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Whole brain radiotherapy for brain metastasis

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Abstract

Whole brain radiotherapy (WBRT) is a mainstay of treatment in patients with both identifiable brain metastases and prophylaxis for microscopic disease. The use of WBRT has decreased somewhat in recent years due to both advances in radiation technology, allowing for a more localized delivery of radiation, and growing concerns regarding the late toxicity profile associated with WBRT. This has prompted the development of several recent and ongoing prospective studies designed to provide Level I evidence to guide optimal treatment approaches for patients with intracranial metastases. In addition to defining the role of WBRT in patients with brain metastases, identifying methods to improve WBRT is an active area of investigation, and can be classified into two general categories: Those designed to decrease the morbidity of WBRT, primarily by reducing late toxicity, and those designed to improve the efficacy of WBRT. Both of these areas of research show diversity and promise, and it seems feasible that in the near future, the efficacy/toxicity ratio may be improved, allowing for a more diverse clinical application of WBRT.

Key Words: Brain metastasis, oncology, prophylactic cranial irradiation, radiation, stereotactic radiosurgery, whole brain radiotherapy

INTRODUCTION

Intracranial metastasis is the most common type of brain tumor in adults, with an overall incidence of approximately 8.3/100,000.[60,89] Until the past few years, the most common primary tumors responsible for brain metastases reported in adults were lung and breast cancer.[58,89] Recently, however, two large studies found that the incidence of intracranial metastasis has shifted with (in descending order) lung cancer, malignant melanoma, renal cell carcinoma, breast carcinoma, and colorectal carcinoma now representing the most common tumors associated with brain metastases.[7,73] This shift might be explained by improved treatments in breast cancer, resulting in fewer patients with

metastatic disease, coupled with the rising incidence and more common screening for intracranial disease in melanoma, which metastasizes rapidly and remains a therapeutic challenge.[46] These factors may also explain the rise in the number of metastatic brain lesions seen in cancer patients over the past few decades. Barring autopsy studies, which have reported postmortem evidence of intracranial metastasis in over 60% of individuals with certain cancers,[44] the most recent studies of living patients with metastatic disease have shown incidences of brain involvement of 10-40%.[31,60,78] This number is significantly greater than the reported incidence of intracranial metastasis half a century ago, with studies citing brain lesions in only as high as 5% of cancer patients.[14] Thus, while cancer therapy and

radiologic imaging have improved dramatically over the past 50-60 years, brain metastases have become a significantly more prominent issue in patient treatment due to increasing incidence, and represents an ongoing therapeutic challenge.

Due to the advanced nature of disease at the time of presentation in patients with intracranial metastases, particularly if symptomatic, treatment options have traditionally been limited. The presence of multiple metastases often preclude the option of surgical resection, and trials using various systemic chemotherapeutic agents have to this point only demonstrated efficacy in treating brain metastases in a very select group of primary tumors that are highly chemosensitive.[33,35,87] In contrast, radiation therapy has been shown to be efficacious in treating brain metastases regardless of the primary tumor histology, including metastases derived from tumors considered to be radioresistant.[14] The ability of radiation to effectively treat brain metastases of any tumor histology is unique among currently available therapies, and thus represents an important palliative option for patients with brain metastases by alleviating symptoms, decreasing the use of corticosteroids needed to control tumor-associated edema,[1,8] and potentially improving overall survival.[30] For these reasons, radiation therapy has become a cornerstone in the treatment of metastatic brain lesions.

HISTORY AND EVOLUTION OF WHOLE BRAIN RADIOTHERAPY

Supportive care for patients with multiple cerebral metastases was the only viable option available to physicians and oncologists for the first half of the 20th century. It was not until the 1950s that the first conclusive publication was released on the possibility of palliation of symptomatic intracranial metastatic disease through the use of external radiation.[14] It was found in this preliminary study by Chao *et al*. that symptoms associated with cerebral metastases could be alleviated in 63% of individuals undergoing therapy, and also that there seemed to be no bias in response among individuals with metastases from tumors thought of as radiosensitive versus those seen in patients with more radioresistant tumors, such as malignant melanoma.[14] Additionally, radiotherapy for intracranial metastasis was found to result in minimal morbidity and toxicity by these early investigators.[63] These initial findings in the treatment of cerebral metastases provided the foundation for whole brain radiotherapy (WBRT) being used in patients with brain metastases today.

While initially deemed effective and minimally toxic, WBRT has seen many improvements and augmentations during its evolution from its modest beginnings in the 1950s, wherein various doses and schedules of radiation were administered on a case-by-case basis,[14] with no sparing of radiosensitive intracerebral structures. By the 1970s, WBRT had become a mainstay treatment for cerebral metastases,[47] and while some of its uses are now being supplanted by stereotactic radiosurgery (SRS), it remains a beneficial adjunct to other therapies, is used as monotherapy in a variety of clinical situations, and is still the treatment of choice in patients with widely disseminated metastases in the brain.

