REVIEW ARTICLE

Brain Metastases: A Modern Multidisciplinary Approach

Philip J. O'Halloran, Enrique Gutierrez, Aristotle Kalyvas, Nilesh Mohan, Soha Atallah, Suneil Kalia, Barbara-Ann Millar, Normand Laperriere, Tatiana Conrad, Gelareh Zadeh, Mark Bernstein, David B. Shultz, Paul Kongkham

ABSTRACT: Brain metastases (BM) are the most common intracranial neoplasm and represent a major clinical challenge across many medical disciplines. The incidence of BM is increasing, largely due to improvements in primary disease therapeutics conferring greater systemic control, and advancements in neuroimaging techniques and availability leading to earlier diagnosis. In recent years, the landscape of BM treatment has changed significantly with the advent of personalized targeted chemotherapies and immunotherapy, the adoption of focal radiotherapy (RT) for higher intracranial disease burden, and the implementation of new surgical strategies. The increasing permutations of options available for the treatment of patients diagnosed with BM necessitate coordinated care by a multidisciplinary team. This review discusses the current treatment regimens for BM as well as examines the salient features of a modern multidisciplinary approach.

RÉSUMÉ : Polychimiothérapie et approche moderne du traitement des métastases cérébrales. Les métastases cérébrales représentent le type le plus fréquent de tumeurs intracrâniennes et posent un sérieux défi clinique dans de nombreuses disciplines médicales. L'incidence des métastases cérébrales est à la hausse, phénomène qui s'explique en grande partie par l'amélioration des traitements des tumeurs primitives qui permet de limiter davantage la dissémination dans l'organisme et par les progrès réalisés en neuro-imagerie par l'arrivée de nouvelles techniques, deux facteurs qui favorisent une pose précoce du diagnostic. Au cours des dernières années, l'arsenal thérapeutique des métastases cérébrales a considérablement changé par l'introduction de la chimiothérapie ciblée personnalisée et de l'immunothérapie, l'adoption de la radiothérapie focale dans les cas de lésion intracrânienne invalidante et la mise en œuvre de nouvelles stratégies chirurgicales. Ainsi, le nombre sans cesse croissant d'associations de traitements nécessite la formation d'équipes pluridisciplinaires pour la coordination des soins. La synthèse ici présentée fait état des différentes formules thérapeutiques pratiquées actuellement dans le traitement des métastases cérébrales ainsi que des points saillants d'une approche pluridisciplinaire moderne.

Keywords: Brain metastases, Surgery, Radiotherapy, Targeted therapy, Immunotherapy, Multidisciplinary

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Introduction

The incidence of brain metastases (BM) continues to increase worldwide, with a reported 25% of cancer patients developing intracranial metastases[1]. Targeted therapies and immunotherapies have led to significant survival benefits in the treatment of systemic disease. Enhanced primary oncological control has been associated with a paradoxical increase in the incidence of central nervous system (CNS) progression. Lung, breast, melanoma, colorectal, and renal cell carcinomas continue to represent the most common primary malignancies to metastasize to the brain[2]. Currently, there is a paucity of high-quality evidence guiding the treatment of BM, however, a combined modality therapeutic approach confers the greatest survival benefit to patients along with lower rates of recurrence and improved quality of life[3].

Many other questions remain unanswered including:

- Is there a benefit to screening for asymptomatic breast cancer BM (similar to other primary cancers such as asymptomatic patients with stage ≥ II non-small-cell lung cancer (NSCLC), as well as stage IIIC–IV melanoma)?
- Is neoadjuvant radiation superior to postoperative radiation after BM resection?
- What is the role of up-front laser interstitial thermal therapy (LITT) in the treatment of BM?
- What is the role of tumor treatment fields (TTF) in the setting of CNS metastatic disease?
- What is the limit regarding the number of BM suitable for stereotactic radiosurgery (SRS) versus whole-brain radiation therapy (WBRT)?
- Can disruption of the blood–brain barrier augment the effectiveness of systemic therapies against BM?
- Will combination versus monotherapy of molecular therapeutic agents be more effective (with/without increased toxicity)?

From the Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, Toronto, Ontario, Canada (PJOH, AK, NM, SK, GZ, MB, PK); and Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada (EG, SA, BAM, NL, TC, DBS)

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Correspondence to: Paul Kongkham, Division of Neurosurgery (Department of Surgery), Toronto Western Hospital, 399 Bathurst St, WW4-450, Toronto, Ontario, Canada, M5T-S28. Email: paul.kongkham@uhn.ca

Table 1: Current recommendations on the role of surgery and radiation therapy in the management of single brain metastases (BM)[65]

Level 1	Surgery plus WBRT is recommended as first-line treatment in patients with single BM with favorable performance status and limited extracranial disease to extend overall survival, median survival, and local control.
Level 3	Surgery plus SRS is recommended to provide a survival benefit in patients with metastatic brain tumors.
Level 3	Multimodal treatments including either surgery plus WBRT plus SRS boost or surgery plus WBRT are recommended as alternatives to WBRT plus SRS in terms of providing overall survival and local control benefits.
Level 3	Gross total resection is recommended over subtotal resection in recursive partitioning analysis of class I patients to improve overall survival and prolong time to recurrence.
Level 3	En bloc tumor resection, as opposed to piecemeal resection, is recommended to decrease the risk of postoperative leptomeningeal disease when resecting single BM.
Level 3	Craniotomy is recommended as a treatment for intracranial recurrence after initial surgery or SRS.

