Teaching Case

Long-Term Imaging Follow-up of Radiation Necrosis After Stereotactic Radiosurgery: A Case Report and Lessons Learned

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Introduction

The management of brain metastases (BMs) is a growing medical issue due to a combination of factors, including advancements in systemic therapy that allow for longer survival of patients with metastatic disease as well as increasing use of surveillance magnetic resonance (MR) imaging.[1,2] Among patients who die from their malignancy, the rate of BM ranges from 10% to 26%.[1,3]

While a diagnosis of BM has traditionally been associated with a relatively poor prognosis,[4] survival outcomes are highly dependent on multiple factors, including histology, receptor status and/or molecular markers, age, functional status, number of BM, and burden of extracranial disease.[5] As an example, for patients diagnosed with BM from breast cancer, the median survival can vary from 3 to 36 months depending on these other factors.[5]

With some exceptions, systemic therapies are often not effective in controlling metastatic disease within the central nervous system. Therefore, management of BM has primarily been through a combination of surgery and/or

radiation.[6] From the radiation perspective, we have historically employed whole-brain radiation therapy (WBRT), which targets the entire brain to treat both visible and microscopic diseases.[7] However, this comes at the cost of significant neurocognitive morbidity.[7] Therefore, over the last 2 decades, the standard of care has shifted to favor stereotactic radiosurgery (SRS) and fractionated SRS (fSRS) in patients with a limited number of BM.[8,9] SRS and fSRS involve the precise delivery of high doses of radiation over a single or limited number of fractions.[10] These modalities have been shown to be effective and generally well-tolerated treatment methods,[11,12] with better long-term neurocognitive outcomes compared to WBRT.[13]

Unfortunately, SRS and/or fSRS still pose a risk of adverse effects, including radiation necrosis (RN). RN is an inflammatory reaction causing tissue death that affects 5% to 10% of patients post-SRS/fSRS and is difficult to differentiate from tumor progression on standard imaging.[14,15] Herein, we highlight how this imaging dilemma can result in diagnostic uncertainty and create challenges and delays in providing appropriate management.

Case Presentation

A 64-year-old woman with a history of locally advanced, right-sided (pT2N2a) estrogen receptor and/or progesterone receptor-positive, human epidermal growth

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal upon request to the corresponding author.

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factor receptor 2-negative breast cancer was treated with curative intent surgery, adjuvant systemic therapy, and locoregional radiation therapy in 2012 for her primary cancer. In late 2018, she was diagnosed with a metastatic recurrence in the brain (Fig. 1a), for which she received fSRS to 6 brain lesions at a dose of 35 Gy in 5 fractions in March 2019.

In April 2019, 1 month after fSRS treatment, surveillance imaging showed no significant residual disease (Fig. 1b). These findings remained stable over the next 15 months. However, follow-up imaging in July 2020 noted a new enhancing lesion in one of the previously treated areas, specifically the right middle frontal gyrus (Fig. 1c). This rim-enhancing lesion increased in size on the subsequent MR imaging scan in September 2020 and was associated with vasogenic edema and local mass effect (Fig. 1d). The patient reported increased fatigue, weakness, headaches, and unsteadiness, for which she was started on dexamethasone 4 mg twice daily with taper for the next 5 weeks. At this point, it was uncertain whether these changes were reflective of disease progression or RN, although it was suspected to be the latter.

To help clarify the diagnosis, short-term interval follow-up with repeat MR imaging of the head with spectroscopy was completed in October 2020, approximately 6 weeks after her prior imaging (Fig. 1e). The perilesional white matter T2 and fluid-attenuated inversion recovery hyperintensity had decreased compared with the September 2020 scan and associated spectroscopy was not suggestive of tumor recurrence. Overall, findings from this study were more suggestive of RN rather than tumor growth. At this point, the patient was still endorsing persistent headaches and an unsteady gait; however, neither of these had worsened. The patient's imaging reports and symptoms were also reviewed at a local tumor board meeting in which clinicians agreed on a most likely diagnosis of RN and recommended continued close-interval surveillance.

An MR imaging with perfusion was completed in late February 2021. Results revealed mild increases in lesion size in the right frontal lobe (Fig. 1f), as well as increased surrounding edema. Notably, perfusion mapping showed decreased blood volume and no increased blood flow, in keeping with a diagnosis of RN. Moreover, the patient did not report any new or worsening central nervous system symptoms. As such, the patient continued on close surveillance.

