Evidence-Based Guidelines for the Management of Brain Metastases

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• Brain metastases • Surgical resection • Radiotherapy
• Stereotactic radiosurgery • Chemotherapy
• Systemic review • Practice guidelines

Metastatic tumors of the brain are defined as secondary lesions that have spread from a primary cancer originating in another system. It is difficult to generate precise data on the incidence of these lesions because they are poorly studied. It is estimated that 1.4 million Americans are diagnosed with cancer every year. Approximately 20% to 40% of these patients with systemic cancer will develop a metastasis to the brain making this disease roughly 4 to 5 times more common than primary brain tumors.[1]

Any attempt to develop strong guidelines based on evidence requires careful definition of the target population, the interventions used, and the measured outcomes. The concept of defining a disease as a metastatic lesion originating from elsewhere implies a wide variation in pathologic presentation and natural course that can depend on several factors. A summary of these variables can be categorized into patient-specific (age, neurologic status, and presence of medical comorbidities), brain lesion-specific (size, location, and number of brain lesions), and tumor-specific (extent and prognosis of the systemic cancer). These 8 variables alone can vary widely from patient to patient, making a rigid algorithm for patient treatment almost impossible to devise given the current state of medical knowledge. Nevertheless, a systematic review of the large number of peer-reviewed publications on this subject can be extremely useful to the practitioners of neurosurgery, radiation oncology, neuro-oncology, and also medical oncology.

The American Association of Neurologic Surgeons (AANS), the Congress of Neurologic Surgeons (CNS), and the AANS/CNS Joint Tumor Section jointly funded an initiative to set up a Management of Brain Metastases Guideline (MBMG) panel to address this issue.[2] The panel included 17 clinical experts from surgical neuro-oncology, radiation oncology, and medical neuro-oncology. A comprehensive electronic literature search from the past 20 years was initiated with articles dating as recently as April 2009. The search yielded 16,966 candidate articles that were subsequently screened for relevance to the particular topic. Screened articles were then reviewed in accordance to the evidence classification adopted by the AANS/CNS (**Table 1**). Each eligible study was assigned to a class based on study design

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alone. The levels of recommendations made (see **Table 1**) were based on aspects of study quality as well as design. If there was a consensus by the panel regarding methodological concerns of certain studies, for example, it would warrant a decrease in the level of recommendation.

The panel organized its review around 8 clinical questions that corresponded to the 8 practice guideline papers[3–10] that form the major subject of this article. The 8 questions were segregated by target population into 3 categories: 4 questions pertained to patients with newly diagnosed brain metastasis, 1 question pertained to previously treated patients who present with recurrent or progressive metastasis, and 3 questions pertained to all patients with brain metastasis.

Table 1
AANS/CNS evidence classes and levels of recommendation

Evidence Classification	
Class I	Evidence provided by 1 or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (eg, case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports, and studies with historical controls
Levels of Recommendation	
Level 1	Generally accepted principles for patient management that reflect a high degree of clinical certainty (usually this requires Class I evidence, which directly addresses the clinical questions or overwhelming Class II evidence when circumstances preclude randomized clinical trials)
Level 2	Recommendations for patient management that reflect clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence)
Level 3	Other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

It is thought that patients with untreated brain metastasis have a median survival of approximately 1 month with mortality usually related to neurologic compromise.[11] The ultimate goal of treatment is to minimize the effects of these lesions while preserving neurologic function. This goal acknowledges the limitations in attempting to prolong overall survival by altering the course of systemic disease outside the nervous system. There are 3 main treatments that are considered for patients presenting with a newly diagnosed brain metastasis: whole brain radiation therapy, surgical resection, and stereotactic radiosurgery. Each is thought to provide benefit in certain clinical scenarios and is the primary focus of the review.