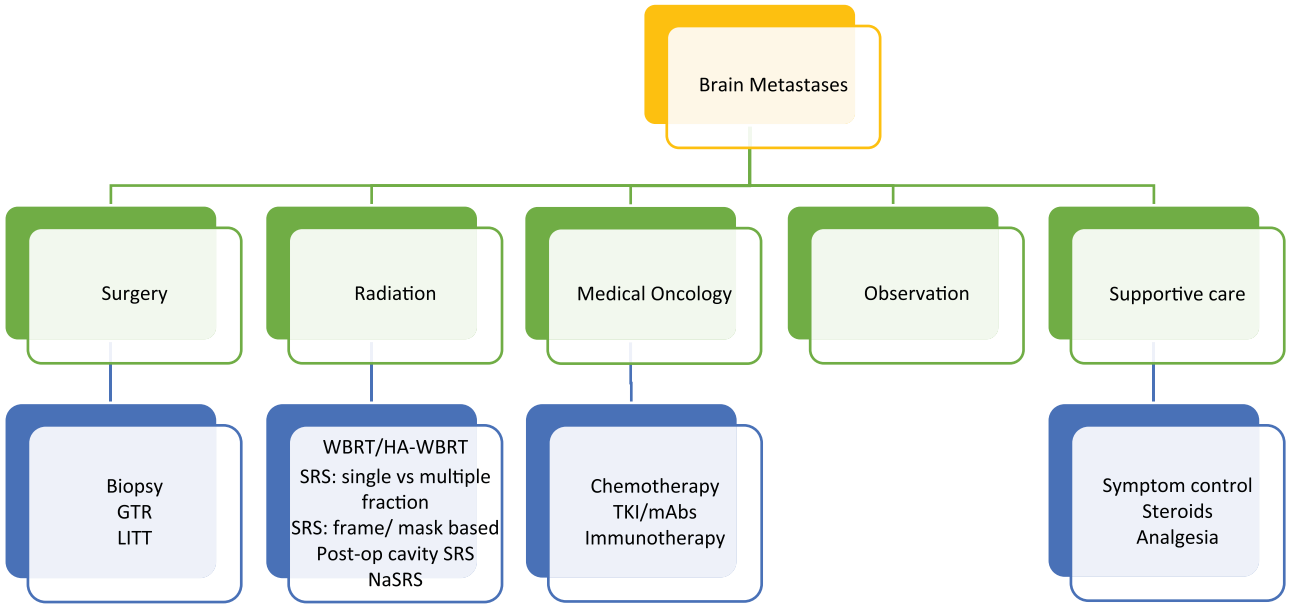

Figure 1: *Brain metastases (BM) treatment options. HA-WBRT=hippocampal avoidance WBRT; mAbs=monoclonal antibodies; NaSRS=neoadjuvant SRS; SRS=stereotatic radiosurgery; TKIs=tyrosine kinase inhibitors; WBRT=whole-brain radiotherapy..*

Herein, we discuss modern treatment options available for patients with BM (Figure 1), highlighting nuances related to treatment considerations and the critical role of a multidisciplinary team approach incorporating neurosurgery, radiation oncology, neuroradiology, and medical oncology.

Diagnosis/Imaging

As with many neurological disorders, imaging plays a pivotal role in the initial diagnosis and assessment of tumor response to treatment for BM. MRI remains the imaging modality of choice, with BM often localized to gray–white matter junctions and demonstrating a characteristic ring-enhancing appearance with surrounding edema. Increasing availability and access to MRI, as well as screening MRI brain studies (often in the context of clinical trial enrolment) have led to increasing numbers of patients diagnosed with BM at a pre-symptomatic stage during which their disease may be more amenable to noninvasive treatment modalities. Furthermore, while BM historically precluded patients from clinical trials, recent advancements in imaging modalities and the development of Response Assessment in Neuro-Oncology (RANO) imaging guidelines for the design of trials involving patients with BM have opened the door to clinical trial inclusion[4]. This has ushered in a new era of investigation in which the response of BM to novel systemic therapies can be elucidated. Novel MRI biomarkers are currently under investigation to examine the cellular and metabolic features of tumors in order to better characterize treatment response including magnetic resonance spectroscopy (MRS), chemical exchange saturation transfer (CEST), quantitative magnetization transfer (qMT) as well as FET PET/MRI radiomics[5].

