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.
Radiation Therapy Oncology Group (RTOG) and was published in the number of patients in the study. It did not reach statistical significance because there were a relatively small number of patients in the study. However, this did not reach statistical significance 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 $\geq 50$, 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 $\geq 70$, 2 to 4 metastatic brain tumors, and tumor diameters $\leq 25$ 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 statistical significance 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 $\geq 70$, and a maximum tumor diameter of 40 mm for the largest lesion and a diameter of $\leq 30$ 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 $\leq 30$ mm in diameter and a KPS $\geq 70$. 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 $30,000/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 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 SRS + WBRT and SRS vs. 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 radiation-related toxicity.

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 \[2\].
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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References

1. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, et al. (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37: 745-751.
2. Elaimy AL, Mackay AR, Lamoreaux WT, Fairbanks RK, Demakas JJ, et al. (2011) Clinical outcomes of stereotactic radiosurgery in the treatment of patients with metastatic brain tumors. World Neurosurg 75: 673-683.
3. Elaimy AL, Mackay AR, Lamoreaux WT, Fairbanks RK, Demakas JJ, et al. (2011) Multimodality treatment of brain metastases: an institutional survival analysis of 275 patients. World J Surg Oncol 9: 69.
4. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, et al. (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322: 494-500.
5. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, et al. (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 33: 583-590.
6. Minta AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, et al. (1996) A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 78: 1470-1476.
7. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, et al. (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280: 1485-1498.
8. Linskey ME, Andrews DW, Asher AL, Burri SH, Kondziolka D, et al. (2010) The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96: 45-68.
9. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC (1999) Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys 45: 427-434.
10. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, et al. (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial. Lancet 363: 1665-1672.
11. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, et al. (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 296: 2483-2491.
12. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, et al. (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomized controlled trial. Lancet Oncol 10: 1037-1044.
13. Lal LS, Byfield SD, Chang EL, Franzini L, Miller LA, et al. (2011) Cost-effectiveness Analysis of a Randomized Study Comparing Radiosurgery With Radiosurgery and Whole Brain Radiation Therapy in Patients With 1 to 3 Brain Metastases. Am J Clin Oncol [Epub ahead of print].
14. Roos DE, Smith JG, Stephens SW (2011) Stereotactic radiosurgery versus surgery, both with adjuvant whole brain radiotherapy, for solitary brain metastases: a randomised controlled trial. Clin Oncol 23: 646-651.
15. Kocher M, Soffietti R, Abacioglu U, Vilia S, Fauchon F, et al. (2011) Adjuvant whole-brain radiotherapy versus observation after surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 29: 134-141.
16. Roos DE, Wirth A, Burmeister BH, Spry NA, Drummond KJ, et al. (2006) Whole brain irradiation following surgery or radiosurgery for solitary brain metastases: mature results of a prematurely closed randomized Trans-Tasman Radiation Oncology Group trial (TROG 98.05).Radiother Oncol 80: 318-322.
17. Muacevic A, Wovra B, Siefert A, Tonn JC, Steiger HJ, et al. (2008) Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neurooncol 87: 299-307.
18. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, et al. (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 77: 655-661.
19. Elaimy AL, Mackay AR, Lamoreaux WT, Fairbanks RK, Demakas JJ, et al. (2010) Brain Metastases: Clinical Outcomes for Stereotactic Radiosurgery (Method). Tumors of the Central Nervous System. Ed. M.A. Hayat. Vol. 3. Ch. 22. pp. 217-226.