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Incidence and outcome of pseudoprogression after radiation therapy in glioblastoma patients: A cohort study

Hanne Blakstad, Eduardo Erasmo Mendoza Mireles, Liv Cathrine Heggebø, Henriette Magelssen, Mette Sprauten, Tom Børge Johannesen, Einar Osland Vik-Mo, Henning Leske, Pitt Niehusmann, Karoline Skogen, Eirik Helseth, Kyrre Eeg Emblem, and Petter Brandal

All author affiliations are listed at the end of the article

Corresponding Author: Hanne Blakstad, MD, Department of Oncology, Oslo University Hospital, P.O. Box 4953 Nydalen, 0424 Oslo, Norway (hanbla@ous-hf.no).

Abstract

Background. Differentiating post-radiation MRI changes from progressive disease (PD) in glioblastoma (GBM) patients represents a major challenge. The clinical problem is two-sided; avoid termination of effective therapy in case of pseudoprogression (PsP) and continuation of ineffective therapy in case of PD. We retrospectively assessed the incidence, management, and prognostic impact of PsP and analyzed factors associated with PsP in a GBM patient cohort.

Methods. Consecutive GBM patients diagnosed in the South-Eastern Norway Health Region from 2015 to 2018 who had received RT and follow-up MRI were included. Tumor, patient, and treatment characteristics were analyzed in relationship to re-evaluated MRI examinations at 3 and 6 months post-radiation using Response Assessment in Neuro-Oncology criteria.

Results. A total of 284 patients were included in the study. PsP incidence 3 and 6 months post-radiation was 19.4% and 7.0%, respectively. In adjusted analyses, methylated *O6-methylguanine-DNA methyltransferase* (*MGMT*) promoter and the absence of neurological deterioration were associated with PsP at both 3 ($p < .001$ and $p = .029$, respectively) and 6 months ($p = .045$ and $p = .034$, respectively) post-radiation. For patients retrospectively assessed as PD 3 months post-radiation, there was no survival benefit of treatment change ($p = .838$).

Conclusions. PsP incidence was similar to previous reports. In addition to the previously described correlation of methylated *MGMT* promoter with PsP, we also found that absence of neurological deterioration significantly correlated with PsP. Continuation of temozolomide courses did not seem to compromise survival for patients with PD at 3 months post-radiation; therefore, we recommend continuing adjuvant temozolomide courses in case of inconclusive MRI findings.

Keywords:

associated factors | chemoradiotherapy | glioblastoma | prognostic factors
pseudoprogression

Glioblastoma (GBM) is an aggressive primary brain tumor and unselected patients have a median overall survival (OS) of about 1 year.[1–3] For patients treated with maximal safe surgical resection followed by partial brain radiotherapy (RT) with concomitant and 6 courses of adjuvant temozolomide, median OS is approximately 15 months.[2,4,5] In patients with tumors harboring methylated *O⁶-methylguanine-DNA methyltransferase* (*MGMT*) promoter; median OS is 21.7 months.[6] A shorter RT course is usually considered for patients above 70 years of age and/or with poor performance status.[7]

Magnetic resonance imaging (MRI) represents the gold standard for disease evaluation.[8] The response assessment in neuro-oncology (RANO) criteria for high-grade glioma are used to evaluate treatment response.[8,9] Pseudoprogression

(PsP) is a post-radiation treatment phenomenon with new or progressive contrast-enhanced MRI signal foci and/or edema within the radiation field that mimics tumor progression.[10,11] These changes typically appear within 12 weeks after radiation therapy and thereafter spontaneously regress or stabilize without any change of anti-neoplastic treatment.[10,11] PsP is subacute with inflammation, edema, and increased abnormal vessel permeability.[12] It has been reported in about one-third of patients with high-grade glioma after standard treatment and is more prevalent in patients with a tumor that harbors methylated *MGMT* promoter.[13–17] Radionecrosis is usually a late post-treatment effect but has also been observed within 6 months post-radiation.[18]

A significant challenge is differentiating PsP imaging features from those of progressive disease (PD). Increased contrast-enhancement and/or increased T2/FLAIR signal present at MRI within the first 6 months after RT should be interpreted with caution.[9] PsP is thought to indicate relative treatment success, whereas PD indicates treatment failure and a need to change anti-neoplastic therapy. Advanced imaging techniques, such as dynamic MRI series, positron-emitting examinations with various isotopes (PET), and machine learning models, show promise for separating post-treatment effects from tumor recurrence but need further validation.[19–23] Also, the limited availability of many of these methods hampers their widespread use.

In case of inconclusive MRI findings within 3 months post-radiation, a common anti-neoplastic treatment strategy has been to continue adjuvant temozolomide courses and shorten MRI follow-up intervals. The rationale for this strategy is twofold; avoid discontinuing a potentially beneficial treatment and appreciate the limited effective treatment options for recurrent GBM. In this population-based study, we re-evaluated post-radiation MRI to assess the incidence and management of, as well as associated factors with, PsP.

