Neuro-Oncology

Neuro-Oncology 17(7), 919–923, 2015
doi:10.1093/neuonc/nov089

The controversy surrounding the use of whole-brain radiotherapy in brain metastases patients

Minesh P. Mehta

University of Maryland School of Medicine, Baltimore, Maryland

Corresponding Author: Minesh P. Mehta, MBChB, University of Maryland School of Medicine, 22 S Greene St, Baltimore MD 21201 (mmehta@umm.edu).

Keywords: brain radiotherapy, cancer, memory, metastasis.

Brain metastases account for the majority of intracranial malignancies and carry an extremely high mortality and, anecdotes aside, are associated with very short survival times. With improvements in treatment including surgery, systemic therapy, and radiotherapy, a tiny minority of patients are living longer. Unfortunately, for an unselected population of patients with brain metastases representing the vast majority of these patients, median survival is still measured in months rather than years. It is well recognized that the therapies and the disease itself can have a significant impact on a patient's cognition and quality of life, even in this short survival duration. One of the more debilitating side effects associated with brain metastases is cognitive decline, most notably affecting memory.

The underlying pathology of cognitive decline in patients with brain metastases is multifactorial. A common cause is the cancer itself and, of course, the occurrence of brain metastases. Medications associated with symptomatic management of the consequences from brain metastases, systemic chemotherapeutic agents, and whole-brain radiotherapy (WBRT) are contributing factors. Additionally, comorbid factors such as anxiety, fatigue, depression, and direct involvement of memory centers in the brain can contribute to memory decline. Various techniques have been and are being developed to prevent or treat neurocognitive decline in brain cancer patients.[1]

WBRT has been integral in the treatment of brain metastases for well over half a century. For example, Chao et al demonstrated symptomatic improvement in 63% of patients treated with this approach.[2] Improvements in surgical and radiosurgical techniques have increasingly led to applying WBRT as an adjuvant treatment following resection or radiosurgery (SRS) to improve local, leptomeningeal, and regional control.[3–7] Over the last decade, an increasing trend has emerged toward utilizing SRS alone for patients with multiple brain metastases and reserving WBRT as a treatment of last resort for salvage of widespread intracranial metastatic disease. In this review, we will scrutinize the evidence suggesting that WBRT can be abandoned in a significant majority of patients, and we posit that this is in fact a dangerous trend that is not adequately supported by the evidence at hand. Further, we will highlight the significant advances in modulating WBRT-associated cognitive deficits, which would be expected to further improve the therapeutic window associated with this modality.

What is the Role of Whole-brain Radiotherapy?

Perhaps the foremost question to address in this review is understanding why we use WBRT in the first place. It is crucial to understand that the typical doses utilized for this (eg, ~30 Gy in 10 fractions) have an effect both on macroscopic or overt metastatic lesions as well as microscopic disease not visible on conventional imaging. The impact on macroscopic disease is not trivial; in various reports and studies, WBRT produces actuarial local control in approximately half of all patients. For example, in a 2015 prospective randomized trial reported to the American Society of Clinical Oncology, WBRT was associated with a 41.2% objective response rate and a median time to radiologic progression of just under 9 months, both measured through a blinded central review.[8] In multiple trials, when WBRT is added to focal therapies, macroscopic local control improves from 31%–73% without WBRT to 73%–100% with it.[3–7] The implication of this is obvious. Focal therapies, irrespective of how aggressive they are, have their primary effect enhanced by the addition of WBRT, implying that WBRT is providing biologic enhancement, or overcoming geographic miss (since microscopic disease cannot be targeted by focal therapies) or accounting for tumor spillage resulting from resection. This phenomenon is essentially reproduced across almost all prospective trials.

