Brain metastases have a prevalence of up to 20% in cancer patients, with lung, breast, melanoma, kidney, and gastrointestinal tract cancers being the most common primary cancer types. As systemic treatments continue to improve, the number of patients with brain metastases has increased. This trend may be partly due to advances in MRI technology, which have improved the ability to detect small tumors. In the United States, more than 100,000 patients are diagnosed with solitary brain metastases each year, and the number of patients with multiple metastases is even higher than the number of patients with a solitary lesion. Reduction of metastatic burden to the brain has been strongly linked to improved neurocognitive function, neurological function, and overall survival (OS); thus, treatments aimed at reducing tumor volume have become mainstays in the management of intracerebral metastatic disease.

Treatment of brain metastases usually entails the use of multiple modalities. Historically, resection was performed, given its ability to acutely alleviate the increased intracranial hypertension, seizures, and progressive neurological deficits associated with brain metastases. The invention of stereotactic radiosurgery (SRS), and the further development of linear accelerator SRS in 1987, offered a less-invasive treatment for intracranial pathology. While patients with a single brain metastasis benefit from longer...
survival and a decreased recurrence rate after resection, the benefit of operative management for multiple metastases may be marginal.\textsuperscript{10,11} By comparison, the precise delivery of high doses of ionizing radiation to regions with multiple brain metastases has shown SRS to be an effective treatment option in patients with fewer than four brain metastases.\textsuperscript{5,12,13}

Previous work has suggested that patients with single or multiple brain metastases undergoing resection may have improved survival outcomes compared with those undergoing SRS.\textsuperscript{14–16} However, in recent years there have been advances in SRS technologies, including improved collimation capabilities and image guidance. Indeed, compared with resection, the precision of SRS makes brain metastases in sites of otherwise high surgical morbidity accessible.\textsuperscript{13,17} Given the lack of conclusive evidence comparing SRS with traditional operative resection in patients with multiple brain metastases, we aimed to perform a systematic review and present a pooled analysis of all published literature on SRS and resection in patients with multiple intracranial metastases.

Methods

Search Strategy

A systematic review of peer-reviewed literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review was not registered, and the review protocol can be accessed by contacting the corresponding author. The following databases were searched from inception through February 2020 for relevant studies: PubMed (MEDLINE), Ovid (MEDLINE), Cochrane CENTRAL, Web of Science, Scopus, and ClinicalTrials.gov. The search strategies combined text words and relevant indexing using appropriate Boolean operators to capture the papers discussing the use of resection and radiosurgery for treatment of multiple brain metastases. The literature search used the following terms (including synonyms and other closely related words): “resection” or “radiosurgery” and “brain” and “metastasis.” The searches were not limited by study design or date of publication but only to references published in the English language. The reference lists of included papers were assessed for additional relevant studies not retrieved in the databases. The template data collection form, extracted data, and analysis data are available by contacting the corresponding author.

Eligibility Criteria

One author identified duplicates to be excluded. Each set of title and abstract was then independently screened by two of five authors. Records deemed eligible by consensus of two reviewers were included for full-text review. Conflicts were also included for full-text review. Each full-text review was completed by one of the above authors, and one author rechecked all eligible records for final inclusion in this review.

Inclusion criteria were as follows: 1) randomized controlled trials, cohort studies, observational studies, clinical trials, and case series (≥ 3 patients) examining surgical treatment (resection, radiosurgery, or both) of multiple brain metastases (> 1 metastasis) in adults; and 2) reporting OS in the study results. Exclusion criteria were 1) non-human studies; 2) pediatric population studies; 3) studies that did not contain ≥ 50% of patients with multiple brain metastases; 4) radiological, histopathological, or autopsy studies; 5) case series with fewer than 3 patients; 6) technical or operative case reports regarding surgical management; 7) editorials, commentaries, meeting abstracts, protocols, or review articles; 8) studies containing republished data or using national databases; 9) studies not written in the English language; 10) inability of extracting data from published results; and 11) full text not available.

