Risk-reduction strategies for late complications arising from brain metastases treated with radiotherapy: a narrative review

Chen'en Ye[1#], Pooja Handa[1#], Arjun Sahgal[2], Simon Lo[3], Balamurugan Vellayappan[1]

[1]Department of Radiation Oncology, National University Cancer Institute Singapore, National University Hospital, Singapore; [2]Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; [3]Department of Radiation Oncology, University of Washington School of Medicine, Seattle, WA, USA

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[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Balamurugan Vellayappan. Department of Radiation Oncology, National University Cancer Institute Singapore, National University Hospital, Singapore, 1E Kent Ridge road, Tower Block Level 7, Singapore. Email: bala_vellayappan@nuhs.edu.sg.

Objective: This review will focus on the late neurological complications from cranial irradiation and relevant mitigation strategies.

Background: Radiotherapy (RT) remains an important pillar in the management of brain metastases. Patients being treated in the modern era do experience longer survival, because of superior intra- and extra-cranial disease control. As a result, they can be more prone to developing and manifesting late complications post-brain radiotherapy.

Methods: A search and narrative review of prospective clinical trials relating to neurological toxicity outcomes was conducted.

Conclusions: Neurological toxicities can be challenging to diagnose and manage and should be considered during consideration of radiotherapy in brain metastasis, hence more emphasis should be placed on prevention and upfront mitigation of these complications, with novel strategies showing promising results in prospective trials being adopted into clinical practice.

Keywords: Radiotherapy (RT); stereotactic radiosurgery; whole-brain radiotherapy; brain metastases (BM); complications

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Introduction

Brain metastases (BM) are the most common central nervous system malignancy, with up to 30% of cancer patients developing BM during the course of their disease (1). The prognosis of patients with BM used to be uniformly poor, with the median survival hovering around 6 months (2). As a result, the detection of BM had been the cue for many clinicians to assume a fatalistic approach, withholding aggressive treatment, as patients were believed to have a poor outcome despite treatment. Naturally, the potential of long-term complications from whole-brain radiotherapy (WBRT), which was then the mainstay, was mostly disregarded.

In the modern era, advances in neurosurgical techniques, neuro-imaging, systemic therapeutics and radiotherapy technology have conferred an improved survival for patients with BM. This is particularly so for patients with good performance status and solitary BM (3). As an example, Nieder reported the 1-year survival if patients treated between 1983–1989 to be 15%, comparatively patients treated between 2005–2009 achieved a 1-year survival of 34% (4). Due to the improved survival of patients, there is an increased concern (both by patients and oncologists) about

the longer-term toxicities, in particular neuro-cognition.

In terms of treatment, radiotherapy (in various forms) continues to remain a cornerstone in the management of BM—spanning from palliative to "locally radical". WBRT is still commonly used as a palliative treatment for patients with multiple BM and/or diffuse leptomeningeal disease. At the other end of the spectrum, stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (HSRT) allows for an ablative dose of radiation to be delivered to well-defined lesion (or lesions), in one or a few fractions, respectively, whilst sparing the uninvolved brain parenchyma. Recent trends demonstrate an increased use of SRS or HSRT for managing BM, even in the setting of multiple BM, compared to WBRT—particularly because of the lesser impact on neuro-cognition with SRS (5).

In general, toxicities of cranial radiotherapy can be divided into 3 main categories based on their timeline: acute, subacute, and late/delayed effects. Acute toxicities occur during RT or within days after RT, with symptoms ranging from headache, nausea and vomiting, drowsiness or worsening of focal neurological symptoms. Subacute toxicities occurs within 6 weeks and up to 6 months after completion of RT (6). Late/delayed toxicities occur more than 6 months after cranial irradiation and are irreversible. More often, late/delayed toxicities can be functionally debilitating and negatively affect quality of life, making it difficult for both patients and their families to cope. Moreover, many patients with metastatic cancer may be treated with systemic therapy (e.g., cytotoxic chemotherapy, targeted therapy, or immunotherapy) before, during and after cranial irradiation. The interaction of systemic therapy and radiotherapy remains unclear, and in certain cases may lead to a potentiation of toxicities, although this has never been proven in clinical trials.

In this narrative review, we will elaborate on the common late complications with cranial irradiation (e.g., WBRT, SRS) for BM. As there is a lack of effective treatment, we will summarise mitigation strategies which can be used to reduce the risk of these late complications. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-121/rc).

Search strategy and study selection

A search was conducted on MEDLINE, on 26th July 2021, using MeSH Major topics "radiotherapy" AND "brain neoplasms/secondary". The search results were limited to prospective clinical trials reported in the English language, from 2010. Studies reporting toxicity outcomes including neurocognitive decline and/or radiation necrosis were selected and presented in *Table 1*.

