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Characterization of pseudoprogression in patients with glioblastoma: is histology the gold standard?

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Abstract

Pseudoprogression (psPD) refers to an increase in size or appearance of new areas of MRI contrast enhancement soon after completing chemoradiation, timely diagnosis of which has been a challenge. Given that tissue sampling of the MRI changes would be expected to accurately distinguish psPD from true progression when MRI changes are first seen, we examined the utility of surgery in diagnosing psPD and influencing patient outcome. We retrospectively reviewed data from adults with GBM who had MRI changes suggestive of progression within 3 months of chemoRT; of these, 34 underwent surgical resection. Three subsets—tumor, psPD or mixed—were identified based on histology and immunohistochemistry in the surgical group and by imaging characteristics in the nonsurgical group. A cohort of patients with stable disease post-chemoRT served as control. PFS and OS were determined using the Kaplan–Meier method and log rank analysis. Concordance for psPD between radiological interpretation and subsequent histological diagnosis was seen in only 32 % of cases (11/34) 95 %CI 19–49 %. A large proportion of patients had a histologically “mixed” pattern with tumor and treatment effect. No significant differences in PFS or OS were seen among the three subtypes. Surgical sampling and histologic review of MRI changes after chemoRT may not serve as a gold standard to distinguish psPD from true progression in GBM patients. Refinement of the histological criteria, careful intraoperative selection of regions of interest and advanced imaging modalities are needed for early differentiation of PsPD from progression to guide clinical management.

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Keywords

Pseudoprogression; Glioblastoma; Glioma; Radiation; Chemotherapy; Surgery

Introduction

Glioblastoma (GBM) is the most common and the most aggressive of primary brain tumors in adults [1]. Stupp et al. showed improvement in overall survival with a regimen using temozolomide (TMZ), an alkylating agent concurrently with radiation (ChemoRT) and followed by 6 months of adjuvant TMZ which has become the standard of care for patients with newly diagnosed GBM [2].

Pseudoprogression (psPD) is a phenomenon originally described in patients with high grade glioma which refers to an increase in size of existing lesions or appearance of new areas of contrast enhancement on MRI studies, soon after radiotherapy, with subsequent improvement without any further specific treatment. [3,4] Even though this entity has been known since the pre-MRI era [5], PsPD remains a confounding factor in clinical management of newly diagnosed GBM. Due to the lack of a validated noninvasive method of distinguishing psPD from true progression, it has been proposed that patients who have imaging changes within the first 12 weeks after ChemoRT should be excluded from clinical trials for recurrent disease [6], unless pathological confirmation of tumor is obtained. [4,6,7] Several factors have limited the ability to differentiate tumor progression from treatment effect including lack of standardized methodology, ambiguity of terminology and particularly, the lack of systematic histological confirmation, conventionally considered the gold standard for accurately characterizing pathological processes [7–10].

Distinguishing treatment effect from tumor progression when a change is detected in radiological studies is critical in deciding the subsequent management of the patient in order to avoid either discontinuing an effective treatment or continuing an ineffective treatment in the setting of unidentified progression. Currently, the determination of psPD is primarily made by radiological assessment with a short-term clinical follow up often with the empiric use of steroids. In certain instances when there is ambiguity about treatment decisions or when progressive symptoms require intervention, the area is sampled surgically to accurately determine whether psPD has occurred. The primary objective of our study was to determine whether histological criteria could indeed serve as a gold standard to distinguish psPD from true progression in patients with GBM.

