CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINE ON THE ROLE OF WHOLE BRAIN RADIATION THERAPY IN ADULTS WITH NEWLY DIAGNOSED METASTATIC BRAIN TUMORS

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Abbreviations

BED:	Biological equivalent dose
BM:	Brain metastases
EGFT:	Epidermal growth factor receptor
HVLT:	Hopkins Verbal Learning test
Gy:	Gray
HA:	Hippocampal avoidance
HER2:	Human epidermal growth factor receptor 2
MMSE:	Mini-mental status examination
NSCLC:	Non-small cell lung cancer
PCI:	Prophylactic cranial irradiation
QOL:	Quality of life
RCT:	Randomized controlled trial
RT:	Radiation therapy
SCLC:	Small cell lung cancer
SIB:	Simultaneous integrated boost
SRS:	Stereotactic radiosurgery
TKI:	Tyrosine kinase inhibitors
WBRT:	Whole brain radiation therapy
WHO PS:	World Health Organization Performance Status

No part of this manuscript has been published or submitted for publication elsewhere.

ABSTRACT

Target population

Adult patients (older than 18 years of age) with newly diagnosed brain metastases.

Question

If whole brain radiation therapy (WBRT) is used, is there an optimal dose/fractionation schedule?

Recommendations

Level 1: A standard WBRT dose/fractionation schedule (i.e., 30 Gy in 10 fractions or a biological equivalent dose [BED] of 39 Gy_{10}) is recommended as altered dose/fractionation schedules do not result in significant differences in median survival or local control.

Level 3: Due to concerns regarding neurocognitive effects, higher dose per fraction schedules (such as 20 Gy in 5 fractions) are recommended only for patients with poor performance status or short predicted survival.

Level 3: WBRT can be recommended to improve progression-free survival for patients with >4 brain metastases.

Question

What impact does tumor histopathology or molecular status have on the decision to use WBRT, the dose fractionation scheme to be utilized, and its outcomes?

Recommendations

There is insufficient evidence to support the choice of any particular dose/fractionation regimen based on histopathology. Molecular status may have an impact on the decision to delay WBRT in subgroups of patients, but there are not sufficient data to make a more definitive recommendation.

Question

Separate from survival outcomes, what are the neurocognitive consequences of WBRT, and what steps can be taken to minimize them?

Recommendations

Level 2: Due to neurocognitive toxicity, local therapy (surgery or stereotactice radiosurgery [SRS]) without WBRT is recommended for patients with ≤4 brain metastases amenable to local therapy in terms of size and location.

Level 2: Given the association of neurocognitive toxicity with increasing total dose and dose per fraction of WBRT, WBRT doses >30 Gy given in 10 fractions, or similar biologically equivalent doses, are not recommended, except in patients with poor performance status or short predicted survival.

Level 2: If prophylactic cranial irradiation (PCI) is given to prevent brain metastases for small cell lung cancer, the recommended WBRT dose/fractionation regimen is 25 Gy in 10 fractions, and because this can be associated with neurocognitive decline, patients should be told of this risk at the same time they are counseled about the possible survival benefits.

Level 3: Patients having WBRT (given for either existing brain metastases or as PCI) should be offered 6 months of memantine to potentially delay, lessen, or prevent the associated neurocognitive toxicity.

Question

Does the addition of WBRT after surgical resection or radiosurgery improve progression-free or overall survival outcomes when compared with surgical resection or radiosurgery alone?

Recommendations

Level 2: WBRT is not recommended in World Health Organization (WHO) performance status 0-2 patients with up to 4 brain metastases because, compared with surgical resection or radiosurgery alone, the addition of WBRT improves intracranial progression-free survival but not overall survival.

Level 2: In WHO performance status 0-2 patients with up to 4 brain metastases where the goal is minimizing neurocognitive toxicity, as opposed to maximizing progression-free survival and overall survival, local therapy (surgery or radiosurgery) without WBRT is recommended.

Level 3: Compared with surgical resection or radiosurgery alone, the addition of WBRT is not recommended for patients with more than 4 brain metastases unless the metastases' volume exceeds 7 cc, or there are >15 metastases, or the size or location of the metastases are not amenable to surgical resection or radiosurgery.

INTRODUCTION

Rationale

Whole brain radiation therapy (WBRT) has long been a standard treatment for patients with brain metastases. Based on preclinical and observational data, some physicians alter dose fractionation or withhold WBRT, based on tumor histology. Concern has also been expressed by clinicians regarding the neurocognitive effects of WBRT, particularly if the metastases are amenable to surgical resection or stereotactic radiosurgery (SRS).

This guideline is based on a systematic review of the evidence available for WBRT dose fractionation regimens and the impact of tumor histopathology on treatment outcomes when WBRT is used for newly diagnosed brain metastases. Due to concerns about neurocognitive toxicity from WBRT, this guideline also reviews the evidence for pharmacologic or technical maneuvers to reduce this toxicity. In addition, this guideline analyzes the data regarding survival outcomes following local therapy with surgical resection or SRS.

Objectives

This guideline will systematically review the evidence available for altered WBRT dose fractionation and the impact of tumor histopathology on treatment outcomes when WBRT is used. The neurocognitive effects of WBRT, and the strategies for reducing these effects, are addressed. In addition, this guideline will also systematically review the evidence for the use of surgical resection plus WBRT compared with WBRT alone in patients with newly diagnosed, surgically accessible, single brain metastases. The studies identified through this process will be used to make evidence-based recommendations for the role of WBRT in the management of patients with newly diagnosed brain metastases.

METHODS

Writing Group and Question Establishment

The writing group was established by the nominating section and Task Force Chair. The writing group jointly developed the 4 questions relevant to WBRT in the current era. The 4 questions were each assigned to a primary writer. To answer the questions, a comprehensive systematic literature review was performed. Two writers evaluated citations found by the search using *a priori* criteria for relevance and documented decisions in standardized forms. Cases of

disagreement were resolved by a third reviewer. The same methodology was used for full-text screening of potentially relevant papers. Studies that met the eligibility criteria were data extracted by one reviewer and the extracted information was checked by a second reviewer.

Literature Review

To update questions raised in the prior guidelines, PubMed, Embase, and Cochrane CENTRAL databases were searched for the period from January 1, 2008, to December 31, 2015. For the new question regarding neurocognitive effects, the search extended between January 1, 1990, through December 31, 2015. A broad search strategy using a combination of controlled vocabulary and text words was employed. The search strategies for each database are documented in Table 1.

Article Inclusion and Exclusion Criteria

For new literature to be included for consideration, studies published in full as peer review papers had to meet the following criteria:

- Be published in English with a publication date within the periods described above.
- Involve patients with newly diagnosed parenchymal brain metastases.
- Involve adult patients (>18 years of age).
- Fully-published peer-reviewed articles.
- Use of WBRT after diagnosis of brain metastases has been made.

Study Selection and Quality Assessment

After an extensive search, 1823 articles were found. The duplicates from the searches in different databases were eliminated. By reviewing the titles and/or abstracts, we excluded all articles referring to leptomeningeal metastases, those discussing exclusively surgery, chemotherapy or radiosurgery *and citations that only referred to* patients <18 years of age. We also excluded publications that discussed exclusively WBRT for treatment of recurrent/progressive brain metastases, and all articles discussing experimental therapy in animal tumor models. The remaining 172 articles underwent full-text review. Only 61 articles met all of the inclusion criteria and were considered in formulating these evidence-based clinical guidelines. The remaining 111 articles that underwent full-text review were excluded for the following reasons: the results were not presented according to treatment type, the study eligibility or reasons for treatment assignment were not clear, a lack of subgroup analysis by histology or molecular

status, the paper was a review, systematic review, letter, or editorial, the study contained too few patients, or the study included a radiographic or non-neurocognitive endpoint.

Evidence Classification and Recommendation Levels

Both the quality of the evidence and the eventual strength of the recommendations generated by this evidence were graded according to a 3-tiered system for assessing studies addressing diagnostic testing as approved by the American Association of Neurological Surgeons (AANS)/ Congress of Neurological Surgeons (CNS) Joint Guidelines Review Committee on criteria (https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology).

Assessment for Risk of Bias

A list of article titles and abstracts was produced by the search, using the search strategies presented in Table 1. To avoid bias due to selective choice of articles, the decision to review and utilize the full article was made by at least 2 authors. The authors of this guideline represent multiple specialties. The decision to classify a study as Class I, II, or III was first made by the primary author of each of the 4 questions, and then reviewed by at least 1 other author. The strength of the recommendation was also proposed by the primary author and then discussed and modified by all authors.

RESULTS

If WBRT is used, is there an optimal dose/fractionation schedule?

In the 2010 guideline, 17 studies met the eligibility criteria for this question.[1] These unique studies fell into 3 evidence class categories as follows: 9 randomized controlled trials (RCT) Class I studies[2-10] and 1 Class II randomized phase I/II trial,[11] 7 other Class II studies[12-17] (retrospective cohort studies), and 1 Class III study[18] (prospective cohort study with historical controls). Since 2008, there have been 3 additional studies that met eligibility criteria: 1 Class I study[19] and 2 Class III studies.[20, 21] Table 2 summarizes the 14 RCT studies from the old and new guidelines that informed the recommendations.

Expressing radiation dosages in terms of the biological equivalent dose (BED) takes into account the total dose of radiation, fraction size, and overall time to deliver the radiation, and presumed repair of irradiated tissue.[22, 23] The 2010 guidelines found no meaningful improvement in any endpoint relative to dose or BED; specifically, survival was not improved. In addition, no dose-

effect was identified for quality of life (QOL) or neurologic function. Given the paucity of Class I studies published since the 2010 guidelines, these BED analyses were not updated.

Despite previously published phase III studies (all Class I studies) finding no disadvantage to very short, accelerated treatments, there have been few recent studies evaluating this further.[2, 6, 10] One recent phase II study of short accelerated radiation therapy (RT), such as 18 Gy given in 4.5 Gy fractions twice daily for 2 days, concluded that this treatment was effective in terms of symptom relief (63%) and median survival time (7 months), but agreed that further phase III studies were required.[24]

One of the evolving techniques of WBRT is to use a simultaneous integrated boost (SIB).[25, 26] The decision to do a SIB may be based on the size of the brain metastases or histology of the primary cancer.[27] Rodrigues et al [25] reported on such a technique for 120 patients with oligometastatic brain metastases (< 7 lesions with cumulative volume < 30 cc) treated at 2 centers between 2005 and 2010. Using an arc-based image-guided system, patients received 20 Gy in 5 fractions WBRT while simultaneously receiving 40 Gy in 5 fractions to the oligometastases. With a median follow-up of 4.7 months, 23% of deceased patients died of intracranial disease. The median survival time was 5.9 months. As in other WBRT studies, poor performance status, lung cancer histology, and the presence of systemic disease were identified as poor prognostic factors. A phase II study comparing this technique to traditional SRS techniques is ongoing in Canada (NCT01543542).

In summary, a standard WBRT dose/fractionation schedule (i.e., 30 Gy in 10 fractions or a BED of 39 Gy_{10}) is recommended because altered dose/fractionation schedules do not result in significant differences in median survival or local control. However, due to concerns regarding neurocognitive effects, higher dose per fraction schedules (such as 20 Gy in 5 fractions) are recommended only for patients with poor performance status or short predicted survival. The more difficult issue is when to recommend WBRT. As seen throughout the following questions, the role of WBRT has declined, because more patients are treated with local therapies (radiosurgery or surgery) or supportive care. Studies of local therapy with or without WBRT have only been conducted in patients with <4 brain metastases.[28] This lead to the Level 3

recommendation of WBRT to reduce progression-free survival for patients with >4 brain metastases. The use of systemic therapy only is addressed more thoroughly in other chapters.

What impact does tumor histopathology or molecular status have on the decision to use WBRT, the dose fractionation scheme to be utilized, and its outcomes?

