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# Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression

M.C.Y. de Wit, MD; H.G. de Bruin, MD; W. Eijkenboom, MD; P.A.E. Sillevius Smitt, MD, PhD; and M.J. van den Bent, MD, PhD

**Abstract**—To determine the frequency of progressive MRI lesions shortly after radiotherapy for glioma with spontaneous improvement or stabilization, the authors studied a cohort of patients treated within two prospective phase III trials with radiotherapy only. In 9 out of 32 patients, the first post-radiotherapy MRI showed progressive enhancement. In 3 of these 9 the MRI improved or stabilized for 6 months without additional treatment. The authors conclude that patients with progressive lesions within 3 months after radiotherapy should not be eligible for phase II trials on recurrent glioma.

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Most phase II and phase III trials on recurrent anaplastic glioma require radiologic evidence of progression as a mandatory inclusion criterion. As a rule, this requires either an increase in area of gadolinium uptake on MRI or the appearance of new lesions. This is unspecific, as radiation therapy induced lesions may mimic recurrent tumor.<sup>1,2</sup> Due to inherent risks and invasiveness of a stereotactic biopsy, it is generally considered unethical to include mandatory repeat tumor biopsies in protocols on recurrent high grade glioma. Most protocols deal with this in part by avoiding patients with an increased risk of radionecrosis by precluding patients treated with high dose radiotherapy, stereotactic radiosurgery, or interstitial radiotherapy.<sup>3</sup>

In the last years we observed several patients with radiologic deterioration on MRI shortly after the end of radiotherapy, which proved to be a transient phenomenon even when no further treatment was initiated. Some articles mention the possibility of early post-radiotherapy changes, but virtually no data on this phenomenon are available.<sup>4,5</sup> Moreover, many phase II studies on recurrent glioma still accept patients with progressive lesions within the first 3 months after radiotherapy. Cases similar to the index patient described below led us to investigate the clinical relevance of this phenomenon by

reviewing a cohort of patients included in prospective phase III trials on newly diagnosed glioma treated with radiotherapy only and for whom strict follow-up at three monthly intervals was available.

**Index case.** A previously healthy 47-year-old man presented with seizures and underwent a gross total resection of a right frontal anaplastic astrocytoma, followed by radiation therapy (64 Gy). A brain MRI made immediately following radiotherapy (figure, A and B) was unchanged compared to the pre-radiotherapy scan, showing the resection cavity but no gadolinium uptake. Two months after the completion of radiotherapy he developed headache, drowsiness, and nausea. Repeat MRI (figure, C and D) showed a new area of gadolinium uptake and edema. Dexamethasone resulted in a complete disappearance of all signs and symptoms; no other treatment was given. Dexamethasone was then discontinued. Follow-up MRI at 12 months after the end of radiotherapy (figure, E and F) showed a complete resolution of the gadolinium uptake and edema.

**Patients and methods.** For this study, we reviewed all patients included in our center in EORTC studies 25951 and 26981. Both studies addressed the value of adjuvant chemotherapy in high-grade glioma (EORTC 26951: PCV-chemotherapy; EORTC 26981: temozolomide); both had a control arm with radiation therapy only. At our center, all eligible patients were routinely asked

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From the Departments of Neuro-oncology/Neurology (Drs. de Wit, Sillevius Smitt, and van den Bent), Radiology (Dr. de Bruin), and Radiotherapy (Dr. Eijkenboom), Daniel den Hoed Cancer Center/Erasmus Medical Center, Rotterdam, The Netherlands.

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Address correspondence and reprint requests to Dr. M.J. van den Bent, Department of Neuro-oncology/Neurology, Daniel den Hoed Cancer Center/Erasmus Medical Center, PO Box 5201, 3008 AE Rotterdam, The Netherlands; e-mail: m.vandenbent@erasmusmc.nl

