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Pseudoprogression versus true progression in glioblastoma patients: A multiapproach literature review
Part 1 – Molecular, morphological and clinical features

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ABSTRACT

With new therapeutic protocols, more patients treated for glioblastoma have experienced a suspicious radiologic image of progression (pseudoprogression) during follow-up. Pseudoprogression should be differentiated from true progression because the disease management is completely different. In the case of pseudoprogression, the follow-up continues, and the patient is considered stable. In the case of true progression, a treatment adjustment is necessary. Presently, a pseudoprogression diagnosis certainly needs to be pathologically confirmed. Some important efforts in the radiological, histopathological, and genomic fields have been made to differentiate pseudoprogression from true progression, and the assessment of response criteria exists but remains limited. The aim of this paper is to highlight clinical and pathological markers to differentiate pseudoprogression from true progression through a literature review.

1. Introduction

Glioblastoma multiforme (GBM), the most common malignant brain primary tumor in adults, represents approximately 60 % of all gliomas (Ostrom et al., 2015, 2013; Ahmed et al., 2014). The incidence of GBM is 3/100,000 in Europe and North America (12,000 patients per year) (Dolecek et al., 2012; Albert et al., 2016; Bleeker et al., 2012). One-third of patients with GBM survive 1 year, with a median survival of 15–18 months, and the survival rate is less than 5% at 5 years (Ostrom et al., 2015, 2013; Stupp et al., 2005; Seystahl et al., 2016). In addition, most patients experience tumor recurrence or progression during follow-up (Ostrom et al., 2015; Stupp et al., 2005; Chinot et al., 2014; Kang

Abbreviations: ATRX, Alpha-Thalassemia/mental Retardation syndrome X-linked; BPTI, International Brain Tumor Imaging; BRAF, V-raf murine sarcoma viral oncogene homolog B1; CDKN2A/B, Cyclin Dependent Kinase Inhibitor 2 A/B; CR, Complete Response; CRT, Chemoradiotherapy; EV, Extracellular Vesicles; EGFR, Epidermal Growth Factor Receptor; FLAIR, Fluid-Attenuated Inversion Recovery; GBM, Glioblastoma; HGG, High Grade Glioma; IDH, Isocitrate Deshydrogenase; IRF9, Interferon Regulatory Factor 9; KPS, Karnofsky Performance Status; MDM2/4, Murine Double Minute 2/4; MGMT, Methylguanine-Methyltransferase; MRI, Magnetic Resonance Imaging; MRS, Magnetic Resonance Spectroscopy; NANO, Neurologic Assessment in Neuro-oncology; NF 1, Neurofibromin 1; OS, Overall Survival; RT, Radiotherapy; PD, Progressive Disease; PDGFRA, Platelet Derived Growth Factor Receptor Alpha; PET, Positron Emission Tomography; PTEN, Phosphatase and Tensine homolog; PFS, Progression Free Survival; PR, Partial Response; PsP, Pseusoprogression; RANO, Response Assessment in Neuro-Oncology; RN, Radionecrosis; SD, Stable Disease; TCGA, The Cancer Genomic Atlas; TERT, Telomerase Reverse Transcriptase; TGF, Transforming Growth Factor; TMZ, Temozolomide; TP, True Progression; TP 53, Tumor Protein 53; TTP, Time to Progression; VEGF, Vascular Endothelial gGowth Factor; WHO, World Health Classification; XRCC1, X-Ray Cross-Complementary gene 1.

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et al., 2011), with a median time of recurrence of 8–9 months (McNeill et al., 2015). In 2005, Stupp et al. proposed a randomized multicenter phase trial that included 573 GBM patients to compare radiotherapy (RT) alone (60 Gy in 30 fractions) and concomitant chemoradiotherapy (CRT) combining RT and temozolomide (TMZ) after a maximal debulking surgery between August 2000 and March 2002. The median age of the included patients was 56 years, and 63 % were male. The median follow-up was 28 months. In the CRT group versus the RT alone group, the median overall survival (OS) was 14.6 months versus 12.1 months ($p < 0.001$), the median progression-free survival (PFS) was 6.9 months versus 5 months ($p < 0.001$) and the two-year survival rate was 26.5 % versus 10.4 %, respectively (Stupp et al., 2005). The authors showed that CRT improves survival in GBM patients without increasing toxicity, and the "Stupp protocol" is now the standard of care for GBM patients (Stupp et al., 2005, 2009).

Conventional gadolinium-enhanced magnetic resonance imaging (MRI) is the cornerstone examination for monitoring treatment response but fails to distinguish true progression (TP) from pseudoprogression (PsP). However, the concordance for PsP between radiological interpretation and subsequent histological features can be as low as 32 % of cases (Melguizo-Gavilanes et al., 2015). Conventionally, PsP MR images show vasogenic edema with increased contrast enhancement (Brandsma et al., 2008; Ellingson et al., 2017a). Some authors have studied potential PsP markers, such as tumor size, shape, number of contrast-enhancing lesions, location, radiation dose distribution, or sharp demarcation, with discordant results (Young et al., 2011; Rowe et al., 2018; Agarwal et al., 2013; Mullins et al., 2005; Kim et al., 2014; Hansen et al., 2018). Conventional MRI has limitations, and some efforts to develop other imaging features are encouraging, particularly in the case of immunotherapy (Aquino et al., 2017). Advanced MRI techniques, magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and multiparametric imaging can provide additional information on cellular, biological, and metabolic parameters when conventional MRI is ambiguous to improve the distinction between PsP and TP (Masch et al., 2016; Gerstner et al., 2009; Lewis et al., 2016; Hyare et al., 2017). However, no single imaging characteristic or combination of features has been validated to date to differentiate PsP and TP, and efforts to create uniform practices and protocols are necessary (Lieberman, 2017). Some efforts have been made to elaborate standardized criteria, resulting in the Response Assessment in Neuro-Oncology (RANO) criteria (Wen et al., 2010), which updated the Macdonald criteria (Macdonald et al., 1990) and defined PsP as a transient 25 % increase in the sum of the product of the perpendicular diameters of measurable contrast-enhanced lesions associated or not with an increase in T2/fluid-attenuated inversion recovery (FLAIR) within 12 weeks after CRT that decreased or disappeared 4 weeks after MRI, without specific treatment.

PsP can be defined as subacute radiographic changes (enlarged or new contrast enhancement within the radiation field) mimicking tumor progression that resolves spontaneously without modifying therapy (Ellingson et al., 2014a; Radbruch et al., 2015; Dietrich et al., 2017). PsP often occurs in the first six months after CRT, and its incidence remains variable (2–50 %) (Abbasi et al., 2018). The identification of PsP is challenging, and repeated follow-up imaging is necessary (Hygino da Cruz et al., 2011; Zhang et al., 2016). The diagnosis of PsP indicates treatment efficacy, and continuing adjuvant TMZ or follow-up should be encouraged. The conclusion of TP means that current treatment must be modified (e.g., antiangiogenic therapy, radiotherapy, surgery, or combination treatment) (Strauss et al., 2019). Differentiation between PsP and TP is required to avoid unnecessary reoperations and the premature discontinuation of TMZ, which can be sources of distress in patients (Peca et al., 2009; Wick et al., 2016; Yoo and Choi, 2016).

In addition to imaging, histopathology and genomic information can help in the diagnosis of PsP. It has already been shown that patients with O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation have a higher incidence of PsP as well as an increase in overall survival (OS) (Brandes et al., 2008). The features of macroscopic images can be combined with genomic features to improve the characterization of GBM and facilitate the diagnosis of PsP or TP (Gutman et al., 2013).

In clinical trials, the criteria to define PsP are often different, as are the time points of the evaluation (Yoo and Choi, 2016). This results in the inclusion of patients with PsP in TP groups because of a false diagnosis of TP as well as a falsely improved PFS. The eligibility for salvage treatment could be hindered in the case of misinterpretation (van den Bent et al., 2009; Delgado-López et al., 2018).

The aim of this review was to identify clinical and pathological markers for differentiating PsP and TP and their impact on the survival rate of GBM patients treated by the Stupp protocol.

2. Materials and methods

A literature search was conducted using the Medline/PubMed, ScienceDirect and Cochrane Wiley databases. Search terms included ("glioblastoma" OR "gliomas" OR "high grade gliomas") AND ("pseudoprogression" OR "pseudo-progression"). Articles concerning PsP in adult patients with glioma, high-grade glioma (HGG) and GBM who were treated with the Stupp protocol were examined. References provided from relevant articles were also examined to identify additional studies to be included. Any irrelevant entries and articles not in English were excluded. Twenty-four articles about response assessment criteria, 29 about the definition of PsP, 58 about PsP incidence, 20 about PsP occurrence delay, 19 about PsP clinical markers, 30 about PsP survival impact, and 35 about PsP molecular markers were included in this review (Table 1).

