Advances in radiotherapy for brain metastases

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Abstract

As novel systemic therapies yield improved survival in metastatic cancer patients, the frequency of brain metastases continues to increase. Over the years, management strategies have continued to evolve. Historically, stereotactic radiosurgery has been used as a boost to whole-brain radiotherapy (WBRT) but is increasingly being used as a replacement for WBRT. Given its capacity to treat both macro- and micro-metastases in the brain, WBRT has been an important management strategy for years, and recent research has identified technologic and pharmacologic approaches to delivering WBRT more safely. In this review, we outline the current landscape of radiotherapeutic treatment options and discuss approaches to integrating radiotherapy advances in the contemporary management of brain metastases.

Keywords

brain metastases | modern management | radiotherapy | stereotactic radiosurgery | whole-brain radiotherapy.

Brain metastases (BMs) are intracranial neoplasms that occur in 10%–20% of adult patients with cancer.[1] Over the years, the frequency of BMs has increased due to the increase in overall survival of cancer patients due to improvements in systemic therapies.[2] Improvements in diagnostic imaging approaches have also led to a further increase in lead time diagnosis of smaller lesions that further increases the detected incidence. Within the brain, the most common sites of metastasis are the cerebral hemispheres (80%), cerebellum (15%), and brainstem (5%).[3] Cancers vary in their proclivity to metastasize to the brain, but in adults, up to 75% of BMs can be accounted for by lung and breast carcinomas and malignant melanomas.[4] Renal carcinomas and colorectal cancers are also common sources of BMs in adults. In children, sarcomas and germ cell tumors are the most likely to metastasize to the brain.[4] Brain metastases tend to develop at the junction between gray and white matter, where the terminal "watershed regions" of arterial circulation reside. Most reach the brain through hematogenous spread and are believed to be entrapped in small size terminal arteries.[4]

BMs may present with focal or generalized symptoms, although up to one-third of BM patients may be asymptomatic.[5] This means many epidemiologic studies may underestimate the true incidence of BMs. Common clinical features include headaches, focal weakness, neurological deficit, and seizures. When neurological symptoms develop in a patient with a known extracranial malignancy, BM must always be considered. Contrast-enhanced MRI is the preferred method for a differential diagnosis between BMs and primary brain tumors.[6] MRI is used for imaging because it can detect lesions as small as 1.9 mm.[5]

BM management varies per patient and should involve multidisciplinary discussion of specific factors including tumor histology, performance status, prognosis, the presence or absence of targetable mutations, BM number and volume, and BM velocity,[7] as well as patient-centered decision making focusing on maximizing tumor control and prioritizing the patient's quality of life. Treatment options include surgical resection, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), systemic therapy (chemotherapy, targeted

therapy, and/or immunotherapy), and best supportive care with symptom management. Supportive treatments frequently used in the management of BMs include corticosteroids, antiepileptics, anticoagulants, antidepressants, and analgesics.

Stereotactic Radiosurgery

Stereotactic radiosurgery is a highly precise radiotherapeutic management approach that has been increasingly employed in BM management. SRS is a treatment delivered with submillimeter precision to BMs localized in 3 dimensions and permitting maximal sparing of normal brain tissue.[8] SRS can be delivered using a single session (single-fraction SRS) or multiple (typically 2–5) sessions (fractionated SRS) of high-dose radiation. One advantage of single-fraction SRS is the use of a stereotactic frame-based approach to cranial fixation, although frameless stereotactic mask-based approaches are increasingly being used. One advantage of fractionated SRS is the time to enable normal-tissue recovery between SRS sessions, which can limit toxicity when treating targets larger in volume or near critical normal tissues such as the brainstem or the optic structures.[9] SRS allows a noninvasive approach that spares most normal brain tissue from radiation exposure and offers a potentially safer treatment option for patients.[10] One downside to SRS is the increased risk of future BM development arising from untreated micro-metastases (distant brain relapses).[11] Close MRI surveillance to monitor for distant brain relapses permits effective salvage treatment prior to the development of symptoms.

SRS was initially a resource-intensive therapy offered only at specialized centers and indicated primarily for patients with a limited number of BMs. In prospective trials, SRS was first introduced as a boost treatment for conventional WBRT. RTOG 95-08 included patients with 1–3 BMs and demonstrated an overall survival benefit in patients with a single BM but no survival benefit in patients with 2–3 BMs with the addition of SRS to conventional WBRT. As secondary endpoints, local control and Karnofsky Performance Status (KPS) were improved with the addition of SRS to WBRT.[12] Similarly, Kondziolka et al.[13] observed significantly improved local control at 1 year with the addition of SRS to conventional WBRT for patients 2–4 BMs.

