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REVIEW

Radiation necrosis or tumor progression? A review of the radiographic modalities used in the diagnosis of cerebral radiation necrosis

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Abstract

Purpose Cerebral radiation necrosis is a complication of radiation therapy that can be seen months to years following radiation treatment. Differentiating radiation necrosis from tumor progression on standard magnetic resonance imaging (MRI) is often difficult and advanced imaging techniques may be needed to make an accurate diagnosis. The purpose of this article is to review the imaging modalities used in differentiating radiation necrosis from tumor progression following radiation therapy for brain metastases.

Methods We performed a review of the literature addressing the radiographic modalities used in the diagnosis of radiation necrosis.

Results Differentiating radiation necrosis from tumor progression remains a diagnostic challenge and advanced imaging modalities are often required to make a definitive diagnosis. If diagnostic uncertainty remains following conventional imaging, a multi-modality diagnostic approach with perfusion MRI, magnetic resonance spectroscopy (MRS), positron emission tomography (PET), single photon emission spectroscopy (SPECT), and radiomics may be used to improve diagnosis.

Conclusion Several imaging modalities exist to aid in the diagnosis of radiation necrosis. Future studies developing advanced imaging techniques are needed.

Keywords Brain metastases · Radiation necrosis · Tumor progression · Stereotactic radiosurgery · Radiation therapy · Neuroimaging

Introduction

Cerebral radiation necrosis is a late complication of brain radiation, and following treatment with SRS, an incidence of approximately 25% has been reported [1]. Radiation necrosis (RN) may be seen months to years following conventionally fractionated radiation or stereotactic radiosurgery (SRS) and is often indistinguishable from tumor progression (TP) on conventional imaging. Manifestations of both diagnoses range from asymptomatic newly discovered intracranial enhancement on surveillance magnetic resonance imaging (MRI) to significant neurologic dysfunction, creating a diagnostic dilemma. Symptoms are dependent on location, but generalized symptoms of increased intracranial pressure including headache, nausea, somnolence, and seizures may be seen [2, 3]. When differentiating radiation necrosis from tumor progression, risk factors associated with radiation necrosis should be considered, although no definitive algorithm exists for confirmation of diagnosis. Factors

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commonly associated with increased risk of radiation necrosis include treatment volume, dose-fractionation schedule, prior brain radiotherapy, radiosensitizing chemotherapy, tumor location, and histology [4–9]. As the literature continues to evolve, there is also mounting evidence supporting an increased risk of RN following SRS in combination with immunotherapy [10, 11].

The gold standard for diagnosis of radiation necrosis is pathologic tissue assessment; however, this is infrequently performed given the potential complications of obtaining tissue. Because of this, advanced imaging techniques such as perfusion weighted MRI, magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) are becoming more frequently used in the diagnostic workup of RN (Table 1). Minimally invasive techniques such as laser-induced thermal therapy (LITT) may also be used following biopsy, which helps with diagnosis. As targeted systemic therapies and immunotherapy continue to evolve, patients with cancer are living longer, and the incidence of radiation necrosis is likely to increase. This highlights the need for understanding and improving diagnostic tools. We sought to provide a review of the radiologic modalities used to diagnose cerebral radiation necrosis, with a focus on brain metastasis evaluation.

Radiologic imaging studies

Magnetic resonance imaging (MRI)

MRI is the standard neuroimaging test used to monitor metastatic brain tumors following radiation therapy. Conventional MRI is widely available and provides excellent spatial and anatomical detail. Multiple sequences are performed as part of the standard MRI protocol, with the most frequently utilized sequences on surveillance imaging including T1-weighted without and with contrast and T2/FLAIR (fluid-attenuated inversion recovery). Contrast enhancement on T1 signifies disruption of the blood brain barrier while increased T2/FLAIR signal represents vasogenic edema. These findings are frequently seen in RN, but are unfortunately non-specific and may also be found in TP. Colloquial descriptions of RN on MRI include "soap bubble," "cut green pepper," or "swiss cheese," though the positive predictive value of these appearances is poor [12–14].