3. Definitions

3.1. Definition of PsP

Many definitions of PsP have been published in the literature. PsP was reported for the first time in 1979 by Hoffman et al. (1979). Then, in 2004, De Wit et al. described PsP as "progressive MRI lesions shortly after radiotherapy with spontaneous improvement or stabilization without additional treatment" (de Wit et al., 2004). In 2007, Chamberlain et al. reported that the use of TMZ in CRT could influence PsP incidence (Chamberlain et al., 2007). Eventually, in 2008, Taal et al. characterized the term PsP as a "progressive MRI lesion immediately after the end of concurrent CRT with TMZ, with spontaneous improvement without further treatment other than adjuvant TMZ" (Taal et al., 2008). Usually, PsP is a subacute secondary effect of treatment that is clinically asymptomatic and mimics progression (Brandsma et al., 2008; Hygino da Cruz et al., 2011; Jefferies et al., 2007). PsP reflects the response to treatment rather than treatment failure (Jahangiri and Aghi, 2012). The definition of PsP can include a component of clinical impairment, but its appreciation remains variable and blurry. Radiological images are often contrasted with minimal neurological deterioration (Reardon and Weller, 2018). Several studies have shown that clinical deterioration in PsP is less severe than that in TP (Rowe et al., 2018; Brandes et al., 2008; Taal et al., 2008). This variability in definition could explain the large variation in published incidence rates, ranging from 2 % to more than 54 % (Chinot et al., 2014; Kang et al., 2011; Brandsma et al., 2008; Young et al., 2011; Rowe et al., 2018; Agarwal et al., 2013; Gerstner et al., 2009; Lewis et al., 2016; Ellingson et al., 2014a; Radbruch et al., 2015; Brandes et al., 2008; Hoffman et al. (1979); de Wit et al., 2004; Chamberlain et al., 2007; Taal et al., 2008; Jefferies et al., 2007; Chappell et al., 1998; Tsien et al., 2010; Nayak et al., 2017; Linhares et al., 2013; Van Mieghem et al., 2013; Kickingereder et al., 2019; Brahm et al., 2018; Kumar et al., 2000; Nasseri et al., 2014; Mangla et al., 2010; Lee et al., 2012; Li et al., 2016; Kong et al., 2011; Baek et al., 2012; Chan et al., 2012; Chang et al., 2014; Gahramanov et al., 2013; Clarke et al., 2009; Roldán et al., 2009; Chaskis et al., 2009; Fabi et al., 2009; Soike et al., 2018; Prager et al.,

Table 1
Literature review.

Authors	Year	Design	N	Criteria assessment	Definition	Incidence	Occurrence delay	Clinical markers	Survival	Molecular markers
Levin et al.	1977	Retrospective	100	X				X		
Hoffman et al.	1979	Retrospective	51		X					
MacDonald et al.	1990	NA	NA	X	X					
Calvo et al.	1993	NA	NA		X					
Hopewell et al.	1993	NA	NA		X					
Chappell et al.	1998	NA	NA	X						
Kumar et al.	2000	Retrospective	148			X				
Sorensen et al.	2001	Retrospective	219	X						
Warren et al.	2001	Retrospective	32	X						
de Wit et al.	2004	Retrospective	32		X	X				X
Hein et al.	2004	Retrospective	16		X					
Chakravarti et al.	2006	NA	NA			X	X			
Galanis et al.	2006	Retrospective	67	X						
Shah et al.	2006	Retrospective	104	X						
Chamberlain et al.	2007	Retrospective	51		X	X				
Jefferies et al.	2007	Prospective	15		X	X	X			
Brandes et al.	2008	Prospective	103			X	X	X	X	X
Brandsma et al.	2008	NA	NA		X	X	X	X		
Henson et al.	2008	NA	NA	X						
Mehrkens et al.	2008	Prospective	31							X
Sorensen et al.	2008	NA	NA	X						
Taal et al.	2008	Retrospective	85		X	X	X	X		
Chaskis et al.	2009	Retrospective	54			X	X			
Clarke et al.	2009	Prospective	85			X				
Fabi et al.	2009	Retrospective	12			X			X	
Gerstner et al.	2009	Retrospective	45			X	X	X	X	
Jensen et al.	2009	NA	NA		X					
Roldán et al.	2009	Retrospective	43			X			X	
Van den Bent et al.	2009	NA	NA	X						
Yang et al.	2009	NA	NA					X		
Mangla et al.	2010	Retrospective	36			X				
Sanghera et al.	2010	Retrospective	104			X			X	
Tsien et al.	2010	Prospective	27	X	X	X		X		
Wen et al.	2010	NA	NA	X	X					
Yaman et al.	2010	Retrospective	67			X			X	
Gahramanov et al.	2011	Prospective	14						X	
Gladwich et al. Gladwish et al.	2011	Prospective	25			X			X	
Gunjur et al.	2011	Retrospective	68			X			X	
Hygino da Cruz et al.	2011	NA	NA		X					
Kang et al.	2011	Retrospective	35			X		X	X	X
Kong et al.	2011	Prospective	90			X				X
Pope et al.	2011	NA	NA	X	X					
Quant et al.	2011	NA	NA	X						
Young et al.	2011	Retrospective	321			X		X	X	X
Yovino et al.	2011	Retrospective	38					X		
Baek et al.	2012	Retrospective	135			X				
Bleeker et al.	2012	NA	NA						X	X
Chan et al.	2012	Retrospective	28			X			X	
Fatterpekar et al.	2012	NA	NA		X					
Hu et al.	2012	Retrospective	25		X					
Jahangiri et al.	2012	NA	NA		X			X		
Kim et al.	2012	Retrospective	20							X
Lee et al.	2012	Retrospective	22			X		X		
Nasseri et al.	2012	Retrospective	61			X			X	
Pouleau et al.	2012	Retrospective	63		X	X				X
Sanghera et al.	2012	NA	NA		X					X
Topkan et al.	2012	Retrospective	63			X			X	
Agarwal et al.	2013	Retrospective	163			X	X			
Choi et al.	2013	Retrospective	117			X				
Chu et al.	2013	Retrospective	20			X				
Danish et al.	2013	Retrospective	131			X			X	
Gahramanov et al.	2013	Prospective	19			X	X		X	
Gutman et al.	2013	Retrospective	75							X
Larsen et al.	2013	Retrospective	19				X			
Linhares et al.	2013	Retrospective	70			X				
Motegi et al.	2013	Retrospective	32			X				X
Neal et al.	2013	Retrospective	58			X				
Song et al.	2013	Retrospective	20			X				
Tran et al.	2013	NA	NA				X			
Van Mieghem et al.	2013	Retrospective	136	X		X				X
Young et al.	2013	Retrospective	95			X				
Chang et al.	2014	Retrospective	55			X	X		X	

(*continued on next page*)

Table 1 (*continued*)

Authors	Year	Design	N	Criteria assessment	Definition	Incidence	Occurrence delay	Clinical markers	Survival	Molecular markers
Chinot et al.	2014	Prospective	463			X		X		
Ellingson et al.	2014	Retrospective	329		X	X			X	
Nasseri et al.	2014	Retrospective	56			X	X		X	
Aldape et al.	2015	NA	NA							X
Galldiks et al.	2015	Retrospective	22							X
Lin et al.	2015	NA	NA	X						X
Melguizo-Gavilanes et al.	2015	Retrospective	34		X				X	X
Prager et al.	2015	Retrospective	68			X				
Radbruch et al.	2015	Retrospective	79	X	X	X	X		X	
Thomas et al.	2015	Retrospective	37						X	X
Ellingson et al.	2016	Retrospective	95	X						
Gzell et al.	2016	Retrospective	49			X			X	
Kebir et al.	2016	Retrospective	26			X				
Lewis et al.	2016	Retrospective	26			X				
Li et al.	2016	Retrospective	145			X		X		X
Oberheim et al.	2016	NA	NA		X					
Qian et al.	2016	NA	NA							X
Wick et al.	2016	Prospective	354				X	X		
Yang et al.	2016	NA	NA	X	X					
Yoo et al.	2016	NA	NA	X	X					
Balana et al. Balaña et al.	2017	Retrospective	256			X		X	X	X
Dietrich et al.	2017	NA	NA		X					
Ellingson et al.	2017	NA	NA	X					X	
Galldiks et al.	2017	NA	NA						X	
Kucharczyk et al.	2017	Retrospective	130	X		X				
Mohammadi et al.	2017	Retrospective	30			X			X	
Monga et al.	2017	NA	NA							X
Wen et al.	2017	NA	NA	X						
Yoon et al	2017	Retrospective	75							X
Abbasi et al.	2018	Meta-analysis	2603			X	X			
Brahm et al.	2018	Prospective	24		X	X				
Jang et al.	2018	Retrospective	79			X	X	X		X
Kebir et al.	2018	Case Report	1							X
Lee et al.	2018	NA	NA							X
Reardon et al.	2018	NA	NA		X					
Rowe et al.	2018	Retrospective	67			X	X	X	X	X
Soike et al.	2018	Retrospective	74			X			X	X
Zikou et al.	2018	NA	NA				X			X
Bani-Sadr et al.	2019	Retrospective	83							X
Kickingereder et al	2019	Retrospective	455	X						
Le Rhun et al.	2019	NA	NA							X
McNulty et al.	2019	Retrospective	86							X
Voss et al.	2019	Prospective	23				X			
Yang et al.	2019	Retrospective	49			X				X
Kessler et al.	2020	Prospective	253							X
Montemurro et al.	2020	NA	NA							X
TOTAL				24	29	58	20	19	30	35

2015; Sanghera et al., 2010; Yaman et al., 2010; Motegi et al., 2013; Song et al., 2013; Choi et al., 2013; Gunjur et al., 2011; Gladwish et al., 2011; Park et al., 2011; Pouleau et al., 2012; Young et al., 2013; Neal et al., 2013; Danish et al., 2013; Balaña et al., 2017; Topkan et al., 2012; Jang et al., 2018; Yang et al., 2019; Mohammadi et al., 2017; Nasseri et al., 2012; Kebir et al., 2016) (Table 2), with a rate of 36 % reported in a recent meta-analysis (Abbasi et al., 2018).

