Magnetic Resonance Imaging Findings of Radiation-induced Changes After Treatment of Malignant Gliomas and Metastases with a Particular Emphasis on Radiation Necrosis

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Abstract

New contrast-enhancing lesions discovered on routine follow-up brain imaging at or near the site of previously treated primary or metastatic brain tumours represent a clinical and radiological challenge, as radiation necrosis and tumoral recurrence often present at standard magnetic resonance imaging (MRI) with overlapping imaging features. Since the advent of combined therapy, including surgery and/or radiotherapy and chemotherapy, the post-treatment radiological assessment has been made earlier, with a subsequent higher incidence of early radionecrosis and a potential risk of mistaking it for disease progression. Therefore, both clinical and imaging follow-up are essential. This article briefly describes and illustrates the temporal patterns and spectrum of MR findings of radiation-induced brain injury and considers practical aspects of conventional and advanced MR sequences (diffusion-weighted imaging, perfusion MR and MR spectroscopy), with a particular emphasis on the distinction between tumoral recurrence and radiation necrosis.

New contrast-enhancing lesions discovered on routine follow-up brain imaging at or near the site of previously treated primary or metastatic brain tumours represent a challenge for radiologists and oncologists, as radiation-induced injuries may have an appearance that is virtually indistinguishable from that of recurrent disease. With standard magnetic resonance imaging (MRI) modalities, a reliable distinction among tumour recurrence, pseudoprogression and radionecrosis (RN) is not always possible.[1–13]

Although primary resection is the mainstay of treatment in gliomas and selected cases of metastases, its extent and feasibility are often limited by the location of the tumour near vital or eloquent brain structures. Therefore, tumour sites are often treated in association with radiation therapy (RT), chemotherapy (ChT) or chemoradiotherapy (ChRT).[8,14,15] ChT protocols include different dosage schemes of various chemotherapeutic agents.[7] RT protocols include whole-brain RT (WBRT) and different schemes of locally administered high doses of radiation (stereotactic RT or radiosurgery), which have resulted in improved outcome but also in a significant incidence of radiation injury to the brain.[1] The risk of late effects leading to functional deficits after brain irradiation limits the total dose that can be safely administrated to patients.[1,5–7,11,16,17]

Nowadays, ChRT with temozolomide (TMZ) is the standard therapy for glioblastoma as it has been shown to improve the survival of newly diagnosed patients.[5] In addition, the post-RT radiological assessment is made earlier than in previous eras when RT was given alone.[5] The possibility of a higher incidence of early RN and the risk of mistaking it for disease progression remain diagnostic challenges.[1,5,18] Histological examination remains the gold standard,[1,3] and re-operation via a biopsy or resection to obtain tissue is the treatment or diagnostic procedure of choice.[4] However, even biopsy may yield the wrong diagnosis in approximately 10% of cases and is not always clinically practicable due to a high risk of morbidity.[3,4,6,11,15,17] Therefore, the distinction between recurrent tumour and treatment-related lesions is made on the combination of clinical course, brain biopsy and imaging over a lengthy follow-up interval, not the specific imaging itself, which may lead to delays in starting treatment.[7–9, 15, 16]

This article briefly describes and illustrates the temporal patterns and spectrum of MR findings of radiation-induced brain injury and considers practical aspects of conventional and advanced MR sequences – diffusion-weighted imaging (DWI), MR perfusion and MR spectroscopy (MRS) – with a particular emphasis on the distinction between tumoral recurrence and RN.

