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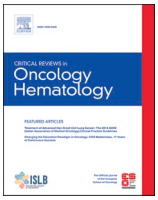

Perioperative imaging predictors of tumor progression and pseudoprogression: A systematic review

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ABSTRACT

In high-grade gliomas, pseudoprogression after radiation treatment might dramatically impact patient's management. We searched for perioperative imaging predictors of pseudoprogression in high-grade gliomas according to PRISMA guidelines, using MEDLINE/Pubmed and Embase (until January 2024).

Study design, sample size, setting, diagnostic gold standard, imaging modalities and contrasts, and differences among variables or measures of diagnostic accuracy were recorded. Study quality was assessed through the QUADAS-2 tool.

Twelve studies (11 with MRI, one with PET; 1058 patients) were reviewed. Most studies used a retrospective design (9/12), and structural MRI (7/12). Studies were heterogeneous in metrics and diagnostic reference standards; patient selection bias was a frequent concern. Pseudoprogression and progression showed some significant group differences in perioperative imaging metrics, although often with substantial overlap. Radiomics showed moderate accuracy but requires further validation.

Current literature is scarce and limited by methodological concerns, highlighting the need of new predictors and multiparametric approaches.

1. Introduction

Radiation therapy is a mainstay in the treatment of primary and metastatic brain tumors (Weller et al., 2020; Niyazi et al., 2023). Recent advances in radiation techniques have allowed a more accurate dose delivery, with subsequent reduction in the irradiated healthy tissue volume (Scaringi et al., 2018). Nevertheless, the need to deliver high doses of radiation to the tumor might lead to adjacent tissue damage, which might manifest at brain imaging as a wide spectrum of radiation-induced changes (Katsura et al., 2020). The differential diagnosis of post treatment radiation effects and true tumor progression is one of the biggest challenges in neuro-oncology, as misdiagnosis might lead to inappropriate interruption of effective treatments, with a negative impact on patient outcome. This is particularly important to avoid in high-grade gliomas, as treatment options are limited and pharmacotherapy has not shown an overall survival benefit at relapse (Weller et al., 2020). In response assessment of high-grade gliomas, enhancement is the most important variable; however, it lacks biological specificity (Wen et al., 2023; Booth et al., 2021). In fact, pseudoprogression might also present as contrast-enhancement. Furthermore, histology shows that post treatment radiation effects may coexist with a variable admixture of viable tumor cells (Kumar et al., 2000; Burger et al., 1979).

Pseudoprogression definition varies among studies, thus leading to differences in findings and reported incidence. It is usually defined retrospectively at brain MRI as a new or enlarging contrast-enhancing

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lesion, which eventually subsides or stabilizes at follow-up scans without any change in treatment; it occurs in up to 35 % of patients undergoing chemoradiation, typically within 3–6 months post-treatment (de Wit et al., 2004; Balaña et al., 2017; Young et al., 2011; Taal et al., 2008; Brandsma et al., 2008; Abbasi et al., 2017; Radbruch et al., 2015).

Clinical presentation alone does not allow the differentiation of pseudoprogression and progressive disease, as up to two thirds of patients with pseudoprogression might present with neurological deterioration (Balaña et al., 2017; Taal et al., 2008). To date, due to the high rate of pseudoprogression in the 12 weeks after the completion of radiation therapy, the Response Assessment in Neuro-Oncology Criteria (RANO) RANO and RANO 2.0 mandate the confirmation of progression within this time frame either with a repeat MRI at least 4 weeks later or with histopathology (Wen et al., 2023). This means that the suggested strategy is to postpone the decision or to perform a new surgery: both approaches might imply severe consequences for patient survival or quality of life. The existence of reliable pre-treatment predictors of pseudoprogression/true progression would address an early differential diagnosis with a prompt therapeutic decision.

In addition, while the Stupp protocol with its standardized radiation schedule has proven to be effective, the occurrence of pseudoprogression and the rate of early progression remain rather high (Stupp et al., 2005). The pre-treatment identification and stratification according to the risk of pseudoprogression or progression could result in a tailoring of radiation treatment with improvement in the progression free survival and quality of life.

O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation greatly increases the occurrence of pseudoprogression (Brandes et al., 2008; Hagiwara et al., 2022; Zhou et al., 2019). Concomitant treatment with temozolomide increases its likelihood, possibly due to the greater sensitivity of MGMT-methylated tumors to this drug (Gerstner et al., 2009). Interferon regulatory factor 9 and X-ray repair cross-complementing 1 genes have been proposed as potential biomarkers of pseudoprogression (Qian et al., 2016a). However, these molecular features are not sufficient to reliably predict its occurrence or require further validation.

Advanced neuroimaging (e.g. radiomics, perfusion, diffusion, and PET) allows the quantitative assessment of structure, perfusion, and metabolism of brain tumors. Radiomics is a recent tool which exploits the high-throughput extraction of image features, which can be harnessed through quantitative analysis enriching the characterization of the disease (Lambin et al., 2017). Diffusion, perfusion, and metabolic imaging have extensively been studied in the differentiation of true tumor progression and post treatment radiation effects with promising results (Henriksen et al., 2022; Booth et al., 2022a). There is growing evidence that pre- and post-operative structural and advanced neuroimaging, and radiomics could help predict both the molecular features of primary brain tumors and disease prognosis (Patel et al., 2017; Suh et al., 2018, 2019; van Santwijk et al., 2022; Lasocki et al., 2021; Xi et al., 2018; Larsson et al., 2020; Pérez-Beteta et al., 2019; Geraghty et al., 2022; Kotrotsou et al., 2018). However, their role in the prediction of pseudoprogression or true progression has been poorly defined. As tumor and pericavitary tissue characteristics are expected to partly explain the variability concerning progression and pseudoprogression, perioperative imaging might have a crucial role in identifying further predictive features before they may be confounded by subsequent treatments (Baine et al., 2021).

