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Modern Multidisciplinary Management of Brain Metastases

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Abstract Ideal management of brain metastases (BMs) requires simultaneous control of the existing brain metastasis (local brain control), prevention of future BMs (distant brain control), and control of the systemic cancer (systemic control). Available tools include whole brain radiation therapy (WBRT), surgery, stereotactic radiosurgery (SRS), and systemic therapies, such as chemotherapies, biologic agents, and radiosensitizing agents. Selecting the combination of these tools is highly individualized and is impacted by numerous factors involving the tumor, patient, provider, and evolving evidence. Historically, patients received WBRT, either alone or with local treatments (surgery or SRS). However, concern about the effects of WBRT, coupled with improvements in local control and survival in select patients, with the combination treatment, has led to a reconsideration of the role of WBRT. Additionally, there have been advancements in the efficacy and tolerance of systemic therapies and clarification regarding the relative risks and symptoms of tumor recurrence versus treatment complications. Thankfully, individualizing modern multidisciplinary management for patients with BMs is being aided by numerous recently completed, ongoing, and planned prospective series.

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Introduction

Secondary metastases to the brain parenchyma (brain metastases [BMs]) are 10 times more common than primary brain tumors and most commonly originate in the lung, breast, skin, kidney, and colon. Twenty percent to 25% of patients with systemic cancer eventually develop symptomatic BMs, which account for about 170,000 new cases diagnosed annually in the United States [1]. There is a 33% chance of BMs presenting as either solitary, oligometastatic (2–3 lesions), or polymetastatic (>4 lesions), and a 80% chance that they will present after the systemic cancer diagnosis [2]. Presenting symptoms include headaches, seizures, encephalopathy, ataxia, and sensory or motor deficits. Patients with BMs may also be asymptomatic.

Numerous factors are likely increasing the incidence of brain metastasis. By 2030, an estimated 20% of the US population will be ≥65 years old, accounting for 70% of all cancers and 85% of all cancer-related mortality [3]. Detection of both symptomatic and asymptomatic disease has increased though the use of T1/T2-weighted gadolinium-contrast MRI. The number of systemic cancer patients living long enough to develop BMs has increased as a result of improved local and systemic therapies. For instance, there has been an increase in survival of colon cancer patients from about 10 to 12 months in the era of 5-flourouracil monotherapy to about 22 to 24 months in the era of combination therapy involving biologic agents [4]. This increased survival coincides with the increased incidence of BMs from 2.3% to between 5% and 6%, respectively [5]. Lastly, the unreliable and likely variable penetration of many systemic therapies through the

blood brain barrier (BBB) undoubtedly facilitates the occurrence of BMs, even in the setting of controlled systemic disease [6].

Factors Determining Response

The use of systemic therapy for the treatment of BMs is limited by factors related to both the brain and the tumor. The BBB, which usually limits the passage of large, hydrophilic molecules (ie, contrast dye, chemotherapy, biologic agents) can be partially disrupted by infection, inflammation, ischemia, trauma, radiation, and tumors [7]. Thus, the presence of contrast within BMs suggests at least a partial and temporary exposure to systemic therapies [8, 9].

Furthermore, agents that modify peritumoral edema or central nervous system (CNS) vasculature, including steroids and vascular endothelial growth factor receptor (VEGFR) inhibitors, may partially and temporarily affect the BBB. To date, attempts to circumvent or disrupt the BBB, such as intra-arterial administration of the chemotherapy or prechemotherapy administration of mannitol, remain experimental [7, 10]. Tumor-related factors also limit the usefulness of systemic therapy, including their relative size, number, chemosensitivity, propensity to mutate, and heterogeneity within the tumor and the surrounding environment [11]. Lastly, patients presenting with disease that is widely disseminated, recurrent, and synchronous with systemic disease do poorly with any therapy [12].

