Review

FET- PET RANO for Radiotherapy Assessment of Gliomas

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FET–PET RANO for Radiotherapy Assessment of Gliomas

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Simple summary: Despite recent advances in molecular diagnostic, glioblastoma is connected with tremendously poor outcomes – median overall survival is 14,6 months and the majority of patients will experience progression. After standard treatment such as resection and radiochemotherapy it is extremely difficult to distinguish treatment related changes or pseudoprogression with true progression. However, growing evidence supports the use of PET with amino acid radiotracers such as FET-PET in brain cancer. Due to limited studies there is high variability in the assessment of FET-PET results.

Abstract: Conventional MRI sequences are standard methods to monitor patients with brain tumors but have significant limitations especially after irradiation. Currently, the role of FET-PET in radiotherapy of glioblastoma is emerging, starting from target definition, response assessment and in distinguishing progression from post-irradiation changes. Recently a PET RANO criteria have been published providing optimal strategy for treatment evaluation with amino-acid PET. Earlier, a PET/RANO group reported contribution of PET imaging to radiotherapy planning and monitoring in glioma patients. Also, increasing evidence have showed advantages of amino-acid PET vs. RANO MRI for prediction of overall survival. In this narrative review we aimed to summarize published data on FET-PET based treatment response assessment to radiotherapy and focused on details in protocols.

Keywords: glioblastoma; amino acid PET; post-treatment changes; tumor progression; response assessment

1. Introduction

Glioblastoma is the most common malignant brain tumor among adults. Standard treatment includes maximal safe resection followed by radiotherapy plus concomitant and adjuvant temozolomide. Despite advances in molecular diagnostic and new WHO classification, glioblastoma is connected with tremendously poor prognosis – median overall survival is 14,6 months and median PFS is 10-12 months [1–4] .

The diagnose of recurrent glioblastoma is usually based on MRI . However, conventional MRI sequences may not distinguish post-treatment changes (such as radionecrosis and pseudoprogression) from actual tumor progression and result in inappropriate therapeutical decisions. In recent years PET has been used to assess response to treatment [5–7]. The most commonly used PET tracer in oncology is ^{18}F-fluorodeoxyglucose ([^{18}F]FGD). However, high physiological glucose uptake in brain decreases its diagnostic value [8,9]. Gliomas have overexpression of L-amino acid transporters compared to normal brain cells [10]. Amino acid tracers used in neurooncology are: ^{11}C-methionine ([^{11}C] MET), ^{18}F-dihydroxyphenylalanine ([^{18}F]F-DOPA) and ^{18}F-fluoroethyl-L-tyrosine ([^{18}F]FET). They have unique ability to cross blood-brain barrier (BBB) and visualize tumor extent beyond areas with contrast enhancement on MRI [11]. PET has higher sensitivity and specificity for neoplastic tissue than MRI, is superior in metabolic

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response to treatment and has higher accuracy in differentiation of progression from radiation-induced changes [12–14]. It has been demonstrated that PET is also useful in brain metastases and meningiomas [15]. Other PET tracers that may be useful in response assessment in neurooncology are: FACBC (anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid or Fluciclovine), FMISO ([18]F fluoromisonidazole) and TSPO (translocator protein) but their role is still under investigation [16–18]. PET RANO 1.0 and RANO 2.0 provide criteria for response assessment in gliomas [19,20]. PET/RANO working group prepared a summary of the available evidence with recommendations for the use of PET imaging for radiotherapy of glioma patients [21]. The aim of this review is to summarize the evidence of FET-PET response assessment to radiation therapy in glioblastoma and to prepare practical recommendations for clinical routine.

2. PET-based response assessment criteria for diffuse gliomas

Published in 2024 report of the RANO group has proposed standardized criteria for evaluation of amino acid PET.

Baseline PET in newly diagnosed patients should be obtained 14 days before postoperative treatment but as late as possible after surgery. In patients without postoperative treatment baseline PET should be performed 4-6 weeks after surgery. Without surgical resection (e.g biopsy only) preoperative PET can be used as baseline but should not be obtained more than 14 days before therapeutic intervention.

In recurrent glioma, PET should be performed as close as possible before any therapeutic intervention (not exceeding 14 days). A postoperative PET should be acquired within 14 days before postoperative treatment.

In follow-up of CNS WHO G4 diffuse gliomas PET should be performed at intervals of 2-3 months, parallel to MRI. For assessment of early metabolic response, additional PET 2-3 weeks after treatment initiation can be considered. If needed, additional PET with MRI can be performed (e.g. worse clinical condition). If PET findings are unclear, PET imaging should be repeated in closer intervals, e.g. after 1-2 treatment cycles.

Background activity on amino acid PET should be assessed in the contralateral healthy-appearing cerebral CNS tissue (including grey and white matter within a crescend-shaped volume in the frontoparietal region). PET-positive disease has been defined as volumes with standardized uptake volume (SUV) of 1.6 x mean background activity or higher. Visual check and manual correction are recommended to avoid encompassing structures with physiological high uptake. The maximal SUV and mean SUV in the PET-positive volume are a ratio to the mean SUV of healthy background and serve as measures for uptake intensity (maximal and mean target-background ratio, TBR_{max}, TBR_{mean}). TBR_{max} and TBR_{mean} can not be obtained if no PET-positive volume can be found.

Measurable disease has been defined as PET-positive disease with volume exceeding 0.5ml. In non-measurable disease visible lesions have intensity below a TBR_{max} of 1.6 or volumes below 0.5ml. No measurable disease is the absence of any increased signal abnormality in PET. Patients without measurable disease can not show a partial (PR) or complete response (CR) to subsequent treatment – they can only have stable (SD) or progressive disease (PD).

