Role of Whole-Brain Radiotherapy

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Introduction

Whole-brain radiotherapy (WBRT) has been integral to the management of brain metastases for several decades. Early studies demonstrated the efficacy of WBRT in relieving neurologic symptoms related to intracranial disease and improving survival for patients with brain metastases. However, concerns over cognitive side effects with conventional WBRT and improvements in local treatment techniques have led to a shifting dynamic in how and when WBRT is used [1]. As a result, focal therapies involving stereotactic radiosurgery (SRS) with or without surgical resection have been increasingly used as an alternative to conventional WBRT in patients with limited brain metastases at a cost of increased risk of distant brain relapse and use of salvage therapies. Subsequent trials demonstrating cognitive preservation using neuroprotective strategies of prophylactic memantine and hippocampal avoidance have led to efforts seeking to redefine the role of WBRT, especially since prior trials comparing cognitive outcomes between focal therapy and WBRT did not include these neuroprotective strategies and no longer apply in the modern WBRT era.

In recent years, multiple attempts have been made to optimize the efficacy of WBRT. The most common dose prescription for WBRT is 30 Gy in 10 fractions, though other dosing regimens have been studied without proven superiority. The use of systemic agents during and following WBRT has also been studied extensively. Although enthusiasm for radiosensitizers was sparked by studies of motexafin gadolinium showing benefits in non-small cell lung cancer, other radiosensitizers have failed to show added value. The use of targeted agents and immune checkpoint inhibitors with WBRT remain areas of active study.

Radiation-related toxicity secondary to conventional WBRT manifests as early, early-delayed, and late delayed forms, with the last one being the most permanent. This toxicity ranges from mild cognitive impairment to rarely dementia and can be a concern for patients and clinicians alike. However, practice-changing clinical trials have demonstrated that prophylactic memantine, combined with minimal radiation

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dose to the hippocampal neural stem cell compartment (hippocampal avoidance), prevents cognitive toxicity in patients undergoing WBRT. This chapter traces the course of the research that established the use of WBRT and discusses the evolving role and delivery of WBRT in contemporaneous management of brain metastases. In order to improve care for patients requiring WBRT, knowledge of the optimal candidates for WBRT and techniques for safer delivery of WBRT are important.

The efficacy of WBRT was noted as early as 1954 when Chao et al. published a case series of 38 patients with symptomatic brain metastases treated with two opposed lateral x-ray fields targeting the whole brain. Chao started with doses of 0.5 Gray (Gy) per fraction and eventually increased to 4 Gy per fraction to deliver total dose up to 35 or 40 Gy. Of these patients, 63% experienced improvement of a variety of symptoms related to tumor shrinkage in the brain. Incontinence, aphasias, and hemiplegia improved or resolved in many of these patients. At least one returned to work and another was able to play the piano again [2]. While limited in many respects, this foundational study was the largest series to date demonstrating the palliative benefit of WBRT and prompted further study to define the role of WBRT. In 1980, Borgelt et al. published the results of two phase III trials—Radiation Therapy Oncology Group (RTOG) 6901 and 7361—demonstrating symptomatic improvement in 43–64% of patients with brain metastases at 2 weeks following WBRT, and noted a threefold increase in median survival time compared to standard supportive care (3–6 months vs 1–2 months). These studies evaluated five different dose schedules ranging from hypofractionated regimens (e.g., 10 Gy in one fraction or 12 Gy in two fractions) to more conventional schedules of 20–40 Gy in 5 to 20 fractions. They did not identify significant differences in outcomes between the different dose schedules [3].

More contemporary studies have confirmed these findings as well. RTOG 9104 assessed 1-year survival and acute toxicity in patients receiving either accelerated fractionation (30 Gy at 3 Gy daily) or accelerated hyperfractionation (54.4 Gy at 1.6 Gy BID). The authors found no difference in survival or toxicity between the two groups [4]. Rades and colleagues retrospectively compared 30 Gy in 10 fractions to either 40 Gy in 20 fractions or 45 Gy in 15 fractions. The alternative dose-escalated schedules did not significantly improve survival or local control [5]. Neider and colleagues demonstrated a 25% complete and 39% partial radiographic response at 3 months after WBRT with 30 Gy in 10 fractions. Radiographic response was associated with improved survival across multiple cancer histologies [6, 7]. Likewise, tumor shrinkage in those with favorable response following WBRT was associated with preserved neurocognitive function relative to those with poor response in both mini mental status exam and specific tests of executive function and fine-motor skills [8, 9].

These seminal studies established WBRT as the standard of care for management of brain metastases and support 30 Gy in 10 fractions as the most standard regimen. More recently, concerns over the neurocognitive sequelae of WBRT have prompted a reevaluation of the technique. Recognizing the connection between memory formation and the production of neural progenitor cells (NPCs) in the subgranular zone (SGZ) of the hippocampal dentate gyrus, a technique was devised that would avoid this highly radiosensitive region [10]. Termed hippocampal avoidance (HA), results from a single-arm phase II trial and subsequently a randomized phase III trial combining this strategy with the neuroprotective agent memantine (NRG-Oncology CC001) showed significant prevention of cognitive toxicity and better preservation of patient-reported quality of life (QoL) [11, 12]. Prior research comparing WBRT to focal therapy modalities, particularly SRS, does not account for these neuroprotective strategies, which is crucial to bear in mind when considering the differences in cognitive toxicity between WBRT and SRS presented below. Though SRS is considered to have a more favorable side effect profile, future trials are being designed to reevaluate this in light of these trials' practice-changing findings.

Conventional Whole-Brain Radiotherapy

Approach

Conventional WBRT is administered through parallel-opposed lateral portals. The inferior field border should be inferior to the cribriform plate, the middle cranial fossa, and the foramen magnum, all of which should be distinguishable on simulation or portal localization radiographs (Fig. 20.1). The safety margin depends on penumbra width, head fixation, and anatomic factors, but should be at least 1 cm, even under optimal conditions. A special problem arises anteriorly because sparing of the ocular lenses and lacrimal glands may require blocking with <5-mm margins at the cribriform plate.

