

Incidence of Early Pseudo-progression in a Cohort of Malignant Glioma Patients Treated With Chemoradiation With Temozolomide

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BACKGROUND. Radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ) is now the standard of care for patients with newly diagnosed glioblastoma. The occurrence of pseudo-progression directly after RT is a recognized phenomenon, but to the authors' knowledge its incidence after combined RT/TMZ is unknown. The occurrence of early pseudo-progression was retrospectively assessed in a cohort of malignant glioma patients treated with RT/TMZ.

METHODS. The pre-RT and post-RT brain scans from patients treated with RT/TMZ for a malignant glioma were reviewed. Scans were made before the start of RT, 4 weeks after the end of RT, and every 3 months thereafter. In addition, information was collected regarding clinical signs and symptoms, dexamethasone dose, histology, and survival.

RESULTS. Eighty-five patients were identified. In 36 patients (42%) the first follow-up scan 4 weeks after the end of RT indicated disease progression. Of these 36 patients, 18 (50%) were diagnosed with pseudo-progression. None of the patients received additional treatment other than TMZ. Six of 18 patients with pseudo-progression and 12 of the 18 patients with real tumor progression developed new clinical signs and symptoms during RT or in the first 4 weeks thereafter.

CONCLUSIONS. Up to 50% of malignant glioma patients treated with RT/TMZ and progression immediately after RT develop pseudo-progression. The current study data support the idea to continue TMZ in the case of progressive lesions immediately after RT/TMZ. Surgery should be considered in symptomatic cases. The inclusion of patients with progressive lesions developing directly after chemoradiation in studies regarding recurrent gliomas will lead to an overestimation of the results. *Cancer* 2008;113:405-10. © 2008 American Cancer Society.

KEYWORDS: glioblastoma, glioma, temozolomide, radiotherapy, chemoradiation, pseudo-progression.

Radiotherapy (RT) and concomitant temozolomide (TMZ) followed by adjuvant TMZ has become the standard of care for patients with glioblastomas since the European and Canadian randomized trial was published in 2005.¹ Despite the improved outcome with combined modality treatment, the overall outcome of this disease remains dismal, with many patients progressing early after RT or during adjuvant TMZ chemotherapy. In recent years, we and other clinicians observed the occurrence of progressive magnetic resonance imaging (MRI) lesions immediately after the end of concurrent chemoradiation with TMZ (RT/TMZ), with spontaneous improvement without further treatment other than adjuvant TMZ. In an earlier study, this phenomenon of early pseudo-progression was investigated in 32 patients with a malignant glioma

who received RT only.² In that study, 3 of 9 patients (33%) with a progressive lesion immediately after RT demonstrated a stabilized or improved lesion during at least 6 months on subsequent scans, without additional treatment. To our knowledge, the incidence of early pseudo-progression in malignant glioma patients treated with RT/TMZ is unknown, nor is it known whether this is clinically symptomatic. (At the time of publication, Brandes et al have since published data regarding the incidence of pseudo-regression and the correlation with the MGMT promoter methylation status in glioblastoma patients.³) We investigated the incidence of early pseudo-progression and its clinical features by reviewing a cohort of patients with newly diagnosed malignant gliomas who were treated with RT plus concomitant and adjuvant TMZ.

MATERIALS AND METHODS

For this study, all malignant glioma patients treated between 2000 and July 2006 with RT/TMZ in the Daniel den Hoed Cancer Center in Rotterdam, The Netherlands, were reviewed. Furthermore, all patients who participated in the European Organization for Research and Treatment of Cancer (EORTC) 22981 study and received chemoirradiation at the University Medical Center Utrecht in Utrecht, The Netherlands, were also reviewed. No patients were excluded. Treatment was comprised of fractionated irradiation at a dose of 2.0 grays (Gy) per fraction given once daily on weekdays over a period of 6 weeks to a total dose of 60 Gy and concomitant TMZ (75 mg/m²/day on all days), followed after 4 weeks by 6, 28-day cycles of adjuvant TMZ (Day 1–5 every 28 days, at a dose of 150–200 mg/m²/day). None of the patients received other treatment, such as gliadel or a focal radiotherapy boost.

