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Teaching Case

Radionecrosis and Complete Response After Multiple Reirradiations to Recurrent Brain Metastases From Lung Cancer Over 10 Years: Is There a Limit?

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Introduction

Lung cancer accounts for 25.5% of all cancer death in Canada.[1] Non-small cell lung cancer with symptomatic multiple brain metastases (mbMets) has very limited survival time.[2] Standard whole brain irradiation (WBI) with or without craniotomy usually cannot prolong overall survival (OS) owing to high frequency of recurrence.[3] Reirradiation to the brain can cause severe neurotoxicity and worsen quality of life. There is a trend toward stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiation therapy (HSRT) for patients with a limited number of brain metastases to avoid neurotoxicity.[4-8]

Radionecrosis is a concerning neurotoxicity from SRS, as reported in the literature. However, it is usually difficult to differentiate it from tumor progression on computed tomography or magnetic resonance imaging (MRI) and also difficult to secure a tissue diagnosis. Without appropriate diagnosis and treatment, radionecrosis carries a poor prognosis. We present a case of multiple complete response (CR) to 2 full courses of WBI, 2 courses of HSRT, and 2 craniotomies for mbMets from lung cancer over a 10-year period with pathologically confirmed radionecrosis and good recovery.

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Case Presentation

We previously reported the case of a 43-year-old nonsmoker female patient who was initially diagnosed with stage T1N2M0 lung adenocarcinoma (American Joint Committee on Cancer 8) positive for anaplastic lymphoma kinase. She had CR initially after concurrent chemoradiation 60 Gy in 30 fractions in 2010. Nine months later, she had biopsy-proven distant metastases. Over a 9-year period, she had multiple recurrent mbMets treated with 2 WBI 20 and 21 Gy, in 5 and 7 daily fractions, respectively (4 years apart); craniotomy to remove a large 4-cm mass from the right brain (pathology-confirmed adenocarcinoma of lung origin); and finally HSRT 20 Gy in 5 fractions every other day to a large solitary metastasis in the right cerebellum (Fig 1). We achieved CR after each radiation and reirradiation. The right cerebellum lesion completely disappeared on computed tomography and MRI (Fig 2). We did not observe any neurotoxicity. She was also treated with 4 different lines of systemic tyrosine kinase inhibitors, that is, crizotinib, ceritinib, alectinib, and lorlatinib (switched to another type whenever there was disease progression).[9]

Ten months after HSRT, the patient fell and was found to have a new 1.2-cm solitary brain metastasis in the left frontal lobe. MRI did not show any other metastasis. She refused craniotomy but consented to a second course of HSRT 20 Gy in 5 fractions (Fig 3). She was able to walk again and do all her housework until about 2 months later, when she had a 10-day deterioration noticed by her

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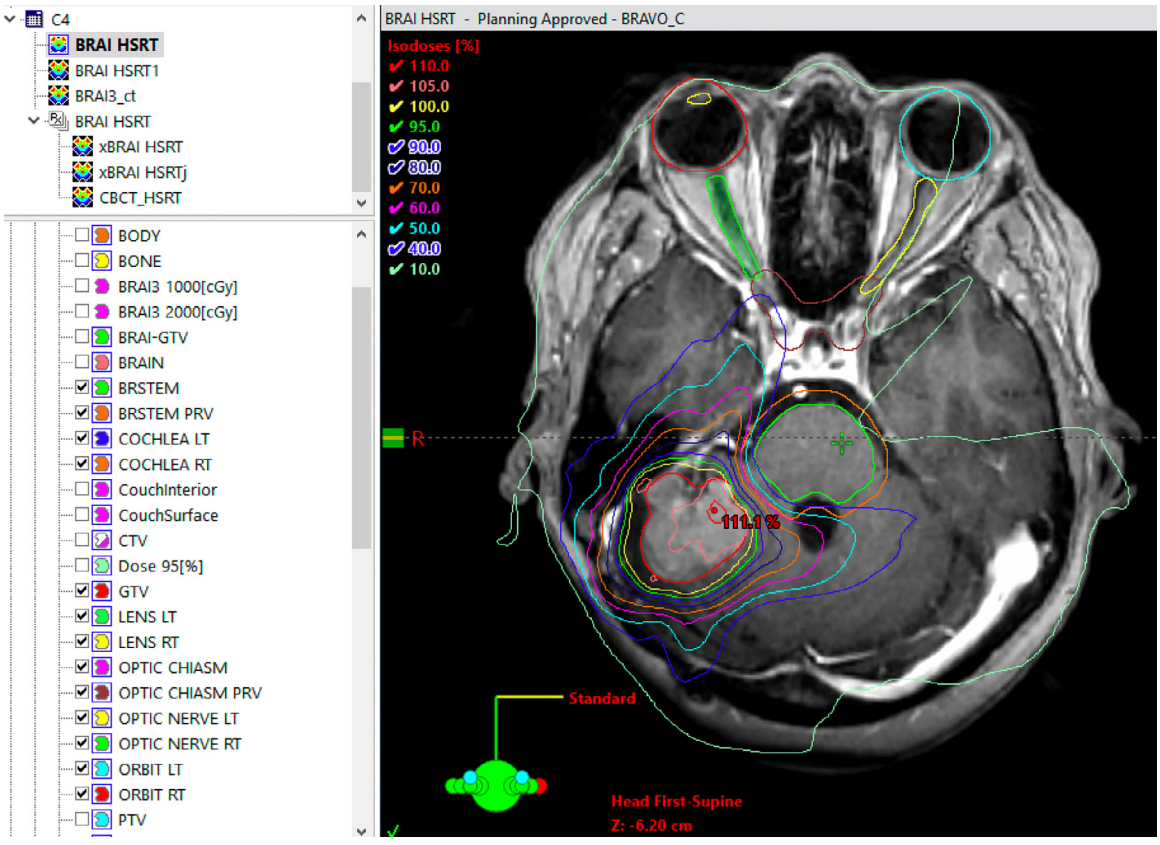

