The Role of Whole Brain Radiation Therapy for Metastatic Brain Tumors

16

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Contents

Abstract

Whole brain radiation therapy (WBRT) has long served as an important treatment modality for patients diagnosed with metastatic brain tumors, both alone and in combination with other therapies including surgical resection. The recently published multidisciplinary treatment guideline by Gaspar and Kalkanis for brain metastases evaluates the evidence for the continued use of WBRT, with recommendations for specific clinical scenarios. We will address the subject of the role of WBRT in brain metastases throughout this chapter.

Introduction

Approximately 1.4 million people in the US are diagnosed with cancer every year according to the American Cancer Society. About 20–40 % of cancer patients will go on to develop brain metastases. The incidence of these secondary brain tumors is about four to five times that of primary brain tumors (American Cancer Society 2006; Gavrilovic and Posner 2005; Linskey and Kalkanis 2010). The mode of spread is primarily hematogenous with local extension also possible. In 11 % of patients with no known cancer history, cerebral metastasis was the presenting symptom (Voorhies et al. 1980). The most common primary sites for brain metastases are lungs and breast. 85 % of brain metastases are found in the cerebral hemispheres, 10–15 % in the cerebellum and 1–3 % in the brainstem.

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Typically the signs and symptoms of brain metastasis are usually slowly progressive. These include headache, focal weakness, mental disturbances, gait ataxia, seizures, speech difficulty, visual disturbance, sensory disturbance and limb ataxia.

Whole brain radiation therapy (WBRT) typically had been the mainstay for treatment for metastatic brain tumor until the 1990s when surgical resection and stereotactic radiosurgery (SRS) became more popular. WBRT has been shown to prolong survival to about 3–6 months compared to the 1–2 months in patients who did not receive any treatment (Patchell et al. 1998; Kondziolka et al. 1999). In 1954, Chao et al. (1954) showed that WBRT increased the median survival of patients with metastatic brain tumors by up to 3–6 months. Other studies (Posner 1977; Zimm et al. 1981) have shown similar improvement in overall survival in these patients. Response rate to WBRT ranges from 50 % to 85 % (Katz 1981).

Tumors that are more sensitive to WBRT are small cell lung ca, germ cell tumors, lymphoma, leukemia, multiple myeloma (Patchell et al. 1990). Highly resistant tumors are thyroid, renal cell, malignant melanoma, sarcoma, adenocarcinoma (Nieder et al. 1997). Patients with metastatic brain tumors who are candidates for WBRT usually receive steroids to decrease the peritumoral edema and WBRT over the course of 2 weeks. Mortality from metastatic brain tumors is mostly due to complications of extracranial tumor activity.

The Role of Surgery Combined with WBRT

Guidelines pertaining to the role of surgery combined with WBRT have been published (Gaspar et al. 2010). Class I evidence supports combined treatment with surgical resection plus postoperative WBRT, compared to WBRT alone or surgical resection alone, in patients who are functionally independent, who spend less than 50 % of time in bed and who have limited extra-cranial disease. There is no unified recommendation for patients with poor performance scores, advanced systemic disease, or multiple brain metastases.

The randomized control trial by Patchell et al. (1998) involved 48 patients with systemic cancer, evidence of single metastasis to the brain and Karnofsky performance scores (KPS) of 70 or greater who had received either needle biopsy and WBRT (radiation group), or complete surgical resection and WBRT (surgical group). Both groups received the same total radiation dose of 36 Gy given in 12 daily fractions of 3 Gy each. Patients with acute neurologic deterioration and radiosensitive tumors (SCLC, germ-cell, lymphoma, leukemia and multiple myeloma) were excluded. Patients in the surgical group were reported to have had complete resection verified by postoperative computerized tomography (CT) scanning. Compared to the radiation group, the surgical group had an increase in the overall length of survival (median 40 weeks vs. 15 weeks; $P<0.01$), increased duration of functional independence and quality of life, and decreased frequency of recurrence of the original tumor. There was no extra mortality noted in the surgical group.