More importantly, WBRT dramatically improves compartmental control. Studies using SRS or resection alone are associated with an inordinately high rate of any intracranial failure approaching 70%–78%, and this is dramatically reduced to 24%–47% with WBRT.[9] Proponents of WBRT avoidance have advocated a policy of SRS alone, followed by MRI-based

Received 6 April 2015; accepted 9 April 2015

surveillance and salvage SRS as needed, but such a strategy can be prohibitively expensive for a patient population in which median survival is still measured in months.[10]

The Survival Question

It has been more or less assumed that WBRT does not enhance survival when added to SRS or resection. In reality, this conclusion deserves serious examination. To understand the issue at hand, it behooves the reader to understand that prophylactic WBRT is employed in the treatment of malignancies with a high propensity for microscopic CNS spread such as small cell lung cancer (for patients with a good response following chemotherapy); not only does WBRT decrease intracranial relapse, doing so actually leads to a direct improvement in overall survival; This is not true prophylaxis but is in fact a crystal-clear example of a significant underlying concept: for patients in whom extracranial disease is controlled, decreasing intracranial compartmental failure/progression translates not only to a benefit in enhanced local control but also an actual benefit in overall survival.[11] With non–small cell lung cancer, the most common cause of brain metastases, prophylactic WBRT has also categorically demonstrated a decrease in intracranial relapse (but without a corresponding increase in overall survival), a reflection of the need to be selective in the judicious application of WBRT to only the highest risk subsets.[12]

The emerging data presented by Sahgal et al—that for patients 50 years or younger with 1–4 brain metastases, there is an overall survival advantage to SRS alone based on a meta-analysis of 3 phase III studies (10 vs 8.2 months)—have cast further doubt on the value of WBRT.[13] These data require thoughtful scrutiny. This analysis was conducted by merging the EORTC 22952–26001, JROSG99-1, and MDACC NCT00460395 datasets. Collectively, these trials included patients with 1–4 brain metastases, who were treated with SRS ± WBRT, with variable entry criteria for each trial as well as considerable dissonance in terms of systemic therapies, variability in enrollment eras, SRS dose, follow-up imaging, and retreatment considerations. Further, the EORTC trial also included patients undergoing resection, at physician discretion. A total of 364 patients are available in this collated dataset, of whom 51% (185) were treated with SRS alone and only 19% (69) were <50 years old. None were prospectively restaged for establishing the extent of systemic disease prior to protocol entry, thereby likely resulting in an unpredictable distribution of patients by systemic burden on the treatment arms. The results demonstrate a curious blend of outcomes; for the post-hoc, not an a priori prespecified subset of these 19% of patients below age 50 years, overall survival was superior for the SRS alone arm (10 vs. 8.2 months); as expected, time to distant brain failure was shorter for patients treated with SRS alone (4.5 vs. 6.5 months), but this was seen only in patients older than 55 years of age, an explanation that defies clear biologic explanation, other than an imbalance in the extent of unrecognized systemic disease burden, which as alluded to above was an unascertained parameter. As would be expected, time to local failure was superior with the use of WBRT (7.4 vs. 6.6 months). It is important to recognize that the recommendation regarding the survival gain in the younger patient category with SRS alone is based on ~35 patients per arm. In a post-hoc analysis which could not assure pre-enrollment balance regarding the extent of systemic disease, systemic burden as a confounder for assessing overall survival could not be eliminated.

Based on lessons learned from prophylactic WBRT, it is reasonable to hypothesize that, in reality, the survival benefit from WBRT is likely limited primarily to patients not succumbing to extracranial disease progression. Unless this question is studied in an enriched cohort, most other studies would likely remain too underpowered to demonstrate a survival advantage. As early as 1998, Pirzkall et al, reporting on a 236 patient retrospective cohort, found that there was a trend toward improved longer-term survival favoring SRS + WBRT (actuarial 1- and 2-year survival: 30 and 14% vs. 19 and 8%). More importantly, however, the median survival was impressively (but not statistically) different at 15.4 vs 8.3 months ($P = 0.08$) in favor of WBRT[14] for patients without extracranial disease.

More recently, Wang et al retrospectively reviewed a database from Columbia University in which 528 (257 lung cancer, 102 breast cancer, 62 melanoma, and 40 renal cell carcinoma) patients were treated between 1998–2013 with SRS alone (206), SRS and WBRT (111), resection followed by SRS (109), or all 3 modalities (102). The overall median survival was 16.6 months; for patients with a single brain metastases, median survival following SRS, SRS + WBRT, SRS + resection, and all 3 modalities was 9.0, 19.1, 25.5, and 25.0 months, respectively. Even for patients with more than one metastases, the corresponding median survival values were 8.6, 20.4, 20.7, and 24.5 months, respectively, demonstrating the survival inferiority of SRS alone as a modality in this cohort. This was validated in a multivariate analysis as being associated with the use of SRS alone as a modality.[15]

