Update to the RANO working group and EANO recommendations for the clinical use of PET imaging in gliomas

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This Policy Review provides recommendations for the use of PET imaging in patients with gliomas and represents a joint effort of the Response Assessment in Neuro-Oncology (RANO) working group for PET and the European Association for Neuro-Oncology. The initial guideline was published in 2016, and summarised the previously established clinical benefit of PET with radiolabelled glucose and amino acid tracers in patients with gliomas. Since then, numerous additional studies have been published on this topic, focusing on differential diagnosis, prediction of molecular information, and prognostication. Further studies evaluated PET for biopsy guidance and delineation of glioma extent for local therapy planning, including resection and radiotherapy. In patients undergoing treatment, PET was studied for the assessment of response to local and systemic treatments and PET-based standardised response criteria (PET RANO 1.0) were proposed. In this Policy Review, the updated recommendations are based on evidence generated from studies that validated PET findings by histomolecular findings or clinical course. This guideline further underscores the previously reported clinical value of PET imaging and the superiority of amino acid PET over glucose PET, providing a framework for the use of PET in the management of patients with gliomas. The guideline also underscores the scarcity of class 1 evidence showing that incorporating PET imaging into clinical workflows improves patient outcomes, highlighting priority areas for future clinical studies designed to address this gap.

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Introduction

Over the past two decades, the role of PET imaging in neuro-oncology has evolved considerably.[1] For various indications in patients with glioma, amino acid PET has gained broader international acceptance as an adjunct to conventional and advanced MRI. This success is consequential to rigorous research efforts, resulting in multiple publications, which prompted expert panel recommendations and clinical and technical guidelines for PET imaging in patients with glioma.[2–5]

Notably, these recommendations and guidelines are the result of the joint effort of experts from major organisations in neuro-oncology—the European Association for Neuro-Oncology (EANO), the Response Assessment in Neuro-Oncology (RANO) working group, and the Society of Neuro-Oncology—and in nuclear medicine—the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging. Moreover, most probably due to the visibility of these highly cited guidelines and the convincing results of the published research, reimbursement by statutory health agencies for PET imaging with radiolabelled amino acids to differentiate treatment-related changes from tumour relapse in patients with gliomas has now been granted in Germany, Denmark, and France, with anticipation that such reimbursement will soon be granted in other European countries.

The first guideline for PET imaging in patients with gliomas was published by the RANO working group for PET, together with the EANO in 2016.[6] This guideline highlighted the superiority of amino acid PET over [^{18}F]fluorodeoxyglucose PET ([^{18}F]FDG-PET) for various clinical applications. Recommendations provided by this guideline were based on the most widely used amino acid tracers for PET imaging targeting system L amino acid transport, including [^{18}F]fluoroethyl-L-tyrosine ([^{18}F]FET), [^{11}C]methionine ([^{11}C]MET), and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine ([^{18}F]FDOPA).

Since the publication of this guideline in 2016,[6] several hundred articles on PET imaging in gliomas have been published, and standardised criteria for assessment of response to treatment have been proposed by the RANO group in 2024.[2] Overall, the initial results were confirmed and refined, the level of evidence improved, newer indications for amino acid PET imaging were established (eg, evaluating its role in paediatric patients with brain tumours), and other radiolabelled amino acids were introduced for clinical use. For example, the alicyclic amino acid anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (fluciclovine) has been proposed for imaging of primary and secondary brain tumours. Fluciclovine transport is mediated by several neutral amino acid transporters, including system ASC and system L, distinguishing its mechanism of uptake from [^{18}F]FET, [^{11}C]MET, and [^{18}F]FDOPA.

The updated guidelines presented in this Policy Review aim to serve medical professionals of all disciplines involved in the diagnosis and care of

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patients with gliomas and provide a framework for the use of PET in neuro-oncology.

Levels of evidence and strength of recommendations

As described previously by the RANO working group for PET,[6] any study that confirmed PET findings with neuropathology (ie, histology, molecular information according to the most recent WHO classifications for CNS tumours,[7,8] and combinations thereof) was considered to represent the highest degree of validation. Next, correlation with conventional MRI (when applicable, according to RANO criteria) and with the patient's clinical course were deemed as the second degree of validation. Only papers constituting levels 1–3 of evidence according to the Oxford Centre for Evidence-Based Medicine were included as bases for our recommendations (table 1). According to the Strength of Recommendations Taxonomy,[9] the RANO working group for PET defined the grade of a recommendation for clinical practice based on the level of evidence and the body of evidence, including the available number of studies and consistency and coherence of these studies (table 2).

Clinical indications

An overview of indications for amino acid PET in patients with gliomas is presented in figure 1.