Surgery

Correct patient selection remains of paramount importance when including surgery in the overall management strategy for BM. Surgery is not typically a stand-alone strategy; suitability for post-operative radiotherapy (RT) is an important consideration. Currently, level I evidence supports the role of surgery in patients with a single BM, particularly for patients with favorable prognostic factors such as Karnofsky performance score (KPS) > 70, <65 years of age, stable primary disease, and lack of extracranial metastases (Table 1).

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Table 2: Current recommendations on the role of surgery and radiation therapy in the management of single BM[65]

Level 1	Surgery plus WBRT is recommended as a superior treatment to WBRT alone in patients with single BM.
Level 3	Surgery plus SRS is recommended as an alternative to treatment with SRS alone to benefit overall survival.
Level 3	It is recommended that SRS alone be considered equivalent to surgery plus WBRT.

Table 3: Current recommendations on the role of surgery in the management of multiple BM[66]

Level 3	In patients with multiple BM, tumor resection is recommended in patients with lesions inducing symptoms from the mass effect that can be reached without inducing new neurological deficits and who have control of their cancer outside the nervous system.

Among data supporting the role of surgical resection for BM is the 1990 landmark study by Patchell et al. This trial prospectively randomized patients to surgical resection plus WBRT versus WBRT alone. Surgery plus WBRT demonstrated an improved overall survival (40 weeks vs. 15 weeks), reduced local recurrence (20% vs. 52%), and enhanced functionally independent quality of life (38 weeks vs. 8 weeks)[3] (Table 2). In addition, the role of reducing intracranial pressure and steroid use are further benefits of surgical resection in patients with accessible lesions[6].

Commonly, patients present with more than one BM creating a clinical dilemma. A reported 80% of patients have more than one BM and approximately 50% have >3 BM at presentation[7]. In this setting, level III evidence recommends that select patients with large, symptomatic, surgically accessible metastases, may be considered for surgical resection without increasing surgical morbidity[8] (Table 3). In certain patients with multiple BM, a single lesion may be immediately life threatening due to mass effect or associated obstructive hydrocephalus. In these cases, while resection of all lesions may not be feasible, resection of the dominant lesion may prevent imminent deterioration, provide histological diagnosis, and offer the opportunity to receive further adjuvant treatment such as radiosurgery or RT.

Modern surgical techniques such as awake craniotomy, intraoperative monitoring, in combination with micro-neurosurgical techniques allow for safe maximal resection with en bloc resection of BM associated with decreased incidence of leptomeningeal disease and local recurrence compared with piecemeal resection without a converse increase in mortality[9].

BM can originate in deep-seated/eloquent areas and, therefore, represent a surgical dilemma due to the increased invasiveness and the inherent surgical risk in accessing the tumor. The risk of surgical morbidity needs to be balanced against the long-term survival benefits, with one overarching goal being the preservation of neurologic function and quality of life. The advent of novel minimally invasive surgical strategies including LITT and channel-based resections has facilitated safer surgical intervention in these situations.

LITT is a minimally invasive procedure that uses kinetic energy to heat the surrounding tissue inducing cell death and coagulative necrosis. (Figure 2). The real-time effects of the interstitial laser can be visualized via MRI thermography. LITT has grown in popularity in recent years as a salvage therapy in BM lesions measuring 1–3 cm, located within deep/eloquent brain tissue, as well as lesions refractory to RT[10,11]. Patient postoperative length of stay in hospital is typically 1 day and patients are treated without any hair shave, through a few mm incision closed with a single stitch. However, the application of LITT is not without its limitations. Post-treatment edema due to the thermal effects of the therapy can cause lesions to expand leading to symptomatic mass effect if large lesions or those with significant preexisting perilesional edema are treated[12]. Although the use of LITT has been reported since the 1990s, further work is required to elicit the role of LITT within the surgical armamentarium available to treat BM.

Channel-based resections employ novel tubular retractor systems that serve to displace critical subcortical white matter functional tracts as one approaches deep-seated tumors. Such retractor systems are combined with improvements in intraoperative navigation and MRI white matter tractography, allowing the surgeon to identify and preserve neighboring critical functional pathways when resecting deep tumors. Despite gross total resection rates ranging from 80% to 100%[13–15], channel-based retractions are technically challenging due to the narrow diameter of the retractor making visualization of the tumor and surrounding structures difficult.

