Radiation necrosis differential diagnosis

Radiation necrosis (RN) may mimic tumor progression both clinically and radiographically. Differences in prognosis and treatment make it important to distinguish between tumor and RN.

Over the years many methods have been championed to differentiate radiation necrosis from recurrent high-grade glioma. None have proven adequately reliable, and this may not even be a useful exercise. Tumor cells are frequently found on biopsy. The decision whether to reoperate is usually based on whether there is a progressive mass effect (regardless of whether it is necrosis or tumor), taking into consideration the patient's neurologic condition, projected longevity, patient desires.

It is widely accepted that the capture, enumeration, and identification of circulating tumor cells (CTCs) hold significant promise for early cancer screening, diagnosis, and prognosis. These cells originate from primary tumors and disseminate to distant sites via the blood [1) 2) 3)]

Differentiating treatment necrosis from tumor recurrence poses a diagnostic conundrum for many clinicians in neuro-oncology. To investigate the potential role of circulating tumor cells (CTCs) detection in differentiating tumor recurrence and treatment necrosis in brain gliomas, Gao et al. retrospectively analyzed the data of 22 consecutive patients with tumor totally removed and new enhancing mass lesion(s) showed on MRI after initial radiotherapy. The 22 patients were finally classified into tumor recurrence group (n = 10) and treatment necrosis group (n = 12), according to evidence from the clinical course (n = 11) and histological confirmation (n = 11). All 22 patients received CTCs detection, and DSC-MRP and 11C-MET-PET were performed on 20 patients (90.9%) and 17 patients (77.3%) respectively. The data of the diagnosis efficacy to differentiate the two lesions by CTC detection, MPR and PET were analyzed by ROC analysis. The mean CTCs counts were significantly higher in the tumor recurrence group (6.10 ± 3.28) compared to the treatment necrosis group (1.08 ± 2.54, $p < 0.001$). The ROC curve showed that an optimized cell count threshold of 2 had 100% sensitivity and 91.2% specificity with AUC = 0.933 to declare tumor recurrence. The diagnostic efficacy of CTC detection was superior to rCBV of DSC-MRP and rSUVmax in MET-PET. Furthermore, they observed that CTCs detection could have a potential role in predicting tumor recurrence in one patient. The research results preliminarily showed the potential value of CTC detection in differentiating treatment necrosis from tumor recurrence in brain gliomas, and is worthy of further confirmation with large samples involved [4)].

CT and MRI

Cannot reliably differentiate some cases of RN from tumor (especially astrocytoma; RN occasionally resembles glioblastoma).

Proton magnetic resonance spectroscopic imaging

Proton magnetic resonance spectroscopic imaging was reliable in distinguishing pure tumor (elevated choline) from pure RN (low choline), but was less definitive with mixed tumor/necrosis [5].

Magnetic resonance perfusion imaging

Magnetic resonance perfusion imaging, particularly Dynamic Contrast-Enhanced (DCE), help in the differential diagnosis by tumor recurrence and radiation necrosis during the follow-up after radiosurgery.

DWI

Mean ADCs were lower with recurrence (1.18 ± 0.13 X 10–3 mm/s) vs. necrosis (1.4 ± 0.17 X 10–3 mm/s) [6] (not all cases biopsy proven).

Nuclear brain scan

Some reports of success with thallium 201 and technetium-99 m brain scans.

Computerized radionuclide studies

PET (positron emission tomography) scan: because positron emitting isotopes have short half–lives, PET scanning requires a nearby cyclotron to generate the radiopharmaceuticals at great expense. Utilizing [18F]-fluorodeoxyglucose (FDG), regional glucose metabolism is imaged and is generally increased with recurrent tumor, and is decreased with RN. Specificity for distinguishing RN from tumor recurrence is >90 %, but sensitivity may be too low to make it reliable [7] Amino acid tracers such as [11C]methionine and [18F]tyrosine are taken up by most brain tumors [8], especially gliomas, and may also be used to help differentiate tumor from necrosis. Accuracy may be increased by fusing PET scan with MRI [9].

SPECT

SPECT (single positron emission computed tomography): “poor man’s PET scan.” Uses radio- labeled amphetamine. Uptake depends on presence of intact neurons and the condition of cerebral blood vessels (including blood brain barrier). Decreased radionuclide uptake indicates necrosis, whereas tumor recurrence has no decreased uptake.

