Novel approaches to the management of patients with 5–15 brain metastases: a narrative review

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Background and Objective: The management of metastatic disease has been greatly influenced by molecular-based tumor classification and associated therapeutic targets, leading to a significant improvement in survival in many cases. This improvement, in both progression free survival and overall survival, has led to an increased incidence of brain metastases (BM) in a population with systemically well controlled disease or patients with promising therapeutic options available. Within this review, we discuss the paradigm of treatment for 5 to 15 BM, and how the treatment has evolved away from short-term palliation towards providing long term intracranial control.

Methods: A review of literature pertaining to treatment of multiple BM was performed. We searched in PubMed to identify literature on treatment of multiple brain metastases. Only English literature published until February 1st, 2022 was reviewed.

Key Content and Findings: The management of 5–15 BM include multi-modality treatment pathways that are tailored towards each individual's primary cancer and burden of disease. Surgical resection of a dominant metastasis is still reserved for large symptomatic lesions, and is combined with post-operative local disease control. Overall, there is a shift away from whole brain radiation therapy (WBRT) due to side effect profile towards stereotactic radiosurgery (SRS). However, advances in WBRT continue to be studied, as well as the use of immunotherapy, targetable mutations, and synergistic effects between SRS and targeted therapies.

Conclusions: The use of SRS to treat 5 to 15 BM is an increasingly acceptable and well-regarded practice, along with a combinatorial approach taking into account systemic options during all treatment timepoints.

Keywords: Brain metastases (BM); stereotactic radiosurgery (SRS); whole brain radiation therapy (WBRT); central nervous system metastases (CNS metastases)

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Introduction

The diagnosis and management of metastatic disease has been revolutionized by our rapidly evolving understanding of molecular-based tumor classification and its impact on therapeutic targets. Traditional cytotoxic chemotherapy has, in many instances, been supplanted by the burgeoning field of targeted therapies, including small molecule inhibitors, with a growing role for immunotherapies as first-line agents, either alone or in combination with targeted inhibitors. The marked improvement in progression-free survival (PFS), and overall survival (OS), afforded by these treatments has resulted in an increasing population of patients who present with brain metastases (BM) and have progressive systemic disease with promising therapeutic options or systemically controlled disease. While pharmacologic therapies that disrupt the signal transduction pathways of protein kinases, like tyrosine kinase inhibitors (TKI) have intracranial activity, only 8.3% of patients with metastatic cancer can be treated with targeted therapies (1,2). Furthermore, immunotherapy for the treatment of BM for many tumor types remains plagued by variable or incomplete responses, necessitating treatment paradigms that provide more robust control for symptomatic or high risk BM (3). The paradigm of treatment for 5–15 BM thus requires a similar evolution in strategy to appropriately address metastases that suboptimally respond to one or more systemic agents, particularly in patients where additional systemic management options exist. These treatment paradigms must incorporate a change in goals away from short-term palliation to providing potential for years of intracranial control to match the control expected with successful systemic treatments, ultimately aiming to optimize quality of life. This shift necessitates fluid strategies to deal with patients presenting with 5–15 lesions in a multi-modal fashion.

Within this review, we discuss the management of 5–15 BM, including the role for surgical resection combined with local treatment, the shifting paradigm away from whole brain radiation therapy (WBRT) towards stereotactic radiosurgery (SRS), advances in WBRT and SRS delivery, as well as targetable mutations, immunotherapy, and synergy between targeted therapies and SRS. The choice to focus in this article on 5–15 BM is because of ample class I data showing superior neurocognitive outcomes and equivalent OS for 1–4 BM treated with SRS compared to WBRT, and because there is still only scant data to guide management of >15 BM. It should, however, be noted that there is no compelling data to suggest that there will be a threshold number of BM at which SRS may provide worse outcomes than WBRT, and that clinical judgement is always going to be required to optimize management. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-15/rc).

Methods

A review of literature gleaned from a search on PubMed that excluded papers not available in English took place from December of 2021 to February of 2022. Decision to include a citation were based on number of citations (as an index of importance), level of evidence and type of study design. In addition, the knowledge and expertise of the senior authors were relied on for compilation of the review. Please see *Table 1* for the journal's search strategy summary.