Materials and methods

Patient cohort

Oslo University Hospital is the only regional referral center for neurosurgery in the South-Eastern Norway Health Region, part of a public single-payer healthcare system, with a population of 3 million, 55% of the Norwegian population. Patients were identified through the Brain Tumor Registry at the Department of Neurosurgery, which includes a consecutive historical cohort of adult patients (≥18 years) who underwent surgical resection of GBM. Inclusion criteria were adult patients with histologically confirmed GBM diagnosed from January 2015 to December 2018, treatment including RT, and a follow-up MRI exam performed more than 2 months after the end of RT. To match the current fifth edition of the WHO Classification of Tumors of the CNS,[24] we did not include patients with isocitrate dehydrogenase (IDH)-mutant tumors classified as GBM according to the at that time used fourth edition of the WHO Classification of Tumors of the Central Nervous System (CNS).[24–26] Patients with secondary GBM following a previously histologically confirmed lower-grade glioma and patients alive without informed consent were not included.

Data collection

Data from the register were verified and expanded from electronic patient journals. Collected patient data included age and sex, tumor characteristics of the location and molecular genetic characteristics (*MGMT* promoter methylation), and treatment data for surgical resection grade and anti-neoplastic treatment administered at primary diagnosis. Surgical resection grade was determined based on radiological evaluation of early (within 48 h after surgery) postoperative contrast-enhanced MRI and classified as gross total resection (GTR, no residual contrast-enhancing tumor), subtotal resection (STR, residual contrast-enhancing tumor), or biopsy. The neurosurgeon's intraoperative assessment assisted in resection classification in cases where radiological findings were ambiguous. Multifocality was registered if at least 2 distinct contrast-enhancing neoplastic foci existed.

Histopathology and molecular pathology

All patients had histologically confirmed GBM according to the fourth edition of WHO Classification of Tumors of the CNS,[25,26] however, patients with IDH-mutant GBMs were not included to match the updated 2021 WHO Classification of Tumors of the CNS.[24] *MGMT* promoter methylation status was evaluated by a polymerase chain reaction and verified by quantitative pyrosequencing. The cutoff frequency for accepting methylation as positive for CpG sites was set to 10%. Sanger sequencing was used to detect mutations in the NADP-dependent isocitrate dehydrogenase genes (*IDH1* and *IDH2*). An unknown *IDH* status was registered if only immunohistochemistry was performed to detect mutation of the IDH1 p^{R132H}.

MRI re-evaluation

MRI examinations included pre-gadolinium T1-weighted, post-gadolinium T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images. First author re-evaluated post-radiation MRIs based on imaging and radiologist description. Re-evaluation was done according to RANO criteria.[9] A slight modification of RANO criteria was used in the retrospective evaluation, as increasing contrast-enhancing changes or significantly increased T2/FLAIR signal in the high-dose radiation volume within 3 months post-radiation were first defined as PD. Cases in which increased MRI changes at 3 or 6 months subsequently stabilized or regressed without change in treatment strategy were re-classified from PD to PsP, whereas PD was maintained if changes further progressed or if death occurred within 6 months (Figure 1). Retrospective assessment was deemed not evaluable in patients still alive with no MRI follow-up exam or if a new therapeutic intervention had been done before the next MRI precluding the assessment. Neurological status was registered as stable/improved or worsened.

