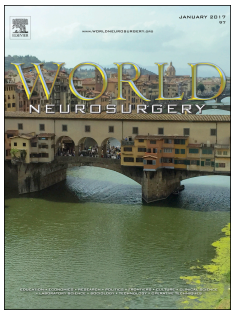
Journal Pre-proof



Differentiation between True Tumor Progression of Glioblastoma and Pseudoprogression using Diffusion-weighted imaging and Perfusion-weighted imaging: A Systematic Review and Meta-analysis.

Charalampos Tsakiris, Timoleon Siempis, George A. Alexiou, Anastasia Zikou, Chrissa Sioka, Spyridon Voulgaris, Maria I. Argyropoulou

PII: S1878-8750(20)31750-2

DOI: https://doi.org/10.1016/j.wneu.2020.07.218

Reference: WNEU 15680

To appear in: *World Neurosurgery*

Received Date: 16 March 2020

Revised Date: 28 July 2020

Accepted Date: 30 July 2020

Please cite this article as: Tsakiris C, Siempis T, Alexiou GA, Zikou A, Sioka C, Voulgaris S, Argyropoulou MI, Differentiation between True Tumor Progression of Glioblastoma and Pseudoprogression using Diffusion-weighted imaging and Perfusion-weighted imaging: A Systematic Review and Meta-analysis., *World Neurosurgery* (2020), doi: https://doi.org/10.1016/j.wneu.2020.07.218.

Differentiation between True Tumor Progression of Glioblastoma and Pseudoprogression using Diffusion-weighted imaging and Perfusion-weighted imaging: A Systematic Review and Meta-analysis.

Charalampos Tsakiris*[1]

Timoleon Siempis*[1]

George A.Alexiou[1]

Anastasia Zikou[2]

Chrissa Sioka[3]

Spyridon Voulgaris[1]

Maria I Argyropoulou[2]

*The first two authors contributed equally to this study.

[1]Department of Neurosurgery, Medical School, University of Ioannina, [2]Department of Radiology, Medical School, University of Ioannina, [3]Department of Nuclear Medicine, Medical School, University of Ioannina, Ioannina, Greece

Corresponding author

George Alexiou, MD

Department of Neurosurgery

University of Ioannina

School of Medicine, Ioannina, 45500

GREECE

Tel.: +30 6948525134

Email: alexiougr@gmail.com

Cc email: alexiougrg@yahoo.gr

Differentiation between True Tumor Progression of Glioblastoma and Pseudoprogression using Diffusion-weighted imaging and Perfusion-weighted imaging: A Systematic Review and Meta-analysis.

Abstract

Background: On brain magnetic resonance imaging (MRI), both diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are used to evaluate cerebral tumors. The purpose of this meta-analysis was to evaluate and compare the diagnostic performance of DWI and PWI in differentiating between pseudoprogression and true tumor progression of glioblastoma.

Methods: We performed a systematic review of the PubMed database from January 2000 to December 2019 for relevant studies. After application of specific inclusion and exclusion criteria, the eligible articles were evaluated for methodological quality and risk of bias using the updated Quality Assessment of Diagnostic Accuracy (QUADAS-2) tool. From the published study results, the pooled sensitivity, pooled specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (DOR) and their corresponding confidence intervals (% CI), and the area under the curve (AUC), were calculated individually for DWI and PWI.

Results: The meta-analysis included 24 studies, with a total of 900 patients. DWI was found to be slightly superior in terms of sensitivity and specificity, 0.88 (% CI 0.83-0.92) and 0.85 (% CI 0.78-0.91) respectively, compared with the respective values of PWI, 0.85 (% CI 0.81-0.89) and 0.79 (% CI 0.74-0.84). On comparison of the overall diagnostic accuracy of the MRI modalities using their respective AUC values (0.9156 for DWI, 0.9072 for PWI), no significant difference was demonstrated between the two.

Conclusion: Both DWI and PWI provided optimal diagnostic performance in differentiating pseudoprogression from true tumor progression in cerebral glioblastoma, and neither technique proved to be superior.

Keywords: Tumor progression; pseudoprogression; recurrence; glioblastoma; diffusion-weighted imaging (DWI); perfusion- weighted imaging (PWI)

Introduction

Glioblastoma is a highly malignant brain tumor, with high mortality rates. Its poor prognosis is attributed mainly to its inevitable recurrence. [1] The 5-year survival rate is <10%, with a mortality rate of close to 100% [2] The current standard care for the management of glioblastoma includes complete surgical resection, when possible, followed by radiotherapy with concurrent and adjuvant temozolomide-based chemotherapy. [3]

After the addition of chemotherapy to the treatment plan, the incidence of detection of progressively enhancing lesions on magnetic resonance imaging (MRI) after the completion of the concurrent chemoradiotherapy (CCRT) increased significantly. Although the MRI of these patients appeared to be deteriorating after treatment, some presented spontaneous clinical improvement, without modification of the therapeutic approach. [4] This treatment-related phenomenon, which is named "pseudoprogression", typically occurs within 3-6 months of the completion of treatment. [5] Radiologically, pseudoprogression appears as a new contrast-enhancing lesion on T1-weighted MRI or growth of the high T2/FLAIR area, thus mimicking early progressive disease (ePD). [6] It is evident that misdiagnosis of gliolastoma recurrence alters the treatment plan dramatically, leading potentially to non-effective second line treatment or unnecessary repeat surgery. [7]

The underlying mechanism behind pseudoprogression is largely unknown, but it has been suggested that the combination of chemotherapy and radiation induce inflammation of epithelial cells and tissue, with edema and anomalous vessel permeability. [8,9] The clinical definition of pseudoprogression is unclear, as the authors of some series propose that the lesion must not show signs of progression for

at least 6 months, while others propose a 2-month interval after the initial scan for the diagnosis of pseudoprogression to be established. [9] This discrepancy might explain the wide variation in the reported incidence of this phenomenon. A recent meta-analysis showed that the pooled incidence of pseudoprogression in newly diagnosed glioblastoma was 36 % (95 % CI 33–40) while tumor progression occurred in 60%. [10]

It is important to underline the differences between pseudoprogression and radiation necrosis, as they represent distinct clinical entities. Their main difference is the time of presentation, as pseudoprogression typically appears 3 to 6 months after the completion of chemoradiotherapy, whereas radiation necrosis presents 6 months to several years after treatment. [11] The time interval between treatment and detection of radiation necrosis differs depending on the radiotherapy technique, being longer when associated with carbon ion therapy than with proton or photon therapy.[12] Specifically, Miyawaki and colleagues reported a mean latency time between treatment and brain necrosis injury onset ranging from 6 to 49 months for proton therapy and 11 to 41 months for carbon ion therapy.[13] Although histopathology is considered the gold standard for the diagnosis of ePD, it has many limitations. Melguizo-Gavilanes and colleagues reported that in a cohort of 34 cases, the histological diagnosis and radiological interpretation of pseudoprogression matched in only 11/34 (32%) of cases (95 %CI 19–49%). Biopsy misdiagnosis highlights the importance of the radiological identification of tumor recurrence. Biopsy sampling has significant limitations; it is an invasive method, and sampling errors may occur. In resection specimens, areas of residual tumor mixed with minor areas of pseudoprogression could be misinterpreted as showing predominantly ePD. [14] Because of the drawbacks of histopathological diagnosis, several imaging modalities

have been developed for the differentiation of true tumor progression from pseudoprogression. MRI techniques, including diffusion-weighted imaging (DWI) and perfusion- weighted imaging (PWI), and nuclear medicine techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used [7], but the diagnostic performance of these imaging modalities has not been systematically evaluated to date.

