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Treatment of Brain Metastases: Past, Present and Future Directions

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Abstract

Brain metastases are the most frequently observed cancerous lesions in the brain and their incidence has grown as advances in imaging technologies and the treatment of extracranial disease has allowed the life expectancy of cancer patients to increase. For this reason, determining optimal treatment regimens for specific subsets of patients with brain metastases is imperative for clinicians. The purpose of this article is to review the randomized controlled trials analyzing patients with brain metastases treated with neurosurgery, WBRT, and SRS to determine future research directions for physicians and scientists. For patients who have a Karnofsky Performance Status (KPS) ≥70 and a single, surgically accessible brain metastasis, surgical resection followed by post-operative WBRT has proven to be a superior treatment modality when compared to WBRT alone and surgical resection alone. Evidence suggests that the addition of WBRT to SRS results in increased levels of survival for patients who have a single brain metastasis and increased levels of local tumor control for patients who have 1 to 4 brain metastases. Questions remain regarding survival and tumor control in patients treated with SRS with or without WBRT, which warrants further clinical investigation into this controversial matter. Although several randomized controlled trials have been published assessing the clinical outcomes of patients with brain metastases treated with a variety of treatment modalities, many studies are limited by poor patient accrual and further randomized evidence is needed to guide clinicians in their future treatment decisions.

Keywords: Brain metastases; Whole-brain radiation therapy; Surgery; Stereotactic radiosurgery; Survival;Tumor control

Introduction

Today, clinicians have a variety of treatment modalities and combinations of treatment modalities to consider for patients who suffer from metastatic brain tumors. We now know from the recursive partitioning analysis (RPA) by Gaspar et al. [1] and several phase III randomized controlled trials that treatment regimens are dependent on the patient's age, Karnofsky Performance Status (KPS), control of primary cancer, and presence of extracranial metastases, as well as the number, location, and size of brain metastases specific patients present with at the time of diagnosis [2].

Historically, whole-brain radiation therapy (WBRT) alone or combined with steroid therapy has been the most common method in the treatment of patients with brain metastases [3]. Tumor resection by means of craniotomy combined with WBRT was proven to be the benchmark treatment for patients with a single metastatic brain tumor who have a KPS ≥ 70 in the 1990's [4-7]. However, many patients with metastatic brain disease are not qualified candidates for neurosurgery or present with more than one lesion. In recent years, stereotactic radiosurgery (SRS) has gained increased popularity as a management approach for patients with brain metastases because it is a minimally-invasive procedure that has the ability to target any region in the brain with accuracy and can be used to irradiate multiple lesions in the same clinical treatment setting. Due to those advantages, SRS has proven to be safe and effective in several randomized controlled trials analyzing its efficacy when used alone or in combination with WBRT or neurosurgery [2,8-17].

Although numerous randomized controlled trials assessing patients with brain metastases have now been published, questions remain regarding treating select patients in specific clinical scenarios due to the numerous baseline characteristics that physicians must account for when prescribing treatment regimens. Furthermore, it has been demonstrated that the prognostic factors for patients with brain metastases is dependent on the primary tumor histology of specific patient subsets [18]. For this reason, the purpose of this article is to review the randomized controlled trials analyzing patients with brain metastases treated with neurosurgery, WBRT, and SRS to determine future research directions for clinicians and scientists.

WBRT alone vs. WBRT + surgery

Three randomized controlled trials have been published analyzing the efficacy of surgical resection followed by WBRT compared to WBRT alone for patients with a single brain metastasis [4-6]. In 1990, Patchell et al. [4] published a study analyzing a total of 48 patients with a single brain metastasis that were randomly assigned by computer-generated random numbers to a surgery with WBRT group (25 patients) and a WBRT alone group (23 patients). All patients had a known primary cancer (excluding small-cell lung cancer, multiple myeloma, lymphoma, leukemia, and germ-cell tumors), a KPS ≥ 70, and did not require urgent focal treatment for an acute neurological deficit. The total prescribed radiation dose for both groups was 36 Gy which was delivered in 12 daily fractions of 3 Gy each. In clinical

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analysis, it was reported that the surgery with WBRT group lived a substantially ($P < 0.01$) longer period of time when compared to the WBRT alone group (median of 40 weeks vs. 15 weeks). Patients in the surgical arm also experienced less frequent tumor recurrence at the original site of metastasis ($P < 0.02$) and exhibited a longer time of functional independence ($P < 0.005$) when compared with the WBRT alone arm (median of 38 weeks vs. 8 weeks).