THE ROLE OF RADIATION

Whole-brain radiation therapy (WBRT) has been the standard treatment for all patients with brain metastasis. The rationale behind treatment outside of the tumor bed is the prevention of widely disseminated recurrent metastases throughout the brain. Because the brain can generally tolerate radiation better than other organs, WBRT also has a role in local tumor control. There are certain histopathologic tumor subgroups (small cell lung cancer, leukemia, lymphoma, germ cell tumors, multiple myeloma) that are considered radiosensitive and treated almost exclusively with WBRT. Conversely, other tumor histopathologies, such as melanoma, renal cell carcinoma, and sarcoma, are radioresistant. Between these extremes lay the vast majority of patients with common tumor histopathologies, such as breast cancer and non-small-cell lung cancer. Given the wide variety of presentations based on the variables previously mentioned, a general guideline cannot be applied to everyone. Rather, it is recommended that the guidelines be taken in the context of a multidisciplinary treatment paradigm to choose the optimal course of therapy. A risk to consider when giving WBRT is the development of neurocognitive deficits. These deficits can be subtle and easily missed on many routine medical examinations or basic mental evaluations, such as the Mini-Mental Status Examination. Nevertheless, they can be disturbing to both patients and families.

WBRT Alone versus Combination Surgical Resection and WBRT

Seven studies were reviewed by the MBMG panel to generate a Level 1 recommendation stating that

Class I evidence supports the combination of surgical resection plus postoperative WBRT, as compared with WBRT alone, in patients with good performance status (functionally independent and spending less than 50% of the time in bed) and limited extracranial disease.[9] There is insufficient evidence to make a recommendation for patients with poor performance scores, advanced systemic disease, or multiple brain metastases.

Optimal Dosing/Fractionation Schedule for WBRT

A total of 23 studies were reviewed by the MBMG panel to generate a Level 1 recommendation stating that Class I evidence suggests that altered dose/fractionation schedules of WBRT do not result in significant differences in median survival, local control, or neurocognitive outcomes when compared with standard WBRT dose/fractionation. (ie, 30 Gy in 10 fractions or a biologically effective dose [BED] of 39 Gy_{10}). This evidence was generated by performing a meta-analysis of the multiple studies by expressing several different radiation schedules in terms of the BED, which takes into account the total dose of radiation, fraction size, and overall time to deliver the radiation and presume repair of irradiated tissue. The standard dose previously mentioned served as the control dose; none of the trials with low-dose regimens or high-dose regimens relative to the control dose showed a significant difference in overall survival.

WBRT in Different Tumor Histopathologies

The MBMG panel was able to identify only 1 Class III article on this subject and was, therefore, unable to support the choice of any particular dose/fractionation regimen based on histopathology.

THE ROLE OF SURGERY

The question of surgical resection arises in patients presenting with brain metastasis. It is the responsibility of the treating neurosurgeon to determine whether it is possible to resect the lesion without causing further neurologic deficit. The brain lesion-specific variables previously mentioned are critically important factors when considering options other than radiation alone. The brain-lesion specific variables of size, number, and location of lesions can be best determined by a gadolinium-enhanced MRI scan or, if unavailable, CT scan with contrast of the brain.

For *size*, surgical resection can be thought of as a cytoreductive strategy to reduce the overall tumor burden for other therapies. In this scenario, tumors less than 0.5 cm in diameter may be too small to warrant an exclusive surgical intervention; whereas, those greater than 3 cm may not be effectively treated by any modality other than surgery. Size may be a complicating factor if there is sufficient mass effect to compromise neurologic function. An easily accessible tumor in the posterior fossa or temporal lobe, for example, can cause significant neurologic compromise because of the risk of compression to adjacent structures. In these scenarios, there may not be sufficient time for nonsurgical therapies to work.

For *number*, it is generally thought that resection of more than 1 lesion via multiple craniotomies is inadvisable. One may consider surgery for multiple, large metastatic lesions with mass effect that may be amenable to surgery or multiple lesions that may be accessible through a single craniotomy. Another indication for surgery in the face of multiple metastases is for biopsy for diagnosis in the absence of a known primary source. Approximately 37% to 50% of patients with brain metastases with primary cancers that are solid tumors will present with only 1 lesion.[1,12,13] Given this statistic, many patients will be candidates for surgical resection.