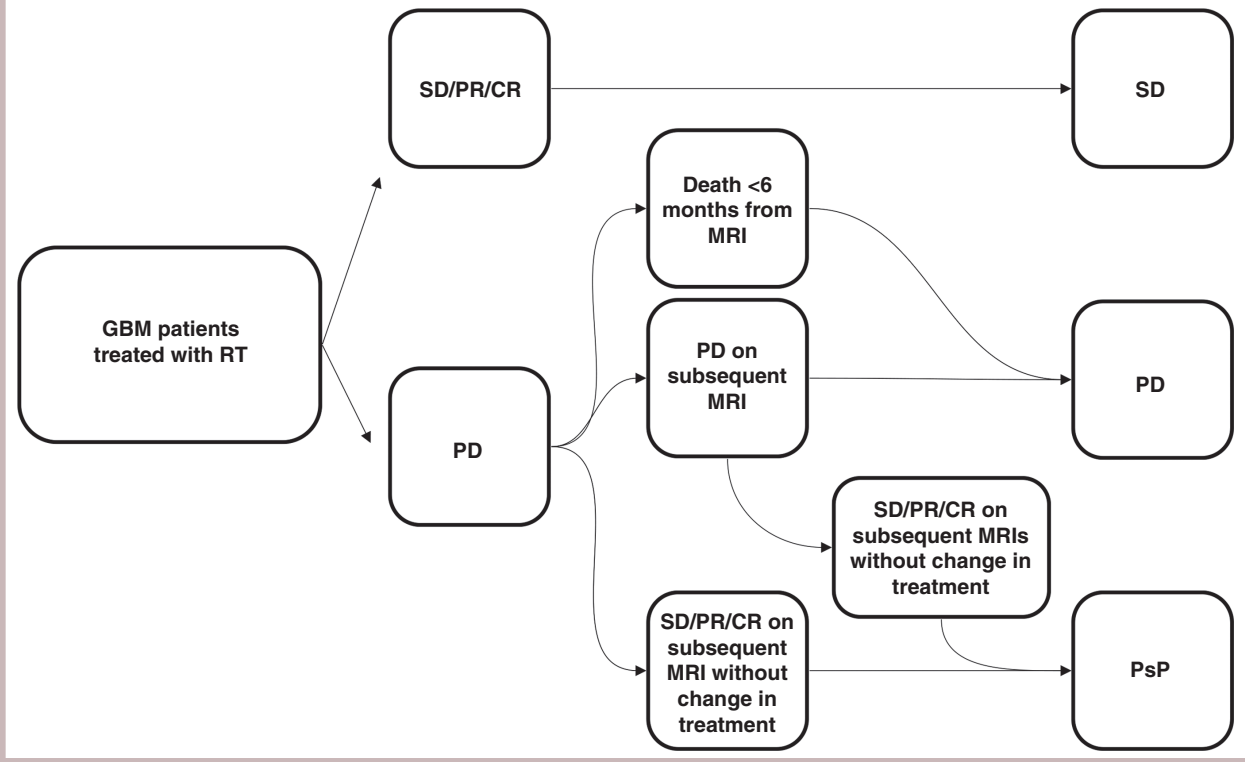

Figure 1. Retrospective assessment of radiological response. GBM = glioblastoma; RT = radiotherapy; SD = stable disease; PR = partial response; CR = complete response; PD = progressive disease; PsP = pseudoprogression.

Statistics

Patients' OS was defined as the time from primary surgery to death of any cause or censoring (December 9th, 2022). The Kaplan–Meier method with a log-rank test was used for survival probability analyses. Cox-proportional hazard regression was used to analyze the effect of multiple risk factors on mortality, and multiple logistic regression was used to analyze associated factors. Correction with the Firth logistic regression method was used in the case of covariates with empty cells that led to separation.[27,28] p Values < .05 were considered statistically significant. A statistician from the University of Oslo was consulted during the statistical analysis. Data analysis was performed using Stata version 17 (StataCorp LLC, Texas, USA).

Ethics

This study was approved by The Regional Committee for Medical and Research Ethics (219194). Informed consent was obtained from live patients.

Results

Patient and tumor characteristics

A total of 406 patients with a tissue-based *IDH* wild-type GBM diagnosis were identified. Of these, 122 patients were excluded based on no informed consent (n = 11), no RT (n = 33), or no MRI follow-up (n = 78). With the exemption of the 11 patients who did not consent, the median OS for the remaining 395 patients was 12.1 months. The median OS of the 111 patients excluded for reasons other than missing informed consent was 3.7 months.

A total of 284 patients were included in the study, with a slight male predominance (n = 172, 60.6%) and a mean age of 62 ± 11 years (range 23–85). The median OS of the 284 included patients was 14.8 months. Patient and tumor characteristics, including their prognostic affect, are shown in Table 1.

Patients younger than 60 years had better prognosis compared to patients in the age groups 60–69 years (p = .020) and 70 years or older (p < .001). Patients with tumors harboring methylated *MGMT* promoters had better prognosis compared to tumors with unmethylated *MGMT* promoters (p < .001). Patients with tumor localization in the left hemisphere had a better prognosis when compared to localization in the right hemisphere (p = .036).

Primary treatment characteristics

Gross total resection (GTR) was achieved in 41.9% (n = 119), STR in 48.6% (n = 138), and biopsy performed in 9.5% (n = 27; Table 1). GTR was associated with a longer median OS of 17.2 months compared to STR (13.9 months) and biopsy (11.0 months), p = .006 and p < .001, respectively.

