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Review

Adjuvant whole brain radiation following resection of brain metastases

David F. Slottje [a,1], Joon-Hyung Kim [a,1], Lisa Wang [b], Daniel M.S. Raper [c], Ashish H. Shah [d], Amade Bregy [d], Michael Furlong [e], Karthik Madhavan [d], Brian E. Lally [f], Ricardo J. Komotar [d,*]

[a] Department of Neurological Surgery, Weill Cornell Medical College, Manhattan, New York, NY, USA
[b] Department of Neurological Surgery, Weill Cornell University, Ithaca, New York, NY, USA
[c] Department of Neurological Surgery, Junior Medical Staff Unit, Royal North Shore Hospital, St Leonards, New South Wales, Australia
[d] Department of Neurological Surgery, Miller School of Medicine, 1095 NW 14th Terrace, Room 2-06, University of Miami, Miami, FL 33136, USA
[e] Department of Neurological Surgery, University of Massachusetts, Amherst, MA, USA
[f] Department of Radiation Oncology, Miller School of Medicine, University of Miami, Miami, FL, USA

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ABSTRACT

Brain metastasis is a common complication of systemic cancer and significant cause of suffering in oncology patients. Despite a plethora of available treatment modalities, the prognosis is poor with a median survival time of approximately one year. For patients with controlled systemic disease, good performance status, and a limited number of metastases, treatment typically entails surgical resection or radiosurgery, followed by whole brain radiotherapy (WBRT) to control microscopic disease. WBRT is known to control the progression of cancer in the brain, but it can also have toxic effects, particularly with regard to neurocognition. There is no consensus as to whether the benefit of WBRT outweighs the potential harm. We review the evidence related to the question of whether patients undergoing surgical resection of brain metastases should receive adjuvant WBRT.

1. Introduction

Brain metastases occur in 10% to 30% of oncology patients, accounting for approximately 170,000 incident cases per year in the United States.[1,2] The median survival time following diagnosis of metastatic disease in the brain is approximately one year.[3] Lung cancer is the most common primary tumor, accounting for 30% to 60% of patients; other common sources include breast cancer, melanoma, renal cell carcinoma, and colorectal cancer.[4] The number of cerebral metastases is of pivotal concern in determining appropriate treatment. Most patients present with three or more central nervous system (CNS) metastatic lesions, and management typically involves whole brain radiotherapy (WBRT) and corticosteroids without surgical intervention.[5,6] In patients with a solitary CNS metastatic lesion, however, surgical resection prior to WBRT can prolong survival as compared to WBRT alone.[7,8] In clinical practice, surgery is also used with good results for patients with multiple metastases in locations amenable to resection.[9] Surgical resection offers the advantages of precise histological diagnosis, relief of mass effect and/or intracranial hypertension, and effective reduction of tumor load. In addition, surgery is indicated when it is necessary to rule out alternative diagnoses, such as intracranial abscess, radiation necrosis, or primary CNS neoplasm.[10] Thus, for a subset of patients with CNS metastases, surgical intervention has a critical role in management.[11,12]

In contrast, the utility of WBRT as an adjuvant treatment following resection is less well defined. WBRT following resection is thought to control residual tumor in the resection bed, as well as distant microscopic metastases elsewhere in the brain.[13] However, WBRT has also been associated with neurocognitive decline, and concerns about the risk-benefit profile have limited clinical uptake of the treatment modality.[14] Some reviewers, therefore, have advocated deferral of adjuvant WBRT until there is radiographic evidence of recurrence.[1] To our knowledge, no prospective randomized controlled trial has demonstrated a survival benefit from adjuvant WBRT following surgical resection, and there is conflicting evidence regarding the effects of adjuvant WBRT on quality of life (QoL) and functional status.[13–15] We have reviewed the published literature to better define the role of WBRT as an adjuvant treatment for patients with metastatic CNS lesions.

2. Current evidence

Two high-quality prospective randomized controlled trials have assessed the effect of adjuvant WBRT. The seminal study was published by Patchell et al. in 1998, and more recently, in 2011, Kocher et al. published results from a trial conducted by the European Organization for Research and Treatment of Cancer (EORTC).[13,14]

* Corresponding author. Tel.: +1 305 243 4058.
E-mail address: RKomotar@med.miami.edu (R.J. Komotar).
[1] These authors have contributed equally to the manuscript.

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Previously, another prospective randomized controlled trial was conducted by the Trans-Tasman Radiation Oncology Group (TROG), but concluded prematurely due to slow accrual of participants.[15] Prior to these studies, the literature surrounding this topic has consisted mostly of retrospective series that reached conflicting conclusions.[16–18]

3. Control of central nervous system disease, survival, and functional independence

Patchell et al. enrolled 95 patients with solitary metastasis to the brain who had undergone complete surgical resection as verified by post-operative MRI.[13] Forty-nine patients were randomly assigned to receive adjuvant WBRT and 46 patients were assigned to observation with salvage treatment only at the time of recurrence at the discretion of the patients' physician. Patients in the WBRT group received 50.4 Gy in 28 fractions, substantially more than is commonly given in clinical practice. Patients were excluded if they had a Karnofsky Performance Scale (KPS) score lower than 70, a history of previous cranial irradiation, immediate need for treatment to prevent acute deterioration, or certain radiosensitive or chemotherapy-sensitive primary tumors (that is, small cell lung cancer, germ cell tumor, lymphoma, leukemia, or multiple myeloma). Recurrence anywhere in the brain was significantly lower in the WBRT group than in the observation group (18% *versus* [*vs.*] 70%, $P < 0.001$). Recurrence at the original site of resection was also significantly lower in patients in the WBRT group (10% *vs.* 46%, $P < 0.001$). Leptomeningeal carcinomatosis or new metastases distant from the original operative bed occurred less frequently among patients receiving WBRT compared to their observed counterparts (14% *vs.* 37%, $P < 0.01$). In spite of these differences, there was no significant difference in overall survival (median survival of 43 weeks in the observation group *vs.* 48 weeks in WBRT group, $P = 0.39$). Patients in the WBRT group were, however, less likely to die of neurological causes, which were broadly defined to include any death that occurred in the context of advancing neurological deterioration. Of the patients in the observation group who died, 44% died of neurological causes, as compared to 14% in the WBRT group ($P < 0.01$). However, there was no significant difference in the length of time to loss of functional independence. KPS scores remained at $\geqslant$70% for a median of 35 weeks in the observation group, compared to 37 weeks in the WBRT group ($P = 0.61$). Therefore, the authors concluded that although WBRT did not improve survival, the significant reduction in neurological death was sufficient to justify its routine use as an adjuvant therapy.

