Amino Acid PET Imaging:

Transforming the Management of Gliomas

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Highlights

- Accurate neuroimaging is critical for glioma management See more →
- MRI has several limitations in characterization of gliomas that can lead to under- or over-treatment of patients due to uncertainty and inconclusive results
  - Incomplete detection of tumor extent can lead to under-treatment See more →
  - Inability to differentiate tumor progression from treatment-related changes (TRC) results in uncertainty and can lead to under- or over-treatment See more →
  - Detection of pseudoresponse during anti-angiogenic therapy can lead to under-treatment See more →
  - The emotional toll of inconclusive imaging results impacts patients, their caretakers, and physicians alike See more →
- PET imaging in glioma management has gained considerable interest due to the extensive utilities of amino acid radiotracers See more →
  - Not all amino acid PET radiotracers are the same See more →
- Amino acid PET radiotracers in clinical practice have already been recommended by society guidelines See more →
- ^{18}F-FET is the most studied and commonly used amino acid PET radiotracer with proven high diagnostic performance and accuracy in a broad range of clinical applications:
  - Differentiation of tumor progression or recurrence from TRC See more →
  - Monitoring treatment response See more →
  - Delineation of tumor extent for treatment planning See more →
  - Differential diagnosis, tumor grading, and prognostication at initial diagnosis See more →
- ^{18}F-FET PET imaging informs physicians to make confident clinical decisions and help resolve clinical dilemmas See more →

Definitions

Glioma is a central nervous system (CNS) neoplasm that originates from glial cells.[1]

Glioblastoma is the highest-grade (grade 4) and the most common glioma that accounts for 48.6% of malignant CNS tumors.[2] It is one of the most aggressive malignancies and a leading cause of adult cancer mortality.[2,3]

Magnetic resonance imaging (MRI) is the gold standard in glioma imaging.[4,5] MRI is acquried before and after an intravenous (IV) injection of a gadolinium-based contrast agent, with areas of contrast enhancement (brightness) indicating sites of blood-brain barrier (BBB) disruption and vascular leakage caused by the tumor.[5]

Amino acid positron emission tomography (PET) radiotracers emerged as a reliable imaging modality primarily due to their high uptake in gliomas and low uptake in normal brain tissue.[4-6] The most commonly studied amino acid radiotracers are[3,5,7]:

- O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET)
- 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (^{18}F-FDOPA)
- [^{11}C]-methyl-L-methionine (^{11}C-MET)

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Gliomas and neuroimaging

Approximately 80,000 primary brain tumors are newly diagnosed each year in the United States. About 20,000 of those (~25%) are gliomas and about 12,000 (~15%) of those are glioblastoma, which is the highest grade (grade 4) and most aggressive form of glioma.[1] Only <5% of patients with glioblastoma survive 5 years following diagnosis.[8] Patients with glioblastoma who are treated with maximal safe tumor resection, radiochemotherapy, and adjuvant chemotherapy have a median overall survival of ~15 months.[3]

Accurate neuroimaging plays a critical role in the management of all gliomas.[3,6] Contrast-enhanced magnetic resonance imaging (MRI) is the primary imaging modality for patients with glioma along the disease journey, including initial diagnosis, presurgical planning, evaluation of residual tumor right after surgery, planning for radiotherapy , and monitoring during chemotherapy, as well as detection and definition of disease progression.[3] However, MRI can be unreliable as a surrogate for tumor size or growth as contrast-enhancement nonspecifically reflects vascular pathology and permeability of the contrast agent across a disrupted blood-tumor barrier.[3]

Limitations of glioma imaging with MRI

Incomplete detection of tumor extent

MRI can underestimate tumor burden in areas of the tumor that lack vascular pathology because it only detects sites of blood-brain barrier (BBB) disruption and vascular leakage.[5] Progression of glioma is almost inevitable and tumor cells can infiltrate beyond the contrast-enhancing component, which makes up the non-contrast-enhancing tumor.[9] Non-contrast-enhancing tumor also has high malignancy potential and greater residual non-contrast-enhancing tumor is associated with poor prognosis.[9] Therefore, inaccurate delineation of the tumor volume can lead to under-treatment during surgical resection and radiotherapy, contributing to poor clinical prognoses and recurrent tumors.[5]

Contrast enhancement on MRI nonspecifically reflects vascular pathology, and thus, it may[3,5]:

- underestimate tumor burden due to its inability to detect non-contrast-enhancing tumor, leading to under-treatment
- falsely detect treatment-related changes as tumor progression, which results in uncertainty and may lead to over-treatment

Inability to differentiate tumor progression or recurrence from treatment-related changes (TRC)

Treatments of glioma, such as radiotherapy, chemotherapy, corticosteroids, antiangiogenic and immunotherapy agents, also affect vascular permeability of tumors and MRI detects these changes

potentially as progression or recurrence.[3] Therefore, the inability of MRI to differentiate between TRC and true tumor progression or recurrence may also result in under- or over-treatment.[4,5,7]

Common scenarios observed by MRI attributed to TRC, but mimicking tumor progression are[4,5,7]:

- Pseudoprogression (PsP), observed in ~30% of cases, is an acute response that manifests within 3 to 6 months after treatment due to tissue inflammation resulting in increased blood vessel permeability
- Radiation necrosis, observed in ~24% of cases, is a delayed effect of radiation therapy due to the damage to the vascular and glial cells leading to cell death

Detection of pseudoresponse

Pseudoresponse is the perceived reduction in the size of lesions by MRI during anti-angiogenic treatment due to restoration of the BBB and reduced vascular permeability rather than an actual impact on the tumor size.[4,10,11] This pseudoresponse adds ambiguity to MRI interpretation and may lead to under-treatment.[12]

The emotional toll of inconclusive imaging results

MRI signal changes may be related not only to treatment-related changes due to radiotherapy or chemoradiation with alkylating agents, but also to infection or neuroinflammation, ischemia, and demyelination.[13] All these changes can be difficult to distinguish from tumor recurrence and require repeat MRIs, resulting in uncertainty of clinical decisions that can last for several months.[13,14] This uncertainty may result in further distress and impacts everyone living with and managing glioma.[14,15] Importantly, it has a substantial emotional toll: patients and their loved ones experience extreme stress and worry as they wait for the results, while the physicians feel disappointed and stressed for not having clear answers or a plan of action.[15]

Amino acid PET, specifically ^{18}F-FET PET, is widely used to complement even advanced MRI methods. This underscores the value of amino acid PET beyond these supplementary MRI techniques.[4,7]

PET imaging in glioma management

PET imaging can guide clinical decision making by providing molecular, functional, and metabolic information and complement the morphological data.[16,17] While ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET is extensively used in imaging of multiple tumor types, it has several limitations in imaging of brain tumors due to high glucose metabolism in normal brain tissue, leading to a high background signal and a decreased tumor-to-background ratio.[5,6,17] Additionally, ^{18}F-FDG PET is fraught with challenges similar to that of MRI in the differentiation of tumor recurrence from TRC due to the elevated glucose metabolism at sites of inflammation, such as those caused by radiation.[5]

Amino acid PET radiotracers have been developed to bridge the gap in the management of gliomas and have primarily been used in Europe in diagnosis, biopsy, and resection as well as radiotherapy planning, treatment monitoring, and response assessment.[3-5,16,17]

Amino acid PET radiotracers

Amino acid PET radiotracers are transported into the tumor cells via amino acid transport systems, most commonly through the L amino acid transport (LAT1 and LAT2).[5,6] LAT1 has increased expression in gliomas, making it a valuable target for PET imaging as well as treatment.[5,6,17-19] LAT1 is also abundantly expressed both on the luminal and abluminal membrane side of the capillary endothelial cells that make up the BBB so it shuttles amino acid radiotracers across an intact BBB.[19] These radiotracers' ability to cross the BBB and their high tumor-to-brain uptake allow for improved accuracy in visualization of tumor extent with amino acid PET imaging.[5,6,17]

Not all amino acid radiotracers are the same.[4,5,7,18,20]

Three of the most commonly used amino acid radiotracers that are transported via LAT1 are ^{11}C-MET, ^{18}F-FDOPA, and ^{18}F-FET.[3,5,7] Another amino acid tracer that has more recently been studied in imaging of brain metastases is anti-1-amino-3-^{18}F-fuorocyclobutane-1-carboxylic acid (^{18}F-FACBC), also known as ^{18}F-fluciclovine, and it is primarily transported via alanine-cysteine-serine transporter (ASCT2).[5,20] Because ASCT2 is only located at the abluminal side of the BBB facing the brain, it cannot shuttle its substrates from the plasma across an intact BBB.[21] In support of this, a recent study revealed that higher uptake of ^{18}F-fluciclovine was associated with tumors that have BBB disruption. Therefore, tumors with an intact BBB may be difficult to detect with ^{18}F-fluciclovine PET imaging.[20]

