




Radiation Necrosis from Stereotactic Radiosurgery—How Do We Mitigate?

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Opinion statement

Intracranial stereotactic radiosurgery (SRS) is an effective and convenient treatment for many brain conditions. Data regarding safety come mostly from retrospective single institutional studies and a small number of prospective studies. Variations in target delineation, treatment delivery, imaging follow-up protocols and dose prescription limit the interpretation of this data. There has been much clinical focus on radiation necrosis (RN) in particular, as it is being increasingly recognized on follow-up imaging. Symptomatic RN may be treated with medical therapy (such as corticosteroids and bevacizumab) with surgical resection being reserved for refractory patients. Nevertheless, RN remains a challenging condition to manage, and therefore upfront patient selection for SRS remains critical to provide complication-free control. Mitigation strategies need to be considered in situations where the baseline risk of RN is expected to be high—such as large target volume or re-irradiation. These may involve reduction in the prescribed dose or hypofractionated stereotactic radiation therapy (HSRT). Recently published guidelines and international meta-analysis report the benefit of HSRT in larger lesions, without compromising control rates. However, careful attention to planning parameters and SRS techniques still need to be adhered, even with HSRT. In cases where the risk is deemed to be high despite mitigation, a combination approach of surgery with or without post-operative radiation should be considered.

Introduction

The delivery of conformal radiation in one (SRS) or 3–5 fractions (HSRT) has been used in brain lesions for > 50 years. It is proven to be effective and convenient and is being increasingly adopted worldwide. This is exemplified in the setting of brain metastases (BM), where the use of whole-brain radiotherapy (WBRT) is decreasing and the use of SRS is increasing [1]. Other conditions commonly treated with SRS include non-malignant tumours (meningioma, pituitary adenoma, vestibular schwannoma) and malignant (recurrent glioma) tumours, arteriovenous vascular malformations (AVM) and functional disorders (trigeminal neuralgia and movement disorders). The principles of SRS/HSRT

involve accurate target localization, meticulous treatment planning with multiple beam angles allowing for conformal dose distribution around the target and image-guided treatment delivery. Multiple commercial platforms are currently available including Gamma Knife, CyberKnife or linear accelerator (LINAC), which are all able to produce a sharp dose fall-off outside the target. However, due to the physical properties of megavoltage radiation, the peri-lesional areas are invariably exposed to low-intermediate doses of radiation, resulting in treatment-related imaging changes which can be indistinguishable from tumour recurrence. These changes may represent radiation necrosis (inflammation

from tissue death), which can lead symptomatic oedema and a decline in the patient's quality of life.

In this focused review, we will elaborate on the pathophysiology, diagnosis and contributing factors for

radiation necrosis. In addition, since established treatments are limited, we will outline mitigation strategies to avoid RN.

Search strategy

We performed a search on MEDLINE using the MESH headings "radiosurgery" and "necrosis" on September 10, 2020. Eighty four citations were retrieved, and relevant studies have been included in this narrative review.

Incidence of RN

The incidence of RN is probably between 5 and 26%, with roughly 1/3–1/2 being symptomatic [2–7]. This large variation exists, in part, due to the varying definitions of RN (some based on radiological changes while others requiring pathological confirmation). The incidence is likely higher amongst contemporary cohorts owing to improved quality of diagnostic imaging, increased awareness of RN and longer survival of patients given improved oncological treatment. The largest series from Cleveland Clinic, assessing 1650 patients with 2843 brain metastases, report a radiographic RN rate (per lesion) of 8% with half being symptomatic [7•].

Pathophysiology of RN

Early animal experiments, using single fractions ranging from 10 to 25 Gy, indicated that the radiation tolerance of brain parenchyma was dependent on radiation dose, irradiated volume and time elapsed post-radiation [8, 9]. Post-mortem analysis demonstrated reduction in vasculature and myelin in the irradiated areas. In addition, these pre-clinical experiments demonstrated that the necrosis free-interval shortens with higher doses.

There are two main theories regarding the pathophysiology of RN:

- Vascular injury theory

Large fraction sizes (typically > 8 Gy) can activate acid sphingomyelinase and cause upregulation of ceramide, leading to endothelial apoptosis [10]. Kamiryo et al. have reported that endothelial changes precede frank necrosis [11]. These changes include reduction of capillary density, increase in capillary diameter and thickening of the capillary basement membrane. In addition, radiation can lead to a pro-inflammatory milieu (involving TNF-alpha, IL-1beta, VEGF, ICAM-1) eventually leading to fibrinoid necrosis of small vessels, resulting in ischemia and cell death of brain parenchyma [12–16].

