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Neurologic Complications of Cranial Radiation Therapy and Strategies to Prevent or Reduce Radiation Toxicity

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Abstract

Purpose of Review Radiation therapy is an important treatment for patients with brain tumors but can have significant neurologic complications. This review highlights the broad spectrum of short-term and long-term neurologic complications that can occur in patients receiving cranial radiation therapy, and strategies to prevent and treat such complications.

Recent Findings Despite significant improvements in radiotherapy delivery, there are neurologic complications that can result from treatment. With increased recognition and understanding of these neurologic complications, novel strategies to prevent and mitigate them are an area of active research with early promising results. Intensive efforts are ongoing to address the risk of radiation-induced neurocognitive changes through advances in radiation technique and therapies targeting relevant molecular pathways.

Summary Neurologic complications from radiation therapy are an important consideration in counseling, treatment, and post-treatment management of patients with brain tumors.

Keywords Radiation toxicity · Radiation injury · Necrosis · Neurocognitive changes

Introduction

Radiation therapy (RT) is an important modality of therapy for patients with primary or metastatic brain tumors in both curative and palliative settings [1]. Cranial RT is most commonly delivered through external beam radiation therapy (X-rays, gamma rays, protons) or brachytherapy with implanted sources of radioactive activity [2]. Radiation dose is measured in gray (Gy). External beam cranial RT can be delivered with two primary techniques: stereotactic radiosurgery (SRS) or fractionated (conventional) RT. SRS arose from interest in applying neurosurgical concepts of stereotaxis to precisely deliver RT to the central nervous system (CNS). It was pioneered by Lars Leksell, who published his landmark paper describing stereotactic radiosurgery in 1951 [3]. SRS relies on maximal precision, accuracy, and reproducibility to deliver high doses of radiation in one treatment [4], and typical doses to treat brain metastases are 18–24 Gy. Stereotactic radiotherapy (SRT) refers to a similar stereotactic approach delivered over two to five treatments. Conventional fractionated radiation therapy, on the other hand, treats a patient over several weeks of daily treatment using multiple small fractions (e.g., 1.8 Gy or 2 Gy a day over 5–7 weeks).

Photon (X-rays, gamma rays)-based radiation is the most accessible and common form of RT employed for brain tumors. Proton and other particle-based RT can also be used for stereotactic and conventionally fractionated treatments. Proton beam therapy is a particle therapy that can deliver a similar biologic dose to targets at the Bragg peak, the point at which protons penetrate deepest in tissue followed by a sharp dose falloff. This phenomenon minimizes radiation exposure of normal tissue beyond the target and decreases the total integral dose to normal tissue. Although proton RT experiences have been reported since 1960s [5], building a proton facility remains expensive and complex with a limited number of facilities around the country.

RT causes its intended effect through DNA damage [6]. Absorption of ionizing radiation by matter produces charged

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particles that can ionize DNA directly (direct action) or ionize water molecules to produce reactive hydroxyl radicals that can react with DNA (indirect action) to mediate damage [7]. Complex and severe damage to DNA that cannot be repaired leads to loss of proliferative ability or cell death via mitotic death, necrosis, autophagy, or apoptosis [8]. While DNA damage is the desired result in tumor, RT effects on normal brain tissue can cause treatment-related neurotoxicity and neurologic complications. Despite advances in treatment planning and delivery of RT, a persistent challenge in the use of cranial RT is the identification of the ideal therapeutic ratio of balancing the therapeutic benefit relative to toxicity. Therefore, to better inform clinical decision making in the treatment of brain tumors, it is necessary to understand RT-induced toxicity.

Radiation complications are often divided into short-term and long-term adverse effects. Acute adverse effects generally occur within 6 weeks of RT and are often self-limited. Late or delayed complications of cranial RT can occur months or years after treatment and are often irreversible. Common neurologic complications of RT are summarized in Table 1.

In this review, we examine neurologic complications commonly associated with cranial RT, their evaluation, and strategies to prevent and treat them.

Acute and Subacute Complications After Cranial RT

Fatigue

Fatigue is a common side effect of RT regardless of treatment modality. Pathophysiology is poorly understood, though it is sometimes attributed to transient demyelination of white matter [9]. Fatigue may be associated with worsening of preexisting neurologic symptoms. In patients receiving fractionated EBRT, fatigue is typically seen 1–2 weeks into treatment with peak fatigue 2–3 weeks after completion of EBRT. While symptoms generally resolve over several weeks, fatigue can persist for many months after RT completion [10].

Evaluation

Fatigue in patients receiving cranial RT is often multifactorial, and it is important to consider cardiac, pulmonary, metabolic, hematologic, postoperative, medication-related or psychiatric factors that can also contribute to fatigue.

Incidence and Risk Factors

Estimates of fatigue and somnolence can vary widely, but modern series suggest that the majority of patients experience some fatigue, with 90% incidence reported in a prospective evaluation of primary brain tumor patients receiving RT [11]. Factors associated with a higher incidence of fatigue include irradiated volume, RT dose, and performance status [10, 12]. Increased fatigue with treatment for primary brain tumors has been associated with worse overall survival (OS) [12]. Recent work in 176 malignant glioma patients suggests that single nucleotide polymorphisms in *ARTNL2* and *PER2*, genes associated with the circadian clock pathway, were significantly associated with incidence of moderate-severe fatigue in brain tumor patients [13].

Prevention and Management

Psychostimulants are often employed for fatigue, but evidence to support this practice is sparse. Prophylactic methylphenidate, a norepinephrine-dopamine reuptake inhibitor, did not improve quality of life measures in a phase III, double-blind, placebo-controlled trial in patients receiving cranial RT [14]. Randomized trials with modafinil [15] and armodafinil [16, 17] similarly did not show a significant decrease in fatigue symptoms.

Cerebral Edema and Exacerbation of Existing Neurologic Symptoms

CNS tumors are often associated with peritumoral edema and can result in generalized symptoms such as headache, nausea,

Table 1 Common neurologic complications of cranial RT

Acute/subacute	Delayed
Fatigue/somnolence syndrome	Neurocognitive effects
Exacerbation of existing neurologic symptoms	Radionecrosis
Headache	Cerebrovascular effects (cerebrovascular accidents, cavernoma, moyamoya,teleangiectasia, intracranial hemorrhage)
Loss of appetite/nausea/emesis	Optic neuropathy, cranial nerve palsies
Acute encephalopathy	Stroke-like migraine attacks after radiation therapy (SMART)
Pseudoprogression	Endocrinopathy
	Secondary malignancy

vomiting, gait instability, or seizures. Cerebral edema, generally vasogenic in nature, is caused by breakdown of tight endothelial junctions of the blood-brain barrier [18]. Cranial RT can increase cerebral edema, and this can be seen several weeks into treatment with conventionally fractionated RT. Radiosurgical approaches can cause more acute increases in edema with increased edema within 12 to 48 h of stereotactic RT [19].

Evaluation

Edema can be visualized with neuroimaging, most commonly as hypodensity on CT imaging relative to surrounding normal parenchyma and T2/FLAIR hyperintensity on MRI imaging. In addition to radiologic correlates, worsening cerebral edema in setting of RT can be diagnosed with clinical exam or responsiveness to dexamethasone.

Incidence and Risk Factors

The landmark Radiation Therapy Oncology Group (RTOG) 90–05 trial evaluated maximum tolerated doses for SRS by evaluating acute severe CNS toxicities. With doses of 12 to 24 Gy based upon size, acute severe CNS toxicity was limited to a maximum of 17–33% incidence [20]. In the treatment of meningiomas with SRS or SRT, 28–50% of patients developed edema, symptomatic in 5–43% of patients [21]. Factors correlating with edema or symptomatic edema include maximum RT dose, greater tumor size or treatment volume, and presence of pretreatment edema [21, 22]. Generally, edema resolves within 6 to 12 months of SRS, although it can persist for 12–16 months after treatment. Multi-fraction SRT is associated with lower risk of treatment-related edema compared to single fraction treatment [22, 23].

Prevention and Management

Since a landmark paper in 1961 [24], steroids have long been used to treat brain tumor patients with cerebral edema, including exacerbations caused by cranial RT. There is wide variability in physician recommendations in the use of steroid and anticonvulsant prophylaxis for SRS treatments with a survey indicating that 53% of radiation oncologists usually or always recommend corticosteroid prophylaxis [25]. However, there is increasing evidence that corticosteroids may interfere with the effectiveness of RT and lead to worse outcomes in gliomas [26]. While corticosteroids should be used if patients are symptomatic from peritumoral edema, routine use of prophylactic corticosteroids in asymptomatic patients undergoing conventional RT should be avoided. Bevacizumab, a monoclonal antibody targeting angiogenesis via vascular endothelial growth factor (VEGF) can also be used for symptomatic edema to reduce toxicity of cranial RT, which has been demonstrated in the setting of fractionated RT, SRS, and re-irradiation [27•, 28, 29, 30].

Pseudoprogression

Pseudoprogression refers to a treatment-related phenomenon where imaging findings after cranial RT or chemoradiation show a transient increase in contrast enhancement due to disruption of the blood brain barrier and inflammation by radiation rather than by progressive disease [31–33]. Pseudoprogression can be associated with new symptoms but usually is asymptomatic [34]. While pseudoprogression is most recognized in gliomas patients after conventionally fractionated RT [34], a temporary treatment-related increase in treated site can also be seen after SRS treatment of benign [35] and malignant entities [36, 37].

Evaluation

Distinguishing between pseudoprogression and true progression of tumor after cranial RT remains a challenge in neuro-oncology [34, 38, 39]. Advanced imaging techniques such as MR perfusion-weighted imaging [40] and PET-based imaging [41, 42] are promising in their ability to distinguish and identify pseudoprogression, but they are still not fully incorporated into routine clinical practice. Pathological confirmation remains the "gold standard" to identify pseudoprogression or true progression, but even this is not always definitive [43].

Incidence and Risk Factors

In glioblastoma, pseudoprogression occurs in 20–30% of cases and the addition of temozolomide to RT is associated with a higher risk [32]. Among glioblastoma patients, MGMT methylated glioblastoma patients were more likely to exhibit pseudoprogression [44] in one study but not in another [45].

Prevention and Management

Distinguishing pseudoprogression from true progression remains an important challenge, particularly in high-grade gliomas. While pseudoprogression can generally be managed with close surveillance, symptomatic management, and continuation of standard therapy, true progression requires a change in therapy. Misclassifying pseudoprogression as true progression can lead to discontinuation of an effective therapy in a disease setting where salvage therapies are meager and ineffective. The Response Assessment in Neuro-Oncology working group has developed criteria for clinical trials in high grade gliomas to address pseudoprogression [32, 46].

Long-Term Adverse Effects of Cranial RT

Late radiation effects are complex and involve target tissue, vasculature, connective tissue, and interplaying interactions with the immune system [47]. Long-term survivors of childhood cancer and patients with benign tumors who received cranial RT as part of treatment have most contributed to our understanding of long-term side effects. We review long-term side effects with an emphasis on the neurocognitive effects of RT. Of note, our understanding of long-term complications of cranial RT derive from patients treated with older RT techniques that may be outdated and less precise than contemporary treatments.

Neurocognitive Changes

There are a well-described spectrum of neurocognitive changes and deficits that can occur months or years after cranial RT. Whole brain radiation therapy (WBRT), used commonly in patients with multiple brain metastases, has been extensively studied with respect to early, delayed and long-term neurocognitive changes. In addition to WBRT, partial brain and SRS/SRT approaches can also be associated with neurocognitive changes [48]. The timeline for neurocognitive changes resulting from RT can first be noticed 3 to 12 months following RT, but changes can occur years later. Improvements in oncological outcomes through new technologies and therapies have magnified the importance of managing long-term sequela associated with cranial RT.