To the best of our knowledge, although many studies have evaluated the radiological differentiation of recurrence from the broad category of "treatment related changes", none has focused on the identification of the early phenomenon of pseudoprogression. Here, we conducted a meta-analysis to evaluate the diagnostic performance of DWI and PWI in differentiating glioblastoma pseudoprogression from true tumor progression.

MATERIALS AND METHODS

Literature selection

This systematic review and meta-analysis adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15], and was written according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.[16] Eligible studies provided both sensitivity and specificity measures of DWI, PWI and PET, compared with the reference standards in the diagnosis of pseudoprogression. A literature search, as shown in **Figure 1**, was made in the PUBMED database up to December 10, 2019 by two independent reviewers (T.S and C.T), using the key words "pseudoprogression" AND "high-grade glioma" OR

"glioblastoma" AND "MRI" OR "PET". In addition, the reference lists of all the included articles were manually examined to identify eligible reports that might have been missed in the initial search.

Inclusion criteria

Studies that met the following criteria were included: (1) Patients with a newly diagnosed high-grade glioma, (2) standard care of treatment with first-line CCRT with temozolomide, followed by adjuvant temozolomide after surgical resection, (3) average interval between CCRT and the emergence of signs of radiological progression on MRI scan did not exceed 6 months, (4) clinico-radiological diagnosis (RANO criteria) and/or histopathology as a reference standard to differentiate between pseudoprogression and true tumor progression, (5) use of PWI and DWI or PET, (6) sufficient data to generate 2x2 tables for sensitivity and specificity, and (7) studies published as original articles.

Exclusion criteria

The exclusion criteria were: (1) non-English or other species articles, (2) case reports/case series and reviews, (3) use of other imaging techniques (PET, Conventional MRI) giving an insufficient sample to pool data, (4) insufficient data for obtaining 2x2 tables, (5) use of other therapeutic strategies, (6) average interval between CCRT and the emergence of signs of progression on MRI scan or on histopathology exceeding 6 months, and (7) low grade or recurrent gliomas. The details of the main studies that were excluded are displayed in Table 1. [17-22]

Data extraction and Quality assessment

The methodological quality of the included studies was evaluated independently using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [23] by two reviewers (T.S and C.T). In the case of disagreement, consensus was reached under consultation with a third reviewer (G.A). The results of the quality assessment are presented in **Figure 2**. With regards to patient selection, consecutive enrollment was reported in nearly all of the included studies. In terms of the index test domain, a prespecified threshold was reported in none of the included studies. This could be attributed mainly to the lack of consensus in published literature about a specific cut-off value to differentiate pseudoprogression from true progression. In many cases, it was unclear whether the imaging findings were evaluated blinded to the reference standard. Regarding the reference standard domain, it was largely unclear whether the results of the reference standard were assessed blinded to the imaging findings. In the flow and timing domain section, a high risk of bias was reported several studies, as the diagnosis was not based on the histopathological examination for all of the included patients, but also on radiological findings or clinical deterioration (RANO criteria).

RESULTS

Quantitative Analysis

The final sample consisted of 24 studies (9 DWI and 15 PWI) comprising a total of 900 patients with a mean age of 53.2 years. The male to female ratio was 1.7/1. The characteristics of the patients in the studies are shown in Table 2. [24-45] In addition, 4 PET studies were evaluated, but no pooled estimates were generated, due to insufficiency of the samples. The details of these studies are shown in Table 3 **[46-49].**

Due to high heterogeneity of the studies included in the meta-analysis, all the pooled parameters, namely sensitivity, specificity, likelihood ratio (LR), negative LR, and diagnostic odds ratio (DOR), were calculated using the random effects model. The pooled sensitivity of DWI was 0.88 (95%CI 0.83-0.92), slightly higher than that of PWI which was 0.85 (95%Cl 085-0.89). Heterogeneity was moderately high in the sensitivity of both DWI and PWI (I^2=61.3% and 64% respectively). The pooled values of the specificity of DWI and PWI were 0.85 (95%Cl 0.79-0.91) and 0.79 (95%Cl 0.74-0.84) respectively [**Figure 3**]. Although the specificity of DWI was higher than that of PWI, the difference did not reach statistical significance. Similarly, the DOR of DWI (DOR: 31.45 95%CI: 2.92-76.58) was found to be superior to that of PWI (DOR= 26.02 95%Cl: 10.97-61.72) The AUC values were 0.9156 and 0.9072 for DWI and PWI respectively [**Figure 4**], and neither study proved to be superior in terms of the AUC (p=0.8194). No statistical difference between DWI and PWI was demonstrated in any parameter [**Figure 5**]. The summary estimates, with their corresponding 95% CI, of the parameters used to compare the two techniques are shown in Table 4.

Subgroup analysis

In the subgroup analysis, we calculated the sensitivity and specificity individually for PWI studies using dynamic contrast enhanced (DCE) and dynamic susceptibility contrast (DSC). The 10 DCE studies showed a pooled sensitivity and specificity of 0.88 (0.83-0.91) and 0.77 (0.79-0.83) respectively, while in the 5 DSC studies) the sensitivity and specificity were 0.81 (0.73-0.88) and 0.82 (0.74-0.89) respectively.

Comparing the individual AUCs of each method, no statistically significant difference was found between the two (p=0.4645).

Discussion

The aim of this meta-analysis was to evaluate the relative effectiveness of DWI and PWI in the distinction between early tumor progression and pseudoprogression in patients with newly diagnosed glioblastoma. The DWI and PWI diagnostic accuracy according to the DORs were 31.45 and 26.2 respectively, showing that both techniques were highly efficient in identifying pseudoprogression. The LR+ values of 4.15 and 4.69 for DWI and PWI, respectively, revealed that patients with abnormal imaging findings were roughly 4 times more likely to have true progression of glioblastoma.

In contrast with other published studies on the differentiation between treatment related changes and tumor progression, our meta-analysis focused only on studies of patients presenting pseudoprogression at an interval not exceeding 6 months after the completion of CRRT. This restriction is important, because the term “treatment-related-changes” is a broad category that includes several distinct clinical entities, including pseudoprogression, but also radiation necrosis and mixed-response. Pseudoprogression occurs predominantly 3-6 months after the termination of CRRT, while radiation necrosis emerges typically from 6 months to several years post-treatment. The early identification of tumor recurrence (within 6 months) enables clinicians to decide whether repeat surgery and/or changes in chemotherapy are necessary in an attempt to improve the patient's course

Conventional MRI has limited utility in identifying tumor progression, as pointed out by Young and colleagues [44] who showed that subependymal

enhancement displayed a sensitivity of just 38.1%. PWI and DWI have therefore been investigated for their potential role in distinguishing early progression from pseudoprogression. Several other studies have assessed the role of MR spectroscopy or amide proton transfer-weighted (APTW) MRI, investigating specific imaging parameters as potential predictors of tumor progression, but due to insufficient numbers, they were not included in the final statistical analysis. Specifically, Ma and colleagues propose the use of APTW for the differentiation between early progression and pseudoprogression, reporting high diagnostic accuracy with sensitivity and specificity of 95% and 91.7% respectively. [23]

PET is also a promising technique, but its results in terms of early progression (within 6 months) are heterogenous. Skvortsova and colleagues [47] reported that PET could identify early tumor progression with a sensitivity of 83.5% and a specificity of 97%, but Brahm and colleagues demonstrated sensitivity and specificity of just 29% and 43% respectively. [48]

In conclusion, on meta-analysis of 24 studies, PWI and DWI were found to be equally effective in differentiating between pseudoprogression and true tumor progression of glioblastoma after CRRT. Thus, if certain centers put emphasis on DWI or PWI they may be better at using this as a diagnostic measure. Given that the imaging differentiation between pseudoprogression and true tumor progression continues to be a challenge, and is crucial to decisions about possible further intervention, additional studies with large samples should be conducted to provide more solid evidence.