- Glial cell theory

Both oligodendrocytes and astrocytes can be affected by radiation, with the former being more sensitive [17]. Direct damage to oligodendrocytes and their

precursors (oligodendrocyte type2 astrocytes) may lead to white matter demyelination and necrosis [18]. Radiation has been shown to cause activation of astrocytes (reactive astrogliosis), contributing to the inflammatory environment which is seen in RN [19].

Diagnosis of RN

The diagnosis of RN can be notoriously challenging, which is a major limitation when interpreting the literature. There lacks a current gold standard, although histopathological confirmation is preferred. In many situations, there can be a co-existence between radiation changes and residual tumour with the relative proportion influencing the final diagnosis [20, 21].

1. Histopathological changes: Endothelial cells are highly susceptible, with morphological changes including fibrinoid necrosis, haemorrhage, hyalinisation and thrombosis of the blood vessels. The necrotic area has scant cellularity, surrounded by gliotic brain tissue containing GFAP-reactive astrocytes demonstrating prominent cytoplasmic ramification. Foamy macrophages and hemosiderophages can be seen, with occasional dystrophic calcification. Radiation-induced cytologic atypia may be encountered—with features of cytomegaly and bizarre-looking bubbly nuclei. In the setting of tumour recurrence with superimposed RN, immunohistochemical staining may be helpful (dependent on the primary pathology) to highlight viable tumour cells.
2. Radiological investigations
 - Magnetic resonance imaging (MRI) is usually the initial investigation for patients with suspected RN. Unfortunately, both RN and tumour recurrence show contrast enhancement and peri-lesional oedema [22, 23]. Temporal changes (e.g. increase in lesion size) are not specific to either diagnosis. Characteristic enhancement patterns seen with RN, such as “swiss cheese” and “soap-bubble”, have a low positive predictive value [24]. Lesion-quotient (LQ) values below 0.3, referring to the ratio of nodule on T2 sequence to the total enhancing area on T1 sequence, have been suggested, but are not uniformly reproducible in other studies [24, 25]. The low predictive value of conventional MRI alone has prompted many groups to explore advanced imaging modalities to improve the diagnostic confidence of RN [26]. For example, serial radiomic changes and time-dependent contrast changes seen with conventional MRI imaging have shown potential to improve the diagnostic accuracy [27–29].
 - MR perfusion: Recurrent tumour has increased vasculature, resulting in higher perfusion and blood volume, compared to RN. An increased relative cerebral blood volume (rCBV) on dynamic susceptibility weighted MRI has been proposed to differentiate recurrent tumour from RN [30, 31]. However, the interpretation can be subjective. Hu et al. reported that $rCBV < 0.71$ of having a 92% sensitivity and 100% specificity for RN [31]. Other authors have suggested a higher rCBV cut-off of 2.1 (100% sensitivity and specificity) [32]. Acknowledging the significant overlap in rCBV cut-off values, Barajas et al. proposed using percentage of signal-intensity recovery as a metric for RN [22].

Intravoxel incoherent motion (IVIM) provides quantitative diffusion and perfusion readouts based on diffusion-weighted imaging and has been shown to be superior to rCBV for the diagnosis of RN [33].

- MR spectroscopy: Intra-lesional metabolite composition may help with the diagnosis of tumour recurrence versus RN. For example, Zeng et al. have found that when both choline creatinine and choline-N-acetyl aspartate values were above 1.71, sensitivity, specificity and diagnostic accuracy were 94.1%, 100% and 96.2% respectively for tumour recurrence [34]. In contrast, an elevated lipid-lactate peak and low levels of metabolites would favour RN [35]. In addition, utilizing multi-voxel spectroscopy has been shown to be more accurate than single voxel [36]. However, MRS is limited by voxel size, requiring the lesion to be larger than 1 cm³, and is subject to sampling errors in heterogeneous tumours. Chemical exchange saturation transfer (CEST) imaging is a novel method looking at endogenous mobile peptides and has been shown to be differentiate RN from tumour recurrence with high accuracy in a small cohort [37].
- Functional imaging: The main drawback of FDG-PET is the high physiological glucose metabolism in the normal brain parenchyma, which may mask tumour recurrences. Amino acid tracers such as carbon-11 methionine (MET), fluoro-1-thymidine (FLT) and fluoroethyltyrosine (FET) have shown promise, as there is selective localization within the tumour, in contrast to normal brain parenchyma [38–41]. However, in a meta-analysis by Li et al., sub-group analysis comparing amino acid tracers and FDG had similar diagnostic accuracy in differentiating recurrent brain metastases from RN [42]. Apart from PET, thallium-201 SPECT has been shown to be useful to distinguish tumour recurrence from RN in brain metastases and high-grade gliomas [43].