The data that call the Sahgal et al meta-analysis most into question come from one of the key sources used within that analysis: JROSG 99-1. At the 2014 annual meeting of the Japanese Society for Radiation Oncology, Aoyama et al presented their own reanalysis of this study, using the now widely accepted disease-specific Graded Prognostic Assessment (ds-GPA) stratification tool.[16] Because the ds-GPA relies on molecular variables for stratifying breast cancer patients, information that was not collected on JROSG 99-1, these patients could not be adequately categorized and were excluded, leaving 88 (of 132 total enrolled patients) non–small cell lung cancer patients who were grouped into favorable (GPA, 2.5–4; $n = 47$) and unfavorable (GPA, 0.5–42; $n = 41$) cohorts. The median survival was 16.7 versus 10.6 months in favor of the WBRT arm ($P = .03$) for the favorable group, but a similar survival improvement was not observed in the unfavorable group. This lends credence to the hypothesis that improved brain control translates to a survival advantage for high GPA patients because they do not die as rapidly from extracranial progression; therefore, the beneficial effects of improved brain control from WBRT actually impact overall survival. This is obviously quite contrary to the current wisdom of reserving WBRT for only the prognostically least favorable group of patients. Should we really be jumping to exclude WBRT in the management of these patients, when appropriate randomized trials have not yet been completed, and there is actually a risk that we might be contributing to diminished survival in exactly the patients in whom we are striving to avoid WBRT? Should WBRT avoidance decisions be based on post hoc, non–prespecified

subset analysis of vanishingly small numbers of patients, when all reasonable prudence would suggest that a survival trial in this context would need several hundred, if not more than a thousand, patients to confirm?

Neurotoxicity Concerns

The use of WBRT in brain metastases can be associated with neurotoxicity. Particularly detrimental to the patient's neurocognitive function is the decline in declarative memory. Chang et al compared patients treated with SRS alone with patients treated with SRS + WBRT and showed a greater decline in memory (as demonstrated by the Hopkins Verbal Learning Test-Revised [HVLT-R]) at 4 months in the SRS + WBRT group.[4] One of the most widely accepted causes of impairment in memory involves the hippocampus. Neural stem cells located in the subgranular and subventricular zones of the hippocampus play a role in regenerative processes, including replenishing depleted neurons. When these cells are damaged, or in a pro-inflammatory environment, the stem cells shift from their classical neuronal differentiation ability to a predominantly glial proliferation pattern, thereby resulting in neurocognitive impairment.[17] Damage is likely mediated through excitotoxicity following radiation, resulting in decreased N-methyl-D-aspartate (NMDA) receptor density and increased gamma-Aminobutyric acid (GABA) receptor density. Animal models have demonstrated this reorganization in the dentate gyrus of the hippocampus, which correlates with impairment in long term potentiation (LTP) and is critical for new memory formation.[18,19]

Brown et al,[20] recently presented the results of the Alliance N0574 trial in which patients with a limited number of brain metastases were randomized to SRS or SRS + WBRT; after accruing 213 patients over 12 years, they demonstrated that witholding WBRT was associated with significantly increased risk of local and distant brain failure, without an obvious decrement in survival (although subset data comparable to the Aoyama analysis are not yet available); multiple neurocognitive and quality of life measures at various time points were reported without a Bonferroni correction for multiple comparisons, and consistent with earlier studies, an early decline in recall memory with WBRT was noted (ASCO 2015, Plenary).

Preventing cognitive decline due to WBRT involves avoiding or limiting the processes that damage healthy brain tissue. A number of strategies have been explored including avoiding WBRT, avoiding the hippocampi during WBRT, protecting brain tissue from excitotoxicity, and preventing neurotransmitter receptor remodeling in the hippocampus.

One possibly effective method for preventing loss of memory function in patients with brain metastases is to avoid WBRT altogether. This could be accomplished by either surgical resection or SRS alone. Avoidance of WBRT would theoretically spare the hippocampal stem cell compartments and prevent the white matter changes seen following irradiation. This would be an ideal strategy for patients whose lesions are amenable to such focal therapeutic approaches and those who simultaneously have a low risk of microscopic spread and hence subsequent emergence of brain metastatic disease. This patient population is likely small. Sawrie et al, upon reviewing a 100 patient cohort treated with SRS alone, concluded that only 18% of the patients could truly be classified as having a low risk of relapsing in the brain when WBRT was avoided.[21] One approach for enhancing the size of this population is to recognize that, for specific subsets of patients, blood-brain-barrier (BBB)-penetrating targeted agents might enhance control of micrometastatic disease, thereby permitting a strategy of controlling the macroscopic disease with SRS and the microscopic disease with targeted BBB-penetrant agents and avoiding or delaying WBRT, but such "window-of-opportunity" trials are currently in their infancy.