Data Extraction

Five authors extracted data with a predesigned spreadsheet. Variables included but were not limited to year of publication, location, treatment modality (surgery or SRS), age, sex, OS (months survived after treatment), progression-free survival, gross tumor volume, Karnofsky Performance Scale (KPS) score, and complications. For studies that included ≥ 50% of patients with multiple brain metastases but did not report their outcome separately for patients with single and multiple brain metastases, only the number of patients with multiple brain metastases was counted when assigning weight. For studies that grouped patients with a low number of brain metastases (for instance, 1–3 metastases) and compared them with patients who had a high number of brain metastases (for instance, ≥ 4 metastases), only data from patients with a high number of metastases were included in analysis.

Statistical Analysis

The primary endpoint analyzed was OS because it was the most uniformly reported outcome measure across all studies. As variance was not uniformly reported for all studies, we chose to perform weighted two-tailed t-tests (weighted for the number of patients in each study) to compare OS, age, sex, and year of publication between the two treatment groups. In addition, a weighted ANOVA test was performed to compare OS between the two treatment groups, adjusted for age, sex, and year of publication. For the creation of forest plots (Supplemental Figs. 3 and 4), the central limit theorem was used to estimate a standard error and subsequent confidence interval for each study; p < 0.05 was considered significant. All data were managed and analyzed in RStudio version 1.2.1335.

Results

The initial search generated 1300 titles, which was narrowed to 833 after duplicates were removed. Among these, 450 articles were selected for full-text review, and 129 were eligible for final inclusion in this article (Supplemental Table 1). The PRISMA flow diagram in Fig. 1 provides additional information on the evaluation process.

The mean year of publication for the included studies was 2011 (with a range of 1992 to 2020). The mean year of publication for only SRS studies was 2012 (range 1993–2020), whereas it was 2004 (range 1992–2018) for surgery studies. The median publication year was 2012 for
SRS studies and 2012 for surgery studies. Of the included studies, 64 were from North America, 39 were from Asia, 25 were from Europe, and 1 was from Australia. The majority (n = 118) of the studies were retrospective cohort studies. Eleven studies were multi-institutional, and 118 were single-institution studies. Five studies were randomized controlled trials. The primary cancer type varied widely across the studies, including 16 of the studies exclusively focusing on non–small cell lung carcinoma (NSCLC), 14 on melanoma, 7 on breast cancer, and the majority of the remaining studies including patients with any one of multiple types of primary cancers, including renal, ovarian, and breast cancer.

A total of 20,177 patients were included in our analysis, with 18,852 patients undergoing SRS and 1325 undergoing resection. The mean age at SRS was 59.8 ± 5.0 years, and the mean age at resection was 57.8 ± 6.3 years. The percentage of female patients who underwent SRS was 50.3% ± 18.5%, and the percentage of female patients who underwent resection was 42.5% ± 17.8% (Table 1). The mean OS for SRS was 10.2 ± 6.0 months, and for resection it was 6.5 ± 3.8 months.

Weighted t-tests demonstrated that the SRS treatment group had a significantly longer OS than the surgical treat-
ment group (p = 0.013). There was no significant difference in age (p = 0.174) or sex (p = 0.057) between the treatment groups, and surgery studies had an earlier publication year than SRS studies (p = 0.0054). A weighted ANOVA test comparing OS with covariates of age, sex, and publication year revealed that treatment group (p = 0.045), age (p = 0.034), and publication year (0.0078) were all independently associated with OS, whereas sex (p = 0.95) was not. Horizontal bar plots and forest plots are shown in Supplemental Figs. 1–4.

Discussion

This is the first systematic review of all published literature on SRS and resection for treatment of multiple brain metastases. We found that across 20,177 patients, SRS may be associated with a longer OS posttreatment compared with resection.