Newly diagnosed brain lesions: differentiation of neoplastic from non-neoplastic lesions

Neoplastic lesions, such as gliomas, typically show considerably higher uptake of radiolabelled amino acids than non-neoplastic lesions, which might aid in presurgical differential diagnosis.[6] Studies evaluating the diagnostic performance of PET with the tracers [^{18}F]FET or [^{11}C]MET for the differentiation of neoplastic from non-neoplastic lesions reported a specificity for a neoplastic diagnosis in the range of 76% to 91%.[10,11] In addition, in newly diagnosed lesions radiographically suggestive for glioma, a pathologically increased [^{18}F]FET uptake (ie, a maximum tumour-to-brain ratio of 2·5 or higher) has been associated with a positive predictive value of 98% for a neoplastic diagnosis.[12] A subsequent study reported a sensitivity and specificity higher than 90% to diagnose a tumour of glial origin with [^{18}F]FET.[13] Evidence for other amino acid tracers like [^{18}F]FDOPA or fluciclovine for the differentiation of neoplastic from non-neoplastic lesions is scarce. Of considerable note is the fact that 20–30% of patients with CNS WHO grade 2 gliomas with an isocitrate dehydrogenase (IDH) gene mutation exhibit no amino acid uptake.[14]

Notably, brain lesions without tracer uptake and MRI findings suggest that CNS WHO grade 2 gliomas might exhibit photopenic defects on amino acid PET, with uptake visually lower than that of normal-appearing brain parenchyma. These lesions might be gliomas, including some tumours with a higher CNS WHO grade.[15] This effect has subsequently been reported for the radiolabelled amino acids [^{11}C]MET and [^{18}F]FDOPA.[16] Although much less common, mild amino acid tracer uptake above background level can occur in non-neoplastic lesions (eg, brain ischaemia, cerebral abscess, or inflammatory foci) or be related to epileptic seizures.[5]

To summarise the most relevant clinical aspects: in newly diagnosed brain lesions, amino acid PET shows high diagnostic performance in differentiating between neoplastic and non-neoplastic lesions in cases that remain uncertain following conventional imaging; a negative amino acid PET scan does not exclude a glioma; and although amino acid PET adds valuable information for the differential diagnosis of suspected CNS lesions for gliomas, neuropathological tissue evaluation remains mandatory to provide a final diagnosis.

Non-invasive prediction of molecular information

Invasive procedures are required to obtain tissue samples to establish specific molecular information, which has prompted the evaluation of various non-invasive

	Evidence level defined in the 2016 guideline[6]	Evidence level defined in this Policy Review (2025)
Differentiation of neoplastic from non-neoplastic lesions	3	3
Delineation of glioma extent for planning of local therapy options	3	2
Differentiation of glioma recurrence from treatment-related changes (eg, pseudoprogression)	3	2
Detection of malignant tumour parts within MRI findings suggestive of non-enhancing gliomas	3	2
Assessment of prognosis in newly diagnosed, untreated gliomas	3	3
Response assessment	3	2
Analysis of cost-effectiveness	NA	2
Paediatric patients with gliomas (ie, for differential diagnosis and follow-up after treatment)	NA	3

Definitions of the evidence levels are as follows: 1 is randomised controlled trial; 2 is prospective cohort study, ecological studies, or outcomes research; and 3 is retrospective study or individual case-control studies. NA=not applicable.

Table 1: **Overview of the 2011 Oxford Centre for Evidence-Based Medicine Levels of Evidence for the use of amino acid PET in gliomas**

	Recommendation	Evidence level	Strength of recommendation category
Differentiation of neoplastic from non-neoplastic lesions	In newly diagnosed brain lesions, amino acid PET can be recommended in differentiating between neoplastic and non-neoplastic lesions in cases that remain uncertain following conventional MRI	3	Moderate
Delineation of glioma extent for planning of local therapy options	Amino acid PET is strongly recommended to provide additional information on the delineation of glioma extent	2	Strong
Differentiation of glioma recurrence from treatment-related changes (eg, pseudoprogression)	Amino acid PET is strongly recommended to provide additional information in differentiating glioma relapse from treatment-related changes in cases that remain equivocal following conventional MRI	2	Strong
Detection of malignant tumour parts within MRI findings suggestive of non-enhancing gliomas	Amino acid PET is strongly recommended to identify the most malignant glioma components	2	Strong
Assessment of prognosis in newly diagnosed, untreated gliomas	Amino acid PET can be considered for the estimation of prognosis in patients with gliomas at the time of initial diagnosis	3	Weak
Response assessment	Amino acid PET can be recommended to assess response to anticancer therapy (eg, alkylating chemotherapy or antiangiogenic therapy); in clinical trials, the use of standardised response criteria as provided by the PET RANO 1.0 criteria is strongly recommended	2	Moderate
Paediatric patients with gliomas (ie, for differential diagnosis and follow-up after treatment)	In paediatric patients with glioma, amino acid PET can be considered in differentiating between neoplastic and non-neoplastic lesions in cases that remain uncertain following conventional MRI and for follow-up after treatment	3	Weak

Strength of recommendation categories are defined as follows: strong means the evidence strongly supports the use of this imaging study; moderate means there is moderate evidence supporting the use of this imaging modality; weak means the evidence is limited. Expert opinion suggests use, but evidence is minimal. RANO=Response Assessment in Neuro-Oncology.