Surgical resection combined with other local treatment

Surgical resection in the setting of multiple intracranial metastases is generally reserved for a dominant lesion causing a significant neurological deficit (4), or for dominant lesions not suitable for primary radiosurgery. Similarly, smaller lesions with significant cerebral edema in eloquent regions may be resected in order to facilitate resolution of the edema, and thus improve the safety profile of SRS. Indications for surgery, in general, include the presence of a tumor greater than 3 cm, significant edema or mass effect, neurological symptoms attributable to the lesion, the need for tissue diagnosis, or removal of a hemorrhagic lesion with risk of rebleed. Following resection, cavities and unresected lesions are treated with RT in the form of either SRS or WBRT, with SRS the favored adjuvant treatment in the post-surgical setting when feasible. Ongoing studies evaluating the use of SRS prior to surgery will continue to shed light on the optimal timing of SRS as either neo-adjuvant or adjuvant therapy. In cases in which the cavity is a suboptimal external beam radiation target, either due to size, poor patient compliance, prior treatment, or proximity to critical structures, brachytherapy seeds, implanted at time of resection, may be an alternative to external radiation (5,6). The use of intracavitary brachytherapy affords potential benefits, including immediate treatment to avoid potential delays in completion of adjuvant irradiation, and avoids the inherent logistical and dosimetric concerns related to targeting large volume surgical cavities. For all patients with

Table 1 Search strategy summary

Items	Specification
Date of search (specified to date, month and year)	12/01/2021 to 02/01/2022
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	"BM", "stereotactic radiosurgery", "whole brain radiation therapy", "CNS metastases"
Timeframe	While no paper was excluded based on date, relevant clinical papers within the last few years were favored given the rapidly advancing field
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Excluded papers not indexed on PubMed or in English
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Decision to include based on number of citations, level of evidence and type of study design, as well as senior author's expertise
Any additional considerations, if applicable	–

Table 2 Summary of investigation into treatment of 5–15 BM

Author, year	Study population	Study type	Treatment	Results
Yamamoto *et al.*, 2014 (11)	Comparison: 2 to 4 BM versus 5 to10 BM	Prospective observational study	SRS without WBRT	No significant difference in survival (P=0.78) or treatment-related adverse events (P=0.89)
Yamamoto *et al.* 2014 (12)	Comparison: 2 to 9 BM versus 10 or more tumors	Case-matched	Upfront SRS	No significant difference in median survival time, neurological death rate, cumulative incidence for neurological deterioration, or SRS-related complications
Hughes *et al.* 2019 (13)	Comparison: 1 versus 2 to 4 versus 5 to 15 BM	Retrospective; single-institutional	Upfront SRS	No significant difference in OS between the groups
Hughes *et al.* 2019 (14)	Comparison: 1 versus 2 to 4 versus 5 to 15 BM	Retrospective; multi-institutional	Upfront SRS	No significant difference in survival between 2 to 4 BM versus 5 to 15 BM
Yamamoto *et al.* 2020 (15)	Comparison: 2 to 4 BM versus 5 to 15	Retrospective; cohort study	Upfront SRS	Significantly increased OS in individuals with 2 to 4 BM (8.1 months) compared to 5 to 15 BM (7.2 months); P=0.0010

BM, brain metastases; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; OS, overall survival.

BM, hybrid treatment should be discussed within a multi-disciplinary treatment team and can often involve the use of surgical resection combined with radiation as well as novel targeted therapies and immunotherapeutics (7).

Shift from WBRT to SRS for multiple BM

Over the last decade, acceptance of utilizing SRS to treat greater than 5 BM has increased. There has been a clear shift away from the use of WBRT towards SRS in patients with multiple BM. This paradigm change has been supported by findings from randomized controlled trials that have demonstrated that SRS alone achieves a similar survival benefit with a lower side effect profile compared to WBRT with SRS (8-10). WBRT in conjunction with SRS has not been shown to improve OS compared to SRS alone for patients with 1 to 4 BM (8). While intracranial relapse rates can be significantly increased when SRS alone is employed, studies have shown no significant difference in neurological functional preservation between the groups due to the use of salvage therapies including repeat SRS for new metastases (9).

Several studies have focused on establishing non-inferiority in SRS outcomes in patients with greater than 4 metastases compared to patients with 1 to 4 BM (*Table 2*).