Patients and methods

Patients

We retrospectively queried the longitudinal patient database of the Neuro-oncology department in MD Anderson for adults diagnosed with GBM consecutively between October 2006 and March 2009 under an HIPAA compliant study which was approved by our IRB. Criteria for inclusion in the study were histological confirmation of the primary diagnosis of GBM, treatment with conventional chemoradiation therapy and radiological

evidence of new or enlarging gadolinium enhancing lesion within 3 months of completion of chemoRT. Patients with an incomplete course of chemoradiation treatments, lack of histologic confirmation or MRI scans, or inadequate follow-up were excluded. The evaluable patients, were further divided into two groups: (i) a test group consisting of patients who underwent surgical resection to definitively determine the nature of new MRI changes of concern for progression; this group was subclassified as psPD, progressive tumor (T) or mixed (residual tumor and treatment related changes) based on initial pathology report and subsequently independently reviewed and redesignated by a neuroradiologist and a neuropathologist and (ii) a control group consisting of patients who did not undergo surgery but either had radiological changes after chemoRT (designated as “progression” in our database) or did not have radiological evidence of concern for progression (stable or “no change” entry in our database). This control group was further reviewed by a neuroradiologist, and a subset of patients initially categorized as “no change” in our system were reclassified into the “progression” group based on radiological findings.

Radiologic studies

MRI studies included conventional multiplanar brain scans at field strength of 1.5 or 3 T with and without contrast. Evaluation was primarily based on changes in enhancement on post-contrast images [11,12]. All available MRI scans were independently reviewed by a neuroradiologist and assigned into three radiological categories: progressive tumor (T), psPD and mixed (radiologic features of both residual tumor and treatment changes) based on comparison between the baseline pre-chemoRT and the first post chemoRT scan. In order to closely approximate the decision making process used in routine clinical practice, Tumor was qualitatively defined as either increase in contrast enhancement of a preexisting enhancing lesion or appearance of a new “solid or nodular” homogeneous or heterogeneous enhancing region either distinct from the primary site or along the margin of the surgical cavity. PsPD was also qualitatively defined as areas of increased or new enhancement which had a reticulated or “soap bubbly” appearance. All other enhancing patterns such as no change in enhancement or a decrease in size of the pre-existing enhancing lesions, linear enhancement along the pericavitary margins, small (<5 mm) foci of enhancement were not considered as suggestive of disease progression and such patients were considered stable.

Histologic studies

Tissue specimens from the second or subsequent surgery that were available only for procedures performed at MDACC, were independently reviewed by a neuropathologist. Based on the histologic features, patients were again grouped into one of three categories: Tumor (T) which included specimens with solid areas of high-grade tumor, occupying at least 70 % of the specimen; psPD including specimens which predominantly showed histologic features typically associated with treatment effect such as bland necrosis, fibrosis, gliosis, edema, demyelination and vascular hyalinization. Additionally, concurrent presence of infiltrating atypical astrocytes or areas of tumor occupying less than 10 % of the specimen were included in this category; Mixed, which included specimens that had both the features described above with at least 30 % of the specimen showing changes in both categories. After histologic analysis, 1–3 representative tissue blocks were selected from each case for

immunohistochemical studies, except in cases where individual patients had not provided consent for use of their tumor specimens for additional research.

Immunohistochemistry

Immunohistochemistry was performed on 5 µm thick paraffin sections using a Bond Max automated stainer (Vision Biosystems, Norwell, MA) with epitope retrieval. Antibodies included p53 (1:100, clone DO-7, Dako), phosphohistone-H3 (PHH3, 1:400, Millipore), MIB-1 (1:100, Dako), and isocitrate dehydrogenase 1 (IDH1, 1:40, Dianova). Slides were counterstained with hematoxylin. Appropriate positive and negative controls were included with each run. Positive reactivity for p53 was detected as distinct brown nuclear staining and estimated manually in deciles as the percent of nuclei stained in either tumor areas or brain adjacent to tumor in the section. pHH3 reactivity was scored based on the number of mitotic figures identified with a nuclear dark brown reaction product on each slide. It was scored semi-quantitatively as 0 (no mitotic figures identified), rare (one or two mitotic figures in the section), + (3 or 4 easily identified mitotic figures in the section) and ++ (more than 10 mitotic figures identified in 10 high power fields). Positive reactivity for MIB-1 was estimated semi-quantitatively based on nuclear dark brown reaction product in either tumor or non-tumor regions of a section. It was scored as + (less than 5 % of nuclei stained-low), ++ (5–15 % of nuclei stained-moderate) or +++ (more than 15 % of nuclei stained-high). IDH1 immunoreactivity was scored as positive (mutant protein present) or 0 (mutation not detected), based on strong nuclear and cytoplasmic staining in tumor cells when mutation is present in the tumor.