Through the use of conventional MRI sequences, several methods have been proposed to aid in diagnosing RN. For example, the lesion quotient (LQ), which is the ratio of the hypointense tumor nodule on T2-weighted imaging divided by total contrast enhancement on T1-weighted imaging, initially was found to be a promising tool for differentiating RN with TP on conventional MRI [14]. LQ < 0.3 demonstrated 80% sensitivity and 96% specificity for diagnosing RN, whereas LQ > 0.6 showed 100% sensitivity and 32% specificity for recurrent tumor. However, this study was repeated and results were not validated [15].

Another method, T1/T2 matching, compares the overlap of contrast enhanced volume on T1-weighted imaging with low signal lesion borders on T2-weighted imaging. Lack of a defined T2-weighted margin compared to the T1 contrast margin was defined as a T1/T2 mismatch. In 68 patients that underwent resection of their metastatic lesion at a median of 7 months following SRS, the authors found that T1/T2 mismatch was associated with RN with a sensitivity of 83% and specificity of 91% [16]. Wagner et al. evaluated time dependent changes in lesion morphology on conventional MRI 2, 15, and 55 min after contrast administration in 31 patients treated with SRS for brain metastases. All instances of radiation necrosis showed a non-enhancing interior area on subtraction imaging for the 15 min minus 55 min scan, whereas all progressive tumors had enhancing components [17]. Though the above methods propose tools to distinguish RN from TP on conventional MRI, practical clinical utility is limited and they are rarely used in practice.

If uncertainty remains after review of T1- and T2-weighted imaging, diffusion weighted imaging (DWI)

Table 1 Summary of radiographic imaging findings used to differentiate radiation necrosis from tumor progression

Radiographic modality	Radiation necrosis	Tumor progression
Magnetic Resonance Imaging (MRI)	↑ contrast enhancement on T1 LQ < 0.3 T1/T2 mismatch present ↑ ADC	↑ contrast enhancement on T1 LQ > 0.6 T1/T2 mismatch absent ↓ ADC
Perfusion MRI	↓ rCBV	↑ rCBV
Magnetic Resonance Spectroscopy	↑ lipid/choline ratio ↑ lactate/creatine ratio ↓ choline/creatine ratio	↓ lipid/choline ratio ↓ NAA/choline ratio
Positron Emission Tomography	↓ radiotracer uptake ↓ tumor/background SUV uptake	↑ radiotracer uptake ↑ tumor/ background SUV uptake

LQ Lesion Quotient, *ADC* Apparent Diffusion Coefficient, *rCBV* Relative Cerebral Blood Volume, *SUV* Standardized Uptake Value