Factors Determining Treatment

Extensive analysis of the factors influencing the survival of patients with BMs has resulted in the development of prognostic nomograms. The Recursive Partitioning Analysis (RPA), developed by the Radiation Therapy Oncology Group (RTOG), categorized patients having received WBRT into one of three prognostic groups. RPA class I (16–20%) represented patients with a Karnofsky Performance Status (KPS) greater than 70, age younger than 65 years, controlled primary tumor, and no extracranial metastases, resulting in a median survival of 7.7 months. RPA class III (10–15%) represented patients with a KPS less than 70, resulting in a median survival of 2.3 months. RPA class II (60–65%) represented the rest of the patients, resulting in a median survival of 4.5 months [13]. However, the RPA is limited by its nonrigorous estimation of systemic tumor control and total BMs, two factors known to influence survival. These are incorporated into the more recent Graded Prognostic Assessment (GPA). The GPA uses four factors (age, KPS, number of BM, and the status of extraneural disease) to partition patients into one of four categories, with median overall survival ranging from 2.6 to 11 months [14]. No nomogram to date has fully incorporated other factors known to influence survival (ie, histology, size, or location of BM) nor has been validated using the full complement of modern therapies. Ultimately, control of the systemic cancer remains the dominant factor impacting overall survival and thus requires a multidisciplinary approach to treatment.

Treatment

The goals of treatment include the palliation of symptoms, the preservation of function, the enhancement of quality of life, and the improvement of survival. Ideally, this requires simultaneous control of the existing BM (local brain control), prevention of future BMs elsewhere in the brain (distant brain control), and control of the systemic cancer (systemic control). The tools, used alone or in combination, to achieve control in these areas include surgery, radiation, and systemic therapy. The specific use of these tools is influenced by patient preference, provider bias, cost, availability, and evolving research. In general, patients considered to have a poor prognosis are more likely to receive symptom management alone or a monotherapy, usually WBRT. In contrast, patients considered to have a good prognosis are more likely to receive multimodality therapy, usually a combination of therapies aimed at local brain control, distant brain control, and systemic control. In general, median survival for patients who receive steroids alone, WBRT alone, or combination therapy are 1 to 2 months, 3 to 4 months, and more than 6 months, respectively [15].

Symptom Management

Symptom management is always an important goal and includes the prevention and treatment of physical, cognitive, and emotional symptoms that result from both the tumor and its treatment. Deep vein thrombosis, infection, pain, safety, and neurologic, cognitive, and emotional dysfunction benefit from aggressive prevention and treatment. Cerebral edema and mass effect are most commonly treated with the steroid dexamethasone, given its potency, CNS penetration, biologic half life, and limited mineralocorticoid effect [16]. Radiation necrosis (RN), a rare but serious complication of various forms of radiation, can be treated with surgical resection of tumor with resultant decompression, steroids, hyperbaric oxygen, anticoagulants, and, experimentally, VEGFR inhibitors [17, 18]. In addition, the occurrence of RN can be minimized by the use of lower total dose, smaller treatment field, and increased dose fractionation [19]. Antiepileptics are used for patients with seizures. The prophylactic use of antiepileptics in the perioperative or other select settings remains highly

individualized and somewhat controversial. However, such use is becoming more common as the detriment of nonconvulsant seizures becomes more apparent and the newer antiepileptics become less toxic and less likely to cause drug–drug interactions [20, 21].

Whole Brain Radiation Therapy

The goals of whole brain radiation therapy (WBRT) include treating the existing BMs and preventing future BMs. The most common US regimen uses parallel-opposed external beams to deliver a dose of 30 Gy, divided in a 10-dose fraction for 2 weeks. Acute complications include encephalopathy, cerebral edema, nausea and vomiting, alopecia, skin reactions, and mucositis. Late complications include RN, dementia, optic and otic toxicities, endocrinopathies, and neurocognitive function (NCF) defects. The relative effect of local and distant brain recurrence versus WBRT complications on NCF are discussed in a separate section below. WBRT is often used alone in RPA class III patients whose alternative is best supportive care. In this setting, both overall response rate and neurologic improvement range from 50% to 60% and survival improves from between 1 and 2 to 4 months in most series [22–24]. WBRT is often used in conjunction with local treatment (surgery or stereotactic radiosurgery) in RPA class I/II patients whose alternative is local treatment alone or local treatment combined with systemic treatment. Outcomes for combination therapy are discussed below.

Surgery

The goals of surgery include establishment of a diagnosis, local control in noneloquent locations, and rapid relief of symptoms (eg, mass effect, hemorrhage, hydrocephalus). Surgery commonly involves intraoperative image guidance, microsurgical techniques, perioperative neurologic monitoring, and advanced medical care. Complications include infection, neurologic deficits, cerebral hemorrhage, cerebral infarction, and death [25]. Surgery is often used in patients with RPA class I/II, a single metastasis, and a minimal or controlled systemic tumor. Prospective surgical series report more than 80% ability to establish a diagnosis and at least partially improve CNS symptoms, yet minimal impact on distant brain control and overall survival [26••, 27]. Outcomes of combination therapy are discussed below.