Among the amino acid PET radiotracers, ^{18}F-FET is the most studied and validated across various clinical applications for gliomas.[3-5,7,17] The longer half-life of ^{18}F (110 min) lends itself to logistical advantages over ^{11}C (half-life: 20 min). ^{18}F-FET has become the most widely used while ^{11}C-MET requires an on-site cyclotron and immediate imaging of ^{11}C.[4,7,18] Furthermore, ^{18}F-DOPA use has been limited due to its high uptake in the striatum leading to a high background and a poor signal-to-noise ratio.[4]

^{18}F-FET is the most validated amino acid PET radiotracer in a broad range of clinical applications.[3,4,7,17]

Tumors with an intact BBB may be difficult to detect with ^{18}F-fluciclovine PET.[20]

^{11}C-MET has feasibility challenges with a short half-life and ^{18}F-DOPA is limited with a high background in the striatum.[4,7,18]

Amino acid PET imaging in clinical practice

Utilization of PET imaging with amino acid radiotracers has been widely recognized and recommended by professional medical organizations.[3,16,17] In 2019, joint EANM/EANO/RANO practice guidelines and SNMMI procedure standards recommended use of PET imaging with amino acid radiotracers across several clinical applications in glioma management (Figure 1).[3]

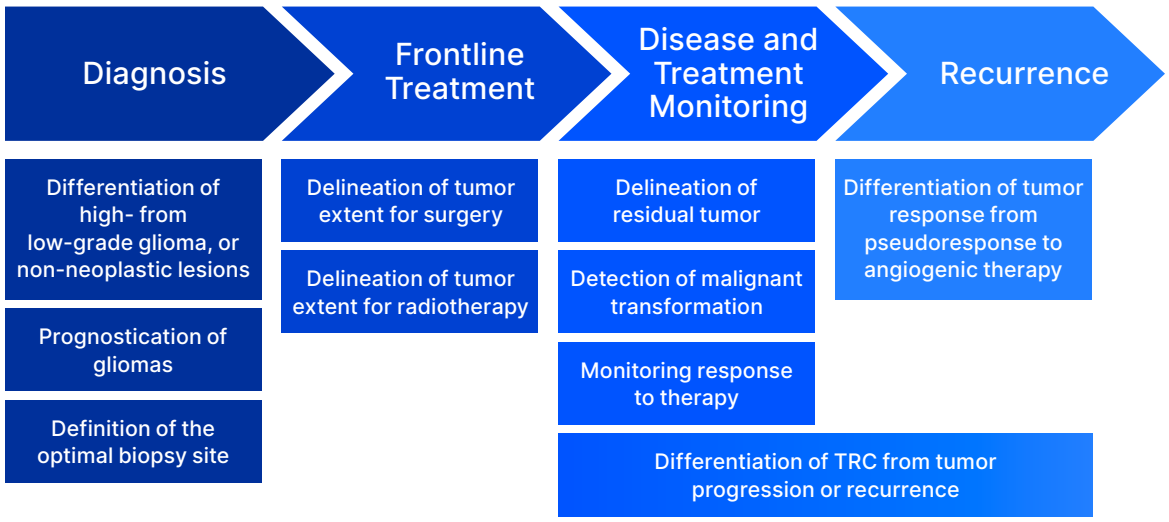


Figure 1: Key milestones in the clinical journey of patients with glioma and various applications of amino acid PET imaging recommended by the joint EANM/EANO/RANO practice guidelines and SNMMI procedure standards.[3]

These recommendations provided extensive information on amino acid PET imaging from radiopharmaceutical preparation to image acquisition and interpretation, including threshold values for PET parameters in various clinical applications such as: biological tumor volume (BTV), static (mean and maximum tumor to background ratios, TBR) and dynamic (time activity curves and time to peak, TTP) PET parameters.[3]

Recently in 2024, PET RANO 1.0 established a set of criteria for a standardized framework in the response assessment of amino acid PET imaging in clinical trials of gliomas.[17] These criteria provide a framework to facilitate implementation of amino acid PET imaging into clinical research and, ultimately, into clinical practice.[17]

EANM/EANO/RANO and SNMMI recommendations for amino acid PET imaging include clinical applications at initial diagnosis, such as definition of high- vs low-grade gliomas, prognostication, definition of the biopsy site, delineation of tumor extent for surgery or radiotherapy, monitoring of

EANM=European Association of Nuclear Medicine; EANO=European Association of Neuro-Oncology; RANO=Response Assessment in Neuro-Oncology; SNMMI=Society of Nuclear Medicine and Molecular Imaging.

treatment response, and diagnosis of tumor progression.[3,17] Below is a summary of ^{18}F-FET PET data in these clinical applications.