Regarding *location*, the question arises as to whether the lesion is accessible through standard neurosurgical approaches with minimal risk of damage to eloquent structures. Again the extremes of a 1-cm lesion in the superficial cortex of the right frontal lobe (resectable) versus in the midbrain (nonresectable) bound a variety of scenarios that should be evaluated on a case by case basis by the treating neurosurgeon.

Combination Surgical Resection Plus WBRT versus Surgical Resection Alone

The MBMG panel reviewed 4 studies, including 1 randomized control trial (RCT). Based on these studies, a Level 1 recommendation stated that combination surgical resection followed by WBRT represents a superior treatment modality, in terms of improving tumor control at the original site of the metastasis and in the brain overall, when compared with surgical resection alone.[5] These patients may still benefit from aggressive local control even with uncontrolled systemic disease. However, they usually have a Karnofsky Performance Score (KPS) greater than or equal to 70. The outcomes of overall survival and time with KPS greater than or equal to 70 were not significantly different. This finding may be caused by progression of systemic disease.

THE ROLE OF STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery (SRS) delivers multiple radiation beams to a specified target volume, thereby delivering a much higher dose compared with the surrounding tissue. It has been used in functional and vascular neurosurgical pathologies as well as neuro-oncology. SRS is a noninvasive modality that can safely target tumor volumes less than 10 mL. Because most metastatic lesions are spherical, this volume approximates to a lesion that is 3 cm in diameter. In addition, the evidence recommendations for SRS do not apply to lesions causing greater than 1cm of midline shift from mass effect. Although SRS has been seen as an alternative to surgery and WBRT, it may also be used in combination treatments. Given the number of variations to this modality, the MBMG panel made several recommendations.

WBRT versus Combination SRS and WBRT

Five studies were reviewed by the MBMG panel. The evidence reviewed generated a total of 4 recommendations that consistently showed the superiority of SRS combined with WBRT compared with WBRT alone, but differed by strength of recommendation as well as by inclusion criteria and outcomes.[6] The first Level 1 recommendation for combination SRS plus WBRT was for patients with single metastases with a KPS greater than or equal to 70, a group which demonstrated significantly longer patient survival compared with patients treated with WBRT alone. The second Level 1 recommendation for combination SRS and WBRT was for patients with 1 to 4 metastatic lesions with a KPS greater than or equal to 70, a group which had better local tumor control and maintenance of functional status compared with WBRT alone. For the outcome of significantly longer patient survival, a Level 2 recommendation stated that the combination of SRS and WBRT is superior in patients with 2 to 3 metastatic lesions. Finally, a Level 3 recommendation stated that there is Class III evidence demonstrating that single-dose SRS along with WBRT is superior to WBRT alone for improving patient survival for patients with single or multiple brain metastases and a KPS less than 70.

Combination SRS and WBRT versus SRS Alone

Given the strong evidence in favor of SRS and WBRT when compared with WBRT alone, the next logical question was to explore what evidence supports the opposite approach. SRS alone may be an advantage to patients in that one therapy session is required. The entire brain is not exposed to radiation in SRS; furthermore, there is a risk of potential neurocognitive deficits with the use of WBRT, although this has not been well studied because the effects may be subtle and variable. The risk, however, is the loss of control of distant tumor recurrence that is thought to be minimized by WBRT. Although it may be tempting to consider SRS as a substitute for surgery, one cannot ignore the fact that it may have biologic effects similar to WBRT. Eleven studies were reviewed by the MBMG panel that generated a Level 2 recommendation stating that SRS alone may provide an equivalent survival advantage for patients with brain metastases compared with combined WBRT and SRS. There is conflicting Class I and II evidence regarding the risk of both local and distant recurrence when SRS is used in isolation and Class I evidence demonstrates a lower risk of distant recurrence with WBRT. Therefore, regular careful surveillance is warranted for patients treated with SRS alone to provide early identification of local and distant recurrences so that salvage therapy can be initiated at the soonest possible time.

SRS Alone versus WBRT Alone

Four Class II studies were reviewed that consistently showed that SRS alone yielded a significant survival advantage when compared with WBRT alone. However, because the supporting data was weak, the MBMG panel generated a Level 3 recommendation stating that single-dose SRS alone appears to be superior to WBRT alone for patients with up to 3 metastatic brain tumors in terms of a patient survival advantage.

