Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas

Dieta Brandsma, Lukas Stalpers, Walter Taal, Peter Sminia, Martin J van den Bent

Since the introduction of chemoradiotherapy with temozolomide as the new standard of care for patients with glioblastoma, there has been an increasing awareness of progressive and enhancing lesions on MRI, noted immediately after the end of treatment, which are not related to tumour progression, but which are a treatment effect. This so-called pseudoprogression can occur in up to 20% of patients who have been treated with temozolomide chemoradiotherapy, and can explain about half of all cases of increasing lesions after the end of this treatment. These lesions decrease in size or stabilise without additional treatments and often remain clinically asymptomatic. Additionally, there is evidence that treatment-related necrosis occurs more frequently and earlier after temozolomide chemotherapy than after radiotherapy alone. The mechanisms behind these events have not yet been fully elucidated, but the likelihood is that chemoradiotherapy causes a higher degree of (desired) tumour-cell and endothelial-cell killing. This increased cell kill might lead to secondary reactions, such as oedema and abnormal vessel permeability in the tumour area, mimicking tumour progression, in addition to subsequent early treatment-related necrosis in some patients and milder subacute radiotherapy reactions in others. In patients managed with temozolomide chemoradiotherapy who have clinically asymptomatic progressive lesions at the end of treatment, adjuvant temozolomide should be continued; in clinically symptomatic patients, surgery should be considered. If mainly necrosis is noted during surgery, continuation of adjuvant temozolomide is logical. Trials on the treatment of recurrent malignant glioma should exclude patients with progression within the first 3 months after temozolomide chemoradiotherapy unless histological confirmation of tumour recurrence is available. Further research is needed to establish reliable imaging parameters that distinguish between true tumour progression and pseudoprogression or treatment-related necrosis.

Introduction

Since randomised trials in the 1970s showed a survival benefit for postoperative 60-Gy whole-brain radiotherapy (WBRT), radiotherapy has been the cornerstone in the management of high-grade gliomas. The introduction of the CT scan in the 1980s and MRI in the 1990s improved tumour delineation and consequently radiotherapy precision. This precision has allowed the use of involved-field radiotherapy for glioma, during which only the tumour area and a 2–3-cm margin (involved fields) are irradiated (figure 1). This technique has resulted in a decrease of radiotherapy-induced neurotoxicity in patients with glioma. Unfortunately, attempts to further improve survival by increasing the radiation dose or by alternative (ie, hyperfractionated and hypofractionated) radiotherapy schedules have failed. By contrast, the addition of concurrent and adjuvant temozolomide to radiotherapy has been shown to further improve survival of newly diagnosed patients with glioblastoma. Nowadays, chemoradiotherapy with temozolomide is the standard of care for patients with glioblastoma and is routinely followed by MR scans to monitor treatment outcome. This monitoring has led to an increased awareness that many patients with progressive lesions shortly after treatment, with or without progressive clinical signs and symptoms, do not suffer from tumour recurrence (figure 2).

An early study noted that patients with malignant glioma had an increase in the size of contrast-enhancing lesions, or new areas with contrast enhancement, immediately after radiotherapy, with subsequent improvement without any further treatment. This occurrence, which mimics tumour progression, has been labelled pseudoprogression. Moreover, a high incidence of radionecrosis (ie, treatment-related necrosis) has been noted in patients who underwent surgery for progressive brain lesions within the first 6 months after combined chemoradiotherapy with temozolomide. Both findings suggest that the mechanisms behind pseudoprogression and treatment-related necrosis are the same. Therefore, pseudoprogression should be considered a treatment effect rather than a tumour progression.
could be consistent with the increased tumour-cell killing caused by the chemoradiotherapy. These progressive lesions have important consequences on the management of patients with progressive lesions immediately after temozolomide chemoradiotherapy. However, this management is complicated by the fact that routinely available MRI techniques do not allow a reliable distinction between tumour recurrence and pseudoprogression or treatment-related necrosis. In this Review, we discuss the clinical and radiological features of pseudoprogression and the possible mechanisms of pseudoprogression and treatment-related necrosis in the treatment of malignant gliomas. Furthermore, we propose a relation between pseudoprogression and other known sequelae of radiotherapy and chemotherapy to the brain.