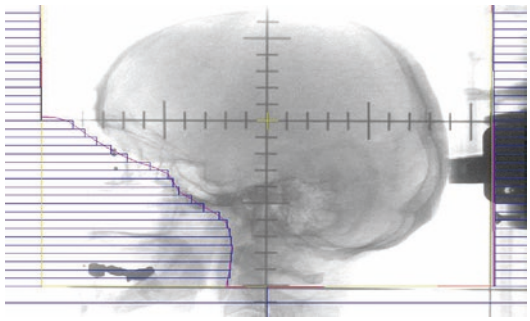

Fig. 20.1 Lateral portal of conventional whole-brain radiotherapy (WBRT) treatment. Conventional WBRT is administered through parallel-opposed lateral portals. The inferior field border should be inferior to the cribriform plate, the middle cranial fossa, and the foramen magnum

The anterior border of the field should be approximately 3 cm posterior to the ipsilateral eyelid for the diverging beam to exclude the contralateral lens. However, this results in only approximately 40% of the prescribed dose to the posterior eye. A better alternative is to angle the beam approximately 3 degrees or more (100- or 80-cm source-to-axis distance midline, but also field size dependent) against the frontal plane so that the anterior beam border traverses posterior to the lenses (approximately 2 cm posterior to eyelid markers). Placing a radiopaque marker on both lateral canthi and aligning the markers permits individualization in terms of the couch angle. This arrangement provides full dose to the posterior eyes. However, the eyelid-to-lens and -retina topography is individually more constant than the canthus, and lateral beam eye shielding is better individualized with the aid of computed tomography (CT) or magnetic resonance imaging (MRI) scans. When in doubt about tumor coverage or lens sparing for tumors in a subfrontal or middle cranial fossa location, CT-based contouring and planning should be considered (Fig. 20.2a).

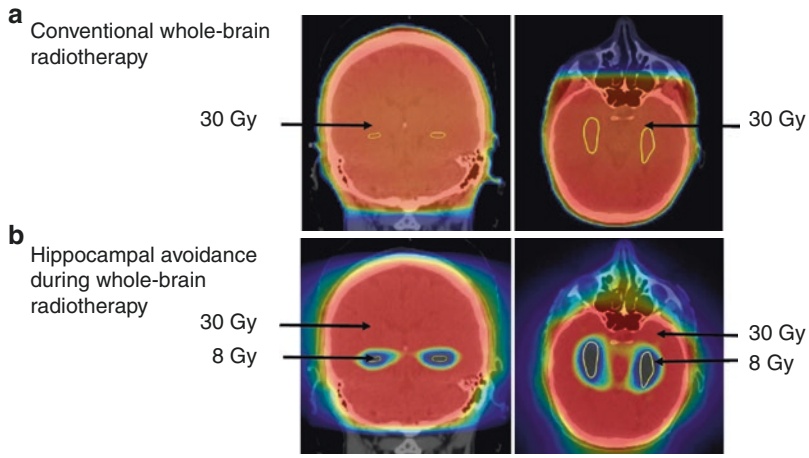

Fig. 20.2 Comparison of treatment plans between (**a**) conventional whole-brain radiotherapy (WBRT) and (**b**) hippocampal avoidant WBRT. Hippocampal avoidance using intensity-modulated radiotherapy during WBRT achieves several-fold reduction in radiation dose to hippocampi (yellow). (Adapted with permission from Brown et al. [12])

Acute, Early-Delayed, and Late-Delayed Complications

Toxicity following conventional WBRT may be categorized as acute, early-delayed, or late-delayed depending on the time of presentation. Acute effects of radiation manifest during the course of treatment or shortly after completion. Common complications include those associated with increased intracranial pressure such as headache, fatigue, nausea, and dizziness. These side effects may be due to interruption of the blood-brain barrier and the development of cerebral edema immediately following radiation exposure. These symptoms generally respond well to corticosteroids [13]. Patients may also acutely experience mild, self-limited dermatitis, and hair loss. Early-delayed toxicity appears weeks to months following treatment and is thought to arise due to transient demyelination. It manifests as weakness, headache, and fatigue [13]. Additional non-neurological side effects include serous otitis media, dry sinuses, and lacrimal gland dysfunction. Lhermitte's sign may be present in some of these patients, identified as the sensation of a shock spreading down the neck and upper limbs with flexion of the neck. Radiation somnolence syndrome is a rare early-delayed complication of central nervous system (CNS) radiation characterized by extreme somnolence accompanied by anorexia, apathy, and headache. The syndrome is commonly associated with prophylactic cranial irradiation in pediatric patients with acute lymphocytic leukemia, but has been described in adult patients undergoing radiation therapy for primary CNS tumors. Management and prevention involve administering corticosteroids during radiation treatment [14].

Late-delayed toxicities appear beginning at 6 months after radiation but can present many years later. They are often the most debilitating and the least likely to improve with time. Permanent neurocognitive dysfunction following conventional WBRT ranges from mild impairment in most cases to severe dementia in rare cases (<5%) [13]. For instance, in the previously mentioned NCCTG N107C/CEC.3, which assessed the impact of adjuvant WBRT after SRS, deterioration of immediate memory, delayed memory, processing speed, and executive function were associated with conventional WBRT [15]. Radiation necrosis is another late complication of WBRT. Necrosis may result in mass-effect-related symptoms that make these lesions difficult to distinguish from tumor recurrence. These lesions can require surgical intervention if unresponsive to corticosteroids. Radiation-related leukoencephalopathy is seen in rare cases and results in severe dementia and cortical atrophy. Higher per-fraction doses (in excess of 3.5 Gy) have been associated with greater risk of radiation-related leukoencephalopathy [16]. The capacity of neuroprotective strategies including prophylactic memantine and hippocampal avoidance during modern WBRT to prevent radiation-related leukoencephalopathy remains unclear.

