radiomics) signatures with an area under the curve (AUC) of 0.94 and 0.86 in the primary and validation cohorts, respectively, while the clinical signature reached AUCs of 0.64 and 0.69, and the fused model reached AUCs of 0.85 in both cases. In addition, the radiomics signature performed significantly better than other signatures in the primary cohort (p value < 0.001 and 0.036, respectively), but the differences in the validation cohort were not significant due to the limited number of patients. The decision curve revealed a net benefit for the radiomics signature at any threshold probability in the primary cohort when compared to the other models. A prognostic analysis was also performed by the authors, revealing that both the MGMT promoter methylation status and the radiomics signature stratified glioma patients into high- and low-risk groups (p value < 0.001 and 0.04, respectively), but the differences within these groups for the methylation status and the radiomics signature did not reach statistical significance.

Li et al. [38] performed a study aimed at developing a model and validating the potential value of features reflecting glioma metabolism for predicting isocitrate dehydrogenase (IDH) genotype and prognosis. By including 127 patients, they developed a radiomics signature with 11 features that were significantly different between IDH-mutated and IDH

wild-type patients, and this signature achieved AUCs of 0.904 and 0.890 in the training and validation cohorts, respectively, higher than the AUCs obtained by the clinical signature (0.705 and 0.664, respectively). A mixed signature using these radiomics features, age, and type of tumor metabolism was also developed, revealing that this combined model achieved the best results, with AUCs of 0.911 and 0.900 for the training and validation cohort, respectively. In addition, this model also showed good predictive performances between different glioma grades, with AUCs of 0.88 and 0.93 in lower grade (WHO II and III) and GBM (WHO IV), respectively. Lastly, the authors performed a prognostic analysis revealing that the combined model was able to divide patients into high- and low-risk groups and significant differences in the overall survival (OS) of test subjects between the two groups in the training and validation cohorts were demonstrated (p value < 0.05).

Focusing on 102 IDH-mutant low-grade gliomas, Zhang et al. [44] evaluated, in a multicentric setting, the ability of a model based on both clinical and radiomic features obtained from [18F]FDG PET/CT and MRI to predict alpha thalassemia/mental retardation X-linked (ATRX) mutation status. The authors developed five single-modal radiomics models from contrast-enhanced T1-weighted imaging (CE-T1WI), T2-weighted imaging (T2WI), apparent diffusion coefficient (ADC), cerebral blood volume (CBV), and [18F]FDG PET. All of them had high AUCs > 0.75 , without significant differences in training and testing groups, and with the model based on PET/CT achieving the highest predictive performance in both groups. Additionally, a radiomics model based on the combination of [18F]FDG imaging and the best bimodal combination of structural and functional MRI features was built. It was composed of [18F]FDG PET+CE-T1WI+ADC and reached AUCs of 0.971 and 0.962 in the training and test groups, respectively. These results were significantly better than all single-modal models (p value 0.021) but not different from the bimodal model (p value 0.490). The Karnofsky performance status, the apparent tumor growth rate, and the speed of functional state deterioration were selected as independent factors to be combined in the mixed model that achieved AUCs of 0.987 and 0.975 in the training and test groups, respectively, both higher than the clinical signatures (p value 0.007). However, this model was not different from the optimal multi-modal radiomics model (p value 0.126) and additionally, the single-modal [18F]FDG model was significantly different from the clinical model (p value 0.021).

The role of [18F]FDG PET-based radiomics in the prediction of proliferative activity of primary gliomas was assessed by Kong et al. [39]. Nine features were selected to build the radiomics signature that achieved AUCs of 0.88 and 0.76 and accuracy of 81.7% and 73.2% for predicting the expression levels of Ki-67 in the primary and validation cohorts, respectively. The clinical signature obtained AUCs of 0.84 and 0.67 and accuracy of 75.6% and 65.9% in primary and validation cohorts, respectively. The mixed signature was built using the selected radiomics features, sex, metabolic patterns, and mean standardized uptake value (SUVmean) and demonstrated AUCs of 0.92 and 0.73 and accuracy of 81.7% and 78% in the primary and validation cohorts, respectively. In addition, significantly better performance of the fusion signature compared to the other two signatures (p value 0.048 for the radiomics and 0.015 for the clinical model, respectively) was reported in the primary cohort, while statistical significance was not reached in the validation cohort. In addition, a prognostic analysis revealed both Ki-67 expression level and radiomics signature as able to stratify between long- and short-survival groups (p value ≤ 0.01); however, the differences within these groups for Ki-67 and the radiomics signature did not reach statistical significance.