The assessment of response in PET should be based on the comparison with the baseline PET or nadir.

PD has been defined as an increase of 30% or more in TBR_{max} or of 10% and more in TBR_{mean}, or of 40% or more in PET volume. Any new measurable lesion is considered as PD. In case of multiple lesions, progression of a least one target is considered as PET-based PD.

PR has been defined as a decrease of 30% or more in TBR_{max} or of 10% and more in TBR_{mean} or of 40% or more in PET volume without PET-based progressive disease. In case of multiple lesions in PR each target lesion must fulfill PR response criteria or there can be CR for one but one target or if no PD or SD criteria are fulfilled.

CR has been defined as complete disappearance of all previously PET-positive disease and the absence of new lesions. A change of lesion status from measurable disease to non-measurable or no measurable disease is considered as PR or CR, respectively.

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SD does not fulfill criteria of PD, PR or CR [19].

3. FET-PET after treatment

A study by Galldiks showed that change of FET-PET parameters is associated with OS and PFS after treatment of glioblastoma. Twenty-five patients had FET-PET and MRI imaging at three different timepoints: after surgery, 7-10 days after radiochemotherapy with temozolomide (R-CHTH) and 6-8 weeks later. FET-PET done early after R-CHTH showed that decrease of TBR_{max} and TBR_{mean} of 10% and more was a prognostic factor for PFS (TBR_{max} 9.3 vs. 4.7 months; p= 0.002; TBR_{mean} 10.3 vs. 5.1 months p <0.001) and OS (TBR_{max} 15.4 vs. 8.5 months; p = 0.001; TBR_{mean} 16.1 vs. 9.3 months, p<0.001). FET-PET done 6-8 weeks later had less significant predictive value of TBR but there was an association of between decreased $T_{VOL1.6}$ and PFS (9.3 vs. 5.1 months; p = 0.002). MRI changes of tumor volume were not associated with survival [22].

Another prospective study by Suchorska showed that smaller biological tumor volume (BTV) before radiation with temozolomide is a prognostic factor for PFS and OS. The cutpoint of BTV was 9.5 cm3 (sensitivity 64%, specificity 70%). Median OS (PFS) for BTV below 9.5 cm3 was 17.5 (8.8) months, and 10.7 (3.9) months, for BTV above 9.5 (p <0.002 and p <0.08). The outcomes were independent of MGMT promoter methylation status and type of surgical intervention (resection vs biopsy). Patients with initially increased TACs (time-activity curves) had longer OS (29.7 vs 12.5 months; p <0.02, HR 2.1) and longer PFS (11.9 vs 5.8 months; p < 0.05, HR 1.8) [23].

A prospective study by Piroth revealed that static FET-PET parameters (20-40min postinjection) are related to survival in glioma patients after R-CHTH. A decrease in the TBR_{max} between FET-PET before treatment and 7-10 after R-CHTH (cutoff 10%) had a significantly longer median PFS (9.3 vs 4.7 months; p =0.002) and OS (18.0 vs 8.5 months; p <0.01) than an increase of TBR_{max}. The results for TBR_{mean} (cutoff 25%) were similar: median PFS (10.3 vs 5.1 months) and OS (22.8 vs 9.3 months) (p < 0.001 for both). However, changes in TTP and the slope of the TAC (10–50 minutes postinjection) after R-CHTH showed no relationship with survival [24].

Another prospective study by Ceccon demonstrated that after R-CHTH and 2 cycles of adjuvant temozolomide a reduction of TBR_{max} and MTV (metabolic tumor volume) were associated with longer OS (24 vs. 12 months; p =0.032, and 29 vs. 12 months; p = 0.005) and PFS (both 11 vs. 8 months; p = 0.031 and 0.007, respectively). The results were independent of MGMT promoter methylation status, extent of resection and baseline MTV and TBR_{max} values. There were no significant correlations between MRI results and OS and PFS [25].

Patients after chemoradiation with concomitant and adjuvant temozolomide at first progression treated with bevacizumab + lomustine had reductions of FET-PET parameters. TBR_{max} reduction of 27% and more was related to improved OS of more than 9 months (sensitivity 92%, specificity 63%; p = 0.036). TBR_{mean} reduction of more than 17% at follow-up PET had the same sensitivity and specificity for differentiating responders from non-responders (p =0.020). Absolute MTV

below 5 ml at follow-up was related to significantly longer OS (12 vs. 6 months, sensitivity 85%; specificity, 88%; p < 0.001). Response assessment based on MRI was not predicted for OS [26].

Response assessment was also compared with RANO criteria I in one prospective study. At the time of response assessment, there was discordance between PET and RANO criteria in 81% of cases. Progressive disease was defined in 72% (8/11) of cases according to RANO criteria but PET showed a partial response in 62% (5/8) of these cases. Responses according to RANO criteria and PET (measured as PD vs. SD or PR) were also examined with respect to survival. Neither factor was significant. However, PD defined by RANO 6 months after treatment was close to significance in terms of association with OS (HR = 3.6, 95% CI, 0.98–13.5; *P* = 0.05). Relative changes in PET volume and PET volume at time of response assessment were associated with OS [27].

Abovementioned studies have been summarized in Table 1.

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Table 1. Overview of studies analyzing FET-PET in treatment response.