Figure 1: Pseudoprogression in a Right Frontal Anaplastic Astrocytoma, Treated With Surgery and Temozolomide Chemoradiotherapy in 2007; and a Second Surgery Followed by Chemotherapy in February 2008 Due to Tumoral Progression
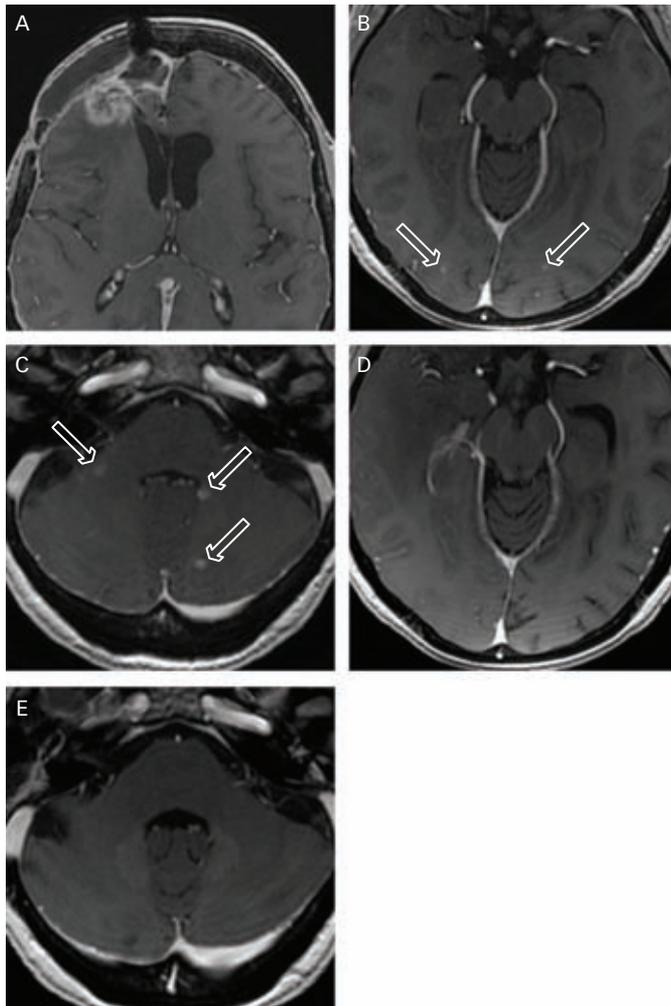
At follow-up contrast-enhanced axial T1-weighted imaging, surgical changes in the tumoral bed were observed (A). New areas of enhancement in the occipital lobes (B) and posterior fossa (C) are depicted (open arrows), mimicking leptomeningeal spread. No signs of leptomeningeal spread were found at lumbar puncture and spine magnetic resonance, and no changes in therapy were made. Four months later, those enhancement foci were no longer present (D and E). These findings suggest pseudoprogression.

Pathophysiology of Radiation-induced Injury

The events leading to radiation-induced injury are the result of a complex, dynamic interplay between the various cells within the irradiated volume (tumoral, endothelial and glial cells).[6]

Endothelial Cell Injury

In acute stages, radiation-induced endothelial cell death results in a breakdown of the blood–brain barrier with vasodilatation and increased capillary permeability, which manifests as vasogenic oedema, hypoxia and ischaemia.[1,4–6,10,18] In chronic stages, vascular hyalinisation, fibrinoid necrosis and thrombosis lead to the development of cytotoxic oedema, infarction and necrosis.[1,4,6,10,13,19] The extension and confluence of multiple peri-vascular necrotic foci result in large serpiginous or 'geographic' zones of parenchymal necrosis,[4,10,20] usually interspersed with tumour cells of unclear viability.[2,6,18] Further histological changes include inflammatory peri-vascular infiltration, low-grade haemorrhage, dystrophic calcifications and malformation-like aggregates of dilated vessels.[18]

Glial Cells

Oligodendrocytes are extremely sensitive to radiation. Their destruction is associated with radiological evidence of demyelination and reactive astrocytic gliosis in peri-lesional white matter.[1,4,5,7,10,13,18] There is sufficient loss of cellular components to account for the observed brain atrophy with hydrocephalus *ex vacuo* seen after RT.[4,7,10,19]

Other Mechanisms

The fibrinolytic enzyme system may also play a role in RN. Decreased tissue plasminogen activator and elevated urokinase plasminogen activator levels have been observed. Their effect on blood vessels may contribute to cytotoxic oedema and tissue necrosis.[7,10] The potential role of autoimmune vasculitis in the response of the central nervous system to radiation-induced damage needs further investigation.[7,10,17] Damage from ChT may occur earlier and be more severe if capillary permeability or cell metabolism are altered.[5,6] Therefore, RT may enhance the efficacy of ChT by maximising drug uptake and activating parallel pathways, leading to an increase of endothelial cell death.[6] This is particularly true for TMZ,[5] such that ChRT is likely to enhance vascular permeability (and therefore gadolinium enhancement),[5,6] along with hypoxia, axonopathy, white-matter demyelination and necrosis.[4]

Radiation-induced Brain Injury

The adverse effects of RT on the brain are classified into three types: acute injury, subacute injury and pseudoprogression, and late radiation-induced injury.

