Whole-Brain Radiotherapy for Brain Metastases: Evolution or Revolution?

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ABSTRACT

An estimated 20% of patients with cancer will develop brain metastases. Approximately 200,000 individuals in the United States alone receive whole-brain radiotherapy (WBRT) each year to treat brain metastases. Historically, the prognosis of patients with brain metastases has been poor; however, with new therapies, this is changing. Because patients are living longer following the diagnosis and treatment of brain metastases, there has been rising concern about treatment-related toxicities associated with WBRT, including neurocognitive toxicity. In addition, recent clinical trials have raised questions about the use of WBRT. To better understand this rapidly changing landscape, this review outlines the treatment roles and toxicities of WBRT and alternative therapies for the management of brain metastases.

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INTRODUCTION

Since the 1950s, whole-brain radiation therapy (WBRT) has been the most widely used treatment for patients with multiple brain metastases, given its effectiveness in palliation, widespread availability, and ease of delivery.¹ Historically, there was limited focus on the toxicities of WBRT, such as cognitive deterioration, because the vast majority of patients with brain metastases had a poor prognosis. More recently, with improvements in both focal and systemic therapies, prognosis has improved for patients with brain metastases, and clinical trials have better defined the toxicity profile of WBRT.^{2,3} In addition, a recent trial in patients with non-small-cell lung cancer (NSCLC) with poor prognosis found no benefit from WBRT compared with best supportive care, which was a significant finding because palliation has been the cornerstone of WBRT.⁴ These advancements and the knowledge gained from these clinical trials have raised questions about the use of WBRT. To better understand this rapidly changing landscape, this review outlines the treatment roles and toxicities of WBRT and alternative therapies for the management of brain metastases.

TREATMENT ROLES OF WBRT

Adjuvant WBRT After Radiosurgery

Several retrospective studies have explored the role of adjuvant WBRT after radiosurgery,

suggesting an increase in tumor control at the radiosurgical sites and a prevention of new brain metastases.^{5,6} To further investigate these findings, the Japanese Radiation Oncology Study Group (JROSG) 99-1 trial randomly assigned 132 patients with one to four metastases to radiosurgery alone or to radiosurgery plus WBRT.⁷ At 12 months, adjuvant WBRT resulted in an increased control rate at the radiosurgical sites of 89% versus 73% for radiosurgery alone ($P = .002$) and a decreased risk for new brain metastases of 42% versus 64% for radiosurgery alone ($P = .003$). No significant reduction in neurologic deaths was observed, and there was no difference in overall survival between the study arms. The European Organisation for Research and Treatment of Cancer (EORTC) 22952-26001 trial was performed to specifically address whether adjuvant WBRT increases duration of functional independence.⁸ Adjuvant WBRT reduced the 2-year relapse rate at initial sites (19% v 31%; $P = .040$) and at new sites (33% v 48%; $P = .023$); however, there were no differences in functional independence or overall survival between the study arms. Adjuvant WBRT was associated with worse quality of life (QOL), predominantly during the early follow-up period.⁹ A phase III trial conducted at MD Anderson Cancer Center (ID00-377) randomly assigned patients with one to three brain metastases to stereotactic radiosurgery (SRS) and WBRT or SRS alone and again found significantly improved intracranial control with the addition of WBRT (1-year freedom from CNS recurrence 73% v 27%; $P = .0003$).¹⁰ However, despite improved

intracranial control with WBRT, the trial was closed early because the patients assigned to SRS and WBRT were more likely to have deterioration in learning and memory function (52% *v* 24%, respectively). An individual patient data meta-analysis of JROSG 99-1, EORTC 22952-26001, and MD Anderson Cancer Center trials found no survival benefit with adjuvant WBRT despite improved intracranial control.¹¹ Potential reasons for the lack of survival benefit from WBRT include the longer interruption of systemic therapy with WBRT compared with SRS and the success of salvage therapy at the time of intracranial progression (necessitating close follow-up with serial imaging with an SRS-alone approach).¹⁰ In addition, prospective trials of SRS alone have shown that extracranial disease progression is the most common cause of death, with < 10% of patients dying as the result of intracranial progression alone.¹²

