MR Imaging Findings of Radiation-induced Changes after Treatment of Malignant Gliomas and Metastases, with a Particular Emphasis on Radiation Necrosis

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Learning objectives

To describe the temporal patterns of treatment-induced changes in malignant gliomas and intraaxial metastases, with a particular emphasis on tumoral recurrence and radiation necrosis.

To illustrate the whole spectrum of findings by means of conventional and advanced MR sequences, with radio-pathologic correlation whenever available

Background

New contrast-enhancing lesions discovered on routine follow-up brain imaging at or near the site of previously treated primary or metastatic brain tumors represent a clinical and radiological challenge, as radiation necrosis and tumoral recurrence often present at standard MR with overlapping imaging features. Since the advent of combined therapy, including surgery and/or radiotherapy and chemotherapy, the post-treatment radiological assessment is made earlier, with a higher incidence of early radionecrosis and a potential risk of mistaking it for disease progression. Therefore, both clinical and imaging follow-up with are essential.

This exhibit briefly describes and illustrates the temporal patterns and spectrum of MR findings of brain radiation-induced injury, and provides considerations on practical aspects of conventional and advanced MR sequences (Diffusion-Weighted Image, Perfusion MR and MR Spectroscopy), with a particular emphasis on the distinction between tumoral recurrence and radiation necrosis.

Imaging findings OR Procedure details

INTRODUCCION

New contrast-enhancing lesions discovered on routine follow-up brain imaging at or near the site of previously treated primary or metastatic brain tumors represent a challenge for the radiologists and oncologists, as radiation-induced injuries may have an appearance virtually indistinguishable from recurrent disease. With the standard MRI modalities, a reliable distinction between tumor 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 tumor near vital or eloquent brain structures. Hence, tumor sites are often treated in association with radiation therapy (RT), chemotherapy (ChT) or chemo-radiotherapy (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 survival of newly diagnosed patients [5]. Besides, the post-radiotherapy radiological assessment is made earlier than before, when RT was given alone [5]. The possibility of a higher incidence of early RN and the risk of mistaking it for disease progression remains a diagnostic challenge [1, 5, 18]. Currently, histological examination remains the gold standard [1, 3], and reoperation 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 tumor and treatment-related lesions is made on the combination of clinical course, brain biopsy, or imaging over a lengthy follow-up interval, not the specific imaging itself, with a possible delay of treatment [7-9, 15, 16].

This article briefly describes and illustrates the temporal patterns and spectrum of MR findings of brain radiation-induced injury, and provides considerations on practical aspects of conventional and advanced MR sequences (Diffusion-Weighted Image (DWI), MR Perfusion and MR Spectroscopy (MRS), with a particular emphasis on the distinction between tumoral recurrence and RN.

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 (eg, tumoral, endothelial and glial cells) [6].

ENDOTHELIAL-CELL INJURY

In acute stages, radiation-induced endothelial-cell death results in breakdown of the blood-brain barrier, with vasodilatation and increased capillary permeability, which
manifests as vasogenic edema, hypoxia and ischemia [1, 4-6, 10, 18]. In chronic stages, vascular hyalinization, fibrinoid necrosis and thrombosis lead to the development of cytotoxic edema, infarction, and necrosis [1, 4, 6, 10, 13, 19]. The extension and confluence of multiple perivascular 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 histologic changes include inflammatory perivascular infiltration, low-grade hemorrhage, dystrophic calcifications, and malformation-like aggregates of dilated vessels [18] (Figure 1). on page 11

GLIAL CELLS

Oligodendrocytes are extremely sensitive to radiation. Their destruction is associated with radiologic evidence of demyelination and reactive astrocytic gliosis in perilesional 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] (Figure 1). on page 11

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 edema and tissue necrosis [7, 10].

The potential role of autoimmune vasculitis in the response of 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 maximizing drug uptake and activating parallel pathways leading to an increase of endothelial-cell death [6]. This is particularly true for TMZ [5], so 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 INJURY OF THE BRAIN

Side-effects of RT to the brain are classified into three types as follows:

ACUTE INJURY
It 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]. By use of currently recommended low fraction doses, symptoms are mostly transient and reversible, and steroids usually alleviate those [6]. MR is not generally needed, as it has little prognosis significance [1, 6, 17].