Yamamoto *et al.* compared outcomes following definitive SRS without WBRT for patients with 5 to 10 BM and patients with 2 to 4 in 1,194 patients. They found no significant difference in survival or treatment-related adverse events between the groups, establishing the principle of non-inferiority in SRS outcomes for patients with 5 to 10 BM (11). Other authors have supported these findings, with comparisons in outcomes for SRS treatment of 2 to 4 BM and 5 to 15 BM demonstrating similar outcomes, and supporting the use of SRS in both settings (13,14). Yamamoto *et al.* also published a study comparing outcomes using SRS alone for 2 to 9 BM versus 10 or more tumors using a case-matching approach (12). This study, comparing 360 patients in each group, found no significant difference between the cohorts with respect to median survival time, neurological death rate, cumulative incidence for neurological deterioration, or SRS-related complications. Importantly, however, Yamamoto *et al.* did find significantly increased OS in individuals with 2 to 4 BM (8.1 months) compared to 5 to 15 BM (7.2 months) (15).

An expert opinion survey published over a decade ago assessed the willingness of physicians attending the Congress and Exhibition of International Stereotactic Radiosurgery in San Francisco or the Annual Meeting of the Japanese Society of Stereotactic Radiosurgery in Sendai to treat 5 or more BM with SRS (16). In the San Francisco cohort, 55% described as reasonable treatment of greater than 5 BM, while 22% described as reasonable treatment of greater than 10 BM with SRS. The three most important factors in clinical decision making were Karnofsky Performance Scale score (KPS), mass effect, and systemic disease control. In the Sendai cohort, 83% described as reasonable treatment of greater than 5 BM, while 57% described as reasonable treatment of greater than 10 BM with SRS. The three most important factors in clinical decision making were size of BM, KPS, and BM location.

The evolution of radiotherapy technology capable of providing radiosurgical treatments with high levels of precision and acceptable throughput rates and its dissemination beyond academic medical centers is certainly a component of why SRS is increasingly offered to patients with BM. The willingness of insurance companies and benefits management intermediaries to authorize these treatments for patients, even when the number of BM is beyond the 1–4 tumors for which randomized controlled trial data is available, is also extremely important.

Impact on quality of life

Whole brain radiotherapy (WBRT) decreases distant brain failures and failures at SRS sites in patients with BM. Because of its association with cognitive decline, its role in the treatment of patients with BM remains controversial. A phase III trial examined neurocognition in patients with 1–3 BM who were randomized between SRS alone or in conjunction with WBRT (17). This study identified that despite improving intracranial control, there were no differences in functional independence at 3 months time or in median OS between the two study arms. In addition, quality of life at 3 months was statistically superior in the cohort not receiving WBRT, despite the higher risk of developing new BM. The risk of cognitive deterioration at 6 and 12 months was statistically significantly higher in the cohort randomized to SRS and WBRT. This National Cancer Institute-sponsored clinical trial took over 11 years to accrue 213 patients, which may indicate a lack of equipoise of many physicians who could have potentially opened this study and offered it to their patients.

Ongoing clinical trials

Despite the many studies demonstrating non-inferiority in treatment compared to treatment of fewer BM, there remains a lack of consensus regarding the use of SRS versus WBRT for the treatment of 5 to 15 BM. In order to more definitively establish the role and efficacy of SRS in the management of patients with >5 BM, a phase III clinical trial, "Stereotactic radiosurgery compared with hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine for 5–15 brain metastases" (NCT03550391) is currently underway with an estimated primary completion date of December 31st, 2022 and study completion date of June 30th, 2023 (18). It is expected that the neurocognitive impact from WBRT will be ameliorated by the use of novel, clinically proven techniques to decrease post-irradiation cytotoxicity (these approaches will be discussed in greater detail in Section "Advances in WBRT" of this article). Until results of that study are available, the decision to treat greater than 5 BM with upfront SRS is based on and inferred from published class I data from trials evaluating SRS and WBRT in patients with 4 or fewer BM.

Small cell lung cancer (SCLC): a disease specific example

While traditionally, a SCLC diagnosis has triggered

treatment with WBRT for central nervous system (CNS) disease, including prophylactic cranial irradiation for limited stage disease or extracranial disease that responds to systemic therapy, paradigm shifts have now questioned this approach as well. A recent paper published in *JAMA Oncology* evaluated the use of SRS versus WBRT for initial treatment of SCLC BM (19). In this population of 710 patients, the median OS was 8.5 months, with a median OS of 8 months, and 5.5 months for individuals with 5 to 10 BM versus 11 or more, respectively. WBRT improved time to CNS progression compared to SRS, but was not associated with a significant increase in OS. A subset analysis that controlled for extracranial disease control status and extracranial metastatic burden demonstrated similar results. Taken together, these results suggest that SRS may be a viable initial therapy for SCLC BM with mild to moderate CNS disease burden, particularly with expected survival of greater than 6 months.