Despite the lack of new or worsening neurological symptoms, a subsequent MR imaging in June 2021 showed further enlargement of the lesions with increased surrounding edema (Fig. 1g). Therefore, an MR imaging with both perfusion and spectroscopy was performed in September 2021. This demonstrated increased perfusion through the lesion in the right frontal lobe (Fig. 1h). MR imagining spectroscopy through this lesion demonstrated increased creatine levels, decreased choline and N-acetyl

aspartate (NAA) levels, and a lipid lactate peak. Overall, the results of the MR imaging studies, including the perfusion mapping and spectroscopy, were now more concerning for tumor growth than RN.

Given the suspicion of malignancy, the patient ultimately chose to undergo surgical resection of the right frontal lobe lesion. However, pathology results following surgical resection in November 2021 showed necrosis with vascular fibrinoid changes, confirming a diagnosis of RN instead.

Serial MR imaging showed stable postsurgical changes following resection of the right frontal lobe mass with no clear evidence of recurrence (Fig. 1i). The patient's most recent scan from March 2024 continues to show stability in the postoperative cavity (Fig. 1j). No new metastases have been identified, and the patient has remained clinically stable with no new or worsening symptoms.

Discussion

The use of SRS and/or fSRS for the treatment of BM has increased over the last 2 decades,[9] with studies demonstrating better neurocognitive outcomes relative to WBRT in patients with limited BM and good local control.[13,16] The American Society for Radiation Oncology guidelines recommend SRS and/or fSRS for patients with good performance status (EOG 0-2) and 1 to 4 BM, and conditionally for 5 to 10 BMs.[16] Research for its role in patients with 10+ lesions is ongoing.

Although effective, SRS and/or fSRS lead to RN in 5% to 10% of treated patients.[14,15] RN results from endothelial cell loss and avascularization which triggers astrocyte hyperplasia, perivascular edema, reperfusion injury, and an inflammatory response that concludes with tissue death.[17]

