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Is There Pseudoprogression in Secondary Glioblastomas?

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Abstract

Purpose—Pseudoprogression (PP) during adjuvant treatment of glioblastoma (GBM) is frequent and is a clinically and radiologically challenging problem. While there are several reports of the frequency of PP in GBM cohorts including mainly patients with primary GBM, there are few data on the incidence of PP in patients with secondary glioblastomas (sGBM). Therefore, the goal of this study was to evaluate the frequency of PP in sGBM.

Methods and Materials—We retrospectively evaluated the incidence of PP in adult patients with sGBM treated with chemoradiation therapy (CRTx) using temozolomide (TMZ) and sought to assess if there was an association between PP and *MGMT* promoter methylation status, *IDH* mutations status, or 1p/19q codeletion. The definition of PP according to the Response Assessment in Neuro-Oncology Working Group was used.

Results—None of the evaluable 15 sGBM patients in our series demonstrated a PP. Of the 9 sGBM patients who received concomitant CRTx with TMZ, 6 patients had the methylated *MGMT* promoter, and 6 patients had *IDH* mutations. There also was no PP identified in sGBM patients who received sequential CRTx, irrespective of *MGMT*or *IDH* status. The median time of follow-up was 3.4 years after diagnosis of an sGBM, and the median overall survival was 18.2 months (range, 14.3–45.2 months). Three of 15 patients had previously received radiation therapy for their

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World Health Organization low-grade 2 glioma, while none of them had received chemotherapy at that stage.

Conclusions—Based on this small series of sGBM patients treated with CRTx (concomitantly or sequentially) the frequency of PP appears to be very low in sGBM, even in those patients with methylated *MGMT* promoter or *IDH* mutations. Our results highlight the differences between primary glioblastomas and sGBM in particular as they relate to PP.

Introduction

World Health Organization (WHO) grade 4 glioblastoma (GBM) represents the most common and aggressive primary brain tumor, with a very poor survival rate (1). The majority of GBM cases (>90%) are primary glioblastomas (pGBM), which manifest rapidly after a short clinical history and without evidence of a less malignant precursor lesion, at an average age of 61 years (2). Secondary glioblastomas (sGBM) are, conversely, less frequent, develop more slowly from lower grade, WHO grade 2 gliomas, and affect younger patients (2). Thus, pGBM and sGBM represent 2 clinically distinct entities with different genetic alterations during their evolutions (3). However, the current standard conventional treatment of both GBM entities includes surgical tumor resection followed by concomitant radiation therapy and chemotherapy (CRTx) with temozolomide (TMZ). While patients were under treatment, a transient enlargement of the enhanced postoperative lesion on magnetic resonance imaging (MRI) was reported in up to 50% of GBM patients (4). If the enlarged lesion does not represent true tumor progression, this phenomenon is referred to as pseudoprogression (PP) (4,5). The Response Assessment in Neuro-Oncology (RANO) working group stated that apparent radiologic progression can be considered true progression within 12 weeks of completion of CRTx only if new lesions have appeared outside the radiation field (beyond the high-dose region or the 80% isodose line) or if pathology confirmation of progressive disease has been obtained (6). However, differentiating between true progression and PP is still challenging for the neuroradiologist and other members of the treatment team. This is based on the fact that there are currently no definitive radiologic criteria, despite the RANO criteria, to differentiate between true progression and PP in GBM. Therefore, the distinction between true progression and PP is made retrospectively by comparing imaging studies longitudinally (5). Furthermore, the recognition of this fact is paramount in avoiding misdiagnosis of recurrent tumors, resulting in an unnecessary second surgery, a change in the patient's treatment, or taking a patient off study. Besides, some studies have demonstrated that PP is associated with improved prognosis of GBM patients, making PP a potential prognostic marker for GBM patients (7,8).

Most data about PP are in relation to pGBM, and, to date, no study has reported on the frequency of PP in exclusively sGBM. We therefore performed a retrospective study to evaluate the frequency of PP in sGBM and to emphasize some of the unique MRI characteristics of sGBM in comparison with pGBM.

Methods and Materials

Study population and treatment

Adult patients who had had surgery for sGBM between 2005 and 2012 were identified and categorized on the basis of histological criteria, provided that a WHO grade 2, low-grade glioma (LGG) tumor had been diagnosed at least 1 year prior to surgery for sGBM. A senior neuropathologist (K.D.G.) performed histopathology. All patients were at least 18 years old at diagnosis and gave informed written consent for molecular analyses of tumor tissue. The study was approved by the local ethics committee.