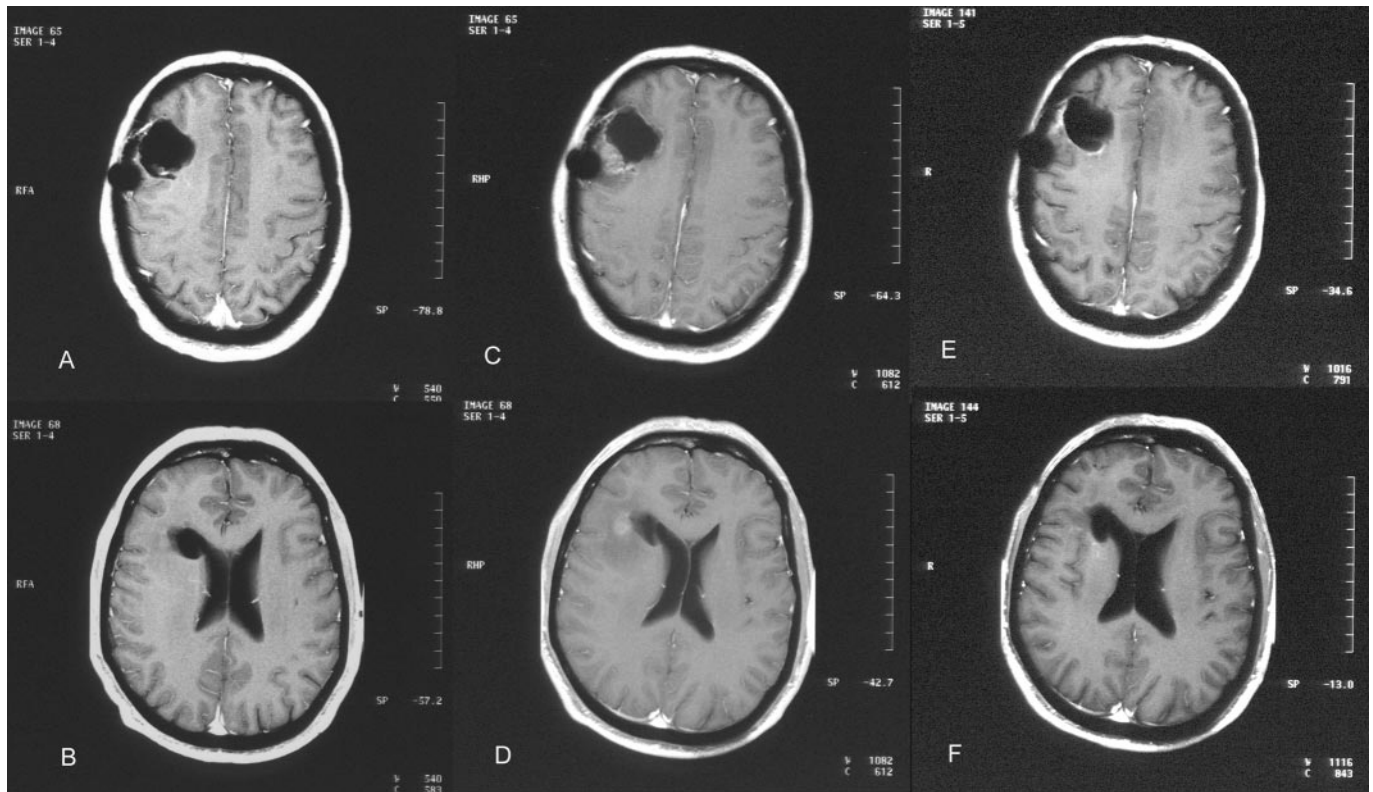


Figure. (A through F) Index case: T1-weighted images after gadolinium administration. (A, B) Immediately following the end of radiotherapy showing the post-resection cavity; (C, D) 2 months after radiation therapy at the time of clinical signs and symptoms showing a new area of gadolinium uptake and edema causing a slight midline shift; (E, F) 1 year after the end of radiotherapy: resolution of edema and enhancement.

to participate, to which the majority consented. Only patients randomized to the control arms were used for the present study.

All pre- and post-radiotherapy brain MRI up to and including the MRIs made after 12 months were reviewed by two independent observers: a radiologist (H.G.d.B.) and a neuro-oncologist

(M.J.v.d.B.). The timing of MRIs was prescribed by the EORTC protocol and is shown for patients with progression on the first post-radiotherapy MRI in the table. The evaluation was primarily based on T1-weighted pre- and postcontrast MR images. Macdonald's criteria were used to assess the response to radiothera-

**Table** Description of demographics, interval between pre-RT MRI and start RT, interval between end of RT and first post-RT MRI, dexamethasone dosage on the day of pre- and post-RT MRI, and outcome in the nine patients with an increasing lesion at the time of the first follow-up MRI scan after radiotherapy

Patients with progression at first post-RT MRI						MRI interval/DXM dose, mgr		MRI changes compared to prior MRI			Survival, mo
	No.	Age, y	Sex	Histology	Surgery	RT	Pre-RT	Post-RT	Post-RT	At 3 mo	
1	36	M	AOA	Partial resection	59 Gy	12/4	2/4.5	PD	PR	SD	33+
2	33	F	AOD	Total resection	59 Gy	0/4	30/2	PD	PR	PR	11.5
3	55	F	GBM	Partial resection	60 Gy	0/16	18/24	PD	SD	SD	16.5
4	46	F	GBM	Biopsy	25 Gy*	9/2.5	7/16	PD	Died		1.5
5	53	M	GBM	Biopsy	60 Gy	2/16	28/24	PD	Died		3
6	63	M	GBM	Partial resection	60 Gy	12/4	35/3	PD	PD	Died	7.4
7	40	M	AOD	Partial resection	59 Gy	2/4	24/8	PD	PD	Died	6
8	53	M	GBM	Total resection	46 Gy*	32/4	0/24	PD	Died		1.1
9	53	F	AOA	Biopsy	59 Gy	33/4	16/2	PD	PD	ND	11.7

\* Radiotherapy prematurely discontinued.