Figure 1 shows the various imaging modalities which can be used to diagnose RN.

Contributory factors for RN

A direct cause effect relationship can be challenging, as the development of RN is likely multifactorial. The underlying condition for which SRS is being used should also be considered. Counter-intuitively, the risk of RN in patients with AVM undergoing SRS is lower than patients with BM, despite the shorter survival seen in patients with metastatic disease [44••].

- 1) Dose-volume interplay: The radiation dose contributes to RN. SRS at doses above 24–25 Gy are at higher risk of causing RN [45]. Shehata et al. reported that in patients treated with prior WBRT, prescription doses exceeding 20 Gy (for brain metastases < 2 cm) increased the risk of Grade 3 or higher (G3+) toxicity [46]. In addition, the volume effect exists within the brain, where small targets can be safely treated to a higher dose, and a dose reduction is needed as the tumour volume increases. A stepwise reduction of safe SRS prescription doses, based on maximum tumour diameter, was determined by early RTOG trials [47]. In a multi-variable analysis from RTOG 90-05, tumour diameter was significantly associated with G3+ neuro-toxicity with tumours between 2

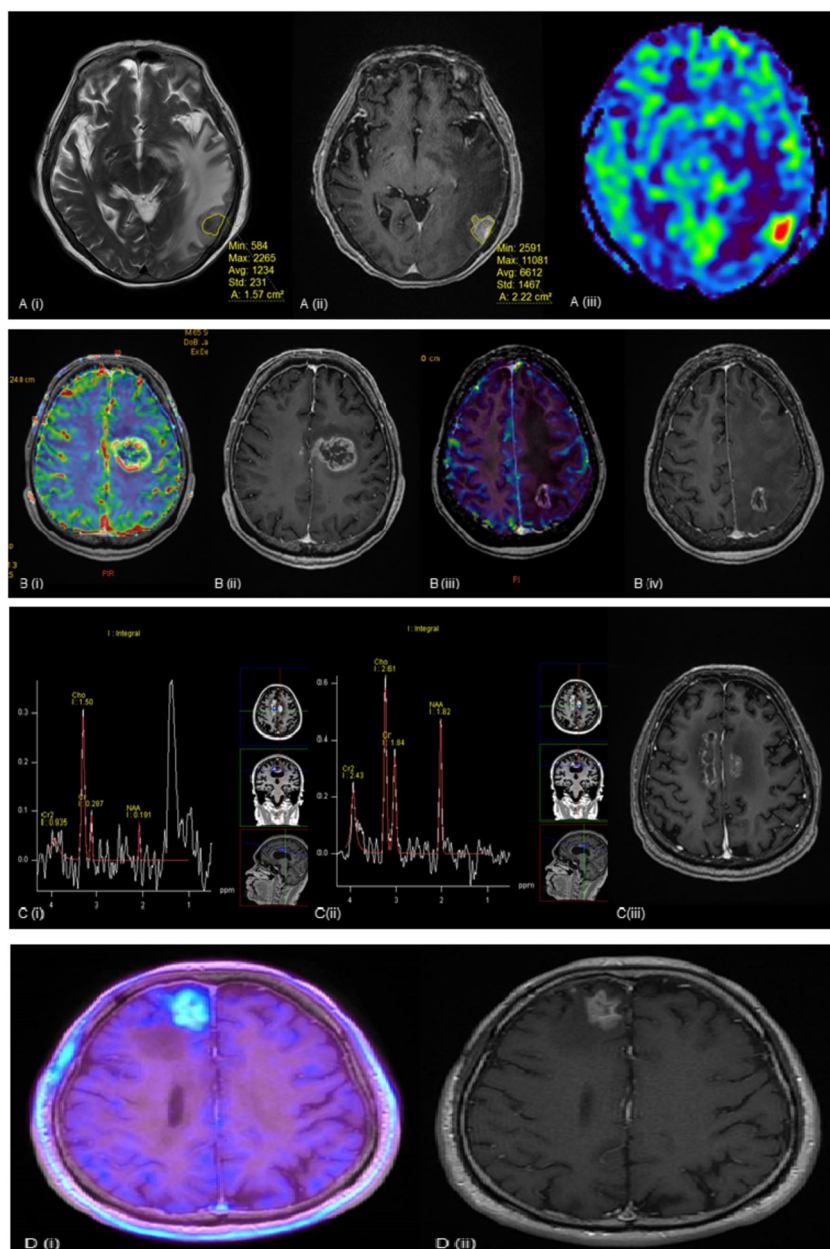


Fig. 1. **a** Tumour recurrence: (i) T2-weighted, (ii) post-contrast T1 and (iii) rCBV (relative cerebral blood volume) MR perfusion sequence of a lesion within the left temporal lobe. The lesion quotient of 0.71 and increased rCBV is suggestive of tumour recurrence. **b** Tumour recurrence: (i) rCBV and (ii) post-contrast T1 showing increased blood flow within the periphery of the lesion, which was histology proven to a tumour recurrence. Radiation necrosis: (iii) rCBV and (iv) post-contrast T1 showing no increase in blood flow. **c** Mixed picture of radiation necrosis and tumour recurrence: (i, ii) MR spectroscopy and (iii) post contrast T1 showing a growing pericallosal lesion post-WBRT. High lipid-lactate peak seen in radiation necrosis at the right cingulum while increased choline:creatinine and choline:N-acetyl-aspartate ratios suggestive of tumour recurrence in the left cingulum. **d** Tumour recurrence: (i) F-18 FET PET showing amino acid tracer uptake within the enhancing lesion, with (ii) demonstrating the lesion on post-contrast T1 (adapted from Vellayappan B, Tan CL, Yong C, Khor LK, Koh WY, Yeo TT, Detsky J, Lo S, and Sahgal A. Diagnosis and Management of Radiation Necrosis in Patients With Brain Metastases. *Front Oncol.* 2018 Sep 28;8:395.doi: 10.3389/fonc.2018.00395. PMID: 30324090; PMCID: PMC6172328)

and 3 cm having a 7.3-fold higher risk and tumours 3 and 4 cm having a 16-fold higher risk (in comparison to tumours < 2 cm) [45].