The second randomized trial evaluating surgery with WBRT compared to WBRT alone for patients with a single brain metastasis was published by Vecht et al. [5] in 1993. The authors randomized 63 patients with a single brain metastasis to a surgical resection with WBRT group and a WBRT alone group by telephone. Eligible patients did not spend more than 50% of their day in bed and were not diagnosed with small-cell lung cancer or lymphoma as a primary cancer. A total radiation dose of 40 Gy was delivered in 2 fractions per day of 2 Gy each. It was reported that the surgery with WBRT group survived a median of 10 months, while the WBRT alone group survived a median of 6 months ($P = 0.04$). Functional independence also favored the surgery with WBRT treatment group ($P = 0.06$).

In 1996, Mintz et al. [6] analyzed a total of 84 patients with a single cerebral metastasis that were randomly assigned by telephone to a surgery with WBRT group (41 patients) and a WBRT alone group (43 patients). Eligible patients were < 80 years of age, had a KPS ≥ 50, and were not diagnosed with small-cell lung cancer, lymphoma, or leukemia as their cancer of primary origin. The total radiation schedule delivered was 30 Gy given in 10 daily fractions of 3 Gy each. In contrast to the studies by Patchell et al. [4] and Vecht et al. [5], the authors reported that the surgery with WBRT group and the WBRT alone group did not statistically differ in overall survival ($P = 0.24$). In addition, the two groups did not differ in patient quality of life or cause of death. This study could be criticized because it contained a larger number of patients with lower KPS values and progressive extracranial cancer, which could have resulted in a higher proportion of patients dying from their primary cancer before the effects of their neurological treatment could be observed [8].

WBRT alone vs. WBRT + SRS

Two randomized controlled trials have been published evaluating the addition of SRS to WBRT for patients with brain metastases [9-10], the first of which was led by Kondziolka et al. [9] at the University of Pittsburgh Medical Center. A total of 27 patients participated in the study, where 13 patients were randomized into the SRS with WBRT group and 14 patients were randomized into the WBRT alone group. Eligible patients had a KPS ≥ 70, 2 to 4 metastatic brain tumors, and tumor diameters ≤ 25 mm. The two treatment arms were similar in terms of age, sex, extent of systemic disease, and primary tumor histology. The primary endpoint the authors analyzed was local tumor control. Since the authors witnessed a drastic difference in tumor control between the two treatment arms, this study was stopped at the 60% accrual point. This is because it was reported that the SRS with WBRT group exhibited a superior local failure rate at 1 year (8% vs. 100%) and median time of recurrence (36 months vs. 6 months) when compared to the WBRT alone group. Median survival also favored the radiosurgery group (11 months vs. 7.5 months). However, this did not reach statistically significant because there were a relatively small number of patients in the study.

The second randomized controlled trial was conducted by the Radiation Therapy Oncology Group (RTOG) and was published in 2004 by Andrews et al. [10]. A total of 333 patients were randomly assigned to a SRS with WBRT group (167 patients) and a WBRT alone group (164 patients). All patients in the study had 1 to 3 brain metastases, a KPS ≥ 70, and a maximum tumor diameter of 40 mm for the largest lesion and a diameter of ≤ 30 mm for the remaining lesions. The two treatment arms were similar in terms of age, sex, KPS, and primary tumor histology. In contrast to the study by Kondziolka et al. [9], the main outcome analyzed was patient survival. It was reported that there were no statistically significant differences in terms of survival between the two treatment groups when compared as a whole. However, patients that were treated with SRS with WBRT who had a single brain metastasis exhibited a superior median survival when compared to the other patients in the study (median of 6.5 months vs. 4.9 months) ($P = 0.0393$).

Surgery alone vs. surgery + WBRT

In 1998, Patchell et al. [7] published the only randomized controlled trial evaluating the efficacy of surgery with WBRT compared to surgery alone for patients with a single brain metastasis. The authors randomized a total of 95 into a surgery with WBRT group (49 patients) and a surgery alone group (46 patients). The two treatment arms were similar in terms of KPS and primary tumor histology. In clinical analysis, it was reported that the two studied groups did not differ in terms of median survival and functional independence. However, patients treated with surgery with WBRT were reported to have a superior prognosis because they exhibited less frequent tumor recurrence at the site of the original metastasis ($P < 0.001$), less frequent tumor recurrence anywhere in the brain ($P < 0.001$), and were less likely to die from neurological causes ($P = 0.003$) when compared to the surgery alone treatment group.