Alliance trial N0574 assessed the effect of adjuvant WBRT on both QOL and cognitive function.³ This trial randomly assigned 213 patients with one to three brain metastases to SRS alone or SRS and WBRT. The primary end point, cognitive deterioration at 3 months, was more frequent after SRS plus WBRT than after SRS alone (92% *v* 64%; *P* < .001). QOL was also worse at 3 months with the addition of WBRT. There was no difference in median overall survival despite improved intracranial control. An analysis of long-term survivors found worse cognitive function at 12 months for those patients treated with adjuvant WBRT. Taking these trials in context, noting the absence of a difference in survival and better cognitive and QOL outcomes, SRS alone is the preferred strategy for the treatment of patients with limited brain metastases.

Adjuvant WBRT After Surgery

Surgical resection of brain metastases, typically performed on larger lesions with mass effect, has been shown to have a survival benefit.¹³ However, even after magnetic resonance imaging–confirmed gross total resection, there is approximately a 50% risk of local recurrence in the surgical bed (Table 1).^{14–16} Postoperative (adjuvant) WBRT reduces the risk of recurrence in the surgical bed and development of new (ie, distant) brain

metastases by more than half, as well as death from neurologic causes; however, these benefits have not been shown to translate into an overall survival prolongation, recognizing that these clinical trials were not powered to assess survival.^{8,14}

There is a growing interest in the use of radiosurgery in the postoperative setting, because radiosurgery has the advantage of sparing patients the acute and late toxicities of WBRT. To assess the effect of radiosurgery on surgical bed control, MD Anderson Cancer Center 2009-0381, a single-institution phase III trial randomly assigned 132 patients to radiosurgery to the surgical cavity or observation after complete resection of brain metastases; the study found that surgical bed control rates were significantly improved after radiosurgery compared with resection alone (surgical bed control at 12 months 72% *v* 43%, respectively; *P* = .015).¹⁵ A multicenter trial (ClinicalTrials.gov identifier: NCT01535209) randomly assigned 59 patients with a resected brain metastasis to radiosurgery or WBRT with no difference in surgical bed control (74% *v* 75%; *P* = 1).¹⁷ The primary end point was neurologic (ie, clinician rated)/cognitive (ie, Mini-Mental State Examination) failure or neurologic death, and the trial did not demonstrate noninferiority of radiosurgery compared with WBRT. An Alliance/Canadian Cancer Trials Group cooperative group, multi-institutional phase III trial, N107C/CEC.3, randomly assigned 194 adult patients with a resected brain metastasis to either radiosurgery or WBRT; for the coprimary end points, the study found better preservation of cognitive function on a battery of tests (Hopkins Verbal Learning Test–Revised [HVLT-R], Trail Making Test [TMT], and Controlled Oral Word Association [COWA]) with radiosurgery and no difference in survival between the study arms.¹⁶ Cognitive deterioration was significantly more frequent in the WBRT arm (52.1% *v* 14.8% at 6 months, respectively; *P* < .001), and QOL was significantly worse despite better intracranial control with WBRT including surgical bed control (80.6% *v* 60.5%; *P* < .001). On the basis of the findings of these phase III trials, radiosurgery in the postoperative setting is a standard of care to improve surgical bed control relative to observation and is a less toxic alternative than WBRT. However, future research is needed to refine the radiosurgery technique (eg, fractionated, preoperative radiosurgery) to further improve on outcomes such as surgical bed control.

Multiple Brain Metastases

Although prior studies of radiosurgery alone have primarily been limited to patients with oligo-brain metastases (ie, one to four brain metastases), significant advances and more widespread adoption of radiosurgical technology have permitted radiosurgical management of multiple brain metastases.^{3,7,8,10} However, because no prospective randomized trial has examined the consequences of its omission, upfront WBRT remains a standard approach for patients with multiple brain metastases. In combination with WBRT, for multiple brain metastases, radiosurgery is commonly reserved for salvage therapy or as consolidative boost therapy for larger lesions or radioresistant histologic types such as melanoma or renal cell carcinoma.¹⁸

Palliative

Historically, palliative treatment has been the primary role of WBRT. Prospective trials have shown complete or partial responses in > 60% of brain metastases treated with WBRT and palliation of

Table 1. Selected Prospective Trials of Patients with Resected Brain Metastases, Intracranial Brain Control Rates, and Survival