TOXICITY: ACUTE, EARLY-DELAYED, AND LATE ADVERSE EFFECTS OF WBRT

Although generally speaking, cranial irradiation is relatively well tolerated, it can cause a number of adverse effects, both over the short- and long-term. Some of the patient characteristics that determine the degree of adverse effects that a patient is likely to experience has been attributed to age (>60 years or <12 years at greatest risk), size of metastases, and tumor-associated edema.[16] In addition, prognosis plays a role, since many of the delayed effects of WBRT typically would occur after the median survival for many patients with brain metastases. WBRT-related toxicities are classified as acute, early-delayed, or late, depending upon when the symptom occurs in relation to the commencement of radiation therapy.[74]

ACUTE TOXICITY

Fatigue is one of the most prominent acute toxicities associated with WBRT, experienced within the first days to weeks of treatment.[16] Other acute effects include radiation-induced alopecia and dermatitis, nausea and vomiting, and decreased appetite. Aside from radiation-induced alopecia, these acute effects are generally self-limited and resolve spontaneously or with medical management.[16] Cerebral edema is another relatively common acute adverse effect of WBRT, but is usually responsive to treatment with corticosteroids.[24]

Although no longer clinically relevant with the use of current dose and fractionation schedules, one described acute complication of WBRT therapy as acute encephalopathy, in which patients may experience severe headache, focal neurologic deficits, obtundation, and in the most severe cases, cerebral herniation (secondary to increased intracranial pressure [ICP]) resulting in death of the patient.[74,91] This clinical entity is most often witnessed in patients undergoing WBRT with dose-fractionation schedules utilizing single-doses of greater than 3 Gy.[91] This dose-dependent potential of WBRT to cause acute encephalopathy was illustrated in an early study on WBRT fractionation, in which 45 patients were irradiated with a single fraction of 10 Gy of gamma radiation, which resulted in the death of three patients (6.7%) within hours of treatment.[38]

EARLY-DELAYED TOXICITY

The adverse effects of WBRT that are experienced by patients within the first weeks to months after beginning treatment are termed "early-delayed" (or "subacute") toxicities. During this period of time, patients may experience continued fatigue, somnolence, neurocognitive deficits such as decline in memory, and other general or focal neurologic symptoms.[4,16] In addition to symptomatology, radiographic changes may be noted during the 1-4 month posttreatment interval. In this scenario, posttreatment contrast magnetic resonance imaging (MRI) may show diffuse contrast enhancement, posing a challenge in determining whether these findings are transient early-delayed changes or progression of disease.[18] When the findings are indeed benign early-delayed effects, the phenomenon is referred to as pseudoprogression, and is commonly associated with higher dosing regimens.[80]

Somnolence syndrome following WBRT has been primarily described in the pediatric population,[28,85] although it has also been reported in adults.[25] In addition to somnolence, manifestations may include fatigue, fever, headache, nausea, vomiting, dysphasia, anorexia, dysarthria, and irritability.[72,85] The syndrome is generally self-limited, and often resolves within 1-3 weeks. In some cases, particularly in children who received prophylactic cranial irradiation (PCI) for Acute Lymphocytic Leukemia (ALL), somnolence syndrome can result in long-term (potentially irreversible) neurologic dysfunction,[12] so prevention of somnolence syndrome with corticosteroids in the pediatric population is ideal.[85]

LATE TOXICITY

Late toxicity from radiation is defined by the Radiation Therapy Oncology Group (RTOG) as any toxicity that occurs after 90 days of commencement of treatment.[37] In modern-day administration of WBRT therapy, late adverse effects are generally the most feared sequelae of treatment. In contrast to the generally self-limited (and often mild) acute and early-delayed toxicities experienced by patients undergoing WBRT with standard dose-fractionation schedules, the late effects of WBRT are not self-limited and may have severe consequences.[16]

Adverse neurocognitive effects are common late findings in patients who have undergone WBRT. Neurocognitive degeneration induced by radiation therapy follows a well-documented biphasic pattern beginning with a transient decline in mental functioning at around 4 months posttreatment, followed by an improvement in neurocognitive functioning, and then an ultimate irreversible return of impairment months to years later;[4] some cases have been reported to occur as late as 33 years after therapy.[21] Although the prevalence of

these effects in patients treated with WBRT has been difficult to quantify due to confounding variables such as persistent brain metastases, paraneoplastic neurocognitive dysfunction, and possible chemotherapy-induced neurocognitive decline, there seems to be sufficient evidence to suggest that it is common enough to be a necessary consideration in the development of a WBRT dose-fractionation schedule appropriate for favorable-prognosis patients.

Only recently has delayed neurocognitive decline become an effect that is followed in clinical trials involving WBRT. A large meta-analysis by Tallet *et al.* analyzed the neurocognitive outcome results from seven recent trials that used WBRT at various prophylactic doses and protocols in patients without brain metastases, and found a decline in neurocognitive functioning of 31-57% at 3 months, and 48-89% at 1 year.[81] Although WBRT seems to cause neurocognitive dysfunction, an observation by Li *et al.* demonstrates that in patients with brain metastases, neurocognitive function is more detrimentally affected by progression of intracranial disease than by WBRT, and thus in patients who require WBRT therapy for cerebral metastases, neurocognitive outcomes are actually improved with WBRT, secondary to successful treatment and tumor regression.[45]

Leukoencephalopathy is another potential late toxicity associated with WBRT, and becomes more prevalent with higher total doses of therapy. The clinical syndrome is characterized by seizures, lethargy, neurocognitive dysfunction, and dysarthria, and occurs within months to sometimes years following treatment with WBRT.[27,66] The diagnosis can be supported by radiographic imaging, which demonstrates diffuse injury to the white matter of the cerebral hemispheres consistent with hyperintensity on T2-weighted MRI (most notable in the periventricular white matter) and hypodensity on computed tomography (CT), as well as noticeable sulcal and ventricular enlargement that are evident on both imaging modalities.[39,86] It is important to note that most patients who have received WBRT will have some degree of similar CT/MRI findings as patients with leukoencephalopathy, but might be entirely asymptomatic.[39,86] Leukoencephalopathy has been shown to be particularly common toxicity in children—a consideration that has led to the more limited use of PCI in childhood ALL.[66]