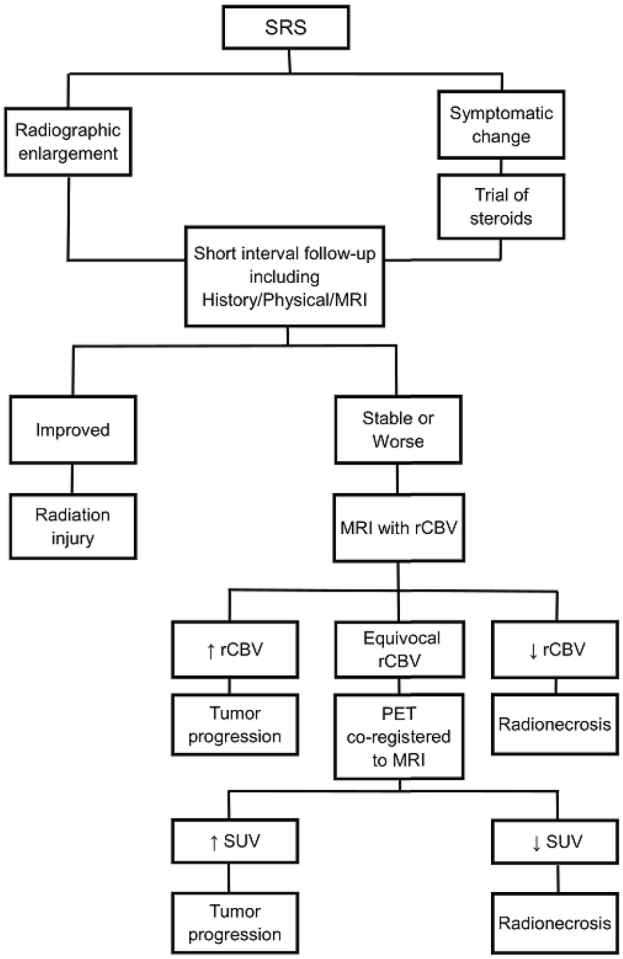

Fig. 1 Modified diagnostic algorithm for differentiating radiation necrosis from tumor progression following stereotactic radiosurgery for brain metastases [59]. *SRS* Stereotactic Radiosurgery, *MRI* Magnetic Resonance Imaging, *rCBV* Relative Cerebral Blood Volume, *PET* Positron Emission Tomography, *SUV* Standardized Uptake Value

with apparent diffusion coefficient (ADC) may be used. This is a commonly available MRI sequence that measures the random motion of water molecules in tissue. Highly cellular tissues, such as recurrent tumor, exhibit a lower ADC due to relatively restricted motion of water molecules whereas radiation necrosis has an elevated ADC ratio. For example, in a small study of 16 patients that underwent brain metastasis resection following radiation, utilizing a three-layer pattern of ADC improved specificity and sensitivity compared to relative cerebral blood volume alone [18].

If diagnostic doubt remains after review of conventional MRI sequences, advanced radiographic techniques must be used to establish an accurate diagnosis. Figure 1 demonstrates the diagnostic algorithm used at our institution. The remainder of this article summarizes these different techniques.

Perfusion magnetic resonance imaging with relative cerebral blood volume (rCBV)

Relative cerebral blood volume (rCBV) is derived from susceptibility weighted imaging and provides information regarding tumor angiogenesis by assessing blood volume, blood flow, and permeability (Fig. 2). At our institution, rCBV is often the first study used if conventional imaging does not provide a clear diagnosis. Recurrent tumor possesses increased neovascularization compared to RN, and as such, perfusion with rCBV is often elevated in the setting of recurrent disease, though data regarding appropriate cutoff values are inconsistent. For example, in a cohort of 27 patients that underwent radiosurgery for brain metastases, the rCBV in patients with recurrence ranged from 2.1 to 10 whereas rCBV in RN ranged from 0.39 to 2.57. The optimal rCBV cutoff was determined to be 2.1 providing a sensitivity of 100% and a specificity of 95% [19]. Hu et al. reported a lower rCBV cutoff of < 0.71 with a sensitivity

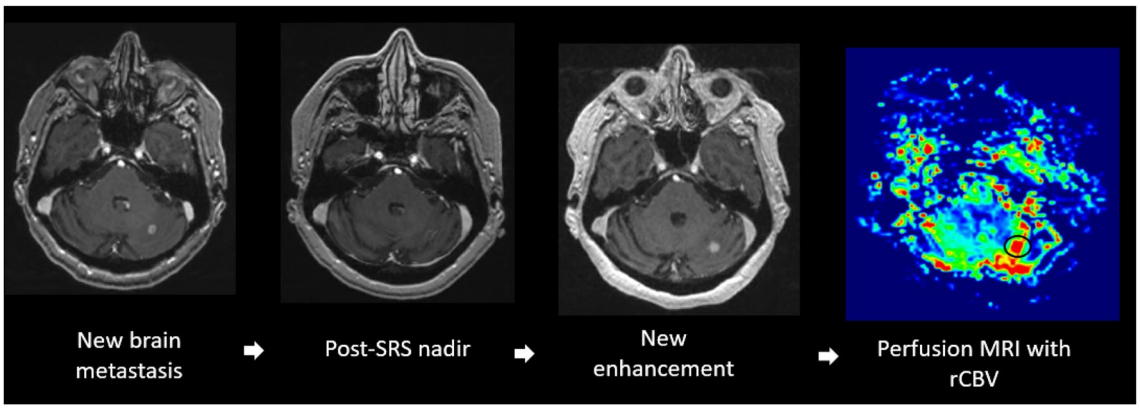

Fig. 2 Perfusion MRI images demonstrating increased rCBV (black circle) in an area of indeterminate tumor progression versus radiation necrosis following stereotactic radiosurgery for a left cerebellar brain metastasis. *MRI* Magnetic Resonance Imaging, *rCBV* Relative Cerebral Blood Volume, *SRS* Stereotactic Radiosurgery