The role and timing of surgical interventions in the treatment of BM continues to evolve. As many BM are treated up-front non-operatively, those that come to surgery are often more challenging in nature or larger in size. These factors may necessitate a surgical strategy of piecemeal resection with an associated risk of tumor dissemination and leptomeningeal seeding during surgery. One strategy to reduce this risk involves neoadjuvant RT prior to resection. Our group is exploring this strategy through a multicenter prospective non-randomized phase II trial of neoadjuvant SRS (NaSRS trial), examining rates of postoperative leptomeningeal dissemination (LMD) and symptomatic radiation toxicity versus a historic cohort of patients treated in the usual fashion with postoperative SRS[16].

Radiation Therapy

Whole-Brain Radiation Therapy

WBRT remains an important treatment modality for patients with BM. WBRT can be used to reduce symptoms associated with intracranial metastases and reduce the likelihood of new metastatic disease[7]. There are multiple dose and fractionation schedules. The most common are 30 Gy delivered over 10 fractions and 20 Gy in 5 fractions. Neither scheme has been shown to have an advantage in survival benefit nor toxicity[17]. However, the choice of a scheme may be influenced by prognosis, functional status, histology, or previous treatment[17]. A shorter course of treatment is generally preferable in patients with a poor prognosis and low-performance status[17].

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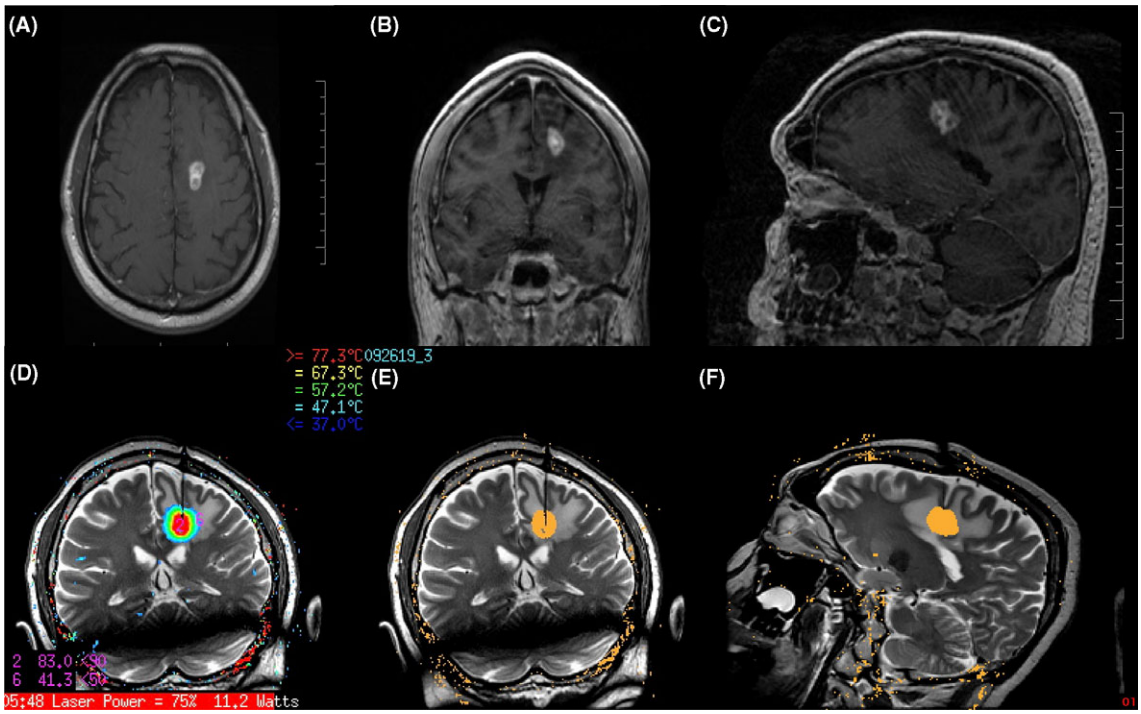

Figure 2: *Laser interstitial thermocoagulation therapy (patient treated in the Toronto Western Hospital). Preoperative MRI (post-gadolinium) demonstrating an enhancing left frontal mass with surrounding edema in a patient with a known primary sarcoma in an axial (A), coronal (B), and sagittal (C) plane. Real-time effects of the interstitial laser heating target tissue visualized via MRI thermography (D) and the subsequent zone of irreversible target ablation outlined in orange (E, F). The thin artifact of the laser catheter, inserted via a 2–3 mm incision, can be seen (D, E).*

WBRT results in a decreased risk of intracranial relapse compared to focal radiation strategies such as SRS[18]. However, WBRT is associated with an increased risk of neurological toxicity (e.g. short-term memory loss) compared to SRS, and decreased quality of life. Neurocognitive toxicity following WBRT has been evaluated using several different tools, such as verbal fluency (Controlled Oral Word Association), memory (Hopkins Verbal Learning Test–Revised), processing speed (Trail Making Test Part A), and executive function (Trail Making Test Part B)[19,20].