Radiation necrosis is perhaps the most extreme local toxicity to occur with WBRT. As the name implies, areas of the brain affected by radiation necrosis represent necrotic, nonreparable tissue. Pathologically, these areas are characterized by fibrinoid necrosis of small arteries and arterioles, which is hypothesized to be the result of extensive damage to the vascular endothelium.[11,86] Although more common in patients being treated with

higher doses of radiation to limited areas of the brain, such as in treatment with SRS, WBRT has also been implicated as a cause of radiation necrosis. However, this late effect is relatively uncommon, as the general threshold to develop radiation-induced necrosis typically exceeds doses used in traditional WBRT dose-fractionation schedules.[22,48]

In addition to smaller-caliber vessel damage responsible for radiation necrosis, large cerebrovascular structures have also been shown to be vulnerable to the effects of WBRT: Particularly the vessels comprising the anterior half of the Circle of Willis.[19] Although quite uncommon with WBRT, the effects on these vessels have been described as similar to those witnessed in a severely atherosclerotic vessel. Moyamoya syndrome can then develop, characterized by weak collateral vessel formation around the sclerotic arteries that are prone to hemorrhage and thrombosis, potentially contributing to worsening dementia and even death.[9,83] The radiographic findings typical of Moyamoya syndrome include the "puff of smoke" on angiography, illustrative of the density of the many small collateral vessels.[79]

THE ROLE OF WBRT IN THE TREATMENT OF INTRACRANIAL METASTASES

WBRT alone

In patients with multiple cerebral metastases, WBRT is generally the treatment of choice, as it addresses both macroscopic and microscopic disease. Studies have shown an improvement in symptoms in 64-83% of patients after treatment with WBRT alone,[10,40,77] and have also demonstrated an increase in median OS from 1 month with no treatment to 3-7 months following WBRT.[30] The most common dose/fractionation schedule used is 30 Gy delivered in 10 fractions over the course of 2 weeks.[10,77] There have been a number of trials that have utilized alternative dose-fractionation schedules, including protocols with both lower and higher doses of overall radiation compared with the control regimens. Most of these studies have failed to show a statistically significant difference, although a trial performed by Davey *et al.* was able to show an increase in time before intracranial relapse of 32 weeks in the experimental dose arm (40 Gy/20 BID fractions) versus 14 weeks in the control arm (20 Gy/5 fractions).[17] Toxicity associated with the alternative dose-fractionation schedules reported in the literature is not significantly different than standard schedules, with the exception of high dose single fraction therapy at doses of 10 Gy, which result in greater toxicity.[38] Overall, sufficient evidence is not currently available to suggest superior efficacy or reduced toxicity of alternative dosing schedules over the accepted and currently used standard WBRT protocols.[82] Therefore, prospective studies with carefully designed

neurocognitive endpoints are still needed to more clearly determine if altered fractionation schedules may be beneficial, particularly in the context of brain metastasis patients with the potential for long-term survival.

In addition to treating patients with known brain metastases, WBRT is also used to treat cancer patients with a high risk of developing brain metastases, termed PCI. The possible utility of PCI for prevention of small cell lung cancer (SCLC)-associated intracranial metastases is one that has been recognized and studied since the 1970s, but individual trials conducted in the mid-1990s were unable to unanimously prove PCI's efficacy in decreasing mortality.[6] In 1999, Auperin *et al.* published the first meta-analysis that was able to demonstrate a survival benefit of PCI.[6] This study analyzed the results of seven randomized clinical trials (RCTs) in which PCI was offered to SCLC patients who had a complete response to therapy, and found that there was a decrease in the incidence of brain metastasis at 3 years in patients who received PCI versus those who did not (33% versus 59%, respectively), along with a decrease in mortality (79.3% versus 84.7%, respectively).[6] Recent trials have attempted to extend these findings in patients with an incomplete response to chemotherapy. A recent study completed by the EORTC demonstrated both a decreased risk of developing brain metastasis and improvement in overall survival at one year in patients receiving PCI.[76] PCI has also been studied in patients with nonsmall cell lung cancer (NSCLC). A trial conducted by the RTOG demonstrated a decrease in the incidence of brain metastasis in the PCI arm (8% with PCI versus 18% in the observation arm), however, there was no statistically significant difference in overall survival.[34]

WBRT as adjuvant to surgery

Some of the first prospective studies evaluating WBRT involved its role following surgical resection. A RCT by Patchell *et al.* compared outcomes in patients who received resection alone versus those who received resection followed by adjuvant WBRT.[61] Efficacy endpoints of the trial included local (site of resection) and regional (other areas of the brain) recurrence, as well as OS. WBRT following resection demonstrated superior local and regional recurrence rates of 10% and 18%, versus 46% and 70% witnessed with resection alone. Although differences in OS were not statistically significant, patients undergoing WBRT did have decreased death associated with neurologic dysfunction (14% of patients who received WBRT, versus 44% of patients who received observation alone).[61] A large RCT conducted by the EORTC included 359 patients with one to three intracranial metastases who were randomized to either receiving surgical resection (or SRS) alone or resection followed by adjuvant WBRT.[42] Of the 160 patients who received surgical resection, consistent with the results

from the RCT performed by Patchell *et al.*, as well as three retrospective studies,[5,36,75] this trial demonstrated that the addition of WBRT to surgical resection reduced both local (59-27%) and regional (42-23%) intracranial recurrence at 24 months, with no OS benefit.[42]