Figure 1 First hypofractionated stereotactic radiation therapy plan with magnetic resonance imaging simulation.

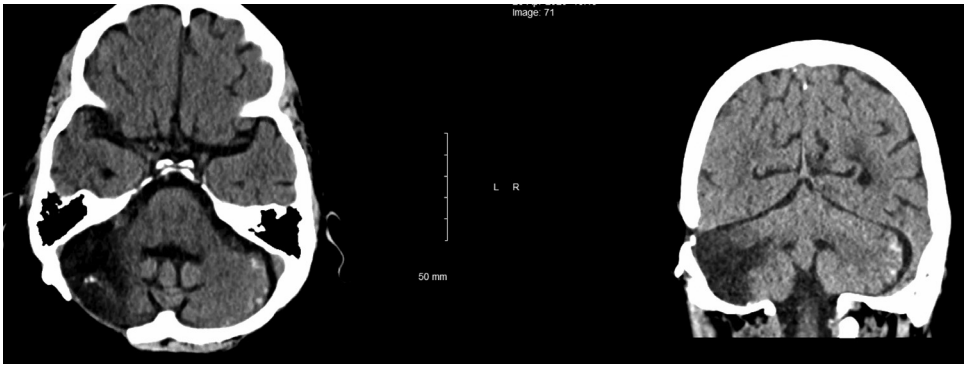

Figure 2 Brain computed tomography showing complete response 9 months after first hypofractionated stereotactic radiation therapy.

family. She completely lost her short memory, fell at home, and could no longer walk.

MRI showed that the left frontal brain lesion progressed to 2.5 cm in size 10 weeks after the second course of HSRT (Fig 4). There was marked increase in vasogenic edema, mild mass effect, and midline shift to the right side for about 0.3 cm. No other suspicious lesions were seen in the brain. Magnetic resonance spectroscopy (MRS) reported borderline low choline to N-acetyl aspartate ratio of 1.78, which is slightly lower than the cutoff value of 1.8 in the literature, favoring radionecrosis over progression of brain metastasis (Fig 5).[10]

Ultimately, she had a second craniotomy, which achieved gross total resection. The pathology confirmed radionecrosis with no viable tumor in the brain. Unfortunately, she had further deterioration of her neurologic symptoms after the surgery for about 4 weeks. She could not stand up and could not remember anything that happened within the last several minutes. Nevertheless, she was started on oral dexamethasone 4 mg twice