References

1. Jeon, H.J., Kong, D.S., Park, K.B., Lee, J.I., Park, K., Kim, J.H., Kim, S.T., Lim, D.H., Kim, W.S., Nam, D.-H., 2009. Clinical outcome of concomitant chemoradiotherapy followed by adjuvant temozolomide therapy for glioblastaomas: single-center experience. Clin Neurol Neurosurg 111, 679–682. https://doi.org/10.1016/j.clineuro.2009.06.013

2. Liu Y, Shete S, Etzel CJ, Scheurer M, Alexiou G, Armstrong G, Tsavachidis S, Liang FW, Gilbert M, Aldape K, Armstrong T, Houlston R, Hosking F, Robertson L, Xiao Y, Wiencke J, Wrensch M, Andersson U, Melin BS, Bondy M. 2010. Polymorphisms of LIG4, BTBD2, HMGA2, and RTEL1 genes involved in the double-strand break repair pathway predict glioblastoma survival. J Clin Oncol. 28, 2467-2474.

3. Stupp, R., Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J.B., Belanger, K, 2005. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. New England Journal of Medicine 352, 987–996. https://doi.org/10.1056/NEJMoa043330

4. De Wit, M.C.Y., de Bruin, H.G., Eijkenboom, W., Sillevis Smitt, P. a. E., van den Bent, M.J., 2004. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. Neurology 63, 535–53 https://doi.org/10.1212/01.wnl.0000133398.11870.9a

5. Taal, W., Brandsma, D., de Bruin, H.G., Bromberg, J.E., Swaak-Kragten, A.T., Smitt, P.A.E.S., van Es, C.A., van den Bent, M.J., 2008. Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide. Cancer 113, 405–410. https://doi.org/10.1002/cncr.23562

6. Wen, P.Y., Macdonald, D.R., Reardon, D.A., et.al, 2010. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J. Clin. Oncol. 28, 1963–1972. https://doi.org/10.1200/JCO.2009.26.3541

7. Alexiou, G.A., Tsiouris, S., Kyritsis, A.P., Voulgaris, S., Argyropoulou, M.I., Fotopoulos, A.D., 2009. Glioma recurrence versus radiation necrosis: accuracy of current imaging modalities. J. Neurooncol. 95, 1–11. https://doi.org/10.1007/s11060-009-9897-1

8. Brandsma, D., Stalpers, L., Taal, W., Sminia, P., van den Bent, M.J., 2008. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol. 9, 453–461. https://doi.org/10.1016/S1470-2045(08)70125-6

9. Thust, S.C., van den Bent, M.J., Smits, M., 2018. Pseudoprogression of brain tumors. J Magn Reson Imaging 48, 571–589. https://doi.org/10.1002/jmri.26171

10. Abbasi, A.W., Westerlaan, H.E., Holtman, G.A., Aden, K.M., van Laar, P.J., van der Hoorn, A., 2018. Incidence of Tumor Progression and Pseudoprogression in High-Grade Gliomas: a Systematic Review and Meta-Analysis. Clin Neuroradiol 28, 401–411. https://doi.org/10.1007/s00062-017-0584-x

11. Zikou A, Sioka C, Alexiou GA, Fotopoulos A, Voulgaris S, Argyropoulou MI. Radiation Necrosis, Pseudoprogression, Pseudoresponse, and Tumor Recurrence: Imaging Challenges for the Evaluation of Treated Gliomas. Contrast Media Mol Imaging. 2018 Dec 2;2018:6828396.

12. Viselner, G., Farina, L., Lucev, F., Turpini, E., Lungarotti, L., Bacila, A., Iannalfi, A., D'Ippolito, E., Vischioni, B., Ronchi, S., Marchioni, E., Valvo, F., Bastianello, S., Preda, L., 2019. Brain MR findings in patients treated with particle therapy for skull base tumors. Insights into Imaging 10, 94. https://doi.org/10.1186/s13244-019-0784-9

13. Miyawaki, D., Murakami, M., Demizu, Y., Sasaki, R., Niwa, Y., Terashima, K., Nishimura, H., Hishikawa, Y., Sugimura, K., 2009. Brain Injury After Proton Therapy or Carbon Ion Therapy for Head-and-Neck Cancer and Skull Base Tumors. International Journal of Radiation Oncology, Biology, Physics 75, 378–384. https://doi.org/10.1016/j.ijrobp.2008.12.092

14. Melguizo-Gavilanes, I., Bruner, J.M., Guha-Thakurta, N., Hess, K.R., Puduvalli, V.K., 2015. Characterization of pseudoprogression in patients with glioblastoma: is histology the gold standard? J. Neurooncol. 123, 141–150. https://doi.org/10.1007/s11060-015-1774-5

15. Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLOS Medicine 6, e1000100. https://doi.org/10.1371/journal.pmed.1000100

16. Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283, 2008–2012.

17. Kebir, S., Khurshid, Z., Gaertner, F.C., Essler, M., Hattingen, E., Fimmers, R., Scheffler, B., Herrlinger, U., Bundschuh, R.A., Glas, M., 2017. Unsupervised consensus cluster analysis of [18F]-fluoroethyl-L-tyrosine positron emission tomography identified textural features for the diagnosis of pseudoprogression in high-grade glioma. Oncotarget 8, 8294–8304. https://doi.org/10.18632/oncotarget.14166

18. Mihovilovic, M.I., Kertels, O., Hänscheid, H., Löhr, M., Monoranu, C.-M., Kleinlein, I., Samnick, S., Kessler, A.F., Linsenmann, T., Ernestus, R.-I., Buck, A.K., Lapa, C., 2019. O-(2-(18F)fluoroethyl)-L-tyrosine PET for the differentiation of tumor recurrence from late pseudoprogression in glioblastoma. J Neurol Neurosurg Psychiatry 90, 238–239. https://doi.org/10.1136/jnnp-2017-317155

19. Kebir, S., Fimmers, R., Galldiks, N., Schäfer, N., Mack, F., Schaub, C., Stuplich, M., Niessen, M., Tzaridis, T., Simon, M., Stoffels, G., Langen, K.-J., Scheffler, B., Glas, M., Herrlinger, U., 2016. Late Pseudoprogression in Glioblastoma:

Diagnostic Value of Dynamic O-(2-[18F]fluoroethyl)-L-Tyrosine PET. Clin. Cancer Res. 22, 2190–2196. https://doi.org/10.1158/1078-0432.CCR-15-1334

20. Philipp Lohmann, Christoph Lerche, Elena Bauer, Jan Steger, Gabriele Stoffels, Tobias Blau, Veronika Dunkl, Christian P Filss, Carina Stegmayr, Bernd Neumaier, Nadim J Shah, Gereon Fink, Karl-Josef Langen, Norbert Galldiks, NIMG-32. Differentiation Of Pseudoprogression From Tumor Progression In Glioblastoma Patients Based On Fet Pet Radiomics, *Neuro-Oncology*, Volume 19, Issue suppl_6, November 2017, Pages vi148–vi149, https://doi.org/10.1093/neuonc/nox168.607

21. Wang, S., Martinez-Lage, M., Sakai, Y., Chawla, S., Kim, S.G., Alonso-Basanta, M., Lustig, R.A., Brem, S., Mohan, S., Wolf, R.L., Desai, A., Poptani, H., 2016. Differentiating Tumor Progression from Pseudoprogression in Patients with Glioblastomas Using Diffusion Tensor Imaging and Dynamic Susceptibility Contrast MRI. AJNR Am J Neuroradiol 37, 28–36. https://doi.org/10.3174/ajnr.A4474

22. Ma, B., Blakeley, J.O., Hong, X., Zhang, H., Jiang, S., Blair, L., Zhang, Y., Heo, H.-Y., Zhang, M., van Zijl, P.C.M., Zhou, J., 2016. Applying amide proton transfer-weighted MR imaging to distinguish pseudoprogression from true progression in malignant gliomas. J Magn Reson Imaging 44, 456–462. https://doi.org/10.1002/jmri.25159

