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MINI - REVIEW

^{18}F-FMISO PET imaging: insights over MRI in patients with glioma

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Abstract

Purpose Hypoxic tumors have been demonstrated to be associated with amplified resistance to radiotherapy, chemo-resistance and less favorable outcome after surgery. Non-invasive identification and quantification of hypoxia in humans affected by glioma can be achieved using PET/CT and MRI techniques, although their use is still limited to the research setting. The objective of this review is to present an update of the literature about the potential clinical utility of FMISO PET imaging for the evaluation of hypoxia in patients with glioma, in comparison with advanced MRI techniques, when available.

Methods A comprehensive search strategy was used based on SCOPUS and PubMed databases using the following terms: "FMISO"/"Fluoromisonidazole" AND "brain tumor"/"glioma" AND "PET"/"Positron Emission Tomography". From all studies published in English, we selected—for this review—the most relevant articles of the last 20 years, evaluating the use of FMISO PET in glioma patients, and comparing PET findings with MRI imaging (when available).

Results The use of PET/CT with hypoxia radiotracers in glioma is still limited due to fragmentary data and scarce number of clinical trials in this setting. The most used PET radiotracer for the quantification of hypoxia brain tumor is ^{18}F-FMISO and advanced MRI techniques may provide additional value, especially to couple perfusion information to hypoxia data obtained by PET. As example, relative cerebral blood volume maps could be integrated with PET imaging results for more precise and integrated evaluation of hypoxia, neo-angiogenesis and necrotic areas.

Conclusion Hypoxia PET imaging has demonstrated potential benefits for grading, diagnostic and prognostic purposes, despite the lack of tangible results able to introduce such method in a wide clinical setting. MRI remains the gold standard in the morphologic evaluation of glioma, but the integration of results provided by ^{18}F-FMISO PET imaging concerning hypoxia might provide new crucial information in patients with glioma.

Keywords PET · Glioma · Hypoxia · FMISO · MRI

Introduction

Hypoxia is defined as an insufficient oxygen concentration to allow the normal execution of biological functions [1, 2]. Hypoxia is one of the most detrimental factors for the outcome of patients with glioma, and particularly high-grade types [3]. Tumor hypoxia mainly occurs due to the altered blood flow, impaired by structural and/or functional disturbances of tumor circulation, coupled with the rapid tumor growth, leading to an increased oxygen demand with unsatisfactory oxygen supply [4]. The assessment of tumor hypoxia is important from a biological and clinical point of view, since hypoxic tumors have been demonstrated to be associated with amplified resistance to radiotherapy, chemo-resistance and less favorable outcome after surgery [5, 6]. Along with hypoxia, the main histological features

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of high-grade glioma (with grade IV glioma being the most lethal brain tumor, formerly known as glioblastoma multiforme—GBM), include cellular and nuclear atypia, increased cellular proliferation, reduced apoptosis, perilesional oedema, microvascular proliferation and necrosis [7].

Imaging and measuring oxygen concentration within a tissue can rely on direct or indirect strategies. The first approach consists of measurements adjusted to a pO_2 value, whereas indirect strategies are based on measurements of a surrogate of oxygen, like the hemoglobin saturation's level [8]. Examples of direct imaging methods include oxygen-sensing probes and phosphorescence imaging, both currently and mainly employed in the preclinical setting [8, 9]. At present, non-invasive identification and measurement of hypoxia in humans can be more practically achieved by the use of Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), although their use is still limited to the research setting [9, 10].

The development of PET tracers for hypoxia has been conducted for decades. The first radiotracer was ^{14}C-misonidazole as a beta-emitting tracer in 1981 [11], followed by ^{18}F-Fluoromisonidazole (^{18}F-FMISO) [12]. To date, although other radiotracers have been examined [10] and few limitations are present (i.e., slow tracer accumulation and slow plasma clearance [13]) ^{18}F-FMISO remains the most widely used radiotracer for imaging hypoxia in patients with brain tumors.

Currently, most MRI techniques have been developed in the effort of mapping and quantifying hypoxic regions, with the goal of providing an indirect measurement of the oxygen level. However, for the majority of these MRI techniques, oxygen measurement could be influenced by external confounding factors [13, 14]. Although MRI techniques are becoming increasingly attractive for the evaluation of hypoxia as a practical alternative, PET imaging represents a precise imaging modality for the quantification of hypoxia in gliomas, with a wide range of available radiotracers.