In the 2010 guidelines, only 1 paper met the eligibility criteria for this slightly modified question.[29] The question was reworded in this guideline to address the issue of timing of WBRT relative to systemic therapy. This updated literature search identified 3 additional papers, all Class II or III.[30-32] In addition, an older Radiation Therapy Oncology Group (RTOG) Class I study primarily asking a question regarding dose/fractionation was considered because it stratified patients according to site of primary cancer (lung vs breast vs other).[33]

Borgelt et al,[33] in a Class II study, concluded that the results of WBRT were no different between 3 histopathology groups: lung, breast, or "other." No regimen was shown to be superior over another regimen according to these histopathology groups. However, a later retrospective analysis of RTOG and multi-institutional data has uncovered diagnosis (histology) specific prognostic factors.[34] This retrospective analysis of 3940 patients with newly diagnosed brain metastases led to the Graded Prognostic Assessment Index that can be used to estimate survival for patients with brain metastases from non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), melanoma, renal cell cancer, breast cancer, or gastrointestinal cancers. Because these patients had undergone a variety of treatments, including WBRT, SRS, surgery, and various combinations, the authors were careful to conclude that although histology may influence prognosis, there were insufficient data to predict the relative benefits of one treatment over another.

Lung cancer has been identified in several studies to have a different outcome when treated with WBRT than other histologies. In RTOG 9508, patients with 1 to 3 newly diagnosed brain metastases were randomized to receive either WBRT or WBRT followed by a SRS boost.[35] The primary study outcome was overall survival, and secondary outcomes were tumor response, local control rates, overall intracranial recurrence rates, cause of death, and performance measurements. No difference between WBRT alone versus WBRT followed by SRS was found

in these primary or secondary endpoints for the study group at large. However, a subset analysis found improved survival, which reached statistical significance in multivariate analysis, for patients who received the combination of WBRT and SRS, as opposed to WBRT alone, in squamous cell and non-small-cell histology, which is usually seen in patients with lung cancer.

The molecular analysis of lung cancer has also brought about significant changes in the approach to brain metastases with either epidermal growth factor receptor (EGFR) mutations or echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase (ALK) rearrangements.[36, 37] Two small institutional retrospective Class III case series of patients with lung cancer brain metastases treated with WBRT attempted to determine the impact of EGFR mutation in treatment outcome.[30, 31] Both studies found that an EGFR mutation was predictive for improved treatment response following WBRT. Gow et al[31] also concluded from a small retrospective study that the addition of a tyrosine-kinase inhibitor to WBRT was independently associated with improved treatment response in EGFR-mutated patients. Small retrospective studies in EGFR-mutated lung cancer patients have found that first-line tyrosine kinase inhibitors (TKI) without WBRT are associated with response or stability in brain metastases, but that intracranial progression requiring WBRT occurs in most patients.[38] Despite the controversy regarding treatment for this subset of lung cancer patients, there are no ongoing phase III studies comparing WBRT to TKIs in EGFR-mutated or echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase rearranged patients.

Molecular analyses in patients with breast cancer have also uncovered the importance of human epidermal growth factor receptor 2 (HER2) status on the outcome of patients with breast cancer brain metastases undergoing WBRT. In a class III study, Wolstenholme et al[32] reported the results of WBRT observed in 88 HER2-positive patients and 93 HER2-negative patients, with heterogeneous chemotherapy regimens, including trastuzumab treatment in 53 of the 88 HER2-positive patients. Twelve patients also received additional SRS. The study concluded that an improved median survival following WBRT was associated with HER2-positive status. However, the results were confounded by the observation that HER2-positive patients may have had more aggressive treatment for their brain metastases.

Though this systematic review of the literature was limited in terms of higher class data that specifically addressed the question of the impact of histopathology/molecular status on treatment outcomes following WBRT, it appears that the use of WBRT has waned, particularly in certain primary histologies. For example, several retrospective Class III case series have concluded that SRS alone for melanoma brain metastases, even if numerous, is associated with a reasonable outcome.[39-41] Prospective studies are needed, and a randomized prospective trial investigating the role of WBRT in melanoma brain metastases is reported to be underway.[42]

In summary, there is insufficient evidence to support the choice of any particular dose/fractionation regimen based on histopathology. Molecular status may have an impact on the decision to delay WBRT in subgroups of patients but there are not sufficient data to make a more definitive recommendation. The role of WBRT, as opposed to SRS alone, is also controversial in many histologies, but particularly for patients with melanoma. RCTs that are histology- or molecular status-specific are necessary to resolve many of these issues.

What are the neurocognitive consequences of WBRT, and what steps can be taken to minimize it?

This is a new question since the prior guidelines were published, reflecting the growing concern about the neurocognitive effects of WBRT. The effects of WBRT on neurocognitive functions can be subdivided into whether or not patients have demonstrable brain metastases at the time of WBRT, or whether WBRT is being used for prophylactic cranial irradiation (PCI). Six studies of the neurocognitive effects of WBRT in the PCI setting for SCLC are summarized in Table 4.[43-48] These studies primarily included patients with SCLC histology, although Sun et al[45] reported on the neurocognitive outcome of PCI in patients with NSCLC.

An early phase III trial by Arriagada et al.[48] reported neurocognition as a secondary endpoint for patients with limited stage SCLC. There was no difference found in the 2-year cumulative incidence of negative change in cognitive "higher functions" (36% if no PCI, vs 30% with PCI, p = NS). This study was given a Class II designation due to the lack of definition for "higher functions" testing, or criteria used to define decline in testing. Gregor et al.[47] also found no difference in neurocognition at 6 months or 1 year following PCI. This RCT was given a Class II designation for several reasons: neurocognition was only a secondary endpoint, and

neurocognitive baseline testing was available in only 40% of patients, leading to potential issues of selection bias and small patient numbers. Slotman et al.[46] reported neurocognition within a phase III RCT for patients with extensive stage SCLC. There was no statistical difference in worsened cognitive functioning at 3 months (PCI: 22.4% versus no PCI: 10%, p = NS). This study had a large number of patients treated with a PCI dose/fractionation scheme not as frequently used in the United States (20 Gy in 5 fractions). Another limitation was that the neurocognitive endpoint was taken from a subset of primarily QOL questionnaires. Sun et al.[45] reported the neurocognitive outcomes in an RCT of PCI or no PCI for NSCLC histology. Patients in the PCI arm had a significant deterioration in memory, measured by the Hopkins Verbal Learning Test-Revised (HVLT-R), at 1 year. However, there was no difference found in global cognition measured by the Mini-Mental Status Examination (MMSE) or QOL between arms. This study represents Class I data due to a relatively large patient population, intact randomization, and the use of more sensitive neurocognitive testing.

Two studies investigated the cognitive effect of various PCI dose/fractionation regimens for patients with PCI.[43, 44] Le Pechoux et al[44] found no significant difference in neurocognitive outcomes between 36 Gy and 25 Gy PCI. However, Wolfson et al[43] reported secondary endpoints of a large randomized phase II trial using a modern battery of neurocognitive assessments and reported a significantly higher rate of neurocognitive decline with 36 Gy versus 25 Gy at 12-months (85 – 89% vs 60%, p = 0.02). Increasing age was also a significant predictive factor for neurocognitive decline. Thus, the class II evidence from the Wolfson et al[43] study allows one to infer that WBRT doses exceeding 30 Gy in 10 fractions (or similar BEDs) are associated with greater likelihood of neurological decline.

Three studies summarized in Table 5 met inclusion criteria for tracking neurocognitive outcome following local brain therapy (primarily SRS) versus local brain therapy and WBRT for patients with known brain metastases.[49-51] Chang et al[50] randomized patients with 1 to 3 brain metastases to SRS alone versus SRS and WBRT. A sensitive battery of neurocognitive assessments was utilized with neurocognition as the study's primary endpoint. The study showed significantly higher rates of deterioration in recall at 4 months with the addition of WBRT (SRS + WBRT: 52% vs SRS: 24%, p(A > B) 96%). Another study by Aoyama et al[49] randomized patients with 1

to 4 brain metastases to SRS versus SRS and WBRT, and used the MMSE as a measure of global cognition. This study found no difference in MMSE preservation rates between arms at both 12 and 24 months. In fact, they showed that intracranial tumor control was the most important factor in cognitive preservation. In a more recent study, Brown et al[52] similarly showed that the addition of WBRT to SRS was associated with significantly higher rates of cognitive decline and memory decline at 3 months (SRS + WBRT 92% vs SRS 64%, $p<0.001$).

Soffietti et al[51] reported the secondary cognitive outcome of local therapy (SRS or surgery) with or without WBRT in an RCT by the European Organisation for Research and Treatment of Cancer (EORTC). The authors reported that WBRT was associated with significantly more decline in 12-month cognitive functioning than local therapy alone. This trial was graded as Class II due to the use of primarily QOL questionnaires to measure cognition and the mixing of post-surgical and SRS local therapy patients into a single group.

Four studies summarized in Table 6 met the inclusion criteria for medications or radiation techniques evaluated for their efficacy in minimizing the neurocognitive effects of WBRT for patients with known brain metastases.[53-56] Three of these trials investigated the use of medications to mitigate the neurocognitive effects of RT in patients with known brain metastases or primary brain tumors.[54, 55, 56] Butler et al[55] reported an RCT of methylphenidate versus placebo, with approximately 50% of patients having metastatic brain tumors. MMSE was used as the primary measure of cognition. There were no differences in MMSE scores between arms $\leq$8 weeks post-radiation. Brown et al[56] reported a phase III RCT of memantine versus placebo in patients with brain metastases treated with WBRT. There was no significant difference in the decline of delayed recall (the primary endpoint) in the memantine arm compared with the placebo arm. However, time to cognitive failure, defined as the first cognitive failure on any of the neurocognitive tests, was found to significantly favor the memantine arm (hazard ratio, 0.78, $p=0.01$). Rapp et al[53] reported a phase III trial of donepezil versus placebo for patients with metastatic or primary brain tumors status post-completion of partial brain RT or WBRT. Patients in both groups showed improved cognitive function at 24 weeks, but there was no significant difference in overall cognitive composite score between the donepezil and placebo arms ($p=0.48$). However, several specific cognitive functions, such as immediate and delayed recall,

did show improvement, and patients with greater baseline impairment were more likely to have the greatest benefit from donepezil.

Gondi et al[54] reported a single arm phase II trial of hippocampal avoidance WBRT (HA-WBRT). The results of this trial were compared with a historical control of conventional WBRT. HA-WBRT was associated with a lower rate of decline in delayed recall at 4 months, 7% with HA-WBRT as opposed to 30% in historical control, p=0.0003.

In summary, there is evidence that the addition of WBRT to local therapy (primarily SRS) is associated with increased risk of significant neurocognitive decline in patients with brain metastases. This decline is apparent as early as 3 months post-WBRT and can persist in long-term survivors. This supports a Level 2 recommendation that local therapy (surgery or SRS) without additional WBRT is recommended for patients with $\leq$4 brain metastases that are amenable to local therapy in terms of size and location. The evidence also supports a Level 2 recommendation that WBRT doses not exceed 30 Gy given in 10 fractions, or similar BEDs except in patients with poor performance status or short predicted survival. WBRT given as PCI also has detrimental effects on neurocognition, although these detrimental effects have to be weighed against the small survival benefit of PCI.[57] There is evidence that higher doses of PCI are associated with higher levels of neurocognitive detriment, particularly in older patients.[43, 44] This supports the Level 2 recommendation that the recommended PCI WBRT dose/fractionation regimen is 25 Gy in 10 fractions, and because this can be associated with neurocognitive decline, patients should be told of this risk at the same time they are counseled about the possible survival benefits.

There is Class I evidence that memantine has a nonsignificant trend towards neurocognitive protection in patients with brain metastases undergoing WBRT. This supports the Level 3 recommendation to place patients having WBRT (given for either existing brain metastases or as PCI) on 6 months of memantine to potentially delay, lessen, or prevent the associated neurocognitive toxicity. The evidence for donepezil is moderate, and there is insufficient evidence that methylphenidate is beneficial. There is additional evidence suggesting that HA WBRT may significantly reduce the risk of neurocognitive decline compared with conventional

WBRT. There are ongoing RCTs of WBRT with or without HA for patients with either known brain metastases or receiving WBRT in the PCI setting.