Clinical outcome and statistical analysis

The influence of the designated histological and radiological grouping on clinical outcome was determined by analyzing the relationship of the groups to progression free survival (PFS) and overall survival (OS). PFS was defined as the period from first post-chemoRT scan to the development of radiologically evident progressive disease or date of last follow up (censored) or death. OS was designated as the period from first post-chemoRT to death, or date of last follow up (censored). The data were analyzed using the Kaplan–Meier method and log rank analysis for significance of differences seen.

Results

Patient characteristics

A total of 295 patients were identified from the database for inclusion in this study; of these, 34 patients were in the test (surgical) group, 107 in the progressive nonsurgical group and 154 in the stable group. Patient characteristics are outlined in Table 1.

Of the 34 test patients, 6 had placement of Gliadel® wafers at the time of initial surgery, but of those only 2 patients were categorized as having PsPD. The second surgical intervention after chemoRT consisted of subtotal or gross total resection in all patients except for one who had a biopsy. In 6 patients, surgery was indicated for edema and increase intracranial pressure associated with the MRI changes whereas in the remainder, it was for diagnostic purposes. In 26 patients (76 %), a clinical decision was made to change to an alternative

chemotherapy regimen for recurrent disease. (Table 2). Of note, 7 patients with histologically characterized PsPD, previously categorized as mixed, had a change in chemotherapy treatment.

Radiological studies

Review of imaging studies in the test group were concordant with histologic findings in only 11/34 cases (32 %) 95 % CI 19–49 %; with agreement in identification of 3 tumors, 7 mixed and 1 psPD (Table 2). An example of the discrepancy between independent imaging and histology is shown (Fig. 1).

Histologic studies

All patients had a confirmed new initial diagnosis of GBM, according to the World Health Organization (2007) criteria [13]. The histology of the second surgery for each of the 34 test cases was reviewed. Each patient was re-classified for this study based on a detailed estimation of specific histologic features noted on all slides available for the case (Table 2). Ten patients were placed into the “tumor” group. Features included high tumor cellularity, nuclear and cytoplasmic pleomorphism, and occasional to marked mitotic activity. Necrosis alone was not considered evidence of tumor. Most cases also showed foci of microvascular proliferation in the areas of tumor. Eleven patients showed histologic features associated with cytotoxic treatment effect, here classified as pseudoprogression (psPD) [14]. These features included areas of bland necrosis with prominent vascular fibrinoid necrosis, reactive gliosis, edema, demyelination and vascular hyalinization. Foci of fibrosis were also seen. Foci of tumor in this group were present in less than 10 % of the total tissue volume or were present as individual infiltrating tumor cells, based on positive immunoreactivity for p53 protein or MIB-1 (Fig. 2). Thirteen patients showed histologic features considered to demonstrate a “mixed” pattern of high-grade astrocytoma and treatment effect.

Immunohistochemistry

Five of the 10 tumor cases had tissue blocks available for immunohistochemistry for p53. Reactivity ranged from <5 % positive to 90 % positive in areas of solid tumor. Of the 7 cases with available tissue in the psPD group, there was reactivity only in the foci of tumor or in infiltrating highly atypical cells, presumed to represent tumor. Percent positivity ranged from scattered infiltrating cells to up to 80 % positive cells, although the foci of tumor were small, amounting to less than 10 % of the tissue. In the “mixed” group, 11/13 cases had tissue available for immunohistochemistry. Patterns were similar to the psPD group and percent positivity ranged from negative (only 1 case) to 80 % positive cells in areas of tumor. Overall, considering all of the tumors tested, 15/23 cases showed positive immunoreactivity for p53 protein.

Immunohistochemistry for MIB-1 identified out of the 11 tumor cases, 4 with available tissue that showed a low labeling, two showed moderate labeling and one showed high labeling. Of the 10 psPD cases, 6 showed low labeling in areas of infiltrating tumor cells and one showed moderate labeling. Of the 13 mixed cases, 5 showed low labeling in tumor, 3 showed moderate labeling, and 3 showed high labeling. No cases with MIB-1 immunohistochemistry were entirely negative.