Acute Injury

Acute injury occurs during radiation or just after completion of RT,[1,4,6,17] presenting as transient worsening of symptoms[1] and signs of increased intracranial pressure.[6] Use of the currently recommended low fraction doses means that symptoms are mostly transient and reversible and can usually be alleviated by corticosteroids.[6] MR is not generally needed as it has little prognostic significance.[1,6,17]

Subacute Injury and Pseudoprogression

Subacute injury occurs within the first 12 weeks of completion of RT,[1,4–7,17,21] presenting as somnolence, fatigue or worsening of pre-existing neurological focal deficits, although patients may remain asymptomatic.[5] Corticosteroids are sometimes needed to control symptoms. Improvement usually occurs within a few weeks or months, sometimes spontaneously.[1,6,17]

MR findings vary from non-enhancing white matter hyperintensities on T2-weighted imaging, representing oedema, to new enhancing lesions or enlargement of pre-existing lesions at first post-radiation MR,[6] noted immediately after treatment. These findings may mimic recurrence or progression[5] and may have an impact on management, resulting in premature discontinuation of effective adjuvant therapy[4–6,21] and inappropriate patient selection for clinical trials on recurrent gliomas.[21]

Therefore, this radiation effect has been called pseudoprogression or therapy-induced necrosis.[5,6] At follow-up, most pseudoprogressive lesions either stabilise or decrease in terms of size and area of enhancement without any change in therapy (see *Figure 1*),[6,19] although some lesions may progress to RN. Hence, pseudoprogression can be considered as a continuum between subacute injury and true RN.[6]

Proposed new response criteria suggest that within the first 12 weeks of completion of RT, progression can be determined only if the majority of the new enhancement is outside the radiation field or there is pathological confirmation of progressive disease.[21] Pseudoprogression and RN not only occur more frequently after TMZ ChT, but also develop earlier if RT is combined with ChT.[5,6,20] The reported incidence rates range between 20 and 30% of patients treated with TMZ ChRT.[6,21] No other risk factors for pseudoprogression have been identified. However, the incidence of pseudoprogression is likely to increase with higher doses of RT.[6]

Late Radiation-induced Injury

Late radiation effects occur months to years post-radiation and are often progressive and irreversible.[1,4–6,17,21] This category includes several entities:[1,4,6,19] vascular lesions (lacunar infarcts, large-vessel occlusion [Moyamoya-like syndrome], telangiectasias), parenchymal calcifications (mineralising microangiopathy), radiation-induced tumours (the most common being meningioma), cranial neuropathy (relatively rare, most often related to necrosis of the optic nerve system), leucoencephalopathy syndrome and RN. Only the last two will be discussed further.

Leucoencephalopathy Syndrome and Disseminated Necrotising Leucoencephalopathy

Leucoencephalopathy manifests as gait and memory disturbances, urinary incontinence and mental slowing.[1,6] The reported prevalence ranges between 38 and 100% of patients receiving RT.[19] It is strongly related to the volume of brain irradiated, the radiation dose, the interval between irradiation and imaging, concomitant medical diseases predisposing to vascular injury, age and concurrent ChT.[1,4,6]

On fluid-attenuated inversion recovery (FLAIR) and T2-weighted imaging, leucoencephalopathy typically presents as diffuse, symmetric hyperintense foci in the periventricular white matter near the frontal or occipital horns, which may lead to a confluent pattern with scalloped outer margins extending from the ventricles to the corticomedullary junction, with no enhancement or significant mass effect (indistinguishable from the deep white matter changes seen in normal older people and patients with risk factors for cerebral vascular disease).[1,4,6,19,20] The corpus callosum and the subcortical arcuate fibers are initially spared. Additionally, cerebral atrophy with hydrocephalus may be seen.[2,4,6,7,10]