of 92% and specificity of 100% for RN [20]. There are several other techniques that use the information gathered from perfusion MRI to help with this differential. Given the fact that there can be overlap between rCBV in patients with RN and TP some recommend the use of percentage of signal intensity recovery (PSR) [21]. PSR is calculated following the administration of contrast bolus and is determined by comparing the lowest signal with the end post-contrast intensity signal. Reduced PSR values reflect tumor recurrence. The addition of intravoxel incoherent motion (IVIM), which is a technique based on DWI that provides diffusion and perfusion measurements, has been shown to improve the diagnostic accuracy in comparison to rCBV [22]. Lastly, the volume transfer coefficient is a pharmacokinetic property of DCE and measures vascular permeability and is elevated in the setting of RN [23].

Magnetic resonance spectroscopy (MRS)

MRS is an imaging modality that utilizes the metabolic composition and concentration of various metabolites within a specific area of tissue. Multiple studies have investigated this modality and proposed different metabolic ratios. For example, Chen et al. found that a lipid/choline ratio > 3 was consistent with RN while recurrence was defined as a neuronal marker (NAA)/choline ratio < 1 and lipid/choline ratio < 3 [24]. Kamada et al. showed an increased lactate/creatine ratio and decreased choline/creatine ratio correlated with RN [25]. In a small study of 25 patients treated with SRS or whole brain radiation therapy (WBRT), Travers et al. evaluated their institutional experience using MRS and PET-CT in distinguishing RN from TP and found MRS to perform better than ^{18}*F-FDG* in distinguishing recurrent tumor from radiation necrosis with an accuracy of 82% [26]. Limitations of MRS include lesion size and location, as small tumors or those near CSF may sample chemical signal outside of the tumor region.

Single photon emission tomography (SPECT)

The use of SPECT nuclear medicine imaging is not common practice at our institution. Thallium-201 and technetium-99 are common radioisotopes used and the use of these results in the emission and detection of γ photons. Using an index score of < 3.0 for RN and > 5.0 for TP based on thallium-201 SPECT, Serizawa et al. demonstrated a sensitivity of 90% and specificity of 91% for detection of RN following SRS [27]. However, another study investigating thallium-201 SPECT reported only a sensitivity and specificity of 50% and 63%, respectively [28]. A systematic review investigating different imaging techniques in the diagnosis of RN included two studies evaluating thallium-201 SPECT for brain metastases and found a pooled sensitivity of 85% and specificity of 80% [29].

Positron emission tomography (PET)

Positron emission tomography is a molecular imaging technique that takes advantage of the cellular and metabolic features of metastases. Fluorodeoxyglucose (^{18}*F-FDG*) PET in combination with computed tomography (CT) or MRI has been investigated on the rationale that proliferating tumor cells uptake increased radiotracer due to increased rates of glycolysis while RN does not. However, PET radiotracers have limitations as normal brain parenchyma and inflammation from RN may result in increased uptake. Because of this, PET imaging is typically performed more than 3 months following radiation therapy to allow for resolution of inflammation. In contrast to ^{18}*F-FDG,* amino acid radiotracers may be utilized based on more selective mechanisms of amino acid uptake in tumor cells, allowing for a better tumor to background ratio. In a report by the Response Assessment in Neuro-Oncology (RANO) working group, the use of amino acid PET imaging is recommended as level 2 evidence for the evaluation and diagnosis of brain metastases following radiation therapy [30].

Fluorodeoxyglucose (^{18}F-FDG) PET

^{18}*F-FDG* is a glucose analog commonly used in the staging and surveillance of several cancer histologies (Fig. 3). ^{18}*F-FDG* uptake is useful because cancer cells are highly proliferative tissues with increased expression of glucose transporters, leading to increased ^{18}*F-FDG* uptake compared to non-cancerous cells. ^{18}*F-FDG* is radiolabeled with fluorine-18, which has a 110 min half-life and thus does not require an on-site cyclotron for its production, making it a widely available radiotracer.