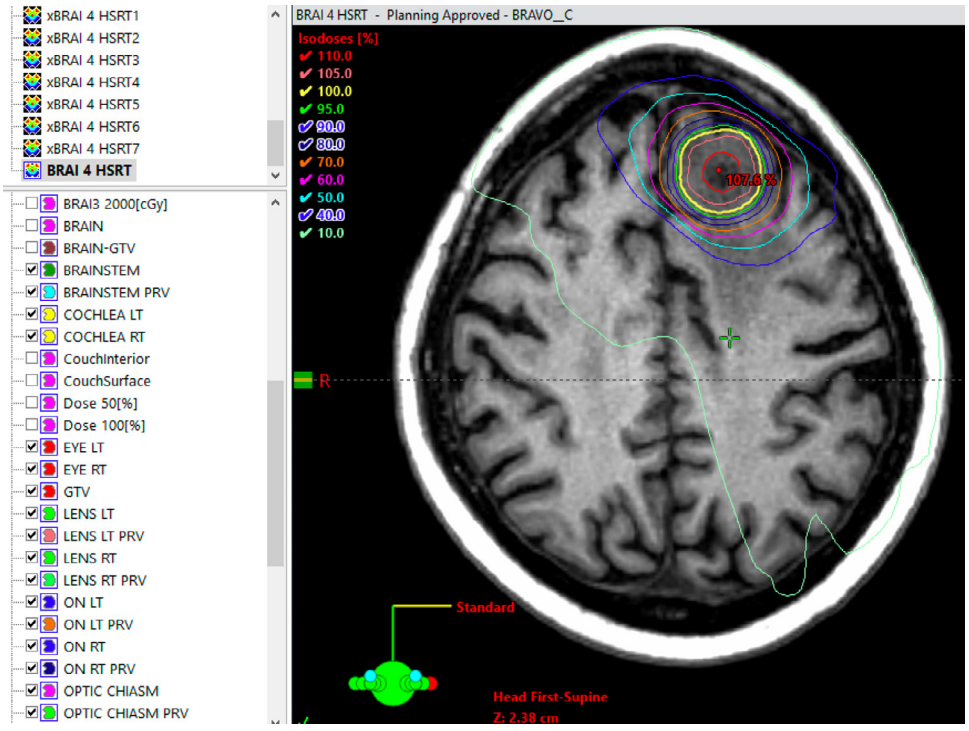

Figure 3 Second hypofractionated stereotactic radiation therapy plan with magnetic resonance imaging simulation.

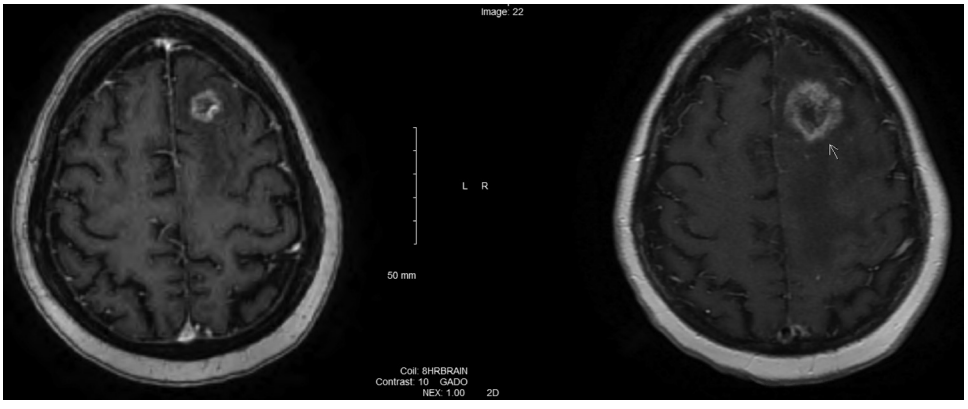

Figure 4 Brain magnetic resonance imaging showing left frontal lesion 2 weeks before (left) versus 10 weeks after second hypofractionated stereotactic radiation therapy (right).

per day and her symptoms improved dramatically. MRI 2 and 6 months postsurgery did not show any residual cancer, new brain metastases, or radionecrosis in the brain (Fig 6).

We tried to wean the patient off of steroids temporarily, but she remains on low-dose oral dexamethasone 2 mg once per day. On the last follow-up, she was able to stand up without assistance. She could even walk without a walker. She no longer needed Foley catheters or a commode beside her bed. She had no further falls. Her short-term memory had partial recovery.

Eleven years after her lung cancer diagnosis, she remains disease free.