Radiation-induced injury of the brain
Radiotherapy in patients with malignant glioma usually consists of fractionated focal irradiation at a dose of 1.8–2.0 Gy per fraction, given once daily for 5 days a week for 6 or 7 weeks until a total dose of 60 GY is reached. Brain metastases are either treated by single-dose high-precision radiosurgery in the case of one to three lesions with a maximum diameter of 3.0–3.5 cm, or by WBRT, usually with five fractions of 4 Gy or ten fractions of 3 Gy. Side-effects of radiotherapy to the brain are discriminated into three different types on the basis of time of occurrence and clinical presentation: acute (during radiation); subacute or early-delayed (up to 12 weeks’ postradiation); and late (months to years postradiation).

Acute and subacute radiation effects
Both the acute and subacute types of radiation-induced injury are presumably caused by vasodilatation, disruption of the blood–brain barrier, and oedema. Clinical symptoms of acute radiation injury are signs of increased intracranial pressure (eg, drowsiness, headache, and emesis). In historical series, two fractions of 7.5 Gy WBRT over 3 days for brain metastases did not prove to be feasible because of severely increased intracranial pressure. By use of the currently recommended low fraction doses, symptoms of acute radiation injury are mostly transient and reversible. Steroids usually alleviate signs and symptoms. In our experience, diffuse brain swelling can be seen, but MRI is usually normal. In the subacute type of radiation injury, patients present with somnolence and fatigue. MRI findings can vary from non-enhancing white-matter hyperintensities on T2-weighted imaging, indicative of oedema, to new or an increased size of contrast-enhancing lesions within the

Figure 2: Pseudoprogression in a 44-year-old man with a biopsy proven glioblastoma in the posterior part of the corpus callosum treated with 60-Gy conformal radiotherapy plus temozolomide. Post biopsy planning MRI was done (A). Patient deteriorated clinically during first course of adjuvant temozolomide. MRI shows a modest increase in size of lesion (B), which is well within the previous high-dose radiotherapy area (red=100% dose area; yellow=95%; green=30%; and dark blue=5%; C). Chemotherapy was suspended, and the patient improved with dexamethasone 1.5 mg daily. Repeated MRI 4 months later showed tumour regression (D). 6 months later the patient developed a frontal syndrome. MRI showed a large recurrence anterior of the corpus callosum despite an ongoing regression of the posterior lesion (E). Courtesy of Jan Wiersma and Charles Majoie.
immediate vicinity of the irradiated tumour volume.9 The occurrence of these effects strongly depends on the fraction dose and the radiation field size. Spontaneous recovery of symptoms of subacute radiation effects usually occurs within weeks. Again, corticosteroids are sometimes needed to control signs and symptoms.9

**Late radiation effects**

Unlike the acute and subacute effects of radiation, late radiation effects are often progressive and irreversible. Late radiation-induced changes of the brain include a leucoencephalopathy syndrome, true radionecrosis, and various other, often vascular, lesions, such as lacunar infarcts, large-vessel occlusion with a moyamoya syndrome, telangiectasias, brain parenchyma calcifications, and enhancing white-matter abnormalities.9,13 Some of these long-term sequelae are typically seen in children after irradiation of the brain.14

**Leucoencephalopathy**

Clinically, leucoencephalopathy is characterised by gait disturbance, urinary incontinence, memory disturbances, and mental slowing.11 Typically, a leucoencephalopathy is recognised by an increased signal intensity of the periventricular white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI, together with atrophy.15 In more severe cases, extensive white-matter changes can lead to a disseminated necrotising leucoencephalopathy.16 Individual non-treatment-related risk factors for radiation-induced leucoencephalopathy are poorly understood, but include concomitant medical diseases that already predispose to vascular injury, such as diabetes, hypertension, and advanced age.6 Concurrent chemotherapy is an additional risk factor for radiation-induced leucoencephalopathy. The most notorious combination in this respect is methotrexate and WBRT, a treatment modality that is used in patients with primary CNS lymphomas.18 The risk of leucoencephalopathy is directly related to the total and fraction dose, the methotrexate dose, and the sequence of administration, with a further increase in risk if radiotherapy is given before methotrexate.19 Furthermore, age is an additional risk factor. More than 90% of patients over the age of 60 years with primary CNS lymphomas treated with methotrexate and radiotherapy will develop a treatment-related diffuse leucoencephalopathy over time. As a rule, this leucoencephalopathy leads to severe dementia and can be fatal.19 In children, the addition of intrathecal chemotherapy to cranial radiotherapy increases the risk of delayed leucoencephalopathy.20