Whole-brain radiotherapy: neurocognitive decline

WBRT is typically delivered using parallel opposed photon beams, targeting the entire skull, meningeal reflections, and brain parenchyma. As with most palliative treatments, WBRT is hypo-fractionated with typical dose-fractionation regimens including 20 Gy in 5 fractions (over 1 week) or 30 Gy in 10 fractions (over 2 weeks). Indications of WBRT include multiple BM (such as patients with a poor prognosis who are deemed unsuitable for SRS), patients with diffuse classic leptomeningeal disease (e.g., sugar coating) or in prophylactic cranial irradiation. WBRT is generally well-tolerated in the short term, with patients experiencing minor acute toxicities (such as radiation dermatitis, alopecia, or xerostomia) (24). The most concerning toxicity from WBRT is that of radiation-related neurocognitive decline. Whilst it is possible that uncontrolled BM may also lead to neurocognitive declines, data from prophylactic cranial irradiation studies suggest that radiation exposure to the uninvolved brain parenchyma is a key causative factor (25). Case in point being the RTOG 0214 randomized controlled trial, which compared PCI (30 Gy in 15 fractions) versus observation in patients with locally advanced NSCLC (26,27). Secondary endpoints of the trial included neurocognitive function and quality-of-life (measured using HVLT, MMSE and activities of daily living). Although, the 1-year rates of BM were significantly better with PCI (7.7% *vs.* 18%, P=0.004), the PCI group reported a trend towards worse cognitive functioning and HVLT scores.

Radiation-induced neurocognitive decline occurs in a biphasic pattern (28,29). Following completion of WBRT, there is an initial subacute transient deterioration which peaks at 4 months post-treatment, in multiple domains of neurocognitive function, and after which there is a transient recovery over the first year (29). Neuroinflammation is suspected to contribute to the initial neurocognitive decline, in which there is an activation of astrocytes and microglia cells leading to an increase in pro-inflammatory cytokines. This may lead to ongoing tissue demyelination and remodeling and eventually resulting in altered neuronal function (30). In longer term, vascular changes in small and medium-sized vessels such as accelerated atherosclerosis and microangiopathy leads to vascular insufficiency and

Table 1 Prospective clinical trials reporting toxicity outcomes

Author, year, trial ID	Trial design	No. of patients	Median follow-up	Technique-dose/ intervention	Toxicity observed/significant findings	Scale	Comments
Neurocognitive decline							
Aoyama *et al.*, 2006–2015 (7,8), JROSG 99-1	Phase III, randomized	67 *vs.* 65	7.8 months	SRS alone (≤2 cm: 22–25 Gy, >2 cm: 18–20 Gy) *vs.* SRS (16.6 Gy) + WBRT (30 Gy/ 10 fractions)	All comers: at 12 months; preservation of NCF: 59% (SRS alone) *vs.* 76% (SRS + WBRT); secondary analysis of NSCLC patients: no difference MMSE scores between the 2 arms, when stratified by DS-GPA	MMSE	Neurocognitive outcomes were optionally assessed using MMSE. Data was available from only 28 patients in total. Improved neurocognitive preservation with WBRT + SRS attributed to improved intra-cranial control
Chang *et al.*, 2009 (9)	Phase II, randomized	28 *vs.* 30	9.5 months	SRS + WBRT *vs.* SRS	Decline in HVLT-R Total Recall, delayed recall & delayed recognition at 4 months: 52%, 22% & 11% (WBRT + SRS) *vs.* 24%, 6% & 0% (SRS) respectively	HVLT-R	The addition of WBRT was detrimental to neuro-cognitive function. WBRT reduced intracranial recurrences, but did not improve survival. 7% risk of biopsy-proven RN in SRS arm
Gondi *et al.*, 2014 (10), RTOG 0933	Phase II, single arm	113 *vs.* historical controls	6 months	HA-WBRT (30 Gy/10 fractions) *vs.* WBRT	At 4 months; mean relative decline in HVLT-R delayed recall: 7% *vs.* mean relative decline in HVLT-R delayed recall: 30%	HVLT-R	First prospective study demonstrating mitigation of neuro-cognitive decline with HA-WBRT
Kepka *et al.*, 2016 (11), NCT01535209	Phase III, randomized	29 *vs.* 30	29 months	Surgical cavity SRT (25 Gy/5 fractions) or SRS (15 Gy/1 fractions) *vs.* WBRT (30 Gy/10 fractions)	Neurologic and cognitive failure (without intracranial progression) seen in: 19% (SRT) *vs.* 31.5% (WBRT)	MMSE*	SRT was not found to be non-inferior to WBRT. Study is underpowered to draw any meaningful conclusion
Berger *et al.*, 2018 (12)	Prospective single arm, cohort study	14	3 months	Post-resection SRS	No significant neurocognitive or QOL changes 3 months following SRS	NeuroTrax computerized neuropsychological battery	Small prospective study, with a short follow-up, which shows preservation of NCF post cavity SRS
De Ruysscher *et al.*, 2018 (13), NVALT-11/DLCRG-02	Phase III, prospective, randomized	86 *vs.* 88	48.5 months	PCI (30–36 Gy/10–12 fractions) *vs.* observation	Increase in: cognitive disturbance (18.6% *vs.* 3.4%); memory impairment (30.2% *vs.* 9.1%)	CTCAE v3.0 (physician scored)	PCI arm had more neurologic adverse events, most of them were low grade (grade 1 and 2)