Discussion

WBI can cause severe neurotoxicity. The current trend is to use SRS or HSRT whenever possible for patients with cancer who have a limited number of brain metastases due to equivalent OS with reduced toxicity, most notably involving neurocognition.[4-8,11-18] However, even though well tolerated, SRS does have adverse effects, including radionecrosis (low rate).[14] There are questions as to whether current low radionecrosis rates apply to metastatic patients who are living longer owing to improvements in systemic therapy, because in the past these patients would have passed away before developing

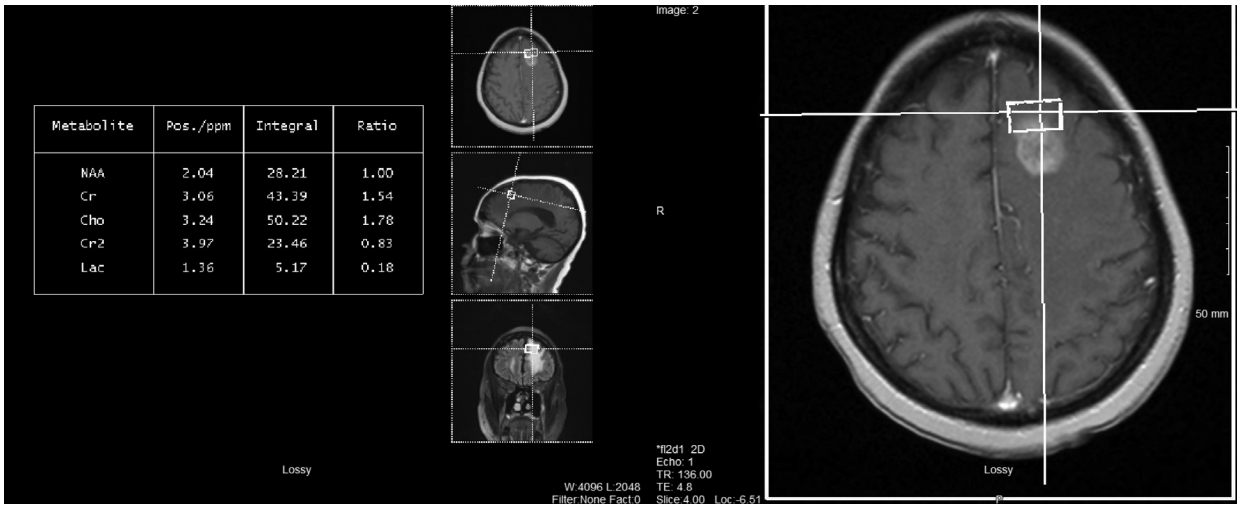

Figure 5 Brain magnetic resonance spectroscopy 2 months after second hypofractionated stereotactic radiation therapy showing radionecrosis with pathologic confirmation.

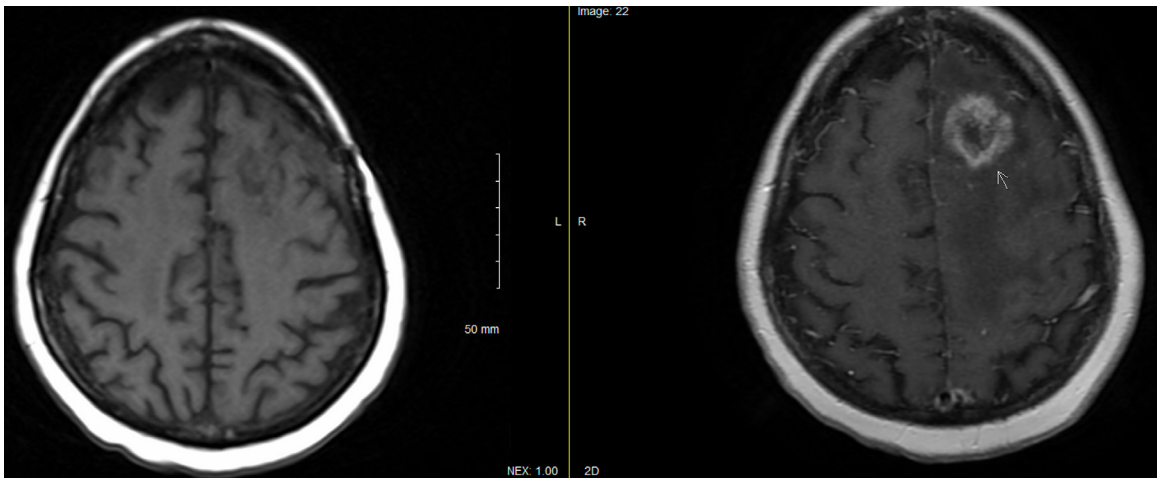

Figure 6 Brain magnetic resonance imaging showing complete response; 2 months after (left) versus 10 days before second craniotomy surgery (right).

late neurotoxicity. As such, there is occasional hesitation to consider reirradiation to mbMets.