Does the addition of WBRT after surgical resection or radiosurgery improve progression-free or overall survival outcomes when compared with surgical resection or radiosurgery alone?

This is a new question raised since the publication of the 2010 guidelines in which there was insufficient evidence to address the value of WBRT following SRS.[1] The previous guidelines only addressed surgical resection and WBRT, or WBRT alone. In this guideline, the authors have expanded the scope of treatment and have the results of studies of local therapy, including either surgery or SRS, with or without WBRT. Prospective RCTs addressing this issue are summarized in Table 7.[28, 58, 59] Sahgal et al[60] published a 2015 meta-analysis evaluating SRS and WBRT compared with SRS alone. While this study was not included in our data table as primary evidence, conclusions gleaned from this study are relevant to this review. Since an earlier question addressed the neurocognitive outcomes of WBRT, this question addresses progression-free or overall survival outcomes.

The first large-scale, prospective RCT demonstrating the efficacy of WBRT following neurosurgical resection of a single solitary BM was reported by Patchell et al[58] in 1998. The primary endpoint was intracranial disease control. Improved local control and cumulative intracranial control were observed in patients who received postoperative WBRT when compared with patients who did not receive the adjuvant therapy. Local tumor recurrence in the resection cavity, as well as distant intracranial metastatic disease, was reduced in the patients who received WBRT, as opposed to those who did not. There was also a significant decrease in the incidence of death resulting from neurological sequelae in patients who received WBRT. Although there was no significant difference found between the adjuvant WBRT versus observation groups in terms of overall survival or length of functional independence, the primary endpoint measured in this study was metastatic recurrence in the brain, and the sample sizes were likely underpowered for these analyses.

An RCT published in 2006 by Aoyama et al[59] (JROSG99-1) randomized 132 patients with 1 to 4

brain metastases, each <3 cm in diameter, to receive either SRS alone or SRS and WBRT. The primary endpoint was overall survival, but secondary outcomes included local recurrence, rate of salvage brain treatment, functional preservation, toxic effects, and cause of death. In the SRS only group, median survival time and the 1-year actuarial survival rate were not significantly different from the SRS and WBRT group. Intracranial recurrence rate at 1 year was higher in the SRS group than the SRS and WBRT group (76.4% vs 46.8%, $p<0.001$). Salvage brain treatment was significantly higher in the SRS alone group; however, the incidence of neurologic-related deaths was not statistically significant. The authors concluded that the addition of WBRT to SRS therapy improved local and intracranial control but did not improve overall survival.

The EORTC 22952-26001 trial, as described by Kocher et al[28] in 2011, randomized 359 patients, WHO performance status of 0-2, who had received local therapy (either SRS or surgical resection of $\leq$3 brain metastases) to either the local therapy only or local therapy followed by WBRT. The primary endpoint was time to decline to WHO Performance Status (WHO PS) > 2. Secondary endpoints included frequency and location of intracranial relapse, progression-free survival, and overall survival. The investigators reported that within the surgical subgroup, adjuvant WBRT reduced the probability of both local and distal relapse to new intracranial sites when compared to patients who did not receive WBRT (59% to 27%, $p<0.001$ and 42% to 23%, $p=0.008$, respectively). In the pooled analyses of surgery and SRS, the median time to WHO PS > 2 was 10.0 months in the local therapy only arm and 9.5 months in the local therapy and WBRT arm ($p=0.71$). In a multivariate analysis, the only factors significantly impacting WHO PS outcomes were the baseline WHO PS (0 vs 2, $p=0.004$) and the presence of macroscopic tumor outside the brain (absent vs present, $p<0.001$). Median progression-free survival was not significantly longer in the WBRT arm when compared with the observation arm (4.6 months vs 3.9 months, $p=0.20$). Overall survival was similar between the two arms. Death resulting from neurologic sequelae was significantly greater in the local therapy arm. Systemic disease progression was the most common cause of death in both arms of the study. The results from this RCT provide further evidence that WBRT is an effective modality to decrease intracranial metastatic recurrence and neurologic death, but this does not translate to an improved duration of functional independence or overall survival. The investigators concluded that in well-

performing patients with stable systemic disease and ≤3 brain metastases, WBRT could be withheld if serial imaging is performed.

The North Central Cancer Treatment Group Alliance N0574 Trial was reported by Brown et al[52] in 2016, falling outside the reference search window, and therefore was not utilized when forming the recommendations.[52] This prospective, multi-institutional RCT was designed to investigate the effect of adjuvant WBRT on cognitive function in patients with 1 to 3 BM treated with SRS. This study was graded as Class II evidence because secondary endpoints included time to intracranial failure, QOL, treatment toxicity, functional independence, individual cognitive assessment outcomes, long-term cognitive status, and overall survival. It was shown that patients who received adjuvant therapy experienced significant deterioration in cognitive function and quality of life at 3 months. Patients receiving adjuvant WBRT had better intracranial control rates; however, this did not lead to improved overall survival. The investigators concluded that in patients with 1 to 3 brain metastases amenable to radiosurgery, SRS alone may be the preferred treatment modality. Retrospective studies were not used to form the recommendation but they also conclude that the addition of WBRT to SRS or surgery is associated with improved local control and distant intracranial control, but not survival.[61, 62]

Lastly, a 2015 meta-analysis by Sahgal et al[60] combined 3 phase III trials to perform a pooled analysis of patients with 1 to 4 brain metastases treated with either SRS alone or SRS + WBRT. The pooled data were individual data obtained from 3 RCTs.[28, 50, 59] Primary outcomes included survival and local and distant intracranial failure. In total, 364 of the pooled 389 patients met the inclusion criteria and were included in the meta-analysis. Fifty-one percent were treated with SRS alone and 49% were treated with SRS + WBRT. The results showed that patients ≤50 years of age had a significant survival benefit when SRS was used alone. The median survival for these younger patients was 13.6 months in the SRS only group as opposed to 8.2 months in the SRS and WBRT group (p=0.04). Furthermore, in patients 50 years of age or less, there was no significant difference between the 2 treatment groups with respect to distant brain failure. In older patients, the risk of observed distant failure was higher in the SRS alone cohort. Additionally, patients of any age with a single brain metastases had a lower chance of developing further brain metastases as compared to those patients with 2 to 4 brain metastases (hazard ratio=

0.63). In all patients, SRS and WBRT was associated with a lower hazard of local brain failure than SRS alone (hazard ratio 2.56). Median time to death in the SRS alone versus SRS + WBRT was 10 versus 8.2 months, respectively. The authors concluded that SRS alone is the recommended initial therapy of patients ≤50 years of age with 1 to 4 brain metastases.

Several Class III studies have addressed the use of SRS alone in patients with > 4 brain metastases and confirmed that overall survival is not different for patients with > 4 brain metastases compared with 1 or 2 to 4 metastases.[63, 64] In 1 study, patients with total tumor volumes > 7 cc or > 7 metastases had significantly poorer overall survival than patients with smaller volumes or number of metastases.[65] However, when comparing survival according to the RTOG-recursive partitioning analysis (RPA) classifications, patients undergoing SRS appeared to have an improved survival compared with the RTOG historical classification groups.[66] Another retrospective study found that overall survival was predicted more by the volume of brain metastases and distant metastases, rather than the number of metastases.[67] Chang et al[64] reached a similar conclusion, in that the overall survival was not significantly different in patients treated with SRS for 1 to 5, 6 to 10, 11 to 15, or >15 brain metastases, with a median survival of 10 months. The overall median progression-free survival was 9 months for thetotal group as opposed to 6 months in patients with >15 lesions (p=0.028). However, patients with more than 15 metastases had a shorter time to progression of new brain metastases.

In summary, compared with surgical resection or radiosurgery alone, WBRT improves intracranial progression-free survival but not overall survival in patients ≤4 brain metastases. This supports a Level 2 recommendation to not proceed to WBRT in WHO performance status 0-2 patients with ≤4 brain metastases because, compared with surgical resection or radiosurgery alone, the addition of WBRT improves intracranial progression-free survival but not overall survival. However, local therapy alone is associated with a higher incidence of both local and distant intracranial tumor recurrence, and prospective randomized studies in patients with >4 brain metastases have not been conducted. This supports the following Level 3 recommendation, “Compared with surgical resection or radiosurgery alone, the addition of WBRT is not recommended for patients with >4 brain metastases unless the metastases’ volume exceeds 7 cc,

or there are >15 metastases, or the size or location of the metastases are not amenable to surgical resection or radiosurgery."

Synthesis of Results

WBRT has been a treatment of brain metastases for many years, and RCTs, summarized in Table 2, have evaluated various dose fractionation regimens. These provide Class I evidence that altered dose/fractionation schedules of WBRT do not result in significant differences in median survival, local control or neurocognitive function when compared with "standard" WBRT dose / fractionation such as 30 Gy in 10 daily fractions. The choice of which dose/fractionation scheme to use is based on a combination of patient convenience and life expectancy. There is concern that WBRT delivered with a high dose per fraction, (ie, >4 Gy per fraction) leads to more frequent or severe neurocognitive impairment, although studies of altered fractionation did not incorporate very robust neurocognitive testing.

Relatively few studies, summarized in Table 3, have been done to evaluate the outcomes of WBRT according to the histopathology or molecular status of the primary cancer. One group of patients who may not benefit from immediate WBRT are NSCLC patients with mutant EGFR or ALK-rearranged cancers. Targeted therapy is an option as initial treatment for asymptomatic brain metastases not amenable to SRS, withholding WBRT until the time of intracranial progression. However, mutant EGFR or ALK-rearranged status is also a positive prognostic factor for WBRT response after WBRT. The question remains as to the optimal timing of WBRT, or whether EGFR or ALK status can be used to predict the benefit of WBRT as opposed to other treatment modalities. Outside of lung cancer, few studies have been done that are relevant to this question. Retrospective studies suggest that HER2-positive patients may have improved outcomes following WBRT compared with HER2-negative patients. The role of WBRT, as opposed to SRS, is also controversial in many histologies, but particularly for patients with melanoma. RCTs that are histology- or molecular status-specific are necessary to sort out many of these issues.

An important addition to this guideline is the question regarding the effect of WBRT on neurocognition. Tables 4, 5, and 6 summarize the neurocognitive effects seen with WBRT or

PCI. They also summarize the studies whose goal was to ameliorate these effects. Class I data demonstrate that the addition of WBRT to local therapy (SRS or surgery) is associated with an increased risk of significant neurocognitive decline in patients with ≤4 brain metastases. This decline is apparent as early as 3 months post-RT and can persist in long-term survivors. Class I evidence also exists to support the Level 3 recommendation to utilize memantine for its nonstatistical tendency of neurocognitive protective effects in patients with brain metastases undergoing WBRT. There is lower level evidence suggesting that HA-WBRT may reduce the risk of neurocognitive decline compared with conventional WBRT.

Table 7 summarizes the additional data used to evaluate the effectiveness of WBRT on non-cognitive endpoints, such as progression-free or overall survival. There are RCTs evaluating the use of surgical resection with or without WBRT in the treatment of patients with 1 brain metastasis. Other RCTs evaluated the use of SRS with or without WBRT for patients with 1 to 4 brain metastases. Withholding WBRT during initial treatment is associated with a higher incidence of both local and distant intracranial tumor recurrence but without a detriment to overall survival or performance status. This led to the Level 1 recommendation of surgical resection or SRS alone as the initial treatment for patients with ≤4 brain metastases. However, there are no Class I studies addressing the benefit of WBRT for patients with more than four brain metastases. Since WBRT improves progression-free survival, this supports a Level 3 recommendation of WBRT following surgical resection or radiosurgery alone.

CONCLUSION AND KEY ISSUES FOR FUTURE INVESTIGATIONS

The use of WBRT has declined over the past 10 years as the use of local and systemic therapies has evolved. A question asked constantly by clinicians is: when is it appropriate to use WBRT? Since the prior publication of this guideline, there have been few studies comparing various dose/fractionation schemes for WBRT. Unless future studies incorporate more sophisticated measures of neurocognitive outcome, there is little need to repeat these studies.