**Radionecrosis**

Radionecrosis is a severe local tissue reaction to radiotherapy, with signs of a disrupted blood–brain barrier, oedema, and mass effect on MRI. Histopathological features include necrosis, oedema, and gliosis in addition to endothelial thickening, hyalination, fibrinoid deposition, thrombosis, and finally occlusion of vessels. Sometimes haemorrhage or dystrophic calcifications are present. On histological examination, necrotic areas are usually interspersed with tumour cells of unclear viability.20 Radionecrosis generally occurs 3–12 months after radiotherapy, but can occur up to years and even decades afterwards.15,22 In adults, the reported incidence of radionecrosis after radiotherapy for brain tumours ranges from 3–24%. Its occurrence is directly related to the irradiated brain volume and delivered dose of radiation, with a steep increase in occurrence when doses exceed 65 Gy in fractions of 1·8–2·0 Gy (figure 3).23–25 A 5% risk of radionecrosis within 5 years after radiotherapy has been estimated to occur after a total dose of 50 Gy to two-thirds of the total brain volume and after 60 Gy to a third of the total brain volume using standard fractionation.21 However, this risk might be underestimated, because many patients die early either due to tumour progression or from a histologically unconfirmed progressive lesion. Indeed, in patients treated with radiotherapy to the brain for malignancies with a favourable survival (eg, childhood leukaemia) high risks of severe late radiation toxic effects have been reported after long-term follow-up.26–28 Additional risk factors for radionecrosis include high fraction doses (ie, >2·5 Gy per day),23,29 hyperfractionation (eg, two fractions of 1·3 Gy per day),1 interstitial brachytherapy and stereotactic radiosurgery,19 reirradiation,15,22 and radiotherapy combined with chemotherapy.19,22–24

The clinical course of radionecrosis is highly variable. Patients can present with progressive focal deficits and signs of increased intracranial pressure, but might also
remain asymptomatic. In some patients, clinical signs and symptoms need surgery and can even be fatal, but spontaneous radiological (and clinical) recovery can also occur (figure 4).

Radionecrosis occurs most frequently at the site that received the maximum radiation dose, usually in the immediate vicinity of the tumour site and the surrounding of the surgical cavity of a partially or totally resected tumour. Most lesions consist of a contrast-enhancing mass on T1-weighted imaging with gadolinium, which is indistinguishable from tumour progression with conventional MR techniques. On T2-weighted images, the solid portion of the radiation-induced necrotic mass has low signal intensity and the central necrotic component has increased signal intensity.12 The predilection place of radionecrosis is the periventricular white matter. This positioning might be due to the poor blood supply of this area from long medullary arteries that lack collateral vessels, leading to a higher vulnerability to ischaemic effects of postradiation vasculopathy.37 Less commonly, radiation-induced lesions are located more remotely from the primary tumour site, such as in the contralateral hemisphere or subependymally.38 Temporal-lobe radionecrosis can occur after radiotherapy for head and neck tumours, in which the temporal lobes receive high doses of radiotherapy.48 Finally, cranial-nerve damage due to radiation-induced necrosis can occur.49 The optic-nerve system is especially vulnerable for late radiotherapy-effects. Optic neuropathy with gadolinium enhancement on MRI can occur when radiotherapy is delivered to tumours in the perioptic regions.48

Pseudoprogression

In several reports, patients with malignant glioma have been described with subacute treatment-related reactions with or without clinical deterioration, showing oedema and sometimes contrast enhancement on MRI, suggestive of tumour progression.45–48 Despite the clinical or radiological suggestion of tumour progression, these patients recovered or stabilised spontaneously, and often without permanent new deficits. Early series described this occurrence in patients treated with hyperfractionated radiotherapy to the brain stem45 and in cerebral gliomas after intra-arterial carmustine chemotherapy, administered alone or with radiotherapy.46 These findings suggested that this event might occur more often in patients who are treated intensively. Because these lesions mimic tumour progression, the subacute radiation effects have been coined pseudoprogression (figure 2).