A multi-centered trial in the Netherlands of patients who had a single brain metastasis randomized 63 patients into surgical resection and WBRT versus WBRT alone (Vecht et al. 1993). Patients in this study were generally ambulatory and did not require continuous nursing care. Patients who received the combined treatment had significantly longer median survivals (10 vs. 6 months) and longer functional independent survival (7.5 vs. 3.5 months). There was no difference in the median survival (5 months) between treatment regimens in patients with poorly controlled systemic disease. The study showed that this benefit was only seen in patients less than 60 years old and without progressive systemic disease who were within 3 months of diagnosis. Three patients were excluded from analysis. Two patients were lost to follow up.

A RCT by Mintz and Cairncross (1998) on 84 patients with a single brain metastasis was published in 1996. Forty-three patients were allocated to undergo radiation alone and 41 patients received

surgery plus radiation. The authors concluded that combined surgery and WBRT is as efficacious as WBRT alone in terms of overall survival, or quality of life. Patients were excluded if they had leukemia, lymphoma, or SCLC.

There have been possible explanations put forth to suggest why the data from this study is different from the other two studies. Most of the patients in this study had either uncontrolled primary or extracranial metastasis which is a relative contraindication to surgery. Also since most of the neurosurgically treated patients died of progression of systemic disease it is likely that there will be difference in outcomes because progressive disease has the same median survival (5 months) irrespective of combined surgery and WBRT versus WBRT alone. Also of note, this trial included patients less than 80 years old and with Karnofsky scores (KPS) of at least 50. This differs from the previous trials in that these patients could spend greater than 50 % of their day in bed. Another reason for this difference could be the lack of mandatory MRI scans in patients included in the study giving rise to the possibility that additional lesions were not seen in pre operative CT scans.

Ampil et al. (1996) retrospectively studied 45 patients at a single institution who had cerebellar metastasis and who received either surgery plus WBRT (11 patients) or WBRT alone (34 patients). Most of the patients who received WBRT alone had additional supratentorial brain metastases. The authors found that patients who received combined treatment had a median survival of 15 months compared to 3 months for patients who received WBRT alone. They concluded that the outcome of patients with metastasis to the cerebellum was significantly improved when the metastatic lesion was resected and when its origin was not from the lung.

WBRT Dosing

Radiation dosages are expressed as tumor response biologically effective dose (BED) to account for total dose of radiation, fraction size, overall time to deliver the radiation, and presumed repair of irradiated tissue. This is calculated with equation: $BED = nd\left[1 + d/(\alpha/\beta)\right]$ where n = number of treatments, d = dose per fraction; and $\alpha/\beta = 10$ Gy for tumor effects of each schedule. The standard WBRT dose is 30 Gy in 10 fractions given over 2 weeks (Gaspar et al. 2010).

In an effort to increase the duration of overall survival and to improve the morbidity from WBRT several randomized controlled trials (RCTs) were conducted to identify the optimal dose of radiation. There is no additional benefit in overall survival, neurologic function or symptom control with altered dose-fractionation schedules compared to the standard (Gaspar et al. 2010; Kalkanis et al. 2010).

In two RCTs by Borgelt et al. (1980), patients were randomly selected to receive one of five WBRT schedules that ranged from 40 Gy for a 4 week duration to 20 Gy for a 1 week duration. The following year, Borgelt et al. (1981) conducted two RCTs where patients were treated with 10 Gy in 1 fraction versus 30–40 Gy in 10–20 fractions, and also 12 Gy in 2 fractions versus 20 Gy in 5 fractions. The authors concluded that there was no statistically significant difference in the overall median survival of patients who received different radiation schedules.