However, technological developments allow WBRT to be delivered with HA to potentially reduce the probability of neurocognitive deficits, which are the most concerning side effect of WBRT. Randomized studies are ongoing to see whether HA does lead to less cognitive

549 impairment without any reduction in intracranial control. Another technological development
550 has been the ability to do an SIB, delivering a higher dose to targeted lesions during a course of
551 WBRT. Prospective trials are ongoing to better support the efficacy of HA and SIB.
552
553 The question of when to recommend WBRT, or whether it is of any benefit at all to patients with
554 certain histopathologic or molecular subtypes remains controversial. Recent studies have
555 indicated that the prognosis of brain metastases is more dependent on histopathology or
556 molecular features of the primary cancer than had been appreciated. The role of WBRT as
557 opposed to SRS is also controversial in many histologies, but particularly for patients with
558 melanoma. Whether these histopathology/molecular marker subtypes are both prognostic and
559 predictive of outcomes of WBRT is less clear. Future prospective randomized trials of issues
560 related to WBRT are likely to be more "targeted" to specific populations, such as specific
561 primary cancers or even specific molecular targets. Examples of possible study groups would be
562 HER2-negative breast cancer, EGFR-mutated adenocarcinoma of the lung, or melanoma.
563 NSCLC cancer patients have been studied in a phase III RCT.[68] Patients with NSCLC and
564 newly diagnosed or progressive brain metastases not amenable to surgical resection or
565 radiosurgery were randomized to either WBRT or supportive care only. There was a broad range
566 of eligibility criteria, but the primary was uncontrolled in approximately two-thirds of patients
567 with extracranial metastases present in >50% of patients and a median Karnofsky Performance
568 Scale score of 60. No significant difference in median survival was found between patients
569 receiving WBRT or supportive care only. The median survival of just 8 to 9 weeks is lower than
570 most prospective studies in brain metastases and raises the question of how patients were
571 selected for the study. In subset analysis, WBRT appeared to provide a survival benefit to
572 patients who were either young, had a controlled primary cancer, or had a low RPA.
573 Nevertheless, this study supports a recommendation of supportive care only for elderly lung
574 cancer patients with a poor Karnofsky Performance Scale score, uncontrolled primary, or
575 progressive systemic disease. Future guidelines will hopefully be able to address this issue in
576 more depth.
577
578 There have also been pharmacologic developments to ameliorate the neurocognitive effects of
579 WBRT. The most promising drug is memantine, started early in the course of WBRT and

continued for ≥6 months. Memantine is well tolerated, and few patients will refuse to take it given the risks and benefits. It has been utilized in a North American study of WBRT with HA.[53] There is also concern for the potential neurocognitive detriment caused by PCI in patients without known brain metastases. There is an ongoing trial to determine if HA would be beneficial in this patient population (NRG-CC003). This trial randomizes patients with SCLC to PCI to 25 Gy in 10 fractions with or without hippocampal avoidance.

The decision regarding local therapies (SRS and surgery) as opposed to WBRT needs further prospective studies when there are >4 brain metastases. Studies have clearly shown that local therapy is sufficient and reasonable for patients with 1 to 4 brain metastases but the treatment of patients with more numerous metastases still needs to be addressed. Technically, large number of lesions can be treated with SRS, but is that necessarily the appropriate treatment? The main reason to use SRS is partly the convenience to the patient of a short treatment but seems primarily related to concerns of neurocognitive deficit following WBRT and many patients will currently refuse WBRT even when it is recommended. Studies of SRS have not yet documented the neurocognitive effects of SRS, particularly if there are >4 lesions. Further studies to evaluate the timing of WBRT relative to local therapies or systemic therapy would be beneficial to develop patient-specific treatment plans.

Potential Conflicts of Interest

The Brain Metastases Guideline Update Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of task force members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The conflict of interest findings are provided in detail in the companion introduction and methods manuscript.

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Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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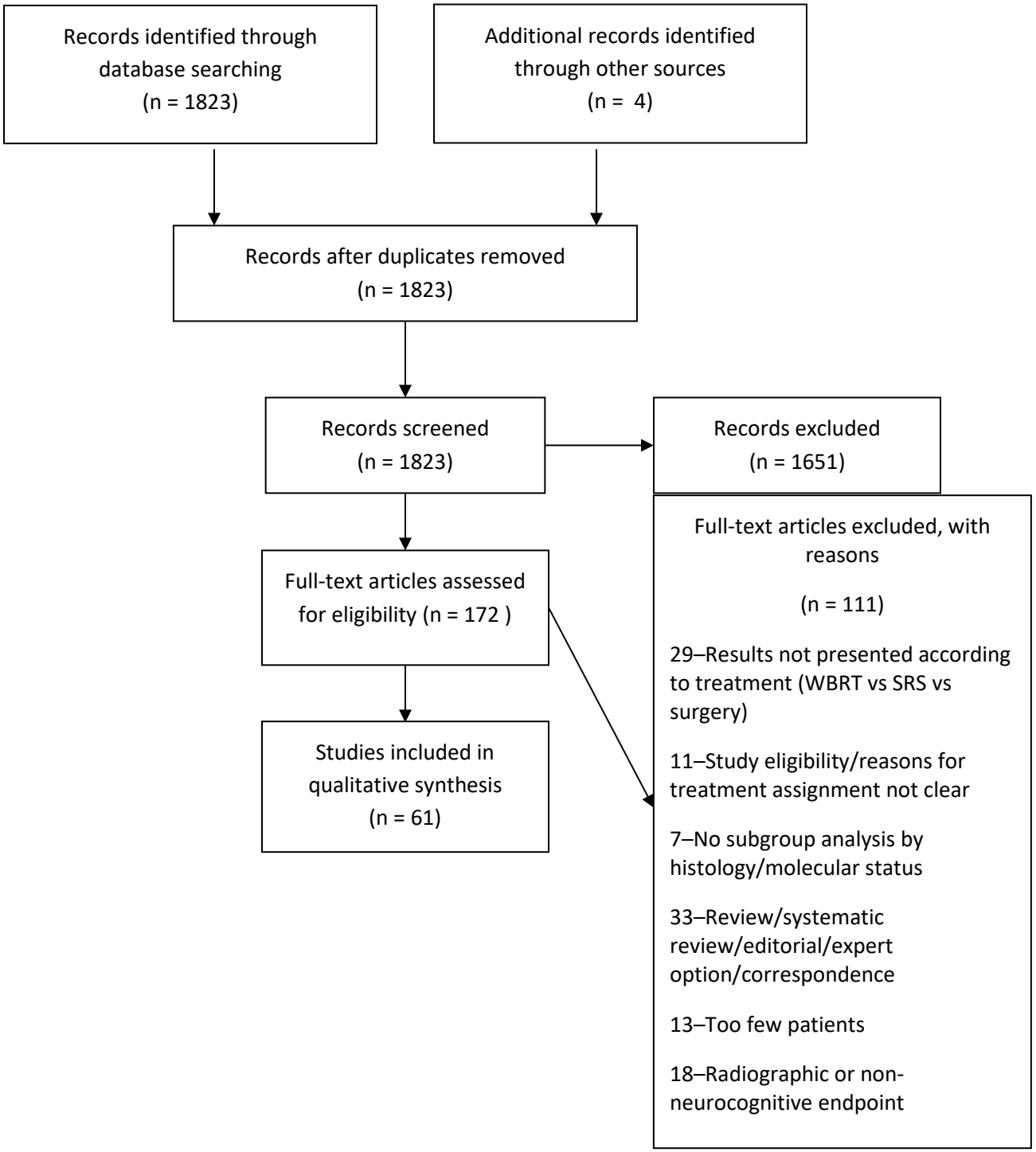
FIGURES

Figure 1 PRISMA Flow Diagram



TABLES

Table 1 Search Strategies

PUBMED (NLM), searched on February 3-4, 2016:
Step 1: Brain Neoplasms [Mesh]
Step 2: (brain OR brainstem OR intracranial) AND (cancer OR tumor* OR tumour* OR neoplasm*) [TIAB]
Step 3: #1 OR #2
Step 4: Neoplasm Metastasis [Mesh]
Step 5: (brain OR brainstem OR intracranial) AND (Metastas*) [TIAB]
Step 6: #4 OR #5
Step 7: #3 AND #6
Step 8: Brain neoplasms/secondary [Mesh]
Step 9: #7 OR #8
Step 10: Cranial irradiation [Mesh]
Step 11: WBRT [TIAB]
Step 12: "whole brain" [TIAB] AND (radiotherap* OR radiation OR radiation therap* OR irradiation) [TIAB]
Step 13: #10 OR #11 OR #12
Step 14: #9 AND #13
Step 15: #14 AND English [Lang]
Step 16: (animals [MeSH] NOT humans [MeSH]) OR case reports [PT] OR review [PT] OR comment [PT] OR letter [PT] OR editorial [PT] OR addresses [PT] OR news [PT] OR "newspaper article" [PT]
Step 17: #15 NOT #16
Step 18: #17 AND ("1990/10/01"[PDAT] : "2015/12/31"[PDAT])
Embase, searched on February 3-4, 2016:
Step 1: 'Brain tumor'/exp
Step 2: ((brain OR brainstem OR intracranial) NEAR/3 (cancer OR tumor* OR tumour* OR neoplasm*)):ab, ti
Step 3: #1 OR #2

Step 4: 'brain metastasis'/exp
Step 5: ((brain OR brainstem OR intracranial) NEXT/3 metastas*):ab,ti
Step 6: #4 OR #5
Step 7: #3 AND #6
Step 8: 'brain radiation'/exp
Step 9: WBRT:ab,ti
Step 10: ('whole brain' NEXT/3 (radiation OR radiotherapy* OR irradiation)):ab,ti
Step 11: #8 OR #9 OR #10
Step 12: #7 AND #11
Step 13: Limits: English, humans, 1990-2015, article OR conference paper NOT case report
COCHRANE, searched on February 3-4, 2016:
Step 1: MeSH descriptor: [Brain Neoplasms] explode all trees
Step 2: ((brain OR brainstem OR intracranial) NEAR/3 (cancer OR tumor* OR tumour* OR neoplasm*)):ti,ab,kw
Step 3: #1 OR #2
Step 4: MeSH descriptor: [Neoplasm Metastasis] explode all trees
Step 5: ((brain OR brainstem OR intracranial) NEAR/3 Metastas*):ti,ab,kw
Step 6: #4 OR #5
Step 7: #3 AND #6
Step 8: MeSH descriptor: [Brain neoplasms/secondary]
Step 9: #7 OR #8
Step 10: MeSH descriptor: [Cranial irradiation] explode all trees
Step 11: WBRT:ti,ab,kw
Step 12: ('whole brain' NEXT/3 (radiation OR radiotherapy* OR irradiation)):ti,ab,kw

Step 13: #10 OR #11 OR #12
Step 14: #9 AND #13
Step 15: Filtered 1990-2015

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643

644 **Table 2.** Outcomes of different dose/fractionation schedules of whole brain radiation therapy
645

Author (Year)	Description of Study	Data Class	Conclusions
Sayed[21] (2015)	*Study description* Prospective nonrandomized study at 1 center to compare 2 WBRT regimens for differences in response and overall survival. *Patient population* 93 patients with MRI scan with >3 brain metastases, good performance status. *Treatment regimen* G1: 20 Gy in 4 Gy fractions (n = 54) G2: 30 Gy in 3 Gy fractions (n = 39)	III	Results *Median survival* G1: 9 months G2: 10 months (p = 0.02) *MRI response at 3 months (partial response or stable)* G1: 85% G2: 87% (p = NS) *Author's conclusions* No significant difference in response or overall survival. Shorter fractionation beneficial to patients with RPA 2 (less time spent in treatment and little concern for late toxicity) and to radiation facilities (quicker throughput). *Comments and conclusions* No neurocognitive testing. Designated as Class III because it was a very small prospective study with "assignment" to 1 of 2 dose schedules. Statistical rationale for the accrual goal not given.