In imaging, PsP is defined as an increase in the size of a preexisting contrast enhancement or a new contrast enhancement in the nontumoral contrast-enhanced area but within the radiation field, with stabilization or resolution without further new treatment, after additional cycles of adjuvant TMZ or follow-up (Radbruch et al., 2015; Brahm et al., 2018; Pouleau et al., 2012; Yang, 2016; Sanghera et al., 2012). These features are associated with tissue damage, remodeling, and inflammatory response to treatment (Ellingson et al., 2014a). PsP can occur in the parenchymal or leptomeningeal brain, and progression images must be correlated with the radiation dose map (Kinger et al., 2019).

The time of appearance is relatively large and cannot be used to differentiate PsP and TP. It ranges from the first 3 months after CRT (Brandsma et al., 2008; Rowe et al., 2018; Wick et al., 2016; Nasseri et al., 2014; Chang et al., 2014; Chaskis et al., 2009; Zikou et al., 2018) to more than 6 months after CRT (Radbruch et al., 2015; Jefferies et al., 2007; Tran and Jensen, 2013). It was also documented after 1 year (Larsen et al., 2013; Voss et al., 2019). Gahramanov et al. analyzed 68 patients with GBM and showed that 35 % of them experienced PsP with a median time of 6 weeks (75 % occurred within 12 weeks, and 25 % occurred after 12 weeks) (Gahramanov et al., 2013). Moreover, Radbruck et al. showed no difference in the incidence of PsP at 1, 4, and 7 months (Radbruch et al., 2015). In addition, Agarwal et al. concluded that there was no difference in appearance time between PsP and TP (Agarwal et al., 2013). To increase the difficulties of differentiation, Abbasi et al., in a meta-analysis, concluded that the mean interval of TP was 10.5 months (range, 1.7–37.6 months) and that the mean interval of PsP was 13.0 months (range, 1.2–40.0 months) (Abbasi et al., 2018). However, Jang et al., using a machine-learning algorithm, showed that the interval between treatment and suspicious progression images was shorter in the PsP group than in the TP group (82 days versus 123.5 days; $p = 0.02$) (Jang et al., 2018).

The incidence of PsP tends to increase with new therapeutics. Many authors have shown that PsP is more frequent after CRT than after RT alone (Brandsma et al., 2008; Gerstner et al., 2009; Brandes et al., 2008; Taal et al., 2008), probably because of the radiosensitizing effect of TMZ

Table 2
Incidence of pseudoprogression (PsP) in the literature.

Authors	Year	Country	Design	N	Incidence of increase of contrast enhancing lesions or new lesions in all study's patients	Incidence of PsP in all study's patients	Interval between end of treatment and PsP
Kumar et al.	2000	USA	Retrospective	148	67 %	13 %	6 months
de Wit et al.	2004	The Netherlands	Retrospective	32	28 %	9 %	3 months
Jefferies et al.	2007	UK	Prospective	15	53 %	20 %	6 months
Chamberlain et al.	2007	USA	Retrospective	51	51 %	14 %	6 months
Taal et al.	2008	The Netherlands	Retrospective	85	42%	21 %	4 weeks
Brandes et al.	2008	Italy	Prospective	103	49 %	31 %	1 month
Clarke et al.	2009	USA	Prospective	85	41 %	12 %	2–4 weeks
Roldán et al.	2009	Canada	Retrospective	43	58 %	23 %	4–6 weeks
Chaskis et al.	2009	Belgium	Retrospective	54	NA	6%	6 months
Fabi et al.	2009	Italy	Retrospective	12	33%	17 %	2 months
Gerstner et al.	2009	USA	Retrospective	45	53%	29 %	2–4 weeks
Sanghera et al.	2010	Canada	Retrospective	104	26 %	7 %	2 months
Yaman et al.	2010	Turkey	Retrospective	67	25 %	6 %	6 months
Mangla et al.	2010	USA Sweden	Retrospective	36	53 %	19 %	1 month
Tsien et al.	2010	USA	Prospective	27	52 %	22 %	1–3months
Kang et al.	2011	Korea	Retrospective	35	51 %	23 %	1 months
Kong et al.	2011	Korea	Prospective	90	66 %	29 %	2 months
Young et al.	2011	USA	Retrospective	321	29 %	9 %	2–4 weeks
Gunjur et al.	2011	Australia	Retrospective	68	60 %	21 %	3 months
Gladwish et al.	2011	Canada	Prospective	25	52 %	20 %	1 month
Park et al.	2011	Korea	Retrospective	48	52 %	23 %	4 weeks
Pouleau et al.	2012	Belgium	Retrospective	63	52 %	11 %	8 weeks
Topkan et al.	2012	Turkey	Retrospective	63	44 %	19 %	≤6 months
Baek et al.	2012	Korea	Retrospective	135	59 %	27 %	4 weeks
Chan et al.	2012	China	Retrospective	28	46 %	18 %	3 months
Motegi et al.	2012	Japan	Retrospective	32	34 %	6 %	6 months
						28 %	≤3 months
Nasseri et al.	2012	USA	Retrospective	61	NA	21 %	>3 months
						49 %	total
Lee et al.	2012	Korea	Retrospective	22	NA	54 %	12 weeks
Young et al.	2013	USA	Retrospective	95	51 %	4 %	2–4 weeks
Neal et al.	2013	USA	Retrospective	58	62 %	21 %	180 days
Linhares et al.	2013	Portugal Brazil	Retrospective	70	60 %	14 %	1 month
Song et al.	2013	Korea	Retrospective	20	NA	50 %	2 months
Choi et al.	2013	Korea	Retrospective	117	53 %	24 %	4 weeks
Agarwal et al.	2013	USA	Retrospective	163	28 %	6 %	12 weeks
Van Mieghem et al.	2013	Belgium	Retrospective	136	60 %	7 %	4 weeks
Danish et al.	2013	USA	Retrospective	131	65 %	24 %	6 months
Chu et al.	2013	Korea	Retrospective	20	NA	50 %	2 months
Gahramanov et al.	2013	USA	Prospective	19	NA	35 %	6 weeks
						34 %	≤3 months
Nasseri et al.	2014	USA	Retrospective	56	52 %	14 %	>3 months
						48 %	total
				301	46 %	23 %	1 month
Ellingson et al.	2014	USA	Retrospective	329	47 %	19 %	2 months
				161	30 %	6 %	6 months
Chang et al., 2014	2014	Korea	Retrospective	55	38 %	9 %	4 weeks
Chinot et al., 2014	2014	International	Prospective	463	NA	9 %	4 weeks
Prager et al., 2015	2015	USA	Retrospective	68	NA	15 %	<6 months
Radbruch et al.	2015	Germany	Retrospective	79	NA	11 %	10 weeks
Gzell et al.	2016	Australia	Retrospective	49	NA	2 %–8 %	6 months
Lewis et al.	2016	UK	Retrospective	26	73 %	15 %	6 months
Kebir et al.	2016	Germany	Retrospective	26	NA	27 %	6 months
Li et al.	2016	China	Retrospective	145	52 %	26 %	3 months
Mohammadi et al.	2017	USA	Retrospective	30	NA	30 %	4 weeks
Balaña et al.	2017	Spain	Retrospective	256	49 %	22 %	2 months
Jang et al.	2018	Korea	Retrospective	79	NA	38 %	NA
Rowe et al.	2018	USA	Retrospective	67	52 %	22 %	12 weeks
Brahm et al.	2018	The Netherland	Prospective	24	58 %	29 %	10 weeks
Soike et al.	2018	USA	Retrospective	74	NA	19 %	NA
Yang et al.	2019	Korea	Retrospective	49	55 %	26 %	3 months

NA: No Available; **UK** : United Kingdom ; **USA**: United State of America.

(Chakravarti et al., 2006). Moreover, new modalities of imaging, improvement in imaging techniques, early imaging follow-up, and reirradiation increase the incidence of PsP.

