

Teaching Case

Severe radiation-induced leukoencephalopathy: Case report and literature review

Michael Cummings MD ^a, David W. Dougherty MD, MBA ^b,
Nimish A. Mohile MD ^c, Kevin A. Walter MD ^d, Kenneth Y. Usuki MD ^a,
Michael T. Milano MD, PhD ^{a,*}

^a Department of Radiation Oncology, James P. Wilmot Cancer Institute, University of Rochester, Rochester, New York

^b Division of Hematology/Oncology, James P. Wilmot Cancer Institute, University of Rochester, Rochester, New York

^c Department of Neurology, James P. Wilmot Cancer Institute, University of Rochester, Rochester, New York

^d Department of Neurosurgery, James P. Wilmot Cancer Institute, University of Rochester, Rochester, New York

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Introduction

Whole-brain radiation therapy (WBRT) remains standard practice for cerebral metastases, either as monotherapy or in conjunction with surgery or stereotactic radiosurgery (SRS).¹ Although potential radiation-induced side effects after WBRT are well described, we report the first (to our knowledge) case of fatal leukoencephalopathy following WBRT and SRS boost.

Case

The patient was, at time of initial diagnosis, a 63-year-old woman with a right lower lobe lung mass incidentally detected during workup for persistent back pain. Medical history was notable only for well-managed

hypertension, hypothyroidism, and esophageal reflux. Subsequent workup disclosed 2 synchronous lung primaries: a right-sided pT1N1 adenocarcinoma and a left-sided pT2aN0 adenocarcinoma, each treated with surgical resection and lymph node sampling. The morphologic subtypes suggested 2 primary cancers versus metastatic disease. She received 1 cycle of full-dose cisplatin/vinorelbine, with further planned cycles aborted because of poor tolerance and functional decline. Approximately 1.5 years after chemotherapy, she developed headaches and right-sided ataxia. Magnetic resonance imaging (MRI) disclosed 5 lesions, with the largest in the left frontal (2.3 × 2.6 cm), right frontal (1.8 × 2.0 cm), and right parietal (1.7 × 1.6 cm) regions. There had been no prior brain imaging; positron emission tomography imaging did not reveal active extracranial disease. Steroids were initiated, after which WBRT (30 Gy/10 fractions) was completed. Because of recurrent headache, she remained on 10 mg dexamethasone daily. One month post-WBRT, the 3 bulkier lesions were treated with frameless, linear accelerator-based SRS; each lesion received 15.5 Gy to isocenter and 13 Gy to the periphery (Fig 1).

Conflicts of interest: None.

* Corresponding author. Department of Neurosurgery, James P. Wilmot Cancer Institute, University of Rochester, 601 Elmwood Ave., Rochester, NY 14642.

E-mail address: michael_milano@urmc.rochester.edu (M.T. Milano).

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Approximately 1 month post-SRS and after resolution of the previously mentioned issues, she developed fatigue, anorexia, failure to thrive, and persistent but minor mental status changes, notable for decreased interactivity. Steadily, her neurocognitive decline progressed with worsening fatigue, inattention, inactivity, decreased personal interactivity, and poor oral intake in the absence of headaches or focal neurologic deficits. Eventually she slept the majority of the day, although she remained arouseable and appropriate in actions and communication during wakeful periods, which continued to diminish in frequency and duration. Magnetic resonance imaging (2 weeks before death) showed regression of the SRS-targeted lesions and decreased perilesional edema; 2 infratentorial lesions (not boosted with SRS) were no longer visualized. There was interval development of cerebral and cerebellar volume loss, with new bilateral deep and periventricular white matter changes (Fig 2). Additional diagnostic testing, including urine and blood cultures, syphilis screening, blood counts, and metabolic panels, were unremarkable. An electroencephalogram showed diffuse background slowing consistent with moderate to severe encephalopathy with no focal or epileptiform abnormalities. Lumbar puncture was not performed. The patient died (2 months after SRS, 3 months after WBRT) under a comfort care approach, with punctate episodes of consciousness prior. Autopsy was declined by her family.