Saha et al[20] (2014)	*Study description* RCT in multiple centers comparing outcome of 2 WBRT regimens. *Patient population* 56 patients with radiologic diagnosis of brain metastases on MRI, good performance status *Treatment regimen* G1: 20 Gy in 4 Gy fractions (n = 26) G2: 30 Gy in 3 Gy fractions (n = 30)	III	Results *Median survival* G1: 26 weeks G2: 29 weeks (p = 0.955) *MRI response at 3 months (complete or partial response or stable)* G1: 81% G2: 93% *Author's conclusions* No significant difference in response or overall survival. 20 Gy in 5 fractions recommended for patients with poor performance status, 30 Gy in 10 fractions for patients with good performance status. *Comments and conclusions* No neurocognitive testing. No significant difference in improvement in ADL between 2 arms, but ADL of both groups improved post-WBRT. Designated as Class III since the patient numbers are small and could account for the nonsignificant finding. Statistical rationale for the accrual goal not given.

Graham et al[19] (2010)	*Study description* RCT in cooperative group (ECOG) to compare intracranial control rate and QOL of 2 WBRT schemes. *Patient population* 113 patients with good performance status; stable, absent, or concurrent presentation of extracranial disease *Treatment regimen* G1: 40 Gy in 2 Gy fx BID (n = 57) G2: 20 Gy in 5 Gy fx (n = 56)	I	Results *Median survival* G1: 6.1 months G2: 6.6 months (p = NS) *Intracranial progression* G1: 44% G2: 64% (p = 0.03) *Author's conclusions* Intracranial disease control was improved and QOL maintained with 40 Gy in 20 twice-daily fractions. Authors recommend this dose/fractionation for patients with better prognosis. *Comments and conclusions* The dose/fractionation regimen was not a significant factor affecting overall survival on MVA. Significant factors for improved survival on MVA were resection, supratentorial location, absent extracranial metastases, younger age. QOL and cognitive function outcomes similar in both groups. Mean scores of QOL and cognitive function were stable to improved in most patients during the 6-9 months following treatment
Davey et al[5] (2008)	*Study description* RCT at 2 centers to compare overall survival following accelerated and conventional hypofractionated WBRT. *Patient population* 90 patients with radiologic features of brain metastases on CT or MRI. Good performance status, life expectancy >6 weeks. *Treatment regimen* G1: 20 Gy/5 daily fractions (n = 45) G2: 40 Gy/20 fractions/twice daily (n = 45)	I	Results *Median survival* G1: 19.1 weeks G2: 19.1 weeks (survival curves: log-rank; p = NS) *Median time to treatment for intracranial relapse* G1:14 weeks G2: 32 weeks (p = 0.03) *Author's conclusions* Although accelerated WBRT may improve intracranial control, this did not lead to improved overall survival. *Comments and conclusions* No QOL or neurocognitive testing. Favorable prognostic factors on MVA were low RPA class and colorectal pathology.

Murray et al[9] (1997)	*Study description* RCT by cooperative group (RTOG) comparing accelerated hyperfractionated WBRT with standard fractionation. *Patient population* 429 patients with brain metastases measurable by CT or MRI scans, Karnofsky scale score ≥70, neurologic function class of 1-2. *Treatment regimen* G1: 30 Gy/10 fractions/daily (n = 213) G2: 54.4 Gy/34 fractions/twice daily (n = 216)	I	Results *Median survival* G1: 4.5 months G2: 4.5 months (*p* = NS) *# pts with recurrence/progression* G1: 109/124 (88%) G2: 105/118 (89%) (*p* value not reported) *Median time to recurrence / progression* G1: 11 weeks G2: 10 weeks (*p* value not reported) *Author's conclusions* 54.4 Gy in 34 fractions not recommended. *Comments and conclusions* No neurocognitive testing. 54.4 Gy delivered as 32 Gy in 20 fractions/twice daily followed by 24.4 Gy boost (visible lesion with 2-cm margin) in 14 fractions/twice daily. Age, performance status, extent of metastatic disease, and status of primary were prognostic factors.
Priestman et al[10] (1996)	*Study description* RCT at 25 institutions comparing 2 WBRT regimens *Patient population* 544 patients with symptomatic brain metastases by CT scan or unequivocal radioisotope scan, or an intracranial biopsy. Required stable dose dexamethasone over week prior to randomization, WHO performance status of 0-3, neurologic status <4 by modified MRC scale *Treatment regimen* G1: 12 Gy/2 fractions (n = 274) G2: 30 Gy/10 fractions (n = 270)	I	Results *Median survival* G1: 77 days G2: 84 days (*p* = 0.04 for entire survival curve, no difference in median survival) *Author's conclusions* For majority of patients, no advantage to longer courses of radiation therapy. *Comments and conclusions* No neurocognitive testing. Small improvement in survival with longer course but not thought by authors to be clinically meaningful. Might recommend longer course in small number of patients with good prognosis (female gender, age <60 years, breast primary, solitary brain metastasis, dexamethasone ≤8 mg/day, WHO performance status <3).

Chatani et al[3] (1994)	*Study description* RCT evaluating 2 different WBRT regimens in patients with normal (<250 U/L) vs high LDH *Patient population* 162 patients with lung cancer (stratified for small vs nonsmall) with CT brain scan. *Treatment regimen* Normal LDH: G1: 30 Gy/10 fractions (n = 46) G2: 50 Gy/20 fractions with field reduction after 30 Gy if possible (n = 46) High LDH: G3: 30 Gy/10 fractions (n = 35) G4: 20 Gy/5 fractions (n = 35)	II	Results *Median survival* G1: 5.4 months G2: 4.8 months (*p* = NS) G3: 3.4 months G4: 2.4 months (*p* = NS) *Author's conclusions* LDH is important prognostic factor. 30 Gy/10 fractions recommended. *Comments and conclusions* No neurocognitive testing. RCT but designated as class II and the patient numbers were small, with no clear inclusion criteria beyond "lung cancer."

Sause et al[11] (1993)	*Study description* Cooperative group (RTOG) phase I/II trial of accelerated fractionation *Patient population* Patients eligible had controlled or absent primary with metastases than brain stable, or only brain metastases with primary uncontrolled. *Treatment regimen* G1: 32 Gy in 1.6 Gy fractions + boost to 48.0 Gy] (n = 62) G2: 32 Gy in 1.6 Gy fractions + boost to 54.4 Gy] (n = 115) G3: 32 Gy in 1.6 Gy fractions + boost to 64.0 Gy] (n = 104) G4: 32 Gy in 1.6 Gy fractions + boost to 70.4 Gy] (n = 53) Fractions administered twice daily	II	Results *Median survival* G1: 4.2 months G2: 5.2 months G3: 4.8 months G4: 6.4 months (p = NS) *Author's conclusions* Nonsignificant improvement in survival in higher dose arms was taken as an encouraging result. *Comments and conclusions* No neurocognitive testing. Used as basis for subsequent RTOG study.[9] Designated as class II since it was a phase I/II randomized phase II study within cooperative group (RTOG)
Haie-Meder et al[6] (1993)	*Study description* RCT at 3 institutions comparing 2WBRT treatment regimens *Patient population* 216 patients with lung, breast, head and neck, or unknown primaries. Diagnosed by CT scan. Age <71 years. Ineligible if Karnofisky scale score <20 or life expectancy <1 month *Treatment regimen* G1: 18 Gy/3 fractions (n = 110) G2: 18 Gy/3 fractions; 4 weeks later a second identical course or 25 Gy/10 fractions (n = 106)	I	Results *Median survival* G1: 4.2 months G2: 5.3 months (p = NS) *Author's conclusions* No difference in overall survival or neurologic response or incidence in complications. A radiation schedule as short as 18 Gy in 3 fractions as good as longer radiation schedules. No neurologic complications occurred among 45 patients living >12 months *Comments and conclusions* Investigators could decide on whether G2 received 18 or 25 Gy in the second course- shortest regimen recommended if poor general or neurologic status. Methods of assessing neurocognitive function in follow-up were not clearly described. Two clinical factors predictive of poor survival were presence of multiple brain metastases and/or extracranial metastases.

Komarnicky et al[7] (1991)	*Study description* RCT by cooperative group (RTOG) evaluating role of misonidazole combined with WBRT *Patient population* 859 patients with measurable disease on CT, 18-75 years of age, Karnofsky scale score ≥40, able to work *Treatment regimen* G1: 30 Gy/10 fractions (n = 193) G2: 30 Gy/6 fractions (n = 200) G3: 30 Gy/6 fractions + MISO (n = 196) G4: 30 Gy/10 fractions + MISO (n = 190)	I	Results *Median survival* G1: 4.5 months G2: 4.1 months G3: 3.1 months G4: 3.9 months (p = NS) *# of pts retreated for BM after protocol therapy* G1: 54/179 (30%) G2: 54/180 (30%) G3: 33/173 (19%) G4: 54/163 (33%) (p = NS) *Author's conclusions* Recommended treatment was 30 Gy in 10 fractions, without misonidazole *Comments and conclusions* No neurocognitive testing. Approximately one-third of patients died of uncontrolled metastases, suggesting the need for more effective therapy.
Chatani et al[4] (1985)	*Study description* RCT at a single institution *Patient population* 69 consecutive patients with metastases from lung cancer *Treatment regimen* G1: 30 Gy/10 fractions (n = 35) G2: 50 Gy in 20 fractions (n = 34)	II	Results *Median survival* G1: 4 months G2: 3 months (p = NS) *Survival at 6 months* G1: 42% G2: 14% ($p < 0.05$) *Author's conclusions* Performance status and LDH were the factors influencing 6-month survival *Comments and conclusions* No neurocognitive testing. Designated as Class II due to small numbers and was limited to lung cancer.

Kurtz et al[8] (1981)	*Study description* RCT by cooperative group (RTOG) *Patient population* 309 patients (255 evaluable) from 31 participating institutions. Ineligible if evidence of other sites of metastatic disease or progressive untreated primary, or poor neurologic function *Treatment regimen* G1: 30 Gy/10 fractions (n = 130) G2: 50 Gy/20 fractions (n = 125)	I	Results *Median survival* G1: 18.2 weeks G2: 16.9 weeks (*p* = NS) *# pts with recurrence/progression in patients with information available* G1: 109/124 (88%) G2: 105/118 (89%) (*p* value not reported) *Author's conclusions* 30 Gy in 10 fractions as effective as 50 Gy. *Comments and conclusions* Excluded patients with evidence of extracranial metastases, uncontrolled primaries, or poor neurologic function. 21% of patients in 50 Gy arm unable to complete therapy. No neurocognitive testing. Authors recommended 20-30 Gy in 5-10 fractions

Borgelt et al[2] (1981)	*Study description* Two large (>900 patients in each study) national RCTs by cooperative group study (RTOG) with optional randomization to very short regimens at small number of institutions. This study is analysis of patients randomized at 4-6 centers that had very short regimens open. *Patient population* Ineligible if lesions too numerous or symptoms too vague to allow for adequate follow-up or assessment. First RCT: 155 patients randomized at 6 institutions Second RCT: 78 patients randomized at 4 institutions *Treatment regimen* First RCT: 30 Gy/10 fractions/2 wks (n = 233) 30 Gy/15 fractions/3 wks (n = 217) 40 Gy/15 fractions/3 wks (n = 233) 40 Gy/20 fractions/4 wks (n = 227) 10 Gy/single fraction: option in 6 institutions (n = 26) Second RCT: 20 Gy/5 fractions/1 wk (n = 31) 12 Gy in 2 fractions (n = 33) *Analysis by group* First RCT: G1: 10 Gy/1 fraction G2: 30-40 Gy over 2-4 weeks Second RCT: G3: 12 Gy/2 fractions G4: 20 Gy over 1 week	I	Results *Median survival* First RCT: G1: 15 weeks G2: 21 weeks (survival curves: log-rank; p = NS) Second RCT: G3: 13 weeks G4: 12 weeks (survival curves: log-rank; p = NS) *Median time to progression (measured by deterioration in neurologic function*): First RCT: Initial NF 1: G1: 9 wks; G2: 14 wks Initial NF 2: G1: 9 wks; G2: 10 wks Initial NF 3: G1: 7 wks; G2: 12 wks (Cox's model; p = 0.07) Second RCT: Initial NF 1: G3: 9 wks; G4: 10 wks Initial NF 2: G3: 11 wks; G4: 8 wks Initial NF 3: G3: 3 wks; G4: 3 wks (Cox's model; p = NS) *Authors' conclusions* Response of patients receiving the ultra-rapid treatment (10-12 Gy in 1-2 fractions) as assessed by the percent who had improvement in neurologic function, was comparable to that of patients receiving the more protracted schedules. Promptness of neurologic function improvement, treatment morbidity, and median survival were also comparable to those of patients receiving the more protracted courses. However, the duration of improvement, time to progression of neurologic status and rate of complete disappearance of neurologic symptoms were generally less for patients treated with ultrarapid treatment. Ultrarapid treatment may not be as effective as higher dose schedules in the palliation of brain metastases. *Comments and conclusions* No neurocognitive testing. Large cooperative group RCT but relatively small numbers of patients in the

			second RCT testing ultrarapid treatment.