3.2. Differentiation with radionecrosis (RN)

Contrary to PsP, which has a radiological definition, RN has a histological definition (Voss et al., 2019). RN corresponds to a severe local tissue reaction to RT and has an incidence ranging from 5 % to 40 % (Ellingson et al., 2017a; Sanghera et al., 2010). RN occurs months to years after irradiation, usually 6–24 months after CRT. Although PsP and RN have distinct clinical and pathological mechanisms, they share histologic similarities that translate into similar imaging characteristics (Prager et al., 2015). However, contrary to PsP, RN is not associated with a better prognosis and progresses without treatment (Ellingson et al., 2017a; Sanghera et al., 2010). Frequent treatments consist of corticosteroids (Shaw and Bates, 1984), bevacizumab (Levin et al., 2011; Delishaj et al., 2017; Furuse et al., 2016) or surgery (Siu et al., 2012).

RN differs from PsP in many ways. Clinically, RN is usually asymptomatic but can also cause irreversible neurological deficits and anatomical injuries. In MRI, RN corresponds to a contrast enhancement ring with a central hypoT1 responsible for edema and a mass effect. On T1 MRI, RN appears in images with features described as “Swiss cheese” or “soap bubble” (Miyatake et al., 2015). RN is a late disease corresponding to white matter necrosis. PsP and RN do not have the same histopathological and biological mechanisms. RN is secondary to chronic inflammation, wall thickening, hyalinization of vessels, and occasional reactive telangiectasia responsible for microvessel collapse around the tumor (Kumar et al., 2000; Miyatake et al., 2015). Radiation targets vascular endothelial cells and oligodendrocytes that lead to clonogenic death, then vascular lesions as the blood-brain barrier breaks down, ischemia, vasogenic edema, and hypoxia. These phenomena stimulate vascular endothelial growth factor (VEGF) and increase vascular permeability, which leads to necrosis and demyelination. Moreover, radiation stimulates glioma cells and activates VEGF, which decreases apoptosis in tumor cells (Jahangiri and Aghi, 2012). Hemorrhages and calcifications can be present (Brandsma et al., 2008). White matter necrosis occurs through multiple mechanisms and three mediators: endothelial cell apoptosis, VEGF, and glioblastoma cell necrosis. Radiation-induced DNA and membrane damage lead to the creation of free radicals and activate ceramides, causing endothelial cell apoptosis. This process provokes blood-brain barrier disruption, demyelination, and tissue necrosis. Hypoxia upregulates VEGF expression, resulting in edema (Yang and Aghi, 2009). Risk factors for RN are high total dose and fractional dose of radiation, hyperfractionation, stereotactic radiosurgery, reirradiation, concomitant chemotherapy and radiotherapy, and volume of radiation (Yang and Aghi, 2009).

4. Clinical markers

4.1. Patients characteristics

Patients developing PsP could be younger than those with TP (Taal et al., 2008), but this factor was avoided in an analysis with machine learning (Jang et al., 2018) or by some logistic regression model (Kang et al., 2011; Tsien et al., 2010; Lee et al., 2012; Li et al., 2016; Balaña et al., 2017). Female patients could develop PsP more often than male patients (Jang et al., 2018), but this observation was largely discussed by other authors (Kang et al., 2011; Li et al., 2016; Balaña et al., 2017). Less deteriorated neurological status was described in patients with PsP (Rowe et al., 2018; Taal et al., 2008), but this has not been found by others (Balaña et al., 2017). In the study by Brandes et al., clinical deterioration was less frequent in the PsP group (34 %) than in the TP group (56 %), without a significant difference ($p = 0.14$) (Brandes et al., 2008). However, World Health Organization (WHO) performance status was not predictive of PsP (Taal et al., 2008) or Karnofsky performance status (KPS) (Tsien et al., 2010; Lee et al., 2012; Balaña et al., 2017). Several scores, such as the Mini-Mental Status Examination (Balaña et al., 2017) and Recursive Partitioning Analysis (RPA) (Tsien et al., 2010), were studied and found not to be related to PsP.

4.2. Treatment features

Gerstner et al. demonstrated in univariate analysis that the extent of surgery (biopsy versus subtotal resection versus gross total resection) was significantly associated with PsP ($p = 0.04$) (Gerstner et al., 2009), but this factor remains disputable (Kang et al., 2011; Young et al., 2011; Taal et al., 2008; Tsien et al., 2010; Lee et al., 2012; Balaña et al., 2017; Yang and Aghi, 2009). The interval between surgery and radiotherapy was not retrieved as a predictive factor (Kang et al., 2011). The time elapsed before the second surgery for progression was not a significant factor of PsP versus TP (Yovino et al., 2011). RT alone provided fewer cases of PsP than CRT, from 10 % to 30 % (Rowe et al., 2018; Gerstner et al., 2009; Brandes et al., 2008; Taal et al., 2008; Jahangiri and Aghi, 2012; Yang and Aghi, 2009). The addition of bevacizumab seemed to decrease the incidence of PsP in the AVAglio phase 3 trial, with comparable patient characteristics in both arms (Chinot et al., 2014; Wick et al., 2016). The RT dose was questionable (Brandsma et al., 2008), as Yang and Aghi concluded that a high dose of RT significantly increased the rate of PsP (Yang and Aghi, 2009), but other authors concluded in its lack of impact (Tsien et al., 2010; Lee et al., 2012). Radiotherapy schedules have not been demonstrated as predictive factors (Kang et al., 2011). The volume of the radiation field was not identified as significantly different between the PsP and TP groups (Taal et al., 2008; Tsien et al., 2010). Schedules of adjuvant TMZ were also suspected but not proven to be predictive factors of PsP (Young et al., 2011).

4.3. Additional treatment

Some authors showed that patients with PsP required fewer corticosteroids than patients with TP (Rowe et al., 2018) and that this treatment at the start of CRT could be related to PsP incidence (Balaña et al., 2017), whereas other authors did not find any correlations with corticosteroids. Anticonvulsant drugs were studied by the authors without any determined correlations (Balaña et al., 2017).

4.4. Influence of PsP on survival

The results of the literature are presented in Table 3.

Some authors showed that patients with PsP had a better prognosis and better treatment response and consequently a better OS or median OS than those with TP (Melguizo-Gavilanes et al., 2015; Ellingson et al., 2017a; Young et al., 2011; Rowe et al., 2018; Gerstner et al., 2009; Ellingson et al., 2014a; Brandes et al., 2008; Nasseri et al., 2014; Chan et al., 2012; Chang et al., 2014; Gahramanov et al., 2013; Roldán et al., 2009; Fabi et al., 2009; Soike et al., 2018; Sanghera et al., 2010; Yaman et al., 2010; Gunjur et al., 2011; Gladwish et al., 2011; Danish et al., 2013; Balaña et al., 2017; Topkan et al., 2012; Nasseri et al., 2012; Galldiks et al., 2017). Few studies did not observe an improvement in OS for patients with PsP compared with those without PsP (Yaman et al., 2010; Mohammadi et al., 2017; Galldiks et al., 2017). Nasseri et al. demonstrated that the median, 1-year and 2-year OS were better for patients with PsP that developed after 3 months of CRT completion than for patients with PsP appearing in the first 3 months after CRT, but the difference did not reach statistical significance ($p = 0.15$) (Nasseri et al., 2012). In the Topkan et al. study, the survival analysis revealed that patients with PsP had higher 1-year OS and PFS rates (100 % versus 70.6 %; $p = 0.03$ and 83.3 % versus 42.2 %, $p = 0.02$, respectively) and 2-year OS and PFS rates (56.8 % versus 25.8 %, $p = 0.007$ and 30 % versus 9.6 %, $p = 0.002$, respectively) (Topkan et al., 2012). Moreover, Radbruch et al. showed that the median OS in patients with stable PsP or PsP

Table 3
Median overall survival (OS) and median progression free-survival (PFS) of patients with pseudoprogression (PsP) or true progression (TP) in the literature.