23. Whiting, P.F., 2011. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Annals of Internal Medicine 155, 529. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

24. Baek, H.J., Kim, H.S., Kim, N., Choi, Y.J., Kim, Y.J., 2012. Percent change of perfusion skewness and kurtosis: a potential imaging biomarker for early treatment response in patients with newly diagnosed glioblastomas. Radiology 264, 834–843. https://doi.org/10.1148/radiol.12112120

25. Bulik, M., Kazda, T., Slampa, P., Jancalek, R., 2015. The Diagnostic Ability of Follow-Up Imaging Biomarkers after Treatment of Glioblastoma in the Temozolomide Era: Implications from Proton MR Spectroscopy and Apparent Diffusion Coefficient Mapping. Biomed Res Int 2015, 641023. https://doi.org/10.1155/2015/641023

26. Cha, J., Kim, S.T., Kim, H.-J., Kim, B.-J., Kim, Y.K., Lee, J.Y., Jeon, P., Kim, K.H., Kong, D.-S., Nam, D.-H., 2014. Differentiation of tumor progression from pseudoprogression in patients with posttreatment glioblastoma using multiparametric histogram analysis. AJNR Am J Neuroradiol 35, 1309–1317. https://doi.org/10.3174/ajnr.A3876

27. Choi, Y.J., Kim, H.S., Jahng, G.-H., Kim, S.J., Suh, D.C., 2013. Pseudoprogression in patients with glioblastoma: added value of arterial spin labeling to dynamic susceptibility contrast perfusion MR imaging. Acta Radiol 54, 448–454. https://doi.org/10.1177/0284185112474916

28. Chu, H.H., Choi, S.H., Ryoo, I., Kim, S.C., Yeom, J.A., Shin, H., Jung, S.C., Lee, A.L., Yoon, T.J., Kim, T.M., Lee, S.-H., Park, C.-K., Kim, J.-H., Sohn, C.-H., Park, S.-H., Kim, I.H., 2013. Differentiation of true progression from pseudoprogression in glioblastoma treated with radiation therapy and concomitant temozolomide: comparison study of standard and high-b-value diffusion-weighted imaging. Radiology 269, 831–840. https://doi.org/10.1148/radiol.13122024

29. Jovanovic, M., Radenkovic, S., Stosic-Opincal, T., Lavrnic, S., Gavrilovic, S., Lazovic-Popovic, B., Soldatovic, I., Maksimovic, R., 2017. Differentiation between progression and pseudoprogresion by arterial spin labeling MRI in patients with glioblastoma multiforme. J BUON 22, 1061–1067.

30. Kazda, T., Bulik, M., Pospisil, P., Lakomy, R., Smrcka, M., Slampa, P., Jancalek, R., 2016. Advanced MRI increases the diagnostic accuracy of recurrent glioblastoma: Single institution thresholds and validation of MR spectroscopy and diffusion weighted MR imaging. Neuroimage Clin 11, 316–321. https://doi.org/10.1016/j.nicl.2016.02.016

31. Kerkhof, M., Tans, P.L., Hagenbeek, R.E., Lycklama À Nijeholt, G.J., Holla, F.K., Postma, T.J., Straathof, C.S., Dirven, L., Taphoorn, M.J., Vos, M.J., 2017. Visual inspection of MR relative cerebral blood volume maps has limited value for distinguishing progression from pseudoprogression in glioblastoma multiforme patients. CNS Oncol 6, 297–306. https://doi.org/10.2217/cns-2017-0013

32. Kong, D.-S., Kim, S.T., Kim, E.-H., Lim, D.H., Kim, W.S., Suh, Y.-L., Lee, J.-I., Park, K., Kim, J.H., Nam, D.-H., 2011. Diagnostic dilemma of pseudoprogression in the treatment of newly diagnosed glioblastomas: the role of assessing relative cerebral blood flow volume and oxygen-6-methylguanine-DNA methyltransferase promoter methylation status. AJNR Am J Neuroradiol 32, 382–387. https://doi.org/10.3174/ajnr.A2286

33. Lee, W.J., Choi, S.H., Park, C.-K., Yi, K.S., Kim, T.M., Lee, S.-H., Kim, J.-H., Sohn, C.-H., Park, S.-H., Kim, I.H., 2012. Diffusion-weighted MR imaging for the differentiation of true progression from pseudoprogression following concomitant

radiotherapy with temozolomide in patients with newly diagnosed high-grade gliomas. Acad Radiol 19, 1353–1361. https://doi.org/10.1016/j.acra.2012.06.011

34. Mangla, R., Singh, G., Ziegelitz, D., Milano, M.T., Korones, D.N., Zhong, J., Ekholm, S.E., 2010. Changes in relative cerebral blood volume 1 month after radiation-temozolomide therapy can help predict overall survival in patients with glioblastoma. Radiology 256, 575–584. https://doi.org/10.1148/radiol.10091440

35. Martínez-Martínez, A., Martínez-Bosch, J., 2014. [Perfusion magnetic resonance imaging for high grade astrocytomas: Can cerebral blood volume, peak height, and percentage of signal intensity recovery distinguish between progression and pseudoprogression?]. Radiologia 56, 35–43. https://doi.org/10.1016/j.rx.2013.02.006

36. Nam, J.G., Kang, K.M., Choi, S.H., Lim, W.H., Yoo, R.-E., Kim, J.-H., Yun, T.J., Sohn, C.-H., 2017. Comparison between the Prebolus T1 Measurement and the Fixed T1 Value in Dynamic Contrast-Enhanced MR Imaging for the Differentiation of True Progression from Pseudoprogression in Glioblastoma Treated with Concurrent Radiation Therapy and Temozolomide Chemotherapy. AJNR Am J Neuroradiol 38, 2243–2250. https://doi.org/10.3174/ajnr.A5417

37. Park, J.E., Kim, H.S., Goh, M.J., Kim, S.J., Kim, J.H., 2015. Pseudoprogression in Patients with Glioblastoma: Assessment by Using Volume-weighted Voxel-based Multiparametric Clustering of MR Imaging Data in an Independent Test Set. Radiology 275, 792–802. https://doi.org/10.1148/radiol.14141414

38. Prager, A.J., Martinez, N., Beal, K., Omuro, A., Zhang, Z., Young, R.J., 2015. Diffusion and perfusion MRI to differentiate treatment-related changes including

pseudoprogression from recurrent tumors in high-grade gliomas with histopathologic evidence. AJNR Am J Neuroradiol 36, 877–885. https://doi.org/10.3174/ajnr.A4218

39. Reimer, C., Deike, K., Graf, M., Reimer, P., Wiestler, B., Floca, R.O., Kickingereder, P., Schlemmer, H.-P., Wick, W., Bendszus, M., Radbruch, A., 2017. Differentiation of pseudoprogression and real progression in glioblastoma using ADC parametric response maps. PLoS ONE 12, e0174620. https://doi.org/10.1371/journal.pone.0174620

40. Song, Y.S., Choi, S.H., Park, C.-K., Yi, K.S., Lee, W.J., Yun, T.J., Kim, T.M., Lee, S.-H., Kim, J.-H., Sohn, C.-H., Park, S.-H., Kim, I.H., Jahng, G.-H., Chang, K.-H., 2013. True progression versus pseudoprogression in the treatment of glioblastomas: a comparison study of normalized cerebral blood volume and apparent diffusion coefficient by histogram analysis. Korean J Radiol 14, 662–672. https://doi.org/10.3348/kjr.2013.14.4.662