Table 1 (*continued*)

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Author, year, trial ID	Trial design	No. of patients	Median follow-up	Technique-dose/ intervention	Toxicity observed/significant findings	Scale	Comments
Hong *et al.*, 2019 (14), ACTRN12607000512426	Phase III, randomized	107 *vs.* 108	48 months	WBRT (30 Gy/10 fractions) (24 patients received HA-WBRT) *vs.* observation	Median time to deterioration of NCF: 5.3 *vs.* 6 months	Neurocognitive battery**	Deterioration in NCF may be due to intracranial disease, or WBRT. Neurocognitive outcomes not reported separately
Brown *et al.*, 2020 (15), NRG CC001	Phase III, randomized	257 *vs.* 261	7.9 months	WBRT + memantine (30 Gy/10 fractions) *vs.* HA-WBRT + memantine	At 6 months: significantly less decline in domains; learning: 24.7% *vs.* 11.5% (P=0.049); delayed recognition: 33.3% *vs.* 16.4% (P=0.02); TMT-B: 40.4% *vs.* 23.3% (P=0.01)	HVLT-R, TMT-B	No difference in OS, intracranial PFS or toxicity. HA-WBRT + Memantine patients reported improved QoL and fewer cognitive symptoms
Radiation necrosis (RN)							
Asher *et al.*, 2014 (16)	Single arm, prospective	47; 51 lesions	12 months	Neo-adjuvant SRS: median dose 14 Gy (11.6–18 Gy)	No RN	Radiological and histopathology co-relation	Neo-adjuvant SRS is a promising new approach to augment the treatment of surgically resected BM with high rates of local control with limited morbidity
Brennan *et al.*, 2014 (17)	Phase II, single arm	49; 50 lesions	12 months	Cavity SRS: 15–22 Gy	RN: 17.5% cavities	Biopsy proven	Post-op SRS is associated with high rates of local control
Kirkpatrick *et al.*, 2015 (18), NCT01017497	Randomized	49; 80 lesions	32.3 months	1 mm PTV margin *vs.* 3 mm PTV margin; SRS 15–24 Gy	RN in 6 lesions: 2.5% (1 mm group); 12.5% (3 mm group), P=0.1	Biopsy proven	Local control equivalent in both groups, but higher RN with larger PTV margin expansion
Ferro *et al.*, 2017 (19), ISIDE-BM-1	Single arm, prospective	30	3 months	WBRT (30 Gy/10 fractions) + SIB as follows (35–50 Gy/10 fractions)	No RN	NR	Use of IMRT–SIB to up to 50 Gy/10# is well tolerable
Bauman *et al.*, 2016 (20)	Phase II, multi-center	87	5.4 months	WBRT (30 Gy/10 fractions) + FSRT (60 Gy/10 fractions); simultaneous boost	2.3% asymptomatic RN, MMSE score deterioration in 16% of patients	Radiological	Patients with 1–3 BM treated with WBRT + SIB boost. OS 5.4 months

Table 1 (*continued*)