Table 2: **Recommendations for the clinical use of amino acid PET in patients with gliomas**

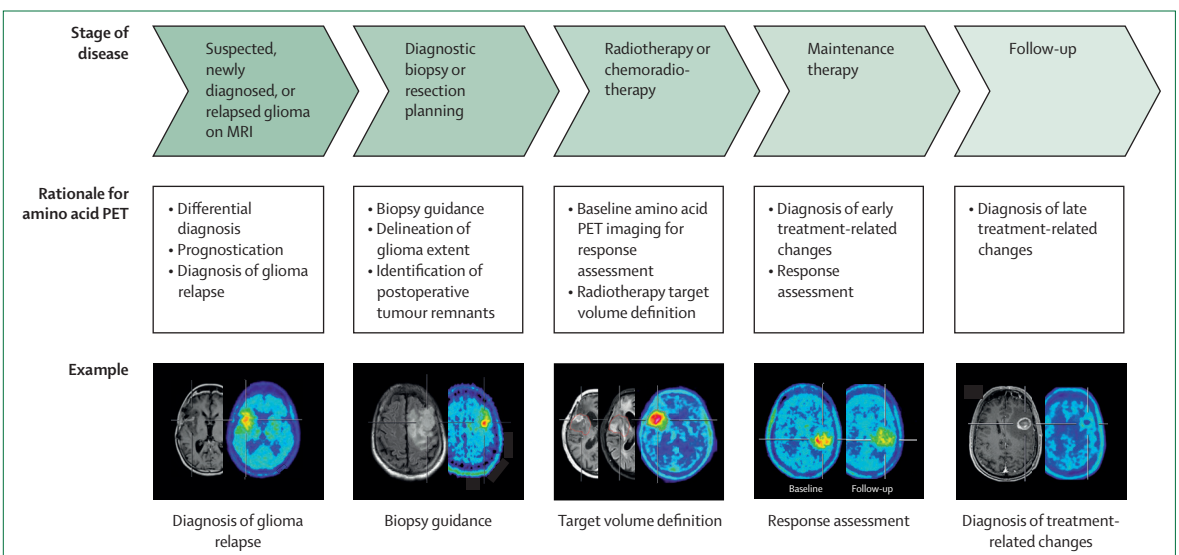

Figure 1: **Overview of indications for amino acid PET in patients with gliomas at any stage of disease**

neuroimaging approaches, including amino acid PET, to accurately obtain information at the molecular level. Such an approach could be useful in scenarios with inconclusive molecular test results or anatomical locations that are difficult to access for resection or biopsy sampling.

The value of dynamic amino acid PET for the prediction of the *IDH* genotype (ie, for prediction in mutations in IDH1 or IDH2) has been investigated for the tracers [^{18}F]FET and [^{18}F]FDOPA.[17,18] These studies showed that, in gliomas with amino acid uptake, there was a correlation between dynamically acquired PET parameters (particularly a short time-to-peak value) and the *IDH* mutational status, which is potentially helpful for the non-invasive prediction of this marker. Furthermore, analyses of perfusion and diffusion MRI metrics combined with static parameters derived from PET with [^{18}F]FET ([^{18}F]FET-PET) or PET with [^{18}F]FDOPA ([^{18}F]FDOPA-PET), such as tumour-to-brain ratios and the biological tumour volume, showed predictive value

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in identifying the *IDH* mutational status (area under the curve >0·9).[19,20]

The role of amino acid PET for artificial intelligence (AI) and radiogenomics applications is being explored.[21,22] Studies using PET with [18F]FET, [18F]FDOPA, and [11C]MET have shown predictive value in identifying the *IDH* genotype,[23,24] 1p/19q co-deletion,[25] *O*-6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status,[26] and telomerase reverse transcriptase (*TERT*) promoter mutation status.[27]

In light of the phase 3 INDIGO trial,[28] PET imaging of therapeutically relevant targets (such as the mutant IDH1 and IDH2 enzymes) for novel anticancer agents in gliomas has gained considerable interest especially for response assessment. Consequently, efforts were initiated to develop selective PET tracers with high specificity for *IDH* mutations to improve the assessment of response to IDH inhibitors such as vorasidenib (Servier, Boston, MA, USA and Suresnes, France), since conventional MRI findings following these agents are frequently unchanged.[28] In 2024, successful labelling of the IDH inhibitor ivosidenib with the positron emitter 18F was reported.[29] Furthermore, the 18F tracer showed excellent metabolic stability in vivo. However, there was no significant difference in tracer uptake between IDH^{mut} and IDH^{WT} tumours in a preclinical mouse model.[29] Further research for PET ligands with high binding selectivity for IDH^{mut} gliomas is warranted.

Overall, although studies provide initial evidence for a potential role of amino acid PET alone and in combination with MRI for the non-invasive prediction of molecular parameters, the validity and generalisability of the results warrant further investigation.