More recent trials have highlighted that SRS can be used as a solo treatment strategy without adjunct conventional WBRT. In a multi-institutional study of SRS with or without conventional WBRT in patients with 1–4 BMs, Aoyama et al.[12] observed improvements in local control, distant brain control, and intracranial control with the addition of conventional WBRT to SRS, but no significant difference in terms of median survival, neurologic death, KPS, or acute or late neurotoxicity. In a trial of surgery or SRS with or without conventional WBRT, the European Organization for Research and Treatment of Cancer also observed improved intracranial control, including local and distant brain control, with adjunct conventional WBRT but no difference in time to performance status deterioration (the primary endpoint) or survival. In addition, the addition of conventional WBRT was found to lead to a greater decline in patient-reported quality of life.[14]

In a single-institution prospective randomized trial of SRS with or without conventional WBRT for 1–3 BMs, Chang et al.[15] observed improved intracranial control with the addition of conventional WBRT to SRS, but also greater decline in cognitive function as assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R) 4 months after treatment. Corroboration of these results was seen in a phase III trial, N05754, for patients with 1–3 BMs randomized to receive SRS + conventional WBRT or SRS alone. While no survival difference was observed between the treatment arms, patients who received SRS alone demonstrated less cognitive deterioration at 3 months. The summation of these studies indicated that SRS alone may be a preferred strategy for patients with limited BM.[16] A review of 54 published trials found that the addition of conventional WBRT to radiosurgery improved local and distant brain control in select patients, but data showed worse neurocognitive outcomes and no difference in overall survival.[17]

Coinciding with the increasing evidence for the management of limited BMs with SRS alone has been the advancement in MRI achieving greater sensitivity for detecting smaller BMs. As a result, close neuro-oncologic MRI surveillance following SRS has permitted the detection of macro-metastatic growth of untreated micro-metastases before symptomatic progression. In addition, advances in SRS technology have permitted more widespread adoption across multiple academic and community centers and relatively efficient development and delivery of SRS treatment plans for multiple BMs (Figure 1). The summation of these efforts has led to broader use of SRS to treat patients with multiple BMs and multiple times during the course of BM patients' lifespan.[18,19]

The appropriate cutoff of BM number or volume to determine who would benefit from SRS versus has not been well defined. Previous cutoffs have ranged from 10 to 15 cc when treating multiple BMs.[7] Several studies have treated patients with large tumor volumes up to 30 cc using SRS alone and achieved successful local control and acceptable toxicity.[20,21] Very small survival differences were found between patients with less than 4 BM versus more than 4 BMs.[20] To address this important management question, the Canadian Cancer Trials Group launched CE.7, a phase III trial randomizing patients with 5–15 newly diagnosed BMs to either SRS or WBRT plus memantine with primary endpoints of overall survival and neurocognitive function. This trial limits accrual to patients with at most 30 cc BM tumor volume. The trial has been amended to include hippocampal avoidance using intensity-modulated radiotherapy (IMRT), as described below.

