Chapter 9

Brain metastases: fractionated whole-brain radiotherapy

TONY J.C. WANG1,2 AND PAUL D. BROWN3*

1Department of Radiation Oncology, Columbia University Medical Center, New York, NY, United States
2Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, United States
3Department of Radiation Oncology, Mayo Clinic, Rochester, MN, United States

Abstract

Brain metastases are the most common malignant adult intracranial tumors, occurring in approximately 10–30% of cancer patients, and generally lead to a poor prognosis. The incidence has been steadily rising, likely due to longer survival from newer systemic therapies and increased utilization of magnetic resonance imaging. Historically, whole-brain radiotherapy has been a standard of care for the management of patients with brain metastases. However, better understanding of both the acute and long-term toxicities associated with whole-brain radiotherapy has led to a more selective use of whole-brain radiotherapy. Herein we discuss the background and prognostication of brain metastases as well as the role of palliative whole-brain radiotherapy, as monotherapy and adjuvant use after resection or stereotactic radiosurgery. We also review refined whole-brain radiation techniques, potential neuroprotective drugs, and ongoing trials.

INTRODUCTION

Brain metastases (BM) are common complications of systemic cancer, with an incidence of approximately 200,000 per year. Despite advances in systemic therapy, surgical and radiotherapy techniques, the prognosis remains poor, with median survival ranging from a few months to over 1 year (Walker et al., 1985; Andrews et al., 2004). Whole-brain radiotherapy (WBRT) has historically been a standard of care for patients with BM. However, better understanding of both the acute and long-term toxicities associated with WBRT has led to a more selective use of WBRT. Due to the heterogeneous nature of BM, including different primary cancers, performance status, number of brain lesions, and numerous treatment options available (e.g., stereotactic radiosurgery (SRS), surgical resection, and systemic therapies), the management of BM remains controversial. In this review, we provide an update on the prognostication, the role of WBRT as monotherapy and as adjuvant therapy, refined radiation techniques, neuroprotective drugs, and ongoing studies on WBRT for BM.

BACKGROUND AND PROGNOSTICATION

The recursive partitioning analysis, an early attempt to understand and prognosticate BM, stratified patients into three classes based on Karnofsky Performance Status (KPS), age, and control of primary disease (Gaspar et al., 1997). Patients with a KPS <70, or recursive partitioning analysis class III, had a median survival of 2.3 months while the most favorable patients, or recursive partitioning analysis class I, with a KPS of 70 or more, primary controlled disease, and age younger than 65, had a median survival of 7.3 months.

Recent studies by Sperduto et al. (2008) have introduced the Graded Prognostic Assessment (GPA), where variables including the number of cranial metastases as well as the presence of extracranial metastases provide easier and more objectives ways of measuring prognosis. There have been ongoing refinements, including the updated Diagnosis-Specific GPA and Lung-molGPA, that take into account mutation status for breast and lung cancers (Sperduto et al., 2012, 2017). As systemic therapies and new advances in BM management continue to
improve survival rates, understanding prognostic variables will improve personalized care and decision making.

**THE ROLE OF PALLIATIVE WHOLE-BRAIN RADIOTHERAPY**

Multiple Radiation Therapy Oncology Group (RTOG, now NRG) trials in the past have examined the optimal WBRT dose fractionation regimen (Komarnicky et al., 1991; Sause et al., 1993; Phillips et al., 1995; Murray et al., 1997). Based on prior and existing data, the typical WBRT fractionation schedule consists of 20 Gy in five fractions, 30 Gy in 10 fractions, or 37.5 Gy in 15 fractions, to have an effect on radiographically observed BM as well as microsurgical disease (Tsao et al., 2012). The impact WBRT has on intracranial disease control (i.e., both local control of known brain metastases and the absence of development of new BM) is significant, ranging from 40% to 80% in multiple randomized trials where WBRT is added on to focal therapies (Patchell et al., 1998; Chang et al., 2009; Kocher et al., 2011; Aoyama et al., 2015).

Additionally, WBRT is associated with improving neurologic signs and symptoms. The early studies from RTOG and Japan found that WBRT improved or stabilized neurologic symptoms in >50% of BM patients (Borgelt et al., 1980; Kurtz et al., 1981; Ogawa et al., 2008; Mulvenna et al., 2016).