The aim of this paper was to present the most relevant ^{18}F-FMISO PET clinical studies, published in the last 20 years, concerning the evaluation of hypoxia in patients with glioma and to offer a comparison, with advanced MRI techniques, when available.

^{18}F-FMISO

^{18}F-FMISO is a lipophilic molecule belonging to the 2-nitroimidazole-based class of compounds, molecules, which passively diffuse into cells with different kinetics depending on their lipophilicity. ^{18}F-FMISO is able to pass the blood–brain barrier (BBB) and slightly accumulates in normal brain tissue; it is excreted through the hepatobiliary system and thus accumulated in the liver and gastrointestinal tract, limiting the analysis of hypoxic conditions in these organs [15]. At present, ^{18}F-FMISO remains the most widely used radiotracer for imaging hypoxia in patients with brain tumors, including gliomas, although other radiotracers are being investigated with promising results [10]. After intravenous injection, FMISO is distributed via the blood flow to the cells, where it captures electrons with a mitochondrial electron transfer system. In hypoxic tissues, due to the lack of oxygen, FMISO keeps extra electrons, form reactive radicals, being irreversibly bound to high-weight molecules [4, 16, 17]. Conversely, in non-hypoxic tissues, oxygen molecules remove the FMISO electron as a strong oxidant, so that FMISO freely exit from the cells. Masaki et al. described an alternative/complementary mechanism of FMISO accumulation [18]. Beyond binding to high-weight molecules, in hypoxic conditions also the glutathione conjugate of amino-FMISO could be related to its accumulation. Tables 1, 2 provide a summary of the main findings and technical aspects of the relevant clinical studies included in the present review.

Methods

Search strategy

A comprehensive literature search of the Scopus and PubMed databases was conducted using the following terms: "FMISO"/"Fluoromisonidazole" AND "brain tumor"/"glioma" AND "PET"/"Positron Emission Tomography". From all studies published during the last 20 years (01.01.2000–01.09.2019), we selected—for this review—the most relevant articles (in cohort of at least 10 subjects), evaluating the use of FMISO PET in patients with glioma, in comparison with MRI imaging (when available). Only articles in the English language were selected. To enlarge our research, references of the retrieved articles were also screened for searching additional papers.

Study selection

Studies or subsets in studies investigating the value of ^{18}F-FMISO PET or PET/CT in patients with glioma were eligible for inclusion. Instead, exclusion criteria were: (a) articles not in the field of interest; (b) review articles, meta-analyses, letters, conference proceedings, editorials, and (c) case reports or small case series (less than 10 patients). Two researchers (RD and DA) independently reviewed the titles and abstracts of the articles, applying the above-mentioned inclusion and exclusion criteria and the same two researchers then independently reviewed the full-text version of the papers to evaluate their suitability.

Table 1 Main findings of selected ^{18}F-FMISO PET clinical studies included in the review