In a systematic study of patients with malignant glioma treated within prospective phase III trials with radiotherapy only, we noted that pseudoprogression occurred in three of 32 (9%) patients.5 In a similar more recent study on 85 patients with malignant glioma treated with temozolomide chemoradiotherapy, pseudoprogression occurred in 18 (21%) patients.35 The pseudo-progressive lesions all occurred on the first MRI done within 2 months after treatment. This timing is earlier than the typical time period in which radionecrosis is described after radiotherapy alone.23,24 In a third of patients treated with temozolomide chemoradiotherapy, the increase in radiological abnormalities was accompanied by new focal signs, but in most patients the increase in radiological abnormalities was clinically asymptomatic.35 With further follow-up most pseudoprogressive lesions either stabilised or decreased in size and area of enhancement. In another study involving 103 patients, pseudoprogression was noted in 32 patients (31%), and was clinically symptomatic in 11 (34%) of these patients. Patients with methylated O6–methyl guanine-DNA methyl transferase (MGMT) showed more frequent pseudoprogression. Whether this latter finding was due to frequent tumour progression shortly after temozolomide chemoradiotherapy in unmethylated and thus unresponsive tumours or indeed is indicative of a higher incidence of pseudoprogression because of a higher sensitivity to treatment remains to be established.26
The occurrence of pseudoprogression within the first 2 months after temozolomide chemoradiotherapy fits with the period in which the acute and subacute somnolence syndrome is normally noted. In one patient with early progression after temozolomide chemoradiotherapy in the study by Taal and colleagues, the lesion increased during further follow-up. At repeated surgery, 4 months after the end of chemoradiotherapy, treatment-related necrosis was noted. Another patient developed radiological progression followed by clinical deterioration after chemoradiotherapy, and needed second surgery within 2 months after the end of radiotherapy. During surgery, extensive necrosis was seen (data not shown). In a systematic study, Chamberlain and colleagues noted surgically confirmed necrosis without evidence of recurrent tumour in seven (14%) of 51 patients with malignant glioma within 6 months after temozolomide chemoradiotherapy. These seven patients constituted half of the 15 patients who were reoperated on within 6 months after radiotherapy because of radiological progression. Taken together, these findings suggest that pseudoprogression represents a continuum between the subacute radiation reaction and treatment-related necrosis. Most likely, pseudoprogression is induced by a pronounced local tissue reaction with an inflammatory component, oedema, and abnormal vessel permeability causing new or increased contrast enhancement on neuroimaging. In less severe cases, this event can subside without further treatment, but in more severe cases it can result, over time, in true treatment-related necrosis. The currently available data indeed suggest that both pseudoprogression and treatment-related necrosis do not only occur more frequently after temozolomide chemoradiotherapy, but also develop earlier if radiotherapy is combined with chemotherapy.

Radiotherapy, temozolomide, and MGMT

Ionising radiation causes its main biological effects by induction of free radicals, which leads to double strand DNA breaks. Most of these lesions are successfully repaired, but some lesions are not, which can lead to clonogenic cell death. Temozolomide is a cytostatic prodrug which is rapidly absorbed after oral administration, can pass the blood–brain barrier, and is spontaneously hydrolysed to its active metabolite methyltriazeno-imidazole-carboxamide (MTIC). In the cell, MTIC methylates DNA at several positions, from which methylation of the O6 position of guanine is regarded as the cell-lethal lesion. The methyl group at the O6 position of guanine can be removed by the suicide DNA repair enzyme MGMT, which is consumed by this event. Cells that are deficient in MGMT have shown an increased sensitivity to temozolomide. The European Organisation for Research and Treatment of Cancer and National Cancer Institute of Canada study on concomitant administration of fractionated radiotherapy and adjuvant temozolomide in patients with glioblastoma showed a significant increase in median overall survival for patients treated with chemoradiotherapy (14–6 months [95% CI 11.2–13.0]) compared with radiotherapy alone (12–1 months [13.2–16.8]). Molecular analysis of glioma specimens from patients included in this trial showed a survival benefit for patients treated with chemoradiotherapy whose tumours had a methylated MGMT gene promoter (2-year survival 46%) compared with those whose tumours had an unmethylated MGMT gene promoter (2-year survival 14%). These data indicate that epigenetic silencing of the MGMT gene promoter, resulting in the absence of MGMT expression, makes tumours more vulnerable to temozolomide.