In severe cases, extensive diffuse white matter injury can lead to disseminated necrotising leucoencephalopathy, which occurs because of the combined effects of ChT and RT.[1,4,19] On MR it is similar to leucoencephalopathy, but presents petechial or ring-shaped haemorrhages and calcification deposits[1] along with areas of contrast enhancement in the white matter at variable distances from the primary tumour[1] (with a predilection for peri-ventricular and, less commonly, cortical involvement). Enhancement patterns can be nodular, linear or curvilinear in varying sizes and can be single or multiple, therefore mimicking tumour progression (see *Figure 2*).[4,10] Leucoencephalopathy and disseminated necrotising leucoencephalopathy may occur together; alternatively, one may follow the other.[1,20] These lesions do not warrant biopsy if they remain stable or regress in size. However, progression to RN should be suspected if the lesions increase in size or are accompanied by oedema and mass effect.[4,10] In the experience of the authors, follow-up should also be recommended if a peripheral restriction of
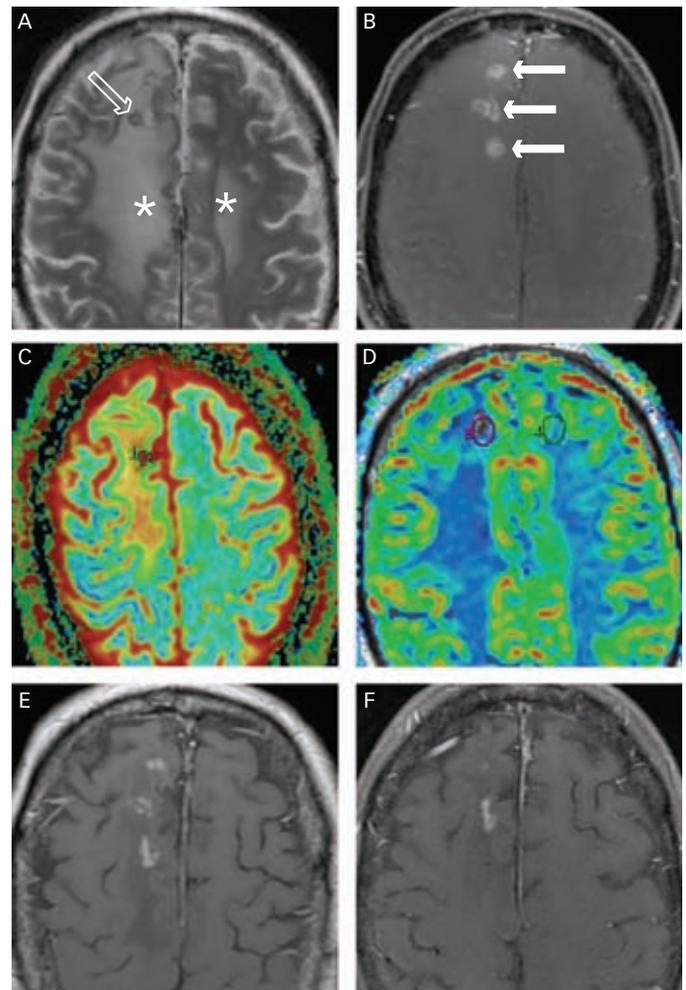
A: Axial T2-weighted image showing diffuse white matter injury (*) secondary to radiotherapy and coarse calcification foci (open arrow); B: Axial contrast-enhanced T1-weighted image showing three lesions with blurred enhancement (solid arrows); C: Apparent diffusion coefficient (ADC) map revealing elevated ADC values – as high as 2.29x10⁻³mm²/second. On diffusion-weighted imaging, these lesions presented homogeneous low signal intensity (not shown); D: On a relative cerebral blood volume (rCBV) map, rCBV values as low as 0.57 were also observed, suggesting post-treatment changes; E and F: Axial contrast-enhanced T1-weighted image at follow-up studies six and 12 months later, respectively, revealed how these lesions regressed in size.

water diffusion is found on DWI, as it may be indicative of a trend towards RN.

Radionecrosis

RN is the end result of confluent perivascular coagulative necrosis affecting the white matter.[10] It generally occurs three to 12 months after RT, but can occur up to years and even decades afterwards.[1,5,6,10,14,18] In adults, the reported incidence of RN after RT for brain tumours ranges between 5 and 24%.[2,4,6–8,10,20] Risk factors include total radiation dose (>6,500–7,000cGy), size of the radiation field and radiation fraction, number and frequency of radiation doses (>200cGy/day), duration of survival, age of the patient at the time of treatment (in older patients, pre-existing vascular pathology and ChRT may have additive effects), treatment duration, re-irradiation and ChRT (increased incidence and earlier appearance).[1,3–7,10,14,20,22] RN is a dynamic pathophysiological process with a highly variable clinical course (progressive functional and cognitive impairments that may