Estimation of prognosis in patients with newly diagnosed, untreated gliomas

Static parameters derived from amino acid PET allow an estimation of prognosis in patients with newly diagnosed, untreated gliomas. The prognostic value of [11C]MET uptake intensity for progression-free survival and overall survival was reported in patients with IDH^{mut} gliomas.[14,30] In the preoperative setting, [18F]FDOPA-PET was used to identify a subgroup of patients at high risk of poor prognosis with gliomas (ie, a maximum tumour-to-brain ratio ≥1·7 combined with a contrast-enhancing volume >1 mL on MRI) who had a three-times shorter overall survival than patients with gliomas without these prognostic factors for worse outcomes.[31] Furthermore, the postoperative biological tumour volume of [18F]FET uptake before radiotherapy of glioblastomas has been reported to be a prognostic factor for progression-free survival and overall survival.[32] In particular, patients with a smaller biological tumour volume (threshold of <9·5 mL) had a significantly longer survival time.[32]

Parameters obtained from dynamic [18F]FET-PET acquisition (eg, time-to-peak values) identified prognostically relevant information (in terms of progression-free survival and overall survival) beyond molecular markers with high prognostic value (eg, *IDH* mutational status).[33,34] Moreover, in patients with CNS WHO grade 2 gliomas, dynamic [18F]FET parameters might help to identify gliomas at risk for less favourable outcomes.[35–37] Of note, these studies were performed before the release of the 2021 WHO classification. As a result, prognostication in such studies might have been imprecisely assessed. [18F]FET-PET radiomics is an emerging approach in the evaluation of amino acid radiotracer uptake distribution and heterogeneity, showing potential in obtaining prognostic information, and is under investigation.[21,22]

In summary, static and dynamic parameters obtained from amino acid PET provide valuable adjunctive information for the estimation of prognosis in patients with gliomas at the time of initial diagnosis and in the postoperative setting. Parameters such as high uptake intensity, large PET-avid volumes (ie, biological tumour volume), and short time-to-peak values obtained from amino acid PET are associated with poorer prognosis.

Delineation of tumour extent

General considerations

Accurate delineation of the glioblastoma extent is of utmost importance in prognosis assessment, surgical and radiotherapeutic planning, and follow-up monitoring. Conventional MRI allows the determination of the tumour only to a limited extent. In particular, the visualisation of the tumour boundaries within the oedema and non-enhancing glioma parts remains challenging. Emerging data suggest that this extent of spread beyond the enhancement, constituting the non-enhancing volume of glioblastomas, has substantial prognostic implications.[38,39] Notably, in over 70% of patients with newly diagnosed glioblastomas, [18F]FET-PET displayed larger tumour volumes than the enhancing volume observed on MRI.[32,40] These results were validated neuropathologically with PET-guided biopsies, showing increased [18F]FET uptake extending beyond the fluid-attenuated inversion recovery (FLAIR) hyperintensity.[41,42] Similar findings were obtained with PET either with [11C]MET ([11C]MET-PET)[14] or fluciclovine (fluciclovine-PET).[43]

Value for diagnostic procedures: biopsy guidance

The added value of integrating amino acid PET with MRI into stereotactic biopsy planning and intraoperative neuronavigation systems to define the extent of newly diagnosed gliomas and to better target the area of biopsy has been described previously.[6,44] Amino acid PET appears to add value in the assessment of potential tumour infiltration in and beyond the FLAIR abnormality,[41,42] and in identifying the most malignant tumour components, especially in non-enhancing gliomas.[45] More prospective studies using well defined and standardised annotation of samples, target imaging, and histomolecular characteristics are still warranted.[46]

Value for treatment planning: resection

Several studies have reported differences in the spatial distribution of amino acid PET tracer uptake and contrast enhancement, potentially modifying resection planning.[14,40–42] This approach might result in either an increase or decrease in the resected volume, defining a resection target that differs from contrast-enhanced MRI. Initial retrospective studies suggested that an absence of residual uptake on amino acid PET was associated with longer overall survival when compared with residual tracer uptake;[47] however, prospective controlled studies are needed to confirm this correlation. Similar findings were reported in a prospective [^{11}C]MET-PET study in patients with newly diagnosed glioblastomas.[48] In line with the concept of supramaximal resection,[38,39] resection of glioblastomas beyond the borders of the surgical target as defined by [^{11}C]MET-PET was also associated with improved overall survival.[49] In another study, [^{11}C]MET-PET identified the largest preoperative volume and showed the highest sensitivity (95%) for detecting residual tumour, outperforming the other modalities.[50]

In a subsequent study, [^{18}F]FET-PET detected larger tumour residual volumes than contrast-enhanced MRI, in early postoperative glioblastomas, with volumes above 4·3 mL associated with worse progression-free and overall survival.[51] Complete resection of 5-aminolevulinic acid fluorescent tissue led to lower metabolic tumour volumes and was linked to improved progression-free and overall survival, highlighting the prognostic value of postoperative [^{18}F]FET uptake for patient outcomes.

Value for treatment planning: target volume definition for radiotherapy

For many years, the standard imaging modality for radiotherapy target volume definition has been conventional MRI with T2-FLAIR and contrast-enhanced sequences. The accuracy of defining tumour volumes continues to improve, with improved biological tumour volume identification with amino acid PET tracers resulting in their increasing integration into radiotherapy planning in Europe,[4,52,53] and active investigation of this application of amino acid PET in the USA.[54–56]