Mechanisms of radiation-induced injury

Vascular injury and vascular endothelial growth factor

The events leading to radiation-induced injury are the result of a complex, dynamic interplay between the various cells within the irradiated volume (eg, tumour cells, endothelial cells, and glial cells). Injury to the vasculature, caused by clonogenic death of endothelial cells, is thought to be crucial for the development of acute and subacute radiation injury. Vascular lesions are also thought to have a major role in late radiation injury of the brain. Wong and van der Kogel postulated that radiation-induced endothelial-cell death results in breakdown of the blood–brain barrier with vasogenic oedema, ischaemia, and hypoxia. Within this process both thrombocytes and leucocytes are thought to have a role. Hypoxia, on its turn, results in upregulation of vascular endothelial growth factor (VEGF), which further increases the permeability of the vasculature with subsequent demyelination and tissue necrosis. The upregulation of VEGF might also account for the increased contrast-enhancement and oedema formation noted in pseudoprogression. Of note, radiotherapy by itself also upregulates VEGF secretion by glioma cells, which was shown to decrease apoptosis of both tumour and endothelial cells, and to increase angiogenesis. This mechanism possibly contributes to glioma-resistance to radiotherapy. In view of the current knowledge about the role of VEGF in high-grade gliomas, inhibition of VEGF-signalling pathways in combination with radiotherapy is an attractive target for therapeutic strategies.

Endothelial-cell apoptosis

In addition to clonogenic cell death, radiation also induces endothelial-cell apoptosis. Apoptotic processes induced by radiation are mainly membrane-damage dependent and less DNA-damage dependent. This process has been described in detail by Rodemann and Blaese. In brief, radiation-induced membrane damage leads to the activation of acid sphingomyelinases and the generation of ceramide. Ceramide mediates the activation of three major cascades: the mitogen-activated protein kinase 8 pathway, the mitochondrial pathway,
Intracellular pathways of endothelial-cell death: membrane and DNA damage-dependent pathways

Ionising radiation activates both mitochondrial and death-receptor pathways (figure 5).62 Ionising radiation does not necessarily lead to apoptosis of endothelial cells. Both in-vitro and in-vivo studies show a strong dependency on the dose of radiation and on the proapoptotic and antiapoptotic signalling cascades.63,64 The detailed information about the several molecular cascades involved in endothelial-cell apoptosis induced by radiotherapy could be exploited for molecular-based prevention and treatment of unwanted effects of radiotherapy. Experimental data show that protein kinase C (PKC) can protect against radiation damage.65 This protective effect is attributed to the PKC-dependent downregulation of acid-sphingomyelinase activity and the inhibition of ceramide-dependent apoptosis. Basic fibroblast growth factor, a stimulator of PKC activity, inhibited radiation-induced endothelial-cell death, both in vitro and in vivo.66 Furthermore, these various molecular pathways might explain the higher incidence of pseudoprogression in patients treated with temozolomide chemoradiotherapy than in those treated with radiotherapy alone. Temozolomide-induced DNA-damage and radiation-induced DNA and membrane damage might activate parallel pathways leading to an increase of endothelial-cell death. Hence, temozolomide chemoradiotherapy is likely to enhance vascular permeability as well as hypoxia and necrosis.

**Individual sensitivity for pseudoprogression**

Up to now, apart from the addition of chemotherapy to radiotherapy, no risk factors for pseudoprogression have been identified. Neither age nor size of the irradiated tumour volume were noted to be related to the occurrence of pseudoprogression.67 However, the incidence of pseudoprogression is likely to increase with a higher dose of radiotherapy (figure 3). Furthermore, speculation could be made that more effective treatments will also result in higher incidences of pseudoprogression. Support for this assumption is the increased occurrence of treatment-related necrosis after chemoradiotherapy or after high doses of radiotherapy with more extensive tissue damage. If this assumption is true, one would expect higher incidences of pseudoprogression in tumours with a methylated MGMT promoter gene treated with temozolomide chemoradiotherapy, or in other (molecularly) more sensitive tumour types. The preliminary data presented by Brandes and co-workers68 suggest this might be the case.