Trial	No. of Patients	1-Year Surgical Bed Control (%)	1-Year Distant Brain Control (%)*	Median OS (months)
Patchell et al ¹⁴				
WBRT	49	88†	93†	11
Surgery alone	46	37†	56†	10
Kocher et al ⁸				
WBRT	81	76†	82†	NR
Surgery alone	79	45†	62†	NR
Brown et al ¹⁶				
WBRT	96	81	89	12
SRS	98	61	65	12
Mahajan et al ¹⁵				
SRS	63	72	42	17
Surgery alone	65	43	33	18

Abbreviations: NR, not reported; OS, overall survival; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

*Distant brain control means that a new brain metastasis did not appear at a site not treated.

†Estimated from figures.

presenting symptoms in more than half of patients; however, cognitive function was not evaluated in these studies.^{1,19} The role of WBRT for patients with poor-prognosis brain metastases was recently assessed by the Quality of Life after Treatment for Brain Metastases (QUARTZ) trial, which randomly assigned 538 patients with NSCLC with brain metastases to either WBRT plus supportive care or supportive care alone.⁴ Patients were only enrolled if they were deemed unsuitable for radiosurgery or surgery and if there was uncertainty about the potential benefit of WBRT.²⁰ A significant proportion of patients enrolled had poor performance status (38% had a Karnofsky performance status < 70), and the vast majority of patients received dexamethasone (median, 8 mg daily) irrespective of presence or absence of neurologic symptoms. There was no difference in median survival (9.2 weeks WBRT *v* 8.5 weeks; *P* = .808), QOL, or corticosteroids use between study arms. However, on further analysis, better-prognosis subgroups, such as patients younger than 60 years, had improved survival with WBRT. The QUARTZ trial suggests that WBRT provides no benefit compared with best supportive care for patients with poor-prognosis NSCLC with asymptomatic brain metastases; however, WBRT remains the primary palliative treatment for the majority of patients with brain metastases.

TOXICITY OF WBRT

Typical acute adverse effects of WBRT include temporary alopecia, mild dermatitis, mild fatigue, and less commonly otitis media or externa. Infrequently, worsening of pretreatment cognitive and neurologic deficits may develop during treatment as the consequence of a transient peritumoral edema, which usually responds to a short-term increase or the initiation of corticosteroids.

Several randomized clinical trials have demonstrated cognitive decline after treatment that includes WBRT.^{3,10,16} These trials have detected cognitive decline with validated, multidimensional, and cognitive tests of episodic memory (HVLT-R), executive function (TMT Part B, COWA), processing speed (TMT Part A), and fine motor control (grooved pegboard). In these studies, 35% to 52% of patients had a 3-standard deviation (SD) drop on cognitive testing 3 to 6 months after WBRT, which was increased relative to 6% to 24% of patients with a 3-SD drop after SRS.^{3,16} Interestingly, these trials have demonstrated a particularly pronounced toxicity of WBRT on episodic memory that is greater than the other domains of cognition assessed.

Although important, demonstration of these cognitive effects has important limitations. It is possible that patients may initially have a decline in cognitive function and later a recovery, because most studies use a time-to-event analysis instead of reporting cognitive function serially over time. However, most patients with brain metastases in these trials did not live beyond 4 to 6 months, diminishing the relevance of such a long-term follow-up question for the vast majority. A small subset of patients enrolled in N0574 survived $\geq$ 12 months and completed cognitive testing that confirmed greater cognitive decline in patients treated with upfront SRS plus WBRT compared with SRS alone.³ As defined populations of patients with brain metastases are identified who have longer survivorship and are treated with radiation, it will be important to carefully evaluate cognitive risks and benefits of different radiation treatment approaches

in the months and years following treatment. Lastly, although trials have demonstrated cognitive and QOL effects from WBRT, one study found both episodic memory decline and self-reported cognitive complaints but limited correlation between decline in tested cognitive function and patient-reported cognitive function.²¹ Discordance between objective cognitive test results and subjective complaints is frequently observed in many neurologic populations, including those with well-known cognitive disorders such as Alzheimer's disease, underscoring the importance of objectively measuring cognition with performance-based neuropsychological tests rather than patient-reported outcomes.²²