		Median OS (months)			Median PFS (months)		
Authors	population	PsP	TP	p value	PsP	TP	p value
Brandes et al., 2008	GBM	38	10.2	<0.001			
Gerstner et al., 2009	GBM	24.4	15.9	NA	22	7	NA
Roldan et al., 2009	GBM	14.5	9.1	0.025			
Sanghera et al., 2010	GBM	27.8	8	0.0286			
Yaman et al., 2010	HHG	NA	NA	NS	7	5	0.004
Young et al., 2011	GBM	10.6	14.7	0.003			
Kong et al., 2011	GBM	21.7	13.5	NA			
Gunjur et al., 2011	GBM	27.4	10.4	0.003			
Gladwich et al., 2011	GBM	19.0	7.2	<0.001			
Topkan et al., 2012	GBM	NA	14.8	0.009	17.5	10.0	0.014
Nasseri et al., 2012	GBM	18–20	8	NA			
Chan et al., 2012	GBM	22	11	NS			
Danish et al., 2013	GBM	18.5	14.1	0.006			
Gahramanov et al., 2013	GBM	34.4	13.4	<0.0001	31.4	8.4	<0.0001
Nasseri et al., 2014	GBM	35.2	14.3	<0.0001			
Melguizo-Gavilanes et al., 2015	GBM	14.4	17.1	0.82	4.8	7.5	0.69
Radbruch et al., 2015	GBM	29.6	15.8	0.012			
Galldiks et al., 2015	Gliomas	16	8	0.006			
Li et al., 2016	GBM	39	12	<0.001			
Balana et al., 2017	GBM	18.9	12.3	0.0001	10.5	5.3	0.01
Soike et al., 2018	GBM	23.8	15.7	0.36	15	7.7	0.08
Rowe et al., 2018	GBM	23.6	13.2	0.032			

NA: not available, **NS:** not significant.

shrinking <50 % versus those with a total disappearance of PsP or PsP decrease >50 % was 35.4 months versus 23.6 months, respectively, but without statistical significance (p = 0.7) (Radbruch et al., 2015). Independent of OS, the PFS and objective response rate were endpoints that were studied according to PsP and TP (Balaña et al., 2017; Ellingson et al., 2017b). PFS was usually shown to be higher for patients with PsP than for patients with TP (Gerstner et al., 2009; Gahramanov et al., 2013; Fabi et al., 2009; Soike et al., 2018; Yaman et al., 2010; Topkan et al., 2012). Some studies showed a statistical advantage of PFS for patients with PsP compared to those without PsP, with a median PFS varying from 7 to 31 months and from 5 to 10 months, respectively (Gerstner et al., 2009; Soike et al., 2018; Yaman et al., 2010; Balaña et al., 2017; Topkan et al., 2012; Gahramanov et al., 2011). However, groups often included a low number of patients, compromising statistical power. Although the difference in median PFS was encouraged, conclusions might be prudent in the absence of controlled prospective trials.

With regard to the median time to progression (TTP), Brandes et al. showed that patients with PsP had a better median TTP than patients with TP (20.7 versus 5.7 months, $p < 0.001$), and the median time interval between recorded PsP and subsequent TP was 16.2 months (Brandes et al., 2008). Kang et al. reported that the median TTP was 7 and 3.1 for patients with PsP and TP, respectively ($p < 0.01$) (Kang et al., 2011). Despite a better median OS in patients with PsP, Balana et al. failed to show a better median post progression survival in the PsP group versus the TP group (7.2 versus 5.4 months; p = 0.43) (Balaña et al., 2017).

For Gunjur et al., better OS can be considered an indication that PsP is a sign of tumoral response rather than a complication of the treatment (Gunjur et al., 2011). Brandes et al. showed that OS was significantly influenced by the detection of PsP (p = 0.045) (Brandes et al., 2008), Soike et al. concluded that PsP was an improved factor of PFS (p = 0.046) (Soike et al., 2018), and Kang et al. showed that PsP was a factor of prolonged median survival time (Kang et al., 2011). Methylation of the MGMT promoter has been identified as improving survival (Brandes et al., 2008; Fabi et al., 2009), but this has been debated (Young et al., 2011). Thomas et al. observed that advantages of better OS were negated when OS was adjusted for several patient characteristics (age, KPS, and MGMT methylation) (Thomas et al., 2015). Gzell et al. demonstrated that survival was reduced when surgical cavity volume and contrast enhancement volume increased ≥5% at 3 and 5 months after CRT (p = 0.006) (Gzell et al., 2016).

5. Morphological markers

5.1. Tumor radiological characteristics

Even if conventional gadolinium contrast-enhanced MRI is the reference exam for the measurement of response to treatment, it lacks efficiency in distinguishing TP from PsP, and advanced MRI, PET scan or multiparametric imaging can provide additional information and improve the distinction between PsP and TP Masch et al. (2016); Gerstner et al., 2009; Lewis et al., 2016; Hygino da Cruz et al. (2011); Law et al. (2019). All the radiological features are described and discussed in another manuscript ("Pseudoprogression versus true progression in glioblastoma patients: a multiapproach literature review. Part 2 – Radiological features", which has been submitted to *CROH* and is currently in revision).

Initial tumor volume or size was not associated with the risk of PsP (Tsien et al., 2010; Balaña et al., 2017), but some authors demonstrated that volume rather than surface or diameter could be predictive of PsP (Gladwish et al., 2011). Tumor location was not correlated with PsP (Tsien et al., 2010; Balaña et al., 2017).

5.2. Response evaluation tools

Uniform rigorous criteria of response assessment and an image standardized protocol in neuro-oncology are necessary (Ellingson et al., 2014a; Reardon et al., 2014; Ellingson et al., 2014b). In 1990, Macdonald et al. proposed the first criteria for response assessment in HGGs based on the Levin criteria (Levin et al., 1977). Radiologic criteria were initially based on computed tomography. These criteria were then extrapolated on MRI, considering the two-dimensional measurements (sum of the product of the perpendicular diameters) of the enhancing tumor area. They were associated with clinical criteria (neurologic symptoms) and the use of corticosteroids (Table 4) (Macdonald et al., 1990). Some limitations of the Macdonald criteria have been raised (van den Bent et al., 2009; Sorensen et al., 2008; Henson et al., 2008). The measurement of enhancing lesions is dependent mainly on irregularly shaped tumors, cystic tumors, or surgical cavities (Yang, 2016). The use

Table 4
Response assessment classifications.

	Macdonald criteria 1990 (29)	RANO criteria 2010 (28)		Modified RANO criteria 2017 (110)
Complete Response (CR)	All Complete disappearance of enhancing lesions least 4 weeks No new lesion No corticosteroids Clinically stable or improved	All Complete disappearance of *measurable and non-measurable enhancing lesions* at least 4 weeks No new lesion *Stable or improved T2/FLAIR lesions* No corticosteroids Clinically stable or improved		All Complete disappearance of measurable and non measurable enhancing lesions at least 4 weeks No criteria on T2/FLAIR lesions No corticosteroids Clinically stable or improved
Partial response (PR)	All Measurable enhancing lesions: ≥50 % decrease in the sum of the product of perpendicular diameters at least 4 weeks Corticosteroids dose stable or decreased Clinically stable or improved	All Measurable enhancing lesions: ≥50 % decrease in the sum of the product of perpendicular diameters at least 4 weeks *No progression of nonmeasurable lesions* *No new lesion* *Stable or improved T2/FLAIR lesions* Corticosteroids dose stable or decreased Clinically stable or improved		All Measurable enhancing lesions: ≥50 % decrease in the sum of the product of perpendicular diameters or ≥65 % decrease in total volume at least 4 weeks No criteria on T2/FLAIR lesions Corticosteroids dose stable or decreased Clinically stable or improved
Stable disease (SD)	No CR nor PR nor PD	All No CR nor PR nor PD *Stable T2/FLAIR lesions* *Corticosteroids dose stable or decreased*		No CR nor PR nor PD
Progressive disease (PD)	Any Measurable enhancing lesions: ≥25 % increase in the sum of the product of perpendicular diameters New lesion Corticosteroids dose stable or increased Clinical deterioration	*<12 weeks after CRT* *New enhancement outside the radiation field (80 % isodose line)* *Histopathological proof of progression*	*≥12 weeks after CRT* Any Measurable enhancing lesions: ≥25 % increase in the sum of the product of perpendicular diameters *Increase in T2/FLAIR lesions* New lesion *Progression of non-measurable lesions that became measurable* Clinical deterioration	Any In two sequential MRI separated by ≥ 4 weeks Enhancing lesions: ≥25 % increase in the sum of the product of perpendicular diameters or ≥40 % increase in the total volume Clinical deterioration

In *italic*, changes between Macdonald and RANO criteria. In **bold** changes between RANO and modified RANO criteria.

of cross-sectional area measurement was poorly reproducible and was considered unusable in the case of multiple lesions. Furthermore, no criteria were available for nonenhancing lesions, multifocal lesions, or gross total resection (Wen et al., 2010). Sorensen et al. proposed FLAIR images in addition to T1 gadolinium images. They also suggested that a stable dose of corticosteroids be considered for an unchanged dose for at least 3 days before imaging. Moreover, they recommended a T1 contrast-enhanced MRI volumetric approach instead of the two-dimensional lesion measurement to decrease the interobserver variability (Sorensen et al., 2008). However, some studies have compared diameter and volumetric measurements with discordant results (Galanis et al., 2006; Shah et al., 2006; Sorensen et al., 2001; Warren et al., 2001; Ellingson et al., 2016). The Macdonald criteria were based on enhancing lesion measurement, but this was not clearly described and was never clearly associated with tumor growth or tumor activity. This observation was especially true when antiangiogenic treatment, radiation therapy, and corticosteroids were used or in post-surgery conditions (van den Bent et al., 2009).