The clinical utility of ^{18}*F-FDG* PET is difficult to interpret, as published studies utilize different imaging methodologies and thresholds for differentiation. Our institution was one of the first to investigate ^{18}*F-FDG* PET, where we found a sensitivity of 86% and specificity of 80% in 32 patients following SRS [31]. However, multiple publications later investigated this modality and found a wide range of outcomes, with sensitivities ranging from 36–95% and specificities ranging from 50–100% [26, 28, 32–36]. The use of dual phase ^{18}*F-FDG* PET showed promising results in a cohort of 25 patients with a sensitivity of 95% and specificity of 100%; however, implementation of this is limited due to a 3.8 h median time between early and late scans [35]. A meta-analysis by Li et al. identified 15 studies that investigated PET for differentiating RN from TP, of which 6 used ^{18}*F-FDG;* the pooled sensitivity and specificity was 85% and 90%, respectively, demonstrating

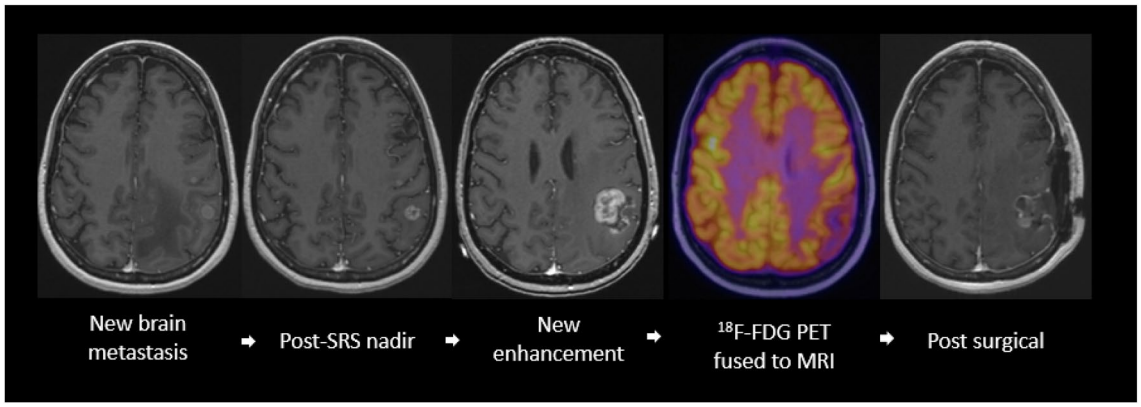

Fig. 3 MRI images showing progressive contrast enhancement following stereotactic radiosurgery. *^{18}F-FDG* PET demonstrated decreased uptake, consistent with radiation necrosis. Surgical pathology confirmed radiation necrosis. *MRI* Magnetic Resonance Imaging, *PET* Positron Emission Tomography, *^{18}F-FDG* Fluorodeoxyglucose, *SRS* Stereotactic Radiosurgery

this can be a useful tool if there is diagnostic uncertainty on MRI [37]. Due to the potential limitations with *^{18}F-FDG*, including a high background physiologic uptake by normal brain parenchyma resulting in a low tumor to background ratio, amino acid radiotracers have been investigated and compared to *^{18}F-FDG*. These are discussed below.