Due to the improvement in both brain-specific and systemic treatments, the prognosis for BM patients has significantly improved. This has led to increased interest in reducing the neurological deterioration associated with WBRT[21]. The recently reported phase III trial NRG Oncology CC001, randomized 518 patients into 2 groups: a hippocampal avoidance (HA)-WBRT plus memantine group and a WBRT plus memantine group; in both groups, 30 Gy was delivered in 10 fractions. The risk of cognitive deterioration was significantly lower in the group that received HA-WBRT plus memantine (adjusted hazard ratio, 0.74; 95% confidence interval [CI], 0.58–0.95; $p = .02$), without a significant difference in OS, intracranial PFS, or toxicity[22]. Despite this evidence, this strategy has not yet been adopted as a standard of care for WBRT (Figure 3).

Stereotactic Radiosurgery

Multiple studies have demonstrated the efficacy and utility of SRS as a single modality or in conjunction with surgery. Thus, SRS is currently the preferred therapeutic option for patients with a limited number of BM (up to 3–4) not requiring surgical resection[23–25] (Table 4). There is also evidence to support the use of SRS for treating a higher number of lesions. A prospective study from Japan that included 1194 patients treated with SRS alone for 1–10 BM demonstrated equivalent median overall survival among patients treated for 2–4 lesions compared to patients treated for 5–10[26]. Notably, a phase III study is currently underway that will compare overall survival and cognitive toxicity following SRS versus WBRT for patients with 5–15 lesions (CE7, Canadian Clinical Trials Group). As established in the RTOG 90-05 protocol[27], SRS treatment dose is inversely proportional to the size of a metastatic lesion target. Hence, the suggested single-fraction dose is 24 Gy for tumors < 20 mm, 18 Gy for tumors 21–30 mm, and 15 Gy for tumors 31–40 mm. This dose reduction reflects the fact that larger tumors are at higher risk for toxicity and radionecrosis. An analysis of lesions treated according to these guidelines revealed that tumor control at 1 year was 85% in lesions treated with 24 Gy, 49% in those treated with 18 Gy, and 45% in those that received 15 Gy[28]. These results suggest the limitations of single-fraction SRS alone for treating larger lesions. However, for smaller lesions, while higher doses can be safely used, it is not clear that they are necessary. A recent retrospective study from our group did not show a difference in local failure and radionecrosis in lesions ≤ 1 cm diameter treated with a dose of 15 Gy or 21 Gy[29]. In lesions greater than 1cm but less than 2 cm diameter, the incidence of local failures was significantly higher in those treated with a dose of 15 Gy.

For larger BM, fractionated radiosurgery treatment schemes may provide equivalent or improved local control with a lower rate of toxicity[23]. Multiple fractionation schedules have been

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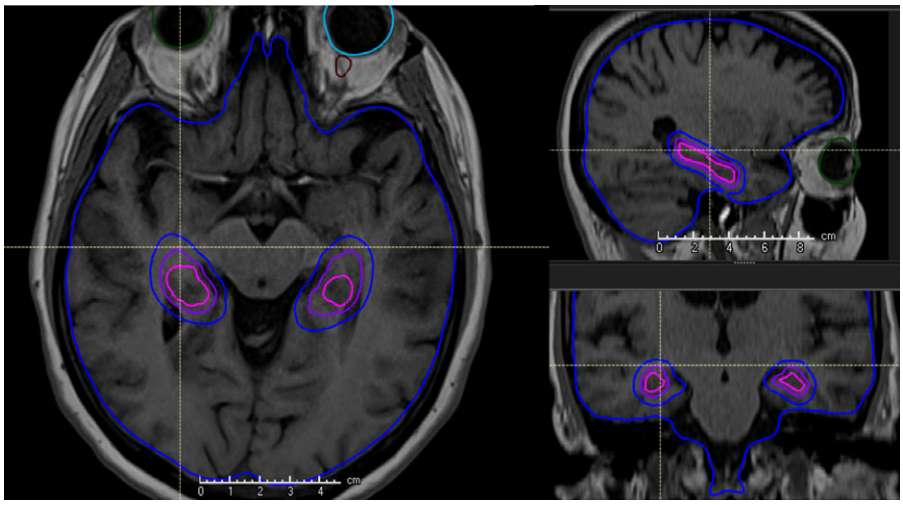

Figure 3: *HA-WBRT treatment volumes.*

Table 4: Current recommendations on the role of radiation therapy in the management of multiple BM[66]

Level 1	In patients with 2–3 BM not amenable to surgery, the addition of stereotactic radiosurgery (SRS) to whole-brain radiation therapy (WBRT) is not recommended to improve survival beyond that obtained with WBRT alone.
Level 2	It is recommended that WBRT can be added to SRS to improve local and distant control keeping in mind the potential for worsened neurocognitive outcomes and that there is unlikely to be a significant impact on overall survival.