Clinically overt, debilitating dementia associated with WBRT manifests in a small minority of patients (< 5%), and is the more severe end of the spectrum of cognitive decline reported in clinical trials.²³ Radiation-induced dementia in its most severe form can be accompanied by other symptoms such as gait instability and urinary incontinence, and more commonly occurs with larger radiation dose per treatment (> 3.5 Gy per treatment) and/or higher total radiation dose.²³

Treatments to Prevent or Ameliorate WBRT Toxicity

Unlike most events that cause cognitive decline, WBRT is planned. Therefore, there is great interest in pharmacologic agents to prophylactically mitigate cognitive toxicity from WBRT. Memantine is a noncompetitive, low-affinity, open-channel antagonist of the *N*-methyl-D-aspartate receptor that blocks pathologic excessive stimulation of *N*-methyl-D-aspartate receptors. In preclinical models, memantine has been shown to be neuroprotective,^{24,25} and in two placebo-controlled phase III trials memantine proved to be a well-tolerated, effective treatment for vascular dementia.^{26,27} The Radiation Therapy Oncology Group trial (RTOG) 0614 randomly assigned 554 patients with brain metastases receiving WBRT to either memantine or placebo.²⁸ The memantine was well tolerated, and rates of toxicity were similar between placebo and memantine. There was less decline in episodic memory (HVLT-R delayed recall) in the memantine arm compared with placebo (0.0 compared with -0.9 SDs) at 24 weeks (*P* = .059). However, the difference was not statistically significant, possibly caused by a lack of statistical power because there were only 149 analyzable patients at 24 weeks as the result of patient death and disease progression. The memantine arm had significantly longer time to cognitive decline (hazard ratio, 0.78; *P* = .01), and the probability of cognitive function failure at 24 weeks was 54% in the memantine arm and 65% in the placebo arm. Superior results were also observed in the memantine arm for executive function, processing speed, and other measures of episodic memory.

If cognitive symptoms arise after radiotherapy, it is important to evaluate potential contributing factors such as tumor progression, fatigue, or depression. For postradiation cognitive symptoms, many pharmacologic agents have been tested and shown little benefit. Donepezil, an acetylcholinesterase inhibitor that is used to treat Alzheimer's dementia, has shown some promise for postradiation cognitive symptoms. In a phase III trial, 198 patients with brain tumors were randomly assigned to donepezil or placebo 6 months after WBRT or partial brain radiation.²⁹ There was no statistically significant difference in the composite neurocognitive scores between study arms at 6 months; however, on subgroup analysis,

patients with greater pretreatment cognitive impairment were found to have benefit with donepezil.

ALTERNATIVE TREATMENTS

Radiosurgery Alone

There is strong evidence supporting radiosurgery alone for patients with limited brain metastases amenable to radiosurgery. For patients with multiple brain metastases, arbitrarily typically defined as five to 10 (or five to 15) lesions, the role of radiosurgery alone is more controversial.³⁰ Japanese Leksell Gamma Knife (JLKG) trial 0901, a multi-institutional prospective observational study, treated 1,194 patients with one to 10 newly diagnosed brain metastases with radiosurgery alone.¹² The patients enrolled in this trial had relatively small-volume brain disease (total cumulative volume ≤ 15 mL). Overall survival did not differ between those with two to four metastases and those with five to 10 metastases ($P = .78$; median overall survival, 10.8 v 10.8 months, respectively). In JLKG0901, although only 9% of patients received salvage WBRT, few suffered a neurologic death and the vast majority died as the result of systemic disease progression, suggesting that a radiosurgery-alone approach may be a reasonable treatment for patients with multiple brain metastases. However, it should be recognized that patients enrolled in JLKG0901 may be different than patient populations in North America or Europe, because mutations in epidermal growth factor receptor (EGFR) are more prevalent among the Japanese population. To our knowledge, there are no published randomized trials evaluating the role of radiosurgery alone with omission of upfront WBRT in patients with four or more brain metastases. However, there are ongoing trials (such as a phase III trial at MD Anderson Cancer Center [[ClinicalTrials.gov](#) identifier: NCT01592968]) that randomly assigns patients with four to 15 brain metastases to WBRT or SRS with primary end points of local tumor control and cognitive function. A similar trial ([ClinicalTrials.gov](#) identifier: NCT02353000) in the Netherlands is currently enrolling patients with four to 10 brain metastases with QOL as the primary end point. Off study, if radiosurgery alone is used to treat multiple metastases it is important to emphasize that close follow-up (eg, every 2 months for the first year) with serial magnetic resonance imaging is warranted, because approximately half of patients will develop new metastases.