Stereotactic Radiosurgery

The goals of stereotactic radiosurgery (SRS) include the convenience of a single outpatient procedure, the ability to treat multiple lesions and nonsurgical candidates, local control for eloquent brain, and relative cost-effectiveness compared with surgical resection. SRS uses head immobilization, computer planning, specialized equipment, and convergent beams to deliver a single dose of radiation with high intensity at the target and rapid dose fall off at the edges. Technical restrictions include indistinct lesions, lesions larger than 3 cm, and lesions too close to the optic apparatus. SRS is usually reserved for patients with a known diagnosis. Complications include RN and the theoretical risk of second malignancies. Retrospective and prospective series (for most histologies) report local control rates of 60% to 75% at 2 years, distant brain control rates of about 46% at 2 years, overall survival of about 10 months, decrease in the need of steroids, and trend toward survival in RPA class I/II patients [26••, 28, 29•]. Across retrospective series, factors predicting distant brain control and improved outcome after SRS alone include female gender, youth, higher baseline KPS, fewer than three lesions, smaller total BM volume, surgery before SRS, nonmelanoma histology, and minimal or controlled systemic disease [29•, 30]. Similar to surgery, there is minimal impact on distant brain control and overall survival. Outcomes of combination therapy are discussed below.

Local Treatment With or Without WBRT

The goals of combining WBRT with local treatments (surgery or SRS) include enhancement of local control of the existing BMs and prevention of future BMs. This combination usually involves the delivery of WBRT after the local treatment, although certain protocols and situations reverse this order. This combination is often used for RPA class I/II patients who have one to three BMs, with at least one benefiting from local therapy, and a relatively radiosensitive histology. Outcomes of this strategy are articulated by multiple retrospective and prospective series.

Several series have demonstrated that the addition of surgery to WBRT results in improved local control and survival over WBRT alone in patients presenting with good prognostic variables and controlled systemic disease. For example, Patchell et al. [31] prospectively randomized patients with a single metastasis to surgery with WBRT versus WBRT alone. Overall survival and functional independence was significantly improved for patients who received combination therapy for 40 versus 15 weeks (P= 0.01) and 38 versus 8 weeks (P=0.005), respectively [31]. Two similar series reported comparable results in patients with good prognoses and stable extracranial disease [32, 33].

In a reverse question, other series have evaluated whether the addition of WBRT to surgery benefits patients. For example, Patchell et al. [27] prospectively randomly assigned patients with a single metastasis to undergo surgery with WBRT versus surgery alone. With a median follow-up of 48 weeks, the combination increased local

control from 54% to 90% (P=0.001), increased distant control from 56% to 86% (P=0.01), and decreased the likelihood of dying from neurologic causes from 44% to 14% (P=0.003). However, there was no difference in overall survival or time to decrease in performance status [27]. Other series have reported similar outcomes [27, 34], including one by Mueller et al. [26••].

Similarly, other series have evaluated whether the addition of SRS to WBRT benefits patients. For example, Andrews et al. [28] prospectively randomly assigned patients from multiple centers with one to three metastases to receive WBRT with or without SRS. Patients with a single metastasis intended for combination therapy (despite 19% not receiving it) yielded increased median survival from 4.9 to 6.5 months (P=0.039). Patients with one to three metastases intended for combination therapy were statistically more likely to have stable or improved performance status at 6 months than those receiving WBRT alone (43% vs 27%, respectively; P=0.03), yet showed no difference in neurologic death rate or overall survival. Multivariate analysis reinforced the importance of RPA class 1 performance status (P<0.0001) and favorable histology (P=0.0121) on outcome [28]. Similar smaller studies have reported comparable outcomes [34].

Recently, a large, multicenter series evaluated whether the addition of WBRT to either local treatment (surgery or SRS) benefits patients. Mueller et al. [26••] prospectively randomly assigned patients with one to three BMs, good performance status, stable systemic disease, and receipt of either surgery or SRS to receive either WBRT versus no further therapy. Regardless of whether patients received surgery or SRS, patients receiving WBRT experienced decreased intracranial progression (15% vs 39% at 6 mo; 31% vs 54% at 24 mo; P=0.0001), decreased neurologic death rate (25% vs 43%; P= 0.0001), yet no difference in functional or overall survival (9.8 vs 10.9 mo, respectively) [26••].