Borgelt et al[33] (1980)	*Study description* 2 RCT by cooperative group (RTOG) to study effectiveness of different WBRT dose fractionation schemes on palliation. *Patient population* First RCT 993 (910 evaluable) and second RCT 1001(902 evaluable) patients with brain metastases established by clinical symptoms, EEG, radioisotope brain scan, arteriogram, pneumoencephalogram, or biopsy. Patients excluded if lesions too numerous or symptoms too vague to allow for adequate follow-up or assessment. *Treatment regimen* First RCT: G1: 30 Gy/10 fractions/2 wks (n = 233) G2: 30 Gy/15 fractions/3 wks (n = 217) G3: 40 Gy/15 fractions/3 wks (n = 233) G4: 40 Gy/20 fractions/4 wks (n = 227) Second RCT: G1: 20 Gy/5 fractions/ 1 wk (n = 447) G2: 30 Gy/10 fractions/ 2 wks (n = 228) G3: 40 Gy/15 fractions/ 3 wks (n = 227)	I	Results *Median survival* First RCT: 18 weeks. No significant difference between G1-4 (range 16-20 wks) Second RCT: 15 weeks. No significant difference between G1-3 (range 14-15 wks) *Brain metastases as cause of death* First RCT: 49%. No significant difference between G1-4 (range 46-54%) Second RCT: 31% No significant difference between G1-3 (range 25-33%) *Palliation of neurologic symptoms* Relief in 60-90% of patients with no significant difference between studies *Improvement in neurologic function at 2 weeks* First RCT: G1: 55% G2-4: 43% ($p = 0.06$) Second RCT: G1: 64% G2-3: 54% ($p = 0.01$) *Author's conclusions* All treatment schedules were comparable with respect to frequency of improvement, duration of improvement, time to progression, survival, and palliation. Important prognosticators of response included initial neurologic function and general performance status. Administration of steroids during irradiation favored more rapid improvement *Comments and conclusions* The administration of steroids was not controlled in either study. Results by treatment regimens not presented separately. Primary site (lung vs breast vs other) had no influence on palliative benefit of WBRT. Palliation reported sooner in shorter WBRT regimens but reporting bias suspected. Relatively small numbers of patients in the second RCT testing ultrarapid treatment. No neurocognitive testing.

ADL, activities of daily living; BID, twice daily; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; LDH, lactate dehydrogenase; MRC, Medical Research Council; MRI, magnetic resonance imaging; MVA, multivariate analysis; QOL, quality of life; RCT, randomized controlled trial; RPA, recursive partitioning analysis; WBRT, whole brain radiation therapy; WHO, World Health Organization.

653 **Table 3.** Effect of histology of primary cancer on outcomes of whole brain radiation therapy

Author (Year)	Description of Study	Data Class	Conclusions
Lee et al[30] (2012)	*Study description* Single institution, retrospective review of impact of EGFR mutation in patients with NSCLC brain metastases treated with WBRT in terms of RPFS and OS *Patient population* 43 patients with NSCLC (40 adenocarcinoma, 1 adenosquamous carcinoma, 2 poorly differentiated carcinoma) EGFR-positive: 30 patients with EGFR mutation (15 with exon 19 deletions, 15 with exon 21 L858R point mutation); EGFR-negative: 13 patients with EGFR wild-type *Treatment regimen* 43 patients underwent WBRT (30-40 Gy in 10-20 fractions, 40% of patients had additional local boost up to 50-60 Gy). EGFR tyrosine kinase inhibitor (TKI) given to 50% of EGFR-positive and 69% of EGFR-negative patients.	III	Results Median follow-up 15 months *Radiographic response to RT* Overall 70% radiographic response rate to RT EGFR-positive: 80% EGFR-negative: 46 ($p = 0.037$) *Multivariate analysis of radiographic response* EGFR mutation was only predictor for treatment response (odds ratio: 4.67, 95% CI; $p = 0.032$) *Median intracranial RPFS* Overall 18 months (95% CI: 8.33-27.68) EGFR-positive: 21 months EGFR-negative: 12 months ($p = 0.009$) *Multivariate analysis for RPFS* EGFR mutation ($p = 0.025$) and RPA class ($p = 0.026$) were 2 predictors for longer RPFS *Overall survival* Median OS 15 months (95% CI: 9.61-20.39 months) Univariate analysis showed that EGFR mutations ($p = 0.061$) and performance status ($p = 0.076$) had a trend to predict OS. *Author's conclusion* Mutant EGFR in NSCLC brain metastasis patients is an independent prognostic factor for better treatment response and longer intracranial RPFS following WBRT *Comments and conclusions* This is a retrospective case series (class III) of patients with brain metastasis from NSCLC treated with WBRT, which found mutant EGFR as a positive prognostic factor for treatment response after WBRT. EGFR TKI given to more than half of these patients and difficult to know how this impacted results. EGFR TKI should not be given to patients known to be EGFR wild-type, since it has been shown in other settings to be associated with poor outcome.

Gow et al[31] (2008)	*Study description* Single institution, retrospective case series of patients with brain metastases from lung adenocarcinoma treated with WBRT, evaluating the role of EGFR mutation status in response to WBRT and survival *Patient population* 63 patients patient with brain metastases from lung adenocarcinoma treated with WBRT EGFR-positive: Positive EGFR mutations (n = 46) EGFR-negative: Wild-type EGFR (n = 17) *Treatment regimen* 63 patients with NSCLC brain metastases received WBRT (30-35 Gy in 15 to 18 fractions); 18 patients received gefitinib treatment (either before or during WBRT treatment). *Pertinent methods of study technique* Univariate and logistic regression models were used to test predictive factors associated with clinical response; log-rank test and cox regression were used to identify factors affecting survival	III	Results *Clinical response to WBRT* Overall response rate 46% EGFR-positive: 54% EGFR-negative: 24% ($p = 0.045$) Both EGFR expression and EGFR tyrosine kinase inhibitor administration were independently associated with response to WBRT ($p = 0.034$ and $p = 0.029$, respectively) *Survival with WBRT* Median survival was 14.7 months (95% CI, 7.5-21.9 months) Better OS in responders vs nonresponders to WBRT (20.7 vs 6.6 months, $p = 0.017$). On univariate analysis, RPA class ($p = 0.025$), KPS ($p = 0.013$), and absence of extracranial metastases ($p = 0.005$) were significant prognosticators for overall survival. EGFR mutation ($p = 0.131$) and administration of EGFR TKI during WBRT ($p = 0.121$) showed a trend but no significant correlation with survival. *Author's conclusion* EGFR mutation and EGFR TKI administration during WBRT are independent predictors of response to WBRT in brain metastases from lung adenocarcinoma. *Comments and conclusion* This retrospective case series (class III) found mutant EGFR expression and TKI administration were predictive of improved response to WBRT, with a trend to improved overall survival but not statistically significant. All patients received WBRT but a small number also received systemic therapy with gefitinib, representing a heterogeneous treatment population.

Wolstenholm et al[32] (2008)	*Study description* Single institution, retrospective case series examining the influence of HER2 status on outcome of patients with brain metastases from breast cancer who received WBRT *Patient population* 181 patients with breast cancer metastasis and known HER2 status receiving WBRT HER2+ (n=88) HER2- (n=93) *Treatment regimen* WBRT regimens included 20 Gy in 5 fractions or 30 Gy in 10 fractions (5 and 2 patients in the HERR2+ and HER2- groups respectively received surgery as primary treatment followed by WBRT, and 11 and 1 patients in the HER2+ and HER2- groups respectively received stereotactic radio surgery (18-22 Gy at the 90-100%) in addition to WBRT. Heterogeneous chemotherapy regimens; trastuzumab treatment in 53 HER2+ patients. *Pertinent methods of study technique* Univariate and multivariate Cox regression analysis of prognostic factors; Kaplan-Meier survival analysis with log-rank test	III	Results *Median survival after WBRT* HER2-: 8 months HER2+: 4 months p=0.008 *Prognostic factors* 8 patients (4% of entire study population) had solitary brain metastases, with significantly improved survival compared to multiple brain metastases (p=0.005); 6 of these patients were HER2+ On univariate analysis performance status was significant predictor of longer survival (p=0.01) On multivariate analysis HER2 status was an independent prognostic factor (p=.02) *Author's conclusion* Improved median survival in patients with HER2+ status following WBRT, which could be attributed to a more aggressive approach to their management with combined cytotoxic chemotherapy and ongoing trastuzumab. *Comments and conclusions* This is a retrospective study (Class III) with no comparison group, with a heterogeneous mix of treatments in addition to WBRT and varied chemotherapy regimens, including use of trastuzumab in a portion of the HER2+ patients.

Sundstrom et al[29] (1998)	*Study description* Single institution, retrospective review of patients treated with WBRT for brain metastases diagnosed by CT or MRI with minimum midline dose to the whole brain of at least 25 Gy. *Patient population* Breast cancer (n=19) Lung cancer (n=35) Renal cell (n=9) Melanoma (n=6) Other (n=6) Extra-cranial metastases Breast: 17/19 Lung: 6/35 Renal cell: 5/9 Melanoma: 4/6 Other: 5/6 *Treatment regimens* WBRT mean dose 30 Gy (range 25–40 Gy) in 1.8– 3 Gy fractions	III	Results *Median survival by primary tumor type* Breast cancer: 7 months (range 1–62 months) Lung cancer: 4 months (range 1–21 months) Renal cell: 4 months (range 2–34 months) Melanoma: 3 months (range 1–6 months) Other: 4 months (range 1–9 months) Survival curves: P-value not reported *Median time to recurrence of brain metastases* Not reported *Tumor control, functional performance, cause of death, adverse events* Not reported by histology *Author's conclusions* Approximately two-thirds of the patients experienced a relief in symptoms allowing a reduction in the dose of corticosteroid medication, which clearly supports the use of whole-brain radiotherapy as a palliative treatment. *Comments and conclusions* Designated Class III since numbers too small to allow meaningful statistical comparison between histologies.

Borgelt et al[33] (1980) and Borgelt et al[2] (1981)	*Study description* 2 RCT by cooperative group (RTOG) to study effectiveness of different WBRT dose fractionation schemes on palliation. *Patient population* First RCT 993 (910 evaluable) and second RCT 1001 (902 evaluable) patients with brain metastases established by clinical symptoms, EEG, radioisotope brain scan, arteriogram, pneumoencephalogram, or biopsy. Stratified by site of primary lesion: lung vs breast vs other, and presence or absence of metastases to sites other than brain; pPatients excluded if lesions too numerous or symptoms too vague to allow for adequate follow-up or assessment. *Treatment regimen* First RCT: G1: 30 Gy/10 fractions/2 wks (n = 233) G2: 30 Gy/15 fractions/3 wks (n = 217) G3: 40 Gy/15 fractions/3 wks (n = 233) G4: 40 Gy/20 fractions/4 wks (n = 227) Second RCT: G1: 20 Gy/5 fractions/ 1 wk (n = 447) G2: 30 Gy/10 fractions/ 2 wks (n = 228) G3: 40 Gy/15 fractions/ 3 wks (n = 227)	II	Results *Median survival* First RCT: 18 weeks. No significant difference between G1-4 (range 16-20 wks) Second RCT: 15 weeks. No significant difference between G1-3 (range 14-15 wks) *Brain metastases as cause of death* First RCT: 49%. No significant difference between G1-4 (range 46-54%) Second RCT: 31% No significant difference between G1-3 (range 25-33%) *Primary site* 60% of patients had lung primaries. Lung cancer patients more likely to have brain as only site of metastases; primary site had no influence on response to WBRT. Time to progression longer for breast cancer patients. Median survival for breast cancer patients longer than for lung cancer patients (21 weeks vs 16 wks, $p < 0.001$). This survival difference between breast and lung cancer not seen in nonambulatory patients. *Author's conclusions* All treatment schedules were comparable with respect to frequency of improvement, duration of improvement, time to progression, survival, and palliation. Important prognosticators of response included initial neurologic function and general performance status. Administration of steroids during irradiation favored more rapid improvement *Comments and conclusions* Primary site (lung vs breast vs other) had no influence on palliative benefit of WBRT. The administration of steroids was not controlled in either study. Palliation reported sooner in shorter WBRT regimens but reporting bias suspected. Relatively small numbers of patients in the second RCT testing ultrarapid treatment. Designated class II since results by treatment regimens not presented separately by histology.