In addition to neuropathological confirmation of tumour extent, clinical outcomes provide evidence for the value of defining and targeting biological tumour volume, with an increasing number of prospective clinical trials correlating, and even modifying, radiotherapy based on this knowledge.[4,52,53] However, to date, conclusive data indicating that this approach meaningfully improves overall survival are scarce, and several trials are attempting to fill this knowledge void. The optimal technique for defining biological tumour volume for radiotherapy planning is being investigated. There are various methods for biological tumour volume definition; regarding [^{18}F]FET-PET, the current guideline recommended a threshold of greater than 1·6–1·8 over the mean background activity, encompassing uninvolved grey and white matter.[2,3] Accordingly, in patients with newly diagnosed glioblastomas, the ongoing TROG 18.06–FIG trial uses a threshold of 1·6 for [^{18}F]FET-PET,[57] and the NOA-28 PRIDE trial uses a threshold of 1·8.[58] In studies using [^{18}F]FDOPA-PET for target volume definition in newly diagnosed glioblastomas, thresholds from 1·2 to 2·0 were applied for the lower dose volume, and for the boost volume a threshold of greater than 2·0 was used.[54] For gliomas at recurrence, an [^{18}F]FDOPA-PET threshold of greater than 1·5 has been used,[55] whereas the GLIAA-NOA 10 trial used a threshold of greater than 1·8 for [^{18}F]FET-PET.[59] The value of fluciclovine-PET for glioma delineation is being investigated.[60] Overall, although optimal thresholds for biological tumour volume definition remain under investigation, current evidence suggests they might vary depending on tracer type and normalisation approach. None of the described thresholds have been validated as a definitive standard for radiotherapy planning in prospective clinical trials.

In a single-arm, phase 2 trial including patients with newly diagnosed glioblastomas, dose-escalated [^{18}F]FDOPA-PET-based irradiation showed better progression-free survival at 6 months and overall survival, particularly in unmethylated glioblastomas, compared with institutional controls (35·5 months *vs* 23·3 months; hazard ratio 0·57, 95% CI 0·33–1·01, p=0·049).[54] Another phase 2 trial in patients with recurrent gliomas reported that when [^{18}F]FDOPA-PET was used for target volume definition, the target volumes increased by 43% compared with MRI-based volumes and resulted in progression-free survival of 50% at 6 months.[55] By contrast, the GLIAA-NOA 10 trial randomly assigned 200 patients with recurrent glioblastomas with contrast-enhanced MRI-based versus [^{18}F]FET-PET-based contours for irradiation (39 Gy in 13 fractions), and did not show any improvement in progression-free survival or overall survival with [^{18}F]FET-PET-based tumour volumes.[61] However, the results of the GLIAA-NOA 10 trial need to be interpreted with caution, as the absence of outcome improvement does not necessarily relate to poor performance of amino acid PET, since PET was used alone, not used in combination with MRI, and since the efficacy of re-irradiation for overall survival has not been shown.[62] In summary, amino acid PET might provide added value for local treatment planning (particularly surgery and radiotherapy) with a performance translating into clinical benefit, especially for patients with glioblastomas. Prospective, well designed studies are warranted to confirm the data reported to date.

Differentiation of glioma relapse from treatment-related changes

Over the past two decades, numerous studies have used amino acid PET to differentiate glioma relapse from treatment-related changes, mostly in patients with glioblastomas. [^{18}F]FET and [^{11}C]MET are the most frequently studied PET probes, and several studies have

shown high accuracy (ranging from 80% to 90%) in identifying early and late treatment-related changes.[63–70] Although less studied, both [18F]FDOPA-PET and fluciclovine-PET have also been shown to differentiate glioma relapse from treatment-related changes with similarly high accuracy to that of [18F]FET and [11C]MET.[71,72] Dynamic [18F]FET-PET acquisition might further improve diagnostic accuracy,[57,64] but this technique requires a longer dynamic acquisition time (40–50 min) compared to static PET acquisition, which might not be feasible in some routine clinical settings.[5]

Overall, amino acid PET has been useful in differentiating glioma relapse from treatment-related changes and might be a valuable adjunct in clinical decision making where available, but further large-scale validation studies are needed. Existing literature shows consistently high diagnostic accuracy. Although [18F]FET is the most widely used radiolabelled amino acid, other amino acid PET tracers, such as [18F]FDOPA, [11C]MET, and fluciclovine, seem to be comparable for this indication. [18F]FDG-PET is of little value in differentiating glioma relapse from treatment-related changes.

Evaluation of treatment response

General considerations

In patients with glioma, increase in contrast enhancement extent on conventional MRI is typically used as an indicator of response or treatment failure.[73,74] In addition, an increase in T2-FLAIR hyperintensity is frequently used for diagnosing non-enhancing tumour progression.[73,74] Nevertheless, these signal changes are non-specific and might be related to oedema, radiation-induced effects, demyelination, cerebral ischaemia, or inflammation, hampering the distinction from non-enhancing tumour.[5,75] Consequently, alternative diagnostic methods, such as amino acid PET, have been evaluated to improve treatment response assessment.

In addition, the PET RANO 1.0 criteria published in 2024 provide a series of specific recommendations on imaging technologies, tracer use, rater qualification, imaging schedules, and, most importantly, predefined thresholds of changes in PET parameters and their interpretation at baseline assessment and follow-up for patients with diffuse gliomas.[2] These criteria define a conceptual framework aiming to facilitate the integration of amino acid PET into clinical trials for patients with this subgroup of brain tumours, and eventually into routine clinical practice.