Improving the efficacy of WBRT

One strategy to improve the efficacy of WBRT involves delivering higher doses of radiation to macroscopic disease, with the most common approach involving SRS. The RTOG recently completed a large Phase III RCT evaluating this approach in 331 patients with good performance status (Karnofsky performance status >70) and one to three brain metastases.[1] This study demonstrated an increase in local brain control from 62% with WBRT alone to 91% when SRS was added to WBRT.[1] Although the addition of SRS to WBRT did not demonstrate improved survival over WBRT alone in patients with multiple intracranial metastases, the study did find an increase in median survival time in patients with single metastases: The median survival in patients treated with WBRT alone was 4.9 months, while in patients treated with WBRT and SRS the median survival was increased to 6.5 months.[1]

Another strategy to deliver higher doses of radiation to brain metastases is by using standard WBRT in conjunction with simultaneous in-field boost (SIB) delivered through helical tomotherapy. Rodrigues *et al.* developed a dosimetric feasibility study that demonstrated the possibility of the administration of an SIB dose of 60 Gy in 10 fractions that is biologically equivalent to a single SRS dose of 18 Gy but superior in terms of normal tissue tolerance; a Phase I trial assessing toxicity has already been accomplished based upon this feasibility study, which demonstrated minimal toxicity.[69] A Phase II trial conducted by the same research group is currently underway, with the goal of comparing the efficacy of helical tomotherapy SIB versus traditional SRS as an adjunct to WBRT.[68]

Lastly, combining WBRT with systemic therapy has been an approach explored to improve clinical outcomes in brain metastases patients. However, since WBRT first became the treatment of choice for intracranial metastasis in the 1970s, there has not been any conclusive evidence that the addition of any chemotherapeutic agent to WBRT imparts a significant benefit in median survival time.[2,41,55,57,64,84] Furthermore, most trials have shown an increased degree of treatment-related toxicity when chemotherapy is used in combination with WBRT.[82] The RTOG-sponsored clinical trial by Knisely *et al.* (RTOG 0118) was one of the more prominent studies to investigate the combination of WBRT and chemotherapy and arrive at such findings. In this trial, 183 patients were randomly assigned to either receive WBRT alone or WBRT with adjuvant thalidomide. While the median

survival was the same (3.9 months), the study was prematurely terminated due to the excessive number of adverse effects witnessed in the chemo-radiation arm.[41]

The radiosensitizing chemotherapeutic agent motexafin gadolinium has also been explored as an adjuvant to WBRT. In a Phase III trial of 554 patients conducted by Mehta *et al.*, it was found that in patients with NSCLC, the interval to neurologic progression could be extended by the concomitant use of WBRT with motexafin gadolinium (24.2 months) versus WBRT alone (8.8 months).[53] It was also demonstrated that there was a statistically significant decrease in the total number of salvage procedures (e.g., SRS, surgical resection) required for management of intracranial disease in patients receiving WBRT with motexafin gadolinium, however, OS was not improved.[53]

Temozolomide is an orally administered alkylating agent that is receiving much attention as an experimental adjunct to brain irradiation in the treatment of brain metastases. While prospective data is limited at this time, there is some evidence of its efficacy in improving response to treatment versus WBRT alone.[2] A recent phase II study by Chua *et al.* found increases in OS and median time to CNS progression in NSCLC patients who received temozolomide with WBRT versus WBRT alone, but this study was flawed due to the patient accrual goal not being met; thus, the authors concluded that temozolomide's role in the treatment of brain metastases should be further investigated, as it remains unresolved.[15] A study by Pesce *et al.* failed to show a survival benefit of temozolomide as an adjunct to WBRT, but instead demonstrated a superior OS in NSCLC patients treated with WBRT and gefitinib (4.9 versus 6.3 months, respectively),[62] an orally administered EGFR inhibitor. The most promising study regarding the use of temozolomide with WBRT was documented in a phase II trial by Gamboa-Vignolle *et al.*, which found WBRT and temozolomide increased the objective response to 78.6% from 48.1% in patients with cerebral metastases who received WBRT alone.[29] Additionally, the median progression free survival was found to be 11.8 months in the temozolomide and WBRT arm, versus 5.6 months in the WBRT alone arm.[29] The inconclusive and often contradictory findings from these relatively smaller studies have led to the development of a large clinical trial that is currently comparing WBRT with temozolomide to WBRT alone, in patients with melanoma (EORTC-18981).[23]

Based on the data currently available, there is no established role of combining chemotherapy with WBRT, and its use therefore remains experimental.[82] However, the concept of applying a systemic agent to improve the efficacy of WBRT continues to be an active area of investigation. The critical determinant for clinical

application of such an agent will be based on its capacity to selectively enhance radiation-induced toxicity in the tumor and not the normal surround brain, thereby improving the therapeutic index of WBRT. There are several, large prospective studies either underway or being planned, designed to test this concept in an effort to improve survival in patients with brain metastases.