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655 EGFR, epidermal growth factor receptor; Gy, Gray; KPS, Karnofsky Performance Scale;
656 NSCLC, non–small cell lung cancer; OS, overall survival; RCT, randomized controlled trial;
657 RPFS, radiologic progression-free survival; TKI, tyrosine kinase inhibitor; WBRT, whole brain
658 radiation therapy.

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660 **Table 4.** Neurocognitive outcomes of prophylactic cranial irradiation versus no prophylactic cranial irradiation for patients without
661 brain metastases
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Author and Year	Description of Study	Data Class	Conclusions
Wolfson et al[43] (2011)	*Study description* Secondary endpoint of multi-institutional phase II RCT SCLC histology (N = 264) Testing different PCI RT schedules for patients with SCLC in complete remission after induction therapy. *Treatment regimens* G1: 25 Gy in 10 fractions (n = 131) G2: 36 Gy in 18 fractions (n = 67) G3: 36 Gy in 24 fractions, 1.5 Gy BID (n = 66) Randomization to 25 Gy vs 36 Gy, then secondary randomization to G2 vs G3. ND defined as a significant decrease at 12 months in at least one neurocognitive test (HVLT, COWAT, or TMT-A and -B) from baseline regardless of brain metastases	II	Results Statistically significant differences for COWAT (p = 0.03) and TMT-A (adjusted p = 0.03) testing at baseline among the 3 groups. *Proportion with ND (regardless of brain metastases) at 12-months:* G1: 62% G2: 85% G3: 89% Significant difference in ND between G1 and G2/3 (p = 0.03) *Proportion with ND without brain metastases at 12-months:* G1: 60% G2: 85% G3: 89% Significant difference in ND between G1 and G2/3 (p = 0.02) Logistic regression model for ND without brain metastases at 12 months showed significantly higher risk with 36 Gy (p = 0.03) and older age (p = 0.005) *Author's conclusion* Due to increased risk of ND with 36 Gy PCI, 25 Gy PCI remains standard of care for this patient population *Comments and conclusions* Formal neurologic testing within prospective trial indicating that ND increased with increasing WBRT dose, and there was no beneficial neurocognitive effect to BID fractionation. Designated as Class II since neurologic decline was a secondary endpoint

Le Péchoux et al[44] (2011)	*Study description* Secondary endpoint of international multi-institutional phase III RCT for SCLC histology. Testing different PCI RT schedules for patients with limited SCLC in complete remission after induction therapy *Treatment regimens* G1: 25 Gy in 10 fractions (n = 360) G2: 36 Gy in 18 daily fractions or 24 fractions of 1.5 Gy BID (n = 360)	II	Results *Proportion of patients with abnormal QoL-cognitive functioning (scale <75) at baseline* (N = 667 with baseline data available) G1: 23% G2: 25% *Proportion of patients with abnormal QoL-cognitive functioning (scale <75) at 24-months* (n = 140) G1: 41% G2: 46% *Proportion of patients with abnormal LENT-SOMA intellectual functioning at 24-months* (n = 144) G1: 20% G2: 28% G1 and G2 showed a similar, mild deterioration across time in communication deficit, weakness of legs, intellectual deficit and memory. This deterioration over time was statistically significant ($p < 0.005$). *Author's conclusion*: Patients should be informed of the potential neurologic and neurocognitive deficits, as well as the benefit of PCI on survival and the incidence of brain metastases. 25 Gy remains the standard of care for PCI for limited SCLC. *Comments and conclusions* Large RCT in cooperative group using validated QOL tools. Designated as class II since neurologic decline was a secondary endpoint.

Sun et al[45] (2011)	*Study description* Secondary endpoint of US multi-institutional phase III RCT in NSCLC histology PCI vs no PCI for patients with stage IIIA/B NSCLC without disease progression after definitive therapy. *Treatment regimens* No PCI (n= 163) PCI 30 Gy in 15 fractions (n = 177) Accrual was 340 eligible patients out of planned 1058 (trial closed early due to poor accrual)	III	Results Baseline neurocognitive results not reported. Baseline used for per patient measurement of decline Proportion with significant deterioration in HVLT-IR at 1 year (n = 90) Control: 7% PCI: 26% (adjusted $p = 0.03$) Proportion with significant deterioration in HVLT-DR at 1 year (n = 90) Control: 5% PCI: 32% (adjusted $p = 0.008$) Proportion with deterioration in MMSE score as defined by reliable change index (n = 95) Control: 18% PCI: 23% (p = NS) *Authors conclusion* No significant differences in global cognitive function (MMSE) or QOL after PCI, but there was a significant decline in memory (HVLT) at 1 year. *Comments and conclusions* This was designated as class III given that it closed with only approximately one third of planned accrual, perhaps accounting for the lack of significant differences

Slotman et al[46] (2009)	*Study description* Secondary endpoint of European multi-institutional phase III RCT SCLC histology, extensive stage with response to induction therapy *Treatment regimen* PCI (n = 143) No PCI (n = 143) Most common PCI dose fractionation regimens: 20 Gy in 5 fractions (62%) 30 Gy in 10 fractions (16%) 30 Gy in 12 fractions (6%) 25 Gy in 10 fractions (5%) HRQOL measured with EORTC Quality of Life Questionnaire C30 (EORTC-QLQ-C30) and EORTC QLQ Brain Cancer Module (EORTC-QLQ-BN20) 268 of 286 with baseline scores available	II	Results *Proportion with worsened global health status (≥ 20-point decline) at 3 months* (n = 188) PCI: 34.7% No PCI: 22.2% (*p* = NS) *Proportion with worsened cognitive functioning (≥ 20-point decline) at 3 months* (n = 188) PCI: 22.4% No PCI: 10% (*p* = NS) Mean difference in cognitive functioning score at 3 months between arms (No PCI – PCI) of 8.8 points (below significance definition of ≥10 points) *Authors conclusions:* PCI should be offered to all responding ED SCLC patients. Patients should be informed of the potential adverse effects from PCI. *Comments and conclusions* The largest mean difference between the 2 arms was observed for fatigue and hair loss. The impact of PCI on global health status as well as on neurocognitive functioning scores was more limited. Designated as Class II since change in cognitive function was a secondary endpoint.

Gregor et al[47] (1997)	*Study description* Secondary endpoint of UKCCCR and EORTC multi-institutional phase III RCT of SCLC histology. Included patients without brain metastases with complete remission after induction therapy *Treatment regimen* PCI (n = 120) No PCI (n = 194) Most common PCI regimens were 30 Gy in 10 fractions, 24 Gy in 12 fractions, and 36 Gy in 18 fractions. Initially 1:1 randomization to PCI:No PCI, then revised to 3:2 (PCI:No PCI) Neurocognitive portion of trial was optional. 125 of 314 patients (40%) with baseline neurocognitive testing available. 59 of 314 patients (19%) with 6-month testing results available	III	Results No significant difference on multiple neurocognitive tests between PCI and No PCI at 6-months and 1-year. Cognitive impairment on study entry was seen on study entry in up to 42% of patients *Authors conclusion:* In both groups, there was similar degree of impairment of cognitive function and QOL before PCI. No difference in neurocognitive detriment between PCI and control in this patient population without brain metastases *Comments and conclusions:* Used simple proportions to compare cognitive decline at each time point. Designated as class III since patient numbers were relatively small at all time points, and neurocognitive testing was only available on 40% of patients at baseline

Arriagada et al[48] (1995)	*Study description* Primary endpoint of multi-institutional French phase III RCT SCLC histology Included patients with SCLC, without brain metastases, with complete remission after induction therapy. *Treatment regimen* PCI No PCI PCI was 24 Gy in 8 fractions Neuropsychologic assessments performed by neurologists, N = 294	II	Results 41% of all patients did not have neurocognitive abnormalities at baseline *Number of patients free from any abnormalities at baseline*: PCI: 50 No PCI: 44 *2-year cumulative incidence of negative change in cognitive "higher functions"* 36% (control) vs 30% (PCI), *p* = NS PCI 30% No PCI 36%, *p* = NS *Authors conclusion* Prophylactic cranial irradiation given to patients with small cell lung cancer in complete remission decreases the risk of brain metastasis threefold without a significant increase in complications. No difference in neurocognitive detriment between PCI and control in this patient population without brain metastases *Comments and conclusions* Used cumulative incidence for cognitive dysfunction endpoint. Designated as class II since "higher functions" were not defined, in addition to the lack of definition of criteria used to define decline

BID, twice daily; COWAT, Controlled Oral Word Association Test; EORTC, European Organisation for Research and Treatment of Cancer; HRQOL, health-related quality of life; HVLT, Hopkins Verbal Learning Test; KPS, Karnofsky Performance Scale; MMSE, Mini-Mental State Examination; ND, neurocognitive decline; NS, not significant; PCI, prophylactic cranial irradiation; QOL, quality of life; RCT, randomized controlled trial; SCLC, small cell lung cancer; TMT, Trail Making Test.

669 **Table 5.** Neurocognitive outcomes of whole brain radiation therapy and local therapy versus local therapy only
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Author and Year	Description of Study	Data Class	Conclusions
Soffietti et al[51] (2013)	*Study description* Secondary endpoint of European multi-institutional phase III RCT *Patient population* Patients with 1-3 brain metastases *Treatment regimen* Local only: local therapy alone with SRS or surgery (n = 179) Local + WBRT (n = 180) Local therapy either SRS (n = 199) or surgery (n = 160) HRQOL measured with the EORTC Quality of Life Questionnaire C30 and the EORTC QLQ Brain Cancer Module N = 341 with baseline HRQOL data	II	Results *EORTC QLQ C30 cognitive functioning score mean difference at 12 months* Local vs local + WBRT mean difference = -10.8 points ($p < 0.05$) *Mean EORTC QLQ C30 cognitive functioning score at 12 months* Local: 80.4 Local + WBRT: 69.7 ($p = 0.05$) *Authors conclusions* Adjuvant WBRT after surgery or SRS of a limited number of brain metastases may negatively impact some aspects of HRQOL, including self-reported cognitive functioning. *Comments and conclusions* Overall, patients treated with surgery or SRS only reported better HRQOL scores than did patients who also received WBRT. Most scores, which differed significantly during the first time points, had a tendency to recover. The positive effect of WBRT in decreasing the rate of intracranial progression and modestly improving the progression-free survival did not translate into an advantage in terms of HRQOL. Designated as class II since cognitive functioning was a secondary endpoint.