Other RCTs (Harwood and Simson 1977; Chatani et al. 1994) and a Cochrane review (Tsao et al. 2012) did not find any statistically significant difference in the outcomes of patients who received varying WBRT schedules. Also, no difference in symptom control, or improvement in neurological function was observed in patients who received doses higher than 30 Gy over 10 fractions (Gaspar et al. 2010). Patients who received lower than that dose fared worse ($p = 0.03$) (Tsao et al. 2012). A RCT study conducted in the UK compared 30 Gy in 10 fractions over 2 weeks versus 12 Gy in 2 fractions on 2 days showed that patients who received 30 Gy in 10 fractions had an improved median survival of 84 days compared to 77 days ($p = 0.04$) (Priestman et al. 1996) with fewer adverse effects.

Whole Brain Radiation Therapy Combined with Other Therapies

Role of WBRT and SRS

A multi-centered RCT (Andrews et al. 2004) by the Radiation Therapy Oncology Group (RTOG) compared patients with one to three solid brain metastases, less than 4 cm in maximum diameter, and KPS > 70 who received WBRT (133 patients) and those who received both WBRT and SRS (139 patients). This study found that patients who received both WBRT and SRS had statistically significant longer survival (6.5 vs. 5.7 months, $p = 0.04$), decreased progression of disease (71 % vs. 82 %), and a higher rate of improved KPS (43 % vs. 27 %, $p = 0.03$) compared to patients who received only WBRT.

Another RCT (Kondziolka et al. 1999) randomized patients with two to four brain metastases no more than 25 mm diameter and KPS scores less than 70 to WBRT alone (14 patients) versus WBRT and SRS (13 patients) evaluating for radiological evidence of local tumor control. They found that patients who received both radiation therapies had longer median time to local failure (36 vs. 6 months, $p = 0.0005$), and longer survival (11 vs. 7.5 months) compared to patients with WBRT alone. This study did not report any neurologic or systemic morbidity related to additional stereotactic radiosurgery. Retrospective studies have also shown improved outcomes in patients who received both single dose SRS and WBRT compared to WBRT alone (Li et al. 2000; Sanghavi et al. 2001; Wang et al. 2002).

WBRT Plus SRS Versus SRS Alone

Aoyama et al. (2006) conducted a multicentered RCT of patients in Japan with no more than four metastastic brain lesions each smaller than 3 cm in diameter and KPS > 70 to compare especially for overall survival, and also brain tumor recurrence. 65 randomly selected patients received both WBRT and single dose SRS and 67 patients received SRS alone. The SRS dose in the combined group arm was reduced by 30 % compared to the SRS only group. It was noted that there was no statistically significant difference in the median survival time between patients who received WBRT and SRS compared to SRS alone. The combined treatment group had a median survival time of 7.5 months compared to 8.0 months for SRS alone. The 1 year distant brain site recurrence rate was significantly higher in the SRS alone group (76.4 % for SRS vs. 46.8 % in the combined group; $p < 0.001$). Also the SRS only group was more likely to require salvage brain therapy of either WBRT or SRS (43.3 % vs. 15.4 %).

Chang et al. (2009) found that patients who received combined SRS and WBRT had a more severe decline in learning and memory function compared to the SRS only group. This trial randomized 30 patients with one to three brain metastases to receive SRS alone, and 28 to receive combined SRS and WBRT but was stopped early because it was noted that the combined group were significantly more likely to show a decline in learning and memory function. It was also noted that the combined group patients had more patients free of recurrence of distant brain metastasis (73 % compared to 27 %, $p = 0.0003$).

Li et al. (2000) conducted a study to compare WBRT, SRS, and WBRT + SRS in terms of local response, survival, and quality of life in patients with squamous cell and non squamous cell lung cancer with single brain metastases < 4.5 cm in diameter and KPS > 60. This study found that both SRS alone and SRS + WBRT were statistically better in terms of prolonging life and improving quality of life than WBRT alone. When the combined treatment arm was compared with the SRS only arm, there was no statistically significant advantage in survival, tumor control, or enhance quality of life except for improved freedom from new brain metastasis in the combined arm.

