Imaging Techniques for the Differentiation of Progression and Pseudoprogression in High Grade Gliomas

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Background

- The current standard treatment protocol for glioblastoma is surgical resection followed by 6 weeks of radiation therapy plus concomitant temozolomide chemotherapy (CCRT) and 6 cycles of adjuvant temozolomide chemotherapy[1]
- A significant challenge post-CCRT is the presence of radiation-induced side effects, such as pseudoprogression (PsP)
- PsP is generally defined radiologically as a new or enlarging area(s) of lesion(s) occurring early after the end of radiotherapy, which subsides or stabilizes without a change in therapy in the absence of true tumor growth (tumor progression, PD)[2]
- PsP is thought to be caused by blood-brain barrier breakdown causing leakage of contrast agent and also treatment-activated immune cells infiltrating the tumor microenvironment[3]
- Enlarged enhancing lesions on conventional MR images may represent PsP in up to 46.8%–64% of cases[4]
- The difficulty in distinguishing PD from PsP impedes clinical decision making in the treatment of patients
- Numerous attempts have been made for discrimination with non-invasive imaging-based techniques

Standard for Imaging Evaluation

- MRI is the current standard for imaging evaluation of GBM for diagnosis and measurement of response in both clinical practice and clinical trials
- The required sequences of the current MRI are three-dimensional T1-weighted images (T1WI), axial bi-dimensional T2-Fluid-attenuated inversion recovery (FLAIR) images, and axial bi-dimensional diffusion-weighted imaging (DWI) before gadolinium-based contrast agent is administered
- After contrast agent administration, the required sequences are axial bi-dimensional T2-weighted images (T2WI) and T1WI[5]
- Macdonald criteria (1990) uses T1WI to measure 2D contrast enhancement of the enhancing lesion
- RANO criteria (2010) uses T1WI and T2/FLAIR to measure 2D contrast enhancement of the enhancing lesion and non-enhancing lesions[7]

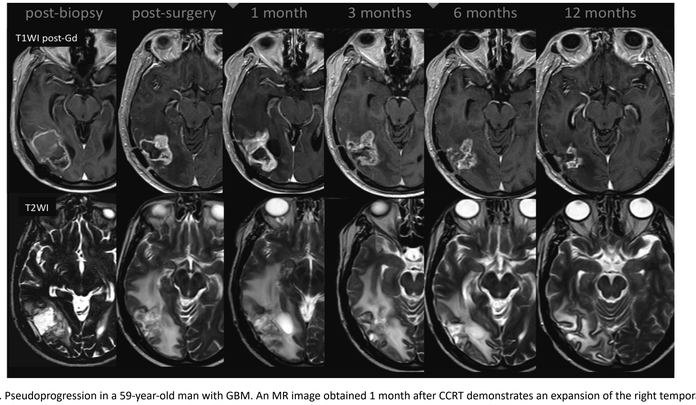

Fig 1. Pseudoprogression in a 59-year-old man with GBM. An MR image obtained 1 month after CCRT demonstrates an expansion of the right temporal lesion. Reductions in both the enhancing lesion (T1WI) and the surrounding abnormal hyperintense area (T2WI) were seen in the follow-up images.[6]

Methods

- Literature were collected through sources referenced by reviews, as well as PubMed and Google Scholar databases using combinations of search terms including “pseudoprogression,” “progression,” “glioblastoma,” “imaging,” “MRI,” “PET,” and “machine learning”

Table of Selected Literature and Meta-analysis

Author (Year)	Predictive Component	Imaging Techniques	Size	Ground Truth	Predictive ability	Conclusions
Tsien et al. (2010)[8]	PRM^{rCBV-} and PRM^{rCBF-}	T1WI-Gd, gradient-echo T2WI	27	Macdonald Criteria	$P(PRM^{rCBV-})$= 0.001; $P(PRM^{rCBF-})$= 0.107	PRM applied to physiologic MRI maps could be an important biomarker in determining PsP from PD
Ismail et al. (2018)[9]	Shape features of lesion habitat from conventional MRI	T1WI, T2WI, FLAIR	105	RANO Criteria	90.85% Accuracy	Local+global shape attributes from the enhancing lesion and perilesional areas from conventional MRI could improve the distinction of PsP from PD
Cha et al. (2014)[10]	Multiparametric histogram analysis using region of interest and rCBV and ADC values	T1W1, DWI, PWI	35	RANO Criteria	94.3% Accuracy	Multiparametric 3D histogram analysis with ADC values and rCBV was useful to evaluate posttreatment glioblastomas
Elshafeey et al. (2019)[11]	Classifier using radiomic features from Ktrans and rCBV maps	DSC, DCE	98	Pathological	90.82% Accuracy	MR perfusion-based radiomic model demonstrates high accuracy, sensitivity and specificity in discriminating PsP from PD
Matsusue et al. (2010)[12]	Multiparametric scoring system from ADC, rCBV, and combined Cho/Cr and Cho/NAA ratio	DWI, DSC, MRS	15	Lesion size change in follow-up MRI	93.3% Accuracy	Quantitative mpMRI ML analysis reveals distinctive posttreatment noninvasive signatures of PD versus PsP
Brahm et al. (2018)[13]	SUV^{max} and T/N ratio from FLT PET	Serial FLT PET	24	Macdonald Criteria	P>0.05 for all values	Further evaluation of FLT PET imaging is warranted to define its predictive ability
Galldiks et al. (2012)[14]	^{18}F-FET PET tumor brain ratios	^{18}F-FET PET compared to T1WI-Gd	25	Macdonald Criteria	n/a	TBR reduction in ^{18}F-FET PET may add valuable information to diagnose pseudoprogression.
Jang et al. (2018)[15]	CNN-LSTM structure ML algorithm using both MR imaging and clinical information	T1WI-Gd	78	Surgical (PD) or pathological (PD/PsP)	0.74 F1 Score	The ML algorithm with 9 selected axial MR images and clinical factors showed acceptable performance in differentiating PsP and PD.
Akbari et al. (2020)[16]	Quantitative ML analysis of mpMRI	T1WI, T1WI-Gd, T2WI, FLAIR, DTI, DSC	63 + 20(ii)	Pathology scores derived from histological analysis	85.5%, 75% (ii cohort) Accuracy	Quantitative mpMRI ML analysis reveals distinctive posttreatment noninvasive signatures of PD versus PsP

Author (Year)	Study Type (35 total)	Size (N=1174)	Results	Conclusions
van Dijken et al. (2017)[17]	Anatomical MRI ADC DSC DCE ASL MRS	5 studies; n=166 7 studies; n=204 18 studies; n=708 5 studies; n=207 2 studies, n=102 9 studies; n=203	Sensitivity 68% (51-81); Specificity 77% (45-93) Sensitivity 71% (60-80); Specificity 87% (77-93) Sensitivity 87% (82-91); Specificity 86% (77-91) Sensitivity 92% (73-98); Specificity 85% (76-92) Sensitivity (52-79 Range); Specificity (64-82 Range) Sensitivity 91% (79-97)); Specificity 95% (65–99)	Highest diagnostic accuracy for spectroscopy and perfusion MRI Meta-analysis supports the incorporation of advanced MRI in high-grade glioma treatment response assessment

Discussion

- Review suggests significant potential in advanced MRI, PET imaging, and ML in developing techniques for distinguishing between PD and PsP, but does not define a singular best method
- There is still a need for a clinically validated and accessible technique, meta-analysis suggests large, multicenter, longitudinal prospective trials
- Imaging comes with many limitations; alternative differentiators should be explored

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