All included patients received RT (Table 1); standard fractionation to 54–60 Gy (n = 230, 81.0%) or hypo-fractionated

Table 1. Prognostic Impact of Patient, Tumor, and Treatment Characteristics

Characteristics	Total	Median OS	Unadjusted analyses		Adjusted analyses	
	n = 284 (%)	Months	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value
Sex						
Male	172 (60.6)	14.3	1	—	1	—
Female	112 (39.4)	15.3	0.75 (0.59–0.96)	**.024**	0.84 (0.65–1.09)	.180
Age (years)						
<60	114 (40.1)	16.4	1	—	1	—
60–69	94 (33.1)	15.0	1.20 (0.91–1.59)	.204	1.41 (1.06–1.89)	**.020**
≥70	76 (26.8)	13.1	1.51 (1.12–2.04)	**.007**	1.85 (1.36–2.51)	**<.001**
Tumor location						
Right side	136 (47.9)	14.3	1	—	1	—
Left side	125 (44.0)	16.3	0.70 (0.54–0.90)	**.005**	0.75 (0.58–0.98)	**.036**
Midline/bilateral	23 (8.1)	11.3	1.76 (1.13–2.75)	**.013**	1.51 (0.79–2.88)	.211
Multifocality						
Solitary	261 (91.9)	15.2	1	—	1	—
Multifocal	23 (8.1)	11.3	2.13 (1.38–3.28)	**.001**	1.14 (0.59–2.23)	.696
MGMT promoter status						
Unmethylated	141 (49.6)	13.3	1	—	1	—
Methylated	101 (35.6)	22.2	0.42 (0.32–0.56)	**<.001**	0.34 (0.25–0.45)	**<.001**
Unknown	42 (14.8)	11.4	1.01 (0.71–1.43)	.953	0.64 (0.43–0.96)	**.031**
Surgical resection						
GTR	119 (41.9)	17.2	1	—	1	—
STR	138 (48.6)	13.9	1.43 (1.11–1.85)	**.006**	1.73 (1.32–2.27)	**<.001**
Biopsy	27 (9.5)	11.0	2.91 (1.90–4.47)	**<.001**	2.79 (1.65–4.71)	**<.001**

CI = confidence interval; GTR = gross total resection; *MGMT* = O^6 methylguanine-DNA methyltransferase; OS = overall survival; STR = subtotal resection.
Significant *p* values highlighted in bold.

to 30–40 Gy (*n* = 54, 19.0%). Median OS was 16.0 and 11.7 months in the 2 treatment groups, respectively. The majority of patients received concomitant temozolomide (*n* = 270, 95.1%). The remaining patients (*n* = 14, 4.9%) did not receive concomitant temozolomide due to either reduced general condition or inclusion in a trial with immunotherapy. Most patients received 6 adjuvant temozolomide courses (*n* = 163, 57.4 %), whereas 97 patients (34.2%) received less than 6 courses, 22 (7.8%) received no adjuvant courses, and 2 (0.7%) received more than 6 courses.

PsP assessed on MRI exam 3 months post-radiation

The mean time from the end of RT to this MRI exam was 3.1 months. Whereas 273 patients had MRI scheduled at 3 months, 11 patients had their first post-RT MRI at 6 months post-radiation. At re-evaluation, 53 patients (19.4%) were found to have had PsP, 113 (41.4%) PD, and 104 (38.1%) as stable disease (SD). In 3 patients, no follow-up MRIs were available, or new therapeutic interventions had been done before the next MRI. Of the PsP patients, 22 (41.5%) had contrast-enhancing T1-weighted signal only, 2 (3.8%) had significantly increased T2/FLAIR signal only, and 29 (54.7%) had an increase of both. Patients with PsP had a median OS of 24.5 months compared to 11.4 months for patients with PD and 18.4 months in patients with SD (Table 2 and Figure 2). The survival difference was significant only when comparing patients with PsP and PD ($p < .001$).

PsP assessed on MRI exam 6 months post-radiation

The mean time from the end of RT to this MRI exam was 6.1 months. The majority of included patients (242 out of 284) had either a subsequent MRI follow-up or their first MRI follow-up at this time, and their median OS was 16.4 months. Re-evaluation demonstrated that 17 patients (7.0%) had PsP, 120 (49.6%) PD, and 104 (43.0%) SD. In 1 patient, disease status was not evaluable. Eight patients in the PsP group were also registered with PsP 3 months post-radiation. Excluding these 8 patients from the PsP group, the incidence of PsP 6 months post-radiation was 3.8%.

Table 2. Overall survival based on neoplastic status as assessed by MRI 3 months post-radiation when compared to pseudoprogression