The Evolving Role of Conventional WBRT

Omission of WBRT

In poor performance status patients with limited survival, there is better understanding regarding the benefit of WBRT versus modern best supportive care. The Quality of Life after Treatment for Brain Metastases (QUARTZ) trial was designed in part to address this question, randomizing 538 patients with non-small cell lung cancer (NSCLC) to either WBRT with optimal supportive care or supportive care alone. Eligible patients had brain metastases that were not amenable to stereotactic radiosurgery or resection. Using quality-adjusted life-years as the primary outcome measure, the trial found that omitting WBRT resulted in a loss of 4.7 days (in terms of QALYs). Overall survival time was also diminished by less than a week for those receiving supportive care alone when compared to those receiving WBRT [17]. While this study is commonly used to dismiss the use of WBRT in the palliative setting, it is important to avoid overgeneralizing the results. First, clinicians were encouraged to recruit patients into the trial if they had doubts regarding the benefit of

WBRT. The median survival on this study was 8–9 weeks, highlighting an extremely unfavorable cohort of patients in both groups. Symptomatic benefit from tumor regression may take 3–6 months; therefore it is not surprising that there was no difference in quality of life for patients undergoing WBRT on this study. Furthermore, subgroup analysis did demonstrate a significant survival benefit to WBRT for patients younger than 60, with a non-significant trend in favor of WBRT observed for patients of better prognosis as measured by recursive partitioning analysis (RPA) and disease-specific generalized prognostic assessment (ds-GPA) scores. Finally, relative to this study, brain metastases may be associated with a better median survival with the emergence of immunotherapy or other systemic therapies or with other types of cancer. Thus, while the QUARTZ trial demonstrated that NSCLC patients with poor prognosis might not benefit from WBRT, those with a better prognosis or a better performance status may experience survival and/or quality-of-life improvements with WBRT. To aid in decision making, Sperduto and colleagues have developed prognostic systems to provide survival time estimates for patients with brain metastases [18]. However, for patients who develop brain metastases in the setting of systemic progression and are not planned for further systemic therapy due to poor performance status and/or limited prognosis, the QUARTZ trial provides a rationale for omission of WBRT to manage the brain metastases.

Conventional WBRT Following Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) offers the ability to deliver targeted, high doses of radiation to discrete foci of metastatic disease within the brain. The hypothesis that SRS followed by adjuvant WBRT for patients with limited brain metastases could achieve superior intracranial control and survival has been tested in multiple phase-III randomized controlled trials (RCTs). Prospective studies conducted by the Japanese Radiation Oncology Study Group (JROSG 99–1) [19], MD Anderson Cancer Center [20], and the European Organization for Research and Treatment of Cancer (EORTC 22852-26,001) [21] demonstrated that adding WBRT does indeed improve intracranial disease control, resulting in a significant reduction in the absolute risk of new brain metastases by between 18% and 22% at 1 year and by 15% at 2 years. Recurrence rates at local sites were also reduced. Notably, the EORTC and MD Anderson studies found reduced quality of life and reduced Hopkins Verbal Learning Test-Revised (HVLT-R) scores, respectively, with the addition of WBRT. In addition, contrary to expectations, the MD Anderson trial identified a survival difference in patients managed with SRS alone, who experienced a median survival time of 15.2 months compared to 5.7 months in patients receiving combination therapy. The differences in survival could have in part contributed to the differences in neurocognition and quality of life observed between the arms [20]. To address these conflicting data on overall survival, Sahgal et al. (2013) analyzed individual patient data from these trials and identified patient age as a significant effect modifier. After stratifying by age, they found that SRS alone was associated with favorable survival outcomes in patients younger than 50 years old, although the majority of this difference was driven by the MD Anderson trial. For patients older than 50, there was no difference between SRS alone and SRS with WBRT. This meta-analysis also identified higher rates of salvage treatment in the SRS alone arm, highlighting the need for regular imaging follow-up with SRS alone [22].

Alliance trial N0574 assessed the impact of adjuvant WBRT after SRS on quality of life, functional independence, and radiation-related cognitive dysfunction at 3 months using a battery of standardized cognitive tests to assess learning, memory, fine motor control, verbal fluency, processing speed, and executive function. Cognitive deterioration—defined as decline greater than 1 standard deviation (SD) below baseline in any of these cognitive domains at 3 months—was more frequent with SRS and adjuvant WBRT compared with SRS alone (91.7% vs. 63.5%, $P < 0.001$). Specifically, patients receiving combined therapy were more likely to experience impairments in immediate memory, delayed

memory, and verbal fluency than those receiving SRS alone. Quality of life was significantly better with SRS alone and functional independence was the same between arms. Overall survival was not different between groups despite the improved intracranial control of combined therapy [23].

Conventional WBRT Following Surgical Resection

Upfront surgery for large or symptomatic brain metastases is associated with survival benefits. However, multiple studies have demonstrated that the rate of local recurrence following MRI-confirmed gross total resection of brain metastases without adjuvant therapy is around 50% [21, 24, 25]. Two large RCTs, a multi-center study published by Patchell et al. in 1998 and EORTC 22952-26001, have investigated the use of surgery with adjuvant WBRT versus surgery alone. Both studies demonstrated a statistically significant improvement in local control, reduction in the incidence of distant brain metastases, and reduced incidence of neurologic death with the addition of adjuvant WBRT [21, 24]. However, these studies did not find a significant difference in survival for adjuvant WBRT over observation following surgery, though they were not powered to do so.

Stereotactic radiosurgery has been shown to improve local control following surgical resection while minimizing the potential for neurocognitive toxicity. A phase III trial of postoperative SRS compared to observation (MD Anderson Cancer Center 2009-0381) demonstrated improved surgical bed control with SRS compared to observation (12-month surgical bed relapse rate: 28% with SRS vs. 57% with observation, $p = 0.015$). While there was no survival advantage to adjuvant SRS, there was a trend toward reduced neurologic death with SRS but this did not reach statistical significance ($p = 0.13$).

A phase III trial from a collaboration between Alliance and the Canadian Cancer Trials Group (N107C/CEC.3) compared surgery with adjuvant WBRT to surgery with adjuvant SRS and examined both overall survival and cognitive side effects. WBRT was again associated with improved local and distant control. Specifically, adjuvant SRS led to a 20% decrement in surgical bed control at 12 months compared to WBRT (60% compared to 80%, $P = 0.00068$). While this improved intracranial control was not associated with an increase in overall survival, this trial lacked a comparison of the rates of neurologic cause of death [15]. With respect to cognitive deterioration, adjuvant WBRT performed significantly worse than adjuvant SRS, with an overall rate of cognitive deterioration of 85% versus 52%, respectively, at 6 months ($P = 0.0003$). Within specific cognitive domains, patients in the WBRT arm had significantly higher rates of deterioration in immediate recall, delayed recall, processing speed, and executive function.

Taken together, the evidence supports the use of postoperative radiotherapy following surgical resection for brain metastasis. Both WBRT and SRS remain effective treatment options but have some limitations [26]. Neuroprotective strategies to prevent cognitive toxicity from WBRT are discussed below. The inferior surgical bed control of SRS remains an area of concern. An Alliance phase III trial of fractionated versus single-fraction radiosurgery to improve local control following surgical resection will seek to address this issue.