Combination Surgery and WBRT versus SRS Alone

The MBMG panel recognized the importance of this comparison. Four studies were found but 1 was noted to be underpowered because it was closed prematurely and the Class II data generated conflicting results. A Level 3 recommendation stated that this evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with the combination of surgery and WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

Combination Surgical Resection and WBRT versus Combination SRS and WBRT

The guidelines presented so far clearly show a significant benefit to combination therapies when compared with individual ones. Given this

information, the question arises as to which combination is superior. In the case of the combination surgical resection and WBRT, versus combinations SRS and WBRT, the MBMG panel identified only 4 retrospective studies on this comparison. The panel issued a Level 2 recommendation stating that both combinations represent effective treatment strategies, resulting in equal survival rates.

The SRS recommendations were based on a single-dose application of SRS. The panel intended to study the role of multidose SRS but the studies found were insufficient to generate recommendations. The situation was also similar for the role of local radiotherapy. Finally, the therapy of surgical resection combined with postoperative SRS to the tumor bed was another topic that did not have enough studies to warrant a review.

THE ROLE OF CHEMOTHERAPY

Although chemotherapy is a standard mode of treatment in many systemic cancers, its use in the brain has been traditionally more limited. The blood-brain barrier (BBB) limits the penetration of most substances into the brain parenchyma. Although there is some breakdown of the BBB around metastatic lesions, it is thought that drug concentrations within these lesions are still limited secondary to active efflux mechanisms.

The guideline panel was interested in the following treatment paradigms[3]:

- WBRT versus WBRT plus chemotherapy
- Chemotherapy versus chemotherapy plus WBRT
- Concurrent WBRT and chemotherapy versus chemotherapy and delayed WBRT
- Chemotherapy first, then WBRT versus WBRT first, then chemotherapy.

The panel concluded that there is no clear survival benefit seen from the addition of chemotherapy to any WBRT paradigm. Therefore, a Level 1 recommendation was made against the routine use of chemotherapy in patients with a newly diagnosed brain metastasis.[3]

There are several points to make regarding this recommendation. First, a complicating factor for any general recommendation on chemotherapy usage in metastasis is that such a recommendation would overlook the variability of different tumor histologies and chemotherapeutic agents as well as the unique interactions that may occur with every possible combination. The panel noted, for example, that metastatic germinomas are chemosensitive and should not fall under this recommendation. Most of the studies reviewed here were limited to non-small cell lung cancer and breast cancer. Second, the panel was unable to find studies that distinguished between chemotherapy naïve patients and those who had prior treatment for their systemic disease. Third, the studies reviewed did not have the same primary endpoint of overall survival. Finally, the panel recommended further enrollment in chemotherapy-based trials.[3]

RECURRENT OR PROGRESSIVE BRAIN METASTASIS

Given the difficulties in variability previously discussed with patients who present with newly diagnosed brain metastasis, one can expect an even greater number of variables to consider when patients develop recurrent metastasis or have progression of growth despite the first line of treatment. For patients who survive long enough to experience this scenario, there is no consensus on how to proceed with therapy.

The MBMG panel first addressed the evidence regarding the use of any of the previously discussed therapies (ie, WBRT, surgery, SRS, or chemotherapy).[10] On this issue, 30 studies were reviewed but no Class I or II studies were found. A Level 3 recommendation stated that treatment should be individualized based on the following factors: neurologic functional status, extent of systemic disease, volume and number of metastases, recurrence or progression at the original tumor site versus a new site, and previous treatments and histopathology of the tumor. Enrollment in clinical trials is encouraged. Considering these factors, the following options can be considered: no further treatment (supportive care), reirradiation (SRS or WBRT), surgical excision, or to a lesser extent, chemotherapy.

Finally, although the MBMG panel wished to examine the impact of differing tumor histopathologies on outcomes in patients with recurrence or progression treated with WBRT, no studies were found to be able to issue any recommendations.