41. Suh, C.H., Kim, H.S., Choi, Y.J., Kim, N., Kim, S.J., 2013. Prediction of pseudoprogression in patients with glioblastomas using the initial and final area under the curves ratio derived from dynamic contrast-enhanced T1-weighted perfusion MR imaging. AJNR Am J Neuroradiol 34, 2278–2286. https://doi.org/10.3174/ajnr.A3634

42. Thomas, A.A., Arevalo-Perez, J., Kaley, T., Lyo, J., Peck, K.K., Shi, W., Zhang, Z., Young, R.J., 2015. Dynamic contrast enhanced T1 MRI perfusion differentiates pseudoprogression from recurrent glioblastoma. J. Neurooncol. 125, 183–190. https://doi.org/10.1007/s11060-015-1893-z

43. Yoo, R.-E., Choi, S.H., Kim, T.M., Lee, S.-H., Park, C.-K., Park, S.-H., Kim, I.H., Yun, T.J., Kim, J.-H., Sohn, C.H., 2015. Independent Poor Prognostic Factors for True Progression after Radiation Therapy and Concomitant Temozolomide in Patients with Glioblastoma: Subependymal Enhancement and Low ADC Value. AJNR Am J Neuroradiol 36, 1846–1852. https://doi.org/10.3174/ajnr.A4401

44. Young, R.J., Gupta, A., Shah, A.D., Graber, J.J., Chan, T.A., Zhang, Z., Shi, W., Beal, K., Omuro, A.M., 2013. MRI perfusion in determining pseudoprogression in patients with glioblastoma. Clin Imaging 37, 41–49. https://doi.org/10.1016/j.clinimag.2012.02.016

45. Yun, T.J., Park, C.-K., Kim, T.M., Lee, S.-H., Kim, J.-H., Sohn, C.-H., Park, S.-H., Kim, I.H., Choi, S.H., 2014. Glioblastoma Treated with Concurrent Radiation Therapy and Temozolomide Chemotherapy: Differentiation of True Progression from Pseudoprogression with Quantitative Dynamic Contrast-enhanced MR Imaging. Radiology 274, 830–840. https://doi.org/10.1148/radiol.14132632

46. Galldiks, N., Dunkl, V., Stoffels, G., Hutterer, M., Rapp, M., Sabel, M., Reifenberger, G., Kebir, S., Dorn, F., Blau, T., Herrlinger, U., Hau, P., Ruge, M.I., Kocher, M., Goldbrunner, R., Fink, G.R., Drzezga, A., Schmidt, M., Langen, K.-J., 2015. Diagnosis of pseudoprogression in patients with glioblastoma using O-(2-[18F]fluoroethyl)-L-tyrosine PET. Eur. J. Nucl. Med. Mol. Imaging 42, 685–695. https://doi.org/10.1007/s00259-014-2959-4

47. Skvortsova, T.Y., Brodskaya, Z.L., Gurchin, A.F., 2014. [PET using 11C-methionine in recognition of pseudoprogression in cerebral glioma after combined treatment]. Zh Vopr Neirokhir Im N N Burdenko 78, 50–58.

48. Brahm, C.G., den Hollander, M.W., Enting, R.H., de Groot, J.C., Solouki, A.M., den Dunnen, W.F.A., Heesters, M.A.A.M., Wagemakers, M., Verheul, H.M.W., de Vries, E.G.E., Pruim, J., Walenkamp, A.M.E., 2018. Serial FLT PET imaging to discriminate between true progression and pseudoprogression in patients with newly diagnosed glioblastoma: a long-term follow-up study. Eur J Nucl Med Mol Imaging 45, 2404–2412. https://doi.org/10.1007/s00259-018-4090-4

49. Grosu, A.-L., Astner, S.T., Riedel, E., Nieder, C., Wiedenmann, N., Heinemann, F., Schwaiger, M., Molls, M., Wester, H.-J., Weber, W.A., 2011. An interindividual comparison of O-(2-[18F]fluoroethyl)-L-tyrosine (FET)- and L-[methyl-11C]methionine (MET)-PET in patients with brain gliomas and metastases. Int. J. Radiat. Oncol. Biol. Phys. 81, 1049–1058. https://doi.org/10.1016/j.ijrobp.2010.07.002

Table 1. Differentiation between true tumor progression of glioblastoma and pseudoprogression using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). Excluded studies with reasons for exclusion

Study Name	Imaging modality	Reason(s) for exclusion
Kebir et.al 2017 [17]	PET	Interval after completion of CCRT>6months
Mihovilovic et.al 2019 [18]	PET	Interval after completion of CCRT>6months
Kebir et.al 2016 [19]	PET	Interval after completion of CCRT>6months

Lohmann et.al 2017 [20]	PET	Not published as a full text
Wang 2016 et.al [21]	PWI	Differentiates ePD from mixed response (not pseudoprogression)
Ma et. Al 2016 [22]	APTW	Insufficient sample of studies to generate pooled sensitivity and specificity

ePD: early progressive disease, CCRT: concurrent chemoradiotherapy, PET: positron emission tomography, APTW: amide proton transfer-weighted imaging

Table 2 Differentiation between true tumor progression of gliomblastoma and pseudoprogression (PsP) using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). Detailed characteristics of the included studies (n=24)

Study Name	Imaging	Time Radiation completed (days)	Diagnosis of Tumor	Patients (N)	Mean Age (years)	Male (N)	Ps (N
Baek et.al 2012 [24]	PWI DSC	28	Clinico-radiological	79	50.6	46	3
Bulik et.al 2015 [25]	DWI	125	Clinico-radiological	24	52.5	17	5
Cha et.al 2014 [26]	PWI DSC	123.5	Clinico-radiological	35	49	18	2
Choi et.al 2013 [27]	PWI DSC	28	Clinico-radiological Histopathology	62	49.3	37	2
Chu et.al 2013 [28]	DWI	23	Clinico-radiological Histopathology	30	50.8	16	1
Jovanovic et.al 2017 [29]	PWI	90	Clinico-radiological	31	49	21	1
Kazda et.al 2016 [30]	DWI	180	Clinico-radiological Histopathology	39	51	28	1
Kerkhof et al 2017 [31]	PWI DSC	120	Clinico-radiological Histopathology	58	60	41	2
Kong et.al 2011[32]	PWI DSC	90	Clinico-radiological	59	50	35	2
Lee et.al 2012 [33]	DWI	97	Clinico-radiological	22	48.5	14	1
Mangla et.al 2010 [34]	PWI DSC	30	Clinico-radiological	19	61	13	7
Martinez et.al 2014 [35]	PWI DSC	180	ClinicalHistopathology	34	47.7	14	1

Nam et.al 2017 [36]	PWI DCE	28	Clinico-radiological - Histopathology	37	58	26	2
Park et.al 2015 [37]	PWI DCE and DWI	63	Clinico-radiological - Histopathology	54	45.5	25	3
Prager et.al 2015 [38]	DWI and PWI	180	Histopathology	51	54.9	38	8
Reimer et.al 2017 [39]	DWI	60	Radiological	35	60	26	7
Song et.al 2013 [40]	DWI	162	Radiological	20	50.8	10	1
Suh et.al 2013 [41]	PWI DCE	30	Clinico-radiologicalHistopathology	79	50.1	43	3
Thomas et.al 2015 [42]	PWI DCE	84	Clinico- radiological	37	63	25	1
Yoo et.al 2015 [43]	DWI	28	Radiological	42	56	27	1
Young et.al 2013 [44]	PWI DSC	80	Clinico-radiologicalHistopathology	20	58	14	4
Yun et.al 2014 [45]	PWI DCE	60	Radiological	33	54.6	22	1

DSC: dynamic susceptibility contrast imaging, DCE: dynamic contrast enhanced imaging

Table 3 Differentiation between true tumor progression of glioblastoma and pseudoprogression. Studies using positron emission tomography (PET) that were not included in the statistical analysis

Study Name	Tracer	Parameter	Cut-off	Sensitivity (%)	Specificity (%)
Galldiks et al. 2015 [46]	^{18}F-FET	TBR max	2.3	100	91
Skvortsova et al. 2014 [47]	^{11}C-MET	Uptake index (UI)	1.9	83.5	97
Brahm [48] et al. 2018	FLT	SUV max	0.25	29	43
Grosu et al. 2011 [49]	^{18}F-FET	Uptake value	0.84	91	100
	^{11}C-MET		0.78	91	100

Table 4. Differentiation between true tumor progression of glioma and pseudoprogression using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). Summary statistics of PWI and DWI.