Figure 3: Conventional Magnetic Resonance Features of Radionecrosis
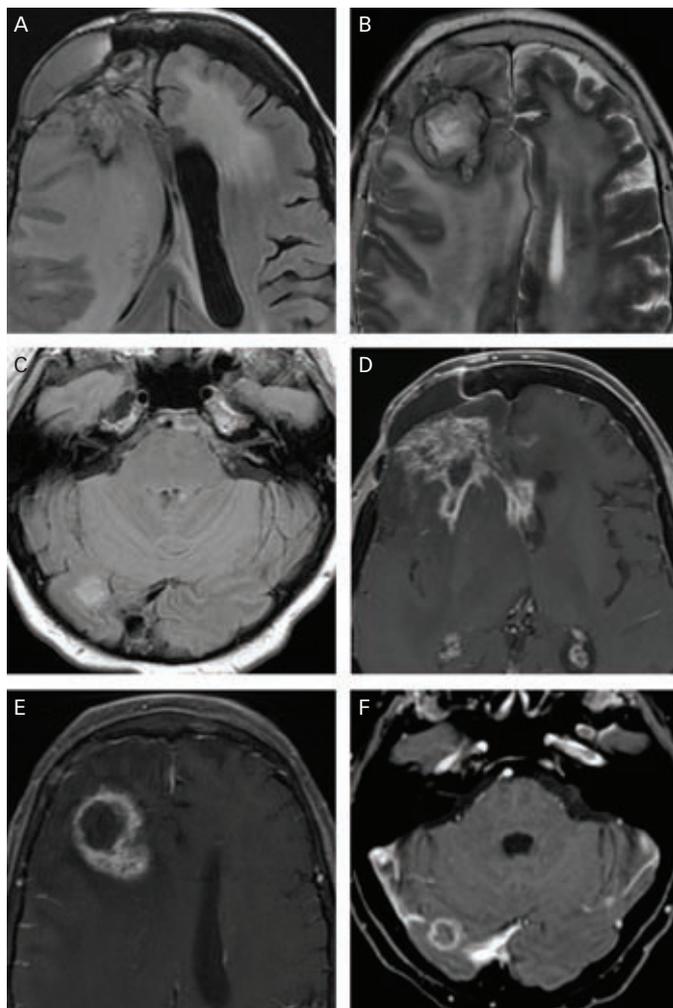
A–C: On axial fluid-attenuated inversion recovery (FLAIR) images, radionecrosis presents as necrotic masses with ill-defined, blurred margins, central high signal intensity (SI) and peripheral (solid-portion) low SI. Typical enhancement patterns are described as 'soap-bubble-like' (D, paired image to A), 'Swiss-cheese-like' (E, paired image to B) and 'cut green pepper' (F, paired image to C).

improve or stabilise; asymptomatic courses may even be seen) and several possible radiological outcomes: lesions may stabilise, regress in size or undergo continued growth with oedema, sometimes with lethal progression.[1,4–7,9,10]

Imaging of Radionecrosis
Conventional Magnetic Resonance Imaging
RN can closely resemble a recurrent tumour because of the following shared characteristics: origin at or close to the original tumour site, contrast enhancement, growth over time, oedema and exertion of mass effect.[1–8,10,11,14–20] RN commonly occurs at the site of maximum radiation delivery (in the immediate vicinity of the tumour site and surrounding the surgical cavity of a partially or totally resected tumour), in the periventricular white matter, or within the corpus callosum.[1,4,6,10,13,15,19,20] Less common patterns include multiple lesions, lesions in the contralateral hemisphere or arising remotely from the primary tumour, subependymal lesions and temporal-lobe RN (after RT for head and neck tumours).[1,4,6,7,10,20]

On T2-weighted imaging, RN presents as necrotic masses with ill-defined, blurred margins. Peri-lesional oedema and scattered calcifications are commonly observed. The central necrotic component has increased signal intensity (SI), while the peripheral, solid portion presents as low SI,[1,4,18] with an intense and irregular peripheral rim of enhancement on T1-weighted imaging with gadolinium.[6,7,10] Commonly seen enhancement patterns are described as 'soap-bubble-like,' 'Swiss-cheese-like' and 'cut green pepper' (see *Figure 3*).[2,4,7,9,15] Swiss cheese lesions are larger, more variable in size, and more diffuse than soap bubble lesions,[4,10] and are the result of diffuse necrosis affecting the white matter and cortex with diffuse enhancement of feathery margins and intermixed necrotic foci.

Perfusion Magnetic Resonance
Relative cerebral blood volume (rCBV) is the most widely used haemodynamic variable derived from perfusion MR. rCBV has been shown to correlate with primary glioma grade and tumour microvascular density.[4,16,22]

High-grade primary neoplasms and brain metastases are characterised by high rCBV values (equal to or greater than those of gray matter), which occur owing to increased angiogenesis. RN has low rCBV values, resulting from endothelial cell damage, thrombosis and fibrinoid necrosis.[4,5,12,14,16]

Normalised rCBV ratios are useful in distinguishing pure RN from pure tumour recurrence. In a study performed by Suhagara et al.,[18] the authors concluded that if the ratio of the enhancing lesion is higher than 2.6 or lower than 0.6, tumour recurrence or RN should be strongly suspected (see *Figure 4*).