Patients were included only if they received either sequential radiation therapy followed by chemotherapy with TMZ or concomitant CRTx (radiation therapy plus continuous daily TMZ followed by 6 cycles of adjuvant TMZ, according to the known standard protocol [1]) after surgical resection with histological verification of a sGBM. No antiangiogenic therapy was performed in any of the patients. Radiation therapy to the contrast-enhancing residual tumor and resection cavity was prescribed, with an anatomically confined 2.5-cm GTV; gross tumor volume-CTV: clinical target volume, expansion and a 0.5-cm CTV: clinical target volume-PTV:planning target volume expansion, to a dose of 58 to 60 Gy in daily 1.8- to 2-Gy fractions using 3-dimensional conformal radiation therapy.

The first MR image was routinely performed immediately after surgery for sGBM (within the first 24–48 hours). MR images were obtained regularly throughout the follow-up period at 3-month intervals. Pseudoprogression was defined according to RANO guidelines (6) as a new or progressing lesion during concomitant CRTx or 12 weeks thereafter, inside the radiation field (defined as the 80% isodose line), which was either stable for at least 4 months or diminished on follow-up MRI, without further treatment. The follow-up MRIs were reviewed until the deaths of all patients.

As a comparison population, 71 pGBM patients were analyzed to determine the rate of PP during and after concomitant CRTx.

IDH1/2 mutations and *MGMT* promoter status assessment

IDH1 and -*2* mutations were assessed using direct DNA sequencing, as reported previously (9–11). The *MGMT* promoter methylation status was determined by methylation-specific polymerase chain reaction (MsPCR), as described by Esteller et al (9–10) and other work (10).

1p/19q codeletion status

Status of 1p/19q codeletion was detected by fluorescence in situ hybridization analysis, using samples of paraffin-embedded tumor tissues, by using probes to detect 1p36.1 to 36.3 (target, red) and 1q25.1 to 25.3 (control, green) for 1p detection, and 19p13.1 to 13.30 (green, control) and 19q13.1 to 13.4 (red, target) for 19q detection (Vysis; Abbot Laboratories, Abbot Park, IL), following the recommendations of the manufacturer. Per case, 1 to 5 punch preparations of 1.2-mm diameter from the respective areas (at least 60% tumor, no pure necrosis or hemorrhage) were then combined in tissue arrays together with

negative and positive controls and with normal brain tissues. Evaluation and documentation were performed by microscopy (Axioplan II microscope with filter sets 49 and 23 and Image Pro software; Carl Zeiss, Jena Germany). For evaluation, depending on the extent of tumor cells, 50 to 100 clearly recognizable tumor cells were evaluated, with a cutoff at 50% positive cells, following the guidelines of European Confederation of Neuropathological Societies (12).

Progression and survival

Progression-free survival was defined as the time interval between first diagnosis of a sGBM and first tumor recurrence or tumor progression seen in the MRI. Overall survival was defined as the interval from the day of first surgery for sGBM until death or the end of follow-up. All patient data were updated on June 16, 2013.

Results

Patient characteristics

According to the aforementioned criteria, the data of 15 patients with sGBM were analyzed (Table 1). Nine patients received concomitant CRTx (radiation therapy plus continuous daily TMZ followed by adjuvant TMZ), and the remaining 6 patients underwent a sequenced radiation therapy followed by chemotherapy with TMZ. Three patients (20%) received radiation therapy after surgical treatment for their LGG. No patients received chemotherapy for their LGG.

The median age at diagnosis of sGBM was 40 years (range, 34.6–55.36 years). The median time of follow-up was 3.4 years after diagnosis of sGBM. On average, the progression-free survival was 10.8 months (range, 3.6–17.9 months) after diagnosis of sGBM. All 15 patients died from tumor progression. The median overall survival of the sGBM patients in our series was 18.2 months (range, 14.3–45.2 months)

Molecular analyses

Ten patients (66.6%) carried an *IDH* mutation as well as methylated *MGMT* promoter status (Table 1). Only 2 patients had 1p/19q codeletion; in these 2 cases, the sGBM tissue exhibited oligodendroglial components.