Clinical records were reviewed concerning the type of surgery performed, histology, radiation field, neurologic signs and symptoms, dexamethasone dose, and survival. Per treatment protocol, brain imaging was performed before RT (median interval of 14 days between the brain scan and the initiation of RT), 4 weeks after the end of RT (median interval of 30 days between the end of the RT/concomitant TMZ), and thereafter every 3 months. Two independent reviewers reviewed all brain scans (HGdB and WT). The evaluation was based on precontrast and postcontrast images and primarily on the changes in the contrast-enhancing area. In the case of disagreement, the scans were jointly re-evaluated. The response criteria developed by Macdonald et al.⁴ were used to quantify all changes in the enhancing lesions on the scan, clinical status, and dexamethasone dose.

TABLE 1
Characteristics at Baseline of 85 Patients With Malignant Glioma Treated With Radiotherapy Plus Concomitant and Adjuvant Temozolomide

Median age (range), y	50 (18–68)
Male/female ratio, %	66/34
Histopathology, no. of patients	
Glioblastoma multiforme	68 (80%)
Anaplastic astrocytoma	11 (13%)
Anaplastic oligodendroglioma	3 (3.5%)
Anaplastic oligoastrocytoma	3 (3.5%)
WHO performance score 0-1 vs 2, %	89/11
Complete or partial resection vs biopsy, %	69/31

WHO indicates World Health Organization.

Early disease progression was defined as progression ($\geq 25\%$ increase) noted on the MRI scan 4 weeks after RT and concomitant TMZ, with or without neurologic deterioration, and on a stable or higher dose of dexamethasone. Real early progression was scored if the patient with early progression developed additional disease progression within the following 6 months. Pseudo-early progression was scored if the patient with early progression 1) had at least a 50% decrease in the enhancing lesion during further follow-up, while remaining neurologically stable and on a stable or decreasing dose of dexamethasone (a 'partial response' according to the criteria of Macdonald et al.⁴) or 2) remained clinically and radiologically stable with a stable or decreased dosage of steroids for at least 6 months after RT/TMZ without any further treatment other than adjuvant cycles of TMZ. Clinical features of the patients with real early progression and pseudo-early progression were compared. Kaplan–Meier survival curves were used to analyze survival in the patients with real early progression and pseudo-early progression.

RESULTS

Eighty-five patients were treated with RT plus concomitant and adjuvant TMZ. The majority of the patients had a glioblastoma multiforme (GBM). Table 1 summarizes the demographic and clinical features of these patients. In 39 patients, the pre-RT/TMZ scan was a computed tomography (CT) scan; in the other 46 patients, MRI was used. All follow-up scans were MRI scans.

Thirty-six of the 85 patients (42%; 95% confidence interval [95% CI], 31.5–52.5%) were identified as having early progression on the first follow-up scan 4 weeks after RT and concomitant TMZ compared with the pre-RT imaging (Table 2). Thirty-one of the 68 patients (45%; 95% CI, 33.2–56.8%) with a GBM and 5 of the 17 patients (29%; 95% CI, 7.4–50.6%) with an anaplastic glioma had early disease

TABLE 2
Description of Demographics, Type of Scan Performed Before RT/TMZ* DXM Dosage on the Day of the Pre-RT/TMZ Scan and Post-RT/TMZ Scan, and Outcome in the 36 Patients With an Increasing Lesion at the Time of the First Follow-up MRI Scan After RT/TMZ