Nevertheless, enhancing masses developing after surgery and ChT and/or RT of high-grade tumours usually demonstrate a combination of both recurrent/persistent neoplasm and RN.[2,18] Accordingly, a large degree of overlapping rCBV values can be observed,[4,12,14,16,18] and there is little consensus in the literature on this matter. Thus, rCBV ratios ranging between 0.6 and 2.6 probably represent a mixture of both tumour and necrosis.[18] In these cases, rCBV plays only a complementary role, and follow-up studies are mandatory.

Magnetic Resonance Spectroscopy
Structural brain degradation after RT can be predicted by early changes in metabolic activity before the development of neurocognitive symptoms or anatomical changes seen on conventional MR.[7] Spectral patterns allow reliable differential diagnosis when either pure tumour or pure RN is found. Unfortunately, in many of the enhancing regions, including those appearing early after treatment, often both tumour cells and radiation injury are present, and the spectral patterns in these cases are less clear.[2,4–7,9] If possible, a spectrum of the tumour should be obtained prior to RT/ChT in order to compare metabolic ratios at follow-up studies.[11] A spectrum of normal tissue should always be obtained to provide an internal standard.[4]

The main spectroscopic features employed in the distinction between tumour recurrence and RN are as follows (see *Figure 4*). First, decreasing or unchanging choline (Cho) levels suggest RN.[5,12,17] In the initial stages, Cho levels may be normal, reduced or elevated (resulting from demyelination, therefore mimicking tumour).[4] Thereafter, decreasing levels of Cho and creatine (Cr) become evident, reflecting a dilution effect of decreased cell density and oedema. At follow-up studies, a decrease in the abnormal Cho/Cr and Cho/N-acetyl aspartate (NAA) ratios and decreasing or unchanging

Figure 4: Radionecrosis in a Right Frontal Anaplastic Astrocytoma Treated with Surgery and Temozolomide Chemoradiotherapy (Same Patient as in *Figure 1*)
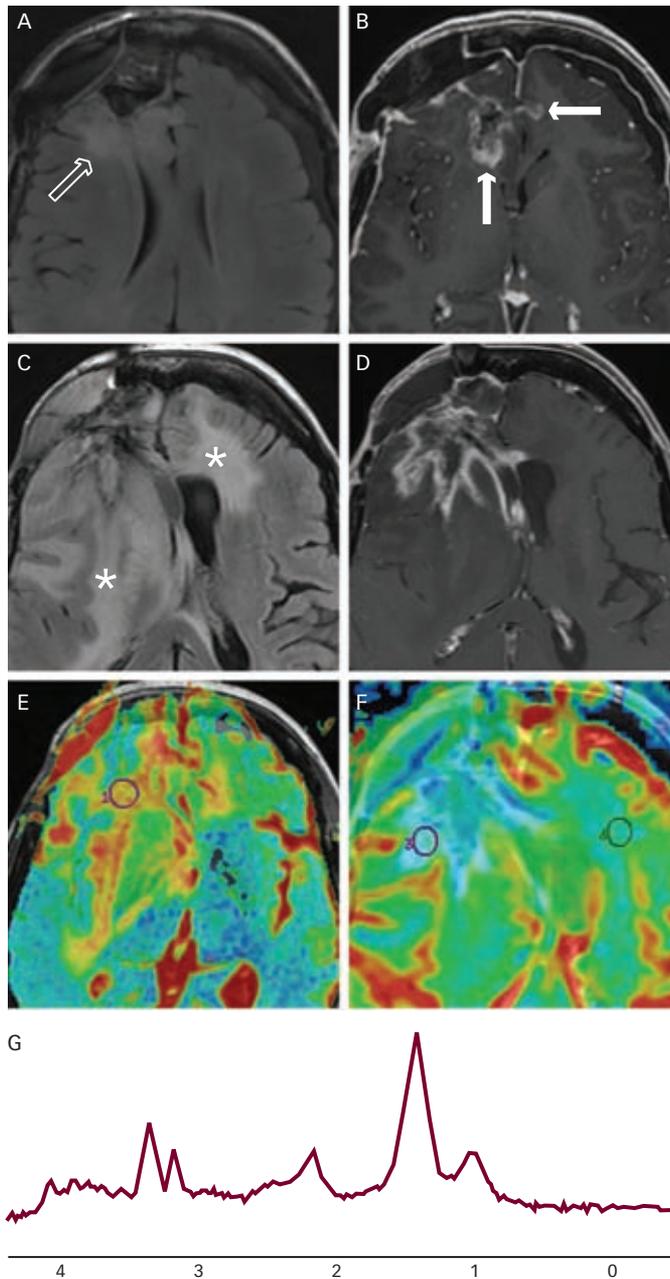
A: Axial fluid-attenuated inversion recovery (FLAIR) image showing elevated signal intensity in the frontal white matter (open arrow); B: Contrast-enhanced axial T1-weighted image revealing irregular and pseudonodular enhancement of the surgical margins, particularly on its posterior aspect and enhancement crossing the mid-line through the corpus callosum (solid arrows); C: Axial FLAIR image at follow-up study demonstrating a markedly increased right parietal and bifrontal oedema (*); D: Paired contrast-enhanced axial T1-weighted image showing increased areas of amorphous, irregular enhancement (Swiss-cheese pattern) in frontal white matter; E: Paired apparent diffusion coefficient (ADC) map demonstrating elevated ADC values as high as $1.81 \times 10^{-3} mm^2/second$; F: Paired relative cerebral blood volume (rCBV) map evidencing values under 0.7; G: Magnetic resonance spectroscopy (single voxel, echo time 35ms) showing slightly increased choline (Cho) levels, decreased N-acetyl aspartate (NAA) levels and large peaks of lipids/lactate (Lip/Lac). These findings are typical of radionecrosis.