Chang et al[50] (2009)	*Study description* Primary endpoint of single institutional phase III RCT *Patient population* Patients with 1-3 brain metastases *Treatment regimen* SRS alone (n = 30) SRS + WBRT (n = 28) WBRT dose: 30 Gy in 12 fractions Primary endpoint: significant deterioration of HTLV-R total recall at 4 months defined as ≥5 points drop from baseline. Bayesian analysis Trial enrollment stopped after 58 patients enrolled due to significant differences.	I	Results *HTLV-R significant deterioration rates at 4 months* *Total recall*: SRS: 24% SRS + WBRT: 52% *Delayed recall*: SRS: 6% SRS + WBRT: 22% Delayed recognition: SRS: 0% SRS + WBRT: 11% *Authors conclusions* Patients treated with SRS + WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone *Comments and conclusions* Significantly longer overall survival in patients treated with SRS alone as compared to SRS + WBRT. Given that this is a finding not found in other studies, thought to possibly be indicative of more favorable prognostic factors in SRS alone group

Aoyama et al[49] (2007)	*Study description* Secondary endpoint of Japanese multi-institutional phase III RCT Patients with 1-4 brain metastases *Treatment regimen* SRS alone (n = 67) SRS + WBRT (n = 65) WBRT dose: 30 Gy in 10 fractions Neurocognition measured with MMSE. 110 of 132 randomized patients (83%) had baseline MMSE scores available.	II	Results Average baseline MMSE did not differ significantly between treatment groups (p = 0.47). Median MMSE score at 12 months SRS alone: 28 SRS+WBRT: 27 *Actuarial rate of MMSE preservation (decline < 3 points) at 12 months* SRS alone: 59.3% SRS+WBRT: 76.1% (p = NS) *Actuarial rate of MMSE preservation (decline < 3 points) at 24 months* SRS alone: 51.9% SRS+WBRT: 68.5% (p = NS) *Average duration until MMSE deterioration* SRS alone: 7.6 months SRS+WBRT: 16.5 months (p = 0.05) *Authors conclusion* Intracranial control is the most important factor for stabilizing neurocognitive function. Addition of WBRT stabilized neurocognition in the intermediate term due to improved intracranial control, however WBRT may be associated with long-term adverse effects on neurocognition. *Comments and conclusions* Designated as class II since MMSE is a relatively insensitive measure of neurocognition and may miss more subtle changes.

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673 **Table 6.** Effect of pharmacologic agents or whole brain radiation therapy techniques on neurocognitive decline
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Author and Year	Description of Study	Data Class	Conclusions
Rapp et al[53] (2015)	*Study description* Primary endpoint of multi-institutional phase III RCT of donepezil versus placebo. *Patient eligibility* Patients with either primary or secondary brain tumors receiving partial brain (60%) or WBRT (40%) of at least 30 Gy ≥6 months before enrollment. 27% metastatic brain tumors 7% PCI 66% primary brain tumors *Treatment regimens* Donepezil: n = 99 Placebo: n = 99 Donepezil single daily 5-mg dose for 6 weeks, which was escalated to 10 mg per day for 18 weeks if well tolerated. Primary endpoint: overall cognitive performance after 24 weeks of therapy	II	Results *24 week results*: Patients in both groups showed improved cognitive function at 24 weeks, but there was no difference in overall cognitive composite score between arms ($p = 0.48$) No significant differences between groups except for memory recognition ($p = 0.027$), memory discrimination ($p = 0.007$), and motor speed and dexterity ($p = 0.016$) The benefits of donepezil greater for those who were more cognitively impaired at baseline. *Author's conclusions:* Treatment with donepezil did not significantly improve the overall composite score, but it did result in modest improvements in several cognitive functions, especially among patients with greater pretreatment impairments. *Comments and conclusions:* Assigned class II since only 40% of patients received WBRT. Donepezil only started 6 months after radiation therapy, providing a source of bias.

Brown et al[56] (2013)	*Study description* Primary endpoint of North American multi-institutional phase III RCT. Primary endpoint was decline in HVLT-R delayed recall at 24 weeks. *Patient eligibility* Patients with brain metastases (number not limited) *Treatment regimens* WBRT + memantine: n = 278 WBRT + placebo: n=276 WBRT 37.5 Gy in 15 fractions Memantine dosing, starting before or during WBRT: Week 1 5 mg qAM Week 2 5 mg BID Week 3 10mg qAM / 5 mg qPM Week 4-24 10 mg BID N = 473 with baseline scores available Only 149 (53%) of 280 alive patients at 24 weeks had neurocognitive assessments and were analyzable.	I	Results *Median decline in HVLT-R delayed recall at 24 weeks* WBRT + memantine: 0 WBRT + placebo: -0.9 (p = 0.059, NS) Probability of cognitive failure at 24 weeks: WBRT + Memantine: 53.8% WBRT + placebo: 64.9% (p = 0.01) *Authors' conclusions* Memantine well tolerated. Although memantine was associated with less decline in the primary endpoint of delayed recall at 24 weeks, this lacked statistical significance possibly due to significant patient loss. Overall, patients treated with memantine had better cognitive function over time; specifically, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBRT.

Gondi et al[54] (2014)	*Study description* Primary endpoint of multi-institutional North American phase II single arm trial of hippocampal avoidance (HA). Results compared with historical control of control arm of previous phase III RCT. Primary endpoint was decline in HVLT-R delayed recall (DR) at 4 months as compared with standard arm of PCI-P-120-9801 phase III trial using WBRT 30 Gy in 10 fractions without HA. Patient eligibility Patients with brain metastases outside a 5-mm margin around either hippocampus. Treatment regiment Patients treated with HA (n=113) during WBRT to 30 Gy in 10 fractions. Hippocampal D100 goal <9 Gy and max point dose goal <16 Gy 100 patients with baseline scores available. 42 patients with scores analyzable at 4 months.	II	Results: 42 patients analyzable for primary endpoint at 4 months (71% of alive patients) *Mean relative HVLT-R DR decline between baseline and 4 months* HA: 7% Historical controls: 30% (p = 0.0003) *Probability of HVLT-R total recall significant deterioration by 4 months* *HA:* 19% *Probability of HVLT-R DR significant deterioration by 4 months* HA: 33% *Intracranial progression within HA region* 5% of patients with intracranial progression 3% of patients overall *Authors conclusions* Conformal avoidance of the hippocampus during WBRT is associated with preservation of memory and QOL as compared with historical series. *Comments and Conclusions* Designated as Class II since it was a Phase II study.

Butler et al[55] (2007)	*Study description* Secondary endpoint of multi-institutional phase III RCT of d-threo-methylphenidate HCl (d-MPH) versus placebo. Primary endpoint was fatigue subscale of the FACIT-F. *Patient eligibility* Patients with either primary brain tumors (n = 33) or brain metastases (n = 35) receiving partial brain RT or WBRT ≥25 Gy *Treatment regimens* RT + d-MPH: n = 34 RT + placebo: n = 34 d-MPH or placebo started by day 5 of RT. Starting dose of d-MPH was 5 mg BID and was escalated by 5 mg BID to a maximum of 15 mg BID. Study drug continued for 8 weeks post-RT. QOL measured with FACT-Brain and FACIT-F and cognition measured with MMSE. Trial closed after accrual of 68 of planned 162 patients due to slow accrual and withdrawal of financial support.	II	Results *Fatigue:* No difference in fatigue assessment at any time point up to 8 weeks post-RT between arms. *Baseline MMSE score* RT + d-MPH: 27.2 RT + placebo: 26.5 (p = NS) *MMSE 8 weeks post-RT* RT + d-MPH: 23.3 RT + placebo: 25.6 (p = NS) *Authors conclusions* Prophylactic use of d-MPH in brain tumor patients undergoing RT did not result in an improvement in QOL. *Comments and conclusions* Designated as Class II due to low patient accrual and reduced statistical power. Only a small number of patients receiving WBRT.

677 **Table 7.** Intracranial progression-free survival and overall survival following local therapy (surgery or stereotactic radiosurgery) alone or local
678 therapy with whole brain radiation therapy
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Author (Year)	Description of Study	Data Class	Conclusions
Kocher et al[28] (2011)	*Study description* RCT comparing WBRT to observation after SRS or surgical resection on duration of functional independence (WHO performance status) *Patient population* 359 patients with 1-3 brain metastases with WHO performance status ≤2 who had previously undergone either surgical resection or SRS prior to randomized intervention *Treatment regimen* SRS + observation (n = 100) SRS + WBRT (n = 99) Surgery + observation (n = 79) Surgery + WBRT (n = 81) Local therapy + WBRT arm (180 total) Local therapy + Observation (179 total) WBRT 30 Gy in 10 fractions	II	Results *Survival with functional independence (time to WHO PS>2)* Observation: 10 months WBRT: 9.5 months (HR = 0.96, p = 0.71) At 2 years, 22.3% and 22.6% were alive and independent in the observation and WBRT arms, respectively. *Progression-free survival* Observation: 3.4 months WBRT: 4.6 months (p = 0.020) *Overall survival* Observation: 10.9 months WBRT: 10.7 months (HR = 0.98, p = 0.89) *Author's conclusions* After surgery or SRS, WBRT reduces the probability of intracranial relapses from 80% to 50%, and is most pronounced after surgery. This is translated into a modest PFS, but no improvement in OS. There was no difference in functional independence between the 2 groups. *Comments and conclusions* In well-performing patients with otherwise stable systemic disease and 1-3metastases, who are initially treated with either radiosurgery or surgery, WBRT can be withheld if serial imaging for follow-up is performed. Regarding the patients undergoing resection of a single lesion, because adjuvant irradiation substantially reduces the risk of recurrence in the tumor bed, postoperative local irradiation should be an option that is investigated. Designated class II since the primary endpoint was functional independence, not PFS or OS.

Aoyama et al[59] (2006)	*Study description* RCT comparing patients with 1-4 brain metastases receiving either WBRT + SRS or SRS alone on overall survival, recurrence, function, and cause of death. Study closed early due to poor accrual. *Patient population* 132 patients with 1-4 brain metastases (each <3 cm in diameter). No surgical resection performed prior to treatment. *Treatment regimen* WBRT + SRS (n = 65) SRS alone (n = 67) WBRT 30 Gy in 10 fractions	III	Results *Survival (median and 1-year actuarial survival rate)* WBRT + SRS: 7.5 months and 38.5% SRS alone: 8.0 months and 28.4% ($p = 0.42$) *Intracranial recurrence rate at 12 months* WBRT + SRS: 46.8% SRS alone: 76.4% ($p < 0.001$) *Salvage intracranial treatment* WBRT + SRS: 10 patients SRS alone: 29 patients ($p < 0.001$) *Cause of death: Neurological causes* WBRT + SRS: 22.8% SRS alone: 19.3% ($p = 0.64$) *Author's conclusions* Compared to SRS alone, the use of WBRT + SRS did not improve survival for patients in this trial, but intracranial relapse occurred more frequently in those not receiving WBRT. *Comments and conclusions* Between both groups, there was no difference in OS, but higher rates of recurrence in the SRS only group lead to the more frequent need for salvage treatment. Assigned class III due to early closure of study due to poor accrual, resulting in lack of statistical power

Patchell et al[58] (1998)	*Study description* RCT comparing patients with single brain metastases who underwent surgical resection followed by postoperative WBRT vs observation on tumor recurrence and survival. *Patient population* 95 patients with single metastases to the brain treated with complete surgical resection *Treatment regimen* Surgery + WBRT (n = 49) surgery + observation (n = 46) WBRT 50.4 Gy in 28 fractions Primary end point: intracranial recurrence Secondary end points: Overall survival, cause of death, and preservation of ability to function independently	I	Results *Tumor recurrence* Surgery + WBRT: 18% surgery + observation: 70% ($p < 0.001$) WBRT prevented recurrence at the site of original metastases (10% vs. 46%, $p < 0.001$) as well as other sites (14% vs. 37%, $p < 0.01$) vs. observation, respectively. *Death from neurological causes* Surgery + WBRT: 14% surgery + observation: 44% ($p = 0.003$) *Overall survival* Surgery + WBRT: 48 weeks surgery + observation: 43 weeks ($p = 0.39$) *Author's conclusions* Postoperative WBRT after complete surgical resection of a single metastasis results in better control of disease in the brain and a reduction in the number of deaths due to neurological causes.Due to the decreased death due to neurologic causes, the authors recommended routine postoperative WBRT. *Comments and conclusions* Despite the reduction in brain recurrence rates and neurologic deaths, postoperative WBRT did not result in an increased survival or improvement in the length of time patients were able to function independently.

Gy, Gray; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; WHO, World Health Organization.

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