	DWI (n=9)	**PWI (n=15)** (95%CI)

	(95%CI)	
Sensitivity	0.88 (0.83-0.92)	0.85 (0.81-0.89)
Specificity	0.85 (0.78-0.91)	0.79 (0.74-0.84)
DOR	31.45 (12.92-76.58)	26.02 (10.97-61.72)
LR+	4.15 (2.74-6.28)	4.69 (2.49-8.86)
1/LR-	5.88 (3.44-10)	4.35 (2.94-6.67)

Figure Legends

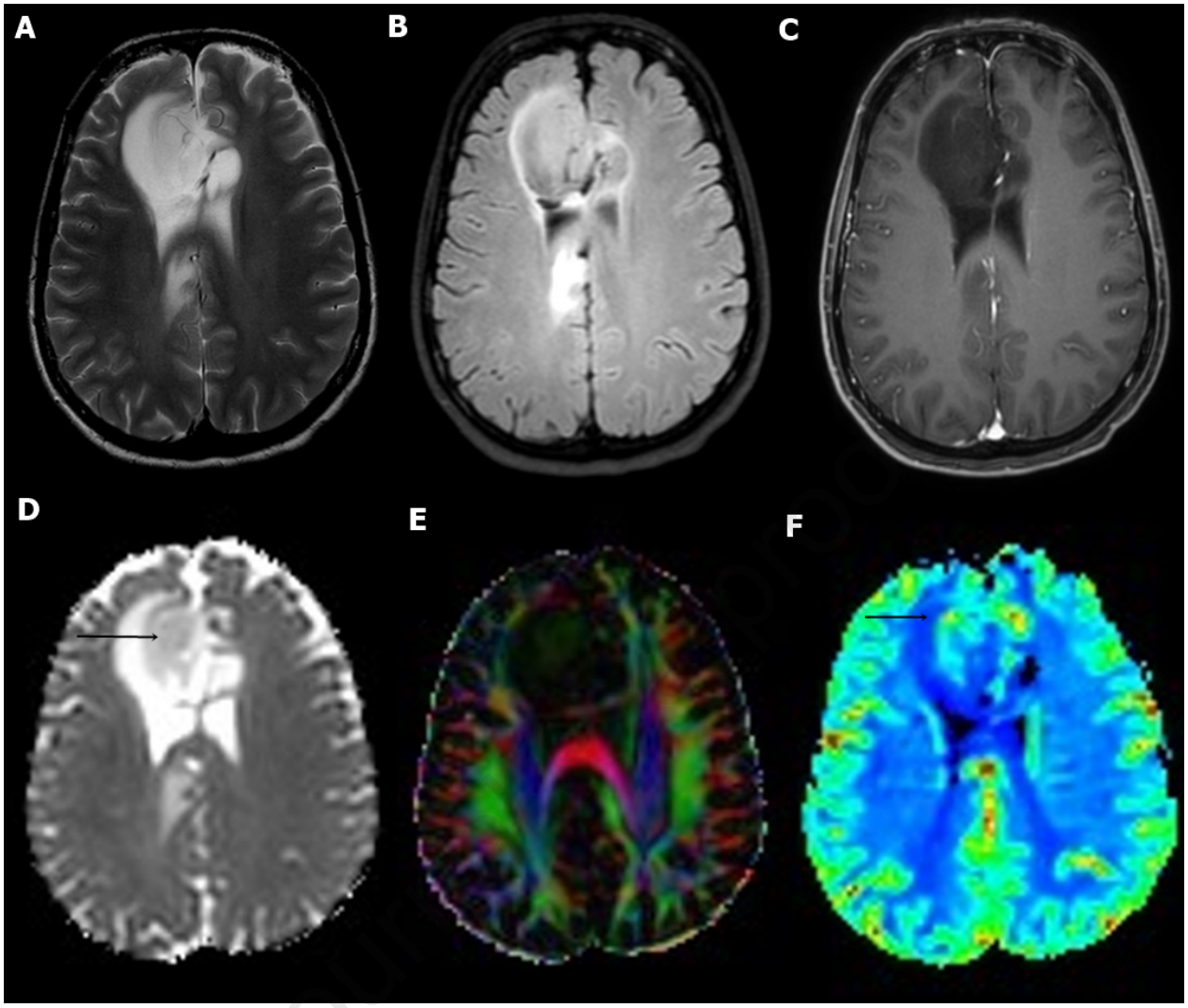
Figure 1. Differentiation between true tumor progression of glioblastoma and pseudoprogression using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). Flow chart presenting the selection of eligible studies

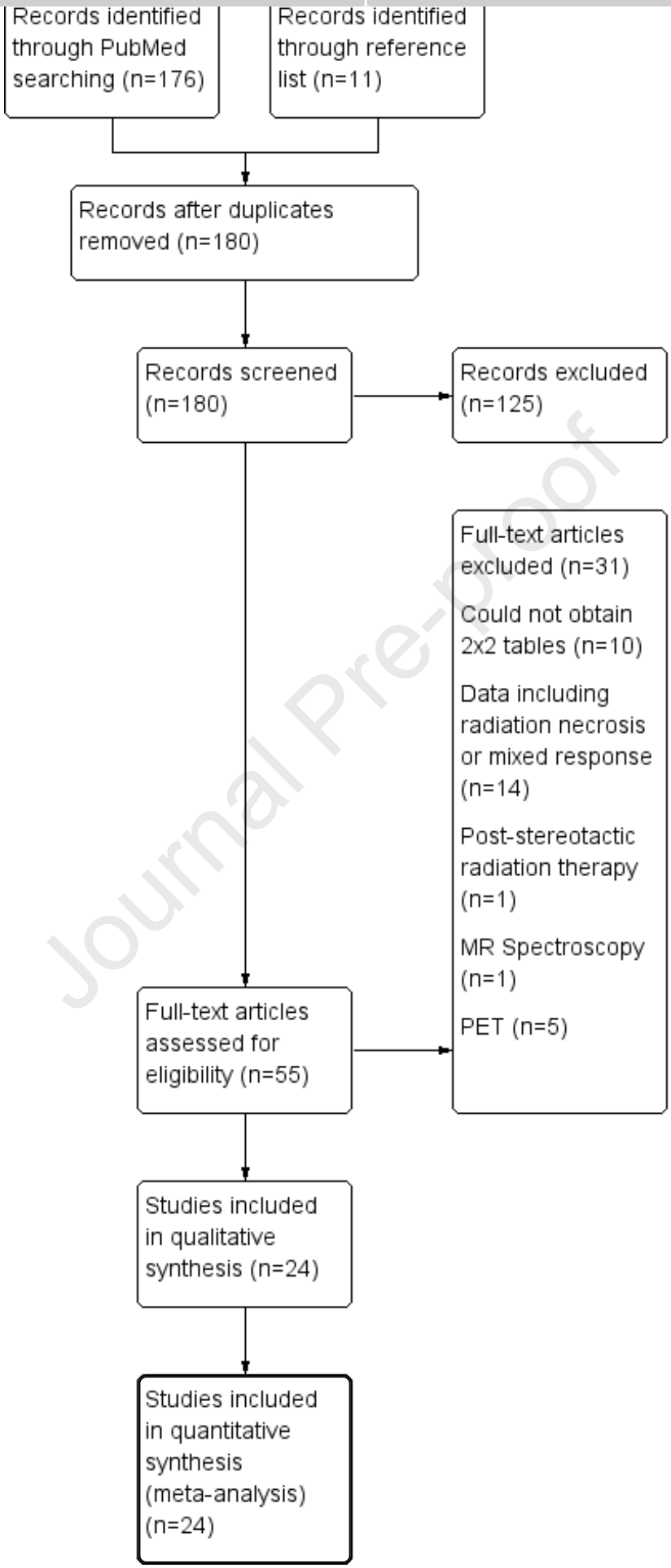
Figure 2. Differentiation between true tumor progression of glioblastoma and pseudoprogression using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). Quality assessment of the eligible studies