Whole-Brain Radiotherapy

Whole-brain radiotherapy has been a cornerstone of BM treatment for decades. This approach delivers radiation to the whole brain, with the intention of treating both macroscopic and microscopic BMs. The primary concern with conventional WBRT is the cognitive toxicity that patients can experience after treatment and that can affect patient's quality of life.
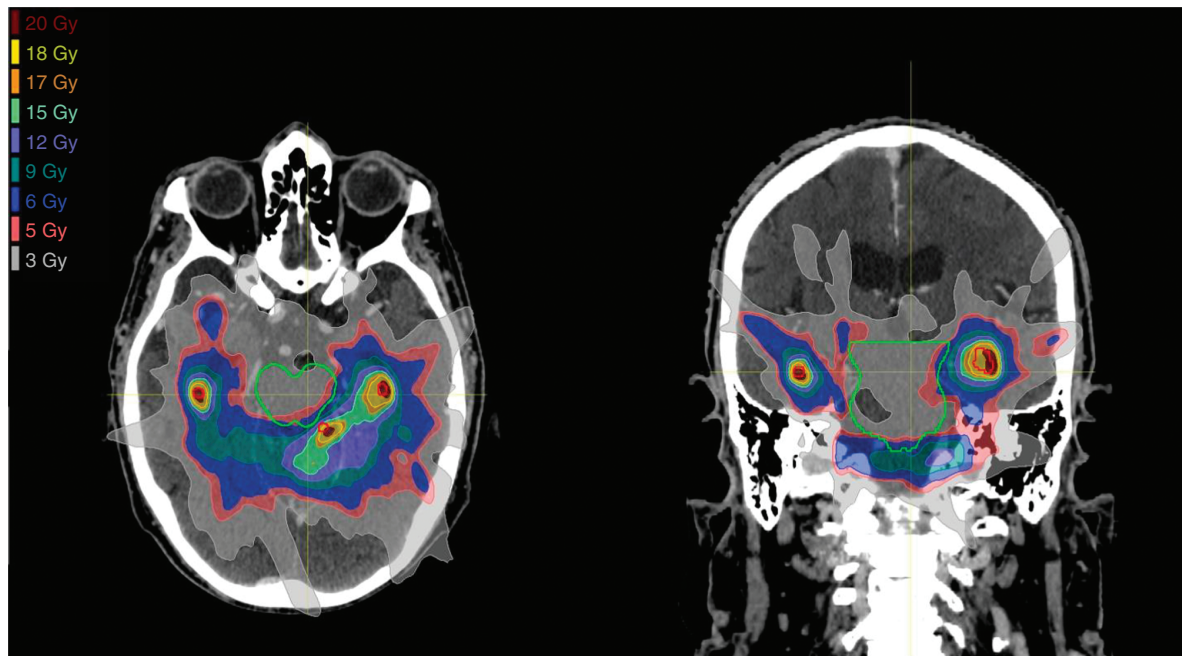
Figure 1. Example of a multilesion stereotactic radiosurgery treatment plan delivered with volumetric modulated arc radiotherapy. In this case of predominantly bilateral temporal lobe lesions, low-dose radiation was able to be purposefully directed away from the brainstem. 18 Gy delivered to all radiographic lesions.

N-methyl-D-aspartate (NMDA) receptor remodeling is one suspected mechanism to explain the neurocognitive effects of conventional WBRT. NMDA receptors are activated by glutamate and are involved in both learning and memory; however, over-excitation can lead to neuronal death. Following radiation exposure, cells in the hippocampal dentate gyrus reorganize their synaptic receptors, decreasing NMDA receptor density and increasing inhibitory GABA receptor density.[22] This alteration in receptor density impairs long-term potentiation (LTP) which is an integral part of neuroplasticity and functional memory. Memantine is an NMDA receptor agonist, which has established use for dementia in patients with Alzheimer's disease.[23] Wu et al.[22] observed in a rodent model that memantine during irradiation was sufficient to prevent this alteration in LTP.

Building off this preclinical work, RTOG 0614 was a randomized, double-blind, placebo-controlled trial to evaluate the role of memantine in preventing cognitive toxicity after WBRT. In this study, the primary endpoint results of HVLT decline did not reach statistical significance ($P < .05$), although there was a trend toward significance for HVLT decline ($P = .059$) as well as a statistically significant benefit seen with the compositive cognitive toxicity endpoint. The lack of statistical significance for the primary endpoint could be attributed to only 149 analyzable patients, compared to the upfront sample size of 508 initial patients, leading to only 35% statistical power for the primary endpoint.[24] The study found that overall patients who received memantine in addition to WBRT had better cognitive function over time and reduced rates of decline in memory, executive function, and processing speed.[24]

Another pathogenic mechanism for radiation-induced neurocognitive toxicities involves radiation-induced selective injury to proliferating neuronal progenitor cells and consequentially a sharp and prolonged decline in neurogenesis in the subgranular zone of the hippocampi.[25–33] These effects seem to be mediated by inflammation in the area surrounding the neural progenitor cells.[34] Neurogenesis within the hippocampus is believed to be responsible for new memory formation. Clinical studies have shown a dose–response relationship between hippocampal radiotherapy dose and the risk of subsequent decline in memory function. The summation of these biological and clinical findings supported the hypothesis that sparing the hippocampal dentate gyrus during WBRT for BMs may provide a cognitive-preservation benefit. Hippocampal avoidance using IMRT during WBRT (HA-WBRT) is a modern radiotherapy technique that has been developed to avoid the cognition-specific and exquisitely radiosensitive hippocampal neural stem cell compartment while delivering therapeutic radiation dose to the remaining whole-brain parenchyma (Figure 2).[35]