[^{11}C]-methyl-L-methionine (^{11}C-MET) PET

^{11}C-MET is one of the most commonly studied amino acid radiotracers for brain metastasis evaluation and utilizes the essential amino acid methionine labeled with carbon-11. Relative to fluorine-18 labeled radiotracers, which take advantage of a 110 min half-life, carbon-11 has a relatively short half-life of 20 min. This results in the necessity of an on-site cyclotron for its development which limits its widespread adaptation. Multiple studies have evaluated the utility of *^{11}C-MET* PET, with sensitivity and specificity values ranging from 78 to 90% and 75 to 100%, respectively [38–41]. Similar to the discussion above for *^{18}F-FDG,* different indices of evaluation are proposed to distinguish RN from TP. For example, Terakawa et al. found the most useful index for differentiation was the ratio of the mean standardized uptake value (SUV_{mean}) of the lesion to the contralateral normal frontal lobe gray matter uptake (L/N_{mean}) [38]. With an L/N_{mean} of 1.41, sensitivity and specificity for metastatic tumor were 79% and 75%, respectively. Yomo et al. found at a maximal lesion SUV to maximal normal tissue SUV ratio cutoff of 1.4, sensitivity and specificity were 82% and 75%, respectively [42]. A meta-analysis including 7 studies showed an overall sensitivity of 70% and specificity of 93% [43].

L-3,4-dihydroxy-6-[^{18}F]-fluorophenylalanine (^{18}F-DOPA) PET

^{18}F-DOPA, an amino acid radiotracer that was initially developed to investigate dopamine synthesis in the basal ganglia for movement disorders, is also used in the management of brain tumors. In a prospective investigation of 106 patients with glioblastoma or brain metastases using MRI and *^{18}F-DOPA* PET for clinical suspicion of relapse or residual disease, the authors found that the addition of *^{18}F-DOPA* changed the diagnosis and treatment plan in 39% and 17% of cases, respectively, highlighting the importance of PET implementation into the diagnostic workup [44].

The use of amino acid radiotracers such as *^{18}F-DOPA* has been suggested to have a higher clinical utility compared with *^{18}F-FDG*. In a report involving 81 patients comparing these modalities, an improved sensitivity of 96% with *^{18}F-DOPA* was found compared with 61% for *^{18}F-FDG* [45]. In another series of 42 patients with indeterminate findings following SRS, *^{18}F-DOPA* was compared to perfusion MRI [46]. Several PET parameters were investigated, with the authors concluding that a maximum lesion to maximum background uptake ratio of 1.59 had the best diagnostic performance with a sensitivity of 90% and specificity of 92% compared to a sensitivity and specificity of 87% and 68% for a rCBV cutoff of 2.1

The long term metabolic evolution of suspected RN following SRS was investigated by Cicone et al., where conventional MRI and *^{18}F-DOPA* PET were obtained every 6 months. They found that the relative SUV, defined as the ratio between the maximum tumor SUV and the maximum background uptake, and the tumor to normal brain (TNB) ratio, defined as a volumetric approach of the ratio between mean tumor SUV and average frontoparietal uptake,

significantly increased over time in progressive lesions while remaining stable in RN [47].

O-(2-[^{18}F]fluoroethyl)-L-tyrosine (^{18}F-FET) PET

^{18}F-FET is another amino acid radiotracer with high diagnostic accuracy [48–50]. *^{18}F-FET* possesses a favorable metabolic stability given its increased retention time in neoplastic tissue after entering cells. Similar to the above modalities, authors have proposed different indices for the differentiation of RN from TP using measurements such as tumor to brain ratio (TBR) max, TBR mean, and time activity curves. Romagna et al. showed that *^{18}F-FET* TBR max and TBR mean ratios yield a sensitivity and specific of 86% and 79%, respectively, while increasing time activity curves were also associated with radiation induced changes. When combined, these provided sensitivity of 93% and specificity of 84% [50]. Ceccon et al. also showed that TBR max and TBR mean are able to differentiate recurrence from RN [48]. In a systematic review that included 4 studies that utilized *^{18}F-FET,* the pooled sensitivity was 79% and specificity was 76% [29]. This was lower than the analysis of 3 studies utilizing *^{18}F-FDG* PET, which showed pooled sensitivity of 91% and 80%, respectively. The previously discussed meta-analysis by Li et al. included 5 studies with *^{18}F-FET PET* with sensitivity and specificity of 83% and 89%, respectively.