Discussion

Radiation-induced leukoencephalopathy is a well-described late sequelae defined clinically by variable neurocognitive changes and radiologically by deep and

periventricular white matter hyperintensities on T2-weighted MRI series in the absence of focal lesions.²

The incidence of leukoencephalopathy is unclear. A retrospective series reported grade 1-3 leukoencephalopathy in 34% of patients 6 months after 40 Gy/20 fractions, with increasing incidence at longer follow-up.³ A series of 94 patients examining late effects after prophylactic cranial irradiation reported periventricular and subcortical lesions on computed tomography (CT) scan consistent with white matter changes in 82% of patients; neuropsychologic impairment scores correlated with the extent of these lesions ($r = 0.7$, $P < .05$), although the number evaluated for assessment was low ($n = 12$) and no standardized grading system was used.⁴ In a prospective study of 92 patients receiving WBRT with regular CT or MRI assessments, brain atrophy developed in 30%, though it did not correlate with changes on the Mini-Mental Status Exam (MMSE); the authors did not report white matter changes.⁵ In a series of 44 melanoma patients undergoing WBRT to 20 Gy/5 fractions ($n = 21$) or 30 Gy/10 fractions ($n = 16$), the incidence of leukoencephalopathy seen on MRI was 5.4%.⁶

The incidence of leukoencephalopathy with SRS plus WBRT is similarly unclear. A Japanese prospective study comparing SRS ($n = 67$) alone with WBRT and SRS ($n = 65$) reported leukoencephalopathy in 9 patients, 7 in the combined modality group and 2 after SRS alone.⁷ A retrospective single-institution series specifically evaluating leukoencephalopathy in patients treated with WBRT alone versus WBRT and SRS reported a significantly higher rate in patients at 1 year after undergoing combination therapy using an investigator-derived grading system (13 vs 92%). Notably, the combination group had greater likelihood of

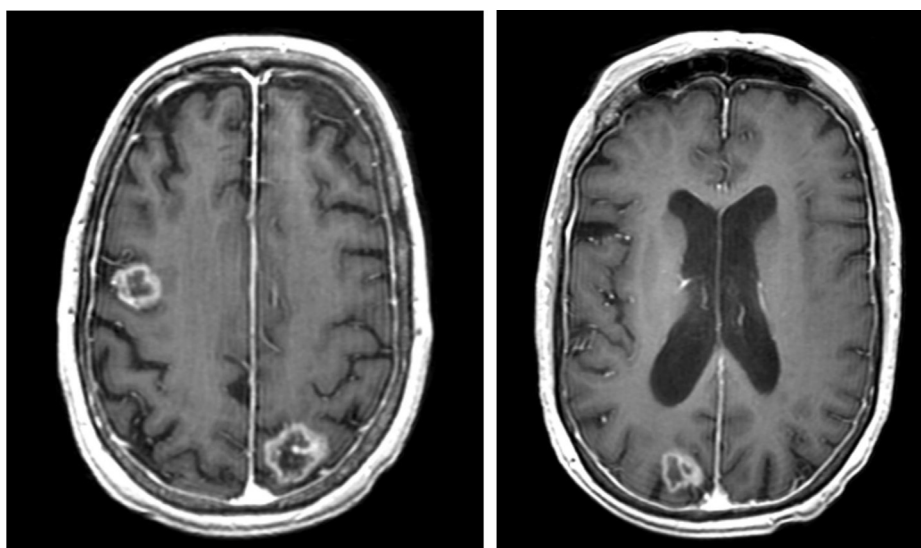


Figure 1 Contrast-enhanced T1-weighted magnetic resonance images 1 month after whole-brain radiation therapy for stereotactic radiosurgery planning.