Characteristics	PsP (*N* = 53)	PD (*N* = 113)			SD (*N* = 104)		
	Median OS	Median OS	Unadjusted analyses*		Median OS	Unadjusted analyses*	
	Months	Months	Hazard ratio (95% CI)	*p* Value	Months	Hazard ratio (95% CI)	*p* Value
All patients							
	24.5	11.4	5.04 (3.50–7.27)	**<.001**	18.4	1.29 (0.91–1.82)	.157
Sex							
Male	22.1	11.8	4.35 (2.74–6.90)	**<.001**	17.3	1.61 (1.03–2.50)	**.037**
Female	27.4	10.4	6.74 (3.64–12.47)	**<.001**	21.3	0.96 (0.54–1.70)	.885
Age (years)							
<60	24.8	11.5	5.63 (3.17–10.00)	**<.001**	21.9	1.23 (0.71–2.14)	.456
60–69	27.4	11.9	5.14 (2.78–9.49)	**<.001**	17.0	1.66 (0.91–3.00)	.097
≥70	18.2	11.1	3.28 (1.45–7.38)	**.004**	16.0	0.76 (0.34–1.69)	.508
Tumor location							
Right side	19.6	11.8	3.44 (2.09–5.65)	**<.001**	17.4	1.25 (0.78–2.01)	.350
Left side	29.4	11.9	7.23 (4.05–12.91)	**<.001**	21.1	1.30 (0.76–2.23)	.336
Midline/bilateral	—	8.1	8.94 (0.90–88.86)	.062	13.1	1.11 (0.12–10.24)	.925
Multifocality							
Solitary	24.5	11.8	4.84 (3.32–7.06)	**<.001**	19.1	1.25 (0.88–1.79)	.214
Multifocal	20.2	10.2	7.36 (1.36–39.82)	**.021**	13.1	1.66 (0.33–8.46)	.542
MGMT promoter status							
Unmethylated	19.6	11.4	6.39 (3.22–12.70)	**<.001**	16.3	2.05 (1.07–3.93)	**.031**
Methylated	23.7	11.9	2.95 (1.66–5.25)	**<.001**	31.8	0.82 (0.50–1.33)	.411
Unknown	35.5	9.5	10.61 (3.29–34.16)	**<.001**	13.1	2.24 (0.79–6.34)	.129
Surgical resection							
GTR	27.4	12.6	4.06 (2.25–7.32)	**<.001**	19.4	1.25 (0.73–2.12)	.417
STR	23.7	11.4	5.26 (3.16–8.76)	**<.001**	18.3	1.29 (0.79–2.10)	.306
Biopsy	20.2	9.5	24.27 (2.14–274.93)	**.010**	11.7	4.11 (0.44–38.01)	.213
Radiotherapy							
60 Gy	25.8	11.8	5.29 (3.55–7.87)	**<.001**	20.2	1.27 (0.87–1.86)	.210
30–40.05 Gy	12.1	9.9	3.18 (1.23–8.23)	**.017**	14.3	0.84 (0.33–2.13)	.713

CI = confidence interval; GTR = gross total resection; Gy = gray; *MGMT* = O^6 methylguanine-DNA methyltransferase; OS = overall survival; PsP = pseudoprogression; PD = progressive disease; SD = stable disease; STR = subtotal resection.
*PsP group is used as reference.
Significant *p* values highlighted in bold.

Median OS for patients in the PsP group was 31.8 months and thus longer than in the PD group (13.0 months) and the SD group (23.7 months, Figure 3). The difference was significant only when comparing patients with PsP and PD ($p < .001$). Patients with *MGMT* promoter methylated tumors had a median OS of 35.9 months in the PsP group and 29.6 months in the SD group. None of the patients who received hypo-fractionated RT were in the PsP group.

Treatment strategy

Anti-neoplastic treatment was changed in 17 (15.0%) patients with real-time suspected and retrospectively assessed PD at 3 months post-radiation. Patients with real-time and retrospectively PD and no treatment change had a median OS of 11.8 months, compared to 12.1 months for patients where treatment was altered ($p = .838$). Treatment was changed based on MRI-diagnosed presumed neoplastic progression in only 2 (3.8%) patients in the PsP group. Both patients underwent a second surgery where histopathology showed reactive tissue and/or necrosis, with no evidence of active neoplastic disease. Discontinuation of temozolomide courses at this point due to clinical deterioration or toxicity was higher in the PD group (14/113, 12.4%) compared to the PsP (1/53, 1.9%) and SD groups (3/104, 2.9%).

Re-resection was performed in 6 patients after the 3 months post-RT MRI and in 10 patients after the 6 months

