Update on Radiotherapy for Central Nervous System Malignancies

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KEYWORDS

• Brain tumors • Glioblastoma • Brain metastases

KEY POINTS

- Although whole-brain radiotherapy (WBRT) remains an important tool for the treatment of brain metastases, strategies for avoidance of the hippocampal neural stem cell compartment and the use of memantine can minimize the cognitive effects of WBRT. Stereotactic radiosurgery (SRS) without WBRT is appropriate in selected patients.
- Adjuvant treatment with alternating cranial electric fields after standard radiotherapy, a new treatment modality, can extend progression-free survival in patients with glioblastoma multiforme.
- Adjuvant procarbazine, CCNU, and vincristine in the treatment of low-grade glioma demonstrates a marked survival benefit.
- In 2016, the World Health Organization (WHO) classification of brain tumors was updated with the addition of various molecular markers prognostic for outcome.

INTRODUCTION

Malignancies arising from the central nervous system (CNS) are rare, representing 1.4% of cancer cases, with approximately 24,000 new cases estimated in 2016 leading to approximately 16,000 attributable deaths.[1] Brain metastases, in contrast, are perhaps the most common neurologic complication of cancer,[2] with an estimated incidence rate of up to 200,000 per year in the United States.[3] Radiotherapy, as part of combined modality therapy, continues to evolve with the advancement of stereotactic radiosurgery (SRS) indications; addition of new technologies, such as alternating electric field therapy; and mounting advances in the complex biology of these entities.

The authors have nothing to disclose.

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BRAIN METASTASES

Decision-making with respect to the treatment of brain metastases is a function of many factors, including patient age, performance status, comorbid conditions, symptoms, extracranial disease extent, and histopathology of the primary tumor. Treatment options include resection, whole-brain radiotherapy (WBRT), SRS, or some combination of these modalities. Work has been done to stratify patients into various prognostic groups, identifying cut-points of three factors prognostic for overall survival: (1) Karnofsky performance status (KPS), (2) age, and (3) presence of extracranial metastases.[4] More recently, a diagnosis-specific graded prognostic assessment (GPA)[5] has been developed, reflective of the strong role of primary tumor histopathology. Algorithms have been proposed using the functional status, systemic disease status, and number of metastases, such that patients with the worst prognosis are identified and recommended WBRT only, in contrast to patients with more favorable factors who may be recommended surgery or SRS, possibly followed by WBRT.[6]

WBRT is a well-established and widely used treatment of brain metastases. In a landmark trial comparing the effect of surgical resection in addition to WBRT, Patchell and colleagues[7] randomized a total of 48 patients with a single brain metastasis to either surgical resection or a biopsy only (in patients with supratentorial disease) followed by WBRT. The radiation was delivered to a total dose of 36 Gy through two parallel-opposed lateral portals, with the treatment field including the entire brain and meninges to the level of foramen magnum. Patients receiving surgery and WBRT had a significantly longer survival than those not receiving surgery, with a median survival of 40 weeks versus 15 weeks, respectively ($P<.01$). On multivariate analysis, only surgical treatment of brain metastasis was associated with a better functional status and quality of life on multivariate analysis.[7] Patchell and colleagues later performed a multicenter randomized trial of treatment of a single brain metastasis with surgical resection followed by radiotherapy versus surgical resection alone.[7] A total of 49 patients were randomized to postoperative WBRT and 46 patients to resection alone, with WBRT given to a total dose of 50.4 Gy via parallel-opposed lateral fields. They demonstrated a significantly decreased rate of recurrence at the operative bed and remainder of the brain with receipt of WBRT. Moreover, patients who received postoperative WBRT were significantly less likely to die of neurologic causes, although no difference in overall survival was shown.

WBRT, however, is associated with long-term permanent neurocognitive effects and adverse effects on quality of life. DeAngelis and coworkers[8] described WBRT-induced dementia causing severe disability in 1.9% to 5.1% of patients receiving a total dose ranging from 25 Gy to 39 Gy, attributing this to large fractions of radiation (3–6 Gy per day) delivered. More recently, Chang and colleagues[9] examined neurocognitive outcomes as assessed by a formal tool, the Hopkins Verbal Learning Test-Revised, in patients with one to three brain metastases randomized to SRS alone versus SRS with the addition of WBRT. Although 73% of patients who received SRS followed by WBRT were free from CNS recurrence at 1 year, compared with 27% who received SRS alone, the trial met early stopping rules because of a significant predicted decline in learning and memory function.

To ameliorate the neurocognitive effects of WBRT, the use of memantine, an *N*-methyl-D-aspartate-receptor antagonist, has been explored in the setting of a randomized, double-blinded, placebo-controlled trial.[10] This randomized patients receiving WBRT to memantine (20 mg/d) versus placebo, for a total of 24 weeks, with the observation of significantly longer time to cognitive decline in patients receiving memantine and a strong trend toward less decline in delayed recall in the memantine arm at