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Evidence-Based Medicine GUIDELINE

The Innovation Oncology

Practice guidelines for amino acid PET in gliomas

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The average annual age-adjusted incidence rate (AAAIR) of all central nervous system (CNS) tumors was 25.34 per 100,000 population. Gliomas accounted for 22.9% of all CNS tumors.

Magnetic resonance imaging (MRI) remains the reference standard for diagnosis and treatment of gliomas, however, it is insufficient for accurate biological characterization. Positron-emission tomography (PET) provides quantitative data on tumor metabolism and proliferation, thereby complementing MRI.[1] In 2016, the first clinical guideline for PET imaging in glioma patients was published, highlighting the clinical relevance of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) and amino acid PET.[2] [^{18}F]FDG PET is limited by high physiological cortical glucose metabolism, which reduces tumor-to-background contrast, whereas radiolabeled amino acid tracers provide superior image contrast due to low uptake in normal brain tissue and high uptake in gliomas. This guideline, therefore, focuses on the clinical applications of amino acid PET in glioma management, outlining its key indications and providing evidence-based recommendations for use.

PRINCIPLES AND RADIOTRACERS

The most widely used amino acid PET tracers include [^{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).[3,4]

Among these, [^{11}C]MET was initially the most widely used amino acid tracer, but its 20-minute half-life requires on-site cyclotron production, limiting wider clinical use. In contrast, [^{18}F]FET permits centralized distribution with longer half-life (110 minutes), [^{18}F]FDOPA is also increasingly used in glioma imaging.

SCOPE, INDICATIONS, AND RECOMMENDATIONS

This multidisciplinary guideline is intended for patients with suspected or confirmed gliomas. Amino acid PET is not routinely recommended for pregnant women, patients unable to cooperate during imaging, or those with severe metabolic disorders.[1]

CLINICAL INDICATIONS AND LEVELS OF EVIDENCE

The main clinical indications of amino acid PET for gliomas contain tumor diagnosis, treatment planning and response assessment, and prognosis assessment. Levels 1-4 of evidence according to the Oxford Center for Evidence-Based Medicine are included as bases for the indications (Figure 1).

PRECAUTIONS FOR THE EXAMINATION

Patients should fast for at least 4 hours prior to the scan. Adequate hydration is recommended, while strenuous physical activity, consumption of high-sugar, alcoholic, or caffeinated drinks should be avoided. Diabetic patients should consult their physician in advance to adjust insulin regimens. Pregnant women should avoid undergoing PET imaging.[5]

CLINICAL INDICATIONS AND CORRESPONDING THRESHOLDS

Diagnosis of gliomas

Histopathological confirmation remains the gold standard for the diagnosis of gliomas. Regarding imaging-based evaluation, amino acid PET provides valuable complementary information for newly diagnosed gliomas (differentiation of neoplastic from non-neoplastic lesions) and recurrent gliomas, particularly when MRI findings are inconclusive.

For differentiating neoplastic from non-neoplastic lesions, both [^{18}F]FET PET and [^{11}C]MET PET have demonstrated diagnostic performance when interpreted alongside clinical and radiological data. In [^{18}F]FET PET, the max tumor-to-background ratio (TBRmax) ≥ 2.5 have diagnostic value for differentiating neoplastic from non-neoplastic lesions (sensitivity, 57%; specificity, 92%). In addition, [^{11}C]MET PET could also differentiate low grade glioma (LGG) from non-neoplastic lesions based on TBRmax (LGG, 1.7 ± 0.6; non-neoplastic, 1.3 ± 0.3). However, mild tracer uptake may occur in non-neoplastic lesions, necessitating strict adherence to defined thresholds.

For differentiating recurrent gliomas from treatment-related changes, [^{18}F]FET PET has shown high accuracy of 93% (sensitivity, 93%; specificity, 100%) with the mean tumor-to-background ratio (TBRmean) ≥ 2.0 or time to peak (TTP) ≤ 45 minutes.

Non-invasive glioma grading

[^{18}F]FET, and [^{11}C]MET PET could provide valuable information for glioma grading.

In [^{18}F]FET PET, optimal differentiation between LGG and high grade glioma (HGG) is achieved with a TBRmax threshold of 2.5 (sensitivity, 80%; specificity, 65%), with higher uptake values (TBRmax > 2.5) favoring HGG. [^{11}C]MET PET could effectively differentiate LGG from HGG using TBRmax (LGG, 1.7 ± 0.6; HGG, 3.0 ± 0.3).

Tumor margin delineation

[^{18}F]FET and [^{11}C]MET PET can assist accurate delineation of gliomas, which is important in surgical and radiotherapeutic planning.

[^{18}F]FET PET-defined tumor volumes regularly exceed those delineated on contrast-enhanced MRI. Histopathological analyses have confirmed the presence of tumor cells within these extended regions, supporting the superior accuracy of [^{18}F]FET PET in delineating tumor boundaries. Supratotal resection guided by [^{11}C]MET PET can improve overall survival (OS) of patients with isocitrate dehydrogenase 1 (IDH1)-wildtype glioblastoma.

Treatment response assessment

The amino acid tracers used for treatment response assessment are [^{18}F]FET and [^{18}F]FDOPA.