In 2009, motivated by the use of antiangiogenic therapies, the RANO working group, initially composed of five volunteer collaborators, proposed criteria for treatment response in HGG to make the design of trials uniform. The RANO criteria includes radiological and clinical criteria and accounts for the use of corticosteroids (Wen et al., 2010). Those criteria included a definition of patients who could participate in a trial and introduced the definition of PsP. Radiological response was evaluated in comparison with the lesion measurement on baseline MRI (pretreatment postsurgical MRI or MRI in which the smallest size of the lesions was observed during the follow-up). The complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) criteria are defined in Table 4. RANO defined measurable lesions as a bidimensional contrast-enhancing lesion with shape demarcation and at least two perpendicular diameters of ≥ 10 mm that were visible on two or more slices. Cystic and surgical cavities were excluded from lesion measurement. Nonmeasurable lesions were defined as unidimensional measurable lesions without a shape demarcation and diameters of ≤10 mm. In the case of multiple contrast-enhancing lesions, lesion size was the sum of the product of the perpendicular diameters from two and five lesions. Because of the high incidence of PsP during the first 12 weeks after CRT, the RANO criteria were proposed to exclude patients from clinical trials who had progression during this period. However, progression could be considered during this period if there was a new enhancement outside the 80 % isodose line or histopathological exam confirming tumor progression. RANO criteria defined PsP as a transient 25 % increase in the sum of the product of the perpendicular diameters of measurable contrast-enhancing lesions associated or not with an increase in T2/FLAIR within 12 weeks after CRT that decreased or disappeared 4 weeks after MRI.

Even though the RANO criteria were developed to standardize the HGG treatment response assessment, some shortcomings remain:

- RANO criteria includes FLAIR assessment to improve the accuracy of the diagnosis of progression in the case of antiangiogenic treatment but do not define objective measurement guidelines for FLAIR imaging as it did for T1-weighted imaging (Yang, 2016; Pope and Hessel, 2011).
- A precise definition of neurological deterioration does not exist, and neurological evaluation is left to the clinician's judgment. However, the authors proposed guidelines for KPS and WHO performance

status score degradation (Table 5), but these scores are not sensitive or specific for treatment response (Wen et al., 2017).

- The threshold of corticosteroid dose to specify an increase, stabilization, or decrease in consumption have not been identified, nor is there a level of change or a time period analysis.
- Patients with progression signs other than histopathological proof of progression or increased enhancement outside of the radiation field within the first 12 weeks after CRT are excluded to avoid including patients with PsP. However, PsP can occur during the first 6 months after CRT completion and even after this period (Radbruch et al., 2015).
- A volumetric approach to measure the contrast-enhancing tumor size or require the use of bidirectional measurements as in the Macdonald criteria was not proposed (Macdonald et al., 1990).
- Postsurgical MRI was chosen as the baseline for the response assessment evaluation, but this could present some issues due to imaging artifacts such as postsurgical bleeding, vascular permeability modifications, or image modification due to a high steroid dose post-surgery, and changes can appear between the postoperative MRI and the MRI used for radiotherapy delineation, often performed some weeks after the postoperative MRI.

In 2017, Ellingson et al. proposed modified RANO criteria to evaluate the radiological response when a treatment affecting contrast enhancement was administered (Table 4) (Ellingson et al., 2017b). Indeed, radiotherapy or cytotoxic chemotherapy increases contrast enhancement (i.e., PsP), whereas antiangiogenic drugs decrease contrast enhancement, inducing a pseudo-response (Pope et al., 2006; Chamberlain, 2006; Kang et al., 2008; Batchelor et al., 2007; Friedman et al., 2009; Vredenburgh et al., 2007a, b). In response to these findings, the authors developed an international brain tumor imaging protocol (BTIP) with sequence and parameter recommendations to standardize the imaging protocol (Ellingson et al., 2015). Moreover, in addition to two-dimensional measurement, a volumetric approach was defined (Chappell et al., 1998). Post-radiation MRI was proposed as baseline imaging instead of post-surgical MRI in the RANO criteria. In the case of suspicion of PsP or pseudo-response, the authors recommended a new imaging control within 4–8 weeks after MRI, as it suggests potential progression. Consequently, the authors introduced the terms “preliminary CR”, “durable CR”, “preliminary PR”, “durable PR”, “preliminary PD” and “confirmed PD”. They removed the T2/FLAIR evaluation from the criteria and considered only measurable enhancing lesions for better interobserver concordance. The T2/FLAIR tumor progression evaluation was too complex, subjective, and controversial to be integrated as a radiographic endpoint. The neurological clinical status could be classified as “stable, better, or worse”, but the clinical evaluation remained subjective. The status of steroid use could be classified as “no” when the patients did not receive corticosteroids or when the corticosteroid dose consumption was physiologic, “increased” if the dexamethasone (or equivalent) treatment dose increased at least 2 mg, “decreased” if the dexamethasone treatment dose decreased at least 2 mg, or “stable” in the other cases.

Table 5
RANO criteria for KPS and WHO status deterioration.

KPS	
Baseline	Deterioration
100 % - 90 %	70 % or less
≤80 %	Decrease 20 % or more
any	50 % or less
WHO status	
Baseline	Deterioration
0 or 1	2 or more
2	3

KPS: Karnofsky Performance Status, **WHO**: World Health Classification.

To respond to critics of the RANO criteria, several more specific scales were designed (Quant and Wen, 2011). The Immunotherapy Response Assessment for Neuro-Oncology (iRANO) suggested that within the first 6 months after the start of immunotherapy, if MRI showed progression without clinical deterioration, immunotherapy could be continued until the next MRI 3 months later (Tsien et al., 2010). The Neurologic Assessment in Neuro-Oncology (NANO) is a more objective and quantifiable neurological symptom score that evaluates supratentorial, infratentorial, and brainstem functions (Nayak et al., 2017). NANO is an objective, relevant, fast, and simple scale developed with the aim of reflecting tumor activity via clinical parameters to identify progression. Wen et al. also exposed RANO-HGG (high-grade glioma), RANO-BM (brain metastasis) (Lin et al., 2015), RANO-LM (leptomeningeal metastasis) (Chamberlain et al., 2017), RANO-LGG (low-grade glioma) (van den Bent et al., 2011), RANO seizures, RAPNO (pediatric), SPINO (spine tumors), RANO meningioma, RANO PET (positron emission tomography), RANO surgery, RANO steroids, RANO PRO (patient-reported outcome), and RANO histologic assessment (Wen et al., 2017), which perpetuated confusion in the evaluation tools.

The importance of criteria to define PsP and TP cannot be ignored. These criteria are essential for patient management and the evaluation of disease prognosis. Linhares et al. underlined the importance of criteria to differentiate PsP and TP. They analyzed data from 70 patients with GBM treated with surgery and CRT and compared the RANO and Macdonald criteria. Thirty-two patients were identified as having TP according to the Macdonald criteria, and 13 patients were identified according to the RANO criteria. Ten patients were identified as having PsP according to the Macdonald criteria, and two patients were identified according to the RANO criteria. According to the Macdonald versus RANO criteria, the median OS for the TP group was 12 months versus 9 months, and the median OS for the PsP group was 24 months versus 13 months. The difference in OS between the PsP and TP groups was significant only for the patients classified with the Macdonald response ($p = 0.01$). The median PFS rates were 6 months for the Macdonald versus RANO criteria in the TP group and 16 months versus 7 months in the PsP group (Linhares et al., 2013). Conclusions of this study remained disputable. The study analysis was performed one month after CRT using restrictive RANO criteria, leading to a small number of patients enrolled in the PsP RANO group, dramatically reducing the statistical power of the results. Similarly, for Kucharczyk et al., the incidence of PsP was 15 % and 19 % using the RANO and MacDonald criteria, respectively (Kucharczyk et al., 2017). Van Mieghem et al. conducted a retrospective study of 136 patients with GBM who underwent CRT or RT alone after surgery. They used two different definitions of PsP: i) the stringent criteria, which defined PsP as a $\geq$ 25 % increase in size or new contrast-enhancing lesion that spontaneously regressed to baseline, and ii) the liberal criteria, which defined PsP as a $\geq$ 25 % increase in tumor volume followed by stable size for at least 6 months. The authors identified 14 % versus 23 % PsPs using the stringent and liberal criteria, with a median OS of 27.7 months versus 32.4 months, respectively (Van Mieghem et al., 2013).

Recently, the use of automated neural networks on MRI for response assessment and TTP in brain tumors was developed and compared with the RANO criteria with great expectation of improving clinical decision making (Kickingereder et al., 2019).

In conclusion, although the RANO and Macdonald criteria tried to be more specific, the impact on the survival of the supposed PsP and TP remains highly disputable. Overlapping values for the median OS and PFS were observed, even if the figures are often higher in favor of the PsP.