Systemic Therapy

Traditional chemotherapy has had a limited role in the management of patients with brain metastases, and its use was usually limited to patients who had experienced disease relapse after use of either WBRT or SRS. However, recent advances in novel agents (eg, tyrosine kinase inhibitors [TKIs] with better blood-brain barrier [BBB] penetration and immunotherapy that results in high responses in brain metastases) has increased the role of systemic therapies in the management of this patient population.³¹

Lung cancer, breast cancer, and melanoma account for the majority of cases of brain metastases, and most of the prospective clinical trials have focused on these malignancies (Table 2).³²⁻⁴⁴ However, most of these trials are single-arm phase II studies rather than randomized clinical trials. First-generation TKIs such as

erlotinib, gefitinib, or crizotinib had more limited BBB penetration; however, next-generation TKIs such as osimertinib, ceritinib, and alectinib have better ability to cross the BBB. The response rates with use of erlotinib, gefitinib, and osimertinib in EGFR mutation-positive lung cancer brain metastases have been reported in prospective trials to range from 50% to 80%, resulting in progression-free survival of 6 to 12 months and overall survival of 15 to 22 months.³²⁻³⁴ The response rates for patients enrolled in prospective trials of crizotinib are approximately 20%, which increase to 50% to 70% with the use of next-generation inhibitors such as alectinib, brigatinib, and ceritinib in *ALK*-rearranged lung cancer brain metastases.^{35, 45-47} A phase II trial of the combination of lapatinib and capecitabine resulted in a response rate of 66% in WBRT-naïve human epidermal growth factor receptor 2-positive breast cancer brain metastases; however, the response rate was 20% in those for whom prior radiation had failed.⁴⁰ A phase II trial evaluating neratinib and capecitabine was associated with 50% response rates in brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer.⁴⁸ A phase II trial of vemurafenib resulted in response rates of approximately 20% to 25% in *BRAF* mutation-positive melanoma brain metastases.³⁷ Response rates of 30% to 38% were reported with dabrafenib in a phase II trial.⁴⁹ The combination of dabrafenib and trametinib in a phase II trial resulted in a response rate of 55% in asymptomatic *BRAF*^{V600E} brain metastases.³⁸ The higher responses were observed in WBRT or radiation-naïve patients compared with those for whom prior radiation had failed.⁵⁰ Although high response rates are observed with the use of TKIs, a limitation of these agents is that the durability of response is < 1 year for most agents. Immune checkpoint inhibitors that target cytotoxic T-lymphocyte-associated protein 4 and programmed cell death (PD) 1 axis have shown initial promise in patients with lung cancer and melanoma brain metastases.⁵¹ In a phase II trial, ipilimumab monotherapy produced disease control rates of 25% in patients who were not receiving steroids and 10% in those who were receiving steroids for melanoma brain metastases.³⁹ A phase II trial of pembrolizumab monotherapy showed a brain metastasis response rate of 22% in patients with melanoma and 33% in patients with NSCLC.⁵² A combination of ipilimumab and nivolumab assessed in a phase II trial was associated with response rates of 45% to 55% in melanoma brain metastases.⁵³ The advantage of immunotherapy is that, unlike TKIs, the responses are more durable (ie, > 1 year).