Much research has focused on the effects of RT on the hippocampus, which contain radiosensitive neural stem cells important to memory formation [49]. Several mechanisms are being actively studied to better understand the pathophysiology of these effects. RT alters the cellular microenvironment, inhibits neurogenesis, and markedly increases microglia within the neurogenic zone [50, 51]. These changes are also associated with a pro-inflammatory environment with overexpression of acute phase agents in experimental models [52]. Radiation may also alter the cellular microenvironment and neurovascular relationships. While most studies have focused on the effect of RT on neuronal precursor cells, RT can also alter mature neuronal function [51]. RT can reduce synaptic efficiency in a dose-dependent manner and reduce dendritic branching, length, and area within the hippocampus [53].

Evaluation

Neurocognition is complex and characterized by several interrelated cognitive domains. In the clinic, a formal evaluation can be useful in some patients. A battery of tests that have been validated to assess neurocognitive function are available [54]. These include the Hopkins Verbal Learning Test-Revised (HVLT-R) [55], Trail Making Test (TMT) A and B [56], and the Controlled Oral Word Association (COWA) test. The Mini-Mental State Examination (MMSE), originally a dementia screening tool, can also be informative, although it is not as sensitive as other assessments [57]. Formal, comprehensive testing allows for greater sensitivity in detecting neurocognitive changes, but the clinical meaningfulness of such changes is not always clear.

Incidence and Risk Factors

Cranial RT-associated neurocognitive decline is associated with patient's baseline neurocognitive function, RT dose, and RT treatment volume [58, 59]. Hippocampal dose volume effects for cranial RT are associated with memory deficits in adults [60] and children [61•]. For pediatric populations, age is associated with long-term decrease in intelligent quotient, with younger patients with more significant treatment-related effects long-term [62]. Other clinical factors associated with neurocognitive function include medications, fatigue, depression, anxiety, intracranial disease burden, seizure status, and unrelated processes (cerebrovascular disease, infection, metabolic, etc.). As neurocognitive function following cranial RT can be multifactorial, careful assessment of mental status and cognition function at baseline and following treatment is important.

Supporting a decrease in the use of WBRT, NCCTG N0574 (Alliance), a large trial of patients with 1 to 3 brain metastases, demonstrated that cognitive impairment was more likely in the patients receiving WBRT (92%) added to SRS compared to patients with WBRT omitted (64%) with decreases in immediate recall, delayed recall and verbal fluency [63••]. Similar results have been seen in several studies evaluating neurocognitive function after WBRT [55, 64, 65•]. In addition to neurocognitive changes, the addition of WBRT is associated with decline in health-related quality of life measures [66].

With partial brain radiation with conventional fractionation, as commonly employed for gliomas, neurocognitive decline can be less pronounced in comparison to WBRT. In a study using MMSE, 5% of patients in a prospective cohort of low-grade gliomas exhibited cognitive deterioration with RT at 7 years of follow-up [67]. An observational study of 195 low-grade glioma patients also did not show a significant decline in cognitive function in patients receiving < 2 Gy per fraction dose [68]. In a study with longer follow-up (mean 12 years), however, cranial RT was associated with progressive decline in attention, executive functioning and information processing speed [69]. In addition to RT dose to the hippocampus, white matter injury is felt to also felt to be associated with neurocognitive decline after hippocampal avoidance WBRT (HA-WBRT) [70].

Prevention and Management

Several strategies have emerged to prevent or mitigate RT-induced neurocognitive decline. With respect to prevention, the avoidance or delay of WBRT through increased use of SRS/SRT for limited number of brain metastases has become the standard of care. The use of SRS/SRT is actively being explored in patients with ten or more brain metastases with the hope of further reducing the use of WBRT [71]. Advances in CNS-penetrant systemic therapies such as agents targeting EGFR, BRAF, ALK, ROS1 mutations and immunotherapy have also created opportunities to omit cranial RT in the care of select patients with brain metastases [72].

When WBRT is indicated, several strategies to reduce RT-induced neurotoxicity have been evaluated (Table 2). Memantine is a non-competitive antagonist of NMDA receptors. Initially approved for Alzheimer's disease and vascular dementia, memantine has been evaluated as an intervention to preserve cognitive function in patients receiving WBRT. In RTOG0614, a randomized placebo-controlled trial of 554 patients, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speech [73]. The study did not meet its primary endpoint for reduction in the decline in delayed recall at 24 weeks, but the study lacked statistical power due to patient death from progressive disease resulting in a small number of patients analyzable at that time point [73]. Since this trial, many consider memantine as a standard of care addition for patients receiving WBRT.

Donepezil is another agent used in Alzheimer's disease and vascular dementia, among other indications, that has been tested in patients receiving cranial RT for brain tumors. In a

Table 2 Prospective, randomized trials evaluating strategies to reduce or minimize radiation-related neurocognitive decline with WBRT

Strategy	Study	Patients (*n*)	Radiation dose/technique	Arms	Cognitive outcomes	Toxicity
Memantine	RTOG0614 Brown et al. 2013; *Neuro-Oncology* (NCT 00566852)	554 adult patients receiving WBRT	WBRT 37.5Gy in 15 fractions	1. WBRT + memantine 2. WBRT alone	- At 24 weeks, no statistically significant difference in delayed recall ($P = 0.059$) - Memantine was associated with: 1) Significantly longer time to cognitive decline (HR 0.78, 95% CI 0.62–0.99) 2) Improvements in processing speed ($P = 0.014$) and delayed recognition ($P = 0.015$) at 24 weeks	- No increase in grade 3–4 toxicity (14% in each arm)
Donepezil	Rapp et al. 2015; *Journal of Clinical Oncology* (NCT00369785)	198 adult patients ≥ 6 months after RT	Partial brain (59%) or whole brain (40%) RT (at least 30Gy)	1. Donepezil 2. Placebo	- At 24 weeks, donepezil did not significantly improve composite cognitive battery score ($P = 0.48$) - Donepezil was associated with improvement in memory [recognition] ($P = 0.027$), memory discrimination ($P = 0.007$), motor speed/dexterity ($P = 0.016$)	- Increased diarrhea (25% vs. 9%) but no other significant differences
Hippocampal avoidance WBRT (HA-WBRT)	NRG CC-001 Brown et al. 2020; *Journal of Clinical Oncology* (NCT 02360215)	518 adult patients receiving WBRT	WBRT or HA-WBRT: 30Gy in 10 fractions	1. HA-WBRT + memantine 2. WBRT + memantine	- HA-WBRT has lower risk of cognitive failure (HR 0.74, 95% CI 0.58–0.95) - HA-WBRT was associated with less deterioration of: 1) Executive function at 4 months ($P = 0.01$) 2) Learning and memory at 6 months ($P = 0.49$) - At 6 months, HA-WBRT was associated with less: 1) Difficulty remembering things ($P = 0.01$) 2) Difficulty speaking ($P = 0.49$) 3) Interference of neurologic symptoms in daily activities ($P = 0.008$) 4) Cognitive symptoms ($P = 0.01$).	- Less fatigue in patients receiving HA-WBRT; no difference in grade 3 or higher toxicity between arms

WBRT = Whole brain radiation therapy

phase III randomized placebo-controlled trial of 198 patients who had received partial or WBRT over 6 months prior, donepezil did not significantly improve the overall composite score encompassing memory, attention, language, visuomotor, verbal fluency, and executive functions at 12 and 24 weeks but did result in modest improvements in several cognitive functions among patients with greater pretreatment impairments. [74].

Given preclinical and clinical evidence supporting role of hippocampal dentate gyrus as a radiosensitive structure at risk [49], RTOG0933 explored the use of HA-WBRT to minimize risk of neurocognitive decline with WBRT. In this single arm phase II trial, there was a 7% decline in HVLT-delayed recall from baseline at 4 months, significantly less than historical controls [75]. A subsequent phase III trial, NRG CC-001, evaluated the use of hippocampal avoidance in WBRT in patients being treated with memantine. With median 7.9 months follow-up, NRG CC-001 demonstrate that hippocampal avoidance reduces risk of cognitive function failure (HR 0.74, 95% CI 0.58–0.95, $p = 0.02$), including HVLT-R total recall, delayed recall, and recognition [76••]. There was less deterioration of executive function at 4 months and learning and memory at 6 months without a significant difference in overall survival, intracranial progression or toxicity [76••]. With these findings, HA-WBRT should gain acceptance as the standard of care approach to eligible patients requiring WBRT with good performance status and without metastases in the peri-hippocampal region.

With a minimal exit dose, an advantage of proton therapy is reduced volume of brain parenchyma receiving low and intermediate dose RT. While prospective randomized trials are not currently available, retrospective data in pediatric populations are mixed on the benefit of proton vs. photon RT on neurocognitive outcomes of pediatric patients [77, 78••]. In a study evaluating longitudinal intelligence data from 79 patients (37 proton, 42 photon) treated with contemporary protocols for pediatric medulloblastoma, however, proton RT-treated patients exhibited superior long-term outcomes in intelligence quotient, perceptual reasoning and working memory compared with the photon RT group [79]. Although promising, additional long-term and prospective data is needed to better clarify clinically meaningful improvements with proton RT.

The renin angiotensin system in the brain is complex and contributes to the blood-brain barrier, learning, memory, and behavioral systems. Radiation-induced effects on the RAS system have been implicated as another mechanism of RT-induced neurotoxicity in animal models. Angiotensin-converting enzyme inhibitors have been associated with reduction in cognitive impairment in cranially irradiated rats [80], and further study may be warranted.

Chronic inflammation also plays a role in RT-induced late effects. Peroxisomal proliferator-activated receptor (PPAR) activation can affect anti-proliferative and anti-inflammatory cellular physiology. In animal models, administration of PPAR-gamma agonist, pioglitazone, to adult rats substantially reduced cognitive impairment from WBRT [81]. A phase I trial in humans established a safe dose to use in trials for humans [82], but further clinical experience is lacking at this time.

Radiation Necrosis

Radiation necrosis can occur as a severe local tissue reaction with evidence of a disrupted blood brain barrier, edema, and mass effect. The pathophysiology is felt to be multifactorial, with contribution from vascular injury [83] through VEGF-mediated pathways and damage to glial cells [84]. With respect to timing, it generally occurs 6–18 months after RT but can develop years later. A case is illustrated in Fig. 1.

Evaluation

Similar to pseudoprogression, differentiating between radiation necrosis and progressive tumor remains a significant clinical challenge because features on conventional MR considerably overlap. Perfusion MR [85, 86], MR spectroscopy [87, 88], and PET-based imaging [89] are promising approaches to distinguish necrosis. The gold standard is pathologic confirmation.

Incidence and Risk Factors

In glioma patients, radionecrosis is uncommon with standard fractionated EBRT though there is greater risk in setting of re-irradiation [90] or dose escalation [91]. Radionecrosis is a larger consideration in SRS/SRT and is considered its most important and dose-limiting complication. In the initial RTOG 90-05 experience with SRS, in patients who had previously received cranial RT, radionecrosis was reported in 11% at 24 months [20]. Modern series report necrosis rates < 5 to 26% [63••, 92], and there may be higher rates in setting of new therapies such as immunotherapy [93].

Since early studies on animals with cranial SRS [94], risk factors for radionecrosis include tumor size, prior cranial RT, and RT dose [92, 95]. Location, tumor histology, and systemic therapies have also been raised as possible risk factors to develop radionecrosis [96]. While many studies discuss radionecrosis in setting of SRS, a growing experience with multi-fraction SRT appears to reduce the risk of radionecrosis [97•, 98].

Prevention and Management

In the absence of symptoms, radionecrosis that is detected radiographically can be followed with surveillance. For symptomatic patients, dexamethasone is first-line treatment and can

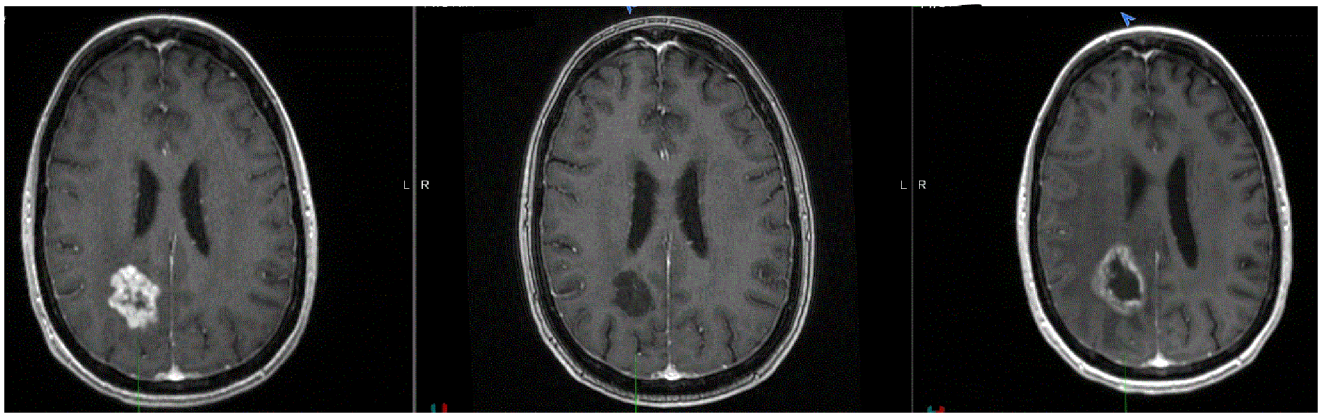

Fig. 1 Case of radiation necrosis. Fifty-three-year-old woman with ER+/PR+/Her2+ breast cancer presented with a right parietal metastasis (**a**). She had received whole-brain radiation 2 years prior. She was treated to this lesion with SRT to 30Gy over 5 fractions. **b** Two months after SRT, there was good response with marked decrease of enhancement. **c** Imaging at 9 months indicated increase in enhancement and associated edema in the right parietal lesion. The patient was taken to surgery and resection pathology indicated brain parenchyma with radiation changes and no evidence of malignancy

have dramatic improvement in symptoms. Bevacizumab can be used for steroid-refractory radionecrosis with a high radiographic response rate and 59–63% decrease in enhancing and T2/FLAIR abnormality [99]. A placebo-controlled randomized trial of 14 patients showed improvement in all patients receiving bevacizumab [100].

Hyperbaric oxygen therapy can promote angiogenesis, but efficacy is unclear with sporadic case reports in the literature [101]. Anticoagulation has also been evaluated with limited evidence to support its use with radionecrosis [102].

If conservative measures fail or diagnostic uncertainty persists, surgical resection can be diagnostic and therapeutic. Laser interstitial thermal therapy is an alternative intervention with prospective evidence supporting safety, preserved quality of life, and reduction in use of steroids [103].

Cerebrovascular Effects

Cranial RT can cause several late effects on the cerebrovascular system including cerebrovascular accidents (CVA), lacunar infarcts, vasocclusive disease, vascular malformation, especially cavernomas, and hemorrhage. The pathophysiology of late vascular events related to cranial RT is a complex process that involves both arterial and capillary damage [104]. Most published evidence is related to fractionated RT, and there is limited data on the long-term vascular effects of SRS/SRT.

CVA

In a prospective study of benign meningiomas, there was a 22% cumulative incidence of CVA at a median of 5.6 years after RT, with most events possibly, probably or definitely due to RT [105]. An increased risk of CVA with RT has been associated with RT to the Circle of Willis or other central arterial circulations [106, 107]. In addition to anatomical consideration, higher doses (e.g., > 30 Gy) in childhood leukemia and brain tumor patients has been associated with greater risk of subsequent CVA [108].

Cavernoma

Cavernomas are benign vascular malformations that can hemorrhage or cause seizures. The incidence has been estimated to be 3.4 to 43% at a median of 6 years, with most patients having a benign course without symptoms or intervention required [109, 110]. Risk factors for cavernomas are not well understood though younger age and higher RT dose are felt to be associated with a higher risk [104].

Other

Moyamoya represents a progressive occlusive vasculopathy with estimated incidence of 0.5% at 8 years in acute lymphoblastic leukemia patients who received prophylactic cranial RT [111]. Telangiectasias and intracranial hemorrhage are other noted late vascular effects.