Amino acid PET imaging, including ^{18}F-FET PET, is already recommended by the EANM/EANO/RANO and SNMMI guidelines in various clinical applications for gliomas.[3,17]

^{18}F-FET PET imaging in management of brain tumors

^{18}F-FET PET imaging in differentiation of tumor progression or recurrence from TRC

Inconclusive MRI results are a common occurrence for many patients with brain tumors.[5] Thus, perhaps the most pressing unmet need that ^{18}F-FET PET imaging addresses in the management of brain tumors is the differentiation of tumor progression or recurrence from TRC.[4] As described earlier, changes in MRI signal suggesting tumor progression or recurrence are frequently observed after radiotherapy and/or chemotherapy or immunotherapy, but whether these changes are in fact related to treatment (ie, TRC) can be uncertain in a sizable patient population.[4,5,7]

Multiple studies have demonstrated high accuracy of more than 95% with ^{18}F-FET PET imaging for differentiation of TRC from tumor progression or recurrence.[22-26] Similar results of more than 90% accuracy have been reported with ^{18}F-FET PET imaging for brain metastases to differentiate TRC from progression or recurrence suspected with MRI.[27-29]

A recent systematic review and meta-analysis of 1206 patients from 21 studies in high-grade gliomas (HGG) and 5 studies in brain metastasis evaluated ^{18}F-FET PET imaging for differentiating TRC from tumor progression or recurrence suspected with MRI.[30] In 6 studies using static TBRmax (cut-off value: 1.9-2.3), the authors reported a pooled sensitivity and specificity of 91% and 84%, respectively. Additionally, a diagnostic accuracy of up to more than 90% was reported using combined static and dynamic ^{18}F-FET PET parameters for the characterization of both recurrent gliomas (4 studies) and brain metastases (all 5 studies).[30]

^{18}F-FET PET imaging complements MRI to address its shortcomings.[3,4,30]

^{18}F-FET PET imaging in monitoring treatment response

^{18}F-FET PET imaging has also proven to be successful for the assessment of treatment response to plan for an optimal treatment strategy and help avoid over-treatment and unnecessary side effects.[7,31]

^{18}F-FET PET imaging after surgery and radiochemotherapy have provided valuable prognostic information.[4,7,31] ^{18}F-FET PET detected residual tumor more frequently than MRI and its results were not influenced if performed >72 hours post-resection.[31,32] Furthermore, higher ^{18}F-FET uptake and

higher residual tumor volume were associated with tumor recurrence and poor overall survival, respectively.[31,33,34]

^{18}F-FET PET imaging has also been evaluated in the assessment of treatment response in glioma. Early reduction in ^{18}F-FET uptake was shown to be a positive prognostic factor following postoperative chemoradiation.[4,7] Early responders identified by ^{18}F-FET PET imaging within 7 to 10 days after chemoradiation were defined as those with more than a 10% reduction in ^{18}F-FET uptake and they were correlated with a significantly longer progression-free survival and overall survival compared with nonresponders.[35,36] Recent evidence also supported the use of ^{18}F-FET PET imaging in patients with brain metastases for monitoring of response to emerging treatments like targeted therapy and immunotherapy.[37]

^{18}F-FET PET imaging provides valuable prognostic information and guidance for an optimal treatment strategy through monitoring of treatment response.[4,7,31]

As described earlier, another limitation of MRI is pseudoresponse to anti-angiogenic therapies because contrast enhancement can be reduced due to restoration of the BBB with these therapies.[4,10,11] ^{18}F-FET PET imaging was also shown to differentiate response to anti-angiogenic therapies earlier than MRI alone.[38-41] In two prospective studies, a response detected by ^{18}F-FET PET predicted a significantly longer overall survival benefit and provided critical information for clinical management while MRI did not.[39,40]