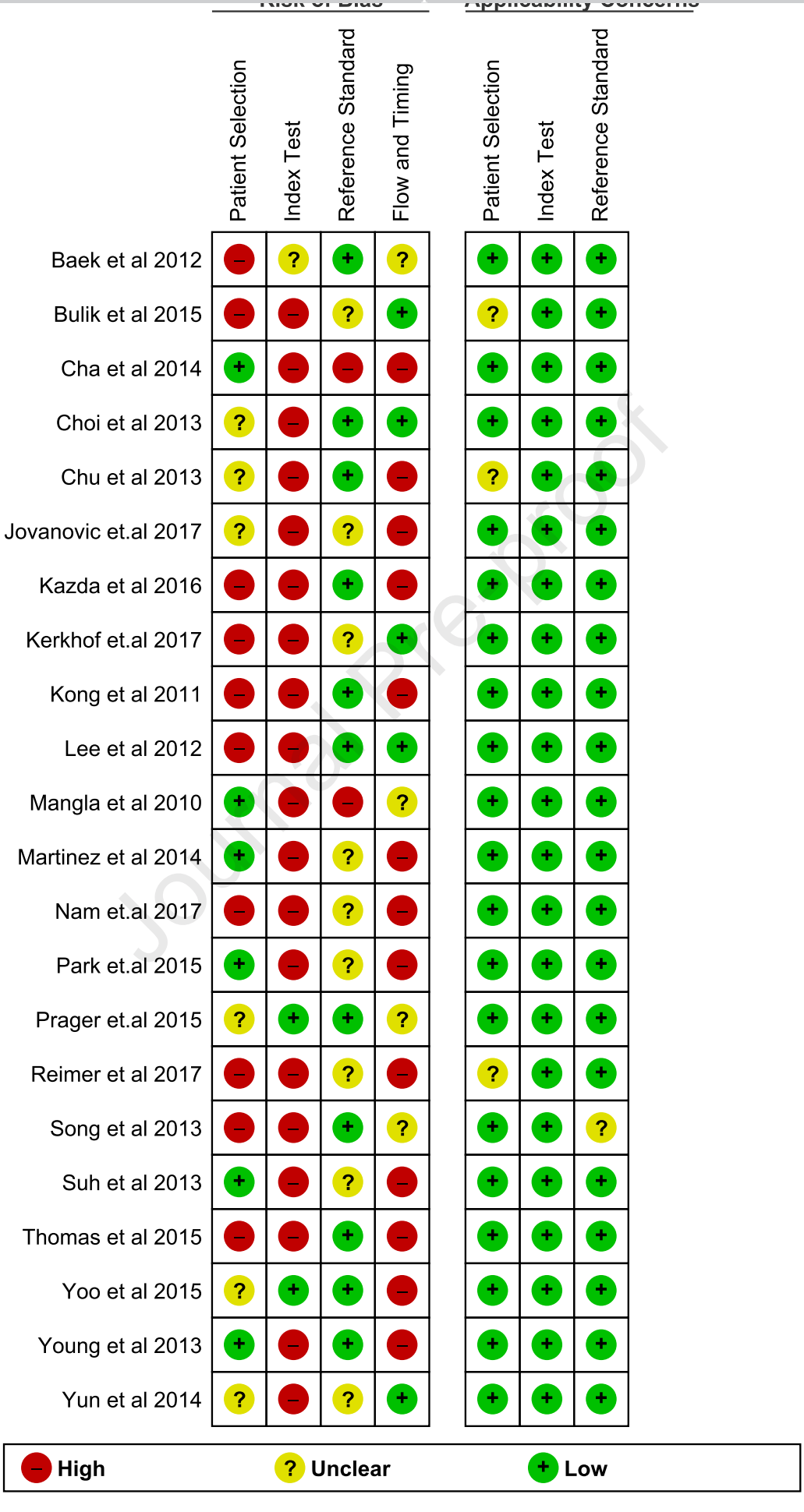
Figure 3. Differentiation between true tumor progression of glioblastoma and pseudoprogression using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). Forest plots of individual study results for DWI and PWI

Figure 4. Differentiation between true tumor progression of glioblastoma and pseudoprogression using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). Summary SROC plot of the diagnostic yield of DWI (A) and PWI (B)

Figure 5. A 63 year-old female patient presented with a right frontal space-occupying lesion suspicious of glioblastoma recurrence. The patient was operated 17 months ago for a right frontal glioblastoma and received postoperative chemoradiotherapy. **A.** Axial T2 and FLAIR (**B**) reveals perilesional oedema. **C.** Contrast-enhanced T1-weighted magnetic resonance (MR) image demonstrates an hypointense right frontal lesion. **D.** Apparent diffusion coefficient (ADC) map showing irregularly shaped lesion with perifocal oedema and areas of restricted diffusion (arrow), indicative of hypercellularity. **E.** The co-registered fractional anisotropy (FA) maps from diffusion tensor imaging (DTI). **F.** Relative cerebral blood volume (rCBV) map reveals areas with increased perfusion (arrow) suggesting the presence of recurrent tumor. The patient was operated on and glioblastoma recurrence was verified.