Finally, no pathology study investigated early phases that precede pseudoprogression and the knowledge of its pathophysiology is very scarce (Qian et al., 2016a; Melguizo-Gavilanes et al., 2015; Wang et al., 2023). Therefore, perioperative imaging could contribute to a better understanding of pseudoprogression pathophysiology by underlining the key differences in structure, perfusion, and metabolism which are associated with this condition.

This systematic review focuses on current literature concerning pre- and postoperative imaging predictors of pseudoprogression in high-grade gliomas aiming at highlighting its limits and potentials.

2. Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Page et al., 2021). One author with three years of experience in neuro-oncologic imaging performed a literature search using the MEDLINE/Pubmed and Embase (OVID interface) databases, selected the studies suitable for inclusion and collected the data. The following search terms were used: ("glioblastoma" OR "glioma" OR "gliomas" OR "brain tumors") AND ("pseudoprogression" OR "radiation necrosis" OR "radionecrosis" OR "post treatment radiation effects"). The search was updated until January 14th, 2024. To be eligible for inclusion, studies were required to investigate in newly diagnosed high-grade gliomas preoperative and/or postoperative (ranging from within 72 hours from surgery till immediately before chemoradiation) imaging predictors of post treatment radiation effects or group differences between patients who will develop true progression or post treatment related effects. Unpublished conference abstracts, duplicates, reviews of the literature, articles not in English, articles whose patients had all received further non-standard therapy (e.g. intraoperative radiation therapy or brachytherapy) before baseline imaging, and articles examining dosimetric criteria but no other imaging features were excluded. After duplicate removal, the selection criteria were first applied to title and abstract screening, and subsequently to the full text of the remaining articles. Whenever a paper included both suitable and unsuitable patients, data extraction of the relevant subjects was attempted. Reference sections of the selected studies were further screened for suitable articles.

Eligible outcomes were true tumor progression and post treatment radiation effects (i.e. pseudoprogression, radiation necrosis, or both). Basic information was extracted from included studies, namely first author's name, year of publication, study design (i.e. prospective or retrospective), numerosity, tumor type, setting (i.e. pre- or post-operative), type of post treatment radiation effect (i.e. pseudoprogression, radiation necrosis, or both), diagnostic reference standard, radiation technique, prevalence of concurrent temozolomide treatment, IDH mutations and MGMT promoter methylation, imaging approach (i.e. sequence or tracer).

Features differentiating tumor progression and radiation effects were collected and included differences among categorical variables (e.g. location, involvement of eloquent area), mean differences between continuous ones (e.g. tumor size, perfusion, tracer uptake) and measures of diagnostic accuracy. All the results that were compatible with each outcome domain in each study were extracted. Studies were grouped according to three main approaches to analysis, i.e. structural imaging, advanced imaging, and radiomics.

Study quality was assessed through the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Whiting et al., 2011).

3. Results

3.1. Characteristics of the included studies

From the 3980 records which were retrieved, 25 studies reached the final stage of our screening; however, thirteen were excluded for the following reasons: unfeasible data extraction due to unclear information about setting (n=3) (Miyashita et al., 2008; Rani et al., 2021; Zeyen et al., 2023), no MRI prior to radiation therapy (n=1) (Reuter et al., 2020), low sample size (n=1) (Rani et al., 2018), addition of brachytherapy to standard treatment (n=2) (Koot et al., 2008; Aiken et al., 2008), metrics needing both perioperative and post-treatment data (n=3) (Neal et al., 2013; Reimer et al., 2017; Qian et al., 2016b), and outcomes other than post treatment radiation effects (n=3) (Nelson

et al., 2016; Bolcaen et al., 2017; Du et al., 2023). Eventually, 12 studies were considered including 1058 patients with high-grade gliomas (Fig. 1).

The majority of these studies (9/12, 75 %) had a retrospective design (Balaña et al., 2017; Hagiwara et al., 2022; Baine et al., 2021; Ari et al., 2022; Mammadov et al., 2022; Ismail et al., 2020; Li et al., 2021; Moon et al., 2021; Roques et al., 2022); the remaining ones used a prospective design (Brahm et al., 2018; Tsien et al., 2010; Regnery et al., 2018). Eight studies (66.6 %) assessed pre-operative predictors, 3/12 studies post-operative predictors and one study both. Among the four studies investigating post-operative predictors, imaging was performed within 72 hours of surgery in one case (Brahm et al., 2018) and within 2 weeks after surgery in one study (Moon et al., 2021); no information about time from surgery was available in the remaining two studies (Li et al., 2021; Tsien et al., 2010). Pseudoprogression was the reported outcome in all studies but one (91.7 %); the remaining one assessed differences between true progression and stable disease (of whom pseudoprogression represented 3/12 cases) (Regnery et al., 2018). The diagnostic reference standard was clinico-radiologic in five cases (41.7 %) (Balaña et al., 2017; Baine et al., 2021; Ismail et al., 2020; Li et al., 2021; Regnery et al., 2018), mixed (i.e. histopathology and clinico-radiologic) in three (25 %) (Ari et al., 2022; Moon et al., 2021; Roques et al., 2022), radiologic in two (16.7 %) (Brahm et al., 2018; Tsien et al., 2010) and clinical in one (8.3 %) (Hagiwara et al., 2022); one study did not report the diagnostic reference standard (8.3 %) (Mammadov et al., 2022). Stupp protocol was applied or preferred in 7/12 studies (Balaña et al., 2017; Hagiwara et al., 2022; Baine et al., 2021; Li et al., 2021; Roques et al., 2022; Brahm et al., 2018; Regnery et al., 2018), 4/12 studies did not report the radiation therapy regimen (Ari et al., 2022; Mammadov et al., 2022; Ismail et al., 2020; Moon et al., 2021), while in one study the majority of patients underwent a dose escalation regimen (Tsien et al., 2010). When data regarding therapy with concurrent temozolomide was available (9/12 studies), the majority of patients (range 74.3–100 %) received this treatment (Balaña et al., 2017; Hagiwara et al., 2022; Baine et al., 2021; Ismail et al., 2020; Li et al., 2021; Moon et al., 2021; Brahm et al., 2018; Tsien et al., 2010; Regnery et al., 2018). Data about MGMT promoter methylation was available only in 7/12 studies (Balaña et al., 2017; Hagiwara et al., 2022; Baine et al., 2021; Li et al., 2021; Moon et al., 2021; Roques et al., 2022; Regnery et al., 2018).