THE ROLE OF ANTICONVULSANTS

Like any mass lesion, brain metastases have been known to cause epileptic seizures. Because of this, many practitioners have been known to routinely start anticonvulsant medications upon diagnosis of these lesions regardless of whether patients have suffered a seizure. As these medications have significant side effects, there is a question of whether the risk of anticonvulsant usage outweighs the potential benefit of seizure prevention. Metastatic brain lesions are thought to possibly have different epileptogenic

characteristics when compared with primary brain tumors, which usually infiltrate brain parenchyma unlike the more circumscribed metastatic tumors.

The review targeted the single question: Do prophylactic anticonvulsants decrease the risk of seizures in patients with metastatic brain lesions who have not had any seizures? The systematic review of this topic found a paucity of eligible studies, with none showing a benefit for prophylactic therapy.[4] Therefore, the Level 3 recommendation was that routine anticonvulsant use should not be recommended.[4]

THE ROLE OF STEROIDS

Corticosteroid therapy has been widely used in brain metastasis treatment. There are typically 3 scenarios in which steroids may be considered for administration. The first is upon initial or recurrent diagnosis, which usually comes about from patients presenting with neurologic symptoms. The second scenario is during the perioperative period for microsurgical or stereotactic radiosurgery to minimize symptoms related to the intervention. The final scenario is during the long-term course of WBRT. In typical patients, these scenarios are likely to overlap in time.

Steroids are thought to reduce edema through their glucocorticoid effect by downregulating proinflammatory transcription factors at the nuclear level; these effects are not instantaneous. There are known risks to chronic steroid use. In addition to the well-known side effects, such as Cushing's syndrome, myopathy, and psychosis, special consideration should be made of the combination of hyperglycemia and immunosuppression in increasing the risk of infection, especially perioperatively. As edema is thought to be the primary pathology that is treatable by steroids, it is also important to recognize the causal link between edema and its associated symptoms along with the capabilities of the steroids to work effectively on an individual basis before judging the success or failure of steroid therapy. For example, the use of steroids to reduce mass effect from a large cerebellar metastasis compressing the fourth ventricle and causing hydrocephalus may not sufficiently reduce the edema before patients undergo herniation. Similarly, consider the idea of steroid use alone on a temporal lobe metastasis in patients presenting with status epilepticus. In both cases, mass effect or peritumoral edema may be the causal agent, but selecting steroids as an exclusive therapy to reduce the neurologic symptoms will likely result in unfavorable outcomes.

Three general concepts were addressed in the review[8]: whether to administer steroids, what dose and kind of steroid to give, and how long the steroid should be administered. The outcome under question was not overall survival, but rather clinical neurologic symptom improvement.

For the question of whether to administer steroids, the target population was stratified according to symptoms relating to mass effect from edema. For clinically asymptomatic patients that demonstrate no mass effect on radiographic studies, there is insufficient evidence to make any recommendation. If patients are experiencing symptoms from mass effect, however, the panel's Level 3 recommendation is that corticosteroids can provide temporary symptomatic relief of symptoms related to increased intracranial pressure. For mild to moderate symptoms, the recommended dosage is 4 to 8 mg/day; whereas, more severe symptoms may have dosages increased up to 16 mg/day.

The panel made a Level 3 recommendation of dexamethasone as the steroid of choice for its low mineralocorticoid effects. As to the duration of therapy, the panel stated that individual factors, such as the severity of symptoms, coupled with an understanding of the consequences of the long-term sequelae should be considered before deciding the length of therapy. However, the panel made a Level 3 recommendation to taper the steroids, once started, over a 2-week period.

Given that steroid therapy alone has little effect on overall survival, the question that requires systematic analysis is whether the benefits of temporary steroid usage outweigh its risks. As the level of evidence is currently Class 3 at best, there is opportunity for addressing the questions of treatment dosages and durations because the panel was unable to identify any ongoing studies on these issues. Another potential avenue for investigation is the role of steroid therapy for symptomatic palliation during SRS, WBRT, or surgical treatment regimens.