^{18}F-Fluciclovine PET

Similar to the above described radiotracers, fluciclovine, known under the brand name Axumin when used to evaluate for prostate cancer metastasis, has uptake mediated by L-type amino acid transporters (LAT) which have high expression in tumor cells. *^{18}F-Fluciclovine* PET is commonly used in the workup of biochemically recurrent prostate cancer, but may also be used in brain metastasis evaluation (Fig. 4). In addition to LAT uptake, fluciclovine also utilizes the alanine, serine, and cysteine transporter 2 (ASCT2), which can be overexpressed in cancer cells leading to an improved tumor to background uptake.

In a small study including 8 patients with 15 lesions, Parent et al. found that *^{18}F-Fluciclovine* PET uptake could

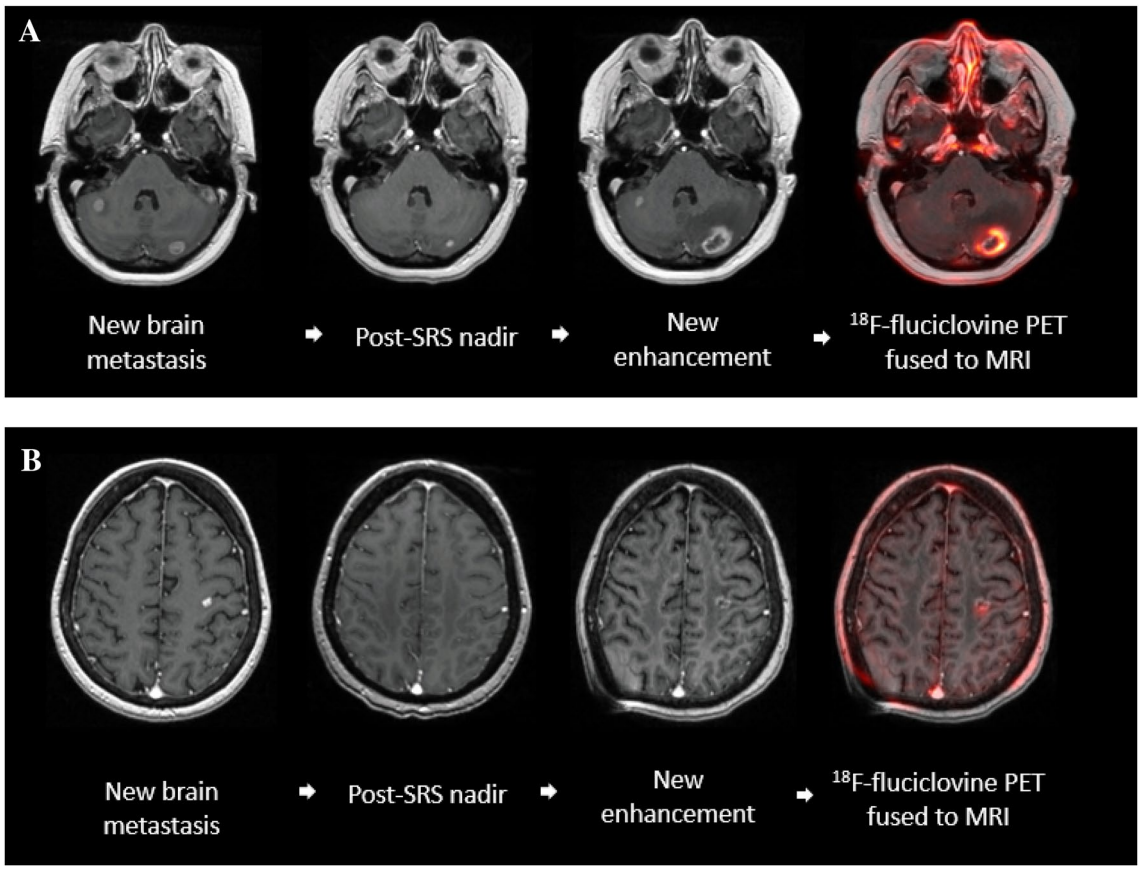

Fig. 4 **A** MRI and Fluciclovine PET images demonstrating tumor progression with a SUVmax of 9.2 following radiosurgery for a left cerebellar brain metastasis. **B** MRI and Fluciclovine PET images demonstrating radiation necrosis with a SUVmax of 2.2 following radiosurgery for a left frontal lobe brain metastasis. *MRI* Magnetic Resonance Imaging, *PET* Positron Emission Tomography, *SUV* Standardized Uptake Value, *SRS* Stereotactic Radiosurgery