- 2) Volume of uninvolved brain parenchyma exposed to intermediate-high dose: This has been shown to be an independent risk factor in some studies [3, 5, 48, 49]. The V12 (volume of brain receiving 12 Gy or higher) metric has been commonly reported to correlate with RN [5, 48]. However, the cut-off values suggested by studies have varied, depending on the underlying condition and how the volumes were defined. It remains unclear if the gross target volume (GTV) should be subtracted from V12 when assessing this metric. This is an important consideration, especially with larger lesions. The recently published HyTEC report suggests a more conservative approach, where the tissue V12 is utilized (i.e. without subtracting GTV) [44••]. Based on their normal tissue complication probability (NTCP) modelling, the risk of RN is approximately 10% or less when $V12 < 5$ cc. SRS for AVM was associated with lower rates of RN, compared to brain metastases, for equivalent V12 values. With the increasing use of HSRT, many single institutional cohorts have reported the rates and dose-volume metrics associated with RN [50–54]. Inoue et al. and Peng et al. have suggested that the volume received by the single fraction equivalent dose of 14 Gy (SFED V14) is to be computed [51, 52, 54]. Assuming an alpha/beta value of 2, this translates to V23 (for 3 fractions) and V29 (for 5 fractions). The probability of G3+ toxicity (requiring surgical intervention) approximates 4% if these values exceed 20 cc [44••].
- 3) Single versus multiple lesion SRS: Recent trials, and guidelines, have suggested SRS to be used in patients with multiple brain metastases [55–57]. Although there is no head-to-head comparison suggesting that the risk of RN is higher in patients with multiple BM undergoing SRS, the intermediate dose spillage to the brain parenchyma is expected to be higher than for a patient undergoing SRS to a single lesion. Previous studies have found the V12 metric to have a linear correlation with total tumour volume, rather than the number of targets [58]. With multiple targets, it remains unclear if the V12 metric should be assessed per lesion, or in totality for the patient (i.e. composite plan). Minniti et al. analysed that patients with >10 targets treated with LINAC-SRS report that the V12 per lesion predicts for post-treatment changes, rather than V12 from the composite plan [59].
- 4) Prior radiation exposure: Re-irradiation, especially with previous SRS, increases the risk of RN significantly [60••]. The largest series from UCSF report a 1-year risk of 20% with re-SRS [4]. In situations where WBRT is used prior to or in conjunction with SRS, the risks of RN range between 4 and 8%, respectively [4]. These findings are not much higher than the rates seen with SRS alone.
- 5) Use of concurrent systemic therapy (including immunotherapy, targeted therapy and chemotherapy): Controversy exists regarding the risk of RN with concurrent immunotherapy. Lehrer leads an individual patient data meta-analysis for patients with brain metastases treated with SRS and immunotherapy [61]. The overall incidence of RN was low at 5.3% (95% CI 0.3 to 15.7%), with ipilimumab being implicated with all cases [62–64]. This is much lower than single institutional studies, predominantly in patients with melanoma brain metastases, reporting RN to range from 14 to