The Benefits and Drawbacks of Combining Local Treatment with WBRT

The decision to combine a local treatment with WBRT continues to be somewhat controversial and evolve as evidence unfolds. Individual patients must weigh the risks and potential symptoms of both the recurrence of the tumor and the complications of treatment. Across series, the benefits of combined therapy generally include improved local and distant brain control, reduction of neurologic decline rate, and stability or improvement of performance status. Conversely, across series, the drawbacks generally include the inconvenience of treatment, the absence of difference in overall survival, the loss of reserving WBRT until subsequent recurrence, and the concern for unnecessary WBRT complications, especially NCF. Until recently, most series did not systematically evaluate the NCF domains of attention, information processing, learning/memory, verbal fluency, executive function, fine motor skills, and dexterity. However, recent series doing so highlight the impact of baseline tumor burden and tumor recurrence on NCF in the context of how NCF is impacted by treatment. For example, Chang et al. [35] prospectively evaluated the NCF of patients with one to three BMs receiving SRS (without immediate WBRT) at baseline and at regular intervals. Interestingly, 67% of patients demonstrated impairment in at least one domain at baseline and more than 50% had progressive impairment in ≥ two domains at 1 month (most commonly executive functioning, motor dexterity, and memory) [35]. In a similar evaluation of BMs patients receiving WBRT with and without a radiosensitizer motexafin gadolinium (MGd), Meyers et al. [36] reported 90% of patients with one NCF deficit and 40% with more than four NCF deficits at baseline. The total volume, response to treatment, and recurrence of BM predicted NCF deficits [36]. Lastly, in the above series by Mueller et al. [26••], neither treatment arm (local treatment with or without WBRT) demonstrated either objective or subjective differences in mood/personality, seizures, headache, somnolence, intellectual deficits, functional competence, and memory, or grade 1 to 3 neurologic deficits.

Systemic Agents

Systemic agents include chemotherapy, radiosensitizers, and biologic agents. The goals of systemic therapy include improving local control, improving distant brain control in a non-WBRT strategy, and improving systemic control. Systemic therapies can be used alone or in combination with radiation and can be selected either for their ability to penetrate the BBB or their evidence of efficacy in specific tumor histologies [37]. Complications include immunosuppression, fatigue, myelosuppression, gastrointestinal dysfunction, or drug-specific toxicities. Outcomes are difficult to generate given that many series include patients with various histologies, uncontrolled systemic disease, undefined numbers of prior recurrences or treatments, and subjectivity in the assessment of progression and response. Nonetheless, several series highlight the emerging role of systemic therapy in BMs, including the improvement of distant brain control in a non-WBRT strategy and, potentially, the improvement of systemic control. [38]

The use of chemotherapy alone has been of increasing interest to clinicians and researchers. Systemic agents are most commonly used alone in the settings of patient or provider preference, contraindication to radiation, or at recurrence after previous radiation. Temozolomide, metho-

trexate, capecitabine, and topotecan have been most commonly evaluated, given their CNS penetration, relative tolerability, sensitivity with tumor histologies that commonly metastasize to the brain, and familiarity by providers. Across diversely performed studies, response rates usually range between 10% and 40%, stable disease rates usually range between 20% to 30%, and rates of palliation or effect on survival range widely. For example, Kim et al. [38] retrospectively evaluated patients with non–small cell lung cancer and synchronous asymptomatic BMs and reported no significant difference in overall survival whether patients had received chemotherapy alone or chemotherapy followed by either SRS or WBRT [38]. When taken collectively, these studies emphasize that more information is needed to define the role of chemotherapy monotherapy in BMs [39, 40].

Biologic agents, including VEGFR or pathway inhibitors, epidermal growth factor receptor (EGFR) inhibitors, platelet-derived growth factor receptor inhibitors, human epidermal growth factor receptor 2, and others are also being evaluated. One of the most studied, bevacizumab, is a VEGFR inhibitor used in the treatment of multiple advanced systemic tumors. Complications include thrombosis, bleeding, poor wound healing, hypertension, and other peripheral and cerebrovascular complications. For these reasons, bevacizumab has historically been excluded in patients with BMs. However, recent evidence suggests that bevacizumab may not only be safe but also efficacious in BMs. For example, three retrospective analyses by Rohr et al. [39] evaluated more than 13,000 patients who had been randomly assigned to one of 17 systemic tumor trials involving bevacizumab and who were subsequently diagnosed with BMs. They reported that the collective incidence of cerebral hemorrhage was less than 1% to 3% compared with the historical incidence of 3.5% to 29% and there was no difference in all-cause mortality [39]. Similarly, Socinski et al. [40] recently reported on non–small cell lung cancer patients with previously treated BMs prospectively who subsequently received bevacizumab-containing treatments safely. Currently, various biologic agents are undergoing prospective evaluation and preliminarily suggest safety, tolerability, and potential efficacy.