The 2024 PET Response Assessment in Neuro-Oncology (RANO) 1.0 criteria suggests that treatment response assessment should be based on PET-identified measurable disease and comparison with tumor measurements

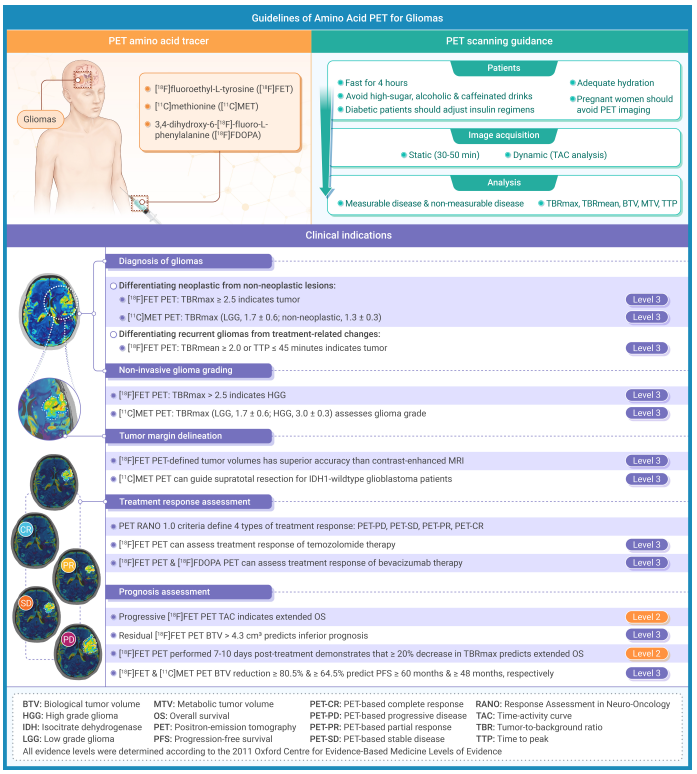

Figure 1. Guidelines of amino acid PET for gliomas.

obtained at baseline. Measurable disease is defined as a PET-positive uptake volume exceeding 0.5 mL. Baseline PET should be performed 4-6 weeks after surgery and within 14 days prior to the initiation of other therapies. Treatment response assessment includes four types: PET-based progressive disease (PET-PD), PET-based partial response (PET-PR), PET-based complete response (PET-CR) and PET-based stable disease (PET-SD).

1. PET-PD is determined by at least one of the following criteria:

- ≥ 30% increase in TBRmax or ≥ 10% increase in TBRmean in any target lesion.
- ≥ 40% increase in PET-positive volume.
- Appearance of a new measurable PET-positive lesion or lesions.

2. PET-PR is determined by at least one of the following criteria, without fulfilling the conditions for PET-PD, PET-SD, PET-CR:

- ≥ 30% decrease in TBRmax or ≥ 10% decrease in TBRmean in any target lesion.
- ≥ 40% decrease in PET-positive volume.
- Complete response in all target lesions but one.

3. PET-CR is defined as the complete disappearance of PET-positive lesions.

4. PET-SD is diagnosed when none of the criteria for PET-PD, PET-PR, PET-CR are met.

[^{18}F]FET PET can assess treatment response of temozolomide therapy in gliomas by measuring metabolic tumor volume (MTV) and TBRmax changes, starting from the second treatment cycle. Therefore, [^{18}F]FET PET provides earlier assessment than MRI. TBRmax can also be used to identify pseudoprogression, which usually occurs within the initial 12 weeks of treatment.

For HGG patients receiving bevacizumab therapy, [^{18}F]FET and [^{18}F]FDOPA PET can assess treatment response, to which PET RANO 1.0 criteria are generally inapplicable. In [^{18}F]FET PET, a decrease in TBRmean > 17% or TBRmax > 27% differentiates responders from non-responders (sensitivity, 92%; specificity, 63%); an MTV < 5 mL has the same effect. In recurrent tumors, [^{18}F]FET PET detects treatment failure 10.5 weeks earlier than MRI. In [^{18}F]FDOPA PET, treatment success is determined by ≥ 35% MTV reduction at 2 weeks post-treatment or ≥ 67% reduction at 6 weeks post-treatment.

Prognosis assessment

Amino acid PET could complement MRI by providing additional prognostic information in glioma management.

For untreated patients, [^{18}F]FET PET time-activity curve (TAC) allows qualitative classification (progressive, mixed, or regressive) of prognosis; a progressive TAC is associated with patients' extended OS. [^{18}F]FDOPA PET parameters play a valuable role in prognostic assessment, as a TBRmax > 1.7 correlates with a reduced OS. In pediatric diffuse intrinsic pontine glioma, [^{11}C]MET PET biological target volume (BTV) < 12.12 cm^3 can independently predict patients' progression-free survival (PFS) and OS.

After surgical resection of World Health Organization (WHO) grade III-IV gliomas, residual [^{18}F]FET PET BTV < 1 cm^3 predicts extended OS (19.3 vs. 13.7 months). Among patients who have undergone gross total resection, residual [^{18}F]FET PET BTV > 4.3 cm^3 predicts inferior prognosis. For patients who have received surgery and temozolomide-based chemoradiotherapy, [^{18}F]FET PET performed 7-10 days post-treatment demonstrates that a ≥ 20% decrease in TBRmax predicts an extended OS (sensitivity, 83%), while a ≥ 5% decrease in TBRmean predicts an extended PFS (10.3 vs. 5.1 months).

For WHO grade II recurrent gliomas with non-enhanced MRI, both [^{18}F]FET and [^{11}C]MET PET show that BTV reductions of ≥ 80.5% and ≥ 64.5% predict PFS ≥ 60 months and ≥ 48 months, respectively.

CONCLUSION

Growing evidence has supported amino acid PET imaging as a promising tool to provide information about glioma diagnosis, treatment and prognosis. However, there is currently a lack of high-level evidence regarding the use of amino acid PET. Thus, more well-designed studies with Level 1/2 evidence should be conducted to establish a gold standard of amino acid PET in clinic practice.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.