37.5% when combining immunotherapy with SRS [65–68]. Martin et al. reviewed single institutional data and reported an increased risk of symptomatic RN with the use of ipilimumab and checkpoint inhibitors, for which only ipilimumab retained statistical significance [69]. Data regarding the safety of concurrent targeted therapy is sparse. In a study by Kim et al., the use of concurrent targeted therapy (defined as administration within five biological half-lives) increased the 12-month cumulative incidence of radiological RN (8.8 vs 5.3%, $p < 0.01$) [70]. This was particularly pronounced with VEGFR tyrosine kinase inhibitors (TKI) and EGFR TKIs. Based on the ECOG consensus guidelines, the use of concurrent BRAF inhibitors do not seem to increase the risk of neuro-toxicity [70]. The use of concurrent chemotherapy, with SRS, has not been shown to increase the risk of RN, ranging from 4 to 17% [7, 71].

- 6) Location of lesion: Certain brain locations may be more prone to developing RN (such frontal and occipital cortex, eloquent brain areas including thalamus, basal ganglia), whereas other locations (e.g. brainstem) are more resistant [72]. Superficial lesions may have a lower risk of RN, as the dose spillage happens within non-brain tissue (such as skull bone, skin) compared to deeper lesions [73].
- 7) Planning target volume (PTV) margin: A larger gross-tumour-volume (GTV) to PTV margin would include a larger volume of normal brain parenchyma in the prescription isodose and therefore predispose to RN [74]. This has been investigated in a randomized controlled trial, comparing 1- and 3-mm GTV-PTV margins [75]. Local control was similar in both groups; however, the 3-mm PTV margin group had a higher incidence of RN.
- 8) Intrinsic radiosensitivity of the patient: Studies from patients undergoing SRS for AVM suggest that the patients who developed RN were more sensitive to radiation [76]. This was shown using in vitro survival curves from skin fibroblasts obtained from patients who ultimately developed RN.
- 9) SRS platform: SRS can be delivered by LINAC-based platforms (using dynamic conformal arcs or VMAT) or dedicated units including Gamma Knife or CyberKnife (using multiple non-coplanar beams). The risk of RN does not appear to vary between SRS platforms despite inherent differences in PTV margin and prescription practices. The frame-based Gamma Knife platform typically uses a 0-mm PTV margin and prescribes the dose to the 50% isodose line. This results in a higher maximum dose/prescription dose ratio (≥ 2), which has been associated with increased neuro-toxicity [47]. LINAC-based platforms, which often use relocatable masks, typically apply a 1–2-mm PTV margin. The dose is usually prescribed to the 60–80% isodose line, leading to less dose heterogeneity. For LINAC SRS, the dose gradient may be related to the prescription isodose line, with steeper gradients (less spillage to normal tissue) seen when the dose is prescribed to the 60–70% isodose line, in comparison to the 90% isodose line [77]. Dose heterogeneity (i.e. hot spots) has been suggested to contribute to RN, in particular if they occur within the GTV-PTV margin where normal brain parenchyma is located [78••]. Between platforms, the Gamma Knife appears to have less dose spillage, in comparison to LINAC, when treating multiple targets [79, 80].

- 10) Lack of a quality assurance program: SRS is a technologically intensive treatment, and the potential for error is a major concern in view of the highly conformal nature, steep dose gradients and large dose per fraction. The lack of a robust end-to-end quality assurance program (i.e. simulation, target delineation, planning, delivery) does increase the risks of treatment-related complications, including RN [81].