StudySStudy	N of pts	Newly diagnosed or recurrence	Time of PET after irradiation	Evaluated parameters	Dynamic vs static acquisition	Prognostic of OS or PFS
Galldiks et al (22)	25	Newly diagnosed	7-10 days and 6-8 weeks after RTH	TBR_{mean}, TBR_{max}, Tvol	Static	A decrease of TBR_{max} and TBR_{mean} in early PET - predictors for longer PFS and OS; 6-8 weeks later T_{vol} decrease related to longer PFS
Suchorska et al (23)	79	Newly diagnosed	4 -6 weeks after RTH and after 3 cycles of TMZ	BTV, TAC	Static and dynamic	Longer OS and PFS in patients with smaller pretreatment BTV. Initially increased TAC associated with longer PFS.
Piroth et al (24)	25	Newly diagnosed	7-10 days and 6-8 weeks after RTH	TBR_{max}, TBR_{mean}, TTP, TAC	Static and dynamic	Decrease of TBR_{mean} and TBR_{max} after RTH – longer PFS and OS. No significant correlation of dynamic parameters and survival.
Ceccon et al (25)	41	Newly diagnosed	7 days before adjuvant TMZ and after 2 cycle of adjuvant TMZ	TBR_{max}, TBR_{mean}, MTV	Static	Reductions of MTV and TBR_{max} predicted longer OS and PFS.
Galldiks et al (26)	21	Recurrence	9-11 days before bevacizumab/lomustine inintiation and after 8-10 weeks	TBR_{mean}, TBR_{max}, MTV	Static	TBR_{max}, TBR_{mean} and MTV reduction correlated with longer OS.
Harat et al (27)	11	Newly diagnosed	3-8 months after RTH	MTV	Static, dynamic	No correlation

RTH – radiotherapy, TMZ- temozolomide, TBR – tumor to background ratio, Tvol – tumor volume, BTV – biological tumor volume, TAC – time activity curve, TTP – time to peak, MTV- metabolic tumor volume, OS – overall survival, PFS – progression free survival.

4. Differentiation of radionecrosis from progression

Differentiating radionecrosis from progression is one of most crucial aspects after irradiation as it may occure in even 30% of patients [28].Reirradiation is being offered widely to progressive gliomas and exact diagnosis is crucial for optimal candidate selection before intervention.

A systematic review summarized the role of PET imaging with different radiopharmaceuticals ([F]FDG, [^{18}F]FET, [^{11}C]MET , [^{11}C]CHO, [^{68}Ga]Ga-PSMA) in differential diagnosis of radionecrosis and glioblastoma recurrence. The authors analyzed three studies with FET-PET. The cohorts were heterogenous and included patients also with lower grade gliomas. Two studies identified comparable TBR_{max} cutoffs - 2.07 and 2.09. Amino acid radiotracers had higher specificity (78–95% for [^{18}F]FET and 78–93% for [^{11}C]MET versus 70–88% for [^{18}F]FDG) and sensitivity that FDG-PET (82–91% for [^{18}F]FET and 78–93% for [^{11}C]MET versus 70–84% for [^{18}F]FDG). Overall specificity and sensitivity was high and improved by the use of dedicated amino-acid tracers [29–32] .

A retrospective study evaluated accuracy of 168 FET-PET scans in 146 patients with suspected glioblastoma recurrence in MRI 6 months after radiotherapy PET parameters were higher in patients with recurrent glioblastoma compared with patients with posttreatment changes – defined as necrotizing tissue (TBR_{max}, 3.2 vs 1.6; TBR_{mean}, 2.0 vs 1.6; and BTV, 14.8 cm3 vs 0.01 cm3; $p < 0.0001$). Optimal thresholds for differentiation between posttreatment changes and recurrent glioblastoma for TBR_{max} and TBR_{mean} were 2.0 and 1.8, respectively and 0.55 cm3 for BTV, with the best performance of TBR_{max} (sensitivity 99%, specificity 94%, accuracy 99%; $p < 0.0001$). Increasing TBR_{max} (HR 1.328, 95% CI: 1.116–1.582; $p = 0.001$) and increasing log BTV (HR 1.303, 95% CI: 1.179–1.439; $p < 0.0001$)

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were connected with shorter OS. The results from PET scans were verified by histopathology or by clinical/radiological follow-up. 166 PET scans were correctly classified [33].

Another retrospective study evaluated static and dynamic parameters of FET-PET and apparent diffusion coefficients (ADC) obtained by diffusion-weighted MRI in 48 high grade glioma patients with suspected findings in MRI. Treatment-related changes (defined as prominent necrosis) were present in 10 of 48 patients (21%). The diagnostic performance of FET PET was significantly higher (threshold for both TBR_{max} and TBR_{mean}, 1.95; accuracy, 83%; $p < 0.001$) than that of ADC values (threshold ADC, 1.09×10^{-3} mm^2/s; accuracy, 69%; $p = 0.13$). TTP cut-off value of 32.5 min was optimal for the differentiation of treatment-related changes from tumor progression (accuracy, 72%; sensitivity, 80%; specificity, 69%; $p < 0.01$). For slope the optimal cut-off value was 0.32 SUV/h had a slightly higher diagnostic accuracy of 74% (sensitivity, 70%; specificity, 75%; $p = 0.02$). Static FET PET parameters with ADC values increased accuracy to 89%. The highest accuracy was achieved by combining static and dynamic FET PET parameters (93%). TBR <1.95 at suspected progression was connected with longer OS ($p = 0.01$) [34].

FET-PET has been showed to be accurate in distinguishing between glioma recurrence and treatment induced changes with a sensitivity of 86.2% (95% CI: 68.3–96.1%) and a specificity of 81.3% (95% CI: 54.4–96.1%), but the cohort included also patients with astrocytoma and oligodendroglioma. The optimal cutoff values for recurrence were TBRmax ≥ 2.1, SUVmax ≥ 3.5, and TTP ≤ 29 min. However, in this analysis no FET-PET parameters were found to impact survival [35].