Decreasing the morbidity of WBRT

In addition to improving the efficacy of WBRT, another area of active investigation involves decreasing its long-term neurocognitive effects. One novel approach that has been proposed applies recent technologic advancements involved in radiation delivery to conformally avoid doses to regions in the brain hypothesized to be particularly sensitive to the effects of radiation. One of the first of these areas to be characterized as a potential candidate for sparing is the hippocampus. As memory loss (particularly the loss of the ability to consolidate new memories) is one of the more common and subjectively detrimental late adverse effects of WBRT, the hippocampus seemed a natural target to avoid. Additionally, metastatic lesions to the hippocampus are extremely rare, and in approximately 86% of patients with cerebral metastases, there exists at least a 15 mm margin between the closest metastasis and the hippocampus, which would allow for effective sparing with modern WBRT without compromising therapeutic efficacy.[32] Sparing of the hippocampal region seems to be particularly important in the pediatric population, as it has been conclusively demonstrated that decrease in IQ and ability to form new memories correlated with radiation exposure to the temporal regions of the brain containing the hippocampus.[54,59] Hippocampal sparing has been shown to be feasible by multiple radiation treatment planning studies, and is likely to receive increasing attention in the future for PCI,[52,67,88] and is already currently being investigated by the RTOG in an ongoing clinical trial.[71] In addition to the hippocampus itself, other contiguous structures of the limbic system have been proposed as candidates for avoidance during administration of WBRT due to their involvement in memory consolidation, emotional processing, and fine motor coordination—all processes that seem to be negatively affected by irradiation of the whole brain. Similar to the hippocampus, the limbic system as a whole seems to only rarely harbor metastatic disease and sparing is dosimetrically feasible.[50,52]

The relatively recent discovery of neural stem cells (NSCs) in two discrete areas of the brain is the impetus behind the most recent potential target for radiation sparing in WBRT. Specifically, these NSCs were identified to be located within a small area of the hippocampus known as the subgranular zone as well as in the subventricular zones.[49] It is proposed that these NSCs are capable of repairing damage to both white and gray matter in the brain, and when destroyed by radiation may prevent neural regeneration and cause subsequent neurocognitive toxicity.[26] NSC sparing has also been shown to be possible by Marsh *et al*. through feasibility studies, and trials of NSC sparing in patients with cerebral metastases have been proposed.[51]

Another area of investigation involved in mitigating the long-term sequelae of WBRT involves neuroprotectors. Memantine is one such neuroprotector that is being studied for this purpose. Acting as an NMDA-receptor antagonist, memantine has been proven effective in slowing or preventing decline in cognitive function through prevention of neurologic excitotoxicity. A recently completed Phase III trial (RTOG-0614) was designed to evaluate memantine's potential to decrease late neurocognitive toxicity from WBRT (as compared with WBRT alone). The primary endpoint of this study is to determine the effect of concomitant memantine with WBRT on cognitive function—specifically memory—at 24 weeks following WBRT therapy. Results from this study are pending.[70]

Localized radiotherapy alone for brain metastases

With recent advancements in radiation delivery, coupled with the lack of survival benefit and both short- and long-term toxicities associated with WBRT, a recent trend in the field of radiation oncology has been toward withholding WBRT and proceeding with a localized approach in the management of patients with brain metastases using SRS. The recent findings of three large prospective randomized studies support this approach. In a study designed to compare WBRT with SRS versus SRS alone in patients with 1-4 brain metastases, Aoyama *et al*. reported a 1-year tumor (locoregional) recurrence rate of 46.8% in the WBRT and SRS group, and a recurrence rate of 76.4% in those treated with SRS alone.[3] In regard to local control alone, combined WBRT and SRS provided local control in 88.7% of patients at 12 months, while SRS alone provided local control in 72.5%.[3] A trial by Kocher *et al*. (EORTC 22952-26001) enrolled 359 patients who were similarly randomized to either SRS alone or SRS with adjuvant WBRT.[42] This study also found an improvement in local and regional control, measured as relapse at 2 years, with SRS and WBRT versus SRS alone (19% versus 31% locally, and 33% versus 48% regionally).[42] Neither the Aoyama study nor the Kocher study reported a statistically significant difference in OS with the addition of WBRT to SRS.[3,42] Conversely, rather than demonstrating an improvement in survival, findings presented by Chang *et al*. actually demonstrated a detriment in overall survival in patients undergoing WBRT.[13] Although this was a well-done, randomized study, the relevance of these findings are still somewhat unclear, as there may have been a higher proportion of patients with favorable prognostic factors in the SRS arm.[90] Additionally, a meta-analysis of the pooled results of the three aforementioned studies found no difference in OS.[82]

In addition to SRS being used as primary therapy for limited brain metastases, this localized approach is also being applied in the postoperative setting. A retrospective study performed by Prabhu *et al.* reviewed the outcomes of 62 patients who received single-dose, postoperative tumor bed SRS (median dose of 18 Gy to surgical margin) following gross resection.[65] This study found a local recurrence rate of 22% after one year, and concluded that due to the highly conformal nature of SRS, these in-field failures were unlikely to be due to geographic misses.[65] Another retrospective study, performed by Do *et al.*, examined the outcomes of 30 patients who received either 15-18 Gy for SRS, or 22-27.5 Gy in 4-6 fractions for stereotactic radiotherapy (SRT).[20] This study described a local recurrence rate of 13.3%, but due to the small number of participants and the various dose-fractionation schedules used, it is difficult to isolate the most effective schedule. Although this localized approach to the postoperative bed has been adopted by many centers, prospective data supporting its efficacy and impact in preserving neurocognitive function are only now being performed.[56]

Lastly, as curtailing healthcare costs has emerged as a dominant theme in recent years, economic considerations will likely play a more important role in dictating which patients may be treated with SRS versus WBRT. This is a point of contention, because although the financial cost of SRS may be significantly greater than WBRT, particularly in the context of multiply recurrent disease, this must be balanced with the potential cost of neurocognitive effects associated with WBRT. In addition, the economic appeal of WBRT may be tempered by its inferiority to SRS in certain clinical circumstances, a view that is posited by Lal *et al.*, which argues that when regarding overall cost-effectiveness, SRS might remain a financially reasonable option.[43] Ongoing and planned prospective trials will hopefully allow physicians to provide treatment recommendations supported by evidence-based medicine for patients with brain metastases, rather than solely through financial consideration and clinician bias.