Sneed et al[15] found previous WBI or SRS can increase the radionecrosis risk to about 20% at 1 year after SRS to the same lesion, and long intervals between reirradiation can reduce that risk. McKay et al[19] also reported repeat SRS as reirradiation for local failure after previous SRS can have durable local control (LC) but high rates of radionecrosis, that is, 11 of 46 brain metastases (24%) had symptomatic radionecrosis. The volume of a lesion receiving 40 Gy (V40 Gy) was statistically significant to predict radionecrosis (P = 0.003). Rae et al[20] suggested that reirradiation to recurrent brain metastases after initial SRS with both SRS and WBI was associated with the highest radionecrosis rate (6/28, 21.42%), whereas no patient had radionecrosis if the salvage treatment was SRS alone (0/31), WBI alone (0/58), craniotomy alone (0/7), or craniotomy followed by radiation (0/8). It should be noted that most radionecrosis in their study had no pathologic confirmation.[20]

Compared with gamma knife (GK), linear accelerator (LINAC)-based SRS is easy to use and lower cost.[21-23] Subgroup analyses of Radiation Therapy Oncology Group 9508 found similar OS comparing GK and LINAC SRS.[6] Sebastian et al[22] reported LINAC SRS has less radionecrosis than GK for treatment of mbMets. However, their definition of radionecrosis was vague and without pathologic confirmation. Meta-analysis of 1887 brain metastases from 24 trials by Lehrer et al[24] also suggested that multifraction SRS or HSRT to large brain metastasis might reduce the risk of radionecrosis (7.3% vs 23.1%, P = .003) while maintaining or improving 1-year LC (92.9% vs 77.6%, P = .18) compared with single-fraction SRS.

Our institution does not have SRS and is located remotely from a GK center. We use a very conservative

LINAC-based HSRT protocol similar to Marcrom et al.[21] We only treat a small number of brain oligometastases (1-4) to 25 to 30 Gy in 5 fractions every other day. Salvage reirradiation with HSRT (for up to 4 recurrent mbMets) or with WBI 21 Gy in 7 daily fractions (if there are more lesions) after upfront WBI 20 Gy is allowed when there is long interval.[9] To our surprise, this patient had excellent response to 4 tyrosine kinase inhibitors and 2 WBI without neurotoxicity. She preferred HSRT over craniotomy after developing further symptomatic oligometastases in the brain. To reduce the risk of neurotoxicity, we did not use standard dose HSRT for the second and third reirradiation. We also used prophylactic steroids during treatment.

The rule of V40 Gy threshold does not apply because the entire brain received 41 Gy before the 2 HSRTs.[19] It is interesting to see the larger lesion in right cerebellum had CR and no radionecrosis, whereas the smaller lesion in the left frontal lobe developed radionecrosis in just 10 weeks. MRS showed a choline to N-acetyl aspartate ratio of 1.78, which is at the borderline of the cutoff value of 1.8 in the literature.[10] However, we favored radionecrosis because it was unlikely to have such rapid tumor progression after the last HSRT. Fortunately, her second craniotomy confirmed the tissue diagnosis and she received prompt proper treatment. It also confirmed CR in the brain.

It is possible that the risk of radionecrosis was reduced by offering reirradiation with HSRT instead of WBI or single fraction SRS, reducing the total dose of HSRT, treating every other day instead of daily, and especially because of the long interval of several years. However, we suspect that we have reached the limit and can no longer offer her more radiation to the brain, either by WBI, SRS, or HSRT. She has received a combined biologically effective dose of 135.34 Gy and equivalent dose for 2 Gy per fraction of 81.2 Gy, using an α/β ratio of 3 for late-responding normal brain tissue.

Although rare, there have been reports of long-term CR and cure after WBI 20 Gy.[25] However, to our knowledge, this is the first reported case of multiple CR to 2 courses of WBI, 2 courses of HSRT, and 2 craniotomies for mbMets from lung cancer over a 10-year period with pathologically confirmed radionecrosis and good recovery.

Conclusions

Reirradiation to the brain can result in severe neurotoxicity, including radionecrosis. However, it might still be considered for patients with cancer with symptomatic mbMets who have the potential for long OS. Reirradiation with HSRT could be a good option to achieve better long-term LC and quality of life if SRS is not available. MRS and craniotomy can help diagnose radionecrosis and thus improve treatment outcome.

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