Structural imaging analysis was the preferred approach in half of studies (Balaña et al., 2017; Hagiwara et al., 2022; Ismail et al., 2020; Li et al., 2021; Moon et al., 2021; Tsien et al., 2010), 4/12 studies used advanced imaging, namely DSC perfusion (Roques et al., 2022; Tsien et al., 2010), chemical exchange saturation transfer (CEST) imaging (Regnery et al., 2018) and PET (Brahm et al., 2018); 3/12 studies used radiomics (Baine et al., 2021; Ari et al., 2022; Mammadov et al., 2022). In 9/12 studies, post-contrast T1 sequences were used to assess differences between patients groups (Balaña et al., 2017; Hagiwara et al., 2022; Baine et al., 2021; Ari et al., 2022; Mammadov et al., 2022; Ismail et al., 2020; Li et al., 2021; Moon et al., 2021; Tsien et al., 2010), FLAIR was used in 4 cases (Balaña et al., 2017; Ismail et al., 2020; Li et al., 2021; Moon et al., 2021), DSC perfusion (Roques et al., 2022; Tsien et al., 2010), and pre-contrast T1 (Mammadov et al., 2022; Li et al., 2021) in 2 cases each, and T2 (Li et al., 2021), nuclear Overhauser enhancement (NOE) and amide proton transfer (APT) in 1 case (Regnery et al., 2018).

3.2. *Quality assessment*

Table 2 summarizes quality assessment according to QUADAS-2 for the selected studies.

In the patient selection domain of QUADAS-2, 6/12 studies had a high risk of bias due to the exclusion of patients i) not able to participate (Brahm et al., 2018), ii) with incomplete data about pseudoprogression (Baine et al., 2021), (iii) with inadequate or missing pre-treatment or follow-up MRIs (Ari et al., 2022; Mammadov et al., 2022; Moon et al., 2021), and (iv) who underwent postoperative complications or confounding treatments (Roques et al., 2022). The latter point needs further

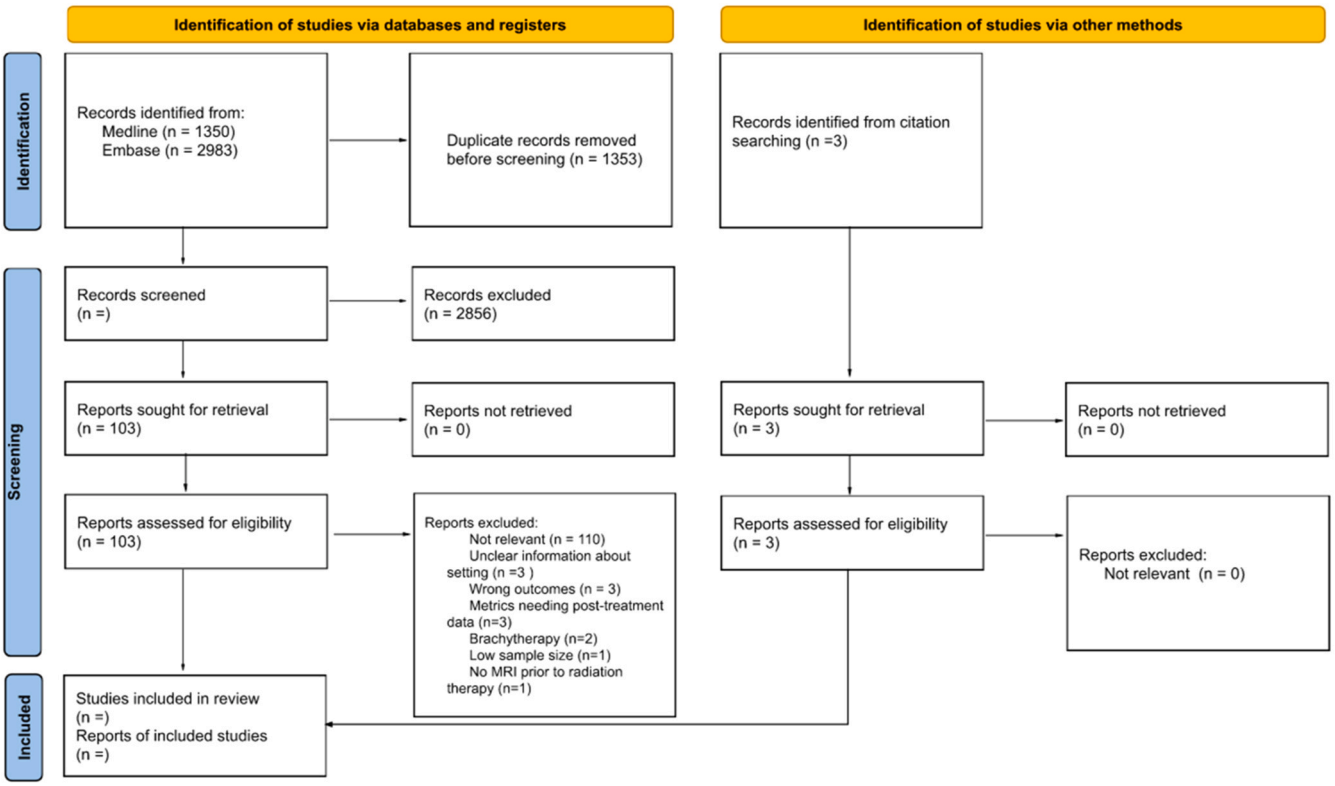

Fig. 1. Flow diagram describing the literature selection process according to PRISMA guidelines.