CONCLUSION

The treatment of brain metastasis has evolved considerably since WBRT first came into popular use in the 1970s. Although some of the uses of WBRT have been supplanted by more focal radiotherapies that introduce less overall toxicity to the normal volume of the brain, WBRT remains the treatment of choice for disseminated intracranial metastasis. The use of WBRT in these clinical situations appears unlikely to be replaced by other therapies in the near future, and thus the clinical trials that are currently attempting to improve the efficacy and toxicity profiles of WBRT will have the potential for strong clinical application.

REFERENCES

1. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, *et al.* Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665-72.
2. Antonadou D, Coliarakis N, Paraskevaidis M, Athansiou H, Sarris G, Synodinou M, *et al.* Whole brain radiotherapy alone or in combination with temozolomide for brain metastases. A phase III study (abstract). Int J Radiat Oncol Biol Phys 2002;54:93-4.
3. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, *et al.* Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA 2006;295:2483-91.
4. Armstrong C, Ruffer J, Corn B, DeVries K, Mollman J. Biphasic patterns of memory deficits following moderate-dose partial-brain irradiation: Neuropsychologic outcome and proposed mechanisms. J Clin Oncol 1995;13:2263-71.
5. Armstrong JG, Wronski M, Galicich J, Arbit E, Leibel SA, Burt M. Postoperative radiation for lung cancer metastatic to the brain. J Clin Oncol 1994;12:2340-4.
6. Auperin A, Arriagada R, Pignon JP, Le Pechoux C, Gregor A, Stephens RJ, *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-84.
7. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit cancer surveillance system. J Clin Oncol 2004;22:2865-72.
8. Bezjak A, Adam J, Panzarella T, Levin W, Barton R, Kirkbride P, *et al.* Radiotherapy for brain metastases: Defining palliative response. Radiother Oncol 2001;61:71-6.
9. Bitzer M, Topka H. Progressive cerebral occlusive disease after radiation therapy. Stroke 1995;26:131-6.
10. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, *et al.* The palliation of brain metastases: Final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1980;6:1-9.
11. Burger PC, Mahley MS Jr, Dudka L, Vogel FS. The morphologic effects of radiation administered therapeutically for intracranial gliomas: A postmortem study of 25 cases. Cancer 1979;44:1256-72.
12. Ch'ien LT, Aur RJ, Stagner S, Cavallo K, Wood A, Goff J, *et al.* Long-term neurological implications of somnolence syndrome in children with acute lymphocytic leukemia. Ann Neurol 1980;8:273-7.
13. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, *et al.* Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. Lancet Oncol 2009;10:1037-44.
14. Chao JH, Phillips R, Nickson JJ. Roentgen-ray therapy of cerebral metastases. Cancer 1954;7:682-9.
15. Chua D, Krzakowski M, Chouaid C, Pallotta MG, Martinez JI, Gottfried M, *et al.* Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small-cell lung cancer: A randomized, open-label phase II study. Clin Lung Cancer 2010;11:176-81.
16. Cross NE, Glantz MJ. Neurologic complications of radiation therapy. Neurol Clin 2003;21:249-77.
17. Davey P, Hoegler D, Ennis M, Smith J. A phase III study of accelerated versus conventional hypofractionated whole brain irradiation in patients of good performance status with brain metastases not suitable for surgical excision. Radiother Oncol 2008;88:173-6.
18. de Wit MC, de Bruin HG, Eijkenboom W, Sillevis Smitt PA, van den Bent MJ. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. Neurology 2004;63:535-7.
19. Desai SS, Paulino AC, Mai WY, Teh BS. Radiation-induced moyamoya syndrome. Int J Radiat Oncol Biol Phys 2006;65:1222-7.
20. Do L, Pezner R, Radany E, Liu A, Staud C, Badie B. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastases. Int J Radiat Oncol Biol Phys 2009;73:486-91.
21. Duffey P, Chari G, Cartlidge NE, Shaw PJ. Progressive deterioration of intellect and motor function occurring several decades after cranial irradiation. A new

facet in the clinical spectrum of radiation encephalopathy. Arch Neurol 1996;53:814-8.

22. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, *et al*. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.

23. EORTC-18981. Phase III randomized study of temozolomide with or without WBRT in patients with stage IV melanoma with asymptomatic brain metastases. Ongoing study. Closed.

24. Evans ML, Graham MM, Mahler PA, Rasey JS. Use of steroids to suppress vascular response to radiation. Int J Radiat Oncol Biol Phys 1987;13:563-7.

25. Faithfull S. Patients' experiences following cranial radiotherapy: A study of the somnolence syndrome. J Adv Nurs 1991;16:939-46.

26. Fike JR, Rosi S, Limoli CL. Neural precursor cells and central nervous system radiation sensitivity. Semin Radiat Oncol 2009;19:122-32.

27. Filloux FM, Townsend JJ. Subacute leukoencephalopathy complicating acute lymphoblastic leukemia. West J Med 1987;146:207-12.