^{18}F-FET PET imaging in delineation of tumor extent for treatment planning

^{18}F-FET PET imaging can also address the MRI limitation of underestimating the tumor burden due to its reliance on BBB disruption for tumor detection.[4,6,7] As discussed earlier, ^{18}F-FET precisely detects increased metabolic activity of the tumor, which is manifested by upregulation of LAT1, and its uptake is independent of BBB disruption.[5,6] As a result, ^{18}F-FET can detect tumor tissue beyond the contrast enhancement of MRI, ie, non-CET component of the tumor.[9] Therefore, ^{18}F-FET PET imaging helps minimize false negative results that mislead biopsies and planning for surgery or radiotherapy, all of which can result in under-treatment and contribute to recurrent tumors and poor clinical prognoses.[4,42]

^{18}F-FET PET imaging is proven to improve the accurate delineation of tumor extent to avoid under-treatment by informing biopsy and treatment planning.[4,6,7,42]

Utility of ^{18}F-FET PET to improve detection of the tumor extent in gliomas, including non-contrast-enhancing gliomas, has been demonstrated in several biopsy-controlled studies.[42-47] Studies that compared ^{18}F-FET PET with conventional or advanced MRI, such as MR spectroscopic imaging, revealed that combination of MRI with ^{18}F-FET PET improved delineation of tumor extent.[43,44,47-49] These results support combined use of ^{18}F-FET PET and MRI to obtain a more accurate delineation of tumor extent for informing individualized biopsy and treatment planning.[43,44,48,49]

^{18}F-FET PET imaging at initial diagnosis

At initial diagnosis, ^{18}F-FET PET has been evaluated for differential diagnosis, tumor grading, and prognostication.[3] Tumor grading with ^{18}F-FET PET is limited to data based on 2007 WHO classification which may no longer be applicable after the significant changes introduced to glioma classification in 2016 and more recently in 2021 based on advances in molecular characterization.[7,50] Also, while there is compelling evidence for prognostically relevant information with ^{18}F-FET PET, such as biological tumor volume and low uptake indicating better prognosis, further research is needed to establish the associated prognostic factors.[4,7]

Nonetheless, ample data support the use of ^{18}F-FET PET in differential diagnosis of neoplastic and nonneoplastic lesions if a lesion is detected by MRI. Evidence suggests that ^{18}F-FET uptake is higher in neoplastic lesions (ie, primary and metastatic brain tumors) than non-neoplastic lesions, such as inflammatory processes, hemorrhage, infarction, and infection.[4,7] In a meta-analysis of 13 studies that included 462 patients confirmed with histopathology comparison, ^{18}F-FET PET had a pooled sensitivity of 82% and specificity of 76% to distinguish primary brain tumors from non-neoplastic lesions.[7,51]

While histological evaluation has been the gold standard to provide an accurate characterization of brain lesions, ^{18}F-FET PET imaging can help with differential diagnosis by evaluation of equivocal brain lesions.[7]