6. Pathological and molecular markers

6.1. Histological and pathological findings

Histopathologic examination was the reference method in the differential diagnosis of progression, PsP, and RN. However, interpreting surgical samples was complex because a large proportion of patients could be categorized as "mixed". These findings failed to resolve the ambiguity of the process and did not inform on progression versus initial tumor Melguizo-Gavilanes et al. (2015). PsP is a continuum between the subacute radiation reaction and treatment-related necrosis (Hein et al., 2004). Some authors supported the idea that RN was the continuum of PsP, but this was debated (Brandsma et al., 2008; Taal et al., 2008; Oberheim Bush et al., 2016). Both pathophysiological mechanisms, vascular injury and cellular effects, are still incompletely understood and characterized (Oberheim Bush et al., 2016). Inflammation and vascular endothelial damage lead to blood-brain barrier disruption, increased permeability, and vasogenic edema, resulting in MRI contrast enhancement (Wen et al., 2010; Oberheim Bush et al., 2016). Cell necrosis and local tissue reaction increased cytokines and proinflammatory mediators that also increased vascular permeability. Endothelial cell apoptosis results from the effects of free radical and cell membrane damage that induce ceramides and apoptotic mechanisms (Sanghera et al., 2012). Cellular hypoxia activates hypoxia-regulated molecules from the tumor and cells and increases permeability and tumor enhancement (Jensen, 2009). The vascular endothelium, blood-brain barrier, and oligodendroglial injuries provoked an exaggerated response to effective therapy, which led to inflammation, vascular dilatation and increased permeability (Yoo and Choi, 2016; Fatterpekar et al., 2012). PsP showed typical pathological findings after radiation, such as perivascular edema, bland necrosis, fibrosis, gliosis, endothelial thickening, hyalinization, platelet fibrin thrombi and occlusion (Melguizo-Gavilanes et al. (2015); Yoo and Choi, 2016; Tsien et al., 2010). Cell analysis showed paucicellularity, scattered little to no atypical cells with a lack of mitotic figures except in inflammatory cells, a reduced number of endothelial cell nuclei, low density of pleiomorphic tumor cells, low mitotic index, hyalinization of vessel walls, fibrinoid necrosis, fibrillary and gemistocytic astrocytes, pleiomorphic astrocytes, and mild perivascular lymphocyte and monocyte infiltrations (Oberheim Bush et al., 2016). There was a preponderance of reactive cells, including astrocytes, microglia and macrophages (Hu et al., 2012). Focal areas of demyelination were secondary to oligodendroglial cell loss (Calvo, 1993; Hopewell et al., 1993). In contrast, recurrent tumors were characterized by the presence of tumor cells, increased cellularity, and vascular proliferation (Hopewell et al., 1993; Wesseling et al., 1997).

6.2. Molecular markers

The Cancer Genome Atlas (TCGA) describes fundamental molecular features of GBM (Brennan et al., 2013). Molecular markers emerged from numerous studies to be relevant to develop new therapeutics in GBM patients with personalized medicine and to be used as biomarkers (Burgenske et al., 2019; McLendon et al., 2008). In a retrospective study on 253 GBM patients, Kessler et al. showed that therapeutic decisions with targeted therapies based on molecular alterations occurred in 38 % of patients, and of them, 70 % were based on MGMT promoter methylation status. Epidermal growth factor receptor (EGFR) amplification/mutation, cyclin-dependent kinase inhibitor 2 A/B (CDKN2A/B) deletions, V-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation, or phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway alterations were less frequently observed. They identified 213 potentially GBM targetable alterations and proposed a therapeutic decision application (Kessler et al., 2020). MGMT promoter methylation was predictive of an alkylating chemotherapy response. It was the most frequent alteration used to guide therapy associated with patient age and KPS (Kessler et al., 2020). Therapy adaptation according to the other alterations was preferentially used at the time of GBM progression, which was characterized by other molecular alterations due to clonal evolution (Wang et al., 2016; Kim et al., 2015). The microenvironment of the tumor could play a role in the treatment response and tumor progression with the influence of the matrix, infiltrative cells, or blood vessels (Lee et al., 2018). VEGF, which influences blood vessel formation, and transforming growth factor (TGF-beta), which participates in immunosuppression, cell migration, cell invasion and angiogenesis or integrin mutations, could orient TP, but data are lacking. Although the GBM molecular profile is now better characterized, the clinical impact remains limited, and more research is needed (Lee et al., 2018).

Three major tumor-intrinsic transcriptional subtypes have been described: proneural, mesenchymal, and classical. The classical subtype is characterized by EGFR amplification and a lack of a TP53 mutation, whereas the proneural subtype mainly presents platelet-derived growth factor receptor alpha (PDGFRA) or isocitrate dehydrogenase (IDH1/2) mutations and mesenchymal subtype neurofibromin 1 (NF1) mutations (Lee et al., 2018; Aldape et al., 2015; Phillips et al., 2006). Soike et al. demonstrated that transcriptional subtypes were not associated with PsP, but this observation remains to be explored (Soike et al., 2018).

Mutant IDH was infrequent in patients with GBM, but patients with lower-grade gliomas showed a higher frequency of mutant IDH (Nobusawa et al., 2009; Wang et al., 2019). IDH wild-type GBM was found in approximately 90 % of GBM patients, corresponding to primary or de novo GBM and mostly affected patients older than 55 years (Siegal, 2015). IDH mutant GBM often corresponded to secondary GBM (85 %), resulting from molecular progression and upgraded malignancy in lower grade gliomas, and mostly affected younger patients (Aldape et al., 2015). IDH encodes tricarboxylic acid cycle enzymes conferring cellular protection against oxidative damage. Mutated IDH reduced enzyme activity with an impact on hypoxia sensing and DNA methylation, increasing oxidative stress susceptibility and the risk of glioma development (Lee et al., 2018; Aldape et al., 2015). Therefore, mutant IDH could promote PsP after CRT. Some authors concluded that IDH status was not associated with PsP (Soike et al., 2018). However, other authors suggested that mutant IDH could be a molecular biomarker for PsP (Li et al., 2016; Balaña et al., 2017; Kebir et al., 2018), with a sensitivity of 67 % and a specificity of 100 % (Motegi et al., 2013).

MGMT promoter methylation was observed in approximately 40 % of primary GBM patients (Lee et al., 2018; Aldape et al., 2015; Montemurro, 2020). MGMT is an enzyme that repairs the DNA damage caused by alkylating agents such as TMZ, which restores guanine from O-6-methylguanine. Injuries to DNA lead to apoptotic cell death. Methylation of the promoter of MGMT reduced the intracellular level of MGMT and inhibited the repair mechanism of DNA, leading to apoptosis and autophagy (Fabi et al., 2009). In the case of the unmethylated MGMT promotor, MGMT induced DNA repair and cell survival (Aldape et al., 2015). RT increased capillary permeability and associated with TMZ to increase DNA and membrane damage, leading to endothelial cell death. Moreover, the authors suggested that endothelial cells presented MGMT promoter methylation or other molecular alterations, making them sensitive to CRT (Li et al., 2016; Motegi et al., 2013). According to those observations, methylation could be needed to impact PsP, favoring cell death. Even if it was not demonstrated at the molecular level, the MGMT methylation status was associated with PsP in clinical literature data. Some authors showed that the unmethylated MGMT promoter was an independent risk factor for TP ($p = 0.005$) (Rowe et al., 2018) or was correlated with the risk of PsP (Brandes et al., 2008; Balaña et al., 2017), but others recused this conclusion (Young et al., 2011; Jang et al., 2018). Patients with MGMT methylation showed more PsP, and approximately two-thirds of MGMT-methylated tumors exhibited PsP (Brandes et al., 2008; de Wit et al., 2004; Van Mieghem et al., 2013; Li et al., 2016; Soike et al., 2018; Balaña et al., 2017; Zikou et al., 2018; Thomas et al., 2015; Galldiks et al., 2015; Yoon et al., 2017). Patients with a methylated MGMT promoter had a 3.5-fold increased risk of having PsP than TP in

the case of MRI, suggesting progression (Balaña et al., 2017). Only a few studies did not show any correlations between MGMT and PsP (Motegi et al., 2013). The sensitivity and specificity of MGMT promoter methylation status for detecting PsP were 66 % and 89 %, respectively (Lin et al., 2015). GBM of patients with PsP more frequently exhibited a methylated MGMT promoter, and conversely, patients with tumors exhibiting a methylated MGMT promoter more frequently developed PsP (Kong et al., 2011; Soike et al., 2018). The higher sensitivity of GBM with MGMT methylation to an alkylating agent such as TMZ could explain the high rate of PsP in these patients (Sanghera et al., 2012).

EGFR amplification is the most frequent alteration in the activation of oncogenic pathways in GBM. EGFR encodes a tyrosine kinase receptor at the cell surface that is involved in DNA transcription, anti-apoptosis and cellular proliferation. EGFR is a prominent oncogene in IDH wild-type GBM, with overexpression in 60 % of patient and amplification in 40 % of patients. Approximately 50 % of GBM with EGFR amplification has an EGFRvIII variant mutation that is supposed to induce tumorigenicity, cell proliferation and resistance to apoptosis (Lee et al., 2018; Aldape et al., 2015; Le Rhun et al., 2019). In numerous studies, EGFR amplification was associated with poor prognosis and high-grade malignancy (Montemurro, 2020; Muñoz-Hidalgo et al., 2020; Dono et al., 2020). EGFR overexpression could promote TP versus PsP (Yang et al., 2019) but is currently not used as a PsP negative biomarker (Li et al., 2016; Bani-Sadr et al., 2019). Although EGFR amplification was the most frequent alteration, other gene amplifications were shown in the oncogenetic pathway of GBM involving tyrosine kinase activity, such as PDGFRA amplification, reflecting the high complexity of GBM alterations.