Prophylactic Cranial Irradiation

WBRT may be used prophylactically (i.e., before disease is radiologically detectable) in select patients with small cell lung cancer (SCLC), who demonstrate up to 80% risk of developing brain metastases 2 years after diagnosis [27]. As such, WBRT is considered the standard of care for patients with limited-stage (LS) SCLC that has responded to chemotherapy, given the potential for prolonged survival. The seminal meta-analysis by Aupérin et al. (1999) demonstrated a significant increase in overall survival (pooled relative risk of death 0.84, $P = 0.01$) and significantly reduced the incidence of brain metastases (0.46, $P < 0.001$) in patients with a complete response (CR) to chemotherapy [28]. These results were reinforced by a 2001 systematic review by Meert et al., which also showed

decreased incidence of brain metastasis (HR of 0.48, 95% CI of 0.39–0.60) and improved overall survival (HR of death 0.82, 95% CI 0.71–0.96) in patients with LS SCLC and CR [29].

Prophylactic WBRT in patients with extensive stage (ES) SCLC is more controversial. A 2007 EORTC trial seemed to demonstrate improved survival for patients with ES SCLC and any positive response to chemotherapy [30]. This study, however, did not include brain imaging as a part of its inclusion criteria, raising the possibility that some patients had asymptomatic brain metastases upon enrollment (making cranial irradiation for these patients therapeutic rather than prophylactic). A later phase III Japanese trial of 224 ES SCLC patients addressed this concern by excluding patients with brain lesions visible on MRI prior to enrollment. This study showed no benefit to overall survival (survival HR 1.27; $P = 0.094$) with prophylactic cranial irradiation (PCI) versus observation and was halted for futility [31]. In light of this most recent trial, prophylactic WBRT for ES SCLC is controversial, and a planned SWOG phase III trial MAVERICK seeks to address this question. SCLC patients in this study will be randomized to PCI with hippocampal avoidance versus MR surveillance; the primary endpoint is overall survival.

Given its success in limited stage SCLC, WBRT has also been studied extensively in non-small cell lung cancer (NSCLC). While no study has demonstrated an advantage to overall survival, two phase III trials have demonstrated significantly reduced incidence of brain metastases [32, 33]. An additional phase III study by De Ruysscher et al. in 2018 confirmed a reduced incidence of brain metastases with PCI versus observation (7% vs 27.2%, $P = 0.001$), albeit with a reduced quality of life with PCI at 3 months post-treatment and a non-significant trend toward QoL benefit to observation at 2, 3, and 4 years [34]. RTOG 0214 was a phase III trial that randomized stage III NSCLC to PCI or observation but did not complete target accrual to detect an overall survival benefit. However, unplanned analyses of longer-term results revealed an overall survival benefit of PCI in stage III NSCLC patients who did not undergo upfront surgical resection.

However, these trials of PCI in NSCLC were conducted prior to the emergence of immune checkpoint inhibitors, now considered the standard of care for most locally advanced and metastatic NSCLC patients. Thus, in the modern era of NSCLC management, the role of PCI remains uncertain. The use of neuroprotective strategies such as hippocampal avoidance during PCI to prevent cognitive toxicity also remains an area of ongoing investigation through the current NRG Oncology CC003 trial.

Modern WBRT

Preceding and concurrent with trials establishing the neurocognitive toxicity of conventional WBRT, several investigations have been pursued to identify approaches to deliver WBRT more safely. These approaches have included both pharmacologic and technologic strategies and have led to practice-changing findings that have ushered in the era of modern WBRT inclusive of prophylactic memantine and hippocampal avoidance.

NMDA Receptor Antagonists (Memantine)

N-methyl-D-aspartate (NMDA) receptors are ionotropic glutamate receptors that mediate synaptic plasticity and memory in the brain, particularly in the neurons of the hippocampus. Overstimulation of these receptors following insults to the brain by ischemia, trauma, or radiation can lead to apoptosis and necrosis via a phenomenon known as excitotoxicity. Preclinical studies have demonstrated that blockade of these receptors by the noncompetitive NMDA antagonist memantine protects against NMDA-receptor-mediated neurotoxicity [35, 36]. Animal studies have also demonstrated that giving memantine ahead of radiation can preserve long-term potentiation—a process involved in synaptic plasticity—in rodents [37, 38]. Phase II clinical studies have demonstrated the effectiveness of memantine in managing vascular dementia [39, 40]. The

apparent neuroprotective effects of memantine generated interest in its use in for managing radiation-related neurotoxicity.

A phase III trial (RTOG 0641) was designed to assess the neuroprotective effects memantine in patients treated with WBRT. Patients were randomized to WBRT (37.5 Gy in 15 fractions) with either memantine or placebo. The dose of memantine was escalated over the course of treatment beginning with 5 mg QD in week 1 of treatment and rising to 10 mg BID for weeks 4 through 24. The full regimen is detailed in Table 20.1. Because memantine is primarily cleared renally, exceptions were made for patients for patients with low creatinine clearance. Those with clearance below 30 mL/min received 5 mg BID and those with clearance less than 5 mL/min were taken off the drug. The primary endpoint was whether memantine preserved memory, as assessed by the HVLT-R Delayed Recall at 24 weeks. Although patients treated with memantine were found to experience less cognitive decline than control patients, this difference was not statistically significant (0 compared to −0.9, $P = 0.059$), possibly due to the high rate of attrition in the trial. Among the positive findings in the trial were a significantly longer time to cognitive deterioration in the memantine arm (HR 0.78, $P = 0.01$) and significantly less deterioration in delayed recognition (measured by the HVLT-R Delayed Recognition) and processing speed (Trail-Making Test A) at 24 weeks [41]. However, when cognitive toxicity was assessed as a composite endpoint, defined as a decline in the reliable change index on the HVLT-R, Trail-Making Test, or Controlled Oral Word Association tests, the use of memantine during WBRT led to a 22% relative reduction in risk of cognitive toxicity. These results, combined with the favorable safety profile of memantine, have made the drug appropriate for use in clinical practice to mitigate the cognitive toxicity of WBRT, particularly in conjunction with hippocampal avoidance as detailed below. It is not known at this time what the optimal dosing schedule and duration of memantine is to attenuate radiation-induced neurotoxicity, and further trials may help guide future management recommendations.