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Author, year, trial ID	Trial design	No. of patients	Median follow-up	Technique-dose/ intervention	Toxicity observed/significant findings	Scale	Comments
Nichol *et al.*, 2016 (21), NCT01046123	Phase II, multi-center, single arm	60; 219 lesions	30.5 months	WBRT 20 Gy/5 fractions, SIB 50 Gy/5 fractions to BM	Crude incidence of severe RN (grade 3–5) 25% for deep metastasis (thalamus, basal ganglia); 1.9% per non-deep metastasis, 10% per patient	Radiological	WBRT with SIB for multiple BM. OS similar for 1–3 BM *vs.* 4–10 BM. Deep BM seen to have a higher risk of RN
Choi *et al.*, 2017 (22), NCT00946673	Phase I, multi-centre	12	12 months	Vorinostat + SRS; SRS dose 20–24 Gy/1 fraction, depending on size	One patient (8%) at the 400-mg dose level with a 2.0-cm metastasis developed grade 4 RN 2 months after SRS	Biopsy-proven	Phase 1 trial to determine the safe dose of vorinostat (histone deacetylase inhibitor)
Miyakawa *et al.*, 2019 (23)	Phase II, prospective	40	7 months	WBRT (30–37.5 Gy/10–15 fractions) followed by low dose GK (12–14 Gy)	2.5% symptomatic RN; 2.5% leukoencephalopathy	NR	Low dose GK followed by WBRT for advanced stage BM has favorable intracranial control and low risk of RN

*, neuro-logical/cognitive failure was defined as a worsening of the MMSE test score by three or more points compared to the baseline score, or neurological death; **, neurocognitive battery includes HVLT-R, COWA, TMT-A and B. MMSE, mini mental state examination; HVLT-R, Hopkins Verbal Learning Test Revised; TMT-B, Trail Making Test-B; SRS, stereotactic radio surgery; WBRT, whole brain radiotherapy; SRT, stereotactic radiotherapy; QOL, quality of life; NCF, neurocognitive function; NR, not reported; PFS, progression-free survival; PTV, planning target volume; SIB, simultaneous integrated boost; RN, radionecrosis; GK, Gamma Knife.

infarction of brain parenchyma, which in turns sets off a milieu of neuroinflammation and accelerated brain atrophy (29,30). The transient improvement in neurocognitive function, is then followed by the second phase of irreversible and progressive decline in memory function (29), which happens months to years after completion of WBRT. This is linked to radiation-induced damage to proliferating neuronal progenitor cells in hippocampus subgranular zone, which have been reported to be relatively radio-sensitive (31). New neurons generated in the hippocampus subgranular zone form an important part of memory function, and the radiation-induced damage to the hippocampus leads to disruption of neurogenesis, hence leading to memory decline after RT. As a summary, the neurocognitive outcomes from prospective clinical trials conducted in patients with BM treated with WBRT and/or focal RT are reported in *Table 1*.

Mitigation strategies

Maintaining neurocognitive function is prioritized by many patients and caregivers, and is intricately linked to quality of life. Mitigation strategies, and if possible, prevention, need to be instituted upfront. These may include use of focal RT (SRS/HSRT alone) in lieu of WBRT, or withholding RT entirely. In situations where WBRT is cleared indicated, then the use of pharmacological agents and/or hippocampal sparing techniques should be considered.

Focal RT alone

One of the main ways to avoid neurocognitive decline would be to consider the use of focal RT alone in patients with limited intracranial metastases. A phase III randomized trial comparing WBRT versus SRS with WBRT (32), demonstrated that cognitive deterioration was more likely in patients (91.7%) when combined with WBRT as compared to SRS alone (63.5%; 90% CI: –41.9% to – 14.4%; P<0.01). Furthermore, there was more reduction in verbal fluency, immediate and delayed recall in patients treated with both WBRT and SRS. The overall survival was not significantly better with the addition of WBRT to SRS (HR =1.02; 95% CI: 0.75–1.38; P=0.92). Hence in the absence of difference in overall survival and the increase in cognitive decline with WBRT, the preferred strategy for limited BM is SRS/focal radiotherapy (32) which can be considered to avoid neurocognitive decline. This is similarly illustrated in the individual patient data meta-analysis by Sahgal *et al.*, looking at randomized controlled trials for patient with limited BM—where the addition of WBRT to SRS did not improve survival, despite distant brain failure being reduced with WBRT (33). Most of the Phase III randomized trials investigating focal RT alone only included patients with up to 3–4 BM. However, there has been a paradigm shift recently, and practice guidelines such as NCCN (34) have not placed a numerical upper limit when recommending focal RT alone. The evidence for this shift primarily stems from the large observational prospective study from Japan (35), where patients with up to 10 BM were treated with SRS alone. Based on their data, they did not find a survival difference between patients who had 2–4 and 5–10 BM.