RTOG 0933 was a phase II trial to first evaluate the use of HA-WBRT for patients with BMs and observed a significant improvement in cognitive outcomes compared to historical controls. Confirming these results was NRG Oncology CC001, a subsequent phase III trial of WBRT plus memantine with or without hippocampal avoidance. This study observed that HA-WBRT plus memantine compared to WBRT plus memantine better preserves cognitive function and patient-reported symptoms, with no differences in progression-free survival or overall survival.[36] The
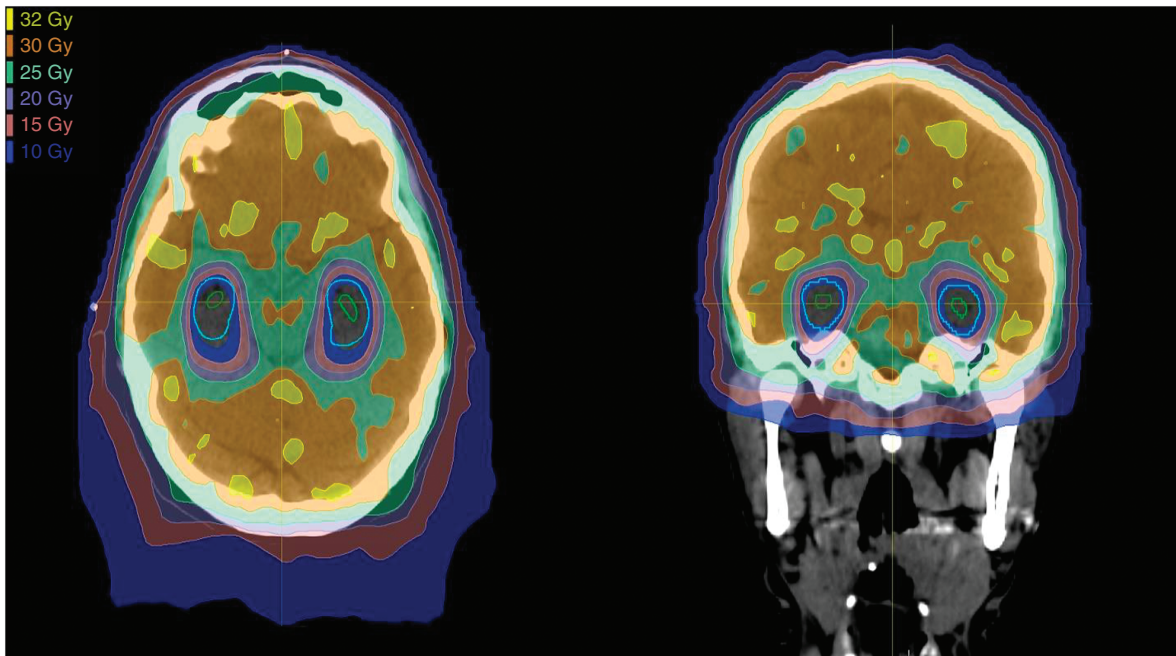
Figure 2. Example of hippocampal-avoidant whole-brain radiotherapy (HA-WBRT) treatment plan delivered with volumetric modulated arc radiotherapy. The hippocampi are spared high-dose radiation and an intermediate gradient of radiation dose is accepted around the hippocampi, known as the planning organ at risk volume. WBRT dose of 30 Gy delivered in 10 fractions.

patients who received HA-WBRT plus memantine reported less fatigue, less difficulty with memory, less difficulty with speaking and, using imputed data, less interference of neurologic symptoms in daily activities, and fewer cognitive symptoms. In a single-blinded randomized trial of WBRT versus HA-WBRT (unlike NRG CC001, neither arm was treated with memantine), patients receiving HA-WBRT demonstrated better preservation of HVLT-R total recall, recognition, and memory compared with patients undergoing WBRT.[37]

Based on these trials, the use of hippocampal avoidance and memantine has been considered the standard of care for patients who are planned to receive WBRT. Importantly, prior trials of conventional WBRT compared to SRS did not include the contemporary neuroprotective strategies of memantine and hippocampal avoidance, raising questions as to which approach is optimal in modern BM management.