Despite improved intracranial tumor control and symptom, the routine use of WBRT for all patients with BM is debatable. The recent QUARTZ trial was a phase III noninferiority trial for nonsmall cell lung cancer patients with BM unsuitable for surgical resection or SRS randomized to optimal supportive care or WBRT (Mulvenna et al., 2016). The primary outcome was quality-adjusted life years. Over 500 patients were accrued, with no difference in survival, quality-adjusted life years, or reduction in steroid use. This study suggests that WBRT provides no benefit compared to best supportive care for poor-prognosis lung cancer patients with asymptomatic BM. It is important to note that a large proportion of the study population had a poor performance status and a poor prognosis.

**ADJUVANT WHOLE-BRAIN RADIOTHERAPY AFTER RESECTION**

The role of adjuvant WBRT after surgery remains controversial, particularly its routine use in patients with limited BM. Patchell et al. (1998) reported one of the earliest randomized trials examining the role of WBRT after surgery for a single BM and found that WBRT was associated with lower rates of intracranial recurrence (18% vs. 70%) and less neurologic death (15% vs. 44%). Despite improvement in intracranial control there was no improvement in overall survival.

The European Organisation for Research and Treatment of Cancer 22952-26001 study was a phase III trial randomizing adjuvant WBRT or observation after surgery or SRS in patients with one to three BM. In patients who underwent surgical resection, WBRT was associated with improved local (73% vs. 41%) and distant control (77% vs. 58%) compared to observation (Kocher et al., 2011).

More recently, Brown et al. (2016a) presented the N107C/CEC.3 study, a phase III trial of postoperative SRS compared with WBRT after resection of a BM. The primary endpoints were cognitive deterioration-free survival and overall survival. Patients were evaluated with a well-established battery of cognitive tests and quality-of-life measures at enrollment and over time. Nearly 200 patients were enrolled and, with a median follow-up of 15.6 months, 6-month cognitive deterioration-free survival was worse in the WBRT group compared to SRS (85.7% vs. 53.8%). Not surprisingly, 1-year intracranial control was better in the WBRT group compared to the SRS group (78.6% vs. 54.7%), but there was worse quality of life after WBRT and it did not lead to any overall survival benefit (Brown et al., 2016a).

These results suggest that SRS after resection in patients with limited BM is a reasonable option that does not compromise overall survival with less impact on cognitive function or quality of life compared to WBRT. Importantly, these studies address BM patients with a limited number of lesions, so the use of adjuvant SRS over WBRT must be carefully weighed in BM patients with numerous metastases.

**STEREOTACTIC RADIOSURGERY AND ADJUVANT WHOLE-BRAIN RADIOTHERAPY**

SRS is an effective and increasingly utilized modality to treat BM. However, SRS does not prevent the development of new BM and the addition of WBRT can increase intracranial control. In an effort to assess the impact of improved intracranial control, there have been four randomized controlled trials examining the addition of WBRT after SRS (Aoyama et al., 2006; Chang et al., 2009; Kocher et al., 2011; Brown et al., 2016b). Notably, despite improvement in intracranial control, none of these four trials has shown a survival benefit of adding WBRT to SRS (Table 9.1). The more recent N0574 trial found worse immediate memory, delayed memory, and verbal fluency and also worse quality of life at 3 months after WBRT compared to SRS alone (Brown et al., 2016b). These results suggest that adding WBRT to
SRS in BM patients with limited BM may provide improved intracranial tumor control but no survival benefit and at the cost of increased risk of neurocognitive and quality-of-life deficits (Sahgal et al., 2015).

**HIPPOCAMPAL AVOIDANCE WHOLE-BRAIN RADIOTHERAPY**

Concerns about long-term sequelae after WBRT have led to novel radiation treatment-planning techniques to preserve neurocognitive and quality-of-life functions, particularly hippocampal avoidance WBRT (Fig. 9.1). The theory is that memory is associated with neural stem cells located in the subgranular zone of the hippocampal dentate gyrus.