Wang et al. [41] performed research aimed at assessing the ability of a radiomics-based model to differentiate between glioma recurrence and tumor necrosis. They reported that the built radiomics signature, including [18F]FDG, [11C]MET, and MRI imaging,

yielded AUCs of 0.932 and 0.910 in the primary and validation cohorts, respectively. The accuracy was significantly higher than the accuracy of the signature built by combining [11C]MET and MRI results and was also higher than the ones obtained by the models using [18F]FDG and MRI or [18F]FDG and [11C]MET, even though without statistical significance. A combined model using age, mean target-to-background ratio (TBR) of [18F]FDG PET images, TBRmax of [11C]MET PET images, and 12 other textural features was also developed, and the score derived from this analysis revealed significantly different values between tumor recurrence and radiation necrosis in both primary and validation cohorts (p value < 0.001 in both cases); in particular, patients with tumor recurrence had higher scores in both cohorts. This integrated model had AUCs of 0.988 and 0.914 in the primary and validation cohorts, respectively, with better diagnostic performances than the model based on [18F]FDG, [11C]MET, and MRI imaging.

Kong et al. [40] evaluated the role of [18F]FDG radiomics features to distinguish between GBM and primary central nervous system lymphomas. The authors demonstrated that 95 radiomics features were significantly different between lymphomas and GBMs (p value < 0.05) and that 31 had better performance than the maximum SUV (SUVmax). Features extracted from the SUVmap demonstrated higher AUCs than features from the further calibrated maps. Thirteen radiomics features that were stable and distinguishable from SUVmax in every circumstance were selected to differentiate lymphoma from GBM, suggesting that lymphoma had a higher SUV in most interval segments, and it is more mathematically heterogeneous than the second neoplasm; these features had AUCs ranging from 0.784 to 0.969.

More recently, Zhang et al. [42] investigated the performances of an integrated radiomics model incorporating DWI and [18F]FDG PET imaging when differentiating between GBM and solitary brain metastases in a study including 100 subjects. This integrated model revealed sensitivity and specificity of 92.5% and 98.7% in the training set, respectively, with an AUC of 0.98, higher than the AUCs of combined radiomics models (DWI + [18F]FDG PET: AUC 0.93, p value 0.014; conventional + DWI: AUC 0.89, p value 0.011; conventional + [18F]FDG PET: AUC 0.91, p value 0.015), the single-radiomics model with conventional MRI (AUC 0.85, p value 0.018), DWI (AUC 0.84, p value 0.017), [18F]FDG PET (AUC 0.85, p value 0.421), and the single non-radiomics method (AUCs 0.57–0.71, p value < 0.05). Similar findings were also reported in the validation set, where the integrated model revealed sensitivity and specificity of 85.3% and 84.9%, respectively. Again, the integrated model had an AUC of 0.93, higher than the combined radiomics models (DWI + [18F]FDG PET: AUC 0.81; conventional + DWI: AUC 0.86; conventional + [18F]FDG PET: AUC 0.83), the single radiomics model using conventional MRI (AUC 0.84), DWI (AUC 0.83), and [18F]FDG PET (AUC 0.84), and the single non-radiomics method (AUCs 0.51–0.67).