Modern Management and Future Directions

With improved survivorship of BM patients due to improved efficacy of systemic therapies, the number of times that a BM patient requires radiotherapeutic intervention has also increased. As illustrated in Figure 3, these clinical scenarios include (1) the initial presentation of BMs, (2) the development of recurrent BMs either as progression of preexisting BMs or as development of distant brain

relapse, and (3) the development of new or recurrent BMs at the end of life when all available systemic therapy options have been exhausted and/or a patient's performance status is too poor to qualify for systemic therapy. At each of these time points, options for modern management include SRS, WBRT including HA-WBRT with memantine, or best supportive care. Modern trials seek to clarify the decision-making process of which approach is optimal. In the survivorship of BM patients, generally, HA-WBRT with memantine can only be used once, whereas SRS can be used multiple times on different lesions. Thus, the question of when to use HA-WBRT to simultaneously treat macro- and micro-metastatic disease becomes even more salient, and the enrollment of brain patients to clinical trials (namely, CCTG CE.7, NRG BN009, and NRG CC009 as discussed below) seeking to address this question in a different patient population becomes a priority.

Newly Diagnosed BMs

CCTG CE.7 is an ongoing phase III trial seeking to evaluate the role of HA-WBRT at the initial presentation of BMs. Endorsed by NRG Oncology and Alliance Oncology, this trial compares SRS to HA-WBRT plus memantine for patients with 5–15 newly diagnosed BMs. Originally designed to compare SRS to conventional WBRT, the emergence of practice-changing results from NRG CC001 led to an amendment to the trial to include hippocampal avoidance on the WBRT arm to provide a more contemporaneous
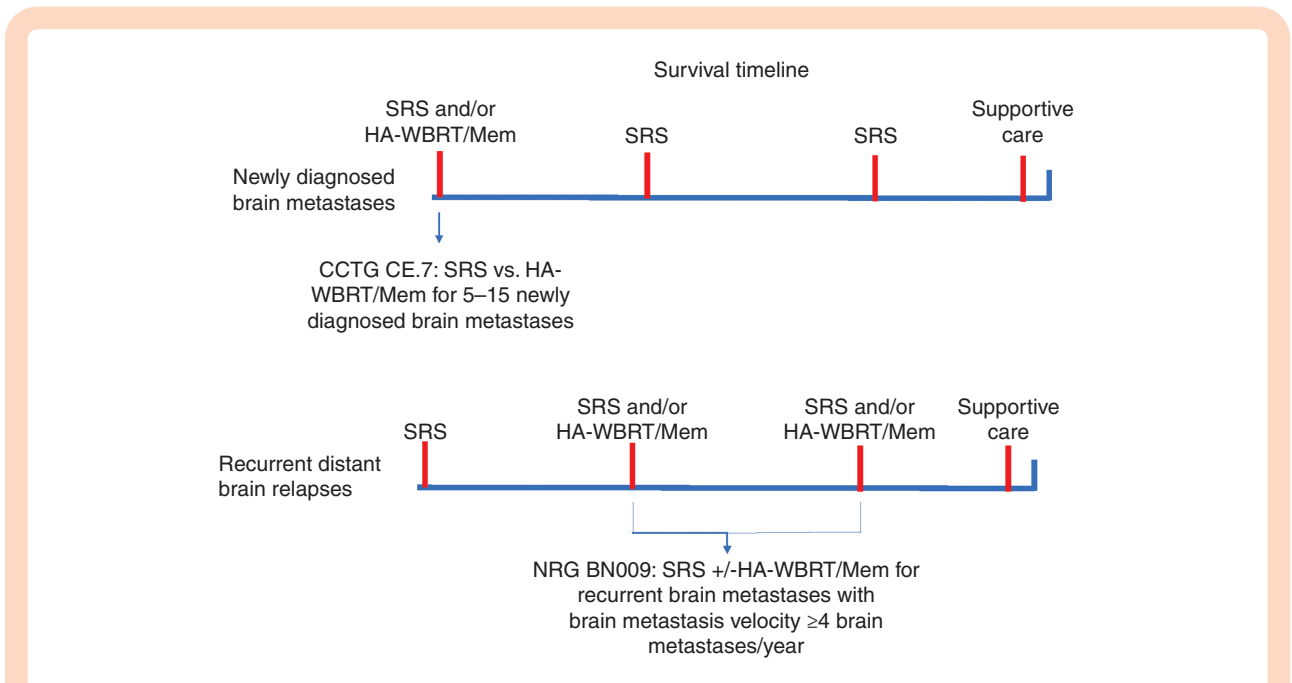
Figure 3. Survivorship timeline of brain metastasis patient, where stereotactic radiosurgery (SRS) can be used multiple times for different lesions, but hippocampal-avoidant whole-brain radiotherapy plus memantine (HA-WBRT + Mem) can be used only once. Ongoing trials CCTG CE.7 and NRG BN009 will help determine the optimal timing of HA-WBRT + Mem.