Cumulative brain metastasis tumor volume

Interestingly, rather than total number of BM, the cumulative BM tumor volume has been shown to be an independent predictor for local control, distant brain failure, and OS (20). Baschnagel *et al.* found that increasing total tumor volume, but not the number of BM, was significantly associated with worse survival. The total tumor volume was also a better independent predictor of OS than the number of BM, specifically with total tumor volume of ≥2 cm being a stronger predictor of OS compared to the number of BM. This becomes particularly true in the case of patients with multiple subcentimeter metastases resulting in low total volume of intracranial disease, as well as with tumors harboring targetable mutations. Therefore, clinicians may consider evaluating the cumulative tumor volume of 5 to 15 metastases in treatment decisions, together with systemic therapeutic options, rather than the number alone.

Considerations for delivery of radiation

Radiosurgery can be delivered as fractionated or single fraction therapy. Examining fractionated versus non-fractionated treatment, a study of 98 patients with BM found that there was no significant difference in local PFS and OS rates (21,22). However, there was an increased rate of toxicity in the single fraction group. Another study found no difference in rate of radiation necrosis or local control in single fraction versus hypofractionated radiation (23). Fractioned treatment is often considered for larger lesions or brainstem pathology, to improve the safety profile while avoiding WBRT. For BM located in the brainstem, SRS is often utilized in a palliative setting (24), but may be considered in the broader context of overall disease burden and tumor volume. In addition, the use of single-isocenter multitarget (SIMT) SRS for the treatment of multiple BM to decrease overall treatment time has been shown in preliminary studies to offer good local control irrespective of distance from isocenter and acceptable toxicity (25-27).

Advances in WBRT

The cognitive and quality of life sequelae after WBRT are a significant deterrent for the use of WBRT in the BM population. The effects are often compounded by the significant intracranial disease burden that individuals already have, placing them at increased risk of confusion, cognitive slowing, and other neurological derangements. To improve cognition after WBRT, the use of HA-WBRT and memantine have both been investigated, with mixed but promising results. In a phase III clinical trial studying HA-prophylactic cranial irradiation with and without HA in SCLC, there was no significant difference in probability of cognitive decline (28). However, a clinical trial investigating the effects of memantine on cognitive function after WBRT for BM found that the group that received conventional WBRT and started memantine 20 mg/d within 3 days of initiating radiation and continued it for 24 weeks, compared to those who received WBRT with a placebo drug, had a significantly longer time to cognitive decline, and a reduced rate of decline of executive function, processing speed, and delayed recognition (29). Similarly, a phase III clinical trial found that subjects with BM treated with HA-WBRT plus memantine had significantly decreased risk of cognitive failure compared to those treated with WBRT plus memantine. This difference was largely seen in decreased deterioration in executive function at 4 months and learning and memory at 6 months (30). There was no difference in OS between groups. Compared to those who received WBRT plus memantine, individuals with HA-WBRT plus memantine reported significantly less difficulty with speaking, fatigue, and difficulty remembering things. The clinical trial concluded that HA-WBRT should be the standard of care for individuals without BM in the hippocampus, with continued use of memantine during subsequent treatment. In patients in whom HA is not an option, memantine may continue to offer significant benefit

when used with WBRT. Memantine has not been tested to see if it assists with neurocognitive preservation in patients undergoing SRS for BM.

Targetable mutations, immunotherapy, and synergy between targeted therapies and radiosurgery

Molecular characteristics of metastatic disease are critical for identifying potential targeted therapeutics and immunotherapies. There are recent reports of improved brain penetration of small molecule targeted therapies with good tumor response, raising the question of synergy between newer therapeutic agents and radiosurgery. For example, a recent meta-analysis studying the efficacy of SRS in combination with BRAF inhibitors for metastatic melanoma found significantly increased OS and local control in the group receiving a BRAF inhibitor plus SRS compared to SRS alone (31-33). However, the use of both BRAF inhibitors and SRS is associated with a significantly increased risk of radiation necrosis compared to SRS alone (34). Prospective studies on the combination of immunotherapy with radiation for metastatic melanoma are ongoing, including a randomized phase II study (NCT03340129) that is comparing combined ipilimumab and nivolumab to this same regimen with SRS (35,36). While initial studies showed the rate of radiation necrosis was higher in the immunotherapy and SRS group, one study reported that a cohort that received this combined therapy had significantly longer survival compared to the SRS group alone (37). The literature base is expanding with reports of BM responses to combination targeted therapy and radiosurgery for common mutations in primary cancers such as EGFR, ALK, and ROS that frequently metastasize to the brain. It is incumbent upon clinicians to weigh the risks of radiation response with the potential benefits of synergies in these patients.