Table 20.1 Memantine dosing in RTOG 0614

	Twice daily dosing[a]		Extended release dosing[b]
Week(s)	Morning dose (mg)	Evening dose (mg)	Daily dose (mg)
1	5	–	7
2	5	5	14
3	10	5	21
4–24	10	10	21

[a]A dosage reduction to 5 mg orally twice daily is recommended in patients with severe renal impairment [creatinine clearance (CrCl), 5–29 milliliters/minute (mL/min)]. No dosage adjustment is needed in patients with mild (CrCl greater than 50–80 mL/min) or moderate (CrCl 30–49 mL/min) renal impairment

[b]A dosage reduction to 14 milligrams (mg) orally daily is recommended in patients with severe renal impairment (creatinine clearance (CrCl), 5–29 milliliters/minute (mL/min)). No dosage adjustment is needed in patients with mild (CrCl greater than 50–80 mL/min) or moderate (CrCl 30–49 mL/min) renal impairment

Hippocampal Avoidance

The hippocampus plays a critical role in the formation of episodic and spatial memory. Its ability to do so stems in part from the production of new neurons by neural progenitor cells (NPCs) within the subgranular zone (SGZ) of the hippocampal dentate gyrus. Animal studies have demonstrated that these NPCs are highly sensitive to radiation and that radioablation of these cells results in deficits in hippocampus-dependent learning and memory tasks [42]. Given this interaction with radiation, it is unsurprising that memory deficits are commonly reported in WBRT patients. One recent study (NCCTG N107C/CEC.3) examining WBRT versus SRS following surgical resection found deterioration of immediate and delayed memory in 49% and 62% of patients, respectively. This was significantly more than in patients treated with focal radiotherapy via SRS [15]. Clinical studies have also demonstrated a clear dose-response relationship between hippocampal radiation exposure and memory deterioration, with a study by Gondi et al. (2013) demonstrating an association between the delivery of 7.3 Gy to 40% of the bilateral hippocampi (in the equivalent of 2 Gy fractions) and long-term deterioration in list-learning delayed verbal recall as

measured by the Weschler Memory Scale-III Word Lists test [43]. Given this association and given the relatively rare rate of metastasis to the hippocampi, a technique was devised using intensity-modulated radiotherapy (IMRT) to limit the dose delivered to the hippocampus (Fig. 20.2b) [10].

A phase II study, RTOG 0933, was designed to evaluate the benefits of this hippocampal avoidance strategy. The study found that compared with historical controls, patients treated with hippocampal avoidance (HA) WBRT experienced significantly less deterioration in delayed memory as measured by the HLVT-R Delayed Recall. Consistent with previous observations, 4.5% of patients experienced progression in the hippocampal avoidance region [44].

A phase III trial, NRG Oncology-CC001, was conducted to validate these findings in patients treated with memantine and WBRT with or without HA. The study recruited and randomized 518 adult patients with brain metastases between July 2016 and March 2018. The primary endpoint was cognitive toxicity, defined as a decline in the reliable change index on the HVLT-R, Trail-Making Test, or Controlled Oral Word Association tests. There was no difference in grade 3 or higher toxicity between the treatment arms. The median follow-up for alive patients was 7.8 months. There was no difference between arms in terms of baseline cognitive function, overall survival (HR = 1.13, 95% CI: 0.89–1.44, p = 0.31), or intracranial progression (HR 1.12, 95% CI 0.90–1.39, p = 0.33).

The addition of hippocampal avoidance to WBRT+memantine significantly prevented cognitive toxicity (Fig. 20.2b) with an adjusted hazard ratio of 0.74, or a 26% relative reduction in risk of cognitive toxicity with the addition of hippocampal avoidance to memantine [12, 26]. The difference was first seen at 4 months and maintained throughout the follow-up period, and was attributable to improvements in executive function at 4 months (p = 0.01) and learning (p = 0.049) and memory (p = 0.02) at 6 months. While age also predicted for prevention of cognitive function failure, test for interaction between treatment arm and age was non-significant (p = 0.67), indicating that the cognitive benefit of hippocampal avoidance does not differ by age.

Importantly, the addition of hippocampal avoidance to WBRT+memantine preserved patient-reported symptom burden, as assessed by the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). Patients on the HA-WBRT+memantine arm experienced less symptom interference and less cognitive symptoms at 6 months (estimate = −1.02, p = 0.008 and estimate = −0.63, p = 0.011, respectively) compared to the WBRT+memantine arm. Cognitive symptom differences were driven primarily by two items: problems with remembering things and difficulty speaking. At 6 months, patients on the HA-WBRT+memantine arm had less difficulty remembering things (mean 0.16 vs. 1.29, p = 0.013) and less difficulty speaking (mean − 0.20 vs. 0.45, p = 0.049) as compared to the WBRT+memantine arm. Greater improvement in fatigue at 6 months was reported in the HA-WBRT+memantine arm as compared to the WBRT+memantine arm (mean 0.93 vs. −0.16, p = 0.036).

Analyses with longer follow-up (median follow-up of 12.1 months) additionally demonstrated better preservation of overall symptom burden (p < 0.0001) at 6 months on the HA-WBRT+memantine arm compared to the WBRT+memantine arm, while continuing to show similar benefits in cognitive function and patient-reported quality of life with hippocampal avoidance.

The summation of these findings remains consistent with cognition-specific hypothesis of hippocampal avoidance but also underscore the palliative intent of brain metastasis management and the capacity of HA-WBRT to provide optimal intracranial control to limit neurologic symptom burden.

Future Directions

All of the trials observing higher cognitive toxicity in patients receiving WBRT were conducted in the conventional era of WBRT without the inclusion of neuroprotective strategies including

memantine and hippocampal avoidance, which have demonstrated significant cognitive toxicity prevention. In the modern era of brain metastasis management, the role of WBRT with neuroprotective strategies remains under investigation. Given the increased requirement for imaging follow-up and the higher rate of salvage therapies associated with SRS alone, modern WBRT may be appropriate for patients who do not wish to undergo extensive surveillance or subsequent salvage therapy. Generally, however, SRS with omission of WBRT can be considered standard of care for patients whose survival is anticipated to extend multiple years, as the capacity of memantine and hippocampal avoidance to prevent the rare occurrence of radiation-related leukoencephalopathy in long-term survivors of WBRT remains unclear.