Figure 5: Radionecrosis in a Right Frontal Cystic Metastasis from Cervical Cancer
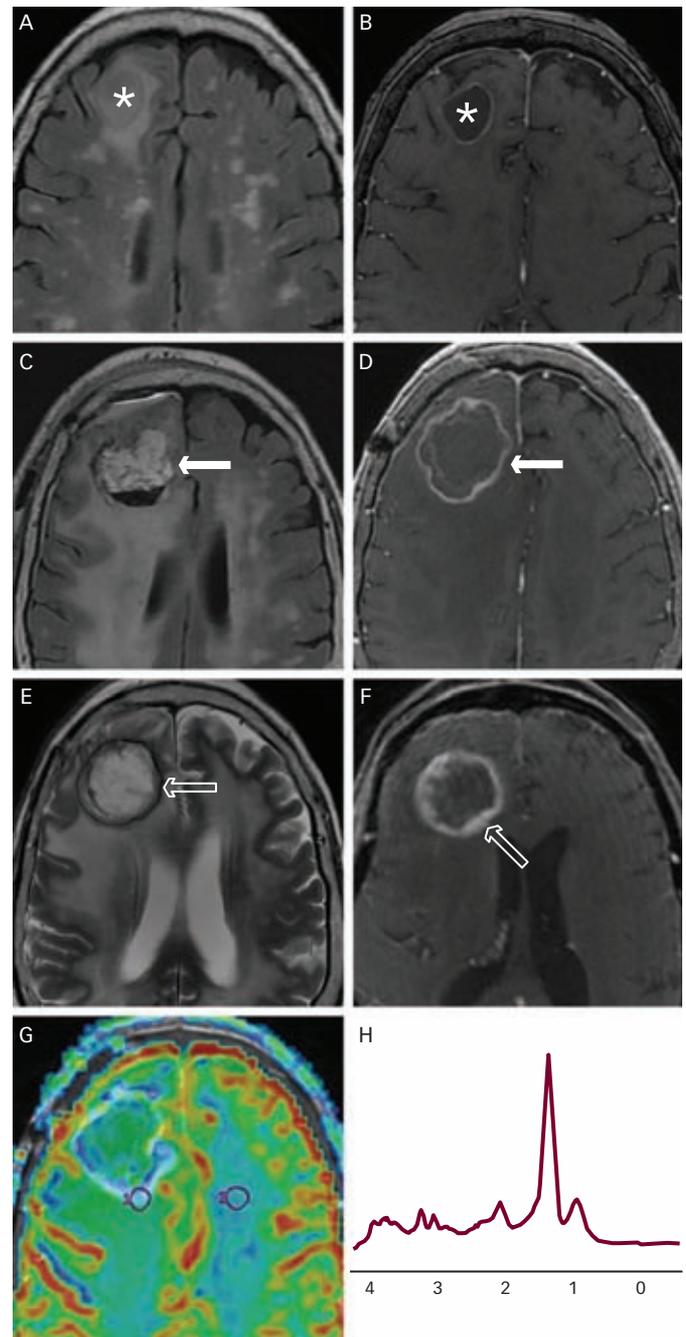
A: Axial fluid-attenuated inversion recovery (FLAIR) image shows a right frontal mass with well-defined margins (*) and mild perilesional vasogenic oedema. Several chronic ischaemic foci in the deep white matter are also observed; B: Axial contrast-enhanced T1-weighted image evidences thin peripheral enhancement of the lesion. The patient underwent whole-brain radiation therapy and radiosurgery followed by surgical resection. Post-surgical axial FLAIR (C) and contrast enhanced T1-weighted images (D) demonstrated surgical changes in the tumoral bed, leucoencephalopathy and irregular peripheral enhancement of the surgical cavity (solid arrows). Four months later, paired axial FLAIR (E) and contrast-enhanced T1-weighted images (F) demonstrate how the surgical cavity presents thicker walls with pseudonodular enhancement. G: Perfusion map evidencing low relative cerebral volume values ranging between 0.31 and 0.72; H: Magnetic resonance spectroscopy (single voxel, echo time 35ms) shows markedly decreased choline levels with prominent lipid and lactate peaks. These findings support the diagnosis of radionecrosis.