Systemic Agents Treatment With or Without WBRT

The goals of combining systemic agents with WBRT include improving response rate, local control, neurologic function, and survival. Many studies have looked at administering these drugs concurrently, before or after radiation. Although the optimal role of combination therapy remains undefined, possible situations include the presence of synchronous brain and systemic disease, the histologies predicted for treatment sensitivity, and the good prognosis patient estimated for extended survival. Numerous chemotherapy agents have been evaluated for combination with radiation, including platinums, nitrosoureas, 5-fluorouracil agents, teniposide, topotecan, and temozolomide. To date, temozolomide has been one of the most extensively studied. For example, Antonadou et al. [41] prospectively randomly assigned newly diagnosed BM patients to receive WBRT, with or without concurrent temozolomide, followed by six cycles of systemic temozolomide. They reported an increase in response rate from 67% to 96% (P=0.017), a decrease in need for steroids and anticonvulsants at 2 months, and a trend toward improved survival with the combination [41]. Similar studies have reported comparable outcomes with combination treatment, including an increase in quality of life at 3 months, decrease in neurologic death rate, increase in CNS progression-free survival, and, collectively, emphasize the importance of good prognosis and extent of systemic disease [42, 43]. In another example, Neahaus et al. [44] prospectively randomly assigned newly diagnosed metastatic patients to WBRT, with or without topotecan, followed topotecan in both arms. Although interpretation of the results are limited by poor accrual, this trial failed to demonstrate significant differences in overall survival or other outcomes [44]. Lastly, it is notable that chemotherapy has been evaluated in combination with SRS, including two prospective trials evaluating temozolomide with SRS [45, 46].

Biologic and radiosensitizing agents have also been evaluated in combination with various types of radiation. For example, Mu et al. [47] prospectively evaluated RPA class 1 patients who received an EGFR inhibitor (gefitinib) with WBRT and reported an overall response rate of 81%, a disease control rate of 95%, and a median survival of 13 months. Similar evaluations are underway with other biologics. Radiosensitizing agents evaluated to date include MGd, supplemental oxygen, platinums, metronidazole, misonidazole, efaproxiral (SR13), bromodeoxyuridine, lonidamine, temozolomide, and others. With the exceptions of temozolomide and MGd, most series report increased toxicity, intolerability, and no difference in tumor control or survival [48]. Notably, several prospective series report an improvement (or delay in decline) of NCF in predominantly non–small cell lung cancer patients receiving WBRT with MGd. This includes a prospective, randomized series by Meyers et al. [36], reporting an improvement in memory and executive function in 63%.

Conclusions

BMs represent a tremendous burden on human society in every way measured. Ideal management of BMs requires simultaneous control of the existing BM (local brain

control), prevention of future BMs elsewhere in the brain (distant brain control), and control of the systemic cancer (systemic control). Tools available to achieve this include WBRT, surgery, SRS, and systemic therapies, such as chemotherapies, biologic agents, and radiosensitizing agents. Selecting the combination of these tools is highly individualized and is impacted by numerous factors involving the tumor, patient, provider, and evolving evidence. Historically, patients received WBRT, either alone or with local treatments (surgery or SRS). However, growing concern over the treatment effects of WBRT, coupled with the improvements in local control, and in select patients, survival, with the combination with local treatment, resulted in reconsideration of the need for WBRT. Simultaneously, there has been clarification over the relative risks and potential impacts of tumor recurrence versus treatment complications. Additionally, advancements in the efficacy and tolerability of systemic therapies may facilitate improved control of both the brain and systemic disease. Although the ideal combination of treatments currently remains undefined, the results of numerous prospective series, discussed above and ongoing, will undoubtedly help to optimize and individualize care. Lastly, research is needed for the prevention of BMs and their recurrence, improvements in the efficacy and tolerability of treatments, prevention and management of complications, and improvements in the design and efficiency of research.

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- •• Of major importance

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