**Management of patients with glioma with early progressive lesions**

**Brain imaging**

With the standard MRI modalities (eg, T2, T1 with gadolinium, and FLAIR), a reliable distinction between tumour recurrence and pseudoprogression or treatment-related necrosis is not possible. Clinically, the question of whether there is active tumour growth or infiltration in addition to, or without, necrosis has important consequences, and a reliable distinction between the two conditions is, therefore, crucial. Magnetic resonance spectroscopy (MRS) can distinguish residual or recurrent tumours from pure treatment-related necrosis, but not from mixed necrosis and tumour tissue.69 Diffusion-weighted imaging (DWI) has also been assessed as an instrument for differentiating between tumour and necrosis after radiotherapy. The apparent diffusion coefficient was noted to be higher in necrotic tissue than in recurrent tumour tissue in several studies.44,45 However, available evidence for this imaging modality is still limited and the specifcity of DWI might be less than with MRS.69 A suggestion has been made that a combination of DWI and MRS can improve the differentiation of recurrent glioma and radiation injury.70 Finally, 18-fluorodeoxyglucose ([18F]FDG)-PET has been shown to be useful in differentiating necrosis from tumour regrowth, but the reported sensitivity and specificity are again low.71 The
limitation of this tracer is the high glucose utilisation of the brain, which results in high background activity. There is limited, but increasing clinical evidence that PET examination with amino acid tracers (eg, 11-carbon methionine and 18F-fluoroethyltyrosine) can discriminate between treatment-related necrosis and tumour recurrence.27 Whether these imaging techniques will also allow a reliable distinction between pseudoprogression and real tumour progression needs to be determined in well-designed prospective series of sufficient size. This research is urgently needed, because a reliable distinction between tumour progression and non-tumoral lesion increase in neuroimaging abnormalities will allow rational patient management in patients presenting with radiological progression. Furthermore, the possibility of this distinction will have important implications for trials on recurrent glioma.

Treatment of patients with early progressive lesions

The frequent occurrence of early pseudoprogression after temozolomide chemoradiotherapy requires a new management approach for patients with early progressive lesions after this treatment. Obviously, in the case of tumour progression, there is no point in the continuation of temozolomide, whereas in the case of pseudo-progression or treatment-related necrosis continuation seems logical. Therefore, in principle, and especially in patients who are free from clinical signs and symptoms, adjuvant temozolomide should be continued. In clinically symptomatic patients surgery should be considered, which might improve the clinical condition of the patient, and which allows a histological diagnosis of the lesion (ie, tumour or extensive necrosis, or both).24 However, the histological interpretation of these cases can be difficult. In the case of treatment-related necrosis, areas with tumour cells are often present between large areas with necrosis and the decision of whether these tumour cells are still viable can be difficult to make.25 If mainly necrosis is seen, continuation of temozolomide is warranted.

Steroids can usually control oedema and increased intracranial pressure, but long-term use is associated with substantial side-effects. Recently, bevacizumab, a humanised murine monoclonal antibody against VEGF, was noted to be effective in eight patients with malignant glioma who were diagnosed with radionecrosis by MRI and biopsy.26 Because treatment-related necrosis can subside spontaneously the interpretation of these findings is difficult. However, the symptomatic control obtained in these patients does support a role for VEGF-signalling pathways in treatment-related necrosis. Further research is needed to see whether anti-VEGF drugs are better than steroids in terms of cost, efficacy, and side-effects in the management of treatment-related necrosis and pseudoprogression. An important scientific consequence of pseudoprogression after temozolomide chemoradiotherapy is that patients with progressive lesions within the first 3 months after treatment should not be included in studies on recurrent malignant gliomas.

Conflicts of interest

MvdB has provided consultancies for, and is a member of, the speakers’ bureau of Schering Plough (New Jersey, USA). All other authors declared no conflicts of interest.

References