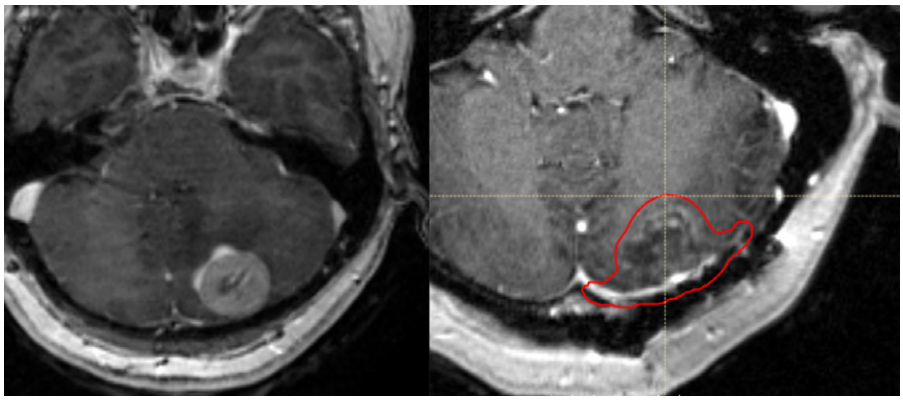

Figure 4: *Pre- and postsurgical MRI of a left cerebellar metastatic lesion. The red line represents the treatment volume of the cavity.*

reported and there is no standard at this time. With regard to RN, multiple studies have demonstrated that a hypofractionated schedule as opposed to single-fraction treatment appears to lower the risk of RN for larger lesions[30,31].

Previous clinical trials have demonstrated that surgical tumor resection alone provides insufficient local control for BM[32]. While the addition of WBRT improves local and distant control, it is associated with cognitive toxicity[33]. Alternatively, single-fraction SRS can be used postoperatively to sterilize the surgical cavity (Figure 4) and increase local control, as shown in the phase 3 trial (NCCTG N107C/CEC·3). This trial randomized 194 patients into 2 groups for postoperative radiation therapy (WBRT vs. SRS), and demonstrated no significant difference in OS between study groups. However, the surgery plus SRS group experienced significantly longer cognitive deterioration-free survival compared to patients assigned to postoperative WBRT (3.7 months vs. 3 months, respectively)[32]. Similarly, fractionated radiosurgery schemes targeting surgical cavities have been shown to provide excellent local control for larger surgical cavities (> 14 cm^3 or >3 cm)[34]. Consensus guidelines for contouring surgical cavities were recently published and describe that the target should include the surgical tract, dura and, in some cases, any adjacent venous sinus. If the tumor was not in contact with dura, CTV should include a 1–5 mm margin of dura along the bone flap. If the tumor was in contact with the dura preoperatively, the CTV should include a 5–10 mm margin of dura along

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Table 5: Radiotherapy (RT) recommendations

Treatment modalities	Prescription dose	Comments
WBRT	Dose 30 Gy in 10 fractions or 20 Gy in 5 fractions	WBRT for patients with > 5–10 lesions.
HA-WBRT plus memantine	30 Gy in 10 fractions	Preferably for patients with good performance status and without hippocampal lesions.
SRS	Single-fraction SRS dosing based on lesion size	For single-fraction radiosurgery, the preferred maximum lesion volume is 4 cc = 2 cm[28]. However, it might still be used for lesions larger than 4 cc at the discretion of the radiation therapy center and radiation oncologist.
Fractionated SRS	3–5 fraction SRS schemes	Consider fractionated SRS schemes in tumors or cavities larger than 4 cc = 2 cm[67] at the discretion of the radiation therapy center and radiation oncologist.
SRS to cavity	Adjuvant treatment modalitySRS dosing based on cavity size 3–5 fraction SRS schemes	Target should include the cavity and surgical tract.If the tumor is not in contact with dura, the CTV should include a margin of 1–5 mm of dura along the bone flap.If the tumor is in contact with the dura preoperatively, CTV should include a 5–10 mm margin along the bone flap[68].

HA-WBRT=hippocampal avoidance WBRT; IMRT=intensity-modulated radiation therapy; SRS=stereotactic radiosurgery; MRI=magnetic resonance imaging; WBRT=whole-brain radiotherapy.

the bone flap. Finally, if the tumor was in contact with a venous sinus preoperatively, a 1–5 mm margin should be added along the sinus. Current radiation therapy recommendations are summarized in Table 5.

Tumor Treatment Fields

The role of TTF in CNS metastatic disease is unclear. Although the electromagnetic therapy has shown efficacy in the treatment of recurrent glioblastoma[35] and newly diagnosed glioblastoma[36] (receiving FDA approval in 2011 and 2015, respectively), no such evidence currently exists in the treatment of BM. The prospective randomized phase III METIS trial (NCT02831959) is currently recruiting comparing the efficacy, safety, and neurocognitive outcomes of TTF in advanced NSCLC patients (1–10 BM) following SRS compared to the best standard of care[37].