RT = radiotherapy, either 59 Gy in 33 fractions or 60 Gy in 30 fractions; DXM = dexamethasone; pre-RT = interval between pre-RT MRI and start RT; post-RT = interval between end of RT and first post RT MRI; PD = progressive lesion; PR = decreasing lesion; SD = stable lesion. Survival is measured in months from the first day of radiotherapy. GBM = glioblastoma multiforme; AOA = anaplastic oligoastrocytoma; AOD = anaplastic oligodendroglioma; ND = not done.

py.<sup>6</sup> In case of disagreement on progressive lesions the scans were jointly re-evaluated. Patients showing radiologic deterioration at the first MRI following radiotherapy were examined more closely, and information was collected on radiation dose, timing of the MRI in relation to the start and end of radiotherapy, clinical performance, dexamethasone dose, histology, and survival.

**Results.** Seventy-three patients were included in these studies by our center; 32 had been randomized in the control arm. Mean age was 49 years, and 22 were men. One patient was lost to follow-up during radiation therapy. In nine patients the first follow-up scan after radiotherapy showed progression as compared to the pre-radiotherapy imaging (see the table). Six of these nine patients developed further progression at further follow-up or died within a year, but two showed subsequent improvement and one stabilized for 6 months without additional treatment (Patients 1–3). Both reviewers identified these three patients as progressive at the first post-radiotherapy MRI. In one case the radiologic progression was accompanied by clinical deterioration, which then stabilized (Patient 3). The individual charts were checked for other explanations of remission, but none were found. In particular, no new treatments had been initiated and changes in dexamethasone dose could not explain the observed changes.

**Discussion.** From this cohort of 32 trial patients treated with radiotherapy only, in three of the nine patients with a progressive lesion at the first tumor evaluation after radiotherapy further follow-up showed that the progressive enhancement was not due to tumor progression. In two patients, the lesions decreased to a PR during follow-up, whereas the third patient remained stable for 6 months. Both decrease and absence of progression for 6 months have been considered endpoints in recent phase II studies on recurrent high grade glioma.<sup>7</sup> With a traditional two-step statistical design used for phase II studies in GBM aiming at a response rate of at least 25% these three out of nine patients would have sufficed to initiate the second step and might have lead to a false positive result of the study.<sup>8</sup> The three patients with transient increased gadolinium enhancement also had a much longer survival than the remaining six patients with a progressive lesion on the first post-radiotherapy MRI. Others have observed apparent tumor progression on radiologic examination followed by spontaneous remission, but the frequency of this occurrence has remained unclear. An article on 51 patients from the pre-MRI era using neurologic examination, brain CTs, and radionuclide scans noted in 25 patients clear deterioration in any of the three tests within the first 18 weeks.<sup>4</sup> Seven of those 25 showed subsequent improvement without any change in therapy, but all patients were treated with adjuvant chemotherapy, which may have contributed to the observed improvement. It is clear though from our series and from other studies that immediate progression after radiotherapy in general heralds a poor outcome.<sup>9</sup> Five of the other six patients with progressive lesion

at the end of radiotherapy died within 8 months from the start of radiotherapy.

The intermediate and late sequelae of radiotherapy to the brain have been well documented.<sup>10</sup> The characteristic difference between the early somnolence syndrome and the patients described in this report is the focal increase in gadolinium enhancement, with or without focal signs and symptoms. The explanation of this early post-radiotherapy deterioration may be manifold, including tumor progression during the first part of radiotherapy and subsequent response, and radiation-induced vascular changes.

The classic article on the WHO-based response criteria for glioma mentions the possibility of early post-radiotherapy changes without further details.<sup>6</sup> The authors advised not to start investigational treatments within the 2 months following conventional radiotherapy. The protocols according to which the patients of this cohort were treated required a first post radiotherapy MRI within 4 weeks after the end of radiotherapy. However, the index case (which was not included in any of the EORTC protocols) shows that such transient increase in size may occur well after these first 4 weeks.

Because the value of metabolic imaging like PET in this situation is unclear, the most prudent approach to this methodologic problem is to exclude patients with progression within the first 3 months of radiotherapy from trials on recurrent glioma, unless histologic proof of the recurrence is obtained. This is already current practice in some cooperative groups (NABTT, NCCTG, EORTC). Our data show that this should be the rule for all phase II studies on recurrent glioma after radiotherapy. For the individual patient an increase in gadolinium enhancement is most likely to represent tumor progression, and they should be managed accordingly, but preferably outside clinical trials.

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