MedCrave
Step into the World of Research

Journal of Cancer Prevention & Current Research

Editorial

Open Access

CrossMark

The Sun has not yet set on WBRT

Volume 5 Issue 3 - 2016

Kunal Sindhu,[1] Timothy Kinsella[2]
[1]The Warren Alpert School of Medicine, USA
[2]Department of Radiation Oncology, Rhode Island Hospital, USA

Correspondence: Timothy Kinsella, MD, Department of Radiation Oncology, Rhode Island Hospital, The Warren Alpert School of Medicine at Brown University, 593 Eddy Street, Providence, RI USA, Tel (401) 444-6203, Fax (401) 444-5335, Email tkinsella@lifespan.org

Received: July 07, 2016 | **Published:** July 28, 2016

Editorial

In spite of all of the progress that has been made in understanding the molecular and cellular principles underpinning the development and treatment of cancer over the past half-century, a diagnosis of metastatic brain cancer remains one of the most devastating diagnoses in all of medicine. In the United States, it is believed that at least 200,000 patients are diagnosed with brain metastases annually.[1] With a predilection for the grey-white matter junction adjacent to the cerebral vasculature, brain metastases are found in the cerebral hemispheres 85% of the time.[2] Over 2/3 of cases result from a primary lung cancer, breast cancer, or melanoma.[3]

Whole brain radiation therapy (WBRT) was first used in 1954 to treat brain metastases.[4] To this day, WBRT continues to be a mainstay of treatment for these patients because it has been shown to offer a survival advantage.[5,6] While most patients with brain metastases do not survive past one year, a small, but increasing minority, are now living longer than they could have in the past. As these patients survive for extended periods of time, concerns have been raised about the potential long-term neurocognitive effects arising from WBRT.

An inevitable side effect of applying radiation to the brain is tissue damage. While modern fractionation schedules have served to limit the risk of more serious side effects like acute encephalopathy or radiation necrosis, a known long-term complication of WBRT is the development of microstructural abnormalities, including demyelination, gliosis, vascular rarefaction, and white matter necrosis.[7] An inevitable consequence of these structural changes is radiation-induced cognitive impairment.

Interestingly, studying long-term cognitive outcomes in patients after WBRT has proved to be challenging. First of all, the median survival of patients with brain metastases, even after receiving corticosteroids and WBRT, is just 6.1 months.[5,6] However, WBRT, in the form of prophylactic cranial irradiation (PCI), has also been used to treat adults with small cell lung cancer (SCLC) and children with acute lymphoblastic leukemia (ALL). While these patients are not strictly analogous to those with brain metastases, they often live longer and may be followed long-term to illuminate some of the late cognitive sequelae associated with WBRT. Secondly, studies that have examined radiation-induced cognitive impairment have used different assessment methods, times to assessment, and definitions of impairment, making it difficult for researchers to draw generalizable conclusions across studies.[8] Thirdly, most patients, both with and without brain metastases, often have cognitive deficits that precede WBRT, making it difficult for researchers to truly isolate the cognitive decline strictly associated with radiation. Lastly, these patients are often on other medications, including chemotherapy and antiepileptics, that can negatively interfere with cognition on their own.

Despite these challenges, prior studies have shown that 50-90% of adult brain tumor patients who survive for at least six months after WBRT experience some degree of radiation-induced cognitive impairment. This cognitive dysfunction is global in nature, affecting verbal and spatial memory, attention, and problem-solving ability .[9]. While the data on neurocognitive outcomes after PCI in patients with SCLC has been mixed, an analysis of patients with locally advanced non-small cell and small cell lung cancer who received PCI found that 45% reported a decline in cognitive function at six months.[10] In children with ALL who have received PCI, broad declines in academic achievement, attention, intellectual function, learning, and memory have been documented, though these deficits may not materialize for at least four years after treatment.[11,12] Consequently, the PCI dose is currently reduced by 2-3 fold while still being effective. Confounding variables regarding delayed cognitive effects of PCI in ALL patients include the age at diagnosis, particularly less than three years, and the use of multiple chemotherapeutic drugs, particularly methotrexate.