Six of the 10 tumor cases had tissue available for immunohistochemistry for PHH3. One case showed no labeled cells, two showed only rare cells (R), and three showed + labeling. In the psPD group, of 7 cases with available tissue, 4 were negative, 2 more showed rare labeling mitoses, and only 1 case showed + labeling. In the mixed group, 11 of 13 cases had tissue available for PHH3. Three cases were negative, 2 showed rare labeled cells, 4 showed + labeling, and 2 showed ++ labeling.

IDH1-R132H immunohistochemistry in the tumor cases showed 1 of the 5 tested cases demonstrated positive reactivity, indicating a mutation. None of the 7 tested psPD cases was positive. One of the 11 tested mixed cases was positive.

Clinical outcome

We initially analyzed survival based on the radiological interpretation of psPD and progression in 32 patients who had sufficient data on radiological studies for this assessment. The median OS based on this analysis for mixed ($n = 16$), psPD ($n = 3$) and tumor ($n = 13$) were 16, 19 and 14 months respectively. Thus, outcome based on radiology-interpretation alone in this subset of patient did not show significant differences among the three categories.

We next analyzed outcome based on the surgical determination of the nature of radiological change. In this surgical group, the median PFS was 4.8, 5.8 and 7.5 months ($p = 0.69$) and the median OS was 14.4, 18.5 and 17.1 months ($p = 0.82$) respectively for psPD, tumor and mixed patients. Thus, there were no significant differences in PFS or OS among these three subtypes (Fig. 3). Similar findings were obtained in the nonsurgical progressive group. However, the median OS for the surgical and nonsurgical group as a whole was 15.2 and 13.2 months respectively whereas that of the post chemoRT stable group was 22.8 months ($p = 0.0001$) which was significantly longer than the other two groups. Data regarding the Karnofsky performance score (KPS) at baseline and at the time of imaging changes suggestive of progression were available for 12 patients. Overall, our data did not support the common clinical assumption that good KPS favors psPD. However, it did indicate that patients who had no changes in their scan (stable scans) after chemoRT had a more favorable outcome. These results may however, be influenced by the small number of patients in this study which precludes drawing definitive conclusions but provide a basis for further assessment of this paradigm.

Discussion

The use of surgery to determine the nature of radiological changes after chemoRT is based on the assumption that it is a “gold standard” for confirmation of tumor progression versus psPD. However, the results of our study demonstrate the complexity of interpreting surgical samples in this setting and highlights that current criteria for histological confirmation may not be a robust standard to distinguish psPD from true progression. We observed that a large proportion of patients were categorized as “mixed” which failed to resolve the ambiguity of the process even after histological examination and did not adequately inform subsequent treatment decisions.

Concordance between radiological interpretation of the increased enhancement on MRI scans and subsequent histological diagnosis was seen in only 32 % of cases. Our results suggest that MRI scans in routine clinical practice cannot be used as a reliable method for detecting psPD especially at a single time-point post chemoradiation therapy and for clinical decision making, consistent with other similar reports [15,16]. It should be noted that we did not examine the impact of delayed psPD that can occur as long after chemoRT as 6 months as most of these patients do not face the same acuity of decision making about treatment planning as the ones immediately after chemoRT.

Surgical sampling and histological examination in the setting of psPD also have notable limitations. When patients with new enhancement on MRI scan post chemoRT are referred for surgical evaluation, the procedure chosen may either be a biopsy or a resection. With biopsies, erroneous diagnoses can result from sampling errors. Additionally, areas of *residualstable* tumor occurring along with a smaller area of psPD in resection specimens may be interpreted as showing predominantly tumor and misinterpreted as representing tumor progression. We also noted discrepancies between the initial pathology reading and a subsequent reassessment by expert tumor neuropathologists using more specific criteria suggesting that there can be interobserver variability even among neuropathologists familiar with psPD [7].