SUBACUTE INJURY AND PSEUDOPROGRESSION

Subacute injury takes place 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, and 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 (WI), representing edema, 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 for recurrent gliomas [21]. Therefore, this radiation effect has been called pseudoprogression or therapy-induced necrosis [5, 6]. At follow-up, most pseudoprogressive lesions either stabilish or decrease in size and area of enhancement without any change in therapy [19, 6], although some lesions may progress to RN (Figures 2 on page 12, 3 on page 13 ,4 on page 14). 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 only be determined if the majority of the new enhancement is outside the radiation field or there is pathologic confirmation of progressive disease [21].

Both pseudoprogression and RN do not only occur more frequently after TMZ ChT, but also develop earlier if RT is combined with ChT [5, 6, 20]. Reported incidence rates range between 20%-30% of patients treated with TMZ ChRT. 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 include several items [1, 4, 6, 19]: Vascular lesions (lacunar infarcts, large-vessel occlusion -Moyamoya-like syndrome-, telangiectasias), parenchymal calcifications (mineralizing microangiopathy), radiation-induced tumors (the most common is meningioma), cranial neuropathy (relatively rare, most often related to necrosis of optic-nerve system), leucoencephalopathy syndrome and RN. Only the two last items will be further discussed.

**LEUCOENCEPHALOPATHY SYNDROME AND DISSEMINATED NECROTIZING LEUCOENCEPHALOPATHY.**

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

On FLAIR and T2WI, leucoencephalopathy typically presents as diffuse, symmetric hyperintense foci in the periventricular white mater 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 (Figure 5 on page 15), with no enhancement or significant mass effect (indistinguishable from 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 necrotizing leucoencephalopathy, which is due to the combined effects of ChRT [1, 4, 19]. On MR, it is similar to leucoencephalopathy, but presents petechial or ring shaped hemorrhages and calcification deposits [1] (Figure 6 on page 16), along with areas of contrast enhancement in the white matter at variable distances from the primary tumor [1] (with predilection for periventricular involvement, and less commonly the cortex). Enhancement patterns can be nodular, linear or curvilinear in varying sizes and can be single or multiple, therefore mimicking tumor progression [4, 10] (Figure 7 on page 17). Leucoencephalopathy and disseminated necrotizing leucoencephalopathy may occur together, but 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 they undergo enlargement or are accompanied by edema and mass effect [4, 10]. In our experience, follow-up should also be recommended if a peripheral restriction of water diffusion at DWI is found, as it may be indicative of a trend towards RN (Figure 8 on page 18).

**RADIONECROSIS (RN)**
RN is the end result of confluent perivascular coagulative necrosis affecting the white matter [10]. It generally occurs 3 to 12 months after RT, but can occur up to years and even decades afterwards [1, 5, 6, 10, 14, 18]. In adults, reported incidence of RN after RT for brain tumors ranges between 5%-24% [2, 4, 6, 7, 8, 10, 20].

Risk factors include [1, 3-7, 10, 14, 20, 22]: 1) Total radiation dose (> 6500-7000 cGy), 2) Size of the radiation field and radiation fraction, 3) Number and frequency of radiation doses (>200cGy per day), 4) Duration of survival, 5) Age of the patient at time of treatment (in older patients, pre-existing vascular pathology and ChRT may have additive effects), 6) Treatment duration, 7) Re-irradiation, and 8) ChRT (increased incidence and earlier appearance).

RN is a dynamic pathophysiologic process with highly variable clinical course (progressive functional and cognitive impairments that may improve or stabilize, and even asymptomatic course) and several possible radiological outcomes: Lesions may stabilize, regress in size or undergo continued growth with edema, sometimes with lethal progression [1, 4-7, 9, 10].

