Cerebral radionecrosis: imaging features, differential diagnosis and developmental characteristics. Experience in our center, pictorial essay and literature review.

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**Learning objectives**

**Radiotherapy (RT)** is a non-surgical treatment that uses radiation to eradicate tumors and to restrict its growth, causing damage to cell’s DNA. Its target is the surgical bed plus a margin around the mass.

Different types of radiation can be used: X rays, gamma rays and ionizing particles.

RT can kill cells or block their proliferation. This action, however, takes place both on tumor cells than on normal. Healthy cells, however, unlike tumor cells, have good mechanisms for repairing damage.

Generally, brain cells are very resistant to irradiation.

**Aim of this work is to evaluate imaging features and developmental characteristic of cerebral radionecrosis as a consequence in treatment of brain and neck neoplasm.**
Background

Radiation treatment (RT) is responsible for cellular damage that affects not only cancer cells but also healthy brain and endothelial cells causing toxic effects on enzyme systems. These effects continue in target organ for many months to reach the maximal effect after at least 3-6 months and in some cases years.

The main factors that increase the risk of neurological toxicity due to radiotherapy are 1) age <65 years, 2) increased volume of treatment or WBRT, 3) total dose > 60 Gy, single fractions > 2.5 Gy, 4) high-LET radiation (e.g. neutrons) or brachytherapy, 5) brain disorders, concomitant vascular or metabolic disease (diabetes, hypertension, dementia, initial collagen), 6) use of chemotherapy (especially pre-exposure to methotrexate).

The CNS effects of RT are known and divided into:

1. **Acute** complications occurring during treatment or shortly after the end, usually transient and reversible, caused by edema and BEE alterations.

   Usually symptoms arise from a mild intracranial hypertension that responds to steroids treatment.

2. **Sub-acute** complications that appear from 3-6 weeks to 3 months, sometimes reversible, but, unfortunately, often permanent, characterized by endothelium toxic effect resulting in increased capillary permeability and thus onset of edema, moreover by oligodendrocytes damage and subsequent demyelination. **Wallerian degeneration** is frequent and extends from site treated in depth, with retrograde progression, affecting axons and their myelin sheaths.

   Clinical is variable: patients may be asymptomatic or present a worsening of neurological symptoms (intracranial hypertension, dysphagia, dysarthria). Sometimes steroid are administered to control symptoms.

3. **Late complications** are evident from 3 months up to 10 years (70% in 2 years), are progressive and irreversible, characterized by endothelial damage that can lead to a series of pathological situations: lacunar ischemia, great vessels occlusion, vascular malformations (cavernous angioma, telangectasia), visual pathways necrosis, leukoencephalopathy, focal necrosis. Generally they are quite common where RT is administered with medium-high doses each fraction, with large irradiation fields and when radiosensitizers medications are administered simultaneously.

   **Symptoms** are characterized by difficulty in walking, mnesic deficits, behavior problems, disorientation, coma.
Although these sequelae in relationship at the time of onset are schematically divided into acute, subacute and late, it's reasonable to assume that they are the result of a dynamic process that, as the case (patient's condition, immune status, integrity vascular tissue, methods of RT used), can turn off out and determine only a scar or can progress until tissue necrosis.

Histopathological radio-induced changes are divided into:

1. **Early** that occur at molecular level and lead to early induction of genes, apoptosis, inhibition of neurogenesis, hypoxia, white matter necrosis and BEE destruction.

2. **Late**, influenced by many variables (dose, fractionation type, individual response, etc. ...) that lead to endothelial injury, hyalinization, fibrinoid necrosis, thrombosis and thus focal necrosis, diffuse white matter alterations, atrophy, mineralizing microangiopathy, telangiectasia, optic neuritis, large vessels wall damage.

Late alterations may also lead to DNA damage, repair mechanisms damage, change in oncogenes expression and then induction of delayed cancer.

**Focal necrosis of the CNS is one of the biggest problems that occurs after RT treatment.** Incidence is variable (5-24%) in relation to various risk factors such as total dose of radiation, radiation field, number and frequency of doses, age at the time of treatment. It may occur as a result of treatment of intracranial tumors, extra-cerebral lesions (meningiomas) and extracranial (eg, nasopharynx, paranasal sinuses, pituitary tumors).

*It can develop months or years after end of RT in relation to not yet clear damage mechanism.* There are several theories proposed: direct injury to irradiated brain tissue, vessels damage, auto-immunization, free radical cellular damage.

*Clinically, symptoms are those of a worsening and expansive lesion. Treatment is represented by steroid therapy or surgical resection.*
Findings and procedure details

In post-RT, diagnostic options available are represented by CT, which is currently underused in follow-up, and especially by morphological and functional MRI, (diffusion, tractography, perfusion, spectroscopy, cortical activation).