THE ROLE OF EMERGING THERAPIES

Given the preponderance of new therapies under investigation, patients and their families will likely question treating physicians regarding these novel treatments that are usually not available outside clinical trials. It is difficult to systematically exhaust all these therapies in an evidence-based review. Nevertheless, the panel did attempt to address some of the emerging and investigational therapies that have been evaluated in clinical trials.[7]

Radiation Sensitizers

These agents are thought to increase the effectiveness of WBRT. The 2 agents reviewed were motexafin-gadolinium (MGd) and efaproxiral

(RSR 13) from data in 5 unique studies. The panel noted that a subgroup of subjects with non-small cell lung cancer who had received MGd early in an RCT had a prolongation of the time to neurologic progression; however, this was not borne out in the overall study population. Therefore, a Level 2 recommendation was made stating that currently these agents have not yet shown sufficient evidence to warrant their use.

Interstitial Therapies

The potential benefit of interstitial therapies is the ability to achieve local control without systemic dissemination of cytotoxic chemotherapy or radiation. However, there is a known risk of toxicity from these treatments. The panel reviewed 11 studies but was unable to generate any Level 1 or 2 recommendations. Currently, there is no evidence to support the use of interstitial modalities outside of clinical trials.

New Chemotherapeutic Agents

The panel reviewed 31 studies regarding the use of novel chemotherapeutic agents. The majority of these were on the subject of temozolomide (TMZ), which is widely used in the treatment of primary brain cancers. The panel issued a Level 2 recommendation stating that the addition of TMZ to WBRT in the treatment of melanoma metastasis is reasonable. Also, a Level 3 recommendation stated that there may be individual circumstances, based on multiple reports, where TMZ or fotemustine can benefit patients. Further investigations are warranted.

Molecular Targeted Agents

Molecular targeted agents have been incorporated into many cancer treatment paradigms in the last decade. There has been considerable progress in laboratory-based development and use of these agents, yet bedside application has lagged. The panel noted 2 molecular pathways that have received considerable attention: the epidermal growth factor and angiogenesis pathways. Six studies were found on the use of gefitinib, which blocks the epidermal growth factor receptor. From these studies, a Level 3 recommendation was made in the use of this agent in the treatment of brain metastases from non-small cell lung cancer. The angiogenesis pathway can be targeted by thalidomide and bevacizumab. No studies were found by the panel investigating their use in brain metastasis.

SUMMARY

Table 2 provides a summary of the number of articles reviewed by topic as well as the number of recommendations made in each section by level of evidence.[3–10] Although there were several overlaps within the review, the key recommendations are that for patients with newly diagnosed metastatic brain lesions, there is strong evidence for the involvement of radiation therapy, surgical therapy, and stereotactic radiosurgery in combination. There does not appear to be an established role for any chemotherapeutic agents at this time. For patients with recurrent or progressive brain metastases, individualization of therapies may be the best approach based on several variables discussed in this article. For all patients with brain metastasis, anticonvulsants can be held in

Table 2
Numerical summary of articles and recommendations by topic

Section Topic	Articles Reviewed	Eligible Studies	Level 1 Recommendations	Level 2 Recommendations	Level 3 Recommendations
Radiation therapy[a]	65	31	3	0	0
Surgical resection[a]	33	15	2	1	1
Stereotactic radiosurgery[a]	56	32	2	3	3
Chemotherapy	30	10	1	0	0
Retreatment	81	30	0	0	1
Anticonvulsant use	4	1	0	0	1
Steroid use	2	2	0	0	4
Novel therapies	125	59	0	2	2
Total	396	180	8	6	12

[a] There is some overlap in the articles reviewed and recommendations in these topics.

patients who have not suffered seizures, steroid use may be tailored to the patient's symptoms though they are not generally considered chemotherapy, and novel therapies currently under clinical investigation cannot yet be integrated into evidence-based guidelines as their efficacy remains unproven. Combination therapies spread across multiple medical disciplines; it becomes clear that single-specialty management of this disease is no longer sufficient to achieve quality care. Finally, there remain several questions to be resolved with evidence-based guidelines. The MBMG panel has indicated the need to review and update the guidelines every 5 years. Included in the panel's review were the names of trials currently underway that will likely make major contributions to future guidelines.

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