Lastly, the ability of different models derived from radiomics features of MRI and [18F]FDG PET imaging to differentiate between solitary brain metastases and GBM was also investigated by Cao et al. [43] in a study including 100 patients. Different models were built, and the integrated models combining both MRI and PET features obtained an average AUC of 0.84; the AUC of the MRI set was 0.8, while the PET set obtained an AUC of 0.71. Significant differences were reported between the integrated and MRI sets (p value 0.008), the integrated and PET sets (p value < 0.05), and the MRI and PET sets (p value 0.003). In addition, each of the combined models from the integrated set had higher AUC values compared to the MRI and PET sets. The integration set was finally selected as the one with the best performance, with an accuracy of 0.67–0.89, sensitivity of 0.66–0.88, and specificity of 0.65–0.92.

4. Discussion

Different studies have evaluated the possible role of [18F]FDG PET-based radiomics and ML for the assessment of gliomas and GBMs, and their values in different settings related to these neoplastic conditions have been studied. First of all, the added value of these fields of research has been proposed for the evaluation of different genetic features, such as the methylation status of the MGMT promoter, the IDH genotype, and the ATRX mutation status [37,38,44]. In addition, the ability to predict the proliferative activity of these neoplasms, with the evaluation of Ki-67, was also assessed [39]. High diagnostic performances were also demonstrated in the differential diagnosis between localization of disease and solitary brain metastasis when focusing on GBM patients [42,43]. Similarly, the ability to differentiate between GBM and primary central nervous system lymphomas was also underlined for these algorithms [45]. In addition, the added value in the differential diagnosis between gliomas or GBM recurrence and tumor necrosis was demonstrated in a single paper [41]. Lastly, the prognostic role of [18F]FDG-based radiomics has been investigated in different manuscripts, even though only a single one revealed a clear value of these analyses in this field [37–39]. Even though some insights on the role of [18F]FDG PET-derived radiomics for the evaluation of gliomas and GBMs could have been underlined by this review, it is mandatory and important to underline the fact that this tracer is not routinely used for the assessment of brain tumors, and its low popularity in this field has to be correlated to the high physiologic uptake that is present in these anatomical regions. For this reason, amino acid PET radiomics could provide more useful information, as amino acid tracers generally have lower physiological uptake in the brain, allowing for better tumor-to-background contrast and potentially improving the accuracy of radiomic analyses [11]. This issue is generally present when we use PET for the evaluation of brain tumors; therefore, one of the main limitations that could arise from the use of radiomics and ML in this specific setting is strictly correlated to this fact. ML is a field that focuses on the learning aspects of artificial intelligence by developing algorithms that best represent a set of data [31]. In this setting, different signatures and models can be obtained with this branch of research, depending on the data that are used to generate them. In general, in all the papers included in the review, different models have been extracted to analyze the role of ML in the specific analyzed setting; in particular, all these manuscripts generally compared the signatures based on radiomics features to models that did not include them. Generally speaking, the mixed models that included both radiomics and other clinico-pathological and imaging features had higher performances compared to models that were based on a single set of data. Interestingly, when focusing on signatures based on a single set of features, most of the studies revealed that [18F]FDG-based radiomics models had better performance compared to others. These findings suggest that, even though [18F]FDG imaging can play an important role in defining some features of gliomas and GBMs or differentiating them from other clinical conditions, a wider approach with ML that also includes other features could be the best approach for these analyses, since this last technique does not focus only on a single characteristic of the patient but takes into account different variables, resulting, therefore, in a more specific and patient-centered approach. Interestingly, only a single paper included in the review reported that the radiomics signature had better performance compared to clinical and fused signatures [37].

An interesting datum that arises from the review is the fact that all the included studies were performed in China. A reasonable explanation for this finding is hard to find and to propose; however, we might hope that future research in this field would be implemented in a global setting, a condition that could strengthen the value of [18F]FDG radiomics-based analysis for the assessment of gliomas and GBM, increasing its reproducibility and adding more insights about its future clinical applications.