CONVENTIONAL MR

RN can closely resemble recurrent tumor because of the following shared characteristics: origin at or close to the original tumor site, contrast enhancement, growth over time, edema and exertion of mass effect [1-8, 10, 11, 14-18, 19, 20].

RN commonly occurs at the site of maximum radiation delivery (immediate vicinity of the tumor site and surrounding the surgical cavity of a partially or totally resected tumor), periventricular white matter or within the corpus callosum [1, 4, 6, 10, 13, 15, 19, 20].

Less common patterns include: a) multiple lesions, b) lesions in the contralateral hemisphere or arising remotely from the primary tumor, c) subependymal lesions and d) temporal lobe RN (after RT for head and neck tumors) [1, 4, 6, 7, 10, 20].

On T2WI, RN presents as necrotic masses with ill-defined, blurred margins. Perilesional edema and scattered calcifications are commonly observed. The central necrotic component has increased signal intensity (SI), while the peripheral, solid portion presents low SI [1, 4, 18], and an intense and irregular peripheral rim of enhancement on T1WI with gadolinium [6, 7, 10]. Commonly seen enhancement patterns are described as: a) Soap bubble-like, b) Swiss cheese-like, and c) Cut green pepper [2, 4, 7, 9, 15]. Swiss cheese lesions are larger, more variable in size, and more diffuse than soap bubble lesions [4, 10]. They are the result of diffuse necrosis affecting the white matter and cortex with diffuse enhancement of feathery margins and intermixed necrotic foci (Figure 9 on page 19).
PERFUSION MR

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

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

Normalized rCBV ratios are useful in distinguishing pure RN from pure tumor recurrence. In a study performed by Suhagara et al [18], they concluded that if the ratio of the enhancing lesion is higher than 2.6 or lower than 0.6, tumor recurrence or RN should be strongly suspected (Figure 10 on page 20). Nevertheless, enhancing masses developing after surgery and ChT and/or RT of high-grade tumors 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 little consensus in the literature is found on this regard. Thus, rCBV ratios ranging between 0.6 and 2.6 probably represents a mixture of both tumor and necrosis [18]. In these cases, rCBV only plays a complementary role, and follow-up studies are mandatory.

MRS

Structural brain degradation after RT can be predicted by early changes in metabolic activity before the development of neurocognitive symptoms or anatomic changes seen on conventional MR [7].

Spectral patterns allow reliable differential diagnosis when either pure tumor or pure RN is found. Unfortunately, in many of the enhancing regions, including those appearing early after treatment, often both tumor 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 tumor should be obtained prior to RT/ChT, in order to compare metabolic ratios at follow-up studies [11]. Spectrum of normal tissue should always be obtained to provide an internal standard [4].

The main spectroscopic features employed in the distinction between tumor recurrence and RN are enlisted (Figure 10 on page 20):
• Decreasing or unchanging choline (Cho) levels suggest RN [5, 12, 17]. At initial stages, Cho may be normal, reduced, or elevated (resulting from demyelination, therefore mimicking tumor) [4]. Thereafter, decreasing levels of Cho and creatine (Cr) become evident, reflecting a dilution effect of decreased cell density and edema. At follow-up studies, a decrease in the abnormal Cho/Cr and Cho/N-Acetyl Aspartate (NAA) ratios and decreasing or unchanging Cho levels are typical for RN [4,7].

• Significant elevations of the Cho/NAA and Cho/Cr ratios (with a concomitant reduction in the NAA/Cr ratio) in contrast-enhancing lesions represent tumor recurrence [8,9,11,12,15,17]. In different studies, cutoff values of 1.71-1.8 (ie, values >1.8 being diagnostic for recurrence) for either the Cho/NAA or Cho/Cr ratio, are considered diagnostic for recurrence [5,9,15], as compared with areas of radiation-injury and normal adjacent tissue [4,7, 9,15].

• The presence of lipids (Lip, which reflects necrosis) and lactate (Lac, which indicates ischemia and necrosis) may suggest both RN and recurrence, but large Lip peaks and Cho/Lip-Lac ratios under 0.3 have high positive predictive value for RN [4, 5, 7, 17].