No.	Age, years	Sex	Histology	Surgery	Pre-RT/TMZ scan	WHO performance score	DXM dose, mg			Scan changes compared with prior scan				Survival, months†
							Pre-RT/TMZ	Post-RT/TMZ	Post-RT/TMZ	Post-RT/TMZ	At 3 months	At 6 months	At 9 months	
1	31	Man	GBM	Resection	CT	1	0	0	0	PD	PR	SD	CR	25+
2	51	Man	AOD	Biopsy	CT	1	0	0	0	PD	SD	PR	SD	13+
3	39	Man	GBM	Resection	MRI	0	0	0	0	PD	PD/SO	PR	SD	22+
4	57	Woman	GBM	Resection	CT	1	0	0	0	PD	SD	SD	SD	15+
5	58	Man	GBM	Resection	MRI	1	0	3.5	0	PD	SD	SD	SD	13+
6	34	Man	GBM	Biopsy	CT	0	0	0	0	PD	PR	SD	SD	38+
7	48	Woman	GBM	Resection	MRI	1	4	16	0	PD	PR	PD	Died	10
8	50	Woman	GBM	Resection	MRI	1	5	4	0	PD	SD	PR	SD	21
9	44	Woman	GBM	Resection	MRI	0	0	0	0	PD	SD	PR	SD	32+
10	34	Man	AOD	Resection	MRI	0	0	0	0	PD	SD	PR	CR	17+
11	47	Man	GBM	Biopsy	CT	2	10	16	0	PD	SD	SD	SD	25
12	38	Man	GBM	Resection	MRI	0	0	0	0	PD	SD	PR	SD	31+
13	32	Woman	AOA	Biopsy	CT	0	0	0.5	0	PD	SD	SD	SD	27+
14	19	Man	GBM	Biopsy	MRI	1	0	1.5	0	PD	SD	SD	SD	17
15	59	Man	GBM	Biopsy	CT	0	0	0	0	PD	NA	SD	SD	19
16	53	Man	GBM	Resection	CT	1	0	0	0	PD	PR	PD	NA	17
17	42	Woman	GBM	Resection	CT	1	3	0	0	PD	SD	PR	CR	23+
18	55	Man	GBM	Resection	CT	1	0	6	0	PD	PR	NA	PD	12
19	58	Man	GBM	Resection	CT	1	0	0	0	PD	SD	NA	Died	11
20	18	Man	GBM	Resection	MRI	1	0	0	0	PD	PD	PD	Died	7
21	37	Man	GBM	Biopsy	MRI	1	8	8	0	PD	SD	SD	Died	11
22	67	Woman	AA	Biopsy	MRI	1	0	16	0	PD	Died	PD	Died	3
23	61	Woman	GBM	Resection	CT	1	4	24	0	PD	NA	NA	NA	14
24	45	Woman	GBM	Resection	CT	1	4	1.5	0	PD	PD	Died	Died	6
25	50	Woman	GBM	Resection	MRI	0	4	6	0	PD	PD	Died	Died	6
26	68	Man	GBM	Resection	CT	1	7.5	3	0	PD	PD	PD	Died	8
27	47	Woman	GBM	Biopsy	MRI	1	4	6	0	PD	SD	PD	NA	15
28	57	Man	GBM	Resection	CT	1	4	0.5	0	PD	SD	Died	Died	6
29	57	Man	AOA	Biopsy	MRI	1	0	8	0	PD	Died	Died	NA	4
30	59	Man	GBM	Biopsy	MRI	1	0	0	0	PD	PD	NA	NA	16+
31	54	Woman	GBM	Biopsy	MRI	2	0	0	0	PD	Died	NA	NA	4
32	54	Man	GBM	Resection	CT	2	0	1	0	PD	Died	PD	OT	5
33	62	Man	GBM	Biopsy	CT	1	2	8	0	PD	SD	PD	PD	16+
34	37	Man	GBM	Resection	MRI	0	1	1	1	PD	Died	Died	NA	2
35	55	Woman	GBM	Resection	CT	1	4	4	0	PD	PD	PD	NA	14
36	60	Man	GBM	Resection	CT	0	0	1.5	0	PD	PD	Died	Died	8

RT/TMZ indicates radiotherapy and concomitant temozolomide; DXM, dexamethasone; MRI, magnetic resonance imaging; WHO, World Health Organization; GBM, glioblastoma multiforme; CT, computed tomography; PD, progressive disease; PR, partial response (decrease in lesion); SD, stable disease; CR, complete remission of lesion; AOD, anaplastic oligodendroglioma; SO, second operation; AOA, anaplastic oligoastrocytoma; NA, not available; AA, anaplastic astrocytoma; OT, other therapy.
 * All follow-up scans were MRI scans.
 † Survival was measured in months from the first day of RT/TMZ onward.

progression. In only 1 patient could the decreased dose of dexamethasone explain the observed progression noted on the MRI scan (Patient 17). Three patients did not continue with adjuvant TMZ because of neurologic deterioration (Patients 22, 31, and 34). All of the remaining patients continued with adjuvant TMZ.