Although there have been many advances in the management of brain metastases with systemic therapy, there needs to be some caution in withholding cranial radiotherapy (SRS or WBRT). For example, a multi-institution retrospective study of 202 patients with EGFR-mutant NSCLC with brain metastases found that treatment with EGFR-TKIs alone and the deferral of radiotherapy was associated with inferior survival compared with those patients who were treated up front with cranial radiotherapy followed by EGFR-TKIs.⁵⁴ Although some data are available, more studies are needed to assess the timing and sequencing of systemic therapy/immunotherapy and cranial radiation, in addition to investigating the efficacy and toxicity of combining the two treatment modalities.⁵⁵ Finally, most of the targeted therapy or immunotherapy

Table 2. Selected Prospective Trials of Systemic Therapies in the Treatment of Brain Metastases, Intracranial Response Rate, Intracranial Progression-Free Survival, and Overall Survival

Drug Studied	Phase	No. of Patients With Brain Metastases	Key Study Features	Median ICRR (%)	Median ICDFS	Median OS
Melanoma						
Dabrafenib (Dummer et al) ³⁶	I-II	Cohort A, <i>BRAF</i> ^{V600E} : 74 Cohort A, <i>BRAF</i> ^{V600K} : 15 Cohort B, <i>BRAF</i> ^{V600E} : 65 Cohort B, <i>BRAF</i> ^{V600K} : 18	Cohort A: Treatment naïve Cohort B: Progressed after prior treatment	39.2 6.7 30.8 22.2	4 months (16.1 weeks) 2 months (8.1 weeks) 4.1 months (16.6 weeks) 4 months (15.9 weeks)	8.2 months (33.1 weeks) 7.7 months (31.4 weeks) 4 months (16.3 weeks) 5.2 months (21.9 weeks)
Vemurafenib (McArthur et al) ³⁷	II	Cohort 1: 90 Cohort 2: 56	Cohort 1: Treatment naïve Cohort 2: Previously treated	18 23	3.7 months 4.0 months	8.9 months 9.6 months
Dabrafenib plus trametinib (Davies et al) ³⁸	II	Cohort A: 76	Asymptomatic, treatment naïve, <i>BRAF</i> ^{V600E} mutant	58	5.6 months	10.8 months
		Cohort B: 16	Asymptomatic, previously treated, <i>BRAF</i> ^{V600E} mutant	56	7.2 months	24.3 months
		Cohort C: 16	Asymptomatic, <i>BRAF</i> ^{V600K/R} positive, treated and/or untreated	44	4.2 months	10.1 months
		Cohort D: 17	<i>BRAF</i> ^{V600E/K/R} positive, symptomatic, previously treated/untreated	59	5.5 months	11.5 months
Ipilimumab (Margolin et al) ³⁹	II	Cohort A: 51 Cohort B: 21	Not receiving steroids during the study period Receiving steroids during the study	24 10	1.4 months 1.2 months	7.0 months 3.7 months
Breast cancer						
Lapatinib plus capecitabine (Bachelot et al) ⁴⁰	II	45	Treatment naïve	65.9	5.5 months	17 months
Lapatinib (Lin et al) ⁴¹	II	242	Previously treated	6	2.4 months	6.4 months
Neratinib (Freedman et al) ⁴²	II	40	Previously treated patients	—	1.9 months	8.7 months
Lung cancer						
Erlotinib (Walsh et al) ³²	II	40	Administered 1 week before and after WBRT	86	8 months	11.8 months
Afatinib (Hoffknecht et al) ⁴³	Compassionate use program	100	Previously progressed while receiving TKI	61	3.6 months	NR
Gefitinib (Ceresoli et al) ³³	II	41	Included both treatment-naïve and previously treated patients	27	3 months	5 months
Osimertinib (Mok et al) ³⁴	Subgroup analysis of phase III study	93	Previously untreated asymptomatic brain metastases	NR	8.5 months*	NR
Crizotinib (Costa et al) ³⁵	Pooled analysis	275	Analysis of patients with brain metastases enrolled in PROFILE 1005 and 1007	18 in previously untreated and 33 in previously treated	5.9 months in previously untreated and 6.0 months in previously treated	NR
Alectinib (Gadgeel et al) ⁴⁴	Pooled analysis	136	Analysis of patients with brain metastases enrolled in NP28761 and NP28673	64	NR	NR

Abbreviations: ICDFS, intracranial progression-free survival; ICRR, intracranial response rate; NR, not reported; OS, overall survival; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

*Overall progression-free survival.

trials have included patients with asymptomatic brain metastases and have not assessed cognitive function, which is critical in trials of neurologic disease and therapies directed at the brain. Hence, the next generation of trials will need to evaluate the combination of these systemic agents with either SRS or WBRT to examine not only the efficacy but also the toxicity associated with such approaches.