First author [references]	Year	Study design	Mean age (range)	Number of patients	M:F	Type of glioma	Main findings	Standard of reference
Cher et al. [20]	2006	Retrospective	49 years (23–76)	17	11:6	Grade I: 1 Grade II: 3 Grade III: 3 Grade IV: 7 Other 3	FMISO uptake correlated with glioma grading, with 18F-FDG uptake and tumor markers of hypoxia, proliferation and angiogenesis Prognostic role of FMISO PET	Histopathology ± MRI
Spence et al. [32]	2008	Retrospective	56* years (41–77)	22	13:9	Grade IV: 22	Prognostic role of FMISO T/B ratio	Histopathology ± MRI
Swanson et al. [33]	2009	Retrospective	54.8 years (37–76)	24	16:8	Grade IV: 24	Complementary role between MRI and 18F-FMISO PET Prognostic role of FMISO T/B ratio	Histopathology ± MRI
Kawai et al. [27]	2011	Prospective	57.8 years (27–72)	10	7:3	Grade IV: 10	Correlation with tumor markers of hypoxia and angiogenesis and aggressiveness measured by MET PET	Histopathology ± MRI
Hirata et al. [21]	2012	Prospective	57 years (31–82)	23	10:13	Grade II: 4 Grade III: 5 Grade IV: 14	FMISO uptake correlated with glioma grading	Histopathology ± MRI
Gerstner et al. [29]	2016	Prospective	59* years (29–77)	42	27:15	Grade IV: 42	Prognostic role of FMISO T/B ratio and SUVpeak	Histopathology ± MRI
Kanoto et al. [19]	2016	Retrospective	57.1 years (N/A)	48	25:23	Grade I: 3 Grade II: 12 Grade III: 8 Grade IV: 25	T/N max and T/N mean in FMISO PET have a positive correlation with primary brain tumor grading	Histopathology
Yamaguchi et al. [34]	2016	Retrospective	63.5 years (27–76)	18	8:10	Grade IV: 18	Evaluation of treatment response after Bevacizumab Prognostic role of FMISO uptake and T/N ratio	Histopathology ± MRI
Toyonaga et al. [31]	2016	Prospective	N/A (30–85)	59	33:26	Grade III: 24 Grade IV: 22 Other: 13	Correlation between qualitative and semiquantitative FMISO PET with necrosis features	Histopathology ± MRI
Bekaert et al. [22]	2017	Prospective	58 years (28–80)	33	24:9	Grade II: 6 Grade III: 3 Grade IV: 24	Correlation with tumor markers of hypoxia and angiogenesis	

M male, *F* female, *N/A* not available, *T/B* tumot-to-blood ratio, *hMTV* hypoxic metabolic tumor volume, *MET* ^{11}C-methionine, *T/N* tumor-to-normal brain tissue

*Age expressed as median value

Data abstraction

For each included study, data were collected concerning the basic study features (author names, year of publication, study design), the main clinical patients features, technical variables (PET device used, radiotracer injected dose, image analysis), number of patients evaluated and the main findings. The main findings of the articles included in this review are reported in the "Results" section.

Table 2 Main technical aspects of ^{18}F-FMISO PET clinical studies included in the review

First author [references]	Device	Mean injected dose (MBq)	Acquisition time (min post injection)	Image analysis	Semiquantitative parameters	MRI/other imaging modality
Cher et al. [20]	PET	18.5/kg	120	Visual and semiquantitative	SUVmax	MRI: T1, T2 and gadolinium contrast enhancement
Spence et al. [32]	PET	3.7/kg	120	Visual and semiquantitative	T/B ratio	MRI: T1 with gadolinium contrast enhancement and T2
Swanson et al. [33]	PET	3.7/kg	120	Visual and semiquantitative	T/B ratio	MRI: T1 with gadolinium contrast enhancement and T2
Kawai et al. [27]	PET	308	120–140	Visual and semiquantitative	SUVmax; SUVmean; T/B ratio	MRI: T1 with gadolinium contrast enhancement ^{11}C-MET PET/CT: 308 MBq injected, uptake time 10 min
Hirata et al. [21]	PET/CT	400	240	Visual and semiquantitative	SUVmax	MRI: FLAIR images ^{18}F-FDG PET/CT: 400 MBq injected, uptake time 60 min
Gerstner et al. [29]	PET/CT	3.7/kg	110	Visual and semiquantitative	SUVmax, SUVpeak, T/B ratio	MRI: DCE, DSC, T1, diffusion and FLAIR images
Kanoto et al. [19]	PET/CT	439.6	240	Visual and semiquantitative	SUVmax, SUV mean, T/N max and T/N mean	N/A
Yamaguchi et al. [34]	PET/CT	400	240	Visual and semiquantitative	SUVmax, T/N ratio	MRI: T1 with and without gadolinium contrast enhancement, T2 and FLAIR images
Toyonaga et al. [31]	PET; PET/CT	400	240	Visual and semiquantitative	T/N ratio	MRI: T1 with and without gadolinium contrast enhancement, T2 and FLAIR images
Bekaert et al. [22]	PET/CT	5/kg	120	Visual and semiquantitative	SUVmax, T/B ratio	MRI: T1 with and without gadolinium contrast enhancement, T2 and FLAIR images

N/A not available, MBq megabecquerel, *T/B* tumot-to-blood, *T/N* tumor-to-normal brain tissue, *DCE* dynamic contrast-enhanced, *DSC* dynamic susceptibility contrast, *hMTV* hypoxic metabolic tumor volume, *hTLG* hypoxic total lesion glycolysis, *HMF* hypermetabolic fraction of hypoxic volume, *MET* ^{11}C-methionine, *FLAIR* fluid-attenuated inversion recovery

Results

The comprehensive computer literature search from the Scopus and PubMed databases revealed 46 articles collected. Reviewing titles and abstracts, 36 studies were excluded because reported data were not inside inclusion criteria. Lastly, 10 papers were selected and screened in the full-text version [19–22, 27, 29, 31–34]. The main features of the included studies are summarized in Tables 1, 2.