Hippocampal avoidance

As mentioned earlier, the hippocampus is crucial for memory formation and learning. Radiation-induced injury to the hippocampal dentate gyrus has been proven to lead to loss in neurogenic capacity associated with memory formation and impaired recall (10). Advances in technology allowed for selective dose reduction to the hippocampi in patients with BM at least 5 mm away from them, through intensity modulated radiotherapy (IMRT), whilst still treating the remaining brain parenchyma and meninges to the required dose (29). This strategy was first evaluated in RTOG0933 (single arm Phase II), which utilized hippocampal-avoidance WBRT (HA-WBRT) 30 Gy in 10 fractions (10). The results were promising as there was a significantly lower neurocognitive decline at 4 months—mean decline in delayed recall of 7% as compared to 30% noted in the historical control group (P<0.001). Hippocampal avoidance was also evaluated, in the setting of prophylactic cranial irradiation for limited stage small cell lung cancer, in the PREMER Phase III trial, where patients received HA-PCI 25 Gy in 10 fractions versus standard PCI. Neurocognitive decline was less in the HA-PCI arm measured by delayed-free recall at 3 months (5.8% *vs.* 23.5%, OR 5, P<0.003) (36).

Pharmacological agents: memantine, donepezil

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist, which competes with glutamate to bring to NMDA receptor, hence reducing excessive NMDA activating and preventing excitotoxicity of the neuron (30). It is largely used in vascular and Alzheimer's dementia and has been proven to improve cognitive performance. This led to a phase III randomized, double-blind, placebo-controlled

trial (RTOG0614) of memantine in patients undergoing WBRT to 37.5 Gy in 15 fractions (37). Patients were assigned to receive either placebo or memantine (which was given in increasing dosage regimen to 20 mg/day) within 3 days of initiating radiotherapy for 24 weeks (37). Patients who received memantine showed significantly longer time to cognitive decline (HR =0.78; 95% CI: 0.62–0.99; P=0.01). Furthermore, the probability of cognitive function failure at 24 weeks was 53.8% in the memantine arm as compared to 64.9% in the placebo arm. Other results from this study which supports the use of memantine included better executive function at 8 and 16 weeks, processing speed and delayed recognition at 24 weeks. Although the RTOG0614 study primary endpoint did not reach statistical significance due to patient dropout, memantine should be considered in patients undergoing WBRT who have a prognosis of >6 months. In general, memantine is well tolerated. Based on a meta-analysis of RCTs (conducted in dementia patients) the likelihood of discontinuation due to intolerability was 11.5% with placebo and 10.1% with memantine (i.e., no significant difference). Common adverse reactions include dizziness (7% memantine, 5% placebo), headache (6% memantine, 3% placebo) and constipation (5% memantine, 3% placebo) (38).

Another pharmacological strategy available is the use of Donepezil, which is a reversible non-competitive inhibitor of acetylcholinesterase that enhances cholinergic-dependent neural communication (39). This has been studied in a phase III randomized, placebo-controlled clinical trial in which patients who were receiving partial- or whole-brain irradiation were randomly assigned to receive either placebo or daily donepezil. After 24 weeks of treatment, overall composite scores did not improve significantly, however there were improvements in several cognitive functions, especially among patients with greater pre-treatment impairment (40).

Hippocampal avoidance and memantine

Building upon the use of both memantine and HA-WBRT, a phase III trial (NRG CC001) evaluated the potential combined neuroprotective effects of hippocampal avoidance WBRT 30 Gy in 10 fractions with memantine (for 24 weeks), as compared to conventional WBRT with memantine. Results showed significantly lower risk of cognitive failure with HA-WBRT plus memantine as compared to WBRT plus memantine (adjusted HR =0.74; 95% CI: 0.58–0.95; P=0.02). The HA-WBRT plus memantine group showed less deterioration in executive function at 4 months, and learning and memory at 6 months. Overall at 6 months, HA-WBRT plus memantine group reported less fatigue, less difficulty with speech and memory, and less interference of neurological symptoms in daily activities (15). With these positive findings, HA-WBRT with memantine should be considered as standard of care for patient for patients requiring WBRT, especially if the expected prognosis is >6 months. Moving forward, there is a currently ongoing phase III randomized trial comparing SRS to HA-WBRT plus memantine for 5–15 BM (NCT03550391) (41). One area of investigation, which is currently unclear, is whether memantine should be continued as a maintenance strategy, for long term survivors.

Avoidance of RT by the use of upfront targeted therapy

There has been a recent trend to use targeted therapy alone for patients with known driver mutations. The advent of new small molecules with intracranial activity has made this possible, particularly in primary cancers such as EGFR-mutation positive lung cancer, Her2+ breast cancer, BRAF V600E mutation positive melanoma. However, this approach is not uniformly adopted by all, as it remains unclear how targeted therapy compares to RT. The retrospective multi-institutional cohort study by Magnusson et al suggested that the survival outcomes, in patients with BM from EGFR-mutation positive lung cancers, were inferior for patients treated with upfront tyrosine kinase inhibitors (TKI) (42). It has to be noted that this study was conducted prior to widespread availability of third generation TKI (e.g., osimiternib), which are known to have better intracranial activity. This topic has been comprehensively reviewed elsewhere (43,44).