5. Differentiation of pseudoprogression from progression

A retrospective study evaluated the role of FET-PET in distinguishing from pseudoprogression and tumor progression in 22 patients with glioblastoma within 12 weeks after standard treatment with suspected MRI findings. Pseudoprogression was confirmed in 11 patients. In patients with pseudoprogression, ^{18}F-FET uptake was significantly lower than in patients with progression (TBR_{max} 1.9±0.4 vs. 2.8±0.5, TBR_{mean} 1.8±0.2 vs. 2.3±0.3; both $p<0.001$). TAC type II (^{18}F-FET uptake peaking at a mid-point; >20–40 min) or III (^{18}F-FET uptake peaking early (≤20 min) followed by a constant descent) was more frequently present in patients with progression ($p=0.04$). The optimal ^{18}F-FET TBR_{max} cut-off value for identifying pseudoprogression was 2.3 (sensitivity 100 %, specificity 91 %, accuracy 96 %, $p<0.001$). TBR_{max} <2.3 was connected with longer OS (median OS 23 vs 12 months, $p=0.046$) [36].

Another retrospective study evaluated FET-PET in similar cohort (26 patients) but 3 months after treatment. Late pseudoprogression occurred in 7 patients, remaining patients showed true tumor progression. TBR_{max} and TBR_{mean} were significantly higher in patients with true progression than in patients with late pseudoprogression (TBR_{max} 2.4±0.1 vs. 1.5± 0.2, $P = 0.003$; TBR_{mean} 2.1±0.1 vs. 1.5±0.2, $p = 0.012$) whereas TTP was significantly shorter (mean TTP 25±2 vs. 40 ±2 min, $p< 0.001$). The optimal cutoff to differentiate between true progression and late pseudoprogression for TBR_{max} and TBR_{mean} was 1.9 (TBR_{max} - sensitivity 84%, specificity 86%, accuracy 85%, $p = 0.015$; TBR_{mean} -sensitivity 74%, specificity 86%, accuracy 77%, , $p= 0.023$). TAC type II or III was more frequently observed in patients with true tumor progression than in patients with late pseudoprogression (sensitivity of 84%, specificity of 100%, and an accuracy of 89%; $p< 0.001$). The author suggest to diagnose late progression when TBR_{max} is higher than 2.4 and late pseudoprogression when TBR_{max} is below 1.0, Values between 1.0 and 2.4 should be interpreted with caution. [37]. In both abovementioned studies there was a higher rate of MGMT metylation in patients wth pseundoprogression than in the patients with true progression. That may suggest that pseudoprogression is a response to radiosensitizing effects of temozolomide.

6. Prognostic value of FET-PET in glioma re-irradiation

A retrospective study evaluated FET-PET in 72 patients with recurrent malignant glioma before and after reirradiation +/- bevacizumab. Re-RT was performed at least 6 months after the first course of RT. Total dose of re-RT was 36Gy in conventional fractions of 2Gy. Patients treated with bevacizumab received a dose of 10mg/kg at day 1. and 15. of re-RT, some patients received

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maintenance therapy. TTP_{min} had prognostic value prior to Re-RT with concomitant bevacizumab - shorter TTP_{min} was connected with shorter PRS (post-recurrence survival) after re-RT (6 months for TTP_{min} <12,5min, 7 months for TTP_{min} 12.5–25 min and 11 months for TTP_{min} >25 min (p=0.027)). Early TBR_{max} and the other conventional PET parameters were not significantly related to PRS [38].

Another study retrospectively evaluated FET-PET in 56 patients with recurrent malignant glioma and re-RT. The most common dose-fractionation scheme of re-RT was 36Gy in fractions of 2Gy. There was a significant decrease of median SUV_{max}/BG after second course of RTH (3.3 vs 2.6, p <0.001) and BTV (13.7 cc vs 7.3 cc , p = 0.006) but without significant influence on PFS. The change of SUV_{mean}/BG did not reach significance (2.2 vs 2.3, p = 0.13). Patients with decreasing pretherapeutic FET kinetics had worse survival than patients with other kinetics (p = 0.01) [39].

A phase I clinical trial evaluated prognostic value of FET-PET in reirradiation of 31 patients with recurrent high grade glioma. FET-PET data were obtained at baseline, during 2nd week of treatment and 4 weeks after RT. The prescribed dose to the PTV were: 35 Gy in 10 fractions (group 1), 35 Gy in 10 fractions plus a 7 Gy simultaneous integrated boost to PET-positive volumes - 42 Gy to PET-GTV (group 2), 29.5 Gy in 5 fractions (group 3) and 35 Gy in 10 fractions to tumor volumes above 100cm3 (group 4). All treatment was delivered with 5 fractions/week. Baseline BTV and baseline MRI volume were prognostic for OS (HR = 1.3 p < 0.01 and HR = 1.3 p < 0.01, respectively). Changes in BTV and T_{max}/B were not connected with survival. There were no significant differences in T_{max}/B and BTV changes between treatment groups [40].

A systematic review summarized prognostic value of amino acid PET (FET/DOPA/MET) versus MRI RANO in prediction of OS in patients with recurrent high grade glioma and bevacizumab therapy. OS was significantly (p < 0.001) lower in the PET + (median = 6.1; n = 39) than in the PET−(median=12.3; n=33) group. OS was marginally (p = 0.052) lower in the MRI + (median = 6.8; n = 18) than in the MRI − (median = 10.5; n = 54) group. The PET+ findings predicted OS at 9 months with a sensitivity and specificity of 76% (95% CI 60–87) and 71% (95% CI 53–83), respectively. Corresponding values for MRI were 32% (95% CI 19–48) and 82% (95% CI 66–92) [41].