Fractionated chemoradiotherapy

In patients with newly diagnosed glioblastomas, prospective studies have assessed the predictive value of early [18F]FET uptake changes 6–8 weeks after postoperative radiotherapy with concomitant temozolomide relative to the baseline scan.[76,77] At follow-up, patients who had a response to [18F]FET-PET, with a decrease of metabolic activity as assessed by tumour-to-brain ratios, had significantly longer overall survival than patients with stable or increasing tracer uptake.

Alkylating chemotherapy

Similar findings to those for fractionated chemoradiotherapy were reported in patients with newly diagnosed glioblastomas early after initiating adjuvant temozolomide chemotherapy with [18F]FET-PET (ie, after two cycles).[78] In contrast to MRI changes consistent with partial response or stable disease according to the RANO criteria,[73,74] only patients for whom a metabolic response was observed on [18F]FET-PET had a significantly longer overall survival. In patients with glioblastoma relapse undergoing lomustine-based chemotherapy, the detection of lesions on follow-up [18F]FET-PET scans spatially located remotely to the tumour at baseline seems to be helpful to identify patients with non-response.[79]

[18F]FET-PET has also been used to assess temozolomide effects in patients with non-enhancing grade 2 gliomas characterised as per the 2007 WHO classification. In patients with a metabolic response, [18F]FET-PET tumour volume reductions after treatment initiation were observed earlier than volume reductions on FLAIR MRI.[80] These findings were confirmed by subsequent [18F]FET-PET studies with a larger number of patients.[81,82]

With [11C]MET-PET, a reliable response assessment to temozolomide chemotherapy and regimens including nitrosoureas was reported, mainly in patients with glioblastomas at relapse.[83–85] Patients who had a response to [11C]MET-PET had a significantly improved outcome compared with patients who did not have a metabolic response.[83]

Antiangiogenic agents

In heavily pretreated patients with glioma relapse, initial studies suggested that [18F]FET-PET and [18F]FDOPA-PET are of value for both identifying patients with response and for diagnosing pseudoresponse following bevacizumab.[86–88] Moreover, in these studies, [18F]FET-PET and [18F]FDOPA-PET also predicted a favourable outcome in patients with gliomas who responded to bevacizumab. A prospective study found that in patients with first glioblastoma progression, [18F]FET-PET identifed patients who had a metabolic response to bevacizumab plus lomustine early after treatment initiation. Here, MRI changes according to the RANO criteria[73,74] were not predictive of a favourable outcome, whereas changes in [18F]FET-PET parameters were associated with an overall survival of more than 9 months.[89]

Other systemic therapy options

Another systemic therapy option with potential efficacy in patients with glioblastoma relapse is the multikinase inhibitor regorafenib, which is characterised by pronounced antiangiogenic activity. Similar to chemoradiotherapy with temozolomide, equivocal MRI findings

were also reported in patients with glioma relapse undergoing regorafenib.[90,91] In addition, initial results suggest that [18F]FET-PET and [18F]FDOPA-PET are of value in the assessment of response to regorafenib.[90,92,93] Nevertheless, interpretation of these results should be considered with caution since the regorafenib group in the GBM AGILE trial was halted after an interim analysis showing little potential for significant improvement in overall survival.[94]

A 2024 case series showed the value of serial [18F]FET-PET in assessing response to inhibitors of mutant IDH, such as vorasidenib in non-enhancing WHO grade 2 or 3 gliomas.[95] Within 5–9 weeks of treatment, three (60%) of five patients showed metabolic response per PET RANO 1.0 criteria, whereas T2-FLAIR signals remained unchanged. This result highlights the potential of this technique in decision making, although further trials are needed to confirm its effect on outcomes.

Despite encouraging initial results in 2012 and subsequent years, the evaluation of amino acid PET parameter changes for response assessment had not been standardised at that time, resulting in the use of different thresholds in those referenced studies. Therefore, a corresponding set of criteria for amino acid PET-based response assessment—the PET RANO criteria 1.0—were defined in 2024. Both retrospective and prospective evaluation of these criteria is warranted.

Value of amino acid PET in paediatric patients with glioma

Considering the little specificity of conventional MRI for neoplastic tissue, [18F]FET-PET and [11C]MET-PET have increasingly been used to metabolically assess CNS tumours in the paediatric population, predominantly gliomas.[96–101] The Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group has recommended the use of amino acid PET rather than [18F]FDG-PET, as amino acid PET provides a higher specificity for neoplastic tissue.[102]

In paediatric patients with CNS tumours, amino acid PET imaging parameters are suggested to provide valuable additional information for clinical decision making, especially for the differential diagnosis of newly diagnosed brain lesions indicative of glioma and in the differentiation of tumour relapse from treatment-related changes following local and systemic treatment options. In a subset of studies, parameters obtained from dynamic [18F]FET-PET acquisition might add further valuable diagnostic information.[96]

Although less studied, [18F]FDOPA-PET has been shown to provide valuable additional information for the management of paediatric patients with brain tumours. Such information can be used in molecular alteration prediction, outcome prediction, and tumour extent delineation.[103–105]

There is no high-level evidence for the use of amino acid PET in each specific type of paediatric brain cancer. There is evidence for the role of amino acid PET in predicting the presence of a histone H3 Lys27Met mutation in diffuse midline gliomas.[103] In paediatric low-grade gliomas, parameters derived from [11C]MET-PET might identify *BRAF*^{V600E} (ie, Val600Glu) mutant tumours.[101]

To enable the simultaneous acquisition of both amino acid PET and MRI in a single session, a hybrid PET-MR scanner (if available) should be used in paediatric patients with brain tumours. In addition to providing multiparametric imaging information, the use of this technology minimises patient discomfort, reduces scanning time, and avoids repeated use of anaesthesia.