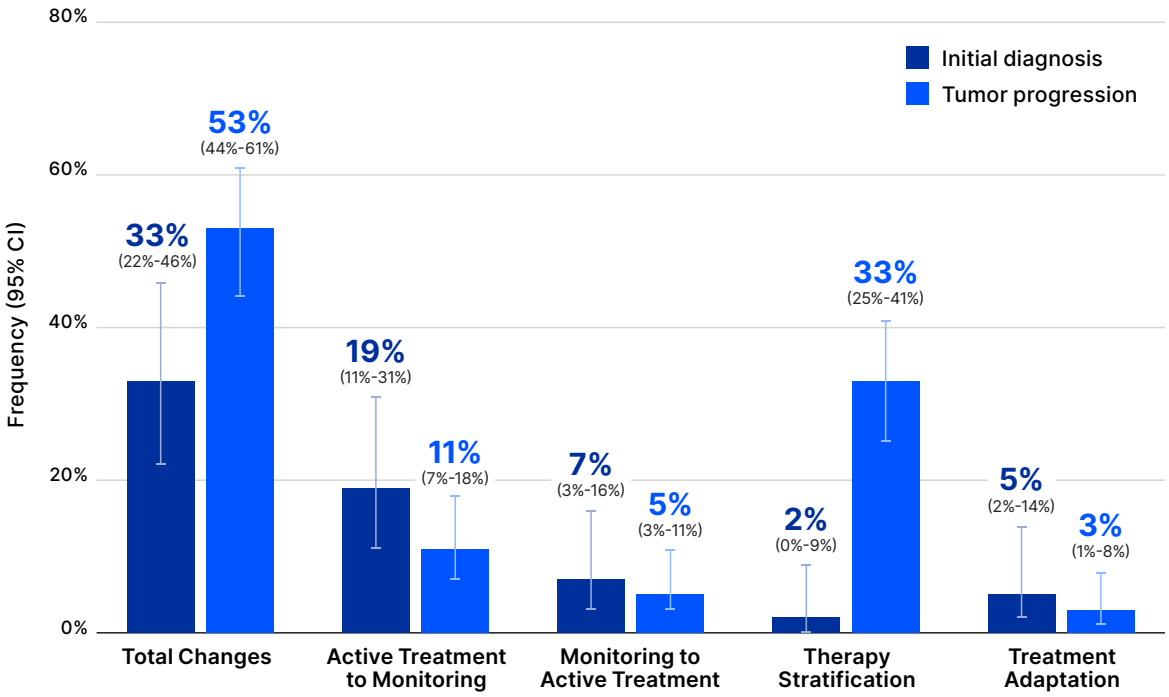
Impact of ^{18}F-FET PET imaging on clinical management

In patients with equivocal findings on MRI, ^{18}F-FET PET/MRI has proven to be a valuable add-on diagnostic tool in brain tumors.[52] Data from studies in routine clinical setup started to unveil the impact of ^{18}F-FET PET/MRI on clinical management in addition to diagnostic performance.[52,53] Such real-world data can address the limited evidence for a direct comparison of ^{18}F-FET PET and MRI due to the challenges associated with randomized, controlled trials.[52]

A retrospective study evaluated the diagnostic performance of ^{18}F-FET PET/MRI and changes in clinical management of patients who had equivocal standard imaging results or clinical course.[52] This study included 189 patients who were newly diagnosed with untreated lesions suspected of malignancy, or who had suspected progression during adjuvant treatment. The authors used histologic confirmation or clinical and standard imaging follow up as the reference standard. At new diagnosis, ^{18}F-FET PET/MRI identified malignancy with an accuracy of 85% and changed the clinical management in 33% of the previously equivocal patients. ^{18}F-FET PET/MRI also identified true progression with an accuracy of 93% and changed the clinical management in 53% of the cases of tumor progression (Figure 2).[52]

Most recently, a prospective study of 80 patients with Grade 3-4 gliomas or brain metastases who had ambiguous MRI results evaluated the diagnostic performance of ^{18}F-FET PET/MRI and its impact on management decisions.[53] Patients were monitored for at least 6 months to confirm the diagnosis using pathology, imaging, and clinical progress. ^{18}F-FET PET/MRI had a sensitivity of 86%, specificity of 87%,

and accuracy of 86% in cases for which MRI had an accuracy of 66%. Detection of tumor progression led to clinical management changes in 88% of cases while clinical management was maintained in 87% of cases when TRC was detected.[53]



Adapted from Brendle C, et al. *J Nucl Med*. 2022;63(4):522-527.

Figure 2: Frequency of clinical management changes based on ¹⁸F-FET PET/MRI outcome at initial tumor diagnosis (dark blue) and at detection of brain tumor progression (light blue).[52] Active treatment to monitoring was defined as waiving of invasive diagnostics for tumor characterization or waiving of surgery/adjuvant therapy during disease course. Monitoring to active treatment was defined as subsequent invasive diagnostics, or treatment start. Therapy stratification was defined as beginning of/waiving additional adjuvant treatment, or waiving planned change and continuing present treatment, or shifting from adjuvant therapy to surgery or vice versa, or changing of adjuvant treatment. Treatment adaptation was defined as change of location/extent of biopsy/resection, or adjustment of irradiation volume/chemotherapy dose.[52]

These real-world results support the use of ¹⁸F-FET PET/MRI to improve confidence in clinical decisions by clarifying equivocal standard imaging results, avoiding unnecessary invasive procedures and distinguishing TRC from tumor recurrence or progression.[52,53]

Recent findings demonstrating the impact on management decisions add to a growing body of evidence that ¹⁸F-FET PET complements and improves MRI results.[52,53]

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