Radiation Necrosis

A subset of patients undergoing high-dose radiosurgery treatment of BM may develop symptomatic edema secondary to radiation necrosis (RN) in the months following treatment. Typically, RN will respond to a short course of oral corticosteroid therapy. In refractory cases, alternate strategies to treat RN must be considered. Among these is the use of bevacizumab, typically at a dose of 7.5 mg/kg for 2 weeks with a median total of four cycles[38]. Hyperbaric oxygen therapy (HBOT) has also demonstrated efficacy in treating steroid-refractory RN in a subset of BM patients[39]. Alternately, up-front HBOT in combination with RT has been explored as a salvage therapeutic strategy on the premise delivering high concentrations of oxygen and reversing the effect of radiation-induced hypoxic microenvironment. Response rates, quality of life, and the incidence of adverse reactions in BM patients treated with HBOT plus RT were significantly improved compared with RT alone[40]. However, further clinical investigations are required for this technique. LITT represents one minimally invasive surgical strategy with demonstrated efficacy in treating refractory RN. In addition, a small subset of patients (under 1% in our patient population) may require open surgical resection to treat SRS-induced RN (unpublished data).

Targeted Therapy

Since Judah Folkman's seminal paper in 1971 examining the efficacy of vascular endothelial growth factor (VEGF) inhibition for targeting the angiogenic microenvironment[41], the exponential growth of molecular therapeutics has led to significant advancements in the oncology field. HER2/ER/PR-targeted therapies are now central to breast cancer treatment and confer a significant survival benefit to patients. Mutations in epidermal growth factor receptor (EGFR), Kirsten Rat Sarcoma Virus, and Anaplastic Lymphoma Kinase rearrangements have been identified in lung cancer while the $BRAF^{V600E}$ mutation has been successfully targeted in metastatic melanoma leading to improved survival. Specifically targeting such oncogenic signaling pathways represents an attractive therapeutic strategy.

Despite several agents such as tyrosine kinase inhibitors (TKIs)/monoclonal antibodies demonstrating efficacy against primary disease, the blood–brain barrier remains a significant obstacle for the delivery of agents into the CNS. Strategies to circumvent this limitation currently being studied include focussed ultrasound leading to the disruption of the BBB thereby facilitating the delivery of systemic agents.

NSCLC/small-cell lung cancer demonstrates the highest incidence of BM[2]. EGFR mutations occur in 15%–35% of primary NSCLC, with a higher proportion identified in an Asian nonsmoking female population[42]. Gefintib and erlotinib (first-generation EGFR TKIs) have demonstrated modest CNS response rates and PFS benefits in the setting of NSCLC BM[43]. In 2018, the phase III FLAURA trial compared osimertinib, a third-generation TKI, to a standard of care first-generation inhibitors in patients lung BM, harboring exon 19 deletion or exon 21 (L858R) EGFR mutation. The median duration of response was 17.2 months with osimertinib versus 8.5 months with standard EGFR TKIs with a reduction in grade 3 adverse reactions with osimertinib[44]. In addition, improved PFS, objective response rate (ORR), CNS response, and reduced LMD using recent third-generation EGFR TKIs, as seen in the phase I BLOOM trial[45], have led to osimertinib receiving a National Comprehensive Cancer Network (NCCN) endorsement as a first-line agent for EGFR-mutant NSCLC, particularly in patients with BM.

Among breast cancer patients, human epidermal growth factor receptor-2 (HER2)-positive breast cancer is found in

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approximately 15% of patients and plays a pivotal role in oncogenic activation of downstream signaling pathways promoting cell proliferation, tumor growth, and creating a pro-invasive microenvironment. HER2-positive breast cancer has a high incidence of BM (with up to 44% of breast cancer BM being HER2 positive[46]), compared to HER2-negetive breast cancers, making HER2 an attractive therapeutic target for breast cancer BM. Lapatinib is a TKI that targets both HER2 and EGFR simultaneously. The phase II LANDSCAPE trial examining the combination of lapatinib and capecitabine in RT-treated and RT-naïve patients reported a 20% and 66% CNS response rate, respectively[47]. Other TKIs targeting HER2 such as tucatinib and ertabinib have also shown promising results in the treatment of HER2-positive breast cancer BM[48].

Direct HER2-positive monoclonal antibodies (trastuzumab) have significantly improved OS in HER2-positive breast cancer patients. Phase III trials have illustrated the synergistic effects of combining lapatinib and trastuzumab with an improvement in OS and PFS, in advanced metastatic HER2-positve breast cancer[48,49].