**DWI**

RN may have variable SI (hypointense, hyperintense, heterogeneous) and non-specific appearance on DWI images [4, 13]. Low apparent diffusion coefficient (ADC) values were reported in some studies, which might reflect early necrosis with abundant polymorphonuclear leukocytes and high viscosity that may restrict water diffusion, as in purulent fluid [4, 13]. SI may also be influenced by the presence of hemosiderin (resulting in low SI because of the T2* effect), calcifications, gliosis, or fibrosis caused by radiation when they occur within the recurrent tumor [3,4,13].

Theoretically, ADC ratios in the contrast-enhancing lesion are lower in recurrent tumor 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 only occurred in RN, while ratios lower than this threshold only occurred in recurrent neoplasm [3].

The presence of a perilesional hyperintense halo, reflecting restriction of water diffusion secondary to perivascular inflammatory changes, should be carefully evaluated, as it may indicate progression towards RN. In our experience, a close follow-up should be recommended.

To sum up, Figure 11 on page 20 shows a clinical example in which every sequence has a complementary role to play in the follow-up evaluation of brain tumors.

**RN AND METASTASES**
In brain metastases, sequential changes identified on MR after RT and/or radiosurgery can be summed up as follows: Temporary exacerbation of the lesion, with perilesional edema and central hypointensity on T2WI. The lesion presents central loss of contrast enhancement and rim-like enhancement at 2-6 months. Blurred marginal enhancement can be observed without tumor progression. With time, this marginal enhancement becomes more discrete, while tumor volume and perilesional signal change (representing glial scarring) usually decrease [22]. The presence of meningeal and dural sinus adhesences should raise suspicion for RN, while the development of a rim of periventricular or ependymal enhancement are more likely related to RN than to metastases growth (Figures 12 on page 21, 13 on page 22). As mentioned previously, the presence of a hyperintense rim on DWI may indicate a trend towards RN; and follow-up should be recommended [22] (Figure 14 on page 23).

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, so that pure RN or pure tumor recurrence are more frequently observed. Therefore, a lower degree of overlapping spectral patterns and rCBV values can be found, providing more accurate diagnostic information (Figure 15 on page 24).