Grading

Hypoxia severity and grading demonstrate a positive correlation in primary brain tumors [19] and ^{18}F-FMISO PET could be used as a non-invasively method to predict tumor grading in newly diagnosed gliomas. Several studies were conducted to evaluate the utility of ^{18}F-FMISO PET in this setting. Firstly, Cher et al. [20] investigated ^{18}F-FMISO PET in a group of 17 patients undergoing also ^{18}F-FDG PET, MRI (using T1 and T2 imaging and gadolinium

contrast-enhancement) and immunohistochemistry. They reported that only grade IV gliomas presented gadolinium enhancement, high ^{18}F-FMISO and ^{18}F-FDG uptake, with only one case (1 out of 3 patients) of stage III glioma showing low ^{18}F-FMISO uptake and either ^{18}F-FDG uptake or MRI gadolinium enhancement. Interestingly, FMISO uptake was not completely restricted to the tumor rim or areas of gadolinium enhancement, or determined by the integrity of BBB and did not match the intensity of ^{18}F-FDG uptake. It follows that ^{18}F-FMISO uptake cannot be predicted by visual assessment of MRI gadolinium enhancement or ^{18}F-FDG uptake. Similarly, Hirata et al. [21] showed a significantly higher ^{18}F-FMISO uptake in stage IV glioma, despite a slight ^{18}F-FMISO uptake in lower-grade gliomas (Fig. 1). Moreover, the authors performed both ^{18}F-FMISO and ^{18}F-FDG PET/CT scans in 23 patients with histological diagnosis of glioma (grade II = 4, grade III = 5, grade IV = 14) and ^{18}F-FMISO PET images were evaluated by visual and semi-quantitative assessment (SUV, lesion–normal tissue ratio and FMISO uptake volume); these analyses demonstrated that ^{18}F-FMISO PET could help to discriminate stage IV glioma from less malignant glioma. Namely, using visual assessment score (low, intermediate and strong) for FMISO PET images, histological diagnosis of glioblastoma was related to a strong ^{18}F-FMISO uptake with sensitivity, specificity and accuracy of 100%; whereas, ^{18}F-FDG PET showed a sensitivity and specificity of 100% and 66%, respectively. In MRI images, gadolinium enhancement was clearly evident in all GBM cases, while it was variable in lower-grade glioma (strong in 3 grade III gliomas; weak in one grade III and two grade II gliomas; absent in one grade III glioma and two grade II gliomas). However, as a major technical difference of this study from the study of Cher et al. [20], the ^{18}F-FMISO PET/computed tomography (CT) scans were acquired 2 h after the radiotracer injection; while Hirata et al. [21] carried out the scans 4 h after ^{18}F-FMISO injection. This different uptake time could explain the low and intermediate uptake found in some low-grade gliomas. Additionally, subsequent papers [17, 21, 22] confirmed the high ^{18}F-FMISO uptake in grade IV gliomas. Namely, Bekaert et al. [22], analyzing 33 patients undergoing both PET and MRI, confirmed that ^{18}F-FMISO uptake was significantly higher in stage IV gliomas ($n = 24$) compared to lower-grade tumors (grade III = 3, II = 6). Furthermore, the authors found a higher level of relative cerebral blood volume (rCBV, $p = 0.006$) in the ^{18}F-FMISO uptake group