Management of RN

In general, asymptomatic RN can be observed closely. Unlike tumour recurrence, RN may resolve spontaneously, with up to 76% of lesions resolving by 18 months [82]. First-line medical therapy for symptomatic patients involves corticosteroids (e.g. dexamethasone). Corticosteroids provide an anti-inflammatory effect and reduce the leakiness of the blood-tumour barrier [83]. Commonly used is a start dose of 4–8 mg/day, with a gradual reduction in dose. Patients may require steroids for prolonged periods of time being subject to steroid toxicities including myopathy, gastritis and immune suppression. Bevacizumab (anti-VEGF monoclonal antibody) can be used as a steroid-sparing agent. A pooled analysis has shown that bevacizumab causes radiographic and clinical improvement in majority of patients [84]. A small double-blinded randomized controlled trial and a multicentre prospective trial have both shown majority of patients having radiographic and clinical improvement with bevacizumab [85, 86]. The duration of effect was durable (median 10 months). Although bevacizumab is promising, the drug-related toxicities including haemorrhage, thrombosis and impairing wound healing must be considered [87]. Other therapies such as anti-coagulants and vitamin E/pentoxifylline have been explored but are yet to be considered mainstream [88, 89]. Hyperbaric oxygen therapy (HBOT) has shown to have potential in the prophylaxis of RN [90]. The use of HBOT to reverse established RN is equivocal with most studies being limited to case reports [91, 92].

Patients who remain symptomatic despite conservative management, or patients with neurological deterioration from mass effect, should be considered for surgical resection [93].

Surgical resection aids in confirming the diagnosis and allows rapid relief of mass effect and a quicker reduction of steroids [94]. However, surgical resection may only be possible for medically fit patients and for readily accessible cortical lesions.

For lesions which are less surgically accessible, a novel intervention using a laser-emitting diode placed within the centre of the lesion called laser interstitial thermal ablation (LITT) has been increasingly used [95]. It is considerably less invasive than an open craniotomy and manages to obtain a tissue diagnosis. Interestingly, LITT has been shown to be effective for both recurrent metastatic lesions and RN [96, 97]. A prospective multicentre study investigated the utility of LITT for lesions which are progressing after SRS. Patients who underwent total ablation for RN ($n = 4$) and recurrence ($n = 4$) had a 3-month control rate of 100% and 75% respectively [98••]. Approximately one in three patients is able to reduce, or stop, steroid use within 3 months of the procedure. Although the sample size is small, these results appear promising.

Mitigation strategies for RN

The diagnosis and management of RN are challenging. Strategies to prevent and mitigate RN should be considered upfront in the clinical management of patients. Our proposed mitigation strategies have been outlined in Table 1. Notably, multifraction SRS (or HSRT) is being increasingly used. Multiple authors have reported the use of HSRT in large lesions to reduce the risk of RN while maintaining control rates [51–53, 99, 100]. Lehrer published an international meta-analysis of 24 trials studying the effects of fractionation and tumour volume [101••]. Fractionation reduced the risk of RN significantly for lesions > 3 cm diameter (7.3% vs 23.1%, $p = 0.003$). There was no significant difference, with fractionation, for lesions < 3 cm (6.5 vs 11.7%, $p = 0.29$). The recently published HyTEC paper confirms the use of HSRT to reduce the risk of RN in larger lesions [44••]. However, the exact cut-off to be used for what is considered large varies from > 2 to > 3 cm in diameter.

Clearly, large brain lesions being treated with single fraction SRS place patients at higher risk of RN. As such, HSRT should be considered. If acceptable dose constraints are not attainable, upfront surgical resection followed by cavity radiation should be considered. Regarding the dose constraints, the HyTEC paper has summarized the available evidence, reporting that if tissue V12 (i.e. including target volume) exceeds 5, 10 and >15 cc, the risk of symptomatic RN approximates 10, 15 and 20% respectively [44••]. This corroborates with QUANTEC recommendation of V12 to be < 5–10 cc and the UK SABR consortium guidelines of V12 < 10 cc [102, 103]. In the setting of HSRT, the HyTEC paper recommends that SFED 14 Gy to be < 20 cc (which corresponds to V23 in 3 fractions and V29Gy in 5 fractions) to limit G3+ toxicity to < 4% [44••]. Clearly, caution should be exercised in patients who have undergone prior SRS [4]. The recovery of brain parenchyma from prior radiation, or the preferred time interval, is still unclear. Using the smallest possible PTV margin, by optimizing the patient setup and the use of image guidance, reduces the volume of normal brain parenchyma exposed to high doses of radiation [75].