Stereotactic radiosurgery (SRS)/hypofractionated stereotactic radiotherapy (HSRT)

Focal radiotherapy (e.g., SRS/HSRT) is increasingly the preferred management for BM, as it is highly effective and convenient. There is minimal disruption of systemic therapy, thereby allowing optimal control of extra-cranial disease. Although rare, late complications can be seen in up to 5% of patients, and may increase particularly in patients who survive more than 1 year. These include radiation necrosis, cranial nerve injury (particularly optic nerve) and brain stem injury. These will be elaborated on below, together with suggested mitigation strategies.

Radiation necrosis (RN)

RN is an inflammatory reaction, due to radiation-induced cell death, that occurs between 6–24 months after completion of SRS (45). Radiologically, RN is difficult to distinguish from intra-cranial disease progression/recurrence on conventional MRI (46) as it commonly occurs in close proximity to original tumour location or in-field. On conventional MRI, RN can appear as a contrast-enhancing lesion on T1 sequence, with peri-lesional vasogenic oedema. Due to the overlapping similarities between RN and tumour recurrences, more advanced imaging techniques are increasingly used to aid in the recognition and diagnosis of RN. Diffusion-weighted MRI imaging such as MR perfusion and MR spectroscopy, has increased sensitivity and specificity for radiation necrosis, hence allowing for accurate diagnosis of RN (47). As normal brain tissue has lower amino acid uptake as compared to tumour cells, specific amino acid tracers such as carbon-11 methionine (MET), fluoro-l-thymidine (FLT) and fluoroethyl tyrosine, are increasingly used in positron emission tomography (PET). These tracers have been reported to have a high sensitivity and specificity (47). However, these novel amino-acid tracers may not be widely available in clinical practice.

Histologically, radiation necrosis is found mainly in white matter with associated endothelial damage, perilesional oedema and gliosis (46). Histopathological findings include coagulation and liquefaction necrosis, with surrounding vessel thickening, hyalinization and thrombosis of blood vessels resulting in hypoxic injury to surrounding parenchyma (47,48). There are 2 main theories explaining the pathophysiology of radiation necrosis. The first theory postulates that necrosis arises due to damage to oligodendrocytes and glial cells, hence leading to demyelination in white matter. The second theory is that radiation leads to vascular injury around the irradiated tumor issues which leads to tissue ischemia. This is associated with increased release of pro-inflammatory factors such as TNF -alpha, VGEF, IL-1 and IL-6. These pro-inflammatory factors leads to increase in blood-brain barrier, increase in leukocyte adhesion and induce endothelial apoptosis (48).

The incidence of radiation necrosis post-SRS ranges between 5–25%. The large variation exists due to varying definitions of RN, and only some studies requiring histological confirmation and/or prolonged follow-up. In a large institutional series, consisting of 2,200 BM treated with SRS, investigators from UCSF reported the incidence of RN to be 5% at 1 year, with approximately half being symptomatic (49). *Table 1* summaries the incidence of RN in prospective clinical trials which have utilized SRS for the management of BM.

Briefly, the usual management of symptomatic radiation necrosis includes a prolonged course of dexamethasone, which serves to reduce inflammation and oedema of necrotic tissue. Bevacizumab, an anti-VEGF antibody, can be used in the treatment of radiation necrosis, with reported 64% reduction in RN volume on radiographical imaging. Furthermore, there is a reduction in steroid requirement, with stability or improvement in RN-associated symptoms (50). MRI-guided laser-induced thermal therapy (LITT) is a minimally invasive ablative technique that generates high temperature with accurate delivery to target cells, resulting in tissue coagulation necrosis, angiogenesis eradication and cellular apoptosis (51). Other possible therapies include anti-coagulants and hyperbaric oxygen therapy, in which the benefits are limited and conservative. Alternatively, surgical resection of RN has to be considered for symptomatic patients who are refractory to medical treatment.