28. Freeman JE, Johnston PG, Voke JM. Somnolence after prophylactic cranial irradiation in children with acute lymphoblastic leukaemia. Br Med J 1973;4:523-5.

29. Gamboa-Vignolle C, Ferrari-Carballo T, Arrieta O, Mohar A. Whole-brain irradiation with concomitant daily fixed-dose temozolomide for brain metastases treatment: A randomised phase II trial. Radiother Oncol 2012;102:187-91.

30. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, *et al*. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745-51.

31. Gavrilovic IT, Posner JB. Brain metastases: Epidemiology and pathophysiology. J Neurooncol 2005;75:5-14.

32. Ghia A, Tome WA, Thomas S, Cannon G, Khuntia D, Kuo JS, *et al*. Distribution of brain metastases in relation to the hippocampus: Implications for neurocognitive functional preservation. Int J Radiat Oncol Biol Phys 2007;68:971-7.

33. Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. Hematol Oncol Clin North Am 2012;26:111-31.

34. Gore E. RTOG 0214: A phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small cell lung cancer. Clin Adv Hematol Oncol 2005;3:625-6.

35. Gremmer R, Schroder ML, Ten Huinink WW, Brandsma D, Boogerd W. Successful management of brain metastasis from malignant germ cell tumours with standard induction chemotherapy. J Neurooncol 2008;90:335-9.

36. Hagen NA, Cirrincione C, Thaler HT, DeAngelis LM. The role of radiation therapy following resection of single brain metastasis from melanoma. Neurology 1990;40:158-60.

37. Herrmann T, Knorr A, Dorner K. The RTOG/EORTC classification criteria for early and late radiation reactions. Radiobiol Radiother (Berl) 1987;28:519-28.

38. Hindo WA, DeTrana FA 3rd, Lee MS, Hendrickson FR. Large dose increment irradiation in treatment of cerebral metastases. Cancer 1970;26:138-41.

39. Johannesen TB, Lien HH, Hole KH, Lote K. Radiological and clinical assessment of long-term brain tumour survivors after radiotherapy. Radiother Oncol 2003;69:169-76.

40. Katz HR. The relative effectiveness of radiation therapy, corticosteroids, and surgery in the management of melanoma metastatic to the central nervous system. Int J Radiat Oncol Biol Phys 1981;7:897-906.

41. Knisely JP, Berkey B, Chakravarti A, Yung AW, Curran WJ, Robins HI, *et al*. A phase III study of conventional radiation therapy plus thalidomide versus conventional radiation therapy for multiple brain metastases (RTOG 0118). Int J Radiat Oncol Biol Phys 2008;71:79-86.

42. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, *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;29:134-41.

43. Lal LS, Franzini L, Panchal J, Chang E, Meyers CA, Swint JM. Economic impact of stereotactic radiosurgery for malignant intracranial brain tumors. Expert Rev Pharmacoecon Outcomes Res 2011;11:195-204.

44. Lassman AB, DeAngelis LM. Brain metastases. Neurol Clin 2003;21:1-23, vii.

45. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. J Clin Oncol 2007;25:1260-6.

46. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. J Invest Dermatol 2009;129:1666-74.

47. Lokich JJ. The management of cerebral metastasis. JAMA 1975;234:748-51.

48. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, *et al*. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10-9.

49. Marsh JC, Gielda BT, Herskovic AM, Abrams RA. Cognitive Sparing during the Administration of Whole Brain Radiotherapy and Prophylactic Cranial Irradiation: Current Concepts and Approaches. J Oncol 2010;2010:198208.

50. Marsh JC, Gielda BT, Herskovic AM, Wendt JA, Turian JV. Sparing of the hippocampus and limbic circuit during whole brain radiation therapy: A dosimetric study using helical tomotherapy. J Med Imaging Radiat Oncol 2010;54:375-82.

51. Marsh JC, Godbole RH, Herskovic AM, Gielda BT, Turian JV. Sparing of the neural stem cell compartment during whole-brain radiation therapy: A dosimetric study using helical tomotherapy. Int J Radiat Oncol Biol Phys 2010;78:946-54.

52. Marsh JC, Herskovic AM, Gielda BT, Hughes FF, Hoeppner T, Turian J, *et al*. Intracranial metastatic disease spares the limbic circuit: A review of 697 metastatic lesions in 107 patients. Int J Radiat Oncol Biol Phys 2010;76:504-12.

53. Mehta MP, Shapiro WR, Phan SC, Gervais R, Carrie C, Chabot P, *et al*. Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients with brain metastases: Results of a phase III trial. Int J Radiat Oncol Biol Phys 2009;73:1069-76.

54. Merchant TE, Kiehna EN, Li C, Shukla H, Sengupta S, Xiong X, *et al*. Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumors including medulloblastoma. Int J Radiat Oncol Biol Phys 2006;65:210-21.

55. Mornex F, Thomas L, Mohr P, Hauschild A, Delaunay MM, Lesimple T, *et al*. A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. Melanoma Res 2003;13:97-103.

56. NCT01372774. Stereotactic Radiosurgery or Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases That Have Been Removed By Surgery. Ongoing study.

57. Neuhaus T, Ko Y, Muller RP, Grabenbauer GG, Hedde JP, Schueller H, *et al*. A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. Br J Cancer 2009;100:291-7.

58. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 1996;78:1781-8.

59. Palmer SL, Goloubeva O, Reddick WE, Glass JO, Gajjar A, Kun L, *et al*. Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. J Clin Oncol 2001;19:2302-8.