PET in this field has however lost much of its weight with advent of new advanced MRI techniques.

These investigations shall be performed within 24-36 h after surgery to get early information useful in following assessment of the patient.

After first control, regular checks are necessary in relation to clinical conditions, to histological examination in order to evaluate the presence of residual tumor or recurrence, but also the typical changes of RT associated with CT.

In acute complications MRI can be negative or may show small T2 and FLAIR hyperintense alterations at cerebral white matter of both emispheres.

In subacute complications MRI shows regions of edema in white matter of both emispheres, basal ganglia and cerebral peduncles in the form of areas of T2 and FLAIR hyperintensity.

In late complications MRI shows extensive confluent T2 and FLAIR hyperintense area in peri-ventricular white matter of both hemispheres and cerebral atrophy.

Criteria for validating RT-induced tumor connexion are represented by irradiated area, histological type different from the pre-existing, elapsed time after treatment, increased incidence of induced tumor type compared to general population.

In cerebral radionecrosis, conventional MRI and CT findings are not specific.

The most common pattern consists of a expansive formation with edema and mass effect, often bleeding, usually with "rim" enhancement. Sometimes CE can be nodular, linear or curvilinear.

Differential diagnosis with tumor recurrence is much important because location is adjacent to lesion treated, there is CE (sometimes simulating secondary lesions), often increasing in size over time, with edema and consequent mass effect increase. Sometimes can be observed multiple lesions, or in the opposite hemisphere or
subependymal and therefore can mimic metastatic lesions, multifocal glioma or multiple sclerosis.

In literature, can be found cases with "swiss cheese" aspect, characterized by extensive white matter marginal CE, involving subcortical "U" fibers with multiple minute necrosis foci inside. This is caused by diffuse necrosis that involves white matter and cortex.

Pathological radio-induced CE is related to moderate intensity vasogenic edema with possible subsequent necrosis. It usually affects periventricular white matter at variable distances from primary tumor with less frequent involvement of cortex. CE can be nodular, linear or curved, single or multiple. Size may remain stable or progress. An increase in size with edema and mass effect associated can suspect progression in radionecrosis.

Radio-necrosis of cranial nerves is more rare and characterized by perineural CE and subsequent atrophy.

At present, conventional diagnostic methods available for the differentiation between recurrence and radiation necrosis are not always clarifying problem even if spatial and temporal patterns can help in solving doubts and suggest radio-necrosis hypothesis in the presence of:

- lesion without CE before surgical treatment that subsequently developed CE inside or at the edges

- CE lesion that develops after primary glioma

- CE lesion that develops in the periventricular white matter, involving corpus callosum

- Lesions with CE "swiss cheese." aspect.

**Spectroscopy** can detect a characteristic metabolic pattern peak of Lac/Lip in absence of other metabolic signal with persistence for several months contrary to what happens in case of recurrence characterized by Cho increase. Cho/NAA and Cho/Cr ratio are discriminant for differential diagnosis, they are in fact significantly higher in recurrence than in RT injur. NAA/Cr ratio has instead an opposite trend.

**ADC** is significantly higher in radio-necrosis respect to recurrence (for the high cellularity) even if there can be some overlap as a result of various factors such as cellularity, viscosity, permeability.

Diffusion tensor imaging (DTI) provides more accurate data, showing lower ADC ratio and and higher FA in recurrence in contrast to RT necrosis.
CBV, being correlated with angiogenesis, is significantly higher in recurrence respect to radio-necrosis, although there is some overlap of findings in relation to non-high spatial resolution, to tissue heterogeneity and to frequent coexistence of vascularized recurrence and radio-necrosis with ierplastic and enlarged vessels.

Presence of petechial haemorrhages in recurrence can cause susceptibility artefacts and reduced CBV. An inaccurate estimation of CBV may also be due to severe damage or absence of BEE.

ON THE SIDE BAR IMAGES OF PATIENT WITH CEREBRAL RADIONECROSIS OCCURRED TWO YEARS AFTER RT IN TREATMENT OF NASO-PHARYNX CANCER
**Fig. 1:** CT axial in emergency.

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Fig. 2: MR flair axial.

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Fig. 3: MR T2 coronal.

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Fig. 4: MR CE T1 coronal.

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Fig. 5: MR CE T1 axial.

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Fig. 6: Control after stheroid therapy.

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Conclusion

Radio-necrosis is one of the most frequent damage from RT. It increases in long-term survivors.

Symptoms are quite similar to those of an expansive lesion.

Predominantly affects the white matter and is characterized by a necrotic center, surrounded by a margin of inflammatory infiltration and glial proliferation. Calcifications, hemorrhagic areas and residual neoplastic tissue can coexist.

Treatment is based on corticosteroids or possibly surgery.
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