It is worth noting too that SRS is being investigated for use in five or more brain metastases, with one prospective observational study demonstrating that survival in patients receiving SRS alone for 5–10 brain metastases was not inferior to that seen in patients receiving SRS alone for two to four brain metastases [45]. Currently, four RCTs are either planned or actively accruing patients to directly compare SRS versus WBRT for four or more brain metastases (up to as many as 20 in one study) [46]. Absent conclusive evidence for non-inferiority of SRS alone to WBRT for patients with more than four brain metastases, modern WBRT with hippocampal avoidance and memantine remains a standard of care for these patients.

Modern WBRT for Newly Diagnosed Brain Metastases

Radiosurgery, for as many as 15 brain metastases, has been found to be safe, notably in a series of 360 patients from Japan [45]. The feasibility and safety of multiple-brain metastasis SRS, as well as studies demonstrating inferior cognitive outcomes following upfront WBRT relative to upfront SRS for one to four brain metastases, have led several institutions to consider SRS alone for patients with more than four brain metastases. However, as mentioned above, these studies were largely conducted prior to the publication of large brain metastasis trials testing pharmacologic and technologic neuroprotective strategies during WBRT and leading to the safer delivery of WBRT. Thus, the appropriate management of patients with multiple brain metastases remains unclear.

To address this question in the newly diagnosed setting of multiple brain metastases, multiple trials have been launched. Originally, a trial comparing SRS to conventional WBRT for patients with greater than five brain metastases was initiated by the North American Gamma Knife Consortium. Although this trial was of interest, it was limited in its scope to only one of the several radiosurgical platforms and limited in its statistical power (39 patients planned to be accrued per treatment arm) and the trial closed long before reaching the total target accrual.

More recently, the Canadian Clinical Trials Group (CCTG) launched a cooperative-group phase III trial of SRS versus conventional WBRT in 5–15 brain metastases with co-primary endpoints of overall survival and neurocognitive progression-free survival. Given the practice-changing evidence from NRG CC001, this trial has subsequently been amended to compare SRS versus modern WBRT with hippocampal avoidance and memantine and has also been endorsed by NRG Oncology and Alliance. The question of whether SRS or modern WBRT with hippocampal avoidance and memantine is the optimal modality in patients with 5–15 brain metastases is significant from a societal and medical resources standpoint since the charges related to SRS and IMRT for HA-WBRT can be considerably higher than those of conventional WBRT. However, examining therapy-associated costs is particularly complex in patients with multiple brain metastases, because such patients are likely to undergo additional salvage procedures for new brain metastases. Therefore, the additional costs of salvage are also important to incorporate into economic comparisons, especially when SRS is anticipated to result in higher intracranial relapse rate and need for salvage therapies [20, 21, 23, 47].

Brain Metastasis Velocity

Brain metastasis velocity (BMV) is a useful measure for predicting outcomes in patients with brain metastases who experience distant brain relapse following their first SRS treatment. It is defined as the cumulative number of brain metastases developed since upfront SRS divided by the number of years following SRS. For example, a patient who develops two brain metastases 6 months after upfront SRS would have a BMV of 2/0.5 = 4. Developed by Farris et al. (2017), BMV was found to be significantly associated with overall survival, neurologic death, and rates of salvage WBRT in a cohort of 737 patients [48]. This remained true when the same analysis was applied to a validation set featuring an additional 2092 patients across multiple institutions [49]. Farris et al. (2017) stratified patients into low (<4), intermediate (4–13), and high (>13 BMV) categories, finding that patients with high BMV experienced a cumulative incidence of neurologic death roughly twice that of low-BMV patients. Neurologic death was defined by the authors as death with progressive neurologic decline, regardless of extracranial disease status [48]. The significant association of BMV with neurologic death, thus defined, makes it a useful marker for predicting intracranial control, as does the association between BMV at first distant brain relapse and BMV at second distant brain relapse. The prognostic value of BMV has since been validated in two additional published series [50, 51].

This predictive ability is of interest for its potential utility in triaging patients at risk for poor intracranial control to optimal intracranial control offered by SRS plus WBRT. With continued refinement, BMV could be used to identify and treat patients who would benefit from the superior intracranial control offered by WBRT. This in turn could reduce both neurologic death and, more generally, the neurological sequelae of a high burden of brain metastatic disease in this patient population. A phase III trial (NRG BN009) of salvage SRS with or without modern WBRT with hippocampal avoidance and memantine for recurrent brain metastases with brain metastasis velocity exceeding four brain metastases/year is being developed through NRG Oncology with anticipated activation in 2020. The primary objective of this trial is to determine if the addition of HA-WBRT with memantine to salvage radiosurgery effectively prevents neurologic death in this high-risk patient population.

Small Cell Lung Cancer Brain Metastases

Intracranial failure is a frequent problem in patients with small cell lung cancer (SCLC). SCLC accounts for approximately 15% of all cases of lung cancer, tends to disseminate earlier in the course of its natural history than non-small cell lung cancer and is more clinically aggressive. As a result, approximately 10–20% of SCLC patients present with brain metastases at the time of initial diagnosis, and an additional 40–50% will develop brain metastases some time during the course of their disease. In addition, brain metastases have an impact on the quality and length of survival. Prophylactic cranial irradiation (PCI) has historically been used as a strategy to reduce the incidence of brain metastases in SCLC; however, the National Comprehensive Cancer Network (NCCN) guidelines recommend caution regarding PCI delivery in older patients and PCI is omitted in up to 40–50% of patients, primarily due to concerns over cognitive toxicity [52, 53]. NRG CC003 is an ongoing phase III trial testing whether the cognitive toxicity of PCI can be prevented with hippocampal avoidance during PCI for SCLC patients.

Due to the high propensity for micrometastatic seeding of the brain, WBRT remains standard of care for patients with SCLC brain metastases. Studies demonstrating cognitive toxicity from conventional WBRT have led to questions as to whether upfront SRS followed by close imaging surveillance for patients with SCLC brain metastases is an acceptable alternative. Importantly, SCLC patients have been excluded from the landmark randomized trials testing SRS for brain metastases [20, 21, 23, 47]. Historic objections to the use of SRS in SCLC

have included the concern for diffuse interval CNS progression, which could potentially result in diminished overall survival.