Abovementioned studies have been summarized in Table 2.

Table 2. Overview of studies analyzing FET-PET in distinguishing between radionecrosis, pseudoresponse and recurrence as well as prognostic value in reirradiation.

Study	N of pts	Newly diagnosed or recurrence	Time of PET after irradiation	Evaluated parameters	Dynamic vs static acquisition	Prognostic of OS or PFS
Bashir et al (33)	146	Recurrence	6 months	TBR_{max}, TBR_{mean}, BTV	Static	Increasing BTV associated with shorter OS PET parameters higher in recurrence than in posttreatment changes
Werner et al (34)	48	Recurrence	16 weeks	TBR_{max}, TBR_{mean}, TTP	Static and dynamic	TBRs <1.95 at suspected progression predicted longer survival
Celli et al (35)	45	Recurrence	12 weeks	TBR_{max}, MTV, TTM, TTP, TAC	Static and dynamic	No impact of FET-PET parameters on OS/PFS.
Galdiks et al (36)	22	Recurrence	12 weeks	TBR_{max}, TBR_{mean}, TTP, TAC	Static and dynamic	TBR_{max} <2.3 correlated with longer OS
Kebir et al (37)	26	Recurrence	3 months	TBR_{max}, TBR_{mean}, TTP, TAC	Static and dynamic	Not assessed
Fleischmann et al (38)	72	Recurrence	6 months	TBR_{max}, BTV, TAC, TTP	Static and dynamic	Longer TTP before reirradiation connected with longer post-recurrence survival

Niyazi et al (39)	56	Recurrence	6 months	SUV_{max}/BG, SUV_{mean}/BG, TAC	Static and dynamic	Increasing TAC prior to re-irradiation correlated with longer survival
Moller et al (40)	31	Recurrence	6 months	BTV, T_{max}/B	Static	Baseline BTV prognostic for OS

TBR – tumor to background ratio, B/BG- background, BTV – biological tumor volume, TAC – time activity curve, TTP – time to peak, TTM – total tumor metabolism, MTV- metabolic tumor volume, OS – overall survival, PFS – progression free survival.

7. Future directions and controversies

PET RANO-stable disease corresponds to a stable uptake after treatment. However, it may still represent a metabolically active tumor. Future studies should examine whether additional therapies to a metabolically stable glioblastoma can improve outcomes. Most papers relate to standard acquisition but new data suggests that early acquisition shows the most aggressive parts of gliomas [42,43].High uptake in early phase is more common in IDH-wildtype gliomas and time to peak may have a positive prognostic impact [44]. Early uptake assessment that localizes tumor extent outside BTV in standard acquisition may provide new insights. Its decrease should be analyzed and correlated with prognosis in future studies. Re-irradiation based on FET PET still requires further studies as based on current evidence FET-PET distinguishes radiation necrosis and may improve target definition adding infiltration areas outside contrast enhancement.

8. Conclusions

Increasing evidence has proved the efficacy of FET-PET in guiding multidisciplinary decisions after irradiation. Most papers have showed that TBR_{mean} and TBR_{max} above 2.0 should be considered as progression or active disease. However, a fraction of tumors after irradiation may present lower uptakes, in those cases additional factors should be analyzed. PET-RANO is a systematic attempt to standardize our opinions based on amino-acid PET results after irradiation in order to increase patient safety and re-treatment efficacy. However, PET-RANO stable disease with biological active tumor needs to be carefully evaluated and optimal strategy for this subgroup remains unclear.

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References

1. Brain and CNS Tumor Statistics 382 CA: A Cancer Journal for Clinicians., doi:10.3322/caac.21693.
2. Stupp, R.; Mason, W.P.; Van Den Bent, M.J.; Weller, M.; Fisher, B.; Taphoorn, M.J.B.; Belanger, K.; Brandes, A.A.; Marosi, C.; Bogdahn, U.; et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma.
3. Louis, D.N.; Perry, A.; Wesseling, P.; Brat, D.J.; Cree, I.A.; Figarella-Branger, D.; Hawkins, C.; Ng, H.K.; Pfister, S.M.; Reifenberger, G.; et al. The 2021 WHO Classification of Tumors of the Central Nervous System: A Summary. *Neuro Oncol* **2021**, *23*, 1231–1251, doi:10.1093/neuonc/noab106.
4. Blumenthal, D.T.; Gorlia, T.; Gilbert, M.R.; Kim, M.M.; Nabors, L.B.; Mason, W.P.; Hegi, M.E.; Zhang, P.; Golfinopoulos, V.; Perry, J.R.; et al. Is More Better? The Impact of Extended Adjuvant Temozolomide in Newly Diagnosed Glioblastoma: A Secondary Analysis of EORTC and NRG Oncology/RTOG. *Neuro Oncol* **2017**, *19*, 1119–1126, doi:10.1093/neuonc/nox025.