differentiate RN from tumor progression at all-time points [51]. Using a SUV_{max} threshold of 1.3 produced 100% accuracy 30 min following radiotracer injection and 87% accuracy after 55 min. At our institution, a prospective pilot study investigating the use of *^{18}F-Fluciclovine* in 15 evaluable patients found that SUV_{max} can accurately differentiate between RN and TP [52]. Using a cutoff of 4.3 provided a sensitivity to identify progression of 100% and a specificity to rule out progression of 63%. SUV_{mean}, SUV_{peak}, and $SUV_{peak/normal}$ also showed the ability to differentiate between the two. The ongoing Study to Establish Image Interpretation Criteria for 18F-Fluciclovine PET in Detecting Recurrent Brain Metastases (PURSUE) and Study to Establish the Diagnostic Performance of 18F-Fluciclovine PET in Detecting Recurrent Brain Metastases (REVELATE), which both recently completed accrual, are looking to answer this question in a larger cohort [53].

Radiomics

Radiomic analysis is a promising and evolving field of artificial intelligence that extracts large amounts of quantitative radiographic features from standard biomedical imaging and uses this information to build predictive models. Several radiomic signatures are under investigation and will likely play a role in the future differentiation of RN from tumor progression [54]. For example, Zhang et al. retrospectively analyzed the radiomic profile of 87 patients with pathologically confirmed RN or TP after SRS and found that the combination of 5 delta radiomic features from contrast enhanced T1- and T2-weighted MRI helped distinguish RN from TP with an overall accuracy of 73% [55] Hettal et al. investigated 1,766 features from contrast enhanced T1-weighted MRI after SRS and compared this with baseline radiomic features using several selection models. They concluded that with their radiomic approach, RN and TP could be predicted with 75% and 91% accuracy, respectively [56]

Laser induced thermal therapy (LITT)

LITT is a minimally invasive surgical technique used in the ablative treatment of RN with promising efficacy. One benefit with LITT is that a biopsy can be done before treatment, which helps guide if adjuvant treatment is needed if biopsy is positive for tumor recurrence. In a meta-analysis comprising 8 studies, 61% of patients had symptomatic improvement following LITT while 44% were able to wean off of steroids [57]. In a study comparing LITT versus medical management in the treatment of biopsy proven radiation necrosis, patients receiving LITT were more likely to wean off steroids (84% vs 53%) at a median of 37 days; patients receiving LITT were less likely to have radiographic progression (5% vs 27%) [58]. Though LITT provides promise in the management of RN, its use remains limited as it is only available at select institutions.

Conclusion

Radiation necrosis is a frequent complication of stereotactic radiosurgery and differentiation from tumor progression is not always possible with conventional imaging. In these scenarios, a multi-modality diagnostic approach is often needed (Fig. 1). The diagnostic workup should begin with short interval follow-up MRI followed by perfusion MRI with rCBV as this is a readily available imaging technique that provides high sensitivity and specificity, especially in the setting of markedly elevated or reduced rCBV values. If uncertainty remains, we next recommend amino acid PET given the selective mechanisms of uptake of these radiotracers, which provide a better tumor to background ratio. If uncertainty still remains, tissue diagnosis with biopsy followed by LITT or surgical resection may be warranted. This review demonstrates that there is not a single standard imaging modality used for the diagnosis of radiation necrosis. Additional non-invasive techniques are needed to accurately diagnose radiation necrosis and allow for appropriate treatment, including advancement in amino acid radiotracers and radiomics.

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Declarations

Conflict of interest Samuel Tay Chao (Research support from Blue Earth Diagnostics and Honorarium from Varian Medical Systems). John H. Suh (Scientific advisory board of Philips, NovoCure, and Neutron Therapeutics). Gene H. Barnett (Speaker for Elekta AB, Consultant for Monteris Medical, Inc.).

Ethical approval This is a review article and no ethical approval is required.

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