**Table 9.1**

Randomized trials of stereotactic radiosurgery (SRS) with or without whole-brain radiotherapy (WBRT)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment arm</th>
<th>Median OS (months)</th>
<th>Intracranial control</th>
</tr>
</thead>
<tbody>
<tr>
<td>JROSG 99-1 (Aoyama et al., 2006)</td>
<td>1–4 BM</td>
<td>SRS</td>
<td>8.0</td>
<td>72.5% 1-year LC; 36.3% 1-year DC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRS + WBRT</td>
<td>7.5</td>
<td>88.7% 1-year LC; 58.5% 1-year DC</td>
</tr>
<tr>
<td>MD Anderson (Chang et al., 2009)</td>
<td>1–3 BM</td>
<td>SRS</td>
<td>15.2</td>
<td>67% 1-year LC; 45% 1-year DC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRS + WBRT</td>
<td>5.7</td>
<td>100% 1 year LC; 73% 1 year DC</td>
</tr>
<tr>
<td>EORTC 22952-26001 (Kocher et al., 2011)</td>
<td>1–3 BM</td>
<td>SRS/Sx</td>
<td>10.9</td>
<td>69% 2-year LC; 52% 2-year DCa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRS/Sx + WBRT</td>
<td>10.7</td>
<td>81% 2-year LC; 67% 2-year DCa</td>
</tr>
<tr>
<td>NCCTG N0574 (Brown et al., 2016b)</td>
<td>1–3 BM</td>
<td>SRS</td>
<td>10.4</td>
<td>50.5% at 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRS + WBRT</td>
<td>7.4</td>
<td>84.9% at 1 year</td>
</tr>
</tbody>
</table>

*aWe report the intracranial control rates of European Organisation for Research and Treatment of Cancer (EORTC) 22952-26001 in patients who underwent SRS, not Sx.*

BM, brain metastases; DC, distant control; JROSG, Japanese Radiation Oncology Study Group; LC, local control; NCCTG, North Central Cancer Treatment Group; OS, overall survival; Sx, surgery.

Fig. 9.1. Hippocampal avoidance whole-brain radiotherapy dosimetry in (A) axial and (B) coronal view.
NEUROPROTECTIVE PHARMACOLOGIC THERAPY

There has been growing interest in potential pharmacologic agents, particularly memantine and donepezil, to prevent cognitive decline after WBRT. Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that blocks pathologic excessive stimulation of NMDA receptors and has been shown to be beneficial in vascular dementia (Lancelot and Beal, 1998) and neuroprotective in preclinical models (Chen et al., 1992; Pellegrini and Lipton, 1993; Chen and Lipton, 1997).

RTOG 0614 was a phase III trial randomizing BM patients undergoing WBRT to placebo or memantine (Brown et al., 2013). The primary endpoint was to determine whether adding memantine preserved cognitive function, specifically memory, measured by HVLT-R delayed recall. Over 500 patients accrued in this study, with approximately a third of patients dying prior to completing 6-month assessments; only 29% of eligible patients completed the 6-month assessment. The study found a not statistically significant decline in HVLT-R delayed recall at 6 months with placebo compared to memantine (p = 0.059), possibly due to the drop in analyzable patients. However, the memantine arm had significantly longer time to cognitive decline and better processing speed and executive function.

Donepezil is an acetylcholinesterase inhibitor that is used to treat Alzheimer dementia. In a phase III study of 198 brain tumor patients, participants received donepezil or placebo 6 months after WBRT or partial brain radiation (Rapp et al., 2015). At 6 months, there was no statistically significant difference in the composite neurocognitive scores between donepezil versus placebo; however, on subgroup analysis donepezil was found to have benefit in patients with pretreatment cognitive impairment.

ONGOING STUDIES WITH WHOLE-BRAIN RADIOTHERAPY

Based on the result of RTOG 0614 and RTOG 0933, there is an ongoing phase III trial, NRG-CC001 (NCT02360215), comparing memantine with WBRT or hippocampal avoidance WBRT for BM patients. The primary endpoint is to determine whether hippocampal avoidance WBRT increases time to neurocognitive failure using a battery of neurocognitive tests. It should be noted that patients with leptomeningeal disease or disease within 5 mm of the hippocampi are excluded from this trial.

CONCLUSIONS

Due to concerns of long-term sequelae from WBRT, its use is diminishing with time and when WBRT is used, it is more frequently used later in the patient’s disease course or for patients with more extensive disease. Nonetheless, this modality remains a cornerstone in the management of BM, particularly in patients with numerable BM lesions or who are not good candidates for SRS or surgery. Improvements with radiation techniques and the use of neuroprotective drugs help address valid concerns of WBRT. With increasing survival, more studies are needed to address the role of WBRT, including novel techniques such as hippocampal avoidance WBRT, with the advent of newer systemic therapies and advances in SRS.

REFERENCES