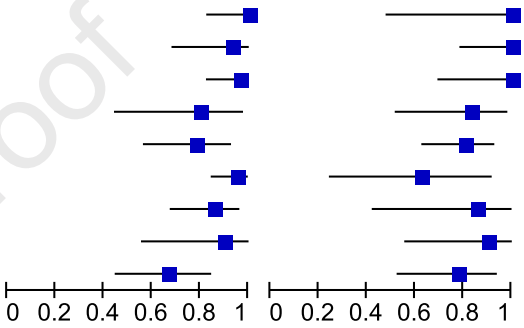

A
B
C
D
E
F





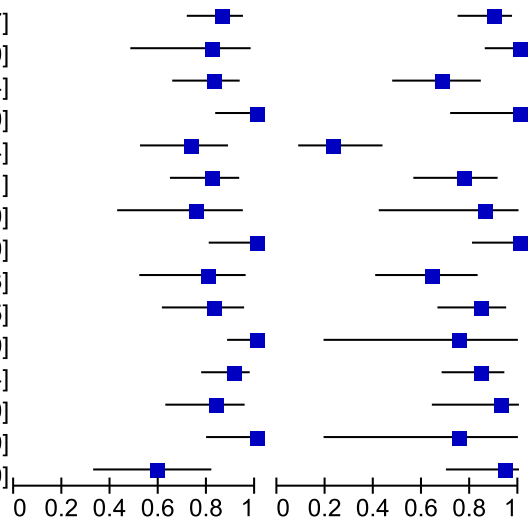
DWI

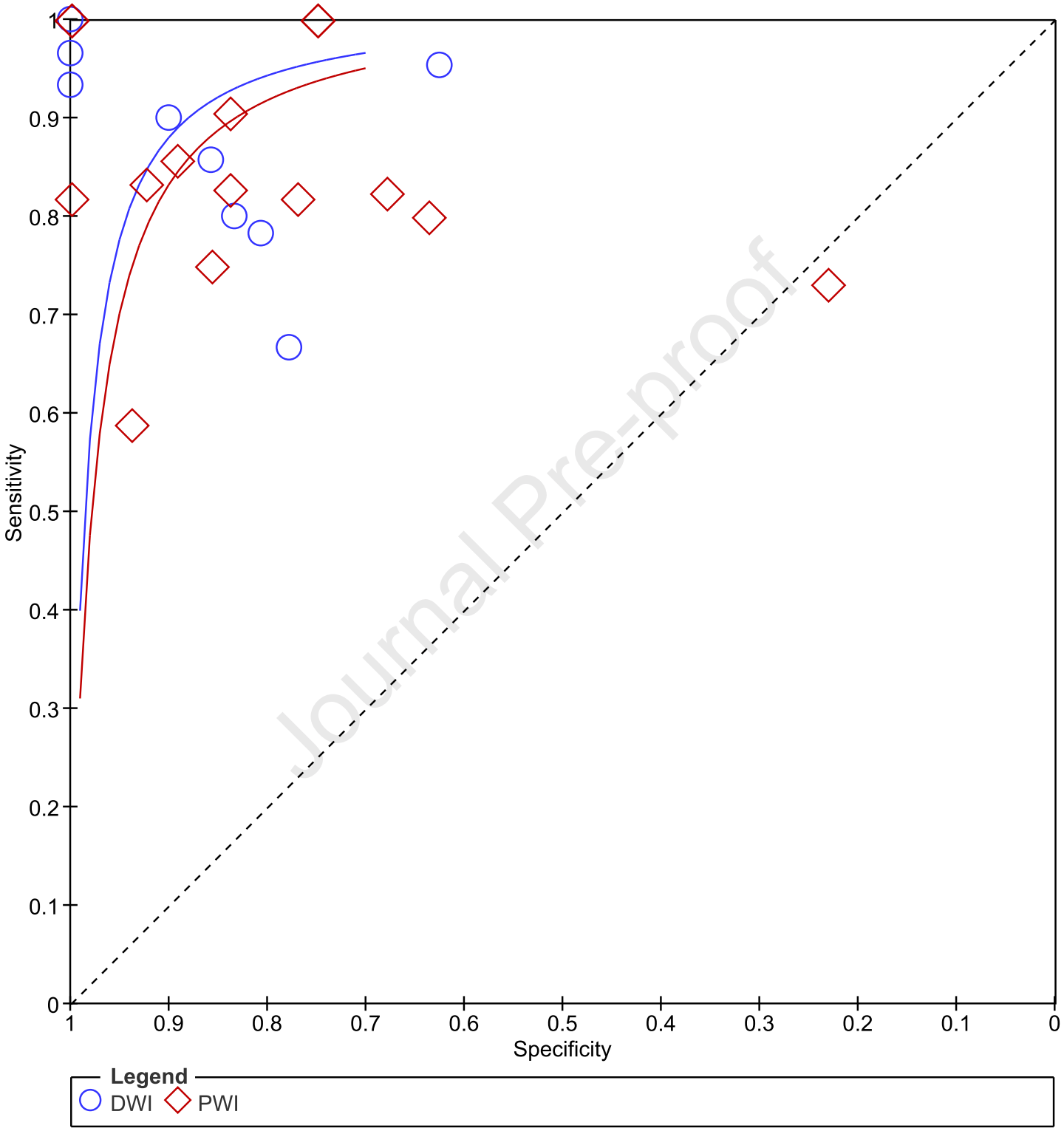
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bulik et al 2015	19	0	0	5	1.00 [0.82, 1.00]	1.00 [0.48, 1.00]
Chu et al 2013	14	0	1	15	0.93 [0.68, 1.00]	1.00 [0.78, 1.00]
Kazda et al 2016	28	0	1	10	0.97 [0.82, 1.00]	1.00 [0.69, 1.00]
Lee et al 2012	8	2	2	10	0.80 [0.44, 0.97]	0.83 [0.52, 0.98]
Park et al 2015	18	6	5	25	0.78 [0.56, 0.93]	0.81 [0.63, 0.93]
Prager et al 2015	41	3	2	5	0.95 [0.84, 0.99]	0.63 [0.24, 0.91]
Reimer et al 2017	24	1	4	6	0.86 [0.67, 0.96]	0.86 [0.42, 1.00]
Song et al 2013	9	1	1	9	0.90 [0.55, 1.00]	0.90 [0.55, 1.00]
Yoo et al 2015	16	4	8	14	0.67 [0.45, 0.84]	0.78 [0.52, 0.94]



PWI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Baek et al 2012	36	4	6	33	0.86 [0.71, 0.95]	0.89 [0.75, 0.97]
Cha et al 2014	9	0	2	24	0.82 [0.48, 0.98]	1.00 [0.86, 1.00]
Choi et al 2013	28	9	6	19	0.82 [0.65, 0.93]	0.68 [0.48, 0.84]
Jovanovic et.al 2017	20	0	0	11	1.00 [0.83, 1.00]	1.00 [0.72, 1.00]
Kerkhof et.al 2017	19	20	7	6	0.73 [0.52, 0.88]	0.23 [0.09, 0.44]
Kong et al 2011	27	6	6	20	0.82 [0.65, 0.93]	0.77 [0.56, 0.91]
Mangla et al 2010	9	1	3	6	0.75 [0.43, 0.95]	0.86 [0.42, 1.00]
Martinez et al 2014	17	0	0	17	1.00 [0.80, 1.00]	1.00 [0.80, 1.00]
Nam et.al 2017	12	8	3	14	0.80 [0.52, 0.96]	0.64 [0.41, 0.83]
Park et.al 2015	19	5	4	26	0.83 [0.61, 0.95]	0.84 [0.66, 0.95]
Prager et.al 2015	29	1	0	3	1.00 [0.88, 1.00]	0.75 [0.19, 0.99]
Suh et al 2013	38	6	4	31	0.90 [0.77, 0.97]	0.84 [0.68, 0.94]
Thomas et al 2015	20	1	4	12	0.83 [0.63, 0.95]	0.92 [0.64, 1.00]
Young et al 2013	16	1	0	3	1.00 [0.79, 1.00]	0.75 [0.19, 0.99]
Yun et al 2014	10	1	7	15	0.59 [0.33, 0.82]	0.94 [0.70, 1.00]





Abbreviations List

^{11}C-MET: ^{11}C-methionine

^{18}F-FET: ^{18}F-fluoroethyl-tyrosine

APTW: Amide Proton Transfer Weight MRI

AUC: Area Under the Curve

CCRT: Concurrent chemoradiotherapy

CI: Confidence Interval

DCE: Dynamic Contrast Enhanced

DOR: Diagnostic Odds Ratio

DSC: Dynamic susceptibility contrast

DWI: Diffusion Weighted Imaging

ePD: Early Progresssive disease

FLT: Fluorothymidine ^{18}F

FN: False Negative

FP: False Positive

GBM: Glioblastoma multiforme

LR: Likelihood Ratio

MRI: Magnetic Resonance Imaging

PET: Positron Emission Tomography

PsP: Pseudoprogression

PWI: Perfusion Weighted Imaging

SUV: Standardized Uptake Value

TBR: Tumor Bioreactor

TN: True Negative

TP: True Positive

UI: Uptake index

Conceptualization GA; Data curation TS, HT,VS, AZ. Formal analysis; GA, MA. Investigation, GA, TS, HT Methodology GA, MA, SV; Supervision; GA, MA, SV. Roles/Writing - original draft; GA, CS, AZ, TS, HT Writing - review & editing GA, AZ, CS, TS, HY.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: