Management of complications from brain metastasis treatment: a narrative review

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Objective: To describe the range of potential side effects associated with modern brain metastasis treatment and provide evidenced-based guidance on the effective management of these side effects.

Background: Brain metastases are the most commonly diagnosed malignant intracranial tumor and have historically been associated with very poor prognosis. The standard treatment for brain metastases until the 1990s was whole-brain radiation therapy (WBRT) alone. Since then, however, numerous advances have established the role of neurosurgical resection, stereotactic radiosurgery (SRS), targeted systemic therapy, and immunotherapy in the multidisciplinary management of brain metastases and led to improvements in intracranial control, survival, and neurocognitive preservation among patients with brain metastases. As a result, however, brain metastasis treatment is associated with a wider range of potential side effects than ever before, and clinicians are tasked with the challenge of effectively managing these side effects without compromising cancer outcomes.

Methods: We performed a narrative review of peer-reviewed articles related to the management of side effects from multidisciplinary brain metastasis treatment and synthesized the data in the context of our clinical experience and practice.

Conclusions: In this review, we summarize the major complications from intracranial radiotherapy, neurosurgical resection, and brain metastasis directed systemic therapy with corresponding evidenced-based, modern management principles to guide the practicing oncologist.

Keywords: Brain metastasis; treatment; complication; toxicity; management

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Introduction

Brain metastases represent the most commonly diagnosed malignant intracranial tumor (1), occurring in up to half of all patients with cancer (2). The incidence of brain metastases is increasing because of improved imaging modalities allowing for more accurate detection of brain metastases, better awareness among oncologists leading to more frequent surveillance imaging, and improved cancer therapies which have led to longer periods of time during which brain metastases may develop (3,4). In addition, improved systemic therapies used in the metastatic setting may not achieve the same effects in the central nervous system (CNS) due to the blood-brain barrier (5).

Historically, brain metastases were near-uniformly associated with poor outcomes. The standard treatment for brain metastases until the 1990s was whole-brain radiation

therapy (WBRT) alone, which was associated with a median survival of 3–6 months (6). Since then, however, a plethora of research and treatment advances has fundamentally transformed the landscape of brain metastasis management. Level I data showed the addition of surgical resection to WBRT for patients with a single brain metastasis improved overall survival (OS), and the addition of WBRT to surgical resection improved local and distant brain control and neurologic death, establishing the role of selective surgical resection in patients with brain metastases (6,7). Multiple trials compared stereotactic radiosurgery (SRS) versus SRS + WBRT for patients with limited brain metastases and found similar OS but better neurocognitive preservation and health-related quality-of-life (QOL) with SRS alone (8-11). Two trials examined the role of post-operative SRS which found improved local control (LC) compared to observation (12) and better QOL compared to WBRT (13).

More recently, targeted systemic agents and immunotherapy have demonstrated clinically meaningful intracranial activity in patients with certain cancer histologies (2,14-17). In some carefully selected patients with brain metastases, systemic agents can be used as a frontline treatment option. Certain novel immunotherapy agents are postulated to have a synergistic effect with radiotherapy and may offer an intracranial control and OS benefit when combined with SRS (18,19).

As patients survive longer following brain metastasis treatment, however, late neurologic complications from brain metastasis directed therapy are also becoming more likely. Furthermore, due to the number of treatment options now available, clinicians are faced with a wide range of potential treatment-related complications in patients with brain metastases from radiotherapy, surgical resection, and systemic therapy and managing these complications appropriately is increasingly complex. In this review, we aim to describe the major potential complications from brain metastasis treatment with an emphasis on modern, evidenced-based clinical management. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-90/rc).

Complications after intracranial radiotherapy

The definition of CNS toxicity is variably categorized into acute versus late or acute, early-delayed, and late by different sources (20). The Radiation Therapy Oncology Group (RTOG) defines acute CNS toxicities as those occurring within 90 days of radiation treatment and late CNS toxicities as those occurring after 90 days of treatment (21). From a radiobiological standpoint, distinct histopathological types of injury have been described in the acute, early-delayed, and late timepoints. Acute injury has been described as occurring within either 30 days after treatment, early-delayed injury as occurring 30 days to 6 months after treatment, and late injury as occurring greater than 6 months after treatment (22,23). For the purposes of this practical review, we will follow the RTOG definition of acute and late CNS toxicity.

Acute complications

Fatigue

Fatigue is common during and after cranial radiotherapy (*Table 1*). In patients receiving WBRT, up to 95% of all patients experience excess fatigue and prospective studies have identified deterioration in validated fatigue scores from baseline to 1 month after WBRT (24,25). However, fatigue is common with brain metastases in general and may be difficult to separate from treatment-related fatigue, as demonstrated in the QUARTZ trial, where 40% of patients who received WBRT *vs.* 44% of patients who received supportive care only reported tiredness (26). On the other hand, fatigue may be less common following SRS, reported by only 28% of patients compared to 95% of patients who underwent WBRT in one series (24).

The primary management of acute fatigue in patients undergoing brain radiotherapy is supportive care, including appropriate steroid taper, advising patients to take steroids earlier in the day (second dose no later than mid-afternoon) to avoid sleep disturbance, and other good sleep hygiene measures. Numerous studies demonstrate that aerobic and resistance exercise can mitigate cancer-related fatigue to an extent, and despite lack of data specifically in patients undergoing brain radiotherapy, we agree with the American Society of Clinical Oncology (ASCO) recommendations for 150 minutes of moderate aerobic exercise (including fast walking, cycling, or swimming) per week with an additional 2–3 sessions of resistance exercise (such as weightlifting), unless contraindicated for medical reasons (27-31). Psychostimulants are not indicated for acute fatigue.

Alopecia and dermatitis

Complete alopecia is common following WBRT and may be acute or chronic, typically beginning during WBRT or up to

Table 1 Radiotherapy complications of brain metastasis treatment and management options

Complication	Management options
Acute toxicity	
Fatigue	❖ Appropriate steroid taper and administration instructions (second dose no later than mid-afternoon) ❖ Sleep hygiene counseling ❖ Moderate aerobic/resistance exercise
Dermatitis	❖ Grade 1–2 without moist desquamation ◆ Gentle hydrophilic moisturizer ❖ Grade 2–3 with moist desquamation ◆ Topical silver sulfadiazine ± foam absorbent dressings
Alopecia	❖ Scalp-sparing radiation techniques ❖ Topical minoxidil 5% BID ❖ Referral for hair prosthesis
Headaches	❖ Mild ◆ OTC analgesics (i.e., acetaminophen) PRN ❖ Moderate ◆ Systemic corticosteroids (dexamethasone 2–4 mg PO BID) ❖ Severe ◆ Emergency evaluation ◆ Systemic corticosteroids (dexamethasone 10 mg IV followed by 4 mg q6 hours)
Nausea/vomiting	❖ Without other signs/symptoms of elevated ICP ◆ Ondansetron 8 mg q8 hours PRN ❖ With other signs/symptoms of elevated ICP ◆ Systemic corticosteroids with dosing based on severity of presentation ❖ Routine nausea/vomiting prophylaxis during RT should be avoided, but if nausea develops immediately after RT treatment, ondansetron can be given prophylactically 1–2 hours prior to subsequent treatments
Late toxicity	
Chronic fatigue	❖ Psychostimulants (including methylphenidate 10 mg BID, modafinil 200 mg QD) can be considered for chronic cancer-related fatigue
Pseudoprogression/radiation necrosis	❖ Clinically directed supportive care and symptom management ❖ Advanced imaging techniques (perfusion MRI, diffusion-weighted MRI, MRI spectroscopy, PET) if concern for tumor recurrence ❖ Close observation with follow up imaging ❖ If symptomatic, systemic corticosteroids with dose based on severity of symptoms and consideration of PPI and infectious prophylaxis as indicated with gradual steroid taper over >4 weeks ❖ If progressive symptoms after corticosteroids or inability to tolerate steroid taper and no medical contraindications, consider IV bevacizumab (either 7.5 mg/kg q3 weeks or 5 mg/kg q2 weeks for up to 4 cycles) ❖ Consider surgical resection for medically refractory or significant diagnostic uncertainty ❖ Insufficient evidence to recommend LITT, HBOT, therapeutic anticoagulation, and/or antioxidant therapy
Neurocognitive preservation	❖ Memantine during and for 6 months after WBRT (maintenance dose of 10 mg PO BID) ❖ SRS with omission of WBRT ❖ HA-IMRT techniques

Table 1 (*continued*)

Table 1 (*continued*)

Complication	Management options
Neurocognitive decline	❖ Psychostimulants (including methylphenidate 10 mg BID, modafinil 200 mg QD) for chronic cancer-related fatigue ❖ Donepezil ≥6 months after cranial irradiation for memory, motor speed, dexterity (maintenance dose of 10 mg QD)
Optic neuropathy	❖ In absence of other effective treatment options, consider HBOT ideally initiated within 72 hours of symptom onset or IV bevacizumab ± dexamethasone (dosing varies) ❖ Insufficient evidence to recommend corticosteroids, therapeutic anticoagulation, or ACE inhibitor therapy ❖ Close clinical and imaging follow up of contralateral optic apparatus
Neuroendocrine dysfunction	❖ Screening for hormone deficiencies triggered by symptoms or beginning 1 year after WBRT

BID, twice daily; OTC, over-the-counter; PRN, as needed; IV, intravenous; ICP, intracranial pressure; RT, radiotherapy; QD, once daily; MRI, magnetic resonance imaging; PET, positron emission tomography; PPI, proton pump inhibitor; LITT, laser interstitial thermal therapy; HBOT, hyperbaric oxygen therapy; WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; HA-IMRT, Hippocampal avoidance intensity-modulated radiation therapy; ACE, angiotensin converting enzyme.

1–2 weeks afterwards. Risk factors for alopecia include older age, radiation dose, volume, and receipt of chemotherapy. In most patients, hair regrowth occurs within 2–4 months after completion of radiation (32). However, in others, chronic alopecia (incomplete hair regrowth >6 months after treatment) may occur. Only patients who experience acute alopecia can develop chronic radiation-induced alopecia (33). In our experience, alopecia is uncommon following SRS, although patchy alopecia is possible with higher doses targeted to peripheral lesions (34).

In patients experiencing chronic radiation alopecia, one study found that topical minoxidil 5% BID improved hair regrowth in 82% of patients and given its favorable safety profile, is a reasonable option for interested patients (35). Patients with significant chronic alopecia can also be referred for hair prosthesis. Scalp-sparing radiation delivery techniques utilizing intensity-modulated radiation therapy (IMRT) have been developed which appear to both reduce the severity of acute alopecia and significantly reduce the likelihood of chronic alopecia (33,36,37). It should be noted that despite a reduction in scalp radiation dose with IMRT, most patients will still experience acute alopecia with >50% hair loss and this technique should therefore be reserved for patients with an expected survival of >4–6 months or for those receiving IMRT for other indications (i.e., hippocampal avoidance).

Radiation dermatitis is highly associated with total radiation dose to the skin. Therefore, while erythema and dry desquamation of the scalp are possible with the range of radiation doses typically used for WBRT (20–37.5 Gy), moist desquamation is unlikely to occur (38). The management of radiation dermatitis of the scalp following cranial radiation is similar to other areas of the body. Patients should be counseled to use sunscreen, avoid sun exposure, and keep the area clean and dry. We typically use a gentle hydrophilic moisturizer (i.e., Aquaphor, Beiersdorf Inc., Wilton, CT, USA; Lubriderm, Johnson & Johnson, New Brunswick, NJ, USA) for grade 1 dermatitis and topical silver sulfadiazine with or without foam absorbent dressings (i.e., Mepilex, Mölnlycke, Gothenburg, Sweden) for grade 2 dermatitis with moist desquamation. Topical corticosteroids, such as hydrocortisone 1% applied once to twice daily, can be used to reduce irritation and itching.

Headaches, vasogenic edema and nausea

Headaches are a common complaint during and after intracranial radiation therapy, including both WBRT and SRS. The pathogenesis is thought to be due to transiently increased vasogenic edema from an inflammatory response to tumor. In general, if headaches are mild, transient, and not associated with any new or progressive neurologic deficits, they can be managed conservatively with over-the-counter (OTC) analgesics such as acetaminophen.

On the other hand, more severe, persistent headaches and those associated with nausea, vomiting, and new or progressive neurologic deficits should prompt concern for vasogenic edema. Edema leading to increased intracranial

pressure (ICP) can be a medical emergency and all patients should be evaluated for signs of elevated ICP and impending herniation, including but not limited to lethargy, nausea/vomiting, severe headache, focal neurologic deficits, cranial nerve palsies, papilledema, and respiratory depression. In the outpatient setting, the mainstay of treatment for vasogenic edema are systemic corticosteroids such as dexamethasone.

The optimal starting dose of dexamethasone depends on the severity of symptoms and underlying vasogenic edema (39,40). In the emergency setting, a loading dose of 10 mg IV followed by 4 mg every 6 hours is commonly used. However, in the outpatient setting, a reasonable starting dose of dexamethasone is 2 to 4 mg PO BID. Clinical improvement typically occurs within 1–3 days, although improvement in vasogenic edema on imaging may lag by 1–2 weeks (41-43). The optimal timing for steroid taper is variable and depends on the status of the underlying condition but should be considered after 7 days of therapy and performed slowly over the course of several weeks. For patients undergoing radiotherapy, we typically continue steroids at least until the end of treatment. Reductions in dose of 50% should occur no more frequently than every 3–4 days (40). Patients should be instructed to return to their previous dose if they experience rebound symptoms such as worsening headache or recurrent neurologic deficits.

In patients presenting with nausea temporally related to radiation therapy without other signs or symptoms, treatment with a 5-HT3 antagonist such as ondansetron, prescribed 8 mg every 8 hours as needed is reasonable. Cranial radiation is categorized as "low risk" for radiotherapy-induced nausea and vomiting and routine anti-emetic prophylaxis should be avoided (44-46). If other signs or symptoms are present that may be explained by underlying vasogenic edema, corticosteroids with or without a 5-HT3 antagonist should be used as a first-line option.

Pseudoprogression

Pseudoprogression describes an imaging finding on magnetic resonance imaging (MRI) which cannot reliably be differentiated from tumor progression on conventional MRI, typically characterized by increasing size, T1-weighted contrast enhancement, and peritumoral vasogenic edema of a treated tumor (47). There may be overlap between pseudoprogression and radiation necrosis, which is a pathologic diagnosis, but the two are distinct entities despite sometimes being used interchangeably in medical literature (48). Pseudoprogression is a radiation dose-dependent phenomenon, common following SRS but rare with WBRT alone, and owing to heterogeneous cohorts and definitions, has a reported incidence ranging from 9–31% (49). Typically, pseudoprogression occurs within 3 months of radiation treatment whereas radiation necrosis can occur months to years afterwards. Numerous studies have found MRI perfusion imaging to be helpful in differentiating pseudoprogression from tumor recurrence (50-52). By definition, most cases of pseudoprogression resolve spontaneously over 2–3 months and if suspected, can be closely monitored with short interval follow-up MRI. Symptoms from increased vasogenic edema can be managed with steroid therapy as previously described. Progression of imaging changes on subsequent imaging should prompt evaluation for radiation necrosis and/or tumor recurrence.

Late complications

Radiation necrosis

Radiation necrosis refers to necrosis of normal brain tissue secondary to radiation treatment. About 80% of cases occur within 3 years after radiation treatment but in rare cases have been reported up to a decade afterwards (53,54). The clinical presentation of radiation necrosis is variable and depends on the anatomic location affected. In general, radiation necrosis can be asymptomatic, cause global symptoms such as headache, nausea, or vomiting from increased ICP, seizures or focal neurologic deficits that localize to the region of radiation necrosis (54). In most cases, tissue is not obtained and therefore imaging and clinical correlates are used to inform diagnosis. The incidence of symptomatic radiation necrosis following SRS ranges from 4–20% and is commonly estimated at 10% overall (55-58). Conversely, the risk of radiation necrosis is minimal (<1%) following WBRT alone and standard dosing regimens.

The imaging diagnosis of radiation necrosis is challenging, and biopsy or resection is required for definitive diagnosis. Some authors advocate for the use of terms such as adverse radiation effect (ARE) and treatment-related imaging changes (TRIC) as broader terms to capture both reversible and irreversible radiation changes (19,57). Advanced imaging techniques, including perfusion MRI, diffusion-weighted MRI, MRI spectroscopy, and positron emission tomography (PET) can be useful as diagnostic

adjuncts (59-65). The objectives in the management of radiation necrosis are to palliate symptoms and prevent progressive neurologic deficits. In asymptomatic patients after initial diagnosis of radiation necrosis, close observation with a repeat MRI in 6–8 weeks followed by spacing to every 2–3 months after lesion stability or regression is reasonable as there is no evidence that treatment at this stage will alter disease course. In many patients, the imaging changes will stabilize and improve over the course of weeks to months.

In patients with symptomatic radiation necrosis, systemic corticosteroids such as dexamethasone are the first-line treatment. For patients with mild to moderate symptoms, a starting dose of 2 to 4 mg dexamethasone PO BID is reasonable (39,40). Patients with severe symptoms should be considered for emergent evaluation and potential inpatient management. Symptom improvement occurs rapidly after initiation of steroids but imaging changes, such as improvement in perilesional vasogenic edema, can lag for several weeks. As such, we typically wait at least 4 weeks prior to obtaining repeat imaging. Steroid dose should be maintained for at least 1–2 weeks, and then gradually tapered afterwards over the course of several weeks. Most patients will not require any additional therapy, but for those with either progressive symptoms or inability to tolerate a steroid taper, more aggressive treatments may be considered.

Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). It has been studied for treatment of radiation necrosis in two randomized controlled trials (66,67). In both trials, high rates of radiographic response (100% and 66%) and neurologic symptom improvement (100% and 62%) were observed, which were significantly better than with corticosteroid therapy alone. A dose of either 7.5 mg/kg every 3 weeks or 5 mg/kg every 2 weeks for up to 4 cycles, lower than those typically used in anti-cancer regimens, can be used. Imaging response can be detected on MRI as early as after 2 cycles. Follow-up MRI can be obtained 8–12 weeks after initiation of therapy and steroid taper can begin around 72 hours after cycle #1. Retreatment with bevacizumab is feasible and appears efficacious but is not well-studied. Rates of serious adverse events with bevacizumab were low but included pulmonary embolism, sagittal sinus thrombus, and ischemic stroke. The studies excluded patients with active or high risk of bleeding, recent intracranial hemorrhage or major surgery/trauma, significant cardiovascular disease, abdominal fistula or perforation, or poorly controlled hypertension.

Surgical resection may be necessary for cases of refractory radiation necrosis with significant symptoms, contraindication to medical therapy, or uncertainty as to whether a lesion represents radiation necrosis or tumor recurrence. Surgery can offer rapid decompression leading to reduced steroid requirement but is also associated with significant morbidity as represented by one contemporary series where overall morbidity from surgery was 54% (68). The authors advocated for the use of surgery for radiation necrosis only in cases where all medical therapy had failed. In recent years, laser interstitial thermal therapy (LITT) has also been used successfully to manage refractory radiation necrosis, and offers a minimally invasive alternative guided by MRI. Retrospective data suggests local outcomes comparable to craniotomy albeit with inferior symptom relief (69).

Hyperbaric oxygen therapy (HBOT) has only been studied in small, retrospective series (70-72). In one cohort of 10 patients who underwent HBOT, all either had stabilization of improvement of symptoms and/or imaging findings without severe toxicities (70). Patients were treated at 2.0–2.4 atmospheres for 20–30 sessions lasting 90–120 minutes each. HBOT should not be used in patients with pneumothorax or at high risk for pneumothorax (i.e., chronic obstructive pulmonary disease, lung blebs/bullae, recent thoracic surgery). Its adoption has been limited due to the need for expensive, specialized equipment and the significant time commitment. Anticoagulants such as warfarin and heparin have also been studied in small retrospective series (73,74). The larger included 8 patients with radiation necrosis, of whom 5 symptomatically improved after anticoagulation for a total of 3–6 months (73). One small, retrospective study of 8 patients with radiation necrosis found improvement in edema volume after treatment with vitamin E and pentoxifylline (75). Overall, the evidence to support HBOT, anticoagulation, and antioxidant therapy for radiation necrosis is weak and these therapies cannot be recommended for routine use.

Neurocognitive decline

Neurocognitive decline is common in patients with brain metastases, both due to tumor progression as well as from brain metastasis therapy. As many as 90% of patients with brain metastases will have one or more impaired neurocognitive functions at baseline (76). The management of neurocognitive decline has primarily been directed at

prevention rather than treatment. The use of fraction sizes >3 Gy with WBRT appeared to lead to higher risk for developing severe dementia (77). Two randomized controlled trials have found better neurocognitive preservation with SRS alone compared to SRS with WBRT with similar OS in patients with limited (1-3) brain metastases (8,9). Later reports have validated the use of SRS alone in patients with up to 15 brain metastases (78,79).

Hippocampal avoidance IMRT (HA-IMRT) has also been demonstrated to have better neurocognitive preservation in a randomized phase III trial, although patients with leptomeningeal disease or metastases within 5 mm of either hippocampus were excluded (80). Due to the time and resource-intensive nature of the treatments, both SRS and HA-IMRT are best suited for patients who are either asymptomatic or only mildly symptomatic from brain metastases and with good performance status. Another scenario where HA-IMRT may be ideal is for prophylactic cranial irradiation (PCI) in small cell lung cancer (SCLC). Two recent randomized trials of HA-IMRT for PCI in SCLC with a dose of 25 Gy in 10 fractions found divergent results with one study finding improved cognitive preservation based on delayed free recall (81), and the other finding no improvement in cognitive preservation based on verbal learning compared to standard WBRT (82). As there was no difference in brain failure, HA-IMRT should be considered for this group of favorable patients without clinically apparent brain metastases.

The use of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine during and for 6 months after WBRT improved preservation of cognitive function, executive function, processing speed, and delayed recognition although its primary endpoint of delayed recall did not reach statistical significance (83). Memantine was started at 5 mg AM for week 1, 5 mg BID for week 2, 10 mg AM and 5 mg PM for week 3, and 10 mg BID for week 4 and maintenance. Due to its favorable side effect profile, memantine should be initiated in most patients receiving WBRT. A randomized trial failed to show benefit of prophylactic methylphenidate on fatigue scores in patients undergoing radiotherapy for primary or metastatic brain cancers and methylphenidate should not be administered prophylactically for this indication (84).

Data regarding treatments for patients who have already developed significant neurocognitive deficits are scarce. A randomized trial comparing a structured multidisciplinary intervention to standard care improved overall patient QOL but failed to show improvement in fatigue in patients receiving radiotherapy (85,86). Psychostimulants such as methylphenidate and modafinil have been successfully used for cancer-related fatigue (87-91). A small, randomized study of methylphenidate (immediate release, 10 mg BID) and modafinil (200 mg qAM) given for 4 weeks in patients with primary brain tumors found improvements in processing speed, executive function, and patient-reported fatigue, mood, and QOL (92). The acetylcholinesterase inhibitor donepezil was studied in a phase III randomized trial among patients ≥6 months after partial or whole brain radiation, which failed to find a difference in its primary composite endpoint, but did result in improved memory, motor speed, and dexterity (93). The dose of donepezil was 5 mg daily for 6 weeks followed by 10 mg daily for 18 weeks. The benefit of drugs such as methylphenidate, modafinil, and donepezil appear to be greatest in patients with worse baseline functioning. These medications can be considered in patients with significant neurocognitive decline following radiation for brain metastases. The choice of a specific agent should be dependent on the side effect profile and tolerability.

Optic neuropathy

Radiation-induced optic neuropathy (RION) is one of the most feared complications of intracranial radiation due to its devastating consequences. RION is characterized by progressive partial to complete monocular or binocular vision loss with corresponding contrast enhancement and thickening of the affected anterior visual pathway on MRI with a history of radiation exposure to that anatomic distribution (94,95). RION is rare below conventionally fractionated radiation doses of 50 Gy or less. The risk of RION is greater when SRS is used to treat brain metastases in close proximity to the optic nerves with an estimated risk of 1% for single fraction SRS doses of >8 Gy and 10% for >12 Gy (96).

Proven treatment options for RION are limited. Corticosteroids and therapeutic anticoagulation have been studied but do not appear to be effective when given alone (97-100). HBOT is controversial for this indication, as some studies have reported improvement in vision with HBOT (101-103), whereas others have found no benefit (100,104,105). When given, treatment should ideally be initiated within 72 hours of symptom onset (102). HBOT delivery regimens are variable but range from 14–30 daily sessions lasting 90–120 minutes each at 2.4–2.8 atmospheres. There are case reports of bevacizumab

improving RION in conjunction with or following a failed trial of corticosteroids (106-108). Farooq *et al.* gave bevacizumab at 7.5 mg/kg q3 weeks for 3 doses with dexamethasone and pentoxifylline while Dutta *et al.* gave bevacizumab 5 mg/kg alone initially followed by 10 mg/kg q2 weeks for up to 6 doses. Animal models have demonstrated efficacy of the ACE inhibitor ramipril in mitigating RION after SRS, but this therapy remains experimental in humans (109,110).

When monocular RION occurs, the contralateral eye should be carefully observed with serial clinical exams and imaging as patients are at higher risk of developing subsequent contralateral RION. Unfortunately, there is no evidence that prophylactic treatment is effective in preventing RION, but early HBOT can be considered if imaging changes develop, even in the absence of clinical symptoms (103).

Neuroendocrine dysfunction

Historically, patients with brain metastases rarely survived long enough to develop clinically significant hypothalamic-pituitary (HP) axis dysfunction following treatment of brain metastases with radiotherapy and HP dysfunction in this population is therefore not well-described in literature. HP dysfunction is related to dose to the pituitary gland and is rare with doses of <20 Gy but occurs frequently with doses of >50 Gy (111). Reported latency times range widely from 1–26 years after radiation treatment, but most cases are thought to occur between 1–5 years after radiation (112). Extrapolating from data in patients with primary brain tumors, it would be reasonable to screen patients with brain metastases surviving longer than 1 year after WBRT annually for endocrine deficiencies with hormone replacement as clinically indicated (113-115).

Complications after neurosurgical resection

The morbidity and mortality of neurosurgical interventions for brain metastases have improved considerably in the last few decades (116,117). An analysis of over 13,500 admissions for metastatic brain tumor resections across the US demonstrated that the mortality rate had decreased by 49% from 1988 to 2000 (118). The mortality risk is now estimated to be approximately 0.7–1.9% based on modern series (119,120). Nevertheless, caring for the neurosurgical patient requires close observation in the immediate postoperative period. A multidisciplinary approach is favored, and care should be delivered by a team comprised of a neurosurgeon, neuro-intensivists, anesthesiologists, and specialized nursing staff (121). Timely detection of neurologic changes is crucial for early diagnosis and quick intervention of any post-surgical complications (*Table 2*).

Neurologic deficit

As many as 20–40% of patients with metastatic brain tumors will present with focal neurologic deficits (122). Surgery aims to remove the tumor and reverse or improve neurologic symptoms, but injury to normal brain structures is possible, which may result in permanent neurologic deficits. Numerous modalities are used to preserve neurological function when possible, including advanced neuro-imaging with diffusion tractography imaging, minimally invasive approaches, awake craniotomy for speech monitoring, and use of cortical and subcortical motor mapping during tumor resection. The overall neurologic morbidity is estimated to be 3.9–6% (120). Patients with new neurologic deficits after surgery should be rapidly assessed to identify potentially reversible causes, including ICH, hematoma, cerebral edema, and seizures. In many cases, however, the probable cause is not discovered, though most deficits improve over time (123). In one study of neurologic deficits after surgery for primary brain tumors, two-thirds of patients were able to make a complete recovery, and another ~15% had a near-complete recovery with no impairment of function (124). Neurological and/or neurocognitive rehabilitation have been associated with improved motor and cognitive function and QOL and should be tailored to each patient's specific impairments and goals (125).

Intracranial hemorrhage

Hypertension and coagulopathy are the main predisposing risk factors for ICH after neurosurgical resection, and efforts should be focused on prevention and early correction to reduce this risk. Hypertension can be precipitated by pain or may be part of the Cushing reflex. Strict blood pressure control is encouraged during surgery and postoperatively. A retrospective study of over 11,000 patients undergoing craniotomy found that patients who experienced hypertension of ≥160/90 during surgery or in the early postoperative period were more likely to have an ICH event (126).

Patients with ICH should be managed in an intensive

Table 2 Neurosurgical complications of brain metastasis treatment and management options

Complication	Management options
Neurologic deficit	❖ Identify and treat potential reversible causes (i.e., intracranial hemorrhage, hematoma, cerebral edema, seizure) ❖ Neurologic and/or neurocognitive rehabilitation program
Intracranial hemorrhage	❖ Strict blood pressure control with goal <140 mmHg systolic blood pressure ❖ ICP lowering measures including elevation of the head of bed to 30 degrees, optimizing pain control, and mild sedation for comfort ❖ For refractory or severe cases, consider invasive ICP monitoring, osmotic therapy, hyperventilation, complete sedation, ventricular drainage, and surgical evacuation
Cerebral edema	❖ Perioperative parenteral corticosteroids followed by oral taper ❖ Close monitoring and management of postoperative blood glucose with goal <180 mg/dL
Post-operative seizure	❖ Identify and treat potential reversible causes (i.e., hypoglycemia, electrolyte disturbances, hypoxemia, hypercarbia, cerebral edema, intracranial hemorrhage, hematoma) ❖ Intravenous benzodiazepines if seizure does not spontaneously resolve within 2–5 minutes ❖ Maintenance anti-epileptic drugs with individualized duration of treatment
Meningitis	❖ Intraoperative antibiotic prophylaxis with cefazolin ❖ CSF gram stain, cell counts, and culture for diagnosis with adjuncts such as cell index, CSF lactate, and procalcitonin ❖ Empiric parenteral antibiotics with vancomycin + anti-pseudomonal cephalosporin or carbapenem

ICP, intracranial pressure; CSF, cerebrospinal fluid.

care unit with close management of blood pressure with a goal of <140 mmHg systolic and ICP lowering measures including elevation of the head of bed to 30 degrees, optimizing pain control, and mild sedation for comfort. More aggressive measures such as invasive ICP monitoring, osmotic therapy, hyperventilation, complete sedation, ventricular drainage, and surgical evacuation are options for refractory patients or severe cases (127).

Cerebral edema

Cerebral edema is commonly seen after craniotomy and may be exacerbated by prolonged brain retraction and hypertension. The symptoms are generally insidious and non-specific (nausea, diffuse headache). Severe cases may be associated with neurologic deficits depending on the location of the edema. Corticosteroids are usually administered at the time of surgery and then transitioned to a short oral taper to reduce the risk of cerebral edema. Typical dosing is 10 mg IV dexamethasone followed by 4 mg every 6 hours, but the dosing is individualized based on the patient's symptoms before and after surgery. Hyperglycemia is a common side-effect of corticosteroids and blood glucose is closely monitored and corrected postoperatively when levels are >180 mg/dL (128,129).

Post-operative seizure

The incidence of postoperative seizure following craniotomy is approximately 5–15% (130). Precipitating medical factors may include hypoglycemia, electrolyte disturbances, hypoxemia, and/or hypercarbia. Prophylactic antiepileptic drugs (AEDs) are not indicated for patients with brain metastases as they have not shown a benefit in seizure reduction, even in the peri-operative setting (130,131). Most acute seizures spontaneously resolve within two minutes, but more protracted seizures may require infusion of intravenous benzodiazepines. An urgent CT scan is recommended if a reversible surgical cause is suspected such as cerebral edema, hemorrhage, hematoma, and/or elevated ICP. In addition to treating the underlying condition, AEDs such as levetiracetam or phenytoin should be added for maintenance in the recovery period. Postoperative seizures have a low risk of progression to epilepsy overall but decisions on length of time to continue AEDs should be individualized.

Meningitis

Infections following a craniotomy can include surgical site infections and, rarely, meningitis. Postoperative meningitis is a severe disease with high morbidity and mortality rates,

making early diagnosis and treatment crucial. The use of indwelling catheters or other CSF draining devices can increase the risk for meningitis. Antibiotic prophylaxis can be used intraoperatively and most guidelines recommend cefazolin as the antibiotic of choice for prophylaxis in craniotomies, but there is no evidence to support continuation after surgery (132).

Symptoms of postoperative meningitis compared to community-acquired meningitis are non-specific and should be suspected with fever and/or an altered level of consciousness (133). The diagnosis is made primarily through CSF gram stain, cell counts, and culture. A positive gram stain should prompt empiric treatment but with a negative gram stain, classic CSF findings of leukocytosis and neutrophilia have low specificity in the postoperative setting. As a result, other lab values may be used to guide clinical decision making. An elevated cell index of ≥5 (a ratio of white blood cells to erythrocytes), high CSF lactate (>4 mmol/L), and elevated procalcitonin have all been associated with bacterial meningitis (133). The treatment is empiric parenteral antibiotics with vancomycin plus either an anti-pseudomonal cephalosporin or carbapenem per the 2017 Infectious Diseases Society of America (IDSA) guidelines (134).

Complications after brain metastasis directed systemic therapy

Checkpoint inhibitor immunotherapy

Checkpoint inhibitors include antibodies against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) such as ipilimumab, programmed cell death receptor 1 (PD-1) such as nivolumab, and programmed cell death ligand 1 (PD-L1) such as atezolizumab. Combination ipilimumab and nivolumab were studied for upfront treatment of melanoma brain metastases (14). Checkpoint inhibitors are associated with a wide range of potential side effects, referred to as immune-related adverse events (irAEs), caused by enhancement of the immune system and the ubiquitous presence of immune cells throughout the body (*Table 3*). Well-documented irAEs include pruritic skin rash, arthralgias/myalgias, colitis, pneumonitis, hepatitis, and endocrinopathies, although many other potential irAEs exist. The incidence of any irAE is as high as 90% while the incidence of severe grade ≥3 irAE ranges from 10–43% depending on the agent, population, and study (135-137). The treatment-related death rate is as high as 2% (138).

Organ-specific practice guidelines exist for management of irAEs (138-140). Most grade ≥2 toxicities should be discussed and managed carefully with appropriate organ specialists. Potential options for irAEs include continued treatment with observation, symptom management, temporary or permanent suspension of immunotherapy, topical or systemic corticosteroids, disease-modifying antirheumatic drugs, and other organ-specific interventions (140).

Immunotherapy can rarely be associated with an autoimmune meningoencephalitis typically occurring between 1–7 weeks following initiation of immunotherapy (141). Meningeal enhancement can be seen on MRI and this must be differentiated from leptomeningeal disease or infectious etiologies with CSF analysis. Autoimmune meningoencephalitis responds to high-dose corticosteroids.

Pseudoprogression of brain metastases after treatment with immunotherapy has also been reported (142). If suspected, the evaluation of pseudoprogression in patients receiving immunotherapy is similar to that of other patients (See above "Pseudoprogression" section). Corticosteroids should be administered when clinically indicated for neurologic symptoms with a slow taper over at least 4–6 weeks, as in other irAEs. A starting dose of either prednisone at 1 mg/kg or dexamethasone equivalent are acceptable options.

There is no consensus on the optimal timing of immunotherapy with radiotherapy. Overall, the toxicity profile of combination therapy is not significantly worse than with immunotherapy alone (143), although some have reported higher rates of radiation necrosis (144). However, as there is no evidence that withholding immunotherapy during radiotherapy reduces side effects, we do not advocate for this approach.

In general, for mild, grade 1 irAEs, immunotherapy can continue with close clinical supervision, and corticosteroids are not necessary. Grade ≥2 events require temporary suspension of immunotherapy with optional administration of low-dose corticosteroids if the irAEs do not promptly improve with discontinuation of immunotherapy. Immunotherapy may be resumed after improvement of the irAE to grade 0–1 and tapering of corticosteroids to a prednisone equivalent of <10 mg/day (139). Grade ≥3 events should be managed with high-dose systemic corticosteroids, possibly as an inpatient, and resumption of immunotherapy should be considered on a case-by-case basis depending on the perceived risk/benefit ratio. Immunotherapy should be permanently discontinued following a grade 4 event.

When initiated, low-dose prednisone is dosed at

Table 3 Systemic therapy complications of brain metastasis treatment and management options

Complication	Management options
Immunotherapy	
irAE	❖ Grade 1 ◆ Symptom management ◆ Continue with immunotherapy treatment with close clinical supervision ❖ Grade 2 ◆ Consider consultation with organ-specific specialist ◆ Temporary suspension of immunotherapy until improvement to grade 0–1 toxicity and tapering of corticosteroid therapy to prednisone equivalent <10 mg/day ◆ Low-dose corticosteroids (0.5–1 mg/kg/day prednisone equivalent) if symptoms do not promptly improve with cessation of immunotherapy with gradual taper over at least 4–6 weeks ❖ Grade 3 ◆ Consider inpatient management ◆ Suspension of immunotherapy with resumption on a case-by-case basis depending on risk/benefit ratio after improvement to grade 0–1 toxicity and tapering of corticosteroid therapy to prednisone equivalent <10 mg/day ◆ High-dose corticosteroids (1–2 mg/kg/day prednisone equivalent) with gradual taper over at least 4–6 weeks ❖ Grade 4 ◆ Inpatient management; permanent cessation of immunotherapy
Small molecule TKIs	
HFSR	❖ Grade 1 ◆ Topical moisturizers and topical urea (20–40%) ◆ Soft gloves and/or socks ❖ Grade 2 ◆ Dose reduction in TKI by 50% until improvement to grade 0–1 toxicity ◆ High-potency topical corticosteroids (i.e., clobetasol 0.05%) and topical 2% lidocaine ❖ Grade 3 ◆ Supportive care as above for grades 1–2 ◆ Hold TKI for at least 7 days and resume at lower dose after improvement to grade 0–1 toxicity; if no recurrent symptoms after 4 weeks, can increase dose
Acneiform rash/folliculitis	❖ Grade 1 ◆ Medium (face) or high (body) potency topical corticosteroids alone ❖ Grade 2 ◆ Add oral minocycline 50 mg BID ❖ Grade 3 ◆ Add prednisone 10 mg QD ×7 days ◆ Hold TKI for at least 7 days and resume at lower dose after improvement to grade 0–1 toxicity; if no recurrent symptoms after 4 weeks, can increase dose
Diarrhea	❖ Loperamide initial 4 mg followed by 2 mg every 2–4 hours after each loose stool, maximum 16 mg/day ❖ Regular clinical fluid status and laboratory monitoring with intravenous fluid and electrolyte repletion as indicated ❖ Hold TKI for persistent (>14 days) or severe diarrhea with resumption at a lower dose after improvement to grade 0–1 toxicity

irAE, immune-related adverse event; TKI, tyrosine kinase inhibitor; HFSR, hand-foot skin reaction; BID, twice daily; QD, once daily.

0.5 to 1 mg/kg/day and high-dose prednisone at 1 to 2 mg/kg/day (139). Corticosteroids should be tapered slowly over at least 4–6 weeks. Although data is still evolving, there does not appear to be a significant negative impact on immunotherapy overall response rate if corticosteroids are initiated after the appearance of irAEs (145).

Small molecule tyrosine kinase inhibitors (TKIs)

Small molecule TKIs are orally bioavailable targeted therapy agents, a number of which have been studied for brain metastasis treatment in recent years including erlotinib, gefitinib, neratinib, and tucatinib (2,15-17). TKIs are associated with a unique dermatologic side effect profile.

Multi-targeted TKIs (i.e., sorafenib, sunitinib) cause a characteristic hand-foot skin reaction (HFSR) in up to 60% of treated patients (146-149). HFSR is characterized by hyperkeratotic, calloused lesions on the palms and soles with surrounding erythema within the first 2–4 weeks of TKI initiation. For grade 1 HFSR, TKI dose can be maintained with supportive care including topical moisturizers, topical urea (20–40%), and soft gloves or socks (148,150). For grade 2 HFSR, TKI dose should be reduced by 50% until improvement to grade 0–1 and high-potency topical corticosteroids (i.e., clobetasol 0.05%) with topical 2% lidocaine given. For grade 3 HFSR, treatment should be interrupted for at least 7 days and supportive treatment as in grades 1–2 HFSR given. After improvement to grade 0–1, the TKI may be resumed at a lower dose and after at least 4 weeks without recurrence or worsening of HFSR, the dose may be increased.

The most common side effects caused by EGFR selective TKIs (i.e., erlotinib, gefitinib) include a dose-dependent acneiform rash/folliculitis and diarrhea (151,152). Acneiform rash is managed according to severity and for grade 1 can be treated with medium-high potency topical steroids alone. Oral minocycline 50 mg BID should be added for grade 2 toxicity and a short course of oral prednisone 10 mg daily × 7 days should be added for grade 3 toxicity (151). Co-management with dermatology should be considered for grade 2–3 rash. Severe rash unresponsive to medical treatment should prompt interruption of TKI therapy with consideration of resumption at a reduced dose after improvement to grade 0–1 toxicity. Severe cutaneous reactions should alert providers to the possibility of Stevens-Johnsons syndrome (SJS)/toxic epidermal necrolysis (TEN) as rare cases have been reported with TKIs (153).

While TKIs concurrent with WBRT may be associated with worse dermatologic toxicity (154), numerous studies have not found TKIs to be associated with worse neurologic toxicity with WBRT or SRS (155). A study in non-small cell lung cancer patients with ≥2 brain metastases randomly assigned patients to either WBRT or WBRT with erlotinib. There was no difference in intracranial PFS or cognitive function with concurrent erlotinib compared to WBRT alone suggesting safety but no justification for adding concurrent EGFR-TKI with WBRT (156). Thus, for treatment-naïve patients with brain metastases, we prefer upfront radiotherapy followed by TKI, but for those patients already receiving TKI administration at the time of radiotherapy evaluation, interruption of TKI therapy may not be necessary. If TKI interruption is preferred, a one-week period before and after radiotherapy is sufficient.

Diarrhea should be managed with supportive care. Loperamide can be used with an initial dose of 4 mg followed by 2 mg every 2–4 hours after each loose stool, titrating to 1–2 bowel movements a day with a maximum daily dose of 16 mg (157-159). In the setting of diarrhea, clinical fluid status assessment should be performed regularly with a low threshold for intravenous fluid administration. Electrolytes should be monitored and repleted as needed, and patients who are acutely ill should be managed as an inpatient. TKI therapy should be withheld for severe or persistent (>14 days) diarrhea with consideration of resumption at a reduced dose after improvement to grade 0–1.

Conclusions

The incidence of brain metastases is increasing due to more advanced imaging modalities, more frequent brain imaging, and improved cancer treatments for metastatic disease. Furthermore, numerous new and effective multimodality brain metastasis therapies have been developed over recent years that have led to both improved survival in patients with brain metastases and better preservation of neurocognitive function. As a result, however, brain metastasis therapies are associated with a greater range of potential side effects than ever before, and clinicians are tasked with the challenge of effectively managing these side effects without compromising cancer outcomes. In this review, we have summarized the major complications from intracranial radiotherapy, neurosurgical resection, and brain metastasis directed systemic therapy and corresponding evidenced-based, modern management principles to guide the practicing oncologist.

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