Table 1
Characteristics of the individual studies included. MGMT = O6-methylguanine-DNA methyltransferase; P = prospective; R = retrospective PsP = pseudoprogression; SD = stable disease; RANO = Response Assessment in Neuro-Oncology; N.A.: not available; CEST = Chemical Exchange Saturation Transfer; T1 C+ = contrast-enhanced T1; DSC = Dynamic Susceptibility Contrast perfusion; FLAIR = FLuid Attenuated Inversion Recovery; [18 F]FLT = 18 F-fluorothymidine; NOE = Nuclear Overhauser Enhancement; APT = Amide Proton Transfer; T1 C- = non-contrast-enhanced T1. *Gross total resection among exclusion criteria; 56.6 % had dose escalation. °Patients who completed treatment; 2 "secondary glioblastoma"; 2 patients excluded due to no uptake at baseline. #"IDH-mutant glioblastoma": n = 1 (5 %); 40 Gy/15 fractions for 5/20 patients.

Authors	Year	Design	Sample size	Type of tumor	IDH status +/unknown (%)	Setting	Post treatment radiation effect	Reference standard	Stupp protocol	Temozolomide	MGMT methylation +/- (% of pts)	Approach or Imaging modality	Sequence or tracer
Tsien et al.	2010	P	14/27*	Glioblastoma: n=23 Anaplastic astrocytoma: n=4	N.A.	Post-op	PsP	Radiologic (MacDonald criteria + follow-up)	44.4 %*	77.7 %	N.A.	Structural, Perfusion	T1 C+. DSC
Balaña et al.	2017	R	256	Glioblastoma	5.5/0	Pre-op	PsP	Clinico-radiologic	All	All	42.5/43.8	Structural	T1 C+, FLAIR
Brahm et al.	2018	P	14*	Glioblastoma	N.A.	Post-op	PsP	Radiologic	All	76.7 %%	N.A.	PET	[18 F]FLT
Regnery et al.	2018	P	20#	Glioblastoma	5/0	Pre-op	"SD" (PsP 3/12)	Clinico-radiologic (RANO)	75 %#	All	35/40	CEST	NOE, APT
Ismail et al.	2020	R	74	Glioblastoma	N.A.	Pre-op	PsP	Clinico-radiologic (RANO + multidisciplinary)	N.A.	All	N.A.	Structural	T1 C+, FLAIR
Baine et al.	2021	R	35	Glioblastoma	11.4/51.4	Pre-op	PsP	Clinico-radiologic	60 %	74.3 %	20/8.6	Radiomics	T1C+
Li et al.	2021	R	234	Glioblastoma	0/0	Peri-op	PsP	Clinico-radiologic (RANO + symptoms)	All	All	41.9/?	Structural	T1C-, T2. FLAIR, T1C+
Moon et al.	2021	R	86	Glioblastoma	0/1	Post-op	PsP	Histopathology Clinico-radiologic (RANO)	N.A.	All	39.5/44.2	Structural	T1C+, FLAIR
Roques et al.	2022	R	25	Glioblastoma	4/0	Pre-op	PsP	Radiologic (RANO: 80 % Histopathology: 20 %	All	N.A.	28/28	Structural, Perfusion	DSC
Ari et al.	2022	R	131	High-grade gliomas	N.A.	Pre-op	PsP	Histopathology Clinico-radiologic (?)	N.A.	N.A.	N.A.	Radiomics	T1C+
Mammadov et al.	2022	R	124	Glioblastoma	N.A.	Pre-op	PsP	N.A.	N.A.	N.A.	N.A.	Radiomics	T1C-, T1C+
Hagiwara et al.	2022	R	169	Glioblastoma	0/38.6	Pre-op	"Clinically-defined" PsP	Clinical	All	All	17.8/61.5	Structural	T1C+

Table 2
Quality assessment of individual studies according to QUADAS-2.

	Risk of bias				Concerns regarding applicability		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Tsien et al.	Low	Low	Low	Low	Low	High	Low
Balaña et al.	Low	Unclear	Low	Low	Low	Low	Low
Brahm et al.	High	Low	Low	Low	Low	Low	Low
Regnery et al.	Low	Low	Low	Low	Low	Low	High
Ismail et al.	Unclear	Low	Low	Low	Low	High	Low
Baine et al.	High	Low	Unclear	Low	Low	Low	Low
Li et al.	Low	Unclear	Low	Low	Low	Low	Low
Moon et al.	High	Low	Low	Low	Low	Low	Low
Roques et al.	High	Low	Low	Low	Low	Low	Low
Ari et al.	High	Low	Unclear	Low	Low	Low	Unclear
Mammadov et al.	High	Low	Unclear	Low	Low	Low	Unclear
Hagiwara et al.	Low	Low	Low	Low	High	Low	High

explanation. Patients enrolled in clinical trials for additional treatments usually have a better clinical status; for this reason retrospective studies excluding subjects who underwent additional treatments might under-represent patients with better prognosis (i.e. with a different clinical course).