Notwithstanding the fact that hormone receptor-positive breast cancer patients are less likely to develop BM[50] and endocrine therapies such as tamoxifen are efficacious, a subset of patients (20%) demonstrate *de novo* resistance to hormonal therapy and over 50% will acquire resistance by the time intracranial metastases develop[51]. Consequently, abemaciclib and other CDK4/6 inhibitors, which have shown promising early results[52], are currently in clinical trials in hormonal-positive-resistant BM (NCT02896335, NCT02308020). In addition, PI3k/mTOR inhibitors are being examined in trials as part of a combination with CDK4/6 inhibitors (NCT03006172, NCT02684032, NCT02389842, NCT02732119, NCT02871791, and NCT02599714).

Triple-negative breast cancer accounts for 10%–15% of all breast carcinomas and is associated with a poor outcome due to the high rate of BM[53]. The lack of targetable receptors makes treatment options limited and often leads to palliative chemotherapeutic approaches.

Bevacizumab lost its FDA approval for the treatment for metastatic breast cancer in 2010 over safety concerns outweighing the possible PFS benefits[54]. In recent years, bevacizumab showed an improved response rate in combination with carboplatin[55] as well as in combination with etoposide and cisplatin in patients progressing post-WBRT[56], although the response rate was not associated with OS/PFS improvements as shown in the ARTemis trial[57].

Novel therapies currently being examined included poly (ADP-ribose) polymerase 1 (PARP1) inhibition, targeting characteristic BRCA1-deficient cells (NCT02595905) as well as nanoparticles, which have also shown promise in clinical[58] and preclinical settings[59].

Metastatic melanoma has the highest risk of CNS dissemination, with approximately 50% of patients developing BM over the course of their disease[60]. *BRAF* mutations were found be to present in half of all melanoma BM, of which 90% were identified as the $BRAF^{V600E}$ variant. The addition of agents targeting this variant such as vemurafenib and dabrafenib have led to the improved median OS of 2 years compared to approximately 6–9 months in historical controls[61]. Consequently, these agents are FDA approved for the treatment of melanoma BM.

Future Trial Design

Historically, patients with BM were often excluded from clinical trials due to the high morbidity and mortality associated with the CNS burden. In 2018, the RANO-BM working group published recommendations on the design of clinical trials examining both local[62] and systemic therapies[63] in patients with BM from solid tumors. Although the identification of clear objectives and endpoints is crucial to the trial design of novel therapeutic strategies, the correct selection of appropriate endpoints tailored for the specific trial is of utmost importance. Overall survival, neurocognitive function, and quality of life analyses are recommended outcomes for late-phase trials of local therapies while local control/brain control should be utilized in early phase trials. Systemic therapies and their respective CNS activity (minimal activity/activity/unknown activity) determine if a patient should be included/excluded in a systemic clinical trial, as follows:

Scenario A: agents that have minimal or no activity within the brain → include patients with stable CNS disease, exclude patients with active CNS disease.
Scenario B: agents with activity within the brain → include patients with stable and active CNS disease.
Scenario C: unknown activity within the brain → incorporate BM patients early in drug design allowing investigators to select scenarios A or B.

As our fundamental understanding of tumor biology increases, the effects of novel therapeutic targets can be mechanistically interrogated by improved translational studies as well as including bucket trials for targeted therapies alone and in combination trials with SRS.

Immunomodulation

Immune checkpoints represent normal innate mechanisms preventing our immune system from attacking normal cells within the body. Many cancers demonstrate an ability to hijack these checkpoint mechanisms. For some cancers, the use of immune checkpoint inhibitors interferes with such inhibitory interactions between cancer cells and immune effector cells, allowing the immune system to mount an appropriate response against the tumor. Monoclonal antibody targeting CTLA-4 (ipilimumab) and PD-1 (nivolumab, pembrolizumab) have demonstrated promising antitumor effects in metastatic lung, melanoma, and renal cell carcinomas, and are subject to many ongoing clinical trials examining their effectiveness in treating brain metastatic disease[64].

Conclusion

With the increasing number of treatment options for BM patients come increasing complexity in determining the most appropriate strategy for each individual BM patient. In this era of personalized medicine for BM patients, the role of the multidisciplinary team is vital to provide the optimum treatment plan in collaboration with the patient. The combined expertise from neurosurgical oncology, radiation oncology, medical oncology, radiation physics, nursing, neuropsychology, and other allied

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health subspecialties is essential in this era of expanding therapeutic modalities among which to choose in managing this patient population.

Conflict of Interest

None of the authors have any conflicts of interest to disclose.

Statement of Authorship

PK and PJOH formulated the idea of this project. PJOH, EG, AK, NM acquired the data collection and performed the literature review. PJOH, EG, SA, DBS drafted the manuscript and completed revisions of the manuscript. SK, PK, GZ, BAM, NL, TC, MB edited and made corrections to the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

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