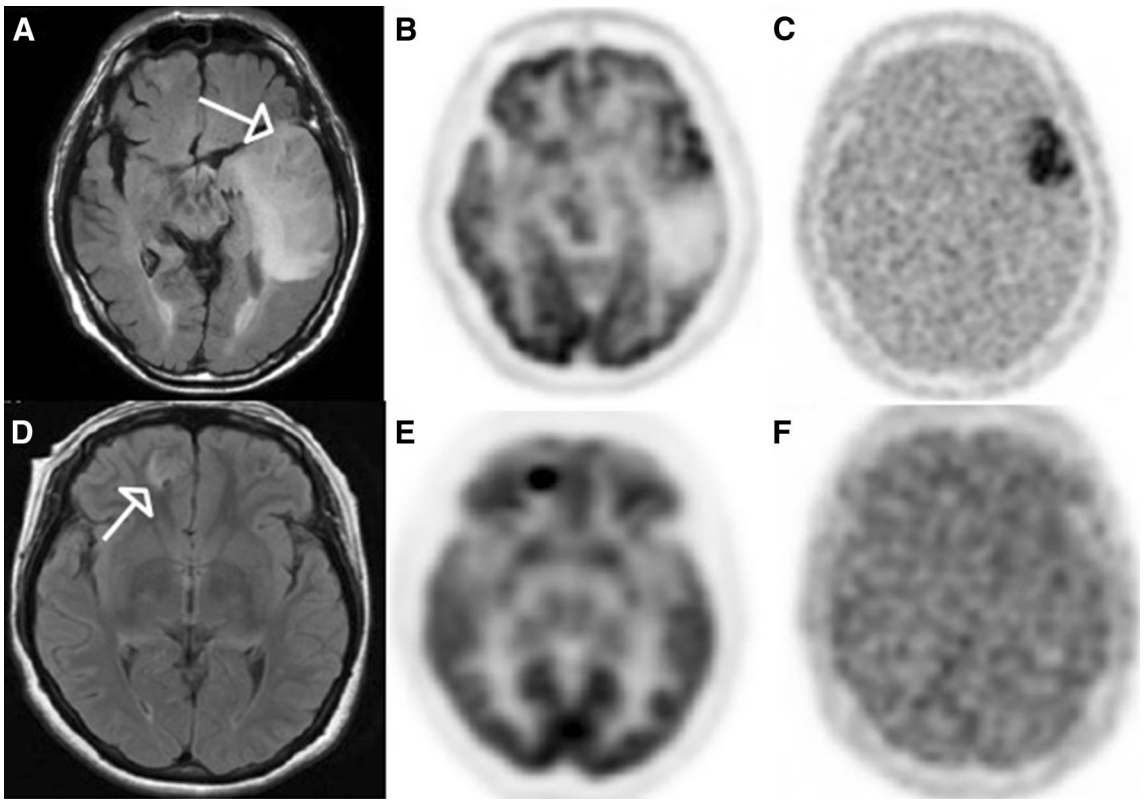

Fig. 1 A representative case of glioblastoma (grade IV) localized at the left temporal lobe detected by fluid-attenuated inversion recovery MRI scan (**a**) with moderate FDG uptake (**b**) and increased FMISO uptake (**c**). Another example of a lesion in the right frontal lobe recognized by MRI (**d**), with high FDG uptake (**e**) but not FMISO uptake (**f**): the final diagnosis was gangliocytoma (grade I). (adapted with the permission of Hirata et al. [21])

than in the "no-uptake" group, thus documenting a correlation between the degree of hypoxia (measured in terms of hypoxic volume—HV—and standardized uptake value—SUV—max) and rCBV. Chakhoyan et al. [23] confirmed the increased rCBV obtained from the perfusion-weighted imaging (PWI) in GBMs, compared to non-GBM tumors (1.4 ± 0.2 vs. 0.8 ± 0.4; $p < 0.001$). In addition, absolute maps of p_tO_2 tissue obtained from ^{18}F-FMISO PET images revealed low values in GBM (4.8 ± 1.9 mmHg). Furthermore, significant inverse correlations were found: a) between ^{18}F-FMISO uptake (in terms of tumor–background ratio—T/B ratio) and affined p_tO2 across tumoral, normal appearing gray matter (NAGM) and normal appearing white matter (NAWM areas) ($R^2 = 0.58$); b) between rCBV and ptO2 ($R^2 = 0.56$) in the same areas; c) between ptO2and lactate/lipid concentrations ($R^2 = 0.66$).