It is worth underlining that, in general, all the radiomics analyses proposed in the studies included in the review are affected by different issues, resulting, therefore, in a low level of the evidence reported. In particular, all the studies taken into account involved low sample numbers of patients, and, in this specific condition, it should be mandatory to have a 50/50 balance between different classes of subjects; some papers achieved this balance; however, some of them did not. In addition, an attempt to reduce the number of radiomics features analyzed by single papers would be useful to strengthen the value of their analyses. However, cross-fold validation has been used in most of the studies considered, a point that strengthens their value, given the problem of limited cohorts, therefore helping to reduce the overfitting. Keeping in mind these limitations, in general, radiomics extracted from different imaging modalities have, in the past, demonstrated promising results for the evaluation of different clinico-pathological characteristics of gliomas and GBMs [45–49]. The findings reported in this systematic review seem to go in the same direction as these results, with a possible role of radiomics and ML analyses based on [18F]FDG PET imaging in the assessment of these neoplasms that could emerge in the future. These findings could have a promising clinical impact on the evaluation of patients affected by these diseases, allowing a more patient-centered approach in the future. However, in order to endorse these future steps, more wider studies need to be performed in this setting, since several intrinsic problems of radiomics and ML technologies need to be overcome. As a matter of fact, the extraction of radiomics features and their subsequent analyses are affected by issues regarding reproducibility and repeatability, a well-known topic in current literature, and therefore, many efforts in these directions need to be performed to resolve these problems. In particular, for PET imaging, it has also been reported that different scanners, partial volume effect, tumor segmentation, reconstruction protocols, and uptake time are able to influence the extraction of radiomics features and, therefore, subsequent ML analyses [28–30,32,36,50–56]. In fact, in the present review, different factors, such as, for example, voxel size, resolution, and acquisition parameters used to acquire PET scans, were different between the included studies. Another interesting point that arises from this review is the fact that different authors had built and used different ML models, but, in general, these models are not completely shared. This fact is an intrinsic limit to the reproducibility of these analyses, which is mandatory in fields of research such as radiomics and ML where, as mentioned, the repeatability of the methods is mandatory to strengthen the value of the findings of a single study and to have a clear impact on a patient's prognosis and management. Therefore, this review could offer an indication in this setting. In this scenario, the data currently available in the literature seem to not offer a clear indication of the added value of the extraction of PET-based radiomics features and ML for the evaluation of gliomas and GBMs. In this setting, its applications in a routine clinical setting are not easy to implement since different and intrinsic limitations of radiomics and ML could impact their spreading in this clinical setting. However, future research in this field should focus on this issue, since these new technologies could have an important impact on daily clinical life. Different limitations affect this review, depending on the studies that were included. First of all, all of them are characterized by a retrospective design. In addition, in a single paper, the number of [18F]FDG and [11C]MET PET scans performed was not specified, an issue that could impact the reported findings. Moreover, some papers included both high- and low-grade gliomas without specifying the number of patients included in these groups, and since gliomas with different grades can have a different prognostic impact, this is another issue that can affect our findings. Most of the fields of application of [18F]FDG-derived radiomics and ML were investigated by a single study included in the review; therefore, the findings reported need to be confirmed with wider studies. This is also closely connected to the aforementioned intrinsic limitations

of radiomics and ML technologies. Moreover, it is worthwhile to underline that most of the papers included in the present review did not include an external validation, which is mandatory to strengthen the result obtained in a monocentric setting and therefore, to clearly assess the clinical significance of their results [28,32,57]. In addition, it is mandatory to point out that all the papers included in the review were performed with different types of radiomics features, and, furthermore, different analyses were used for their selection, which is again an important issue to compare their results. Lastly, as mentioned before, one of the most important limitations that affect most of the papers analyzed in the review is the fact that they were performed on cohorts with limited subjects, which is a big issue for a clear evaluation of the potential radiomics analyses.

5. Conclusions

In conclusion, in general, [18F]FDG-based radiomics and ML could have promising results in the evaluation of some characteristics of gliomas and GBMs, but the general quality of the papers included in the review does not completely support this statement. Additionally, these findings need to be confirmed and standardized in wider settings since most of them were investigated in single studies with limited cohorts, which is a major limitation for the application of these technologies in a clinical setting.

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