comparison of modern radiotherapy management approaches. The co-primary endpoints of the study are overall survival and neurocognitive progression-free survival. As of May 2021, 55 of target 206 patients have been accrued.

Recurrent BMs

The concept of brain metastasis velocity (BMV) was recently developed to identify a high-risk cohort of BM patients whose rapidly progressive BM disease puts them at risk for neurologic death. BMV is defined as:

$$BMV = \frac{[\text{Total number of new brain metastases since upfront SRS}]}{[\text{Time interval (in years) since upfront SRS}]}$$

In a cohort of 737 BM patients from a single institution, Farris et al.[38] observed that BMV at first or second distant brain relapse after upfront SRS predicted for overall survival. In a larger validation dataset of more than 2000 BM patients from 9 other institutions, BMV remained prognostic with nearly identical median survival outcomes. Specifically, patients who had a BMV of ≥4 BMs/year had a 7-month shortening in median survival as compared to patients with BMV of less than 4 BMs/year ($P < .0001$). BMV at first distant brain relapse was also predictive of BMV at second distant brain relapse, highlighting the ability of BMV to serve as a surrogate marker for intracranial progression. The prognostic value of BMV has since been validated in 2 additional published series.[39,40]

Importantly, using a centralized definition of neurologic death, BMV at first or second distant brain relapse after upfront SRS predicted for neurologic death following salvage

SRS.[38] Patients with BMV ≥4 BMs/year were nearly 2-fold more likely to suffer neurologic death than patients with BMV less than 4 BMs/year. A recent analysis of BM patients treated with SRS in the immunotherapy era confirmed that BMV remained prognostic for both overall survival and neurologic death, with more than 7-fold increased risk of neurologic death in patients with BMV ≥4 BMs/year ($P = .005$).[41]

The summation of these findings underscores the capacity of BMV following upfront SRS to distinguish a subset of patients (BMV ≥4 BMs/year) for whom optimizing intracranial control with combined HA-WBRT plus SRS may prevent neurologic death from being a primary contributor to survival.

Seeking to test this hypothesis, NRG Oncology BN009 is a phase III trial of salvage SRS versus HA-WBRT plus SRS for first or second distant brain relapse after upfront SRS with BMV of ≥4 BMs/year. The primary objective is to determine if SRS plus HA-WBRT following upfront SRS prevents neurologic death as compared to salvage SRS alone.[42]

End of Life

In most cancer types, the frequency of BM increases with age. This pattern is largely due to increased risk of cancer as people age, but also can be attributed to the low frequency of BM in cancers more common in young people.[43] In general, increased age comes with more comorbidities, and quality of life is generally already worse. End-of-life treatment addresses the efficacy of supportive treatment alone or combined with WBRT. The importance of estimating prognosis is demonstrated in the Quality of Life

after Treatment for Brain Metastases (QUARTZ) trial. In this trial, non-small cell lung cancer (NSCLC) patients with BM unsuitable for surgical resection or SRS were randomly assigned to optimal supportive care (OSC) or optimal supportive care plus WBRT (OSC + WBRT). OSC included administering the steroid dexamethasone. They found that there was no significant difference in overall survival or quality of life in patients who received OSC + WBRT compared to those who only received OSC.[44] This study demonstrates that for patients with poor prognosis, WBRT offers little benefit. Best supportive care is a reasonable consideration for patients with poor performance status and uncontrolled extracranial disease who cannot receive systemic therapies.[44]