Clearly, there can be multiple contributory causes to RN, and ultimately the clinical manifestation may be due to a combination of these factors. Dose received by the uninvolved brain parenchyma plays a major role. The HyTEC group of investigators have recommended, tissue volumes (including target volume) receiving 12 Gy (single fraction) to be kept below 5 cm^3 for the symptomatic RN risk to be kept below 10% (52). Similarly, for multi-fraction treatments, they have recommended 20 Gy (3 fractions) or 24 Gy (5 fractions) to be kept below 20 cm^3 for the symptomatic RN risk to be below 10%. Prescription practices vary between SRS delivery platforms (e.g., Gamma Knife versus LINAC-based), however the risk of RN has not been shown to be different. For example, the 50% isodose line is typically selected for the Gamma Knife platform, whereas the 60–80% isodose line is selected for LINAC-based platforms. This typically results in higher maximum doses and steeper dose gradients for the Gamma Knife platform. Frameless radiosurgery platforms typically utilize a planning target volume (PTV) margin of 1 to 3 mm. Kirkpatrick *et al.* conducted a randomized controlled trial, and reported that the use of a 3 mm (*vs.* 1 mm) results in higher rates of RN (18). Dose heterogeneity has been suggested to contribute to RN, in particular if they occur within GTV-PTV margin where normal brain parenchyma is located (53). *Table 2* outlines other contributory factors, and the suggested mitigation strategies (54).

Table 2 Contributory factors and mitigation strategies for radiation necrosis [adapted from (54)]

Contributing factor	Mitigation strategy	Reference
Dose-volume interplay	SRS dose should be lowered for larger volume lesions	(55)
	However, tumour control is compromised as a result	(56)
	Large volume targets should be considered for the following	
	(I) Surgical resection, in addition to SRS. Both pre-operative and post-operative SRS approaches are valid options	(57,58)
	(II) HSRT in preference to SRS	(56,59)
Volume of uninvolved brain parenchyma exposed to intermediate-high dose	Attention should be given to the intermediate dose spillage (e.g., 80% and 50% isodose volumes)	
	This is especially important when multiple isocentres are used to treat multiple targets	(60,61)
	Dedicated SRS platforms seem to perform better at reducing dose-gradient index, compared to single arc VMAT	(62)
	A reduction in prescription dose (of 1–2 Gy) may be required when multiple targets are being treated simultaneously	(63)
Prior radiation exposure	In the setting of recurrent tumour, alternatives should be explored (surgery resection, chemotherapy/targeted therapy)	
	If re-SRS is attempted, a fractionated approach or dose reduction is favoured	
Use of concurrent systemic therapy	Caution should be exercised with certain agents such as ipilumumab, VEGFR TKI and EGFR TKI	(64)
	Admittedly, the data regarding increased neuro-toxicity is unclear and may be partially related to the target volume	(65)
	If possible, a washout period of 5 half-lives should be allowed before SRS (approximately 5–7 days for common agents such as sorafenib, pazopanib and gefitinib)	
	There are no guidelines when these agents can be restarted. A period of 2–4 weeks may be sufficient to ascertain that there are no acute side effects from SRS	
Large PTV margin	End-to-end testing should be undertaken at each SRS centre to determine the minimum PTV margin	
	Technologies which allow a smaller PTV should be preferentially used	(66)
Planning parameters	A dedicated SRS team builds experience and is recommended	(67-71)
	A higher degree of variation is to be expected with LINAC-based platforms, especially with smaller targets	
	Parameters such as conformity index, dose gradient index and conformity/gradient index should be assessed during plan evaluation	
Lack of quality assurance (QA) program	A protocolized and evergreen quality assurance program is needed at both the departmental level and a patient-specific level	(72)
	For patient-specific QA, target volume delineation should ideally undergo peer review prior to treatment (especially for complex targets such as resection cavities), and pre-treatment verification using film dosimetry is highly recommended	(73-76)
Non-modifiable factors including: (I) intrinsic radiosensitivity; (II) location of lesion	It is challenging to determine intrinsic radiosensitivity prior to treatment. Alternatives to SRS can be considered such as surgical resection or systemic therapeutics	(77)
	A gentler approach with HSRT may be warranted in these cases	

SRS, stereotactic radiosurgery; HSRT, hypofractionated stereotactic radiotherapy; VMAT, volumetric modulated arc therapy; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor; PTV, planning target volume; LINAC, linear accelerator.

Radiation-induced optic neuropathy

The optic nerve can be divided into 4 segments: intra-ocular, intra-orbital, intra-canalicular (within optic canal) and cisternal (within supra-sellar cistern) segments. The optic nerve is a special sensory nerve which transmits visual information regarding brightness, color and contrast. Radiation-induced optic neuropathy (RION) is a late complication which can present with painless visual impairment progressing rapidly over a few weeks. RION usually occurs months or years after radiation therapy, with average onset of approximately 18 months after treatment (78,79). Visual impairment may be bilateral for injuries located near the optic chiasm. Symptoms of RION may include impairment of colour vision, visual field deficit or worsening visual acuity. Clinical signs may include a relative afferent pupillary defect, optic disc pallor and/or swelling. Typically, contrast-enhancement (within the optic nerve) can be seen on T1 sequence, with a high signal on T2 (79).