One study had an unclear risk of selection bias due to exclusion criteria not being reported (Ismail et al., 2020). In the index test domain, 2/12 studies had an unclear risk of bias as the authors did not state whether imaging was assessed in a blinded fashion (Balaña et al., 2017), or they did not mention which sequence out of four was used to assess structures' involvement (Li et al., 2021). In the reference standard domain, one study had an unclear risk of bias as this item was not mentioned (Mammadov et al., 2022); its companion study also had an unclear risk due to unclear wording when defining the diagnostic standard for pseudoprogression (Ari et al., 2022). Another study had an unclear risk of bias in the reference standard domain as tumor board consensus was the diagnostic standard with no further explanation about the response assessment criteria (Baine et al., 2021). In the flow and timing domain, no concerns about the risk of bias were noted.

Regarding applicability, one study scored a high concern in the patient selection domain due to a clinical definition of pseudoprogression based on residual overall survival (Hagiwara et al., 2022). In the index test domain, the two DSC perfusion studies (Roques et al., 2022; Tsien et al., 2010) had a high applicability concern as their acquisition and post-processing methods did not follow current consensus recommendations (Boxerman et al., 2020). In the reference standard domain, 2/12 studies had a high concern regarding applicability, respectively due to the decision to classify patients as stable disease rather than pseudoprogression (Regnery et al., 2018), and to the use of a clinical definition of pseudoprogression based on residual overall survival (Hagiwara et al.,

Table 3
Summary of structural imaging findings. PD=progressive disease; PsP=pseudoprogression; AUC=area under the curve; OR=Odds ratio; CI=confidence interval; T1C+= contrast enhanced T1 sequence; FLAIR=Fluid Attenuated Inversion Recovery sequence; bold character used for significant findings.

Authors	Sample size	Sequence	Tumor Location	Tumor Size	Other characteristics	Notes
Tsien et al.	14	T1C+	Frontal/temporal: PD 57 % vs PsP 43 % (p=0.71) Other: PD 57 % vs PsP 43 % (p=0.71)	PD: 46.9±22.6 cm3 vs PsP: 23.1±19.1 cm3 (p=0.06)		Gross total resection among exclusion criteria
Balaña et al.	256	T1C+, FLAIR	No difference	No difference	No difference in involvement of eloquent areas	
Ismail	74	T1C+, FLAIR	**Voxel-wise differences**: PD: parietal; PsP: frontal, temporal, insula, putamen			
Li et al.	234	T1C-, T2, FLAIR, T1C+	Frontal location more common in PsP (47.5 vs. 25.0 %, not confirmed at multivariate regression analysis)		**Subventricular infringement: PD 53.3 % vs. PsP: 36.7 %, (p=0.016)**	
Moon et al.	86	T1C+, FLAIR			PsP more common in edema-dominant than in tumor-dominant FLAIR lesions (51.2 % vs 28.9 %, non significantat multivariate analysis	**Post-op contrast-enhancement evolution pattern** independent predictor at multivariate analysis
Roques et al.	25	T1C+		PD: 36.1±28.4 cm3 vs PsP: 53.9±31.9 cm3 (p=0.17)		Volume including central necrosis;
Hagiwara et al.	169	T1C+	**Voxel-wise differences: PD more common in right internal capsule, thalamus, lentiform nucleus, temporal lobe**	**PD: 14.0 (6.3–25.1) mL vs PsP: 7.3 (4.3–13.3) mL (p=0.002)** median [interquartile range]		Radiomics model using MRI at progression

2022). In the same domain, the two studies by the same group had a high concern regarding applicability due to the lack of definition of the reference standard, and unclear wording, respectively (Ari et al., 2022; Mammadov et al., 2022). To note, when every item is accounted for, no study had both a low risk of bias and low concerns regarding applicability in every domain. The results of the individual studies are reviewed in the following sections according to the imaging analysis approach.

3.3. Structural imaging

A summary of structural imaging studies is reported in Table 3.

Tsien et al. included data concerning baseline post-contrast T1 size differences between patients who will develop progression, pseudoprogression, and non-progressors in a prospective cohort of 27 newly diagnosed high grade gliomas. Patients received 60 Gy or more, as the majority was enrolled in a dose escalation study, and were classified according to MacDonald criteria and follow-up MRIs. There were no differences in location (assessed as frontal/temporal and "other") and initial tumor volume (Tsien et al., 2010), even though the 8 patients with subsequent progression had a trend for a larger size at baseline compared to the 6 patients with pseudoprogression (46.9±22.6 cm^3 vs. 23.1±19.1 cm^3, p=0.06).

In contrast, Roques et al. investigated a retrospective cohort of 25 glioblastomas and reported a larger initial tumor volume in the pseudoprogression subgroup (53.9±31.9 cm^3 vs 36.1±28.4 cm^3) though the difference did not reach statistical significance (p=0.17) (Roques et al., 2022).

Balaña et al. retrospectively evaluated 256 glioblastoma patients who underwent chemoradiation treatment according to the Stupp protocol. Patients were stratified as early progressors, pseudoprogressors and non-progressors based on the appearance or enlargement of a lesion at the first MRI evaluation, follow-up imaging, and/or clinical deterioration. T1contrast-enhanced and T2/FLAIR images were assessed for size of the tumor (smaller or larger than 5 cm), its location (3 groups, taking into account laterality and hemispheric vs. deep lesions), and the involvement of eloquent brain areas. No significant differences were found between the three groups. Our subgroup analysis of early progressors and pseudoprogressors did not disclose any differences (p>0.25 for every feature) (Balaña et al., 2017).