In cases which showed pure treatment effect or florid tumor, diagnosis is relatively straightforward. However, determining whether tumor seen in a mixed specimen is active or residual stable disease is particularly challenging using conventional histologic studies. To examine if additional markers could help further refine the histologic diagnosis, we used four immunohistochemical markers to better identify the presence of viable tumor.

The low levels of staining for mutant IDH1 was expected given that these patients had primary GBM which infrequently demonstrate this mutation [17] as opposed to lower grade gliomas that show high frequency of mutant IDH1 [18]. Recently, Motegi et al reported that GBMs with IDH1 mutation may be more likely to be associated with psPD [19]. Juratli et al. reported that psPD did not occur frequently in patients with secondary GBM who received chemoRT [20]. Our series included only patients with primary GBM and since only two patients had tumor with mutant IDH1 expression, we could not utilize this marker for any useful analysis.

Pouleau et al. have reported that high levels of cellular proliferation found in the original tumor predicted psPD in GBM patients. [21] The MIB-1 index and PHH3 reactivity, contrary to our expectations did not reveal clear differences between tumor and mixed specimens. In the psPD specimens showed minimal staining and only in areas with tumor cells as expected. The relatively low level of proliferative activity in the recurrent GBM group in our study could potentially be due to the cytostatic effect of chemoradiation in these patients as recently suggested by Kim et al. [22]; however, the reliability of the MIB-1 index as a measure of the behavior of GBM is less well established compared to their usefulness in lower and intermediate grade diffuse astrocytoma [23].

No significant differences in clinical outcome were seen among the three groups in this study even after histologic confirmation of tissue process. Furthermore, our patients with histological confirmation of psPD appeared to have a trend to a higher rate of progression and worse outcome in contrast to reports by other investigators of a survival benefit with imaging-based definition of psPD. [9,24] Our results are in contrast to previous reports that suggested improved outcome in patients who were diagnosed with psPD. This could be due to the low number of surgical patients in each group. Given that we did not have data on *MGMT* promoter methylation, the relevance of this correlate on outcome in the patients of this study could not be analyzed. An alternative explanation for this discrepancy may be that the previous reports of association between psPD and outcome were based primarily on radiological determination of psPD. Our results show that such purely radiological assessments often do not correlate with histological findings. An additional explanation could be that patients who are referred for surgical evaluation of MRI changes may represent a diagnostically more challenging set of cases whose scans are not clearly interpretable leading to hesitation in continuing standard of care due to concern for tumor recurrence. This is supported by the fact that only a small number of patients in the surgical group were diagnosed to have unequivocal psPD. These findings are also in support of our assertion that surgical sampling may not serve well as a standard for diagnosis of psPD.

Our study has limitations including the known biases inherent to any retrospective analysis and the small size of our surgical patients. It is possible that subsequent treatment decisions could also have influenced progression free and overall survival. We also did not have data regarding additional molecular markers such as *MGMT* promoter methylation or advanced imaging studies since these were not routinely obtained in our patients. However, the patients were selected consecutively from a large longitudinal database and the data reviewed using pre-specified criteria by specialists with expertise in brain tumors. To our knowledge, this is the largest reported series of surgically analyzed specimens from patients suspected to have psPD and could provide a foundation for future studies.

The detection of psPD is in itself less relevant clinically given that it is a reversible process which commonly requires no additional intervention. Its importance lies in the fact that it can be indistinguishable on routine noninvasive imaging techniques from early recurrent tumor which portends a very poor prognosis. Advanced imaging methods show promise in diagnosis and differentiation between tumor recurrence versus radiation necrosis [25–28] and psPD, [29–33] but are not yet validated. In cases where surgical sampling is decided upon, careful pre-surgical planning and close communication between team members is essential. Along with these measures, routine implementation of advanced imaging methods and improvement of biological markers are required in prospective clinical trials to determine the utility of surgical sampling and to improve diagnosis and management of psPD.

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Fig. 1.
Conventional gadolinium-enhanced MRI scans of two patients with increased enhancement surrounding the surgical cavity following chemoradiation therapy that was histologically proven to be pseudoprogression

Fig. 2.