Common management of RION includes the use of steroids, anti-coagulation, hyperbaric oxygen (78) and pentoxifylline. Hyperbaric oxygen therapy is believed to increase fibroblastic activity, collagen synthesis and neovascularization of irradiated tissues, and may help in RION if initiated within 72 h. However, it requires multiple sessions (over 6 weeks) which may be inconvenient for patients. Till date, the benefits and effectiveness of these management measures have shown limited results. Emerging evidence is suggestive that a course of bevacizumab can be helpful in RION, but more data is required (80). Clearly, as no effective treatment is available, more emphasis needs to be placed on prevention by proper patient selection and radiotherapy planning.

Contributing factors and mitigation strategies

The dose received by the optic nerve is the single most important factor for RION. Early reports have recommended the maximum point dose to the optic nerve is recommended to be kept to below 8 Gy (81). Data from Mayo Clinic has suggested that this may be overly conservative, and that the risk of RON is ~1% for patients receiving up to 12 Gy (82). Doses exceeding 12 Gy lead to a 10% risk (83). The recently published HyTEC data (52) offers guidance in terms of dose selection, to keep the risk of RION below 1%. The maximum dose should be kept to below 12 Gy (ideally 10 Gy) in a single fraction, 20 Gy in 3 fractions and 25 Gy in 5 fractions. It is not clear if a volume-effect exists for the optic nerve, but the general principles of ALARA should be adhered to. Data from Stanford has shown that the optic chiasm is subject to physiological motion, and thereby receiving up to 14% more dose that predicted. They have recommended to add a 0.5–0.75 mm planning at risk volume (PRV) margin to this structure during plan optimization (84). Whether underlying vasculopathic risk factors (such as diabetes mellitus, hypertension) contribute to RON remains controversial (79,85).

Appropriate contouring using high-resolution MR (e.g., ensuring no gaps between the optic nerve and chiasm), dose selection and rigorous radiotherapy planning should be used to reduce the risk of RION (86-88). In cases where the lesion is abutting the optic apparatus, single fraction SRS may not be considered appropriate if the maximum point dose to optic apparatus cannot be limited to 12 Gy or lower. In such situations, a 3 to 5 fractions approach should be considered to maximise the therapeutic window. In lesions where the optic nerve is compressed, decompressive surgery can be attempted prior to SRS, or a more conservative dose limit should be used.

Brain stem injury and mitigation strategies

Brainstem metastases only accounts for 5% of all BM. However, the consequences of brainstem injury can be devastating. The clinical manifestation depends on the location of the necrosis, as there are many cranial nerve nuclei and long tracts that pass through the brainstem. The diagnosis is made clinically, with correlative imaging findings. Enhancing foci may be seen on contrast enhanced MRI, similar to parenchymal RN, together with an abnormal T2 signal corresponding to the area of high dose. The overall incidence is low, as most practitioners will compromise tumor coverage instead of overdosing the brainstem. Similar to RION, mitigating brainstem injury is predicated on accurate contouring of the brainstem (using MRI) and adhering to known dose constraints (86,87). Based on studies in patients with brainstem metastases, doses of 15–20 Gy SRS have been used with relatively low complication rates (89,90). Data on brainstem tolerance from hypofractionated RT are obtained from treatment of skull base tumors, where early studies using a regimen of 42 Gy in 6 fractions reported a 5% complication rate (91). With modern planning and delivery, brainstem injuries have been very rare at doses of 20–21 Gy in 3 fractions, 22 Gy in 4 fractions and 25 Gy in 5 fractions (92-95). QUANTEC data recommends maximum point doses are 12.5 Gy

in a single fraction, 21 Gy in 3 fractions or 25 Gy in 5 fractions (96). Fractionated schedules should be considered if constraints cannot be achieved with a single fraction SRS. Although not supported by strong clinical data, the periphery of the brainstem (especially if a small volume is exposed) has been suggested to be more tolerant (97).

Conclusions

Survival of patients with BM continues to improve. Although the focus is usually on intra-cranial control, serious treatment-related complications can occur impairing patient's quality of life. Consequently, the use of WBRT is declining, and being substituted with focal RT, even in the setting of multiple BM. However, WBRT can still be used selectively, and may still have a role in patients with diffuse intracranial disease. Upfront mitigation strategies such as hippocampal avoidance and memantine should be instituted for these patients. With focal RT being performed for more patients, the risk of RN must be anticipated and counselled to patients. Fractionated focal RT (e.g., hypo fractionated stereotactic RT) is an attractive option which maximizes the therapeutic window. With an increase in awareness of these complications, more prospective trials are being conducted to investigate the effect of these mitigation strategies.

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