The PI3K-AKT-mTOR pathway has a role in metabolism, proliferation, migration and invasion and can also be altered in GBM with a phosphatase and tensine homolog (PTEN) deletion in 30 % of patients, NF1 deletion in 10–20 % of patients or PIC3CA/PIC3R1 mutation in less than 10 % of patients (Brennan et al., 2013; Lee et al., 2018; Montemurro, 2020; Le Rhun et al., 2019). The role of PTEN, NF1, and PIC3CA/PIC3R1 mutations in distinguishing PsP versus TP remains to be demonstrated, but we can suppose that they contribute to TP (Li et al., 2016).

TP53 is a tumor suppressor gene that is important in the cellular response to DNA damage, cell cycle progression and apoptosis induction. TP53 is mutated or deleted with a frequency of 30 % in primary GBM and 70 % in secondary GBM (Rodriguez et al., 2016). It can also be neutralized by murine double minute 2/4 (MDM2/4) amplification in 20 % of GBM (Le Rhun et al., 2019). The role of tumor protein 53 (TP53) in PsP is debated. Its impact on PsP versus TP could be related to its role in apoptosis. TP53 mutations were more frequent in PsP tumors than in TP tumors and could influence the development of PsP (Kang et al., 2011; Yang et al., 2019), but in contrast, the authors concluded that the expression level of TP53 was not predictive of PsP (Pouleau et al., 2012).

Ki67 is a marker of cellular proliferation and was identified as a marker of OS (Henker et al., 2019). Ki67 could be a prognostic marker to distinguish PsP from TP, with a higher rate in tumors of patients who developed PsP than in tumors of those with TP (Pouleau et al., 2012). Nevertheless, this observation was disputable because other studies observed the opposite results (Mehrkens et al., 2008), and some articles did not reveal any clear differences in Ki67 between PsP and TP (Melguizo-Gavilanes et al., 2015; Kim et al., 2012).

Telomerase reverse transcriptase (TERT) influences proliferation, cell survival and oncogenesis via its role in telomerase. In 70–90 % of GBM patients, TERT is overexpressed due to promotor mutations associated with poor prognosis. The role of TERT in distinguishing PsP versus TP has not been proven (Aldape et al., 2015; Montemurro, 2020; Le Rhun et al., 2019). BRAF, alpha-thalassemia/mental retardation syndrome X-linked (ATRX), 1p19q deletion, interferon regulatory factor 9 (IRF9), and X-ray cross-complementary gene 1 (XRCC1) have also been studied with conflicting or isolated results, making definitive conclusions impossible (Li et al., 2016; Yang et al., 2019; Qian et al., 2016; McNulty et al., 2019; Monga et al., 2017).

In GBM, several alterations are associated with high complexity and heterogeneity, such as cyclin-dependent kinase 4 (CDK4) and MDM2 deletion, NF1 deletion and CDKN2A/B deletion, TP53 mutation and PTEN deletion, and IDH1 mutation inversely correlated with EGFR amplification. This could explain the failure of current targeted treatment in GBM management to improve outcomes. Instead of using single targeting drugs, multitargeting drugs against a combination of different molecular pathways that are altered and against the tumor microenvironment seemed more efficacious and efficient (Sharifi et al., 2019). The role of molecular alterations in the occurrence of PsP versus TP is undeniable, but more research, understanding and clinical proof are needed to identify positive or negative biomarkers of PsP (Kessler et al., 2020; Lee et al., 2018; Aldape et al., 2015; Le Rhun et al., 2019).

6.3. *Blood-based biomarkers*

Classically, brain tumors are characterized by histopathological and molecular analyses via tissue samples. Because of the heterogeneity of gliomas, a biopsy or a sample analysis of the tumor could not reflect all characteristics of the tumor. Therefore, liquid biopsy from blood or cerebral spinal fluid, which is a quick, inexpensive and noninvasive method, could be more representative of the entire tumor and its heterogeneity (Klekner et al., 2019; Zachariah et al., 2018) and could be useful for GBM diagnosis and tumor monitoring (Yekula et al., 2020). Limitations of liquid biopsy include the lack of consensus and standardization of the biological fluid type, nucleic acid types, and analytical technique (Klekner et al., 2019). Circulating biomarkers correspond to circulating tumor cells, circulating tumor DNA or extracellular vesicles (EVs). Even if circulating tumor cells are rare and challenging to isolate, they can provide information on protein, DNA and RNA levels. Circulating tumor DNA is easier to detect but has a short half-life. The levels correlate with disease stage. EVs are not exclusively released from tumor cells but can provide information on DNA, RNA and miRNA (Müller Bark et al., 2020).

In the case of diagnosing PsP and TP and avoiding surgery, blood-based methods could help to orient the diagnosis by genomic analysis. The isolation of circulating tumor cells (Sullivan et al., 2014) could be useful during follow-up (Zachariah et al., 2018; Sullivan et al., 2014; Haber and Velculescu, 2014; Macarthur et al., 2014; Müller et al., 2014) as a complement to radiographic features (Gao et al., 2016). Circulating microRNA analysis could be interesting for identifying TP versus PsP because miRNA accurately identifies cancer tissues (Zachariah et al., 2018; Garcia et al., 2017) via circulating tumor stem cells (van Schaijik et al., 2019; Liu et al., 2018), circulating cell-free nucleic acids (Klekner et al., 2019) or circulating tumor cell clusters (Krol et al., 2018). EVs contain many of the same transcripts as primary tumor cells and have proven a high sensitivity and specificity to identify, for example, BRAF, KRAS, or EGFR mutations. EV analysis could be promising in the differentiation between PsP and TP (Koch et al., 2014). The authors demonstrated higher EV plasma levels in GBM patients could guide diagnosing GBM and monitoring response assessment to treatment with a decrease after surgery and an increase in the case of progression (Osti et al., 2019). However, the utility of differentiating PsP from TP needs to be proven, but there is potential to use EVs to identify tumor cell proliferation and invasion, angiogenesis, and biomarkers and to evaluate the response to treatment exists. Implementation in clinical practice could improve personalized medicine in terms of diagnosis, treatment, and follow-up.

7. Conclusion

Currently, in routine clinical practice, the only way to distinguish between PsP and TP is surgery with pathological confirmation, but follow-up MRI is less invasive and thus mostly used. The diagnosis of PsP with certainty poses considerable diagnostic challenges to clinicians and

radiologists. False interpretation of treatment-related changes in TP induces the premature discontinuation of efficient treatment and unnecessary surgery. Clinical, morphological, and molecular features could help in the differentiation between PsP and TP, but they remain insufficient. Clinical data such as sex, age, neurological deterioration, KPS and treatment data revealed discordant results as PsP biomarkers. Noninvasive imaging methods could be used to help identify and diagnose PsP, but further studies are needed to determine the optimal solution for PsP identification. Potential molecular markers of PsP are numerous and difficult to isolate. Authors often studied only one marker or one molecular pathway, neglecting that GBM is a complex tumor integrating several molecular pathway alterations, leading to incomplete and inapplicable results. Moreover, studies were often conducted in a retrospective way and lacked statistical power. MGMT promoter methylation was the most studied with a tendency to favor PsP after CRT, but the results regarding the other molecular markers were too discordant to conclude and persisted as assumptions. Even if data must be improved, molecular markers appear to be an interesting and promising field of research. Today, the RANO and modified RANO criteria remain the most applicable in routine clinical practice and are best known by the medical community. Several potential biomarkers of PsP are discussed in this manuscript. In conclusion, we must unfortunately recognize that data in the literature were discordant and not sufficiently consistent to design a definitive conclusion. To improve the uniformity in diagnosing PsP, efforts are needed, and machine learning models integrating clinical data, genomics and radiomics could provide interesting data and help to improve PsP diagnostics.

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Clara Le Fèvre: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization, Writing - review & editing, Resources, Data curation. **Benoît Lhermitte:** Methodology, Validation, Writing - review & editing. **Guido Ahle:** Validation, Writing - review & editing. **Isabelle Chambrelant:** Investigation, Writing - review & editing. **Hélène Cebula:** Validation, Writing - review & editing. **Delphine Antoni:** Validation, Writing - review & editing. **Audrey Keller:** Validation, Writing - review & editing. **Roland Schott:** Validation, Writing - review & editing. **Alicia Thiery:** Sofware, Methodology, Formal analysis, Validation, Writing - review & editing, Supervision, Project administration. **Jean-Marc Constans:** Methodology, Formal analysis, Validation, Data curation, Writing - review & editing, Visualization. **Georges Noël:** Conceptualization, Methodology, Validation, Writing - review & editing, Resources, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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