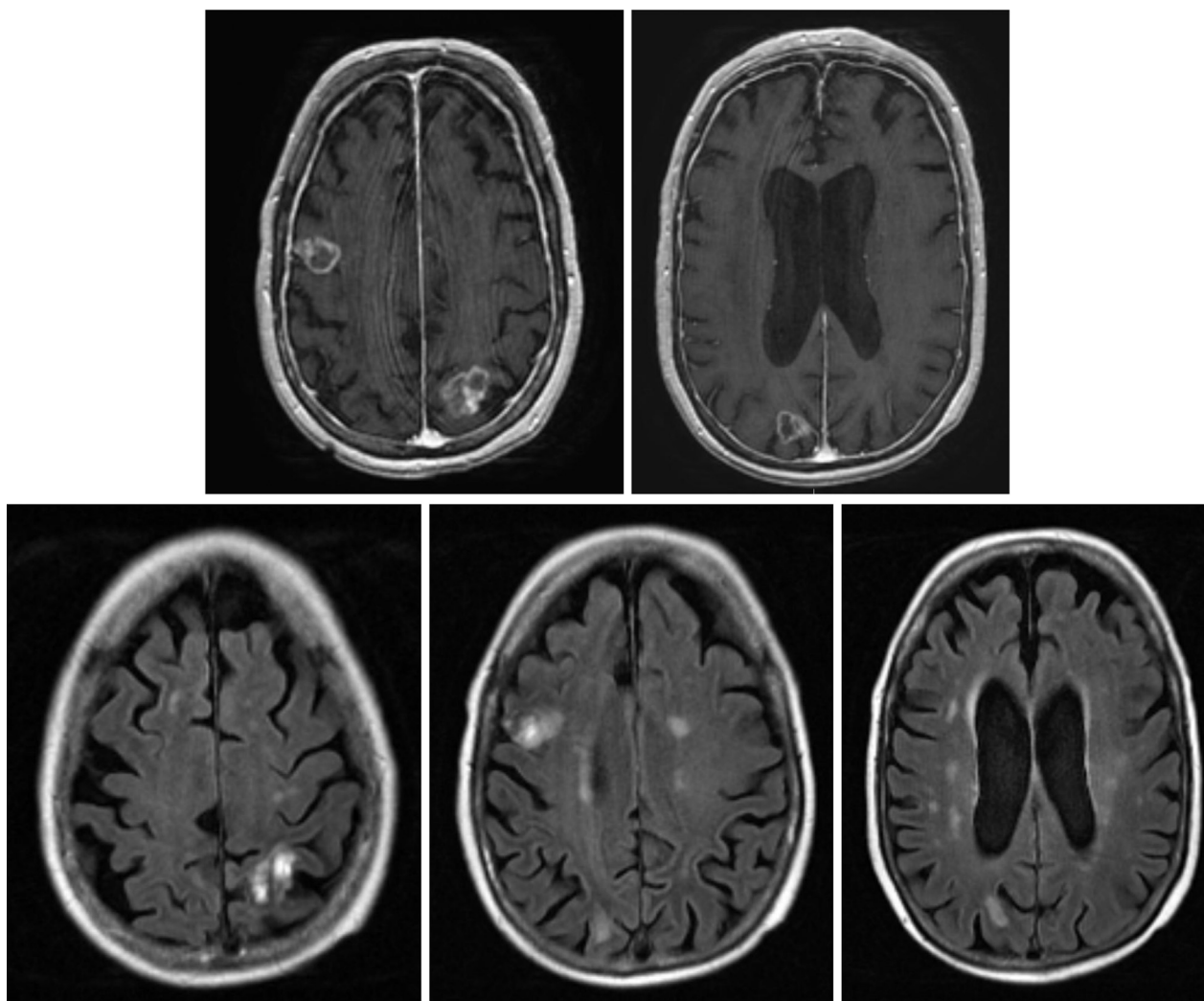


Figure 2 Magnetic resonance images during patient's final hospitalization. Axial T1-weighted postcontrast images showing regression of treated lesions (top). Axial T2-weighted fluid attenuated inversion recovery images showing diffuse subcortical white matter hyperintensities (bottom).

chemotherapy use, a higher cerebral disease burden, and received more SRS treatments.⁸ A retrospective series examining 103 patients who had undergone at least 2 courses of radiosurgery found that both WBRT and a higher integral dose were associated with an increased likelihood of developing leukoencephalopathy on MRI.⁹ These series suggest SRS after WBRT can exacerbate leukoencephalopathy, possibly as a simple function of dose. Hypothetically, SRS may trigger an immune or inflammatory reaction that precipitates demyelinating changes “primed” after WBRT in a uniquely susceptible patient; however, to our knowledge, such an effect has not been described.