Pretreatment MRI characteristics of sGBM

The sGBM characteristic features in the persurgical MRI (Table 2 and Fig. 1) were frontal localization in 10 cases (66.6%); bihemispheric involvement in 4 cases (26%); insular involvement in only 3 cases (20%); infiltration of the corpus callosum in 6 cases (40%); subependymal involvement in 6 cases (40%); huge mass effect with a midline shift greater than 10 mm in 4 cases (26%); large extent of edema spreading over two lobes in 4 cases (26%); intratumoral cysts in 5 cases (33.3%); intratumoral necrosis in only 2 cases (13.3%); tumor microsatellites in 5 cases (33.3%); and reduced enhancement manner in the contrast-enhanced T1-weighted images (no enhancement, point, or ring enhancement) in 14 cases (93.3%), whereas only 1 patient showed spread heterogeneous enhancement.

Progression assessment in the follow-up MRIs of sGBM patients

Four of 15 patients (26.6%) developed an early recurrence within 3 months after surgery and immediately after completing the concomitant CRTx (Fig. 3). In 1 of these cases, a second surgical procedure followed, confirming the short-term recurrence. In the 3 remaining cases, new remote enhancing lesions occurred, so that a second surgery was not necessary for histological confirmation. Except for these 4 cases, none of the remaining 11 patients exhibited any suspicious lesions during the 3-month period immediately after concomitant treatment. On those patients' MRIs, no contrast enhancement was shown over a relatively long time (Fig. 2). However, after the occurrence of a new local or distant contrast enhancement on MRI, the tumors grew explosively in a multifocal manner, and the patients died a short time after recurrence from clinical deterioration and massive tumor progression, making a true progression very likely. In 3 cases, the patients even developed a meningeal seeding of the GBM.

A pathological confirmation was achieved in 5 patients, through a second surgery, showing a true tumor progression.

Pseudoprogression rate in sGBM

None of the 15 patients in our series demonstrated PP during the 3-month period immediately after treatment according to the criteria defined earlier. Of the 9 sGBM patients who received concomitant CRTx with TMZ; 6 patients carried methylated *MGMT* promoter, and 6 patients carried IDH mutations. No case of PP was identified. Similar results were found in sGBM patients who received sequential CRTx, irrespective their molecular analyses results (Table 1). Also no case of PP was identified on MRI during quarterly follow-ups. Similar results were demonstrated in sGBM patients, who received sequential CRTx, irrespective of their molecular analyses results (Table 1). Even if the definition of PP were extended to 6 months or longer, no case of PP in our study population was identified. All patients died because of their massive tumor progression after a sometimes short, sometimes long "rest period," with high probability of true progression.

Intrainstitutional comparison with a primary GBM population

Of 71 patients with pGBM (26 patients with methylated and 45 with unmethylated *MGMT* promoter), 19 patients (26.7%) had evidence of PP during the first 6 months after concomitant CRTx with TMZ (Fig. 4, see Supplementary material). Of those, 26 patients had methylated *MGMT* and 6 had unmethylated *MGMT* promoter status. In a subgroup of 14 young pGBM patients (median age, 43.8 years), there were 4 cases of PP (Table 3), whereas none of the patients in our young sGBM patients' population (median age, 40 years) showed evidence for PP.

Discussion

Based on this small series of sGBM patients treated with CRTx (in concomitant or sequential manner), the frequency of PP is very low (in none of the included 15 sGBM cases), which highlights the biological differences between pGBM and sGBM in terms of

their incidence of PP. We did not find other studies of the rate of PP in sGBM as a rare entity of GBM.

Retrospective data suggested that PP may occur more commonly in GBM patients with a methylated *MGMT* promoter (>90%) than in those with unmethylated promoter (approximately 40%) and is associated even more with improved survival (13). However, as shown in our study, despite the fact that most of the patients in our series had a methylated *MGMT* promoter (66.6%), none of them showed any sign of PP. *MGMT* promoter status appears not to be associated with the incidence of PP in sGBM. The *MGMT* promoter methylation status might therefore not predict the incidence of PP in sGBM, as it does in pGBM.

A further aspect is the *IDH* mutation, which is very common in sGBM but not in pGBM (3,10,14,15). A recently published work postulated that the *IDH1* mutation is a potential novel marker for distinguishing PP from true progression in patients with GBM treated with CRTx (16). In contrast, our series of 10 sGBM patients harboring an *IDH* mutation, including 2 patients with oligodendroglial components exhibiting 1p/19q codeletions, did not support the latter hypothesis, as none of them had PP. Thus, we conclude that *IDH* mutations are not associated with PP in sGBM.