In recent years, with the increasing popularity of stereotactic radiosurgery (SRS), the necessity of WBRT, in light of its neurocognitive sequelae, has rightly been questioned. SRS offers high rates of progression-free survival and is less dependent upon tumor histology than that of WBRT.[13,14] Additionally, it has been shown that adding WBRT to SRS in patients with 1-4 brain metastases does not improve survival.[15] An intriguing large observational study in Japan found that SRS, without WBRT, may be an appropriate initial treatment for patients with up to 10 brain metastases.[16]

Does this mean that WBRT is now obsolete? Despite the progress made in treating patients with SRS, WBRT is still a valuable tool in the treatment of some patients with metastatic brain cancer. At this time, patients receiving SRS alone, without adjuvant WBRT, are at higher risk of treatment failure in areas of the brain that are not treated.[13,14] Additionally, for patients with more than four brain metastases, WBRT continues to be a valuable therapeutic tool. Given that the overall median survival of patients with brain metastases is still less than one year, the neurocognitive sequelae of WBRT remains a secondary concern.

However, as SRS and other therapeutic modalities become more refined, there is a real possibility that WBRT may no longer be as widespread in the near future. As its use declines, and the risk of global cognitive impairment from radiation fades, a greater effort must be made to protect those patients who are still clinically indicated to

receive WBRT. Greater use of meantime, an N-methyl-D-aspartate (NMDA) receptor antagonist that may extend the time to cognitive failure in patients receiving WBRT, and hippocampal-sparing WBRT, which may reduce cognitive decline in patients without poor performance receiving WBRT, must be adopted.[17,18] While we may be nearing the end of WBRT as a therapeutic modality, it is important that we do not forget those patients for whom it still provides benefit.

Acknowledgments

None.

Conflicts of interest

The author declares no conflicts of interest.

Funding

None.

References

1. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J Neurooncol*. 2005;75(1):5–14.
2. Tsao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev.* 2012;18(4):CD003869.
3. Platta CS, Khuntia D, Mehta MP, et al. Current treatment strategies for brain metastasis and complications from therapeutic techniques:a review of current literature. *Am J Clin Oncol.* 2010;33(4):398–407.
4. Chao JH, Phillips R, Nickson JJ. Roentgen–ray therapy of cerebral metastases. *Cancer.* 1954;7(4):682–689.
5. Noël G, Tallet A, Truc G, et al. Whole brain radiation therapy for brain metastases:Advantages and controversies. *Cancer Radiother.* 2015;19(1):30–35.
6. Sundstrom JT, Minn H, Lertola KK, et al. Prognosis of patients treated for intracranial metastases with whole–brain irradiation. *Ann Med.* 1998;30(3):296–299.
7. Brown WR, Blair RM, Moody DM, et al. Capillary loss precedes the cognitive impairment induced by fractionated whole–brain irradiation:A potential rat model of vascular dementia. *J Neurol Sci.* 2007;257(1):67–71.
8. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases:actual assessment. *Radiat Oncol.* 2012;7:77.
9. Greene–Schloesser D, Robbins ME, Peiffer AM, et al. Radiation–induced brain injury:A review. *Front Oncol*. 2012;2:73.
10. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self–reported cognitive functioning after prophylactic cranial irradiation for lung cancer:pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys.* 2013;86(4):656–664.
11. Conklin HM, Krull KR, Reddick WE, et al. Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. *J Natl Cancer Inst.* 2012;104(18):1386–1395.
12. Annett RD, Hile S, Bedrick E, et al. Neuropsychological functioning of children treated for acute lymphoblastic leukemia:impact of whole brain radiation therapy. *Psychooncology.* 2015;24(2):181–189.
13. Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases:a systematic review. *Radiat Oncol.* 2015;9:155.
14. Gorovets D, Rava P, Ebner DK, et al. Predictors for Long–Term Survival Free from Whole Brain Radiation Therapy in Patients Treated with Radiosurgery for Limited Brain Metastases. *Front Oncol.* 2015;5:110.
15. Halasz LM, Uno H, Hughes M, et al. Comparative effectiveness of stereotactic radiosurgery versus whole–brain radiation therapy for patients with brain metastases from breast or non–small cell lung cancer. *Cancer.* 2016;122(13):2091–2100.
16. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901):a multi–institutional prospective observational study. *Lancet Oncol.* 2014;15(4):387–395.
17. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole–brain radiotherapy:a randomized, double–blind, placebo–controlled trial. *Neuro Oncol.* 2014;15(10):1429–1437.
18. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem–cell compartment during whole–brain radiotherapy for brain metastases (RTOG 0933):a phase II multi–institutional trial. *J Clin Oncol.* 2014;32(34):3810–3816.