Eighteen of 36 patients (50%; 95% CI, 33.7–66.3%) with early disease progression were diagnosed with pseudo-early progression. Pseudo-early progression was noted in 15 of the 31 patients (48%; 95% CI, 30.4–65.6%) with a GBM and in 3 of the 5 patients (60%; 95% CI, 17.0–100%) with an anaplastic glioma. In 17 of the 36 patients with early disease progression, the enhancing lesion on subsequent MRI scans stabilized for at least 6 months (Patients 4, 5, 11, 13, 14, and 15), decreased (Patients 2, 6, 7, 8, 9, 12, 16, and 18) (Fig. 1), or disappeared completely (Patients 1, 10, and 17). Because these 17 patients were also clinically stable or improved and were receiving a stable or decreasing dose of dexamethasone, they were scored as having pseudo-early progression. One of the 36 patients with early progression underwent a re-resection 3 months after RT and concomitant TMZ because of further deterioration; at surgery, only necrosis was found (Patient 3). The patient continued with 3 more cycles of adjuvant TMZ and remained stable for another 15 months.

To investigate whether the percentage of patients with pseudo-early progression was artificially high because of the use of a CT scan rather than an MRI scan before RT, we separately analyzed the patients diagnosed with early disease progression who had been evaluated with MRI scans both before and after RT. In this group, 8 of 17 patients (47%) were subsequently diagnosed with pseudo-early progression compared with 10 of 19 patients (53%) who had a pre-RT CT scan.

The individual charts of the patients with pseudo-early progression were re-examined for other explanations of disease remission, but none were found. In particular, no new treatments had been initiated other than adjuvant TMZ.

Neurologic deterioration was found in 6 of the 18 patients (33%) with pseudo-early progression and in 12 of the 18 patients (67%) with real early progression during RT or in the first 4 weeks thereafter. The mean age of the patients with real early progression was significantly higher compared with that of the patients with pseudo-early progression (55 years vs 46 years, respectively; $P = .0342$). The World Health Organization (WHO) performance status was not found to be significantly different between the patients with real early progression and those with