The relationship between white matter changes and severity of clinical symptoms is unclear. An early retrospective series reported a correlation between severe white matter changes on MRI and clinical symptoms, though also reporting leukoencephalopathic symptoms in

patients with mild radiologic changes.¹⁰ A secondary analysis of Radiation Therapy Oncology Group 9104 (a randomized study of WBRT with or without motexafin gadolinium) investigated neurocognitive impairment after WBRT. The authors showed that larger lesion volume and poorer response to therapy were significant predictors of worse neurocognitive impairment.¹¹ In a planned secondary analysis of the previously mentioned Japanese randomized trial, neurocognitive function was evaluated by MMSE ($n = 92$); of 7 patients with leukoencephalopathy (all SRS + WBRT patients), 4 had a significant drop from their baseline MMSE. This represented a small number of the overall study population who had an observed MMSE decline. Although similar MMSE declines were observed in both cohorts, the WBRT + SRS group experienced a longer median time to deterioration (12 vs 6.6 months) and the decline was attributed to therapy in 5 patients (40%), whereas in the

SRS alone group, 11 patients (92%) had MMSE decline attributed to recurrent disease.¹² Taken together, these reports suggest that leukoencephalopathy can cause variable clinical effects that are difficult to predict or quantify.

There are clinical data indicating that combination therapy can lead to worse neurocognitive outcomes. A randomized trial from MD Anderson Cancer Center evaluating SRS alone compared with SRS with WBRT in 58 patients with 1 to 3 brain metastases with prospective neurocognitive assessments was terminated after an interim analysis showed decreased short-term memory at 4 months, which was the study's primary endpoint.¹³ The Alliance/NCCTG N0574 randomized trial of 208 patients with 1 to 3 brain metastases reported declines in delayed recall, immediate recall, and verbal fluency after WBRT + SRS versus SRS alone.¹⁴ Notably, both studies showed intracranial control was superior with combination therapy, though no effect on overall survival was observed. Leukoencephalopathic changes were not specifically reported in these studies.

It is possible that fatal leukoencephalopathic events after WBRT ± SRS in the past that were either not recognized as toxicities or not deemed worthy of reporting in peer-reviewed literature; however, with decades of experience using similar biologically equivalent doses in routine practice, it is unlikely that similar events would go unreported. In the reported case, there was no clear etiologic process that could otherwise explain the neurocognitive changes observed. Whether leukoencephalopathy was the only pathology involved cannot be definitively stated without autopsy confirmation, but the severity of neurocognitive changes in proximity to therapy in conjunction with characteristic MRI changes strongly suggest a severe reaction in this patient.

In summary, clinicians should be aware of potential severe radiation-induced leukoencephalopathy after combination WBRT and SRS, which manifested as a fatal complication in our patient with bulky brain metastases. We do not advocate changing clinical practice based upon a case report. Even after our experience with this patient, we would treat another steroid-dependent brain metastasis patient similarly, because WBRT can best address acutely symptomatic intracranial disease with SRS providing more durable intracranial control. Although the utility, in terms of survival and quality of life, of WBRT in non-small cell lung cancer patients who were ineligible for SRS has been called into question since the results from the UK Medical Research Council QUARTZ (Quality of Life after Treatment of Brain Metastases) randomized trial were reported,¹⁵ more data are needed to best address which patients would benefit from withholding radiation therapy. Nevertheless, we advocate against routine use of WBRT in patients with limited brain metastases, as

recommended by the American Society of Radiation Oncology's Choosing Wisely campaign (<http://www.choosingwisely.org/astro-releases-second-list/>).

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