For delayed radiation injury, image analysis has considerably advanced, but neuropathological findings are still required to establish diagnosis. A patient who had received radiation therapy for pineal germinoma at age 14 developed neurological and psychiatric abnormalities after 15 years as a late delayed radiation injury. Autopsy at age 59 revealed diffuse changes in the white matter consisting in order of severity of myelin pallor, demyelination, and necrosis which were characterized by a lack of glial reaction. The cerebral cortex was relatively well preserved. As delayed radiation injuries, hyalinous changes in the vascular wall, angiomatous lesions and, fresh and old petechial hemorrhages were found. Moreover, vascular changes associated with arteriosclerosis were also present. Furthermore, a focal glial nodule was detected which was considered to be a new radiation-induced neoplasia. These findings suggest that late delayed radiation injury may slowly develop over 30 years and may involve damage to neuroglial stem cell compensation. It is also evident that arteriosclerotic changes and newly induced neoplasia may develop in delayed radiation injury cases [10)].

A purely radiological diagnosis of recurrence or progression can be hampered by flaws induced by pseudoprogression, pseudoresponse, or radionecrosis.

Radiation necrosis (RN), or its imaging equivalent, treatment-related imaging changes (TRIC), is an inflammatory reaction to high-dose radiation in the brain.

Patients who receive immunotherapy (IT) alone may have an increased rate of RN/treatment-related imaging changes (TRIC) compared with those who receive chemotherapy (CT) or targeted therapy (TT) alone after stereotactic radiosurgery, whereas receiving any CT may in fact be protective against RN/TRIC. As the use of immunotherapies increases, the rate of RN/TRIC may be expected to increase compared with rates in the chemotherapy era [11)].

References

1)
Pantel K., Brakenhoff R.H. Dissecting the metastatic cascade. Nat. Rev. Cancer. 2004;4:448. doi: 10.1038/nrc1370.
2)
Pantel K., Speicher M.R. The biology of circulating tumor cells. Oncogene. 2016;35:1216–1224. doi: 10.1038/onc.2015.192.
3)
Woo D., Yu M. Circulating tumor cells as “liquid biopsies” to understand cancer metastases. Transl. Res. 2018;201:128–135. doi: 10.1016/j.trsl.2018.07.003
4)
Gao F, Zhao W, Li M, Ren X, Jiang H, Cui Y, Lin S. Role of circulating tumor cell detection in differentiating tumor recurrence from treatment necrosis of brain gliomas. Biosci Trends. 2021 Apr 29. doi: 10.5582/bst.2021.01017. Epub ahead of print. PMID: 33952802.
5)
Rock JP, Hearshen D, Scarpace L, Croteau D, Gutier- rez J, Fisher JL, Rosenblum ML, Mikkelsen T. Correla- tions between magnetic resonance spectroscopy and image-guided histopathology, with special attention to radiation necrosis. Neurosurgery. 2002; 51:912–9; discussion 919-20
6)
Hein PA, Eskey CJ, Dunn JF, Hug EB. Di usion- weighted imaging in the follow-up of treated high- grade

gliomas: tumor recurrence versus radiation injury. AJNR Am J Neuroradiol. 2004; 25:201–209
7)

Thompson TP, Lunsford LD, Kondziolka D. Distinguishing recurrent tumor and radiation necrosis with positron emission tomography versus stereotactic biopsy. Stereotact Funct Neurosurg. 1999; 73:9–14
8)

Ericson K, Lilja A, Bergstrom M, et al. Positron emis- sion tomography with ([11C]methyl)-L-methionine, [11C]D-glucose, and [68Ga]EDTA in supratentorial tumors. J Comput Assist Tomogr. 1985; 9:683–689
9)

Thiel A, Pietrzyk U, Sturm V, et al. Enhanced Accuracy in Differential Diagnosis of Radiation Necrosis by Positron Emission Tomography-Magnetic Resonance Imaging Coregistration: Technical Case Report. Neurosurgery. 2000; 46:232–234
10)

Tanikawa S, Kato Y, Tanino M, Terasaka S, Kurokawa Y, Arai N, Nagashima K, Tanaka S. Autopsy report of a late delayed radiation injury after a period of 45 years. Neuropathology. 2019 Jan 4. doi: 10.1111/neup.12528. [Epub ahead of print] PubMed PMID: 30609132.
11)

Colaco RJ, Martin P, Kluger HM, Yu JB, Chiang VL. Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? J Neurosurg. 2015 Nov 6:1-7. [Epub ahead of print] PubMed PMID: 26544782.