SRS alone vs. SRS + WBRT

There have been three randomized controlled trials published analyzing if the addition of WBRT to SRS will provide patients with brain metastases a superior prognosis when compared to patients treated with SRS alone [11-13], the first of which was published by Aoyama et al. [11] in 2006. The authors randomized 67 patients into a SRS alone treatment group and 65 patients a the SRS with WBRT treatment group All patients had 1 to 4 brain metastases ≤ 30 mm in diameter and a KPS ≥ 70. The two treatment arms were similar in terms of age, sex, primary tumor histology, and control of extracranial disease. The median time of survival for the SRS alone group (8 months) and SRS with WBRT group (7.5 months) did not statistically differ ($P = 0.42$). However, patients treated with SRS with WBRT exhibited a superior 12-month brain tumor recurrence rate ($P < 0.001$) and underwent salvage therapy ($P < 0.001$) less often when compared to the SRS alone group.

A study published in 2009 by Chang et al. [12] analyzed differences in neurocognition between patients treated with SRS alone and patients treated with SRS with WBRT by using the Hopkins Verbal Learning Test-Revised Scale at four months following treatment. A total of 58 patients with 1 to 3 brain metastases were randomly assigned to a SRS alone group (30 patients) and a SRS with WBRT group (28 patients). The authors stopped the study early due to a 96% probability that patients in the SRS with WBRT treatment arm would have worse neurological deficits when compared to the SRS alone treatment arm at four months of follow-up. Central nervous system (CNS) tumor recurrence favored the SRS with WBRT group, with 73% of patients in the SRS with WBRT group being free from CNS tumor recurrence, while 27% of patients in the SRS alone group were free from CNS tumor recurrence ($P = 0.0003$). Despite the increased levels of CNS tumor control observed in the SRS with WBRT treatment group, patients in the SRS alone treatment group exhibited an increased period of survival, with a 1-year survival rate of 63% compared to 21% in the SRS with WBRT treatment group (P = 0.003). The authors do not give a satisfactory explanation why patients in the SRS alone group survived a longer period of time.

In the most recent randomized controlled trial to date, Lal et al. [13] randomized a total of 58 patients with 1 to 3 newly diagnosed brain metastases into a SRS with WBRT treatment group (27 patients) and a SRS alone treatment group (31 patients) and compared the cost-effectiveness between the two patient groups. Treatment arms were similar in terms of age, sex, ethnicity, number of metastases, and primary tumor histology. Similar to the results reported by Chang et al. [13], patients treated with SRS alone survived a greater period of time when compared to the patients treated with SRS with WBRT (median survival of 15.2 vs. 5.7 months) (P = 0.003). In addition, the authors reported that SRS alone was a cost effective treatment modality and was associated with an incremental-cost-effectiveness ratio of less than $50,000/quality-adjusted life years.

Surgery + WBRT vs. SRS + WBRT

Recently, Roos et al. [14] published the only randomized controlled trial evaluating if SRS with WBRT is as effective as surgery with WBRT for patients with a single brain metastasis who are qualified candidates for both procedures. A total of 21 patients were analyzed, where 11 were treated with SRS with WBRT and 10 were treated with surgery with WBRT. This study; unfortunately, was closed early due to slow patient accrual. However, the authors did report that the two studied groups did not statistically differ in terms of median overall survival (P = 0.20) and median failure-free survival time (P = 0.20).

Surgery or SRS vs. surgery or SRS + WBRT

Two randomized controlled trials have been published analyzing patients randomized to WBRT following either surgery or SRS [15,16]. Kocher et al. [15] randomized 359 patients with 1 to 3 brain metastases after surgery or SRS into a WBRT group (surgery + WBRT = 81 patients; SRS + WBRT = 99 patients) or an observation group (surgery alone = 79 patients; SRS alone = 100 patients). Eligible patients had 1 to 3 brain metastases from solid tumors (excluding small-cell lung cancer), a stable systemic cancer or asymptomatic primary tumors, and an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 to 2. In addition, patients treated with SRS were eligible if they had a single metastasis measuring ≤ 30 mm in diameter or 2 to 3 metastases measuring ≤ 25 mm in diameter. The authors reported that the two studied groups did not statistically differ in terms of time to achieve an ECOG-PS > 2 (P = 0.71) and overall survival (P = 0.89). However, patients who received WBRT experienced a reduced two-year relapse rate at the initial site (P < 0.001) and at distant sites (P = 0.008). In addition, the patients who were treated with SRS in addition to WBRT were reported to have a reduced progression rate at both the original site (P = 0.04) and at distant sites (P = 0.02).