Since the hippocampi are infrequently involved with metastatic disease, and they are central in their role in postradiation cognitive changes, it is reasonable to avoid them during WBRT. Hippocampal-avoidance WBRT (HA-WBRT) is a technique that involves conformal avoidance of the hippocampal stem cell compartments. Specifically the subgranular zones of the hippocampi are contoured, and the dose to this region is reduced, while the remaining brain parenchyma receives a typical WBRT dose. RTOG-0933, a phase II clinical trial analyzed the impact of HA-WBRT on declarative memory.[22] Of the patients analyzed at 4 months, there was a mean decline from baseline in HVLT-delayed recall (HVLT- DR) of 7% compared with 30% observed in historical controls treated with traditional WBRT ($P = .0003$). This low rate is also highly comparable to that observed with SRS alone at a similar point in time in the prospective Chang et al trial.[4]

Mitigating the excitotoxicity in the hippocampus following radiation is another area of active research in the preservation of memory function. NMDA receptors in the hippocampus are activated by glutamate and play a role in learning and memory. Overexcitation of these receptors during radiotherapy causes an alteration in the ratio of NMDA to GABA receptors and may lead to neuronal cell death. This has been demonstrated in preclinical models following cranial irradiation and shown to impair long-term potentiation (LTP) critical for memory formation.[19] Prophylactic application of the noncompetitive NMDA open-channel blocker memantine has been shown to prevent receptor remodeling and preserve LTP in animal models.[19] The neuroprotective potential of memantine following irradiation was examined in RTOG 0614. The study demonstrated a nonsignificant trend towards less decline in HVLT-DR at 24 weeks ($P = .059$) in the treatment arm compared with placebo. Treatment with memantine also demonstrated a significantly longer time to cognitive decline for the treatment arm ($P = .01$). Superiority was also shown in the memantine arm for specific tests of executive function, processing speed, and memory.[23]

Conclusions

The potential of cognitive decline associated with the use of WBRT has led to a reduction in the utilization of this approach. As valid as this concern is, a more granular analysis reveals 2 other key points whose importance needs to be underscored. First, omission of WBRT is almost universally associated with subsequent compartmental brain failure. Second, an abundance of data demonstrates that cognitive decline is also associated with progressive disease/failure in the brain. In fact, in at least one randomized trial, the incidence of decline in minimental status examination scores and the time to such

decline were both greater in the arm in which WBRT was withheld, underscoring that recurrence in the brain is not cost free in terms of cognition.[6] This issue was evaluated in a recently completed randomized trial (North Central Cancer Treatment Group [NCCTG]-N0574/Radiation Therapy Oncology Group [RTOG] 0671), the results of which are awaited. A second ongoing trial (RTOG 1270) of postoperative stereotactic radiosurgery SRS versus WBRT will shed further light on this question.

Using a handful of retrospective reviews, substantially underpowered trials, and a meta-analysis based on these underpowered trials, it has been widely concluded that the omission of WBRT does not decrease overall survival. However, other factors contributing to the lack of a survival difference include the fact that systemic progression is a significant competing cause of mortality, and this was not adequately addressed. Moreover, a diligent review of the available data would caution against jumping to such a conclusion, since the supporting data are relatively weak and contradictory data have recently emerged, which allow one to posit the very reasonable hypothesis that a certain proportion of patients with brain metastases are destined to succumb to intracranial progression and that enhanced control of intracranial progression will lengthen their survival. This was observed in a contemporary cohort (1998–2013) of 528 patients with brain metastases treated with SRS, either alone or in conjunction with resection, WBRT, or both, which revealed that the median survival for the single-metastasis cohort was 9 months for SRS alone and 19.1 months with the addition of WBRT.[15] Finally, a recent reanalysis of the randomized Japanese Radiation Oncology Study Group (JROSG) 99-1 trial, using the validated Graded Prognostic Assessment (GPA) stratification model to evaluate all non–small-cell lung cancer (NSCLC) patients in the trial, revealed an MS of 16.7 months vs 10.6 months in favor of WBRT + SRS (compared with SRS alone; $P = .03$) for the favorable-prognosis subgroup (GPA = 2.5–4), providing further support for the idea that intracranial control matters and that one accepts a lower rate of such control at the potential risk of reducing overall survival.[16]