Prevention and Management

Known late vascular effects of cranial RT are part of rationale for using smaller RT doses and volumes. The use of proton therapy likewise may reduce such late effects with less integral dose to normal brain, although rigorous evidence is lacking. Management of vascular late effects is generally extrapolated from standard practice in patients without cranial RT.

Optic Neuropathy

Cranial nerve palsies can be caused by RT, and optic neuropathy is one of the most feared. This is a rare complication that can impair vision months to years after treatment. The mechanism is related to free radical damage to endothelium and neuroglial cell progenitors [112].

Evaluation

Formal ophthalmologic evaluation is important to evaluate the optic disk and nerve to assess for RT-induced optic neuropathy. MRI can show abnormal enhancement along the optic nerve or chiasm.

Incidence and Risk Factors

Peak incidence is at 2 years after RT, and risk factors include age, comorbidities (e.g., diabetes, retinopathy), and RT dose [113]. For fractionated RT, recent experience suggests that RT-induced optic neuropathy risk of < 1% with dose < 59 Gy (relative biologic effectiveness, RBE), and 5.8% with ≥ 60 Gy (RBE) [114]. For SRS with < 10 Gy to the optic nerve, incidence of optic neuropathy has been reported as 0 to < 2% in multiple series [115, 116], while > 10 Gy can be associated with risk > 25% [115].

Prevention and Management

Steroids, anticoagulation, hyperbaric oxygen therapy, and bevacizumab have been used with unclear benefit with respect to reversing or halting vision loss. Given a lack of good management options, prevention is felt to be key. Dose constraints of 54–55 Gy with fractionated RT and 8–10 Gy for SRS for optic structures are conservative metrics with low risk of RT-induced optic neuropathy.

Other Late Effects

Stroke-like migraine attacks after radiation therapy (SMART) is a rare syndrome that presents with headaches, possibly with neurologic symptoms including seizures. Symptoms can occur years after RT with MRI findings of enhancement and/or worsening edema. SMART is managed with supportive care and anti-epileptic therapy as needed with resolution of symptoms characteristically over weeks [117].

Endocrinopathy

Among late effects, late endocrinopathies are fairly common in patients receiving cranial RT. Pituitary or hypothalamic dysfunction after RT involving relevant structures can occur in up to 84% of patients [118–120], and regular endocrine function surveillance is important for patients after treatment. For fractionated RT, maximum dose > 50 Gy to the pituitary is associated with higher rates of endocrine dysfunction [120].

Ototoxicity

Cochlear RT dose and older age are associated with sensorineural hearing loss, with increased risk with ototoxic chemotherapy (e.g., cisplatin) [121, 122]. For fractionated RT, mean RT dose < 45 Gy is associated with preserved hearing.

Secondary Malignancy

Secondary malignancy is a devastating complication of cranial irradiation. Among survivors of childhood cancer, cranial RT is the strongest known risk factor of a subsequent CNS neoplasm with one study indicating an odds ratio (OR) 6.8 for glioma and OR 9.9 for meningioma compared to the general population [123]. The risk for secondary malignancy is associated with dose and younger age [124].

With SRS, there appears to be a low risk of secondary malignancy, and a recent multi-institutional study of 4905 Gamma Knife SRS patients for benign indications revealed an incidence of secondary malignancy of 6.9 per 100,000 patient-years [125•], while another study of 1837 patients did not have any RT-induced tumors with long-term follow-up [126].

Conclusion

Radiation therapy is important in the treatment of CNS tumors despite the possibility of short term and long-term complications. Adverse events are not always well documented, and this has been a limitation in our ability to better identify strategies to mitigate these risks. Ongoing efforts to develop strategies to prevent or reduce risk are increasingly important with advances in oncologic care that have increased survivorship in brain tumor patients.

The field of radiation oncology has made dramatic strides to harness advancing technologies and image-guidance to improve precision and conformality of treatments. We would expect that the incidence of long-term adverse events in contemporary patients should be lower than what has been seen historically. Moving forward, rigorous collection of long-term radiation toxicity data and randomized trials to evaluate emerging strategies that mitigate risks will be critical. As data emerges on RT-associated neurotoxicity, clinicians must individualize care based upon available data to inform counseling of the rationale, benefits, and possible complications from cranial RT.

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