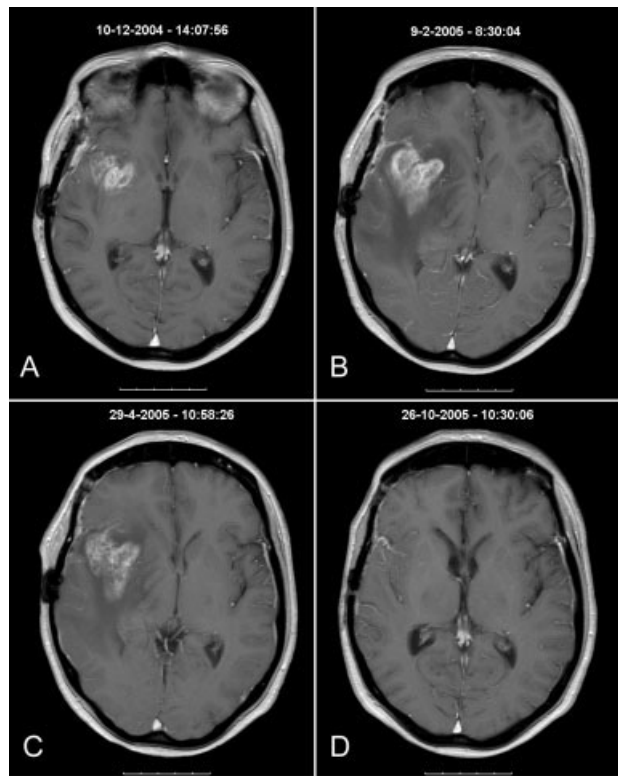


FIGURE 1. Patient 8 was a 50-year-old female who was diagnosed with a right temporal glioblastoma. Debulking surgery was followed by radiotherapy and concomitant temozolomide (RT/TMZ). Compared with (A) the pre-RT/TMZ scan, the (B) scan of the brain taken 4 weeks after RT/TMZ demonstrated disease progression within the area of gadolinium uptake. The patient remained clinically stable and was receiving a stable dose of dexamethasone. She continued with 3 cycles of adjuvant TMZ and the dexamethasone dose was gradually lowered and withdrawn. (C) The magnetic resonance imaging (MRI) scan taken 3 months after RT/TMZ was unchanged and she received another 3 cycles of TMZ. (D) The MRI scans taken 6 months and 9 months, respectively, after RT/TMZ demonstrated a diminishing lesion. The patient developed disease progression 12 months after RT/TMZ.

pseudo-early progression (Table 2; $P = .313$, chi-square) The volume of the radiation field was not found to be significantly different between the patients with real early progression, pseudo-early progression, and no early progression (data not shown). Pseudo-early progression was observed in 6 of 26 patients who underwent a biopsy (23%; 95% CI, 6.8–39.2%) and in 13 of 59 patients who underwent a partial or complete surgical resection (22%; 95% CI, 11.4–32.6%) The extent of surgical resection could not be taken into consideration because no direct postoperative scans were made.

The survival curves of the patients with early disease progression (split between those with pseudo-early progression and those with real early progres-

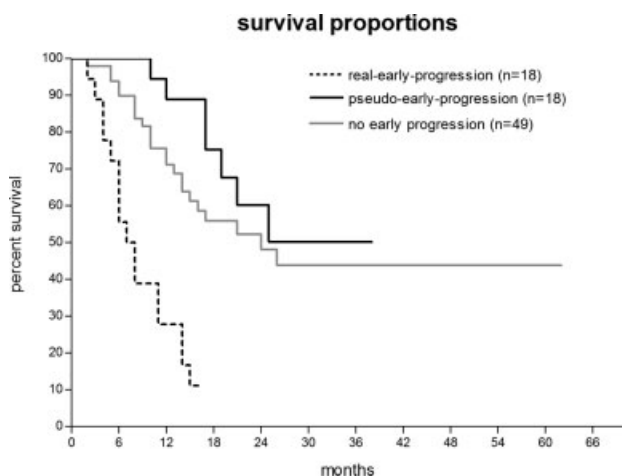


FIGURE 2. Kaplan-Meier survival curves of malignant glioma patients treated with chemoradiation with temozolomide. Survival curves of patients developing disease progression 4 weeks after radiotherapy and concomitant temozolomide, split into patients with further disease progression (real early progression), patients who remained stable for at least 6 months or improved (pseudo early progression), and patients without early disease progression (no early progression), are shown.

sion) and patients with no early progression are shown in Figure 2.

DISCUSSION

In the past decades, the sporadic occurrence of early clinical deterioration with increasing imaging abnormalities immediately after RT with spontaneous recovery have been described.⁵ Since the introduction of chemoradiation with TMZ for GBM, there has been an increasing awareness of this phenomenon. From our cohort of 85 patients treated with chemoradiation with TMZ, the progressive enhancement was not found to be because of tumor progression in 18 of the 36 patients (50%) with a progressive lesion at the time of first tumor evaluation after chemoradiation. Although the pre-RT/concomitant TMZ scan was a CT scan in approximately half of these patients, it is unlikely that this influenced the results because the outcome was the same in patients who underwent an initial MRI scan. In addition, the patients with pseudo-early progression were found to have a similar survival compared with patients without early progression (Fig. 2). A recent report examining surgery performed within 6 months from RT/concomitant TMZ in patients with GBM corroborated our findings regarding the frequency of nontumoral increase in enhancement.⁶ In that study, 26 of 51 GBM patients demonstrated disease progression within 6 months after the completion of RT/

concomitant TMZ. Fifteen of these 26 patients underwent surgery again and 7 of them were diagnosed with radiation necrosis.