The risk of RN can be estimated by the prescribed dose and lesion volume.[15,18] Specifically, the HyTEC study showed that the risk of radiation-induced toxicity following SRS for BM is low when the volume of normal brain receiving at least 12 Gy (V12Gy) is less than 5 mL but increases with larger treatment volumes.[18] When treating these larger volumes, fractionated treatment can reduce the risk of RN. The risk of RN for volumes of 5 mL, 10 mL, and 20 mL has been predicted to be 3.6%, 4.8%, and 8.6%, respectively, for V24Gy and 4.1%, 6.0%, and 12.1%, respectively, for V28Gy.[18] In this case, the V24Gy was 17 mL, corresponding to an expected toxicity rate nearing 8.6%. The V28Gy was 9.8 mL, corresponding to approximately a 6.0% toxicity rate. Additionally, the V30Gy for a normal brain was 7.4 mL, which is below the 10.5 mL constraint used to predict RN by another recent publication.[19] Although the V30Gy data were not published at the time of treatment, the SRS plan for this patient would still meet current-day constraints, thereby aligning with best practices to mitigate RN risk.
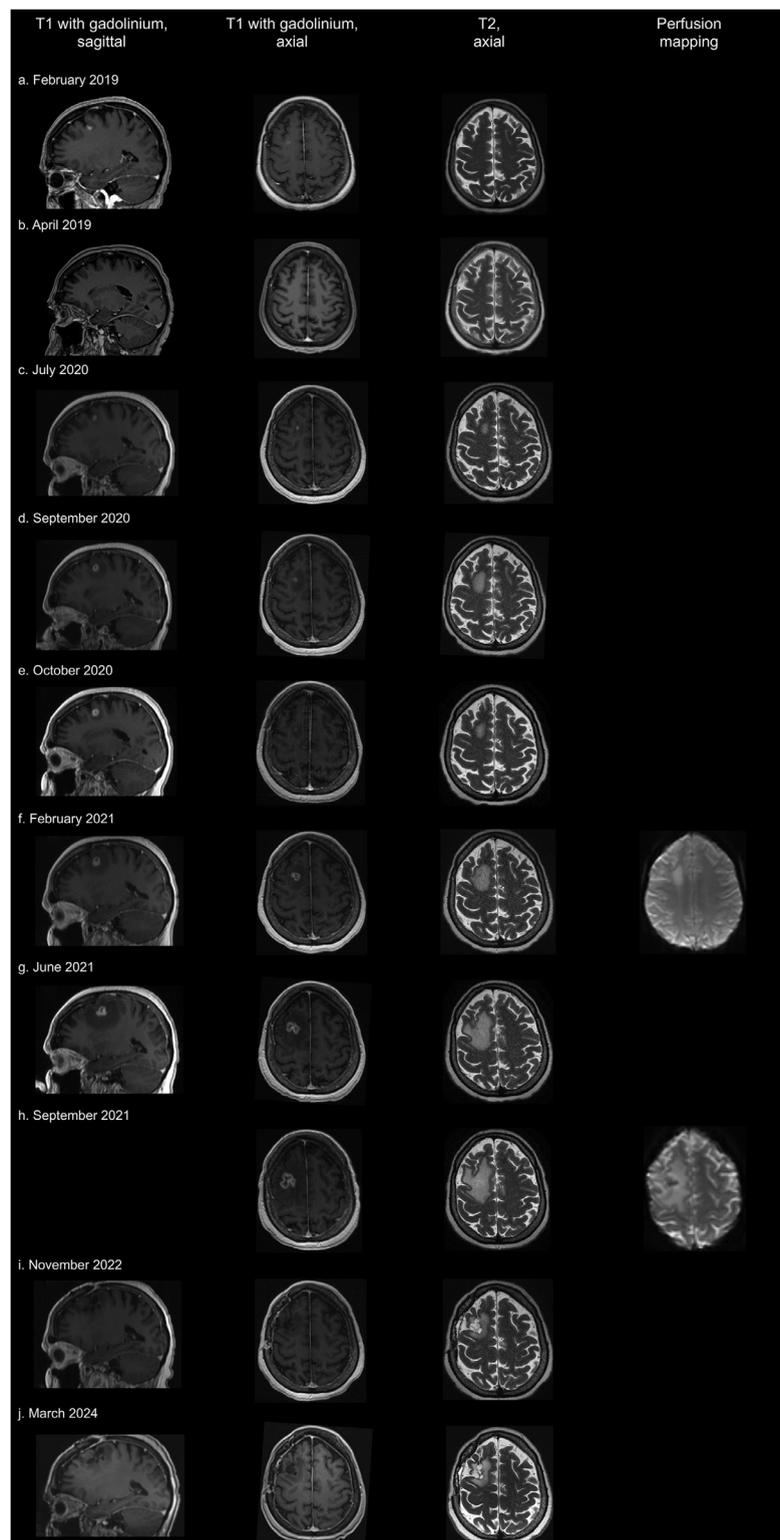
Figure 1 Magnetic resonance imaging (MRI) of the head illustrating changes in lesion volume and perfusion in the months prior to and following fractionated stereotactic radiosurgery (fSRS). (a) MRI head showing an enhancing lesion 2 months prior to fSRS (2 months prior; February 2019). (b) MRI head showing resolved and improving lesions one month after fSRS (1 month; April 2019). (c) MRI head showing a new enhancing lesion in the right middle frontal lobe measuring 5.5 mm (15 months; July 2020). (d) MRI head showing a rim-enhancing lesion in the right superior frontal lobe measuring 8.7 mm (17 months; September 2020). (e) MRI head showing enhancing lesion in right superior frontal lobe measuring 9 mm (18 months; October 2020). (f) MRI head showing an enhancing lesion in the right frontal lobe measuring 13 mm. Perfusion mapping illustrates no changes in

The diagnosis of RN posttreatment is challenging. On imaging, RN often appears as a contrast-enhancing lesion with peri-lesional edema at the site of SRS and/or fSRS treatment. These imaging findings are similar to those seen with tumor progression, making the 2 diagnoses difficult to differentiate. RN can also present with symptoms similar to progressive disease, such as headaches, fatigue, weakness, and numbness, as well as language and memory impairment,[17] further confounding the follow-up and management processes.

Follow-up after SRS and/or fSRS most commonly relies on MR imaging, which has high spatial resolution and sensitivity for tumor-induced structural alterations in the brain.[20] However, this modality also produces overlapping features between disease progression and RN, which include: (1) contrast-enhancing lesions; (2) vasogenic edema; (3) mass effect; and (4) growth over time.[21,22] Overall, no single feature or combination of features has been established as a reliable discriminator between these 2 diagnoses, suggesting that structural MR imaging offers only limited power to differentiate between these clinical phenomena.