Histopathological findings of pseudoprogression: **a** Fibrinoid necrosis and hyalinization of blood vessel walls with reactive gliosis, **b** low MIB-1 proliferation index in an area of low cellularity, representing infiltrating tumor MIB-1 immunohistochemistry, $\times 20$. **c** Small vessels in an area of reactive gliosis. Endothelial cells are plump, but not consistent with microvascular proliferation. H&E, $\times 20$

Fig. 3.

Kaplan Meier curves for progression free survival (*left*) and overall survival (*right*) for patients in the surgical group (n = 34) based on the three subgroups identified by independent histology review: Tumor (GBM), n = 10; Mixed, n = 13 and psPD, n = 11

Table 1

Baseline patient characteristics

Characteristic	Surgery (n = 34)	Non-surgery (n = 107)	Stable (n = 154)
Age (years)			
Median	53	61	57
Range	22–75	20–77	19–78
Sex			
Male	21	64	87
Female	13	43	67
KPS			
Median	90	90	90
Range	60–100	70–100	70–100
Histopathology, No (%)			
Tumor	10 (29.4)		
PsPD	11 (32.3)		
Mixed	13 (38.2)		
Imaging, No (%)			
Tumor		52 (48.5)	
PsPd		14 (13.0)	
Mixed		41 (38.3)	
ChemoRT dose(Gy)			
Median	60	60	60
Range	54–76	45–70	40–70

KPS Karnofsky performance score; *PsPd* pseudoprogression; *ChemoRT* chemoradiation; *Gy* gray

Table 2

Test (surgical) group analysis, outcome and clinical decision making

No.	Independent histology	Independent imaging	Surgery 1	Surgery 2	KPS pre-chemoRT	KPS at progression	DXM dose	OS (months)	PFS (months)	p53 IHC (% cells + ve)	MIB IHC	PHH3 IHC	IDH1 IHC	Clinical decision
1	Mixed	T	Resection	Resection	90	60	4 mg	7	3	50	+++	+	0	Change: recurrent clinical protocol
6	Mixed	Mixed	Resection	Resection	Unknown	Unknown	Unknown	10	3	20	++	+	0	Change: dose dense TMZ/accutane
7	Mixed	Mixed	Resection	Resection	Unknown	Unknown	Unknown	45	36	80	++	0	pos	Continue: adjuvant TMZ
11	Mixed	Mixed	Biopsy	Resection	90	70	8 mg	10	7	Infiltrating tumor cells+	+	+	0	Change: recurrent clinical protocol
14	Mixed	psPD	Resection	Resection	80	70	16 mg	32	4				NT	Change: recurrent clinical protocol
21	Mixed	Mixed	Resection	Resection	Unknown	Unknown	Unknown	25	9	Negative	+++	++	0	Change: avastin-cpt 11
25	Mixed	Mixed	Resection	Resection	Unknown	100	0	17	9				NT	Change: avastin-cpt 11
26	Mixed	Mixed	Resection	Resection	Unknown	90	0	12	4	50	+	0	0	Continue: TMZ/accutane
27	Mixed	T	Resection	Resection	80	Unknown	2 mg	14	11				NT	Change: dose dense TMZ
29	Mixed	psPD	Resection	Resection	Unknown	Unknown	Unknown	19	11	< 5	+	R	0	Change: saha/accutane
31	Mixed	Mixed	Resection	Resection	Unknown	Unknown	unknown	8	3	80	+++	++	0	Continue: adjuvant TMZ
33	Mixed	T	Resection	Resection	Unknown	100	2 mg	10	10	50	++	+	0	Change: dose dense TMZ/accutane
34	Mixed	T	Biopsy	Resection	Unknown	Unknown	Unknown	16	2	50	+	R	0	Change: recurrent clinical protocol
5	psPD	Mixed	Resection	Resection	80	90	4 mg	28	5	Infiltrating tumor cells+	+	0	0	Change: recurrent clinical protocol
8	psPD	Mixed	Resection	Resection	100	90	6 mg	15	5	50	+	R	0	Change: recurrent clinical protocol
9	psPD	T	Resection	Resection	90	100	2 mg	8	6	< 5	+	0	0	Change: avastin-cpt 11
12	psPD	Mixed	Resection	Resection	Unknown	Unknown	Unknown	13	2				NT	Continue: adjuvant TMZ
16	psPD	T	Biopsy	Resection	Unknown	Unknown	Unknown	30	3				NT	Change: dose dense TMZ/accutane
17	psPD	T	Biopsy	Resection	Unknown	80	16 mg	11	3	Infiltrating tumor cells+	+	0	0	Continue: adjuvant TMZ
18	psPD	T	Resection	Resection	Unknown	Unknown	Unknown	6	3				NT	Continue: adjuvant TMZ
19	psPD	T	Resection	Resection	Unknown	Unknown	Unknown	14	4	80	++	R	0	Change: 6thio, TMZ, accutane
28	psPD	Mixed	Resection	Resection	Unknown	Unknown	Unknown	17	10	20	+	+	0	Continue: TMZ/accutane
30	psPD	psPD	Resection	Resection	90	Unknown	0	11	3	20	+	0	0	Change: recurrent clinical protocol
32	psPD	T	Resection	Biopsy	90	100	0	18	18	< 5	+	0	0	Change: dose dense TMZ/steroids
2	Tumor	Mixed	Resection	Resection	100	90	0	8	5				NT	Change: recurrent clinical protocol
3	Tumor	T	Resection	Resection	90	90	0	15	3	< 5	+	0	0	Change: new chemoRT
4	Tumor	Mixed	Resection	Resection	100	90	0	26	18	40	++	+	0	Change: TPC
10	Tumor	T	Resection	Resection	90	90	0	23	23		+		NT	Change: TMZ, accutane, 6-thioguanine