Although we hypothesized that pseudo-early progression would occur more frequently after RT/concomitant TMZ compared with RT only, the incidence we observed (18 of 85 patients [21%]; 95% CI, 12.5–29.9%) is still within the range de Wit et al.² observed after the use of RT only (3 of 32 patients [9%]; 95% CI, –0.7–19.5%). One possible explanation for the increased awareness of the phenomenon of pseudo-early progression could be that most GBM patients are now treated with RT/TMZ and therefore are more closely followed. Conversely, in cell lines, synergy between TMZ and RT has been demonstrated in *MGMT* promoter gene methylated tumors.⁷ It may well be that this synergistic antitumoral effect causes more profound tumor necrosis and inflammation with vascular changes, leading to a deficient blood-brain barrier mimicking enhancing tumor on a scan. Further research will explore whether there is indeed a correlation between *MGMT* methylation status and the occurrence of pseudo-early progression. (At the time of publication, Brandes et al have since published data regarding the incidence of pseudo-regression and the correlation with the *MGMT* promoter methylation status in glioblastoma patients.³) The increase in radiation necrosis noted to occur if chemotherapy is given after RT in patients with brain tumors also suggests that more intensified treatments cause more severe local reactions.⁷ This is also the likely explanation for the earlier occurrence of radiation necrosis noted after combined chemoradiation with TMZ.^{6,8} Most likely, pseudo-early progression and early radiation necrosis are a continuum, with more severe local reactions leading to new focal signs and symptoms and true radiation necrosis.

The precise mechanism of this early post-RT/concomitant TMZ deterioration is unknown. The underlying mechanism may be varied and in addition to the above-mentioned radiation-induced (and perhaps vascular endothelial growth factor [VEGF] signaling-dependent) vascular and necrotic changes, tumor progression during the first part of RT and subsequent response could also be an explanation.

Although to our knowledge the exact nature of this pseudo-early progression is unknown, these observations have important consequences for trials of recurrent malignant glioma. Of the 36 patients in the current study with early progression (according to the response criteria of Macdonald et al.), 3 achieved a complete response and 8 achieved a partial response, whereas 6 fulfilled the criteria for stable

disease at 6 months. Six-month progression-free survival (PFS) is currently considered the most valid endpoint for phase 2 studies of recurrent GBM.⁹ If the presently reported patients with immediate disease progression would all have been entered in a phase 2 trial of recurrent GBM, this would have led to a false-positive study result with a 6-month PFS rate of 50%.

From the clinical perspective, an important question is how to differentiate between pseudo-early progression and real early progression immediately after RT. Because of the inherent risks and invasiveness of a stereotactic biopsy, it is not very attractive to obtain histologic proof of these lesions. Moreover, it is not clear whether all cases with pseudo-early progression will show only necrosis at biopsy because tumor cells may still be present. Clinical deterioration during or within the 4 weeks after RT/concomitant TMZ cannot be used to distinguish between these entities because clinical deterioration was also observed in the group of patients with pseudo-early progression, although less frequently (33% vs 67%). WHO performance score, biopsy versus surgical resection, and volume of the radiation field also cannot be used to discriminate between pseudo-early progression and real early progression. The median age in the group of patients with real early progression was found to be higher (56 years vs 46 years), which could simply reflect the higher likelihood of disease progression in elderly patients. Again, this finding is also of no value in individual patients. Furthermore, pseudo-early progression was also noted in 3 of 17 patients with anaplastic glioma (17%; 95% CI, -0.9-34.9%) versus 15 of 68 GBM patients (22%; 95% CI, 12.2-31.9%).

To our knowledge, to date it has been unclear whether modern imaging techniques such as positron emission tomography, magnetic resonance spectroscopy, or diffusion-weighted and perfusion imaging can be used to make a distinction, although some data appear to be promising.¹⁰ Patients with real early progression have a terrible outcome associated with continuing standard TMZ (Fig. 2); future efforts to better identify these patients are critical so that a potential opportunity to salvage them with an alternative therapeutic intervention is not lost. Until

then, we advise continuing adjuvant TMZ in patients with early disease progression and not to include these patients in studies of malignant gliomas that recur within 3 months after RT/TMZ. Surgery should be considered in the case of patients who develop early clinical signs and symptoms and a progressive lesion. If mainly or only necrosis is found at the time of surgery, treatment with TMZ should be continued.

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