60. Patchell RA. The management of brain metastases. Cancer Treat Rev 2003;29:533-40.

61. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, *et al*. Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. JAMA 1998;280:1485-9.

62. Pesce GA, Klingbiel D, Ribi K, Zouhair A, von Moos R, Schlaeppi M, *et al*. Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). Eur J Cancer 2012;48:377-84.

63. Posner JB. Management of central nervous system metastases. Semin Oncol 1977;4:81-91.

64. Postmus PE, Haaxma-Reiche H, Smit EF, Groen HJ, Karnicka H, Lewinski T, *et al*. Treatment of brain metastases of small-cell lung cancer: Comparing teniposide and teniposide with whole-brain radiotherapy: A phase III study of the European Organization for the Research and Treatment of Cancer Lung Cancer Cooperative Group. J Clin Oncol 2000;18:3400-8.

65. Prabhu R, Shu HK, Hadjipanayis C, Dhabaan A, Hall W, Raore B, *et al*. Current dosing paradigm for stereotactic radiosurgery alone after surgical resection of brain metastases needs to be optimized for improved local control. Int J Radiat Oncol Biol Phys 2012;83:e61-6.

66. Price RA, Jamieson PA. The central nervous system in childhood leukemia. II. Subacute leukoencephalopathy. Cancer 1975;35:306-18.

67. Prokic V, Wiedenmann N, Fels F, Schmucker M, Nieder C, Grosu AL. Whole

brain irradiation with hippocampal sparing and dose escalation on multiple brain metastases: A planning study on treatment concepts. Int J Radiat Oncol Biol Phys 2013;85:264-70.

68. Rodrigues G, Yartsev S, Tay KY, Pond GR, Lagerwaard F, Bauman G. A phase II multi-institutional study assessing simultaneous in-field boost helical tomotherapy for 1-3 brain metastases. Radiat Oncol 2012;7:42.

69. Rodrigues G, Yartsev S, Yaremko B, Perera F, Dar AR, Hammond A, *et al.* Phase I trial of simultaneous in-field boost with helical tomotherapy for patients with one to three brain metastases. Int J Radiat Oncol Biol Phys 2011;80:1128-33.

70. RTOG-0614. A Randomized, phase III, double-blind, placebo-controlled trial of memantine for prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy. Ongoing study.

71. RTOG-0933. A phase II trial of hippocampal avoidance during whole brain radiotherapy for brain metastases. Ongoing study.

72. Ryan J. Radiation somnolence syndrome. J Pediatr Oncol Nurs 2000;17:50-3.

73. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer 2002;94:2698-705.

74. Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. Int J Radiat Oncol Biol Phys 1980;6:1215-28.

75. Skibber JM, Soong SJ, Austin L, Balch CM, Sawaya RE. Cranial irradiation after surgical excision of brain metastases in melanoma patients. Ann Surg Oncol 1996;3:118-23.

76. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, *et al.* Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-72.

77. Sneed PK, Larson DA, Wara WM. Radiotherapy for cerebral metastases. Neurosurg Clin N Am 1996;7:505-15.

78. Soffietti R, Ruda R, Mutani R. Management of brain metastases. J Neurol 2002;249:1357-69.

79. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol 1969;20:288-99.

80. Taal W, Brandsma D, de Bruin HG, Bromberg JE, Swaak-Kragten AT, Smitt PA, *et al.* Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide. Cancer 2008;113:405-10.

81. Tallet AV, Azria D, Barlesi F, Spano JP, Carpentier AF, Goncalves A, *et al.* Neurocognitive function impairment after whole brain radiotherapy for brain metastases: Actual assessment. Radiat Oncol 2012;7:77.

82. Tsao MN, Lloyd N, Wong RK, Chow E, Rakovitch E, Laperriere N, *et al.* Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev 2012;4:CD003869.

83. Ullrich NJ, Robertson R, Kinnamon DD, Scott RM, Kieran MW, Turner CD, *et al.* Moyamoya following cranial irradiation for primary brain tumors in children. Neurology 2007;68:932-8.

84. Ushio Y, Arita N, Hayakawa T, Mogami H, Hasegawa H, Bitoh S, *et al.* Chemotherapy of brain metastases from lung carcinoma: A controlled randomized study. Neurosurgery 1991;28:201-5.

85. Uzal D, Ozyar E, Hayran M, Zorlu F, Atahan L, Yetkin S. Reduced incidence of the somnolence syndrome after prophylactic cranial irradiation in children with acute lymphoblastic leukemia. Radiother Oncol 1998;48:29-32.

86. Valk PE, Dillon WP. Radiation injury of the brain. AJNR Am J Neuroradiol 1991;12:45-62.

87. van den Bent MJ. The role of chemotherapy in brain metastases. Eur J Cancer 2003;39:2114-20.

88. van Kesteren Z, Belderbos J, van Herk M, Olszewska A, Lamers E, De Ruysscher D, *et al.* A practical technique to avoid the hippocampus in prophylactic cranial irradiation for lung cancer. Radiother Oncol 2012;102:225-7.

89. Walker AE, Robins M, Weinfeld FD. Epidemiology of brain tumors: The national survey of intracranial neoplasms. Neurology 1985;35:219-26.

90. Weiss SE, Kelly PJ. Neurocognitive function after WBRT plus SRS or SRS alone. Lancet Oncol 2010;11:220-1.

91. Young DF, Posner JB, Chu F, Nisce L. Rapid-course radiation therapy of cerebral metastases: Results and complications. Cancer 1974;34:1069-76.