Kocher et al., in the EORTC trial, compared patients undergoing open surgery with or without WBRT, and patients undergoing radiosurgery with or without WBRT.[14] Here we focus on patients who underwent surgery, although some endpoints in the study were presented as a pooled analysis of open surgery and radiosurgery. The surgery group had 160 patients enrolled with one or two patients with completely resected brain metastases (the vast majority of patients had solitary metastases) of solid tumors (excluding small cell lung cancer and germ-cell tumors), with stable systemic disease, and World Health Organization (WHO) performance status scale of 0 to 2. A total of 81 patients were randomly assigned to receive adjuvant WBRT (30 Gy in 10 fractions) and 79 patients were assigned to observation. The protocol allowed any type of salvage therapy, including WBRT, for recurrences at the discretion of the patients' physician. At the two-year follow-up, tumor recurrence at the original site of metastasis was lower in the WBRT group compared to the observation group (27% *vs.* 59%, $P < 0.001$). Incidence of new distant metastases was also lower in the WBRT group (23% *vs.* 42%, $P < 0.01$). There was no significant difference between the groups with regard to survival with functional independence, the main endpoint of the study, which was defined as time to WHO performance status >2 or death. Combining the surgery and radiosurgery arms, the median time to WHO performance status >2 was 10.0 months in the observation group, compared to 9.5 months in the WBRT group ($P = 0.71$). Although there was a small increase in progression-free survival in the WBRT group compared to the observation group (4.6 months *vs.* 3.4 months, $P < 0.05$), overall survival did not differ (10.7 months *vs.* 10.9 months, $P = 0.89$). In patients receiving open surgery or radiosurgery, WBRT reduced neurological death, broadly defined as any death with intracranial failure as a component (44% in observation group *vs.* 28% in WBRT group, $P < 0.002$). These results were highly concordant with earlier findings by Patchell et al., but Kocher et al. reached a different conclusion and suggested that WBRT can be withheld at the time of surgery if serial imaging is performed for follow-up.

Last, Roos et al. evaluated the effects of adjuvant whole brain irradiation (30–36 Gy) after surgery or radiosurgery in the TROG trial, but it ended prematurely due to slow accrual of participants.[15] Nineteen patients with solitary metastasis to the brain were randomized to either WBRT ($n = 10$) or observation ($n = 9$) following surgery or radiosurgery. Neither duration of CNS failure-free survival nor overall survival established any statistically significant difference between the WBRT and observation groups. An outcome that came closest to reaching statistical significance was CNS relapse rate. Recurrence in the brain was seen in 78% of patients in the observation group and 30% of patients in the WBRT group ($P = 0.12$). The study also attempted to discern any effects of WBRT on QoL with serial questionnaires and the Mini-Mental Status Examination (MMSE), but failed to reach any statistical significance between two groups. Based on these limited results, Roos et al. cautiously supported the use of WBRT to decrease CNS recurrence.

When we weighed the results from these three prospective randomized controlled trials, adjuvant WBRT appears to decrease the recurrence of cancer in the brain both at the operative bed and distant sites (Fig. 1). Furthermore, WBRT decreases death due to neurologic causes (Fig. 2). However, WBRT does not effect overall survival (Fig. 3). The effect of WBRT on functional independence is somewhat less clear. Inherently, this is a subjective endpoint, and the various metrics used to render quantifiable data (KPS scale, WHO performance status, MMSE) are inevitably blunt instruments. Acknowledging the limitations of these scales, no study has demonstrated any statistically significant difference in survival with functional independence.

In the absence of any concrete evidence that correlates WBRT with increased survival, whether WBRT increases QoL is an

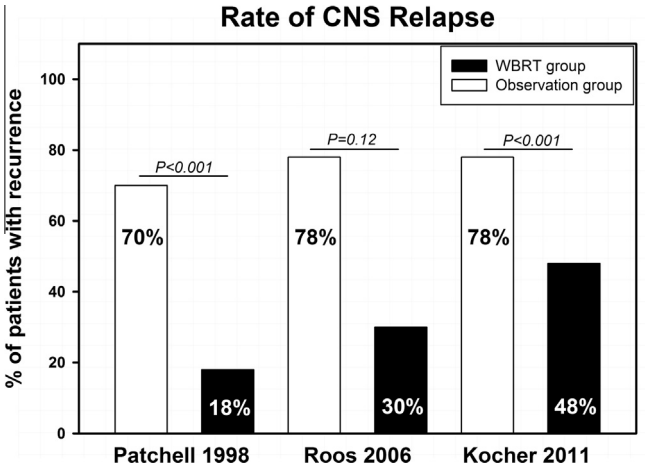

Fig. 1. Column graph showing in three studies that adjuvant whole brain radiotherapy (WBRT) appears to decrease the recurrence of cancer in the brain in patients with recurring cancers compared to a control group.