The mechanism of PP is still poorly understood and is thought to be due to injury of the endothelial cells of the blood–brain barrier (BBB) as reaction of the subacute radiation process and treatment-related necrosis (5). Thus, PP seems to be induced by a pronounced local tissue reaction with an inflammatory component, vasogenic edema causing abnormal vessel permeability, and subsequently, new or increased contrast enhancement on neuroimaging (17). However, as sGBMs are known to show a lower extent of enhancement in contrast-enhanced T1-weighted images and intratumoral necrosis (15), as is also shown in our series (Table 2 and Fig. 1), an explanation for the lack of PP in this study might be based on these 2 facts. In other words, the reaction of the tumor to radiation and the chemotherapy necrosis are less vigorous and the BBB, which might generally be less affected in sGBM with less contrast enhancement in the MRI, avoid such acute damage of the tissue, making PP in this subtype of tumors unlikely. Another aspect is the patients' age by first GBM diagnosis and radiation. It has been shown that older patients' normal brains tolerate radiation more poorly, both radiographically and functionally (18,19). It might be that older individuals are more prone to PP following combined CRTx. However, in a subgroup comparison of our "young" sGBM group with a similar "young" pGBM population, we found several cases of PP in the latter group.

Conclusions

Finally, our study is limited by its retrospective manner and low number of sGBM patients. While only 3 patients received radiation therapy for their low-grade WHO grade 2 glioma and 12 of 15 patients had not, it remains possible that previous treatment might contribute to our observation that the PP is rare in sGBM. Therefore, more work and larger series are needed to confirm that the rate of PP in sGBM is indeed very low.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Pseudoprogression (PP) is common in patients receiving adjuvant chemo-radiation therapy for primary glioblastoma (GBM). We retrospectively evaluated the incidence of PP in 15 secondary GBM patients treated with chemoradiation therapy and its association with *MGMT* promoter methylation and *IDH* mutation status. In this small series, there was no PP in sGBM observed (0 of 15 cases), not even in patients with methylated *MGMT* promoter (0 of 10) or *IDH* mutations (0 of 10), suggesting that PP might be an infrequent event in secondary GBM.

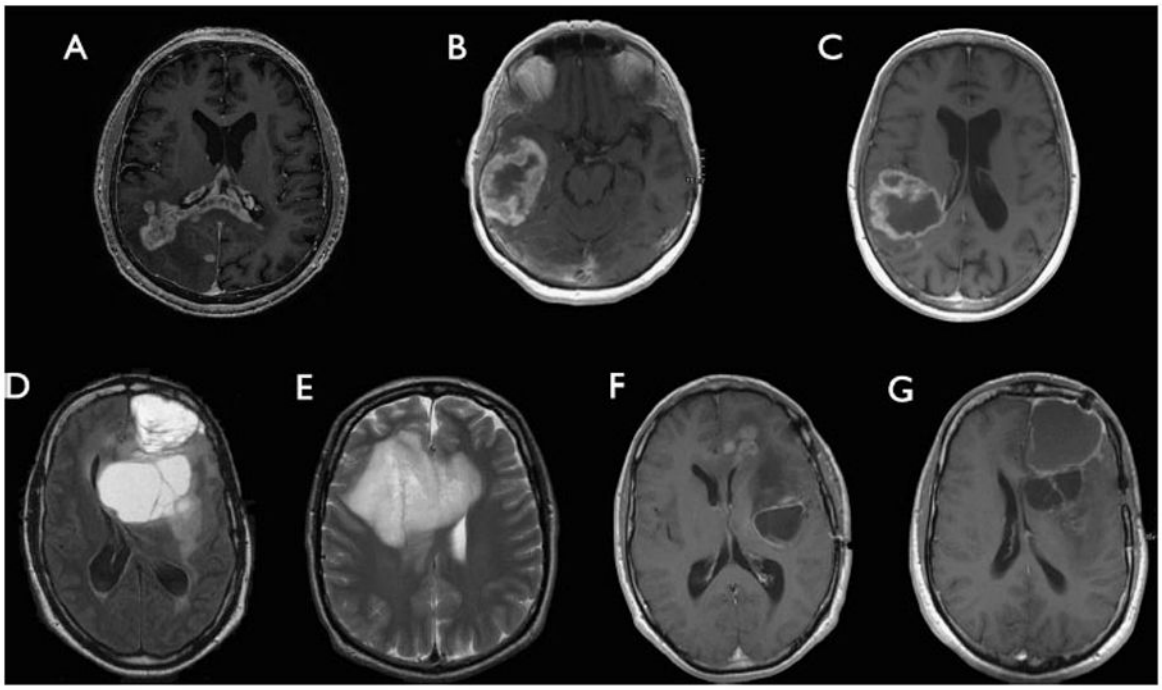

Fig. 1.