With refinements in WBRT techniques resulting in lower rates of cognitive decline,[22,23] it is truly time to ask why we should avoid WBRT when it categorically reduces compartmental failure and could result in improved survival. The alternative (ie, focal therapy) only needs more rigorous testing in terms of lack of cognitive sequelae, especially for consequential relapse in the brain as well as the perspective of societal cost. Clearly, in well-selected subsets, this might be a reasonable strategy, but lots of hard work needs to be done to properly define these subsets before jumping on the bandwagon.

Disclosures

Leadership: Pharmacyclics; stock or other ownership: Pharmacyclics; consulting: Cavion, Elekta, Novartis, Novocure; research funding: Novocure, Novellos.

References

1. Dye N, Gondi V, Mehta M. Strategies for preservation of memory function in patients with brain metastases. *Chinese Clin Oncol*. In press.
2. Chao JH, Phillips R, Nickson JJ. Roentgen-ray therapy of cerebral metastases. *Cancer*. 1954;7(4):682–689.
3. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96(1):17–32.
4. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037–1044.
5. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280(17):1485–1489.
6. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483–2491.
7. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952–26001 study. *J Clin Oncol*. 2011;29(2):134–141.
8. Chabot P, Hsia TC, Ryu JS, et al. Results of a randomized, global, multi-center study comparing veliparib and whole brain radiation therapy (WBRT) versus placebo and WBRT in subjects (subjs) with brain metastases (BM) from non-small cell lung cancer (NSCLC), 2015, ASCO, (in press, May 2015).
9. Mehta M. The dandelion effect: treat the whole lawn or weed selectively? *J Clin Oncol*. 2011;29(2):121–124.
10. Ogiwara H, Kalakota K, Rakhra SS, et al. Intracranial relapse rates and patterns, and survival trends following post-resection cavity radiosurgery for patients with single intracranial metastases. *J Neurooncol*. 2012;108(1):141–146.
11. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664–672.
12. Snider JW 3rd, Gondi V, Brown PD, et al. Prophylactic cranial irradiation: recent outcomes and innovations. *CNS Oncol*. 2014;3(3):219–230.
13. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys*. 2015;91(4):710–717.
14. Pirzkall A, Debus J, Lohr F, et al. Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. *J Clin Oncol*. 1998;16(11):3563–3569.
15. Wang TJ, Saad S, Qureshi YH, et al. Outcomes of gamma knife radiosurgery, bi-modality & tri-modality treatment regimens for patients with one or multiple brain metastases: the Columbia University Medical Center experience. *J Neurooncol*. 2015;122(2):399–408.
16. Aoyama H, Tago M, Shirato H on behalf of Japanese Radiation Oncology Study Group 99-1 (JROSG99-1) investigators. Stereotactic radiosurgery with or without upfront whole brain radiation therapy for one to four brain metastases: Secondary analyses of the JROSG 99-1 randomised study after post-stratification by the diagnosis-specific Graded Prognostic Assessment. *JAMA Oncology*. 2015; Published online ahead of print May 14, 2015.
17. Wu PH, Coultrap S, Pinnix C, et al. Radiation induces acute alterations in neuronal function. *PLoS One*. 2012;7(5):e37677.

18. Gondi V, Tome WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol*. 2010;97(3):370–376.
19. Son Y, Yang M, Wang H, et al. Hippocampal dysfunctions caused by cranial irradiation: A review of the experimental evidence. *Brain Behav Immun*. 2015;45(1):287–296.
20. Brown PD, Asher AL, Ballman KV. NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. *J Clin Oncol*. 2015;33(suppl; abstr LBA4).
21. Sawrie SM, Guthrie BL, Spencer SA, et al. Predictors of distant brain recurrence for patients with newly diagnosed brain metastases treated with stereotactic radiosurgery alone. *Int J Radiat Oncol Biol Phys*. 2008;70(1):181–186.
22. 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.
23. 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*. 2013;15(10):1429–1437.