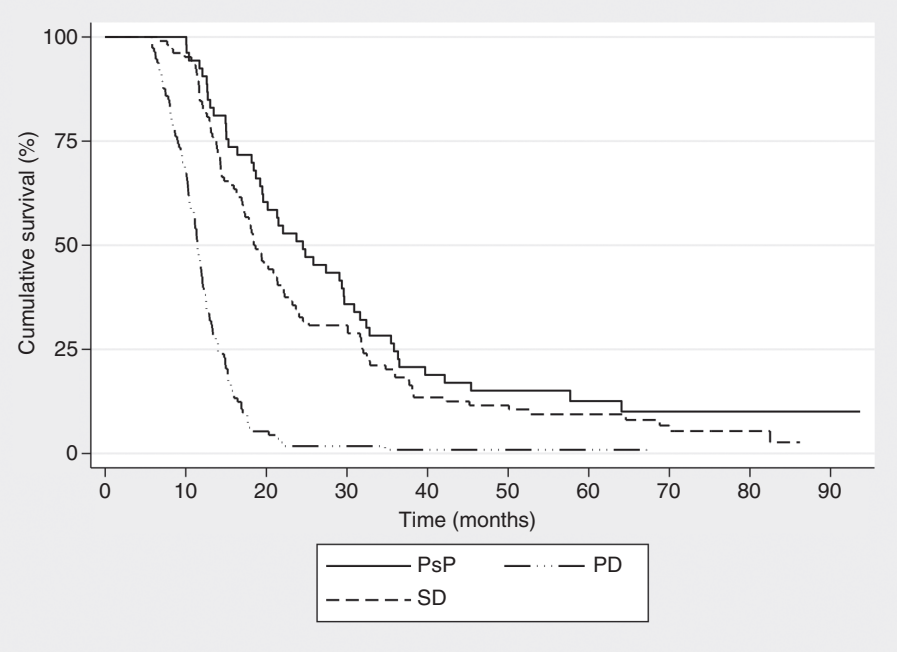

Figure 2. Survival based on retrospective evaluation of MRI 3 months post-radiation. PsP = pseudoprogression; PD = progressive disease; SD = stable disease.

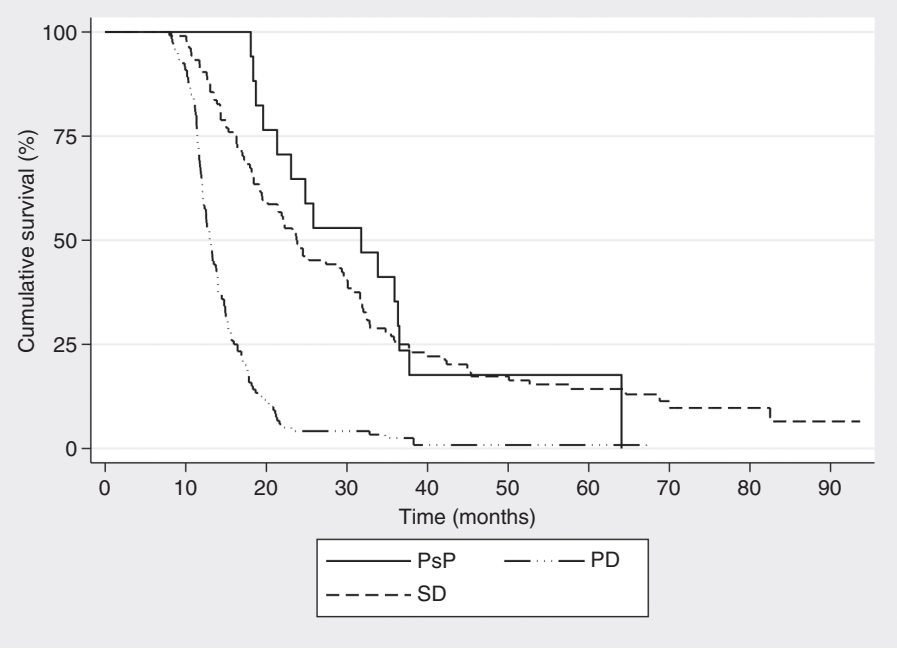

Figure 3. Survival based on retrospective evaluation of MRI 6 months post-radiation. PsP = pseudoprogression; PD = progressive disease; SD = stable disease.

post-radiation MRI. The mean time from the end of RT to the second surgery was 5.7 months. GTR was achieved in 9 (56.3%) and STR in 7 (43.7%) patients following second surgery. Histopathology showed reactive tissue only in 2, neoplastic tissue in 9, and a combination of both in 5 patients. The median OS of these patients was 15.3 months from the time of the first surgery and 7.6 months from the time of second surgery.

Table 3. Predictive Impact for Pseudoprogression 3 Months Post-radiation of Patient, Tumor, and Treatment Characteristics