In select patients, the use of a targeted therapy alone may suffice to cause regression of BM, potentially reducing the number of lesions (and volume of metastases) that need to be targeted to obtain CNS control. It is not clear whether adding radiation to targeted therapies will improve survival, though there is evidence that this may be the case (38). Development of tailored approaches to patients with BM is a growing area of interest. In selected patients, the possibility of CNS response to systemic agents may allow for a more nuanced radiosurgery treatment plan, which focuses on larger lesions (>5 mm) and those in eloquent areas, with the option of monitoring smaller lesions with low risk of causing deficit. This approach may expand the population of patients eligible for radiosurgery compared to WBRT, by focusing upfront treatment on high-risk disease, and allowing for evaluation of systemic response without significantly increasing the risk of symptomatic progression. For individuals with 5 to 15 BM, it is important to evaluate the histology and molecular status of the primary cancer to evaluate if a combinatorial approach may improve outcome, and may decrease the overall radiation volume. In cases of combinatorial therapy, close monitoring should be employed given the potential for an increase in the risk of adverse radiation effects in this setting.

Also of interest is the potential that SRS may provide advantages in off-target tumor control in patients undergoing immunotherapy. An active area of investigation is utilizing targeted radiation therapy to increase abscopal effect, to the ability of radiation to initiate a systemic antitumor response (39,40). Retrospective single-institution series have shown improved survival and acceptable toxicity for patients who are treated with SRS and immune checkpoint inhibitors (41,42). However, similar to results seen with small molecule inhibitors, immunotherapies have been associated with an increased incidence of radiation necrosis compared to both cytotoxic chemotherapy and targeted therapy, with further studies needed to establish a role for modulating the administration of radiosurgery and dosing during concurrent immunotherapy (43). Safely exploiting the immune system to improve intracranial control of macroscopic and microscopic disease when treating macroscopic disease with radiosurgery will facilitate the management of multiple BM, and clinical trials to evaluate the potential for this approach are needed for malignancies that are responsive to immune checkpoint inhibition.

Conclusions

For the treatment of oligometastatic BM, there has been a dramatic movement over the last two decades away from WBRT to SRS for 1 to 4 BM due to similar survival outcomes with a more favorable side-effect profile (8,10). This shift has increasingly been adopted for patients with 5 to 15 BM (11-14). The availability of improved technology has facilitated providing SRS in academic as well as community settings. For patients with potential survival of one or more years, the recognized morbidity of WBRT, including diffuse alopecia and scalp dryness, radiation-induced hearing loss, impairment in sense of taste

and decreased appetite, as well as cognitive impairment, is significant. Furthermore, the improvement in local control afforded by SRS compared to WBRT is increasingly driving SRS as the new standard of care, even in cases of multiple BM. This is particularly true for newly diagnosed metastatic disease, or even in cases of advanced metastatic disease in which there remain systemic options.

The preservation of function and quality of life is an independent indication for surgery or radiosurgery for large lesions or those in eloquent regions. Surgery is now seen as a tool to create safe, favorable targets for radiosurgery, and avoid, or at least postpone, WBRT. The indications for WBRT are continuing to narrow, and in many centers WBRT is reserved for cases of leptomeningeal disease, high volume of tumor burden, innumerable metastases, or in patients with expected survival of less than 3 months. Despite these trends in care, standardized guidelines continue to lag behind this rapidly evolving field.

While clinical trials directly comparing the efficacy of SRS versus WBRT as the initial treatment for 5 to 15 BM are ongoing, the general consensus is that SRS can be used as a safe and effective therapy in multiple BMs. Important considerations when managing individuals with 5 to 15 BM include determining if there is an operative lesion, estimating the total tumor volume, and determining the benefit of initiating a targeted therapy along with SRS. Timing and extent of SRS in patients with expected response to systemic agents remains an ongoing question, and current treatment is focused on preventing high risk progression in these cases. For individuals who are not candidates for SRS, HA-WBRT with memantine has been shown to reduce cognitive side effects compared to WBRT alone. At our own institution, the preferred practice is to treat 5 to 15 BM with initial SRS instead of WBRT, using a multi-disciplinary, combinatorial approach considering systemic options at all times of intervention. Further studies are needed to better elucidate how to optimally leverage combined approaches while minimizing toxicity.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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