5. Lohmann, P.; Stavrinou, P.; Lipke, K.; Bauer, E.K.; Ceccon, G.; Werner, J.-M.; Neumaier, B.; Fink, G.R.; Shah, N.J.; Langen, K.-J.; et al. FET PET Reveals Considerable Spatial Differences in Tumour Burden Compared to Conventional MRI in Newly Diagnosed Glioblastoma., doi:10.1007/s00259-018-4188-8/Published.
6. Hygino Da Cruz, L.C.; Rodriguez, I.; Domingues, R.C.; Gasparetto, E.L.; Sorensen, A.G. Pseudoprogression and Pseudoresponse: Imaging Challenges in the Assessment of Posttreatment Glioma., doi:10.3174/ajnr.A2397.
7. Van Den Bent, M.J.; Dhermain, F.G.; Hau, P.; Lanfermann, H.; Jacobs, A.H. Advanced MRI and PET Imaging for Assessment of Treatment Response in Patients with Gliomas. *Lancet Neurol* **2010**, *9*, 906–926, doi:10.1016/S1474.
8. Fletcher, J.W.; Djulbegovic, B.; Soares, H.P.; Siegel, B.A.; Lowe, V.J.; Lyman, G.H.; Coleman, R.E.; Wahl, R.; Paschold, J.C.; Avril, N.; et al. Recommendations on the Use of 18 F-FDG PET in Oncology. *J Nucl Med* **2008**, *49*, 480–508, doi:10.2967/jnumed.107.047787.
9. Dunet, V.; Pomoni, A.; Hottinger, A.; Nicod-Lalonde, M.; Prior, J.O. Performance of 18 F-FET versus 18 F-FDG-PET for the Diagnosis and Grading of Brain Tumors: Systematic Review and Meta-Analysis., doi:10.1093/neuonc/nov148.
10. Nawashiro, H.; Otani, N.; Uozumi, Y.; Ooigawa, H.; Toyooka, T.; Suzuki, T.; Katoh, H.; Tsuzuki, N.; Ohnuki, A.; Shima, K.; et al. High Expression of L-Type Amino Acid Transporter 1 in Infiltrating Glioma Cells. *Brain Tumor Pathol* **2005**, *22*, 89–91, doi:10.1007/s10014-005-0188-z.
11. Najjar, A.M.; Johnson, J.M.; Schellingerhout, D. The Emerging Role of Amino Acid PET in Neuro-Oncology. *Bioengineering* **2018**, *5*, doi:10.3390/BIOENGINEERING5040104.
12. Lohmann, P.; Stavrinou, P.; Lipke, K.; Bauer, E.K.; Ceccon, G.; Werner, J.-M.; Neumaier, B.; Fink, G.R.; Shah, N.J.; Langen, K.-J.; et al. FET PET Reveals Considerable Spatial Differences in Tumour Burden Compared to Conventional MRI in Newly Diagnosed Glioblastoma., doi:10.1007/s00259-018-4188-8/Published.
13. Roelcke, U.; Wyss, M.T.; Nowosielski, M.; Rudà, R.; Roth, P.; Hofer, S.; Galldiks, N.; Crippa, F.; Weller, M.; Soffietti, R. Amino Acid Positron Emission Tomography to Monitor Chemotherapy Response and Predict Seizure Control and Progression-Free Survival in WHO Grade II Gliomas., doi:10.1093/neuonc/nov282.
14. Rachinger, W.; Goetz, C.; Pöpperl, G.; Gildehaus, F.J.; Kreth, F.W.; Holtmannspötter, M.; Herms, J.; Koch, W.; Tatsch, K.; Tonn, J.C. Positron Emission Tomography with O-(2-[18F]Flouroethyl)-L- Tyrosine versus Magnetic Resonance Imaging in the Diagnosis of Recurrent Gliomas. *Neurosurgery* **2005**, *57*, 505–511, doi:10.1227/01.NEU.0000171642.49553.B0.
15. Galldiks, N.; Lohmann, P.; Albert, N.L.; Tonn, J.C.; Langen, K.J. Current Status of PET Imaging in Neuro-Oncology. *Neurooncol Adv* **2019**, *1*, 1–11, doi:10.1093/NOAJNL/VDZ010.
16. Hirata, K.; Terasaka, S.; Shiga, T.; Hattori, N.; Magota, K.; Kobayashi, H.; Yamaguchi, S.; Houkin, K.; Tanaka, S.; Kuge, Y.; et al. 18F-Fluoromisonidazole Positron Emission Tomography May Differentiate Glioblastoma Multiforme from Less Malignant Gliomas. *Eur J Nucl Med Mol Imaging* **2012**, *39*, 760–770, doi:10.1007/S00259-011-2037-0/FIGURES/6.
17. Albert, N.L.; Nelwan, D. V; Fleischmann, D.F.; Quach, S.; Von Rohr, K.; Kaiser, L.; Teske, N.; Unterrainer, L.M.; Bartos, L.M.; Ruf, V.C.; et al. Prognostic Value of TSPO PET Before Radiotherapy in Newly Diagnosed IDH-Wild-Type Glioblastoma. *J Nucl Med* **2023**, *64*, 1519–1525, doi:10.2967/jnumed.122.265247.
18. Castello, A.; Albano, D.; Muoio, B.; Castellani, M.; Panareo, S.; Rizzo, A.; Treglia, G.; Urso, L. Diagnostic Accuracy of PET with 18F-Fluciclovine ([18F]FACBC) in Detecting High-Grade Gliomas: A Systematic Review and Meta-Analysis. *Diagnostics* 2023, *13*.
19. Albert, N.L.; Galldiks, N.; Ellingson, B.M.; van den Bent, M.J.; Chang, S.M.; Cicone, F.; de Groot, J.; Koh, E.S.; Law, I.; Le Rhun, E.; et al. PET-Based Response Assessment Criteria for Diffuse Gliomas (PET RANO 1.0): A Report of the RANO Group. *Lancet Oncol* **2024**, *25*, e29–e41, doi:10.1016/S1470-2045(23)00525-9.
20. Wen, P.Y.; Van Den Bent, M.; Youssef, G.; Cloughesy, T.F.; Ellingson, B.M.; Weller, M.; Galanis, E.; Barboriak, D.P.; De Groot, J.; Gilbert, M.R.; et al. RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults. *Journal of Clinical Oncology* **2023**, *41*, 5187–5199, doi:10.1200/JCO.23.01059/SUPPL_FILE/DS_JCO.23.01059.PDF.
21. Galldiks, N.; Niyazi, M.; Grosu, A.L.; Kocher, M.; Langen, K.-J.; Law, I.; Minniti, G.; Kim, M.M.; Tsien, C.; Dhermain, F.; et al. Contribution of PET Imaging to Radiotherapy Planning and Monitoring in Glioma Patients-a Report of the PET/RANO Group. *Neuro Oncol* **2021**, *23*, 881–893, doi:10.1093/neuonc/noab013.
22. Galldiks, N.; Langen, K.-J.; Holy, R.; Pinkawa, M.; Stoffels, G.; Nolte, K.W.; Kaiser, H.J.; Filss, C.P.; Fink, G.R.; Coenen, H.H.; et al. Assessment of Treatment Response in Patients with Glioblastoma Using O-(2-18 F-Fluoroethyl)-L-Tyrosine PET in Comparison to MRI. *J Nucl Med* **2012**, *53*, 1048–1057, doi:10.2967/jnumed.111.098590.
23. Suchorska, B.; Jansen, N.L.; Linn, J.; Kretzschmar, H.; Janssen, H.; Eigenbrod, S.; Simon, M.; Pöpperl, G.; Kreth, F.W.; La Fougere, C.; et al. Biological Tumor Volume in 18FET-PET before Radiochemotherapy Correlates with Survival in GBM. *Neurology* **2015**, *84*, 710–719, doi:10.1212/WNL.0000000000001262.
24. Piroth, M.D.; Liebenstund, S.; Galldiks, N.; Stoffels, G.; Shah, N.J.; Eble, M.J.; Coenen, H.H.; Langen, K.J. Monitoring of Radiochemotherapy in Patients with Glioblastoma Using O-(2-[18F]Fluoroethyl)-L-Tyrosine