Characteristics	PsP *N* = 53	PD *N* = 113	Unadjusted analyses		Adjusted analyses	
	N (%)	*N* (%)	Odds ratio (95% CI)	*p* Value	Odds ratio (95% CI)	*p* Value
Sex						
Male	32 (60.4)	67 (59.3)	1	1	1	—
Female	21 (39.6)	46 (40.7)	0.96 (0.49–1.86)	.894	0.68 (0.29–1.55)	.353
Age (years)						
<60	23 (43.4)	45 (39.8)	1	1	1	—
60–69	22 (41.5)	38 (33.6)	1.13 (0.55–2.34)	.737	0.88 (0.36–2.15)	.784
≥70	8 (15.1)	30 (26.6)	0.52 (0.21–1.32)	.169	0.61 (0.16–2.42)	.485
Tumor location						
Right side	27 (50.9)	51 (45.1)	1	1	1	—
Left side	25 (47.2)	48 (42.5)	0.98 (0.50–1.93)	.962	1.01 (0.44–2.28)	.989
Midline/bilateral	1 (1.9)	14 (12.4)	0.13 (0.02–1.08)	.059	0.08 (0.01–1.73)	.106
Multifocality						
Solitary	51 (96.2)	100 (88.5)	1	1	1	—
Multifocal	2 (3.8)	13 (11.5)	0.30 (0.07–1.39)	.124	5.04 (0.34–74.06)	.238
MGMT promoter status						
Unmethylated	14 (26.4)	70 (61.9)	1	1	1	—
Methylated	32 (60.4)	21 (18.6)	7.62 (3.44–16.87)	**<.001**	9.13 (3.78–22.02)	**<.001**
Unknown	7 (13.2)	22 (19.5)	1.59 (0.57–4.44)	.375	3.15 (0.90–11.06)	.073
Surgical resection						
GTR	23 (43.4)	34 (30.1)	1	1	1	—
STR	28 (52.8)	60 (53.1)	0.70 (0.34–1.38)	.294	0.81 (0.36–1.82)	.603
Biopsy	2 (3.8)	19 (16.8)	0.16 (0.03–0.73)	**.019**	0.18 (0.02–1.36)	.096
Radiotherapy						
54–60 Gy	47 (88.7)	89 (78.8)	1	1	1	—
30–40.05 Gy	6 (11.3)	24 (21.2)	0.47 (0.18–1.24)	.128	0.53 (0.12–2.25)	.388
Neurological status						
Improved/stable	45 (84.9)	65 (57.5)	1	1	1	—
Worsening	8 (15.1)	48 (42.5)	0.24 (0.10–0.56)	**.001**	0.35 (0.14–0.90)	**.029**

PsP, pseudoprogression; PD, progressive disease; *MGMT*, O^6 methylguanine-DNA methyltransferase; GTR, gross total resection; STR, subtotal resection; Gy, gray.
Significant *p* values highlighted in bold.

Factors associated with pseudoprogression 3 months post-radiation

In unadjusted analyses, significant factors associated with PsP were methylated *MGMT* promoter ($p < .001$) and absence of neurological deterioration ($p = .001$) (Table 3). Biopsy was significantly associated with PD at 3 months compared to GTR ($p = .019$). In adjusted analyses, methylated *MGMT* promoter and absence of neurological deterioration were significantly associated with PsP when compared to PD ($p < .001$ and $p = .029$, respectively). The start or increase of steroids was inversely associated with PsP in unadjusted analysis (OR 0.28, 95% CI: 0.12–0.65; $p = .003$). Hemispheric laterality was not significant. However, tumor location in the frontal lobe was significantly associated with PsP compared to location in the temporal lobe (OR 4.31, 95% CI: 1.68–11.10; $p = .002$). The significance persisted when adjusted for variables shown in Table 3 (OR 4.35, 95% CI: 1.41–13.45; $p = .011$).

Factors associated with pseudoprogression 6 months post-radiation

In unadjusted analyses, methylated *MGMT* promoter ($p = .001$) and absence of neurological deterioration ($p = .015$) were significantly associated with PsP. In adjusted multivariate analysis, methylated *MGMT* promoter and absence of neurological deterioration were significantly associated with PsP compared to PD ($p = .045$ and $p = .034$, respectively). In unadjusted analysis, the initiation or increase of steroids was inversely associated with PsP (OR 0.29, 95% CI: 0.01–0.49; $p = .014$).

Discussion

A continued and unmet need in neuro-oncology is a reliable tool to differentiate PsP and PD. These 2 very different conditions are essential to separate for further anti-neoplastic decision-making and optimal patient care. We retrospectively evaluated MRIs at 3 and 6 months post-radiation in 284 consecutive GBM patients to assess the incidence, management, and prognostic impact of, as well as factors associated with, PsP. All patients in our study had undergone surgical resection or biopsy with subsequent standard or hypo-fractionated RT. Most patients received adjuvant temozolomide, but the now recommended 12 courses following a hypo-fractionated RT in patients above 70 years of age were not implemented in our clinical practice at the time of treatment of these patients.[7]

Patient age and tumor *MGMT* status were independent prognostic factors consistent with previous studies.[6,29,30] Resection grade is also a well-known prognostic factor.[29–31] In this study, the patients who received surgery with GTR had better prognosis compared to STR ($p < .001$), and to biopsy ($p < .001$) in adjusted analyses. Tumor localization in the left hemisphere was a favorable independent prognostic factor compared to tumor localization in the right hemisphere ($p = .036$), this is in contrast to the results of a large retrospective study where laterality did not impact prognosis.[30]

In this study, the incidence of PsP was 19.4% and 7.0% at 3 and 6 months post-radiation, respectively, and the overall incidence was 21.5%. The incidence drop from 3 to 6 months post-radiation reflects that most cases with PsP presents within 3 months post-radiation.[12] This explanation is supported by a study by Taal et al. in which as many as 50% of patients (18/36) with increasing MRI changes at 4 weeks post-radiation had PsP.[11] The incidence of PsP at 3 months post-radiation found in our study is similar to previous reports ranging from 17 to 23%,[15,32–37] although others have reported higher incidence.[17,38] The same was true for PsP incidence 6 months post-radiation,[39,40] confirming that real-world practice PsP incidence is similar to or slightly lower than reported.