A European trial (Kocher et al. 2011) was conducted to evaluate if patients with brain metastasis who were post-surgery or post-SRS had increased length of functional independence after adjuvant WBRT. The patients included in this

study had one to three brain metastases and WHO performance status (PS) of zero to two. Patients who had prior treatment with surgery or SRS were randomized to receive adjuvant WBRT or placebo. There was no difference observed in the overall survival between both groups. WBRT reduced the 2-year relapse rate both at initial metastasis site (surgery: 59–27 %, P < .001; radiosurgery: 31–19 %, P = .040) and at new sites (surgery: 42–23 %, P = .008; radiosurgery: 48–33 %, P = .023). The adjuvant WBRT had reduced relapse rate and less salvage therapies.

Role of Sensitizers

Sensitizers are agents that in conjunction with radiotherapy increase the cytotoxic effects and improve the therapeutic ratio. Motexafin gadolinium is a metallotexaphrin that accumulates within tumors in significantly higher concentration than in normal tissue. Efaproxiral is thought to cause a modification of the 3D structure of hemoglobin decreasing its oxygen binding capacity hence allowing more free oxygen to be available to tumor cells. Increased oxygen is thought to be destructive to the tumors. Several RCTs (Eyre et al. 1984; DeAngelis et al. 1989; Komarnicky et al. 1991; Phillips et al. 1995; Mehta et al. 2003; Suh et al. 2006) investigated outcomes in terms of overall survival, KPS and neurologic function involving the use of radiosensitizers such as motexafin, RSR13 (efaproxiral), lonidamide, metronidazole, misonidazole, gadolinium, and bromodeoxyuridine (BrdU). When used in conjunction with WBRT, these radiosensitizersdid not provide any added survival benefits andin fact, there were increased side effects.

WBRT and Chemotherapy

There have been studies (Eyre et al. 1984; DeAngelis et al. 1989; Komarnicky et al. 1991; Phillips et al. 1995; Postmus et al. 2000; Mehta et al. 2003; Suh et al. 2006) that evaluated outcomes of patients with brain metastasis who had WBRT and chemotherapeutic agents for changes in survival. These studies failed to demonstrate any improvement in median survival duration when chemotherapy was given in addition to WBRT.

WBRT Treatment Outcome by Histopathology

A retrospective study (Sundstrom et al. 1998) evaluated 75 patients with brain metastases from solid tumors, who received 25 Gy WBRT, for differences in outcomes based on histopathology. The primary cancers included 35 cases of lung cancer, 19 cases of breast cancer, 9 cases of renal-cell cancer, 6 cases of melanoma and 6 cases of other primary sites. In general, patients with breast cancer had better survival than patients with other primary cancers. There are however no formal recommendations concerning the effectiveness of WBRT for one histopathological type versus another (Kalkanis et al. 2010) due to the low number of studies addressing this topic.

Discussion

Surgical resection plus post-operative WBRT has been shown to produce better outcomes compared to WBRT alone in patients with limited extra-cranial disease and with good functional status. Surgical resection and WBRT also produces better local and distant brain control when compared to surgical resection alone. This recommendation however does not apply to relatively radiosensitive tumors histologies such as small cell lung cancer, leukemia, lymphoma, germ cell tumors and multiple myeloma (Gaspar et al. 2010; Kalkanis et al. 2010). The standard dose/fractionation scheme for WBRT is 30 Gy in 10 fractions. Other doses and fractionation schedules have not shown improved local control, neurocognitive outcomes or median survival.

WBRT combined with single dose SRS results in improved local tumor control, functional status, and longer survival, compared with WBRT alone for patients with one to four metastatic lesions

who have KPS scores greater than 70. Single dose SRS with WBRT may be just as efficacious as single dose SRS alone as long as there is regular surveillance for local and distant recurrence so salvage therapy could be initiated promptly. Adjuvant chemotherapy after WBRT has not been shown to increase survival. Radiation sensitizers have not been shown to improve outcomes in patients receiving WBRT. Also due to the relative paucity of data there are no recommendations to be made regarding the efficacy of WBRT for different tumor histology. Further investigation is required for future recommendations.

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