(A–C) Examples of contrast-enhanced T1-weighted MR images of primary glioblastomas showing ring enhancement, necrosis, and superficial (subpial) growth are shown. (D–G) Examples of secondary glioblastoma with an *IDH* mutation. FLAIR and T2-weighed images (D, E) show a large tumor in a frontal location, bihemispheric involvement, and intratumoral cysts. Contrast-enhanced T1-weighted images (F–G) depict a relatively reduced enhancement and tumor microsatellites. FLAIR, fluid attenuated inversion recovery; MR, magnetic resonance.

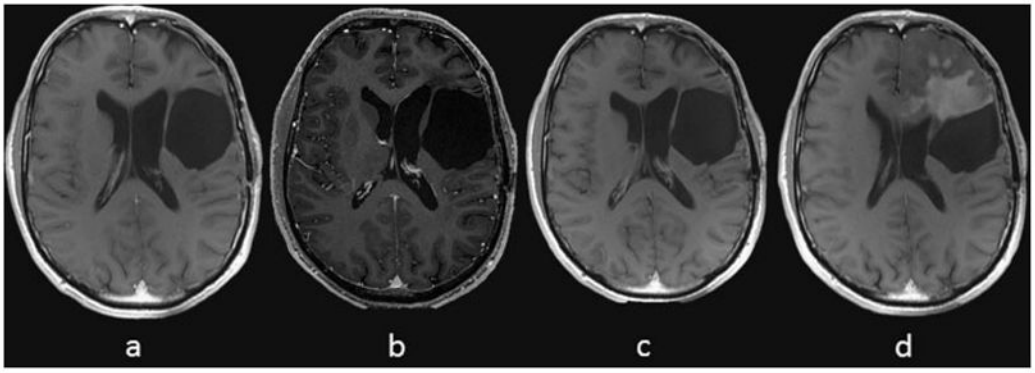

Fig. 2.

Local patterns of recurrence in a sGBM patient treated with CRTx are shown postcontrast T1-weighted MRI scans over 18 months. MRIs were obtained at 3 months (a), 6 months (b), and 15 months (c) after concomitant CRTx showed no contrast enhancement. After 18 months, there is a dramatic example of “sudden” local recurrence with increased “diffuse” areas of enhancement (d). CRTx, chemoradiation therapy; MRI, magnetic resonance imaging; sGBM, secondary glioblastoma.

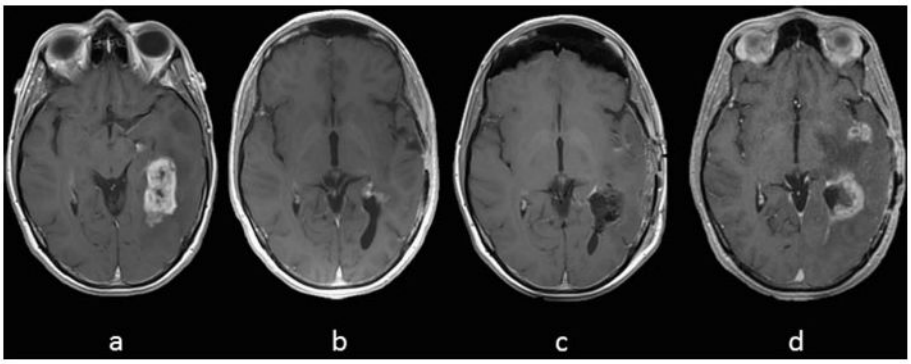

Fig. 3.

Early recurrence of a sGBM immediately after completing the concomitant CRTx shown in postcontrast T1-weighted MRI scans. A preoperative MRI (a), a postoperative MRI scan 1 month after completing concomitant CRTx with a local recurrence (b), a postoperative MRI after the second surgical procedure with histological confirmation of GBM tissue (c), and a follow-up MRI after 2 cycles of adjuvant TMZ with multifocal enhancing recurrence are shown. CRTx, chemoradiation therapy; MRI, magnetic resonance imaging; sGBM, secondary glioblastoma.