Ismail et al. investigated whether the location of newly diagnosed tumors differed between progression and pseudoprogression in a retrospective cohort of 74 glioblastoma patients classified according to RANO criteria and multidisciplinary tumor board evaluation. Enhancing lesions on post-contrast T1 and perilesional hyperintensities on FLAIR were used to construct atlases quantifying the frequency of occurrence of the two conditions and to compute voxel-wise significant differences. Frequency maps for both sequences showed that tumors subsequently undergoing progression were more likely distributed in the parietal and occipital lobes, whereas lesions undergoing pseudoprogression showed a multifocal distribution in the frontal and temporal lobes, insula, and putamen (Ismail et al., 2020).

Li et al. studied 234 consecutive retrospective cases of glioblastoma: pseudoprogression and true early progression were defined according to RANO criteria and symptoms. The MR protocol included pre- and post-contrast T1, T2, and FLAIR, but it was not specified which sequence was used to assess structures' involvement. Frontal location (Odds Ratio [OR]: 2.56, 95 % Confidence interval [CI]: 1.28–5.12, p=0.008) and non-subventricular zone infringement (OR: 10.94, 95 % CI: 5.06–23.64, p<0.001) were more common in pseudoprogression; however, frontal lesions were MGMT promoter methylation enriched (53.3 % vs. 36.7 %, p=0.016) and multivariate regression analysis validated only non-subventricular zone infringement as anatomical predictor (OR: 8.77, 95 % CI: 3.30–23.28, P < 0.001). Non-subventricular zone infringement, together with MGMT promoter methylation levels and extent of resection, was used to build a random forest model from perioperative data to differentiate progression and pseudoprogression (AUC: 0.937) and a nomogram to estimate the probability of pseudoprogression (concordance index = 0.911 in the validation subset) (Li et al., 2021).

Moon et al. retrospectively evaluated 86 IDH wild-type glioblastomas before and after chemoradiotherapy to assess whether non-enhancing lesion type could better predict pseudoprogression. FLAIR lesions on post-surgical MRI were classified as edema-dominant or tumor-dominant according to signal intensity, gray matter involvement, anatomic constraints, parenchymal expansion, and mass effect. Pseudoprogression and true progression were defined according to histopathology or clinicoradiologic follow-up in the 6 months after concurrent chemoradiotherapy following RANO criteria. In patients with new measurable or enlarging lesions, pseudoprogression rate was lower in the tumor-dominant type than in the edema-dominant type (28.9 % vs 51.2 %, p=0.047). A multivariate analysis including age, sex, performance status, contrast-enhancement evolution pattern and non-enhancing lesion type (but not gross total resection that was more frequent in edema-dominant lesions (p=0.023)) showed that the edema-dominant type was the only independent predictive marker for pseudoprogression (OR=0.26, 95 % CI=0.00–0.52, p=0.046) (Moon et al., 2021).

Hagiwara et al. retrospectively reviewed 169 glioblastoma patients from the control arm of a multicenter phase III trial who were treated according to the Stupp protocol and developed progressive findings at imaging within 6 months from radiation therapy. The authors grouped patients in "clinically-defined pseudoprogression" and "true progressive disease", according to whether or not the residual overall survival was longer than 12 months. "Clinically-defined pseudoprogression" was associated with postoperative smaller enhancing tumor volume, and a better neurological performance. Voxel-wise analysis identified a cluster that was more likely to occur in "true progressive disease" in right internal capsule, thalamus, lentiform nucleus, and temporal lobe (Hagiwara et al., 2022).

3.4. Advanced neuroimaging

3.4.1. Perfusion

Tsien et al. assessed post-operative differences in mean rCBV and rCBF though methodological and sample size concerns are present (see Tables 2 and 3). Patients with progression showed significantly higher mean rCBV values than patients with stable disease (3.1±0.6 vs 1.3 ±0.1) but not than those with pseudoprogression (3.1±0.6 vs 2.0±0.4) (Tsien et al., 2010).

Roques et al. investigated DSC perfusion in a retrospective cohort of 25 glioblastomas. Pseudoprogression was determined longitudinally by RANO criteria, or by histopathology. They found that the preoperative fraction of tumor with rCBV>2 was significantly lower for patients who developed pseudoprogression than for those with subsequent tumor progression (57.5 % vs. 71.3 %, p=0.03) (Roques et al., 2022).

3.4.2. Chemical exchange saturation transfer

Regnery et al. prospectively investigated chemical exchange saturation transfer (CEST) MRI at 7 Tesla in 20 untreated glioblastoma patients to predict treatment response to standard chemoradiation (Regnery et al., 2018). Nuclear Overhauser Effect (NOE) and Amide Proton Transfer (APT) CEST signals are novel contrast mechanisms which are related to protein concentration, pH, and cellularity (Jones et al., 2013; Togao et al., 2014; Zhou et al., 2003). Pre-treatment tumor NOE and APT values differed between progression and stable disease classified according to RANO criteria. NOE-Lorentzian Difference signal provided the highest diagnostic performance (AUC=0.98, p=0.0005, sensitivity=91 %, specificity=100 %). Stable disease included 3/12 patients rated as pseudoprogression.

3.4.3. PET

Brahm et al. evaluated the differences in postoperative uptake of [18 F]FLT, a tracer reflecting proliferative activity, in a cohort of 30

patients who underwent surgery for glioblastoma (WHO 2016). Patients were classified as progressors or pseudoprogressors based on Macdonald criteria and size changes at 10 and 22 weeks. In the 12 patients eligible for analysis, no difference in baseline postoperative SUVmax was found between progressors and pseudoprogressors (2.01 ± 1.08 vs. 1.96 ± 1.00, p=0.93) (Brahm et al., 2018).