Patients retrospectively evaluated as PD 3 months post-radiation had no survival benefit from treatment change ($p = .838$), presumably reflecting the aggressive biology of GBM and limited alternative treatment options. This finding should be interpreted cautiously since there was a small sample size and no information on lesion size. In nearly half of the patients who underwent surgical re-resection ($n = 7$, 43.8%) histopathological examination revealed reactive tissue only or in combination with tumor cells. This is not surprising as it is well-known that histopathological evaluation of surgical samples at this time point is complex, differentiation of PsP and PD is not always possible, and the coexistence of both is common.[41,42] The small number of patients who underwent re-resection is a limitation and hampers the study conclusion.

Methylated *MGMT* promoter is well known to correlate to PsP.[12] We also found that methylated *MGMT* promoter significantly correlated with PsP at both 3 and 6 months post-radiation ($p < .001$ and $p = .045$). In the PD group, 48 of 113 patients (42.5%) had worsened neurological status at 3 months post-radiation, compared to only 8 of 53 patients (15.1%) with PsP. The absence of neurological deterioration was significantly associated with PsP when compared to PD at 3 and 6 months post-radiation ($p = .029$ and $p = .034$, respectively). Previous findings differ, as some studies[11,37] found that less deterioration in neurological status was associated with PsP, whereas in other studies[13,15] a significant difference between the PsP and PD group was not found. Laterality was not associated with PsP, but tumor location in the frontal lobe was independently associated with PsP compared to location in the temporal lobe ($p = .011$).

Based on the retrospective MRI evaluation at both 3 and 6 months post-radiation, patients categorized as PsP had longer median OS compared to both SD and PD patients although statistical significance was reached only for comparison with PD patients ($p < .001$ and $p < .001$). This significant survival difference between PsP and PD patients is consistent with previous reports.[13,15,16,37,38] Survival of patients evaluated 6 months post-radiation is biased since they were still alive and in sufficient condition to have an MRI evaluation; immortal time bias.

Radionecrosis is often described as a late post-treatment effect (PTRE), typically occurring 6–18 months post-radiation in 6%–25% of patients but may also be present within 6 months post-radiation.[18,43–46] The distinction between radionecrosis and PsP has not been firmly established, but it is postulated that both conditions exist at different time points along the same spectrum of PTRE.[12] It could therefore be argued that we should have categorized some of the re-resected patients as radionecrosis.

This study is limited by the known biases inherent to retrospective analysis. Retrospective real-world data collection and interpretation is challenging but feasible. Missing MRIs at 3 and 6 months post-radiation reflect real-world data and GBM patients' poor prognosis. Some patients who retrospectively were deemed to have PD may have had PsP, especially if they had a prolonged post-progression survival. This dilemma reflects that without proper discrimination between the 2 conditions, PsP falsely diagnosed as PD will overestimate the treatment effect in recurrent GBM studies.

This study concluded that one-third of all GBM patients with increasing MRI changes 3 months post-radiation had pseudoprogression. Furthermore, a methylated *MGMT* promoter, previously shown to be a predictive factor for temozolomide response, was significantly associated with pseudoprogression.[13,47] We also found that continuing adjuvant temozolomide courses did not seem to compromise survival for patients with PD. Based on these findings, a conservative strategy is recommended.

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Conflict of interest statement

None declared.

Affiliations

Department of Oncology, Oslo University Hospital, Oslo, Norway (H.B., L.C.H., H.M., M.S., T.B.J., P.B.); Institute of Clinical Medicine, University of Oslo, Oslo, Norway (H.B., L.C.H., E.H.); Department of Neurosurgery, Oslo University Hospital, Oslo, Norway (E.E.M.M., E.O.V-M., E.H.); Vilhelm Magnus Laboratory, Institute for Surgical Research, Oslo University Hospital, Oslo, Norway (E.E.M.M., E.O.V-M.); Cancer Registry of Norway, Oslo, Norway (T.B.J.); Department of Pathology, Oslo University Hospital, Oslo (H.L., P.N.); University of Oslo, Oslo, Norway (H.L.); Division of Cancer Medicine, Oslo University Hospital, Oslo (P.N.); Department of Radiology, Oslo University Hospital, Oslo, Norway (K.S.); Department of Physics and Computational Radiology, Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway (K.E.E.); Institute for Cancer Genetics and Informatics, Oslo University Hospital, Oslo, Norway (P.B.)

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