However, there is growing evidence to suggest that SRS alone may be safe and appropriate for some patients with SCLC brain metastases. A multi-institutional retrospective analysis of 293 patients treated with SRS for SCLC brain metastases observed the risk of radiation necrosis to be <5% [54], comparable to outcomes following SRS for brain metastases from other histologies. Serizawa et al. (2002) [55] compared the outcomes of SCLC (N = 34) and NSCLC (N = 211) patients with brain metastases treated with SRS alone and found comparable rates of overall survival, central nerve system control, and neurologic mortality in SCLC and NSCLC patients. Yomo and Hayashi (2015) [56] reported on 70 SCLC patients treated with SRS (including 46 without prior PCI or WBRT), with a median overall survival of 7.8 months and encouraging 1-year and 2-year neurologic mortality free survival of 94% and 84%, respectively. A recent analysis of the National Cancer Database compared upfront WBRT with upfront SRS for SCLC patients with brain metastases and reported favorable overall survival with SRS both overall and after propensity-score matching [57].

Although retrospective analyses are subject to cofounding from selection bias, they do suggest that some patients may be safely and effectively managed with a strategy of SRS alone. Overall, there is growing equipoise regarding the role of SRS versus WBRT in the management of SCLC brain metastases, and prospective randomized data are urgently needed to address this knowledge gap especially given practice-changing evidence demonstrating the cognitive preservation benefits of hippocampal avoidance and memantine as neuroprotective strategies during WBRT. NRG Oncology is currently developing a phase III trial of SRS versus modern WBRT with hippocampal avoidance and memantine for 10 or fewer brain metastases from small cell lung cancer with a primary endpoint of cognitive toxicity. There is data from Switzerland that is raising questions about HA-WBRT for PCI that this proposed trial may help examine, specifically a single-institution retrospective analysis that identified more significant leukoencephalopathy in patients treated with PCI using HAWBRT than conventional WBRT [58] and a multi-institution phase II trial of early HA-PCI that saw similar neurocognitive outcomes as PCI using conventional WBRT techniques [59].

Alternating Electric Field Therapy

Alternating electric fields—commonly called tumor treating fields or TTFields—have been increasingly used as part of management for glioblastoma. The low-intensity, intermediate frequency fields are applied via an adhesive cap consisting of an array of transducers and serve to interrupt cell replication by two principal mechanisms. First, TTFields interact with the strong electric dipole moments of the microtubules forming the mitotic spindle, disrupting spindle formation and stalling mitosis. Second, the fields have been shown to destroy cells nearing the end of cytokinesis, rupturing the cell membrane and generating membrane blebs that resemble the products of apoptosis. These results were observed in vitro in both glioma and melanoma cell lines [60].

A phase III trial comparing TTFields with temozolomide to temozolomide alone in patients with glioblastoma (GBM) has demonstrated a survival advantage to adding TTFields. Patients treated with TTFields were exposed to low-intensity, 200-kHz alternating electric fields for at least 18 h per day via a portable device. These patients had an overall median survival of 20.9 months compared to 16 months in those treated with temozolomide alone (P < 0.001). Systemic adverse events occurred at about the same rate in each arm with the most common side effect of treatment being mild-moderate skin irritation of the scalp in 52% of patients in the TTFields arm [61]. Prompted by this success in the management of primary CNS malignancy and by preclinical data showing effectiveness in non-CNS malignancies, a phase III trial is currently underway to evaluate the use of TTFields in conjunction with radiosurgery for patients with 1–10 NSCLC metastases. The METIS trial (ClinicalTrials.gov identifier: NCT02831959)

will evaluate as its primary outcome the time to intracranial progression and, as a secondary outcome, track cognitive function in patients receiving this novel therapy.

Concomitant Systemic Agents

Since the 1980s, a variety of systemic therapies have been investigated for use in conjunction with WBRT for patients with brain metastases. The imidazoles such as metronidazole and misonidazole were among the first agents to be tested in this context. Neither agent added any survival benefit over WBRT alone [62]. More recently, a trial of sodium glycididazole did demonstrate improved intracranial control and longer progression-free survival, but did not find a benefit to overall survival [63]. One area of success has been with the use of motexafin gadolinium (MGd), a redox modulating agent that catalyzes the oxidation of various intracellular metabolites, increasing the toxicity of reactive oxygen species and limiting the cell's ability to repair itself. While one phase III trial of MGd in patients with brain metastases demonstrated no overall benefit in survival time or time to neurologic progression overall, a subset of patients with NSCLC did experience a benefit in time to neurologic progression [64]. The phase III trial that followed compared WBRT with or without MGd in NSCLC patients and demonstrated that patients initiating WBRT within 28 days of brain metastasis diagnosis experienced a significant improvement in time to neurologic progression with the addition of MGd. This effect was identified on geographic subgroup analysis when it was found that patients in North America (where investigators were more likely to initiate WBRT earlier) had a significantly longer time to neurologic progression than the overall cohort [65]. Based on these data, MGd was deemed an appropriate adjunct therapy in NSCLC patients, provided that WBRT is initiated promptly, but has not been widely accepted.

Temozolomide (TMZ) is a DNA alkylating chemotherapeutic agent that is notable for its high blood-brain barrier (BBB) penetrance. This property has prompted a number of trials evaluating the efficacy and toxicity of WBRT with adjuvant TMZ. A phase III study from Antonadou et al. (2002) demonstrated a significantly higher radiographic response rate with combined therapy versus WBRT alone (53.4 vs. 33.3%, $P = 0.039$). The difference in response rate was even more dramatic in patients <60 years of age and with a Karnofsky performance score of 90–100 (70.6 vs. 32.4%, $P = 0.003$ in the latter group). The study found no difference in neurological response or median survival, however [66].

A later phase III trial in NSCLC patients from Sperduto et al. (2013) investigated WBRT and SRS with or without TMZ or erlotinib. The authors again found no significant survival advantage with the addition of temozolomide. They also found no difference in time to progression [67]. A 2016 meta-analysis of seven trials (including those discussed above) comparing radiotherapy with TMZ to radiotherapy alone found no advantage in survival to adding TMZ, despite a significant increase in response rate on combination therapy. Patients treated with TMZ were more likely to experience grade 3 to 4 nausea and grade 3 to 4 thrombocytopenia [68]. As TMZ has not shown a survival benefit and is accompanied by an increase in toxicity, it is not recommended for use in clinical practice for patients with brain metastases.

Inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase are under investigation for adjuvant use with WBRT. Erlotinib is one such (EGFR) inhibitor with known radiosensitizing properties. Recent trials of this agent highlight the importance of patient selection with respect to pathway-specific mutations. While a preliminary trial from Welsh et al. (2013) suggested a benefit for adjuvant erlotinib with WBRT in lung cancer patients, subsequent trials have contradicted this [69]. The above-mentioned study from Sperduto et al. (2013) showed that adding erlotinib provided no benefit to overall survival or time to progression [67]. Another study from Lee et al. (2014) again found that adding erlotinib had no effect on neurological progression-free survival or overall survival [70]. Notably, however, over 50% of the patients in Welsh et al. with known tumor EGFR mutation status possessed EGFR mutations. Patients in that study with EGFR-mutated tumors had a median

survival time of 19.1 months compared to 9.3 months in those with wild-type EGFR tumors. With a total sample of only 17 patients, however, this difference was not significant ($P = 0.534$). In contrast, Sperduto et al. did not assess EGFR mutation status and in the study from Lee et al. only 1 of the 35 patients with known tumor EGFR mutation status possessed a mutation. The SATURN trial investigating the use of erlotinib in patients with advanced NSCLC demonstrated that although erlotinib provided a benefit to NSCLC patients generally, those with EGFR mutations derived the greatest benefit from it [71]. It seems likely then that erlotinib is most effective in intracranial metastases in which a mutated EGFR drives cancer growth and proliferation. As such, further study is warranted in this patient subpopulation. Other EGFR inhibitors such as gefitinib and icotinib have also been investigated as adjuvant therapy with WBRT with similarly mixed results. A study of icotinib versus WBRT with chemotherapy in patients with EGFR-mutant NSCLC demonstrated superior intracranial progression-free survival in the icotinib arm (10 vs 4.8 months, $P = 0.014$) [72]. It is worth noting, however, that a phase II study of NSCLC patients has shown a survival advantage to icotinib with WBRT compared to WBRT alone, with a particular advantage for patients with EGFR-mutated tumors [73]. This suggests a possible benefit to combination therapy rather than icotinib alone.

RTOG 1119 is an ongoing study assessing the treatment of HER2-positive breast cancer patients with WBRT plus adjuvant trastuzumab and lapatinib. Lapatinib is a dual EGFR and HER2 inhibitor that, unlike trastuzumab, can cross the BBB and has shown preclinical promise. Until more persuasive clinical evidence emerges, however, the benefit of combining WBRT and targeted therapies for the purpose of improving intracranial control remains unclear.

A retrospective analysis of NSCLC patients in whom radiation therapy was deferred provides further reason for clinicians to exercise caution before omitting radiation treatment. The study found that patients who received upfront SRS for brain metastases had a significantly longer median survival time than those receiving upfront erlotinib. There was also trend toward a survival advantage to WBRT over erlotinib, though this was not significant [74]. Given the intracranial activity of osimertinib as a newer generation EGFR-targeting agent [75, 76], and its establishment as first-line therapy for EGFR-mutated non-small cell lung cancer, treatment with osimertinib and omission of upfront radiotherapy for small asymptomatic brain metastases is increasingly being utilized, although further study is needed.

The use of immune checkpoint inhibitors in conjunction with brain radiotherapy is a matter of active and ongoing study. A retrospective analysis of patients with melanoma brain metastases receiving ipilimumab (an anti-CTLA-4 monoclonal antibody) with either SRS or WBRT did not demonstrate a survival advantage for combined WBRT-ipilimumab therapy compared with historical controls treated with WBRT and bortezomib. The authors did find an advantage to SRS and ipilimumab versus SRS alone [77]. There are, however, currently no published RCTs investigating the use of WBRT with immunotherapy compared to WBRT alone or immunotherapy alone. Future trials of immune checkpoint inhibitors and other targeted agents should consider not just efficacy, but toxicity as well. In particular, with significantly improved survivorship with the use of immune checkpoint inhibitors for melanoma and non-small cell lung cancer brain metastases, cognitive side effects become a significant component of both brain metastatic disease and associated therapies, and new treatments should be evaluated for impact on these symptoms.

Optimal Patient Selection: Summary

Recent research has helped identify which patients may stand to benefit the most from WBRT versus or in conjunction with other definitive treatment modalities for brain metastases. WBRT should be considered as primary treatment for patients with good performance status and with systemic therapy options for managing extracranial disease when metastatic lesions within the brain are not amenable to surgical resection or SRS. This can occur when a metasta-

sis is too large for SRS and is located in an unresectable region, when the burden of metastatic disease is too extensive for other techniques (≥ 5 metastases), in the case where there is diffuse disease (extensive dural, pachymeningeal, or leptomeningeal metastases), or in cases where there is a possibility for microscopic metastatic disease (particularly for limited-stage SCLC responsive to chemotherapy or high brain metastasis velocity after upfront SRS). These patients, at high risk for developing or experiencing progression of multiple brain metastases that may cause neurologic and cognitive impairment, may benefit the most from modern WBRT which can alleviate these symptoms and improve survival. Neurocognitive protective strategies of hippocampal avoidance and memantine can effectively prevent WBRT-associated cognitive toxicity.

Summary

WBRT remains a valuable asset in the management of brain metastases. Several trials of SRS versus conventional WBRT demonstrated inferior cognitive outcomes of WBRT in the setting of one to four brain metastases. These findings have led to a declining use of WBRT and rapidly rising use of SRS alone. However, practice-changing evidence demonstrating preservation of cognitive function with hippocampal avoidance and memantine has ushered in the modern era of WBRT. Importantly, prior trials demonstrating inferior cognitive outcomes with conventional WBRT did not include these neuroprotective strategies and thus have limited relevance in the modern management of brain metastases.

Several phase III trials are currently accruing or under development to better define the role of modern WBRT either in lieu of SRS for newly diagnosed 5–15 brain metastases or small cell lung cancer brain metastases or adjunctive to SRS for recurrent brain metastases with high brain metastasis velocity. In addition, as improvements in systemic therapy continue to prolong survival in brain metastasis patients, the impact of optimizing brain metastasis control and minimizing associated neurologic and quality-of-life sequelae will become even more apparent, and the appropriate usage of modern WBRT will be further refined.

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