Alternating Electric Field Therapy

Extensively tested in the setting of newly diagnosed and recurrent glioblastoma, tumor-treating fields (TTFields) represent a noninvasive and potentially novel approach to treating intracranial micrometastatic disease, potentially without the cognitive effects of WBRT (Fig 1). Through the placement of transducer arrays on the shaved scalp, TTFields deliver alternating electric fields with low intensity and intermediate frequency to the brain parenchyma. These alternating electric fields have antimitotic activity against tumor cells through the disruption of mitotic spindle formation during metaphase and through the dielectrophoretic dislocation of intracellular constituents, resulting in apoptosis. In the setting of newly diagnosed glioblastoma, studies demonstrating antimitotic activity of TTFields *in vitro* and *in vivo* have translated into a phase III trial demonstrating an overall survival benefit with the addition of TTFields to conventional chemoradiotherapy.⁵⁶ Similarly significant activity of TTFields has been observed in preclinical models of NSCLC.⁵⁷ Building upon these promising preclinical results, METIS ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02831959) identifier: NCT02831959) is an ongoing phase III trial of radiosurgery alone versus radiosurgery plus TTFields for patients with one to 10 brain metastases. The primary objective of this currently enrolling study is to determine whether TTFields prolongs the time to first intracranial progression. Importantly, cognitive

function is also being evaluated in this trial of a new therapeutic approach.

Hippocampal-Avoidance WBRT

The generation of new neurons from mitotically active neural stem cells located within the subgranular zone of the hippocampal dentate gyrus has been observed to be central to new memory formation.⁵⁸ Preclinical studies have demonstrated that injury to these neural stem cells from relatively modest doses of radiation may contribute to radiotherapy-induced cognitive toxicity and have been supported by additional clinical studies observing a dose-response relationship between dose received by the hippocampus and risk of post-radiotherapy decline in episodic memory.⁵⁹ Modern intensity-modulated radiotherapy techniques have been developed to conformally avoid this hippocampal neural stem cell compartment while delivering therapeutic radiation dose to the remaining whole-brain parenchyma (Fig 2). These techniques, often referred to as hippocampal-avoidance WBRT, were tested in a single-arm phase II trial in patients with brain metastases.²¹ The primary end point of this trial, the mean relative decline in HVL-R delayed recall score from baseline to 4 months, was 7%, which was significant compared with the 30% mean relative decline in HVL-R delayed recall with the historical control ($P < .001$). The trial found that hippocampal-avoidance WBRT was associated with highly promising preservation of memory and QOL compared with historical controls. To validate these phase III findings, NRG Oncology-CC001 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02360215) identifier: NCT02360215) is an ongoing phase III trial of WBRT with memantine with or without hippocampal avoidance for patients with brain metastases, with the primary outcome of time to neurocognitive failure. In addition, NRG Oncology-CC003 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02635009) identifier: NCT02635009) is an ongoing randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer, with the primary outcomes of intracranial relapse rate and time to deterioration in episodic memory.

SUMMARY

The management of patients with brain metastases is rapidly evolving; WBRT is no longer the default treatment for patients with brain metastases. Because of the recent better understanding of the effect of WBRT on cognitive function and QOL, the use of WBRT should be judicious and considered in the context of other treatment options such as radiosurgery. In addition, if clinically appropriate alternative treatment options are available, many clinicians will follow a treatment paradigm of delaying WBRT to later in a patient's disease course. Treatment options will continue to increase, especially with the exploitation of the molecular characteristics of tumors. With the complexities of treatment decisions for this patient population, a multidisciplinary approach is needed to optimize management of patient care. Finally, with the detrimental effect of brain metastases, further research is needed to improve the therapeutic ratio of interventions^{21,28} and to prevent the development of brain metastases in patients with cancer.⁶⁰

Fig 1. Tumor treating fields are administered by four transducer arrays placed on the shaved scalp and connected to a portable device.

Fig 2. (A) The hippocampal avoidance region (blue) is generated by expanding the hippocampal contour (orange) by 5 mm. (B) Color wash dose distributions for hippocampal-avoidance whole-brain radiotherapy are shown on representative axial, sagittal, and coronal images.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Conception and design: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Whole-Brain Radiotherapy for Brain Metastases: Evolution or Revolution?

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