Table 1

Patients' characteristics, treatment modalities, and molecular analyses of the sGBM patient group

Patient	Sex	Histology	Age at sGBM diagnosis (yr)	Pseudoprogression	Concomitant CRTx	Sequenced RT or CT	Carries the *IDH* mutation	Methylated *MGMT* promoter	1p/19q Codeletion
P1	F	sGBM	46	No	Yes	No	Yes	No	No
P2	F	sGBM	40	No	Yes	No	Yes	Yes	No
P3	M	sGBM	36	No	Yes	No	Yes	No	No
P4	M	sGBM	36	No	Yes	No	No	Yes	No
P5	M	sGBM*	49	No	Yes	No	Yes	Yes	Yes
P6	F	sGBM	54	No	Yes	No	No	Yes	No
P7	M	sGBM	35	No	Yes	No	Yes	Yes	No
P8	M	sGBM*	38	No	Yes	No	Yes	Yes	Yes
P9	M	sGBM	54	No	Yes	No	No	No	No
P10	M	sGBM	34	No	No	Yes	Yes	No	No
P11	M	sGBM	48	No	No	Yes	Yes	Yes	No
P12	M	sGBM	53	No	No	Yes	Yes	Yes	No
P13	F	sGBM	39	No	No	Yes	No	Yes	No
P14	F	sGBM	71	No	No	Yes	No	No	No
P15	F	sGBM	34	No	No	Yes	Yes	Yes	No

Abbreviations: CRTx = chemoradiation therapy; CT = chemotherapy; RT = radiation therapy; sGBM = secondary glioblastoma.

*With oligodendroglial components.

Table 2

Presurgical MRI characteristics of sGBM patients

Patient	Tumor location	Bihemispheric involvement	Insular involvement	Involvement of corpus callosum	Subependymal involvement	Mass effect	Extent of edema*	Intratum. cysts	Necrosis	Tumor enhancement manner†	Micro satellite
P1	Temporal	No	No	No	Yes	No	Low	Yes	No	Ring	No
P2	Frontal	No	No	No	No	No	Low	No	Yes	Ring	No
P3	Temporal	No	No	No	Yes	No	Low	No	No	No	No
P4	Temporal	No	No	No	No	No	Low	No	No	Ring	No
P5	Frontal	Yes	No	Yes	No	No	Low	No	No	Point	No
P6	Frontal	No	No	Yes	Yes	Yes	Large	No	Yes	Ring	Yes
P7	Frontal	No	No	No	Yes	No	Low	No	No	Heterogeneous	Yes
P8	Frontal	No	Yes	No	No	Yes	Low	Yes	No	Ring	No
P9	Temporal	No	No	No	Yes	No	Low	No	No	No	No
P10	Frontal	No	Yes	No	Yes	No	Large	No	No	Ring	Yes
P11	Temporal	No	No	Yes	No	No	Large	No	No	Nodular	Yes
P12	Frontal	Yes	No	Yes	No	Yes	Low	Yes	No	No	No
P13	Frontal	Yes	Yes	Yes	No	Yes	Large	Yes	No	Ring	Yes
P14	Frontal	Yes	No	Yes	No	No	Low	Yes	No	No	No
P15	Frontal	No	No	No	No	No	Low	No	No	No	No

*Large extent of edema: involvement of 2 or more lobes.

†Enhancement manner in presurgical contrast-enhanced T1-weighted images.

Table 3

Patient characteristics, treatment modalities, and *MGMT* promoter status of a young pGBM patient population

Patient	Sex	Histology	Age at pGBM diagnosis (yr)	Pseudoprogression	Concomitant CRTx	Methylated *MGMT* promoter
P1	F	pGBM	38	No	Yes	No
P2	F	pGBM	39	No	Yes	No
P3	M	pGBM	39	No	Yes	No
P4	F	pGBM	41	Yes	Yes	Yes
P5	M	pGBM	41	No	Yes	No
P6	F	pGBM	42	No	Yes	Yes
P7	M	pGBM	42	Yes	Yes	Yes
P8	F	pGBM	44	No	Yes	No
P9	F	pGBM	45	No	Yes	Yes
P10	F	pGBM	47	No	Yes	No
P11	M	pGBM	48	No	Yes	Yes
P12	M	pGBM	48	Yes	Yes	Yes
P13	M	pGBM	48	Yes	Yes	No
P14	M	pGBM	48	No	Yes	Yes

Abbreviations: CRTx = chemoradiation therapy; pGBM = primary glioblastoma.