Importantly, the clinical experience from several thousand [18F]FET-PET investigations in adults showed no side-effects, which supports the safety profile of this imaging agent and its potential for use in paediatric patients. Therefore, the potential benefits of accurate disease assessment are considered to outweigh the risks associated with the investigation (ie, radiation exposure).[96]

Overall, at a lower level of evidence, the available literature suggests that radiolabelled amino acids might have similar use in paediatric and adult patients. There is a crucial need for further evaluation of the available diagnostic indications for amino acid PET in paediatric neuro-oncology.

Recommendations

General recommendations based on the levels of evidence and strength of recommendations for the clinical use of amino acid PET in patients with gliomas are summarised in tables 1 and 2. Figure 2 provides recommendations for priority (ie, high or optional) and timing of the various amino acid PET indications over the course of disease.

Limitations

As of 2024, no radiolabelled amino acids have been approved by the US Food and Drug Administration (FDA) for diagnostic brain tumour imaging in the USA, limiting amino acid PET research to a few academic centres and restricting its use in routine clinical care. Reimbursement is inconsistent, with insurance often not covering costs and pre-authorisation presenting barriers. Some PET studies rely on outdated WHO classifications of gliomas,[10,12,35–37] and despite growing evidence since 2016 (table 1), class 1 evidence remains scarce. However, after the FDA's approval of [18F]FET as a medical drug, this agent could become more widely available in the USA, potentially enabling randomised controlled trials involving amino acid PET.

In Europe, [18F]FET-PET or [18F]FDOPA-PET for patients with gliomas are approved in Switzerland, France, and Poland. Reimbursement across Europe varies, although studies showing clinical and economic benefits potentially support broader coverage, as will be discussed later. [11C]MET-PET has logistical challenges due to the 11C labelling, as 11C has a half-life of 20 min, requiring a cyclotron on-site.

When interpreting PET images, some limitations need to be considered. [18F]FDG-PET is generally discouraged for brain tumours due to high glucose uptake in healthy brain tissue, resulting in poor lesion-to-background contrast. Radiolabelled amino acids are preferred for PET imaging and are increasingly used in clinical practice and trials. Limitations of amino acid PET tracers include non-specific uptake in non-neoplastic lesions, absence of uptake in some non-enhancing gliomas (~30%) and *IDH*^{WT} gliomas (<10%, often molecular glioblastomas), increased uptake in non-glial tumours (eg, lymphomas), and challenges in interpreting photopenic defects in gliomas. A 2024 report of the PET RANO group discussed these limitations in more detail.[5]

Outlook

In the future, imaging of gliomas will be expanded and supplemented by PET. In addition, further validation of PET-derived information by use of both standardised, image-guided biopsies and standardised clinical outcome measures will also uncover and reduce diagnostic pitfalls.[5,46] Novel and more specific ligands will be helpful to further analyse biological properties in glial tumours, and PET imaging might gain more importance in the follow-up of targeted therapies (eg, in the response assessment after IDH inhibition).[1]

In addition to typical clinical endpoints of PET studies, such as diagnostic performance, research into the cost-effectiveness of amino acid PET is ongoing, with model-based approaches being used to evaluate the number needed to diagnose to avoid false diagnoses. The use of [18F]FET-PET, in particular, is well justified, due to its clinical accuracy and cost-effectiveness.[106–108] The expense of [18F]FET-PET is balanced by its clinical benefits, as it enables the discontinuation of ineffective and costly anticancer agents.

To date, most publications regarding PET imaging in gliomas refer to adult patients (aged >18 years). Nevertheless, over the past decade, reports have explored the potential value of amino acid PET imaging of gliomas in the paediatric population. Most likely, the clinical value of this imaging technique for children with CNS tumours will be similar to that of adults. Although PET imaging of the spine with standard PET-CT scanners is scarce, initial results in the paediatric, adolescent, and young adult population are promising.[99,109] In addition, the advent of long-axial field-of-view PET-CT scanners allows increased body coverage due to their extended field of view, with high-resolution imaging of the entire neuraxis, which might considerably improve imaging of spinal gliomas in the future.[1,110] Another advantage of this technology is the higher image quality, which results in substantially improved lesion detection and a notably shorter acquisition time.