Systemic Therapy

The role of systemic therapy in the management of BMs has recently evolved. Historically, systemic therapy was limited to chemotherapy, which has variable central nervous system (CNS) penetration due to the blood–brain barrier (BBB).[7] As driver mutations have been identified and multiple agents with modest CNS penetration of the BBB have been developed, systemic management is being utilized alone or in combination with RT. About 10% of NSCLC patients have mutations in the EGFR gene and 5% have ALK translocations.[7] Drugs targeting tyrosine kinase inhibitors (TKIs) that penetrate the BBB are currently being explored. Combinational SRS and EGFR-TKIs yielded the longest OS in a multicenter retrospective report, whereas EGFR-TKI alone had the lowest survival.[45] The synergistic benefit from TKIs is unclear related to local control, but TKIs offer a potentially more effective modality for controlling microscopic disease in the brain compared to SRS alone.[46] Concurrent RT and ALK-TKIs have been shown in preclinical studies to have a synergistic effect on tumor growth and microvessel density.[46] Numerous clinical trials are currently ongoing to evaluate SRS in combination with various targeted agents, some of which may give more concrete evidence of the potential of these therapies.

Small Cell Lung Cancer BMs

Historically, BMs from small cell lung cancer (SCLC) have been excluded from BM trials since SCLC patients were often treated with prophylactic cranial irradiation, after which WBRT is rarely utilized again. In addition, exclusion of these patients was based on observations that patients with SCLC are more likely to develop micro-metastatic seeding of the brain at the time of initial macro-metastatic presentation in the brain. However, the widespread adoption of thin-slice volumetric postcontrast MRI has improved the sensitivity of detecting millimetric distant brain relapses following SRS, raising the question as to whether WBRT to treat micro-metastatic disease is warranted. The FIRE-SCLC study, a large retrospective study analyzing data from 710 SCLC BM patients from 28 centers treated with upfront SRS (without prior PCI or WBRT), observed favorable survival outcomes following SRS as compared to a large contemporary WBRT cohort.[47] In addition, prevention of cognitive toxicity with neuroprotective strategies of prophylactic memantine and

hippocampal avoidance demonstrate that WBRT can be delivered more safely. Thus, SCLC BM patients have become an important patient population in which to study and compare these treatment approaches. NRG Oncology CC009 is a recently activated phase III trial comparing SRS to HA-WBRT plus memantine for 10 or fewer BMs from SCLC with a primary endpoint of cognitive function failure.

Simultaneous Integrated Boost During HA-WBRT

Simultaneous integrated boost (SIB) during HA-WBRT plus memantine represents a novel radiotherapy approach to optimizing control of both gross macro-metastases as well as micro-metastases in the brain, while maximally preserving cognition and quality of life (Figure 4). In a single-arm phase II trial, Westover et al. treated 50 BM patients with HA-WBRT to 20 Gy in 10 fractions with SIB to 40 Gy in 10 fractions and observed improved cognitive outcomes compared to historical outcomes following conventional WBRT and comparable intracranial control to modern series of WBRT plus SRS.[42]

Similarly, favorable results have been reported in other single-institution trials: Popp et al.[48] evaluated the use of HA-WBRT 30 Gy in 12 fractions with SIB 51 Gy/42 Gy in 12 fractions for intact metastases/surgical cavities and Lebow et al.[49] evaluated the use of HA-WBRT 30 Gy in 12 fractions with SIB 37.5 Gy in 10 fractions for intact metastases. This approach is also being evaluated in HIPPORAD,[50] a randomized phase II trial of HA-WBRT + SIB versus WBRT + SIB for patients with at least 4 BMs and at least one but not exceeding 10 BMs ≥5 mm (none within 7 mm of the hippocampus). This trial is being conducted by the German NOA, ARO, DKTK-ROG cooperative groups. HA-WBRT/WBRT is 30 Gy in 12 fractions, and SIB is 51 Gy in 12 fractions (42 Gy in 12 fractions to the surgical cavity). The primary endpoint is the neurocognitive function at 3 months.