Characterization of tumoral microenvironment features (hypoxia, perfusion, necrosis)

It is well known that gliomas, and particularly GBM, are cerebral neoplasm characterized by hypoxic tissue and necrotic areas. The complex tumoral microenvironment is influenced by the hypoxic signaling cascade [24]. Hypoxia activates the transcription of many genes through the hypoxia-inducible factor 1 (HIF-1), including angiogenic factors, as the vascular endothelial growth factor (VEGF), able to induce vascular proliferation, promoting cell survival, invasiveness and aggressiveness. There is large evidence in the literature regarding the link between hypoxia, necrosis and angiogenesis. This relationship could be considered paradoxical because angiogenesis should lead to a more vascularized tumor with higher oxygen supply and, therefore, less hypoxia and necrosis. However, during the tumor growth in GBM, angiogenesis-derived blood vessels are functionally and structurally abnormal, leading to ineffective perfusion [25], being associated with both poor prognosis and resistance to several therapies [25, 26].

^{18}F-FMISO uptake correlates with the angiogenic expression of VEGF-receptor 1 (VEGF-R1) factor, as demonstrated by Cher et al. in a study including 14 of 17 patient with suspected glioma, who performed also cerebral ^{18}F-FDG PET/CT and gadolinium contrast-enhancement MRI [20]. A significant correlation between tumor markers of hypoxia, proliferation and angiogenesis (Ki67 and VEGF-R1, respectively) and ^{18}F-FMISO or ^{18}F-FDG uptake was found ($p < 0.005$).

With the purpose to clarify the biological link between hypoxia, tumor-induced neovascularization and aggressiveness, Kawai et al. [27] analyzed spatial and volumetric information of viable tissue assessed by ^{18}F-FMISO PET relative to neovascularization in T1-weighted gadolinium-enhanced MRI and tumor aggressiveness assessed by ^{11}C-methionine (MET) PET in 10 patients with newly diagnosed GBM. The volumetric analysis demonstrated that the viable hypoxic tissue, assessed by ^{18}F-FMISO PET, is related to the neovascularization in MRI and to the tumor aggressiveness evaluated by MET PET. The spatial analysis showed that the metabolically active tumor may be substantially underestimated by gadolinium-enhanced MRI (77% of the mean metabolically active volume as shown by a MET uptake index > 1.3).

More recently, Bekaert et al. [22] found a strong correlation between ^{18}F-FMISO uptake and molecular expression of HIF and VGF. They performed ^{18}F-FMISO PET and MRI including rCBV. The authors found correlations between the degree of hypoxia (hypoxic volume and SUVmax) and the rCBV and the level of expression of molecular markers (HIF, carbonic anhydrase—CAIX, angiopoietin-2—Ang2, and VEGF). This evidence was in line with the results of subsequent papers [28, 29], which evaluated GBM patients quantifying and localizing hypoxia by means of ^{18}F-FMISO PET, correlating hypoxia with MRI markers of angiogenesis. Lately, Gerstner et al., in a study of 50 GBM patients, found a strong correlation ($R^2 = 0.5$, $p < 0.001$) between HV and normalized cerebral blood flow (nCBF) to the mean of the region of interest (ROI) in NAWM. In a subsequent study, in a cohort of 17 patients, the same group of researchers found, conversely, a lack of association between metabolic markers, measured by MRI Spectroscopy (MRSI), hypoxia (measured by ^{18}F-FMISO PET), and tumor perfusion markers (e.g., nCBF and median K^{trans}) [30]. All these data highlight the complex metabolic microenvironment of GBM.

The relationship between the amount of tissue necrosis and ^{18}F-FMISO uptake was investigated by the study of Toyonaga et al. [31]; it should be remembered that ^{18}F-FMISO accumulates in viable tissues but not in necrotic tissue core. Conversely, wide-ranging necrosis can be clearly detected by conventional MRI. The authors studied 59 patients with brain tumors, including 45 gliomas. In the visual analysis, 26 of the 27 ^{18}F-FMISO-positive patients presented necrosis; whereas, 28 of the 32 ^{18}F-FMISO-negative patients showed no necrosis. Using a cut-off for the tumor–normal tissue ratio of 1.67, the authors showed that the occurrence of necrosis could be predicted with a sensitivity of 96.7%, specificity of 93.1%, and accuracy of 94.9%. This finding suggests that ^{18}F-FMISO uptake can reveal small clusters of hypoxic tissue even within necrotic areas.