Images for this section:
**Fig. 1:** Figure 1. Photomicrograph (original magnification, ×10; hematoxylin-eosin stain) of a pathologic specimen of RN, which shows hyalinized blood vessels, gliosis and interspersed areas of necrosis.
**Fig. 2:** Figure 2: Pseudoprogression in a right frontal anaplastic astrocytoma, treated with surgery and TMZ ChRT in 2007; and a second surgery followed by ChT in Feb 2008 due to tumoral progression. At follow-up contrast-enhanced axial T1WI images, surgical changes in the tumoral bed are 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 punctures and spine MR, and no changes in therapy were made. D, E: Four months later, those enhancement foci were no longer present. These findings suggest pseudoprogression.
Fig. 3: Brain metastases from lung cancer (solid arrows in (A) sagittal T1WI and (B) gadolinium-enhanced sagittal T1WI) in a 61-year-old (yo) woman. The patient underwent whole-brain RT and ChT. Five moths later, follow-up MRI showed all the lesions had diminished in caliber (open arrows in (C) sagittal T1WI and (D) gadolinium-enhanced sagittal T1WI), except for right frontal lesions (* in C and D), which had turned larger secondary to hemorrhage (pseudoprogression).
**Fig. 4:** Figure 4. Right parietal parasagittal glioblastoma multiforme in a 57-yr-old woman. Surgical resection was incomplete, and the patient underwent adjuvant ChRT with TMZ. At follow-up MR after the end of treatment, local persistence of the tumor is depicted (solid arrows in gadolinium-enhanced axial T1WI (A) and (B). A contralateral enhancement focus was also depicted (arrowhead in (A). Ten months later, enlargement of the parietal lesion was observed (open arrows in in gadolinium-enhanced axial T1WI (C) and (D), meanwhile the contralateral enhancement area was no longer present. This finding suggests pseudoprogression.
**Fig. 5:** Figure 5. Leucoencephalopathy. Axial FLAIR images (A) and (B) show the typical imaging features of leucoencephalopathy, presenting 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.
Fig. 6: Figure 6. Disseminated necrotizing leucoencephalopathy. Left temporal anaplastic astrocytoma (grade III) in a 34-yo man, treated with surgery + ChT+ RT in 2004. Note the presence of a focal area of white matter hyperintensity on T2WI secondary to white matter demyelination (*) in A and B) and multiple hemosiderin deposits in the left hemisphere on gradient echo weighted images (arrows in C and D).
**Fig. 7:** Figure 7: Disseminated necrotizing leucoencephalopathy in a right frontal glioblastoma multiforme treated with surgery and TMZ ChRT. A: Axial T2WI shows diffuse white matter injury (*) secondary to RT, and coarse calcification foci (open arrow). B: Axial contrast enhanced T1WI shows three lesions with blurred enhancement (solid arrows). C: ADC map revealed elevated ADC values, as high as $2.29 \times 10^{-3}$ mm$^2$/sec. On DWI, these lesions presented homogeneous low SI (not shown). D: On rCBV map, rCBV values as low as 0.57 were also observed, suggesting post-treatment changes. E and F: Axial contrast enhanced T1WI at follow-up studies 6 and 12 months later respectively revealed how these lesions regressed in size.
Fig. 8: Figure 8. Right frontal glioblastoma multiforme in a 58-yo woman, treated with surgery and ChRT. Gliosis (*) and calcification foci (arrow) in the surgical cavity are depicted on axial T2WI (A). On contrast-enhanced axial T1WI (B), a peripheral, pseudonodular area of enhancement is also observed (arrowhead). Note the presence of peripheral restriction of water diffusion on DWI (C). Although this sign is inespecific, a close follow-up should be recommended because, in our experience, it may be associated with progression towards RN.
**Fig. 9:** Figure 9: Conventional MR features of RN. A, B, C: On axial FLAIR images, RN presents as necrotic masses with ill defined, blurred margins, central high 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).

![Fig. 9 Images](image_url)

**Fig. 10:** Figure 10: RN in a right frontal anaplastic astrocytoma treated with surgery and TMZ ChRT (same patient as in Figure 1). A: Axial FLAIR image shows elevated SI in the frontal white matter (open arrow). B: Contrast-enhanced axial T1WI reveals irregular and pseudonodular enhancement of the surgical margins, particularly on its posterior aspect, and enhancement crossing the midline through the corpus callosum (solid arrows). C: Axial FLAIR image at follow-up study demonstrate markedly increased right parietal and bifrontal edema (*). D: Paired contrast-enhanced axial T1WI shows increased areas of amorphous, irregular enhancement (Swiss-cheese pattern) in frontal white matter. E: Paired ADC map demonstrated elevated ADC values as high as 1.81 x 10^{-3} mm²/sec. F: Paired rCBV map evidenced values under 0.7. G: MRS (single voxel, TE: 35 ms) showed slightly increased Cho levels, decreased NAA levels, and large peaks of Lip/Lac. These findings are typical for RN.

