B. Understanding radiation- and chemotherapy-induced changes after treatment of brain tumours

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Authors: Y. Özsunar; Aydin/TR
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Learning objectives

MRI is the imaging modality of choice for the investigation of after treatment brain changes. Radiotherapy (RT) and chemotherapy (CT) in cancer treatment are standard approach. Radiation necrosis (RN) may occur as late side effects of radiotherapy. The main dilemma is the differential diagnosis of tumor recurrence and necrosis. Because of this, cutting edge MRI are usually applied for reliable diagnosis of the remnant brain lesion. Those include perfusion, diffusion and spectroscopic MRI examination. In this review, we aimed to explain causes, pathophysiology and radiological characteristics' of post radiotherapy and chemotherapy changes after treatment of brain brain tumors.
1. RADIATION (RT) INDUCED CHANGES

RT-related neurological changes are observed in various clinical and radiological findings. These clinical pictures can be classified as, acute side effects during RT, subacute side effects, late side effects after RT (1) (Figure 1). Radionecrosis (RN) is a late complication of RT which mainly affects white matter (2,3) and is a severe radiation-induced complication that is neuropathologically defined as necrosis with severe vascular lesions (stenosis, thrombosis, haemorrhage, fibrinoid vascular necrosis).

The vascular changes play a major role during the management of intracranial lesions with RT. Following RT, vascular endothelial thickening, thrombosis, fibrinoid necrosis of the vascular wall and inflammatory response adjacent to vessels may be observed. Paranchymal changes in the brain are visible with conventional diagnostic tools especially as the ischemia and inflammation of white matter progresses in the meantime (4-6).

IMAGING FINDINGS

A - CONVENTIONAL MR FINDINGS

Focal radionecrosis or paranchymal atrophy - leucoencephalopathy are generally observed in brain parenchyma up to 1/3 of the cases. During the early phase of RT, corpus callosum and subcortical WM is not affected. One of the long term results of RT treatment is disseminated necrotizing leucoencephalopathy (Figure 2-3). However, it usually seen during combination with chemotherapy.

It has been stated that, all radiological findings are detected on RT tract (Figure 4). A simple conventional MRI may be insufficient to differentiate between recurrence and normal tissue changes.

Radionecrosis (RN) may be visible with progressive enlargement with mass effect, which also brings out high suspect for tumor recurrence (6). Given to the findings of Kumar et al (5) The MR imaging features commonly seen in RN are a soap bubble-like and Swiss cheese like. On the other hand, Swiss cheese pattern may also be seen as a result of diffuse necrosis of white matter and the cortical border. Compared to the soap bubble lesions, Swiss cheese lesions are prominent and variable in size. Therefore, Swiss cheese or spreading wavefront pattern are closely related to radiation necrosis (5) (Figure 5). Following RT, central opacification starts to be obvious after 5 to 18 months for benign, and 2 to 3 months for malignant tumors.
B- FUNCTIONAL MR FINDINGS

The most sensitive diagnostic tool to differentiate RN and tumor is perfusion MRI with a proven sensitivity of 80-95% (7). Perfusion of the irradiated tumor is related to angiogenesis and microvascular proliferation. So, radiotherapy regresses the tumor by effecting microvascular density and capillary perfusion. Therefore, rCBV threshold value of 1.3 seems as an indicator of perfusion in differential diagnosis of tumor (8). In addition to rCBV threshold value, the sensitivity of ASL is also high (94%) (Figure 6-7).

Increased tumor cellularity, which can inhibit the effective motion of water molecules, thereby can cause to restricted diffusion. In diffusion MRI (DWI) ADC values are decreased in recurrent tumor. Hein et al (9) showed that ADC value is very low in tumor, while ADC values are higher in RN (Figure 8).

The role of MR spectroscopy (MRS) in distinguishing recurrent tumor from RN has also been extensively discussed in the literature. Spectroscopic scale of the lesion is extremely important to understand the nature of the lesion, given to the increased Choline/Creatine (Cho/Cr) value (i.e. 3) in malignant lesions. In contrast, Cho/Cr ratio below 2 is not diagnostic for recurrent tumor but possibly for RN (10,11) (Figure 9).

2. CHEMOTHERAPY INDUCED CHANGES

Among reversible clinicoradiologic syndromes, posterior reversible encephalopathy syndrome (PRES) is a the most frequent one that causes cortical and subcortical white matter changes after chemotheraphy (12). PRES usually shows hyperintensity on FLAIR images in the parietooccipital and posterior frontal cortical and subcortical white matter. Therefore, imaging findings of PRES are most apparent on the brainstem, basal ganglia and cerebellum (13) (Figure 10).