Positron Emission Tomography: Is Dynamic Imaging Helpful? *Mol Imaging* **2013**, *12*, doi:10.2310/7290.2013.00056.

25. Ceccon, G.; Lohmann, P.; Werner, J.-M.; Tscherpel, C.; Dunkl, V.; Stoffels, G.; Rosen, J.; Rapp, M.; Sabel, M.; Herrlinger, U.; et al. Early Treatment Response Assessment Using 18 F-FET PET Compared with Contrast-Enhanced MRI in Glioma Patients After Adjuvant Temozolomide Chemotherapy., doi:10.2967/jnumed.120.254243.
26. Galldiks, N.; Dunkl, V.; Ceccon, G.; Tscherpel, C.; Stoffels, G.; Law, I.; Henriksen, O.M.; Muhic, A.; Poulsen, H.S.; Steger, J.; et al. Early Treatment Response Evaluation Using FET PET Compared to MRI in Glioblastoma Patients at First Progression Treated with Bevacizumab plus Lomustine. *Eur J Nucl Med Mol Imaging* **2018**, *45*, 2377–2386, doi:10.1007/s00259-018-4082-4.
27. Harat, M.; Blok, M.; Miechowicz, I.; Wiatrowska, I.; Makarewicz, K.; Małkowski, B. Safety and Efficacy of Irradiation Boost Based on 18F-FET-PET in Patients with Newly Diagnosed Glioblastoma. *Clinical Cancer Research* **2022**, *28*, 3011–3020, doi:10.1158/1078-0432.CCR-22-0171/698881/AM/SAFETY-AND-EFFICACY-OF-IRRADIATION-BOOST-BASED-ON.
28. Siu, A.; Wind, J.J.; Bryan Iorgulescu, J.; Chan, T.A.; Yamada, Y.; Sherman, J.H. Radiation Necrosis Following Treatment of High Grade Glioma-a Review of the Literature and Current Understanding., doi:10.1007/s00701-011-1228-6.
29. Ninatti, G.; Pini, C.; Gelardi, F.; Sollini, M.; Chiti, A. The Role of PET Imaging in the Differential Diagnosis between Radiation Necrosis and Recurrent Disease in Irradiated Adult-Type Diffuse Gliomas: A Systematic Review. *Cancers (Basel)* 2023, *15*.
30. Vidmar, M.S.; Doma, A.; Smrdel, U.; Zevnik, K.; Studen, A. The Value of FET PET/CT in Recurrent Glioma with a Different IDH Mutation Status: The Relationship between Imaging and Molecular Biomarkers. *Int J Mol Sci* **2022**, *23*, doi:10.3390/ijms23126787.
31. Sogani, S.K.; Jena, A.; Taneja, S.; Gambhir, A.; Mishra, A.K.; D'Souza, M.M.; Verma, S.M.; Hazari, P.P.; Negi, P.; Jadhav, G.K.R. Potential for Differentiation of Glioma Recurrence from Radionecrosis Using Integrated 18F-Fluoroethyl-L-Tyrosine (FET) Positron Emission Tomography/Magnetic Resonance Imaging: A Prospective Evaluation. *Neurol India* **2017**, *65*, 293–301, doi:10.4103/NEUROINDIA.NI_101_16.
32. Pyka, T.; Hiob, D.; Preibisch, C.; Gempt, J.; Wiestler, B.; Schlegel, J.; Straube, C.; Zimmer, C. Diagnosis of Glioma Recurrence Using Multiparametric Dynamic 18F-Fluoroethyl-Tyrosine PET-MRI. *Eur J Radiol* **2018**, *103*, 32–37, doi:10.1016/J.EJRAD.2018.04.003.
33. Bashir, A.; Jacobsen, S.M.; Henriksen, O.M.; Broholm, H.; Urup, T.; Grunnet, K.; Larsen, V.A.; Møller, S.; Skjøth-Rasmussen, J.; Poulsen, H.S.; et al. Recurrent Glioblastoma versus Late Posttreatment Changes: Diagnostic Accuracy of O-(2-[18F]Fluoroethyl)-L-Tyrosine Positron Emission Tomography (18F-FET PET). *Neuro Oncol* **2019**, *21*, 1595–1606, doi:10.1093/neuonc/noz166.
34. Werner, J.M.; Stoffels, G.; Lichtenstein, T.; Borggrefe, J.; Lohmann, P.; Ceccon, G.; Shah, N.J.; Fink, G.R.; Langen, K.J.; Kabbasch, C.; et al. Differentiation of Treatment-Related Changes from Tumour Progression: A Direct Comparison between Dynamic FET PET and ADC Values Obtained from DWI MRI. *Eur J Nucl Med Mol Imaging* **2019**, *46*, 1889–1901, doi:10.1007/s00259-019-04384-7.