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No.	Independent histology	Independent imaging	Surgery 1	Surgery 2	KPS pre-chemoRT	KPS at progression	DXM dose	OS (months)	PFS (months)	p53 IHC (% cells + ve)	MIB IHC	PHH3 IHC	IDH1 IHC	Clinical decision
13	Tumor	No Imaging available	Biopsy	Resection	Unknown	Unknown	Unknown	13	5			R	NT	Change: concurrent chemoradiation
15	Tumor	T	Resection	Resection	80	80	4 mg	27	12	30	+	R	0	Change: avastin-cpt 11
20	Tumor	No Imaging available	Resection	Resection	Unknown	Unknown	unknown	13	3				NT	Change: recurrent clinical protocol
22	Tumor	Mixed	Resection	Resection	Unknown	90	8 mg	22	6	90	++	+	0	Change: recurrent clinical protocol
23	Tumor	Mixed	Resection	Resection	Unknown	100	0.5 mg	26	23	80	+++	+	pos	Change: TMZ/accutane
24	Tumor	Mixed	Resection	Resection	Unknown	Unknown	unknown	7	4		+		NT	Continue: adjuvant TMZ

Resection: includes gross total resections and subtotal resections

T tumor; *psPD* pseudoprogression; *KPS* Karnofsky performance status; *chemoRT* chemoradiation therapy; *DXM* dexamethasone; *TPC* 6-thioguanine/procarbazine/CCNU, accutane, isotretinoin; *TMZ* temozolomide; avastin, bevacizumab; cpt 11, irinotecan; saha, vorinostat; *p53 IHC* p53 protein immunohistochemistry; number indicates percent of tumor cells with positive nuclear reactivity; *MIB-1 IHC* MIB-1 immunohistochemistry; +++ high labeling index; ++ moderate labeling index; +low labeling index; *PHH3 IHC* phosphohistone H3 immunohistochemistry; 0 negative, *R* 1–2 stained nuclei per section, + 3–4 stained nuclei per section, ++ more than 10 stained nuclei per 10 high power fields; *IDH-1 IHC* isocitrate dehydrogenase immunohistochemistry; *NT* not tested, 0 no mutation detected, *pos* mutation detected