Resection Bed Radiosurgery

Resection of BM is typically reserved for larger lesions with mass effect and has been shown in select circumstances to have a survival benefit.[51] However, following gross total resection with modern surgical techniques, there is approximately a 50% risk of local recurrence in the surgical bed.[52,53] Postoperative WBRT reduces the risk of recurrence in the surgical bed by more than half and increases intracranial control.[52,54] In an effort to avoid the toxicities of conventional WBRT, yet improve surgical bed control, SRS to the surgical bed has been used in the postoperative setting and was evaluated in 2 prospective phase III trials. One of these trials was a single-institution, phase III trial that observed improved surgical bed control rates post-resection radiosurgery compared to post-resection observation.[53] A cooperative group, multi-institutional phase III trial, N107C/CEC.3, randomized 194 adult patients with a resected BM to either radiosurgery or conventional WBRT and found better preservation of cognitive function with radiosurgery and no difference in survival between the study arms.[55] These phase III trials established postoperative SRS as a standard of care to improve surgical bed control relative to observation and a less toxic alternative than conventional WBRT.
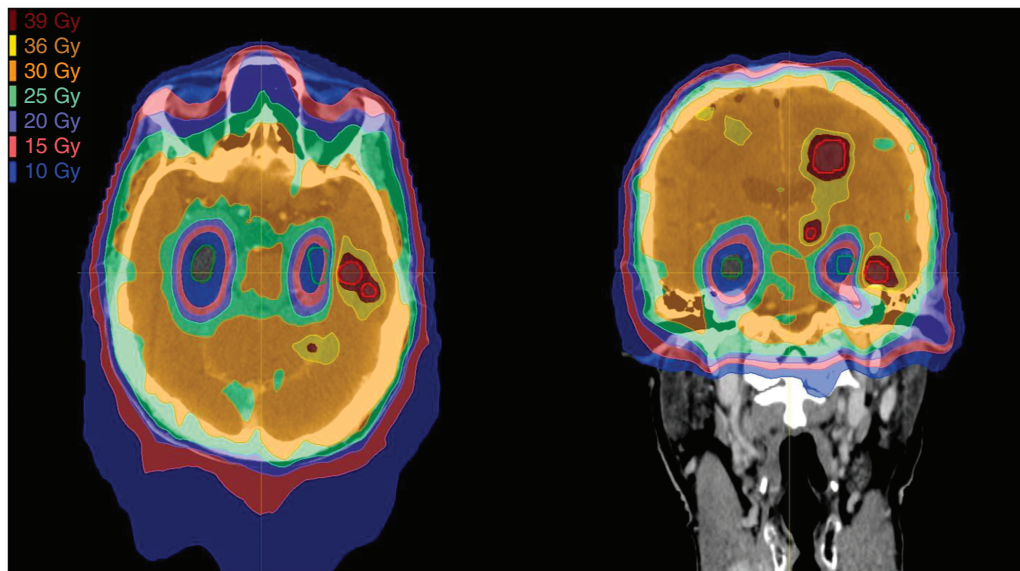
Figure 4. Example of hippocampal-avoidant whole-brain radiotherapy with a simultaneous integrated boost (SIB-HA-WBRT) to the radiographic brain metastases, delivered with volumetric modulated arc radiotherapy. The hippocampi are maximally spared but not at the expense of radiographic disease coverage. WBRT dose of 30 Gy and brain metastases boost dose of 39 Gy, together delivered in 10 fractions.

However, one major shortcoming of post-resection SRS is the relatively poor surgical bed control compared to the historic standard of care of conventional WBRT.[56] As discussed above, fractionated SRS has emerged as an opportunity to dose-escalate the resection bed and/or treat wider microscopic margins to improve surgical bed control, while exploiting the radiobiologic advantages of fractionation to permit safer treatment.[9] Retrospective studies of fractionated SRS in patients with resected BMs have observed better local control and lower rates of radiation necrosis compared to single-fraction SRS.[53,55,57–66] Alliance A071801 is an ongoing phase III trial of fractionated SRS versus single-fraction SRS for resected BM with a primary endpoint of surgical bed control.

In addition, postoperative SRS does not adequately prevent the risk of leptomeningeal dissemination (LMD), an unintended consequence of resection that can compromise survival, quality of life, and cognitive function.[56] In order to potentially reduce the risk of LMD, data suggests the use of preoperative SRS in order to preemptively sterilize microscopic disease that seeds viable tumor cells outside the treated cavity.[67] One major limitation of neoadjuvant SRS is the lack of pathological confirmation prior to SRS. NCT03741673 is an ongoing phase III trial investigating the 1-year LMD-free rate among patients randomized to preoperative SRS versus postoperative SRS.

Conclusions

Significant advances in radiotherapy technology and techniques have enhanced the effectiveness and safety of the 2 most commonly employed treatments for BMs: SRS and WBRT. With improved survivorship of BM patients resulting from novel systemic therapies, the appropriate timing of application of these radiotherapy treatments in a BM patient's survivorship remains under investigation, and we strongly recommend enrollment of patients in ongoing prospective trials to address this and other clinically significant questions.

Conflict of interest statement. The authors declare no conflicts of interest related to the published work.

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