35. Celli, M.; Caroli, P.; Amadori, E.; Arpa, D.; Gurrieri, L.; Ghigi, G.; Cenni, P.; Paganelli, G.; Matteucci, F. Diagnostic and Prognostic Potential of 18F-FET PET in the Differential Diagnosis of Glioma Recurrence and Treatment-Induced Changes After Chemoradiation Therapy. *Front Oncol* **2021**, *11*, doi:10.3389/fonc.2021.721821.
36. Galldiks, N.; Dunkl, V.; Stoffels, G.; Hutterer, M.; Rapp, M.; Sabel, M.; Reifenberger, G.; Kebir, S.; Dorn, F.; Blau, T.; et al. Diagnosis of Pseudoprogression in Patients with Glioblastoma Using O-(2-[18 F]Fluoroethyl)-L-Tyrosine PET. *J Nucl Med Mol Imaging* **2015**, *42*, 685–695, doi:10.1007/s00259-014-2959-4.
37. Kebir, S.; Fimmers, R.; Galldiks, N.; Schafer, N.; Mack, F.; Schaub, C.; Stuplich, M.; Niessen, M.; Tzaridis, T.; Simon, M.; et al. Late Pseudoprogression in Glioblastoma: Diagnostic Value of Dynamic O-(2-[18 F]Fluoroethyl)-L-Tyrosine PET. *Clinical Cancer Research* **2016**, *22*, 2190–2196, doi:10.1158/1078-0432.CCR-15-1334/268068/AM/LATE-PSEUDOPROGRESSION-IN-GLIOBLASTOMA-DIAGNOSTIC.
38. Fleischmann, D.F.; Unterrainer, M.; Bartenstein, P.; Belka, C.; Albert, N.L.; Niyazi, M. 18F-FET PET Prior to Recurrent High-Grade Glioma Re-Irradiation—Additional Prognostic Value of Dynamic Time-to-Peak Analysis and Early Static Summation Images? *J Neurooncol* **2017**, *132*, 277–286, doi:10.1007/s11060-016-2366-8.
39. Niyazi, M.; Jansen, N.; Ganswindt, U.; Schwarz, S.B.; Geisler, J.; Schnell, O.; Büsing, K.; Eigenbrod, S.; La Fougère, C.; Belka, C. Re-Irradiation in Recurrent Malignant Glioma: Prognostic Value of [18F]FET-PET. *J Neurooncol* **2012**, *110*, 389–395, doi:10.1007/s11060-012-0980-7.
40. Moller, S.; Law, I.; Costa, J.; Poulsen, H.S.; Engelholm, S.A.; Engelholm, S. Prognostic Value of 18 F-FET PET Imaging in Re-Irradiation of High-Grade Glioma: Results of a Phase I Clinical Trial. *Radiotherapy and Oncology* **2016**, *121*, 132–137, doi:10.1016/j.radonc.2016.08.014.
41. Chaban, A.; Waschulzik, B.; Bernhardt, · Denise; Delbridge, C.; Schmidt-Graf, F.; Wagner, · Arthur; Wiestler, B.; Weber, W.; Yakushev, I. Amino Acid PET vs. RANO MRI for Prediction of Overall Survival in

Patients with Recurrent High Grade Glioma under Bevacizumab Therapy. *Eur J Nucl Med Mol Imaging* **123AD**, doi:10.1007/s00259-024-06601-4.

42. Harat, M.; Rakowska, J.; Harat, M.; Szylberg, T.; Furtak, J.; Miechowicz, I.; Małkowski, B. Combining Amino Acid PET and MRI Imaging Increases Accuracy to Define Malignant Areas in Adult Glioma., doi:10.1038/s41467-023-39731-8.
43. Albert, N.L.; Winkelmann, I.; Suchorska, B.; Wenter, V.; Schmid-Tannwald, C.; Mille, E.; Todica, A.; Brendel, M.; Tonn, J.-C.; Bartenstein, P.; et al. Early Static 18 F-FET-PET Scans Have a Higher Accuracy for Glioma Grading than the Standard 20-40 Min Scans., doi:10.1007/s00259-015-3276-2.
44. Mittlmeier, L.M.; Suchorska, B.; Ruf, V.; Holzgreve, A.; Brendel, M.; Herms, J.; Bartenstein, P.; Tonn, J.C.; Unterrainer, M.; Albert, N.L. 18f-Fet Pet Uptake Characteristics of Long-Term Idh-Wildtype Diffuse Glioma Survivors. *Cancers (Basel)* **2021**, *13*, doi:10.3390/cancers13133163.