3.5. Radiomics

Baine et al. retrospectively identified 35 patients (pseudoprogression, n=8) with glioblastoma who underwent postoperative radiation therapy. Pseudoprogression was defined as post-treatment imaging findings which resolved at follow-up imaging either spontaneously or with steroids. 841 imaging features, and clinical features were extracted from preoperative post-contrast T1 sequences to build radiomic models. The optimal model combination including two radiomic features (wavelet_HHL_firstorder_Mean and original_firstorder_Minimum) was able to predict pseudoprogression with a mean Area Under ROC Curve (AUC) of 0.82. No test sample or independent validation cohort were used (Baine et al., 2021).

Two studies by the same group applied radiomics to more than 120 high-grade gliomas, using 107 features extracted in one study from preoperative contrast-enhanced T1, and in the other both from non-contrast-enhanced and contrast-enhanced T1 sequences, respectively. Diagnostic criteria of early progression and pseudoprogression included histopathology but were unclear. The optimal model combinations, both based on post-contrast T1 images and including 6 variables, yielded a good accuracy in the prediction of pseudoprogression with AUC, sensitivity, specificity, and accuracy of 0.73, 0.72, 0.80, 0.76 (independent validation data) in the one study and 0.82, 0.82, 0.72, and 0.77 (independent test sample) in the other. To note, 2 out of 6 features were different among models and there were some minor differences concerning their order of importance (Ari et al., 2022; Mammadov et al., 2022).

4. Discussion

Early appropriate management of pseudoprogression and true tumor progression is crucial in the postoperative management of high grade gliomas as the two conditions require strikingly different therapeutic approaches. The quest for reliable predictors is therefore high in the routinary clinical setting in order to avoid further injury to the brain and provide the best chances of prolonged survival. Nevertheless, perioperative imaging predictors of pseudoprogression have seldom been the main aims of studies. Therefore, current literature on this topic is scant and is characterized by several limits regarding the heterogeneity of metrics and by methodological concerns. The subsequent paragraphs will deal with the main difficulties raised by the present review.

4.1. Heterogeneity of studies limits the generalizability of findings for pseudoprogression predictors

To date, only 12 studies have investigated the role of perioperative neuroimaging in the prediction of post treatment radiation effects in high-grade gliomas (Balaña et al., 2017; Hagiwara et al., 2022; Baine et al., 2021; Ari et al., 2022; Mammadov et al., 2022; Ismail et al., 2020; Li et al., 2021; Moon et al., 2021; Roques et al., 2022; Brahm et al., 2018; Tsien et al., 2010; Regnery et al., 2018). None of these studies scored both a low risk of bias and low concerns regarding applicability in every domain of QUADAS-2. Patient selection accounted for the majority of biases and concerns, underlining the difficulty of designing inclusion and exclusion criteria which reflect clinical practice and the heterogeneity of neuro-oncological patients. In addition, the low number of prospective studies (3/12) represents a clear shortcoming of the literature.Finally, few studies investigated post-operative imaging (3/12) that would have taken into account a pivotal factor such as the extent of tumor removal.

4.2. Size, subependymal involvement and non-enhancing lesion type might predict true progression

Concerning structural imaging, difference in location was the most reported finding (5/6 studies), with inconsistent results. Studies which treated anatomy as a categorical variable found no difference in the distribution of lesions which would undergo progression or pseudoprogression (Balaña et al., 2017; Li et al., 2021; Tsien et al., 2010). On the other hand, studies which used voxel-wise methods found significant but conflicting differences in location (e.g. temporal lobe and putamen being factors favoring pseudoprogression according to Ismail et al. and progressive disease according to Hagiwara et al.) (Hagiwara et al., 2022; Ismail et al., 2020) These inconsistencies might be partially due to the "clinical definition" of pseudoprogression by Hagiwara et al. and warrant further investigation in adequately powered prospective studies with the up to date definition according to RANO 2.0 (Wen et al., 2023); however, whether voxel-wise differences could translate into a clinically useful marker remains unclear.

A larger volume has been found in tumor progression compared with pseudoprogression both in low and high grade gliomas (Sidibe et al., 2023; van West et al., 2017). In glioblastoma, four studies have assessed the differences in size between patients who would develop progression and pseudoprogression disclosing conflicting results. Balaña et al. found no difference when classifying size as a binary variable, Hagiwara et al. found a smaller preoperative volume in "clinical pseudoprogression" patients, Tsien et al. reported a similar trend in the postoperative setting, while Roques et al. had a larger initial volume in patients with pseudoprogression (Balaña et al., 2017; Hagiwara et al., 2022; Roques et al., 2022; Tsien et al., 2010). Although the perioperative results are consistent with a larger size at progression, difference in size is unlikely to translate into a clinically reliable metric due to the substantial overlap in the volume distribution between the two groups.

Subventricular zone involvement is more likely to be present at baseline in patients developing true progressive disease rather than pseudoprogression according to two studies (Hagiwara et al., 2022; Li et al., 2021). These results are consistent with findings by Young et al., who reported subependymal enhancement to be much more common in true tumor progression (Young et al., 2011). Therefore, periventricular involvement before chemoradiation could be a promising predictor of true tumor progression, but it requires further validation.

Moon et al. found that baseline non-enhancing tumor type was the only independent predictor for pseudoprogression (Moon et al., 2021). Recently published RANO 2.0 criteria evaluate non-enhancing lesion burden only in selected cases, as its assessment does not improve the correlation between progression free survival and overall survival at least in the follow-up period (Wen et al., 2023; Youssef et al., 2023). As Moon et al. also found that tumor-dominant non-enhancing lesions were also associated with shorter time to progression but not with overall survival, non-enhancing lesion type could be a promising diagnostic predictor of pseudoprogression, but its impact on prognosis could be limited.