Cho levels are typical of RN.[4,7] Second, significant elevations of the Cho/NAA and Cho/Cr ratios (with a concomitant reduction in the NAA/Cr ratio) in contrast-enhancing lesions represent tumour recurrence.[8,9,11,12,15,17] In different studies, cut-off values of 1.71–1.8 (i.e. values >1.8 being diagnostic of recurrence) for either the Cho/NAA or Cho/Cr ratio are considered diagnostic of recurrence[5,9,15] compared with areas of radiation injury and normal adjacent tissue.[4,7,9,15] Third, the presence of lipids (Lip), which reflects necrosis, and lactate (Lac), which indicates ischaemia and necrosis, may suggest both RN and recurrence. However, large Lip peaks and Cho/Lip-Lac ratios under 0.3 have a high positive predictive value for RN.[4,5,7,17]

Diffusion-weighted Imaging

RN can have variable SIs (hypointense, hyperintense, heterogeneous) and a non-specific appearance on DWI.[4,13] Low apparent diffusion coefficient (ADC) values have been reported in some studies; this might reflect early necrosis with abundant polymorphonuclear leukocytes and high viscosity, which could restrict water diffusion, as in purulent fluid.[4,13] The SI may also be influenced by the presence of haemosiderin (resulting in a low SI because of the T2* effect), calcifications, gliosis or fibrosis caused by radiation when it occurs within the recurrent tumour.[3,4,13]

Theoretically, ADC ratios in the contrast-enhancing lesion should be lower in recurrent tumour than in RN,[3–7,13,22] but there is a relatively broad range of overlapping ADC values.[4] In a study by Hein et al., mean ADC ratios higher than 1.62 occurred only in RN, while ratios lower than this threshold occurred only in recurrent neoplasm.[3]

The presence of a peri-lesional hyperintense halo, reflecting restriction of water diffusion secondary to peri-vascular inflammatory changes, should be carefully evaluated as it may indicate progression toward RN. In the experience of the authors, a close follow-up should be recommended.

Radionecrosis and Metastases

In brain metastases, sequential changes identified on MR after RT and/or radiosurgery can be summed up as temporary exacerbation of the lesion, with peri-lesional oedema and central hypointensity on T2-weighted imaging. The lesion presents central loss of contrast enhancement and rim-like enhancement at two to six months. Blurred marginal enhancement can be observed without tumour progression. With time, this marginal enhancement becomes more discrete, while tumour volume and peri-lesional signal change (representing glial scarring) usually decrease.[22] As mentioned above, the presence of a hyperintense rim on DWI may indicate a trend towards RN, and follow-up should be recommended.[22] The presence of meningeal and dural sinus adherences should raise suspicion of RN, while the development of a rim of peri-ventricular or ependymal enhancement is more likely related to RN than to metastasis growth.

The previously mentioned parameters of advanced MR sequences are also applicable to metastases. However, it is important to highlight that metastases are more likely to be completely treated with ChRT, such that pure RN or pure tumour recurrence are more frequently observed. Therefore, a lower degree of overlapping spectral patterns and rCBV values can be found, providing more accurate diagnostic information (see *Figure 5*).

Conclusion

RN and tumoral recurrence often present at MR with overlapping imaging features; therefore, both clinical and imaging follow-up with conventional and advanced MR sequences are essential. If possible, a spectrum of the tumour should be obtained prior to RT and ChT.

Nevertheless, sometimes the diagnosis can be made solely on the basis of histopathological analysis. In the future, validated prediction models combining multiple metabolic ratios, with or without clinical data, will allow rational patient management, resulting in a reduction of the number of patients subjected to unnecessary invasive procedures or treatment. Furthermore, the possibility of this distinction will have important implications for trials on recurrent glioma. ■

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