Although resection is the standard of care for patients with solitary brain metastases, it is limited by the number and location of the tumors.13,15,18 SRS overcomes this limitation, allowing for treatment of multiple distant or surgically inaccessible lesions.19-22 A randomized controlled trial found that, compared with those undergoing whole-brain radiation therapy (WBRT) alone, patients with multiple brain metastases who received combination SRS and WBRT had increased time to local failure (tumor spread) and improved KPS scores at 6 months.23 Interestingly, another randomized controlled trial compared SRS plus WBRT with SRS alone in patients with single and multiple brain metastases and observed that the combination therapy was associated with a rapid decline in memory and overall neurocognitive function.20 Thus, SRS alone may be the preferred treatment in certain populations. However, it should be noted that SRS plus WBRT treatment was associated with a lower recurrence rate, and this combination continues to be used particularly in patients with primary cancers that have a predilection for intracranial spread.20 Most recently, a multi-institutional prospective observational study on SRS found that OS and treatment-related adverse events are not negatively impacted when a patient has more metastases.23

The increased availability of SRS for multiple brain metastases has allowed for large institutional analyses. Serizawa and colleagues retrospectively analyzed 1508 patients across two institutions and showed a 9.36-month survival length associated with SRS.24 Similarly, in a retrospective analysis of 817 patients, Cho and colleagues determined that female sex and younger age (< 65 years old) were significantly associated with greater OS.25 SRS has also shown efficacy in treating brain metastases from a variety of primary sites, including the lung, breast, and kidney.25 Brown and colleagues showed favorable SRS outcomes in classically radioresistant primary tumors, such as melanomas.26 However, the impact of SRS on metastases from different primary sites is not equal; patients with NSCLC showed greater survival benefits than those with combined renal cell carcinoma and melanoma as well as when compared with patients with other types of lung cancers.27 However, another study showed that, despite observed differences between primary cancer types (breast, NSCLC, and gastrointestinal tract) in OS and tumor reduction rates in response to SRS, there were no differences in tumor progression rates or radiation necrosis rates between primary cancer types.27

Our analysis suggests that younger age may be associated with longer survival. Research on the possible correlation between SRS outcomes and age has thus far mainly focused on patients with vascular malformations and primary brain tumors.28,29 There is not yet consensus that age is a predictor for radiosurgery outcomes. Indeed, in one cohort of patients who underwent SRS for multiple breast cancer metastases to the brain, age was not of prognostic relevance.30 Importantly, older, frailer, ill patients who are not surgical candidates may still be candidates for SRS.31

Limitations were present in our analysis. Resection for metastatic disease has been a therapeutic option for a longer period of time compared with SRS, and this is reflected in the earlier range of publications regarding resection compared with SRS. As with all reviews, we were limited by the quality of reporting of the published data we used, which limited our ability to analyze patient factors that can influence treatment effect, such as tumor volume, histopathology KPS scores, or number of metastases. Additionally, our included studies had wide heterogeneity of primary tumor type, which can cloud conclusions, as different primary tumors have different metastasis incidence rates, radiosensitivity, and systematic treatment paradigms. The quantity of published studies was skewed with more SRS studies, making a balanced comparison difficult. Indeed, treatment for multiple brain metastases is made on a case-by-case basis (e.g., if the patient tolerates a longer or staged operation, or favorable prognosis, age, or functional status). Finally, we acknowledge that, although this survival benefit of SRS compared with resection is statistically significant, it may not be clinically significant: 10.2 compared with 6.5 months represents a 57% increase in survival length but only 3.5 months.

Conclusions

For patients with multiple metastases, SRS and resection are effective treatments to prolong OS, with published data suggesting that SRS may trend toward longer survival outcomes. We encourage additional work examining treatments for multiple metastases, with consideration for patients with multiple large metastatic lesions in surgically accessible locations to be considered for resection of multiple metastases.

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References


**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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**Supplemental Information**

Online-Only Content

Supplemental material is available online. [Supplemental Table and Figures](https://thejns.org/doi/suppl/10.3171/2022.8.FOCUS22369).

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