![Fig. 10 Images](image_url)
Fig. 11: Figure 11. Right frontal anaplastic astrocytoma in a 42-yo man, treated with surgery and ChRT. June 2008: (A, B) Enhancing margins of the surgical cavity (arrow) and a small amount of peripheral gliosis (*) are shown. (C) ADC map shows ADC values ranged between 0.76 - 0.86 x 10^-3 mm²/s. (D) rCBV map shows a ratio of 1.23-1.4 between the surgical area and normal contralateral white matter. September 2008. (F, G) 3 months later, the enhancement area presents thicker and more irregular margins. Perilesional edema is also observed. (H) ADC values were still low, ranging between 1.17-1.34 x 10^-3 mm²/s. (I) rCBV ratio was 2.7-3. (E and J) Paired MRS (single voxel, TE: 35 ms) show changes in the spectral pattern of the lesion, with decreasing NAA levels, slightly increased Cho levels and increased peaks of Lip/Lac. These findings, along with increased rCBV and low ADC values, suggest tumor progression.
Fig. 12: Figure 12. Brain metastases from breast cancer in a 45-yo woman treated with WBRT and radiosurgery. A to F: contrast enhanced axial T1 images. (A, B) May 2007. Contrast-enhancing lesions in the right parahippocampal gyrus (arrow) and left frontal lobe (arrowhead) are observed. (C, D) Jan 2008. Absence of enhancement in the frontal lesion (arrowhead), which presents only minimal residual gliosis (not shown). The right parahippocampal lesion (arrow) is smaller, and presents low central SI and peripheral enhancement. (E, F) Feb 2009. No supratentorial enhancement. A peripheral enhancement within the right parahippocampal area is depicted. Note the development of a rim of enhancement surrounding both margins of the temporal horn and ependymal enhancement (open arrows), not previously found. These findings are more likely related to progression to RN than to metastases growth. Finally, the patient underwent surgery of the lesion, and histopathologic analysis confirmed the diagnosis of RN.
Fig. 13: Figure 13. Right occipital lobe metastases from breast cancer in a 50-yo woman. The lesion was treated with WBRT and radiosurgery in August 2007. At follow-up study in Jan 2008, axial FLAIR (A) and coronal T2WI (B) images show bilateral leucoencephalopathy (*) and the occipital lesion, which has rather ill defined, blurred, margins (arrows). Paired axial and coronal contrast-enhanced images C and D reveal irregular peripheral enhancement of the lesion, which is adjacent to the right tentorium and presents partial adherence to the right transverse sinus. These findings should raise suspicion for RN. The lesion was surgically resected in Feb 2008, and RN was histologically confirmed. Eight months later, paired axial and coronal contrast-enhanced images E and F show Swiss-cheese like-enhancement at surgical margins, extending along the right tentorium and right transverse sinus.
**Fig. 14:** Figure 14. Right occipital metastases from lung cancer in a 44- yo man. The patient underwent WBRT. Axial FLAIR image (A) shows vasogenic perilesional edema. Axial contrast-enhanced image (B) shows irregular peripheral enhancement of the lesion. Note the presence of a hyperintense rim on DWI image (C). This finding represents restriction of water diffusion secondary to perivascular inflammatory changes, and might indicate a trend towards RN. Therefore, a close follow-up should be recommended.

**Fig. 15:** Figure 15: RN in a right frontal cystic metastases from cervical cancer. A: Axial FLAIR image show a right frontal mass with well defined margins (*) and mild perilesional vasogenic edema. Several chronic ischemic foci in the deep white matter are also observed. B: Axial contrast enhanced T1WI evidence thin peripheral enhancement of the lesion. The patient underwent WBRT and radiosurgery, followed by surgical resection. Post-surgical axial FLAIR (C) and contrast enhanced T1WI (D) images point surgical changes in the tumoral bed, leucoencephalopathy and irregular peripheral enhancement of the surgical cavity (solid arrows). Four months later, paired axial T2WI (E) and contrast enhanced T1WI (F) images demonstrate how the surgical cavity presents thicker walls with pseudonodular enhancement. G: Perfusion map evidenced low rCBV values ranging between 0.31 and 0.72. H: MRS (single voxel, TE: 35 ms) shows markedly decreased Cho levels, with prominent Lip and Lac peaks. These findings support the diagnosis of RN.
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 tumor should be obtained prior to RT and ChT. Nevertheless, sometimes the diagnosis can be made solely on the basis of histopathologic analysis. In the future, validated prediction models combining multiple metabolic ratios, with or without clinical data, will allow rational patient management, resulting in 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.

Personal Information

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She studied at the Universidad Complutense de Madrid, where she graduated in Medicine in 2004, and completed her residency in radiology at Hospital Universitario Doce de Octubre (Madrid, Spain) in 2009. She is a member of the Sociedad Española de Radiología Médica (SERAM) and the European Society of Radiology (ESR).

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