The reasons of acute toxic leukoencephalopathy (ATL) in heavily medicated patients are chemotherapy, immunosuppressive therapy, and overuse of antimicrobial medications (e.g., metronidazole) Clinical outcome is sometimes better as the effects of drug-induced ATL is potentially reversible.

Methotrexate and 5-flourouracil injures microvasculature of the WM and may also have indirect effects (Figure 11). The agents that are commonly associated with leukoencephalopathy are shown on Table 1. (14-16). The acute changes develop during therapy, such as transient diffuse WM hyperintensity. Long term effects of chemotherapy ranges from asymptomatic white matter hyperintensities to necrotizing
leukoencephalopathy. Patchy involvement of the periventricular white matter and centrum semiovale are diagnostic findings of MR imaging. Symmetrical calcifications are seen around basal ganglia (Figure 12).

The combination intravenous and intrathecal chemotherapy may cause necrotizing leukoencephalopathy and aseptic menengitis (Figure 13).

CONCLUSION

Magnetic resonance imaging (MRI) is a useful noninvasive modality for evaluating post treatment brain tumors. Both conventional and functional MRI methods The signal intensity, morphology, and location of findings on MRI can be used to provide more accurate diagnoses, to guide treatment, and to follow therapy-related changes.
Fig. 1: The clinical syndrome that encounter during and after radiotheraphy over time

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**Fig. 2:** Vasogenic edema and sulcal paucity are observed in FLAIR-MRI during radiotherapy. The findings consistent with acute encephalopathy

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Fig. 3: Signal increase was observed in mesencephalene and white matter in radiated case on DWI (A-B). At 18th month after RT (C-D) enlargement of perimesencephalic cistern due to generalised atrophy.

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Fig. 4: The white matter MRI signal changes are detected on parietooccipital RT tract (arrow) on FLAIR (A) T2W (B) Postcontrast T1W (C) and DWI (D-E) images

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**Fig. 5:** The radiation necrosis cavity is enhanced on noncontrast (A) and contrast (B) T1 W imaging (*). Swiss cheese enhancement (arrow) was observed adjacent to the lesion

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**Fig. 6:** The patient was operated for brain tumor located in occipital lob. The recurrent tumor was highly perfused and located subcutaneously (red arrow). However, the location of the tumor was observed as an empty cavity (yellow arrow).

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**Fig. 7:** A 47-year-old man with a history of attempted resection of grade IV glioma and proton-beam therapy with new abnormal enhancing lesion on follow-up. Positron emission tomographic imaging (A) shows hypermetabolism at the site of the lesion on contrast-enhanced T1 axial imaging (B). Arterial spin-labeled (ASL) (C) and dynamic susceptibility contrast-enhanced cerebral blood volume (DSCE-CBV) (D) images show hyperperfusion that correlates with the axial postcontrast T1-weighted image. Note that the lesion is more conspicuous on ASL than on DSCE-CBV imaging. Subsequent surgical resection confirmed predominantly tumor recurrence.


**Fig. 8:** Breast cancer metastases that shows restricted diffusion in right cerebellum. Restriction decreases after radiotherapy and chemotherapy

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**Fig. 9:** MRS evaluation: Cho/Cr ratio is over 3 in patients with recurrence while this ratio is under 2 in radionecrosis. In addition, lipid lactate peak is evident in radionecrosis.

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Fig. 10: PRES in occipital lobe (T2 and FLAIR images)

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**Fig. 11:** Periventricular white matter changes is shown after chemotherapy in breast cancer case T2 (E), FLAIR (D) and DWI (B-C) signal increase

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Table 1: The agents that causes leukoencephalopathy following overuse.

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Fig. 12: Symmetrical calcification in basal ganglia following chemotherapy

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**Fig. 13:** Figure 10: Aseptic menengitis is shown in T1 W CE images after intrathecal chemotherapy (Metotrexate and Cytarabine) and radiotherapy

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Yelda Özsunar Prof. Dr. Department of Radiology, Adnan Menderes University School of Medicine, Aydin, Turkey; yeldaozsunar@gmail.com

Özüm Tunçyürek Assist Prof, EDIR Department of Radiology, Adnan Menderes University School of Medicine, Aydin, Turkey; ozum.tuncyurek@gmail.com

Ersen Ertekin Assist Prof, Department of Radiology, Adnan Menderes University School of Medicine, Aydin, Turkey; drersen@hotmail.com
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