Prognostic value

^{18}F-FMISO PET imaging holds also the potential to predict the prognosis in patients with glioma, as demonstrated by several studies in literature [20, 22, 29, 31–34]. In this scenario, Cher et al. [20] demonstrated that positive ^{18}F-FMISO PET was associated with poor outcome in a subset of 14 patients with suspected glioma,

followed up until death or, if alive, for a median follow-up of 68 months (range: 58–83); out of the 8 patients who died, 7 subjects had positive ^{18}F-FMISO uptake and one presented equivocal uptake. Conversely, among the 6 alive patients, ^{18}F-FMISO uptake was negative or equivocal.

Beyond the qualitative analysis, also the semi-quantitative analysis of ^{18}F-FMISO PET images and MRI-derived parameters seemed to correlate with outcome. Maximum tumor–blood ratio (T/Bmax), HV, the surface area of HV and surface area of T1-gadolinium showed to be associated with worst survival in 11 cases of preoperative glioblastoma [33]. Similarly, in another study, HV and T/Bmax correlated with survival and time to progression (TTP); whereas, T1-gadolinium volume correlated only with survival in 22 glioblastoma patients before radiotherapy [32].

In 2016, a prospective clinical trial involving 11 centers [29], included 42 patients with GBM, who performed baseline MRI and ^{18}F-FMISO PET/CT scan. Their analysis showed that a high ^{18}F-FMISO uptake (expressed as SUVpeak, SUVmax and T/B ratio) significantly correlated with shorter OS and PFS at 1 year along with increased tumor perfusion, vascular volume and vascular permeability measured by MRI. In contrast, Bekaert et al. [22], in 33 patients with glioma of different grades prospectively recruited, demonstrated no relationship between ^{18}F-FMISO visual-semiquantitative parameters and outcome survival (in terms of progression-free survival—PFS, and overall survival—OS—). At univariate analysis, ^{18}F-FMISO uptake (positive vs. negative) correlated with PFS and OS, but at multivariate analysis including grade, extent of resection, age and performance status, no significant correlation was confirmed.

Only one study evaluated the potential role of ^{18}F-FMISO PET/CT in the evaluation of treatment response after immunotherapy with Bevacizumab [34], a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting the VEGF-A [35], commonly used for therapy of recurrent GBM. The authors reviewed MRI and ^{18}F-FMISO PET/CT scans before and after 3–4 courses of Bevacizumab in 18 patients with recurrent high-grade glioma. MRI revealed partial response in 14 patients, 9 of which demonstrating decreased ^{18}F-FMISO uptake ("MRI-FMISO double responders"); 5 patients with partial response at MRI but stable or increased ^{18}F-FMISO uptake ("MRI-only responders") and 4 without MRI and PET/CT response ("non-responders"). "MRI-FMISO double responders" showed significantly longer OS than the other two groups (median 12.4 months vs. 5.7 months; $p < 0.001$), whereas there was no survival difference between the "MRI-only responders" and the "non-responders" groups (median OS, 5.7 and 4.8 months; $p = 0.58$). Considering the main pre-treatment clinical and radiological/metabolic variables, high ^{18}F-FMISO T/N ratio was the only significant prognostic factor for OS.

Conclusion

Despite the need of larger cohort, prospective and multicenter study in the clinical scenario of glioma patients, FMISO imaging PET has demonstrated its potential benefits for grading, diagnostic and prognostic purposes. MRI remains the gold standard in the evaluation of high-grade gliomas but the integration of MRI results with PET imaging of hypoxia might provide new crucial information.

Author contributions Laudicella R, Quartuccio N: literature search, literature review, manuscript writing, manuscript editing, content planning; Alongi P, Albano D, Gazzilli M, Durmo R: literature search, literature review, manuscript writing; Baldari S, Bertagna F: manuscript editing, content planning.

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Compliance with ethical standards

Conflict of interest Laudicella Riccardo, Quartuccio Natale, Alongi Pierpaolo, Albano Domenico, Gazzilli Maria, Durmo Rexhep, Bertagna Francesco and Baldari Sergio declare no conflict of interest related to this work.

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