Some advanced MR imaging techniques have been reported to successfully differentiate between the 2 aforementioned outcomes. When employing perfusion-weighted MR imaging (PWI), reduced tissue perfusion favors RN, whereas increased perfusion caused by angiogenesis favors tumor recurrence.[22] Reported PWI sensitivity and specificity range from 70% to 100% and 95% to 100%, respectively.[23-25]

MR spectroscopy (MRS) is another advanced imaging technique that has also been increasingly successful at distinguishing tumor recurrence from RN. MRS measures the relative compositions of NAA, choline, creatine, lipid, and lactate. Prior publications have reported that tumor recurrence is associated with higher choline:NAA and choline:creatine ratios as well as higher regional cerebral blood volume. In contrast, RN has been linked with decreased NAA levels and variable changes in choline and creatine levels intensities over time.[21,26] Specifically, choline levels may increase during the initial months postradiation but will subsequently decrease once necrosis develops.[21,26] MRS sensitivity and specificity have been reported to be near 100%.[27]

In the present case, suspicion of malignancy was based on the increased perfusion on PWI and associated lipid lactate peak on MRS. Elevated lactate and lipid levels are commonly present in cases of recurrent disease.[28] However, MRS showed decreased choline levels as well. In the long run, low choline level has been associated with RN, while high choline level is associated with recurrent disease.[28]

Recent guidelines published by the International Stereotactic Radiosurgery Society (ISRS) outline an approach to the management of RN.[29,30] Briefly, for asymptomatic patients with no prior corticosteroid use (grade 1), close surveillance with repeat imaging in 6 to 12 weeks is recommended, while the use of steroids can be considered. For patients who have no prior corticosteroid use but are symptomatic (grade 2), they recommend dexamethasone at 4 to 8 mg/d with a gradual taper, along with close imaging follow-up. For steroid-refractory RN (grade 3), bevacizumab is strongly recommended. Finally, for RNs with neurologic impairment and progression despite conservative treatment (grade 4), surgical resection is recommended.

These guidelines were published several years after this case. In retrospect, the patient's RN would have been ISRS grade 2 when she presented in July 2020. However, while her symptoms responded to a course of dexamethasone, her imaging findings continued to evolve. As highlighted in these ISRS guidelines, surgical resection should be considered even for ISRS grade 1 to 2 diseases if pathologic diagnosis is urgently required to guide management. Perhaps this patient could have continued with close surveillance for longer given her lack of neurologic compromise; however, prior close surveillance and conservative management had not provided a clear diagnosis, and her imaging findings were apparently progressing.

Conclusion

This case highlights the diagnostic uncertainties in differentiating recurrence versus RN, even when using advanced MR imaging like PWI and MRS. These imaging modalities can aid in decision-making but are not diagnostic. Over-reliance on such can lead to premature diagnoses and invasive treatment. Rather, management of such cases requires continuous evaluation of patient symptoms, serial advanced MR imaging, and the involvement of multidisciplinary tumor boards. Certainly, surgical intervention can play a role in these scenarios because resection can be both diagnostic and therapeutic. Delayed intervention caused by radiological uncertainty could yield suboptimal outcomes and greater symptom burden; however, surgical resection carries its own risks, including the risk of neurological deficits.[31] This leads to our final learning point: the importance of relying on patient symptoms to guide decision-making. When imaging

perfusion (23 months; February 2021). (g) MRI head showing an enhancing lesion in the right frontal lobe measuring 19 mm (26 months; June 2021). (h) MRI head showing an enhancing lesion in the right frontal lobe measuring 21 mm. Perfusion mapping illustrates increased perfusion through the lesion in the right frontal lobe (28 months; September 2021). (i) MRI head showing stable postoperative changes related to prior right frontal craniotomy for right frontal mass resection (43 months; November 2022). (j) Most recent MRI head showing sustained stability in the postoperative cavity (60 months; March 2024).

indicates lesion enlargement in an asymptomatic patient, short-interval imaging surveillance should be considered over reirradiation or surgery. Only when symptoms emerge or when significant growth causes concern for imminent symptom development should surgical intervention be discussed. Allowing symptoms to guide management can be uncomfortable for providers in the face of radiographic tumor growth; however, having restraint in these clinical scenarios is important to ensure surgery or reirradiation are not undertaken prematurely. In asymptomatic patients, a watch-and-wait approach may be most appropriate.

Disclosures

Timothy K. Nguyen reports a relationship with Need that includes consulting or advisory fees and equity or stock options. No other conflicts of interest.

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