Since 2024, the integration of AI and radiomics in neuro-oncology has opened promising avenues, including for PET imaging.[21,22] For AI to be effective, it must have high accuracy and reliability, which rely heavily on large, multicentre datasets to develop and validate robust models. However, these requirements present a challenge in brain tumours due to restricted patient numbers and available datasets. Despite this challenge, the volume and complexity of data across the disease course—especially from multimodal neuroimaging, including PET—are expanding. Overall,

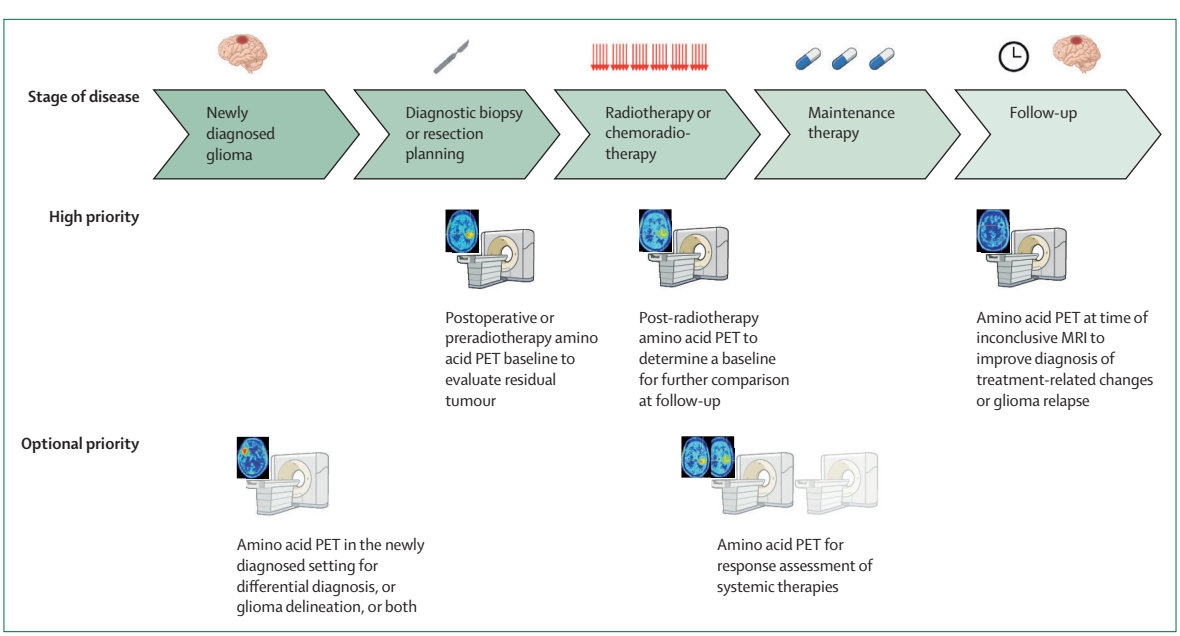

Figure 2: **Recommendations for the prioritisation of amino acid PET indications, categorised as high or optional priority, along with their optimal timing throughout the course of disease**

Search strategy and selection criteria

The information retrieved from a PubMed search of literature published between Jan 1, 2004 and Dec 31, 2024 with a combination of the search terms "glioma", "glioblastoma", "astrocytoma", "oligodendroglioma", "brain tumor", "PET", "FDG", "FET", "MET", "FDOPA", "fluciclovine", "FACBC", or "Axumin", and combinations thereof, along with information from articles identified through searches of the authors' own files, was evaluated by the working group with respect to the level of evidence and the grade of validation of the PET studies examined and were included based on originality and relevance to the scope of this Policy Review. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the scope of this Policy Review.

AI and radiomics hold substantial potential to improve diagnostic precision and personalised treatment in neuro-oncology.

Another important future prospect is theranostics. With the combination of diagnostic molecular imaging and targeted radionuclide therapy, exciting developments in the treatment of gliomas, both in newly diagnosed settings and at relapse, will be expected. Prospective clinical trials are underway.[111]

Contributors

NG and NLA contributed to the conceptualisation, methods, project administration, visualisation, and writing of the original draft of this Policy Review. NG, MA, RFB, WGB, JI, DRJ, TJK, MMK, PL, MJM, GM, MMü, AN, JDP, RR, MS, NT, SEMVvZ, MCV, J-MW, J-CT, and NLA contributed to writing of one or more manuscipt subsections. MvdB, SMC, K-JL, IL, JM, MMe, MP, SCS, RS, MV, MW, PYW, and J-CT contributed to the methods, review, and editing of this Policy Review. All authors approved the final version of this Policy Review.

Declaration of interests

NG: honoraria for lectures from Blue Earth Diagnostics, for advisory board participation from Telix Pharmaceuticals and Servier, and for consultancy services from Telix Pharmaceuticals. PL: honoraria for lectures from Blue Earth Diagnostics and for advisory board participation from Servier. MA: research funding from Blue Earth Diagnostics, Cellectar, and US National Institutes of Health and National Cancer Institute (R01CA275767 and R21CA259964). RFB: honoraria from Telix Pharmaceuticals for consultancy services. WGB: honoraria for consultation or advisory board participation from GE Healthcare and Miltenyi Biomedicine (paid to institution). Research funding from Wayshine Biopharm. JI: research funding from GE Healthcare, Curium Pharma, and Novartis Pharmaceuticals (funds paid to institution). Travel supoport from Siemens Healthineers. DRJ: honoraria for consultation or advisory board participation from Novartis, Telix Pharmaceuticals, and Cellectar Pharmaceuticals. 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