In the other randomized controlled trial, Roos et al. [16] randomized 10 patients to adjuvant WBRT and 9 patients to observation following surgery or SRS of single brain metastases. This study; however, was stopped prematurely due to slow patient accrual. After analyzing the 19 patients who participated in the study, the authors reported that the WBRT group and observation group did not statistically differ in terms of median overall survival, median CNS failure-free survival, median progression-free survival, and time to achieve an ECOG-PS > 1. A trend indicating reduced levels of CNS relapse in the WBRT group was observed (30 vs. 78%), but did not reach statistical significance (P = 0.12) because there was a limited number of patients in the study.

SRS alone vs. surgery + WBRT

To date, the only randomized trial comparing patients treated with SRS alone with patients treated with surgery with WBRT was published by Muacevic et al. [17] in 2008. A total of 64 patients with a single brain metastasis ≤ 30 mm in diameter, a KPS ≥ 70, and a stable primary cancer were randomly assigned to a surgery with WBRT group (33 patients) and a SRS alone group (31 patients). The two treatment arms were similar in terms of age, sex, KPS, primary tumor histology, and extent of systemic disease. This study; however, was stopped at the 25% accrual point. The authors did report that the two treatment groups did not differ in terms of survival, death due to neurological causes, and freedom from local tumor recurrence. In addition, the SRS alone treatment group experienced more frequent distant tumor recurrences when compared to the surgery with WBRT group (P = 0.04). However, this difference was not significant after salvage therapy was administered.

Radiation-Related Toxicity

When prescribing treatment regimens for patients with brain metastases, it is imperative for physicians to counsel patients on the potential toxicity associated with WBRT and SRS. Following WBRT, the acute side-effects following treatment are headache, fatigue, erythema, nausea, impaired sense of taste, alopecia, and hyperpigmentation and the long-term side effects are radiation necrosis, alopecia, behavioral changes, hearing loss, ataxia, urinary incontinence, potential somnolence syndrome, and a decrease in neurological function [19]. The most common acute side-effects following SRS result from the stereotactic headframe that is attached to the patient's skull and include headaches and soreness at the screw site [2]. Acute side-effects from the radiation are seizures and decreased neurocognitive function for a limited period of time [2]. Long-term side-effects following SRS are not as prevalent as acute-side effects and include edema, radiation necrosis, the worsening of existing neurological deficits, and the creation of new neurological deficits [2].

Future Directions

This review highlights six important issues for future clinical analysis. First, since current randomized evidence has predominately focused on patients who have a KPS ≥ 70, investigation into the clinical outcomes of patients who have a KPS < 70 and undergo a variety of treatment regimens is warranted. Second, further randomized evidence assessing overall survival in patients with 2 to 4 brain metastases treated with WBRT with or without SRS is warranted due to the inconclusive statistical evidence reported by Kondziolka and colleagues [9]. Third, since SRS as a treatment for patients who are diagnosed with > 4 brain metastases is growing in popularity, randomized evidence is needed to assess the durability of treating patients in specific clinical scenarios in comparison with WBRT alone. Fourth, due to poor patient accrual in the study by Roos and colleagues [14], further randomized evidence is needed comparing patients who have a single brain metastasis treated with surgery + WBRT and SRS + WBRT. Fifth, further randomized evidence is needed comparing patients treated with SRS alone with patients treated with surgery with WBRT due to poor patient accrual by Muacevic and colleagues [17]. Sixth, two of the three randomized controlled trials analyzing patients treated with SRS with or without WBRT reported a survival advantage in patients treated with SRS alone [12,13]. These results are questionable due to the reported tumor control benefits from the addition of WBRT to SRS and warrants further clinical investigation [11,12].

Conclusion

For patients who have a KPS ≥ 70 and a single, surgically accessible brain metastasis, surgical resection followed by post-operative WBRT has proven to be a superior treatment modality when compared to WBRT alone and surgical resection alone. Evidence suggests that the addition of WBRT to SRS results in increased levels of survival for patients who have a single brain metastasis and increased levels of local tumor control for patients who have 1 to 4 brain metastases. Questions remain regarding survival and tumor control in patients treated with SRS with or without WBRT, which warrants further clinical investigation into this controversial matter. Although several randomized controlled trials have been published assessing the clinical outcomes of patients with brain metastases treated with a variety of treatment modalities, many studies are limited by poor patient accrual and further randomized evidence is needed to guide clinicians in their future treatment decisions.

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