4.3. Advanced techniques: hypervascularized tumor fraction might predict true progression

DSC perfusion is the most widely studied advanced neuroimaging technique for differentiating tumor progression and pseudoprogression (Henriksen et al., 2022) however, its role as early predictor of these conditions seem to be poor. Both perfusion studies included in this review were limited by low sample size and suboptimal acquisition and post-processing. This issue might have impacted metrics estimates, thus leading to a decreased discriminatory power of mean and maximum perfusion values (Roques et al., 2022; Tsien et al., 2010). Nevertheless, Roques et al. found that patients who would undergo true tumor

progression had a higher volume fraction of hypervascularized tumor at preoperative MRI (Roques et al., 2022). This result is consistent with increased perfusion parameters at true progression compared to pseudoprogression (Patel et al., 2016; Hu et al., 2012; Iv et al., 2019). As high grade gliomas have a striking biological heterogeneity (Moffet et al., 2023), MRI metrics like hypervascularized tumor fraction, which take into account such variability, might be better suited to reveal pre-existing biological differences and might yield a higher predictive accuracy. The findings by Roques et al. need to be validated in a larger prospective cohort defining a threshold predictive of pseudoprogression or true progression; in addition the same approach could be pursued with other imaging techniques (e.g. diffusion, Dynamic Contrast-Enhanced perfusion, PET).

CEST MRI is a relatively new technique whose signal is related to protein concentration, pH, and cellularity (Zhou et al., 2003; Togao et al., 2014). Regnery et al. found differences between CEST metrics in patients who would undergo progression or remain stable. This study was included as the identification of predictors of true progression might help to indirectly identify pseudoprogression. However, although it might serve as a proof of concept, the required ultra-high field strength and the inability to disentangle pseudoprogression from other patients with stable disease limit the applicability of these findings to the prediction of pseudoprogression, at least in the clinical setting.

Using [18 F]FLT PET, Brahm et al. found no differences in tracer uptake at postsurgical baseline between patients who developed true progression and pseudoprogression (Brahm et al., 2018). However, as blood brain barrier disruption seems to be a prerequisite for [18 F]FLT uptake, increased tracer activity might be explained by post-surgical phenomena such as subacute hemorrhages and ischemia rather than tumor cell proliferation (Nowosielski et al., 2014). Surprisingly, although many PET tracers are used in oncology, only one study met our inclusion criteria. Further studies with more specific amino acid tracers would be valuable, as they are also fostered in glioblastoma follow-up by the recent PET RANO 1.0 criteria (Ouyang et al., 2023; Albert et al., 2024).

4.4. Radiomics

The three studies using radiomics have shown moderate diagnostic accuracy in differentiating progression and pseudoprogression based on preoperative imaging (Baine et al., 2021; Ari et al., 2022; Mammadov et al., 2022). Their predictive performance is comparable to that of prognostic radiomics models for overall survival based on preoperative MRI (Pease et al., 2022; Choi et al., 2021). A recent review of radiomics studies using machine learning in the differentiation of tumor progression from its mimics has been performed. Despite good pooled sensitivity and specificity, the implementation of such techniques into clinical practice is currently far-fetched, as most of these studies have a relatively small number of subjects, a high risk of selection bias, and unclear diagnostic criteria (Booth et al., 2022b). Similar concerns regarding sample size and risk of bias are present in the three studies addressed in our review and limit the generalizability of the radiomics in the prediction of pseudoprogression based on preoperative MRI. An additional issue to solve is the lack of consistency between the features extracted by Baine et al. and the other two studies. Larger multicenter comparative studies between models with well established diagnostic criteria are therefore needed.

4.5. Limitations

This literature review has some limitations. First, negative findings may be not included in the abstract leading to relevant finding exclusion in our review. For this reason, each study mentioning post treatment radiation effects in gliomas was retrieved and carefully read before exclusion. Second, no objective measures of data heterogeneity could be given due to the small number of studies and to the different types of predictors (i.e. group differences vs. measures of diagnostic accuracy). Third, this review included only cross-sectional neuroimaging metrics that might appear unsatisfactory for reliable prediction; actually, so far, longitudinal assessment has been used for early distinction instead of prediction of tumor progression and treatment effects (Reimer et al., 2017; Nazem-Zadeh et al., 2014).

4.6. New perspectives

Pseudoprogression remains a challenge during follow-up of glioma patients and a main topic during multidisciplinary tumor boards. Together with the refinement of the diagnostic tools for progression recognition, the identification of reliable perioperative predictors of pseudoprogression could be pivotal for the optimal management of these patients. The available literature is scarce and limited by mostly retrospective study design, inadequate sample size or conflicting/non-conclusive results. Moreover, current studies treat pseudoprogression as a 'black-or-white' phenomenon, whereas pathology shows that tumor cells frequently coexist with post treatment radiation effects (Kumar et al., 2000; Burger et al., 1979).

The main cornerstones of development in this field are therefore the adoption of prospective study design on large samples of glioma patients, the search for new MR sequences or new software for quantitative imaging analysis and the implementation of techniques that integrate morphological and metabolic features such as PET-MRI or DSC-derived fractional tumor burden (Hu et al., 2012; Iv et al., 2019; Albert et al., 2024).

5. Conclusions

Current literature about perioperative imaging predictors of pseudoprogression in high-grade gliomas is scant and is limited by methodological concerns and by the variability of assessed metrics. Although several perioperative differences between patients who will undergo true tumor progression and pseudoprogression exist, the overlap between such metrics in the two conditions might limit their clinical utility. Current studies have relied on a limited amount of imaging approaches and none of them has investigated the combination of different contrast mechanisms. Therefore, larger prospective studies using RANO 2.0 criteria and multiparametric imaging are needed both to validate current findings in real life prospective cohorts and to search for more reliable predictors.

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Declaration of Competing Interest

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.

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