Novel approaches, which are currently investigational, such as angiotensin receptor blockers (single institutional retrospective cohort) and ultra-high dose rate (FLASH) radiation (pre-clinical), have shown some signals in reducing the radiation-induced inflammatory responses [104, 105].

Summary

Symptomatic RN tends to be permanent and continues to be challenging to manage—as such the premise lies in mitigation and, if possible, prevention. Clearly, rigorous SRS techniques (including immobilization, target visualization, treatment planning and delivery) and adherence to known dose limits are important. Additional mitigation strategies will need to be considered in situations where the baseline risk of RN is expected to be high—such as large target volume or re-irradiation. These may involve reduction in the prescribed dose or employing strategies such as surgery with or without radiotherapy or

Table 1. Mitigation strategies to reduce the risk of RN

Contributing factor	Mitigation strategy	Reference
Dose-volume interplay	SRS dose should be lowered for larger volume lesions. However, tumour control is compromised as a result	[45] [99]
Volume of uninvolved brain parenchyma exposed to intermediate-high dose	Large volume targets should be considered for the following 1) Surgical resection, in addition to SRS. Both pre-operative and post-operative SRS approaches are valid options	[106, 107]
	2) HSRT in preference to SRS	[44, 99]
Prior radiation exposure	Attention should be given to the intermediate dose spillage (e.g. 80% and 50% isodose volumes)	[108, 109]
	This is especially important when multiple isocentres are used to treat multiple targets	
	Dedicated SRS platforms seem to perform better at reducing dose-gradient index, compared to VMAT	
Use of concurrent systemic therapy	A reduction in prescription dose (of 1–2 Gy) may be required when multiple targets are being treated simultaneously	[111]
	In the setting of recurrent tumour, alternatives should be explored (surgery resection, chemotherapy/targeted therapy) If re-SRS is attempted, a fractionated approach is favoured	[7•]
Large PTV margin	Caution should be exercised with certain agents such as ipilimumab, VEGFR TKI and EGFR TKI	[112]
	Admittedly, the data regarding increased neuro-toxicity is unclear and may be partially related to the target volume	[112]
	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)	
Planning parameters	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	[113]
	End-to-end testing should be undertaken at each SRS centre to determine the minimum PTV margin	
Lack of quality assurance (QA) program	Technologies which allow a smaller PTV should be preferentially used	[114–118]
	A dedicated SRS team builds experience and is recommended	[119]
Non-modifiable factors including 1) Intrinsic radiosensitivity 2) Location of lesion	A higher degree of variation is to be expected with LINAC-based platforms, especially with smaller targets	
	Non-modifiable factors including 1) Intrinsic radiosensitivity 2) Location of lesion	Parameters such as conformity index, dose gradient index and conformity/gradient index should be assessed during plan evaluation
A protocolized and evergreen quality assurance program is needed at both the departmental level and a patient-specific level		
Non-modifiable factors including 1) Intrinsic radiosensitivity 2) Location of lesion	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	[124]
	It is challenging to determine intrinsic radiosensitivity prior to treatment. Alternatives to SRS can be considered such as surgical resection or systemic therapeutics	
	A gentler approach with HSRT may be warranted in these cases	

fractionated approach. Notably, the vast majority of reported RN is retrospective in nature, typically from single institutional series. Multi-institutional prospective registries with clear, consensus-based, endpoints would be useful to guide clinical practice.

Declarations

Conflict of interest

Matthew Foote has received travel and honoraria from Elekta, consulting fee from Varian. Kristin Redmond has received research funding and travel expenses from Accuray, has received research funding from Elekta, has received honorarium from AstraZeneca and acts as a consultant for Medtronic. Simon Lo has received research support from Elekta AB for Gamma Knife ICON Expert Group. Balamurugan A. Vellayappan declares that there is no conflict of interest. Tresa McGranahan declares that there is no conflict of interest. Jerome Graber declares that there is no conflict of interest. Lynne Taylor declares that there is no conflict of interest. Vyshak Venur declares that there is no conflict of interest. Richard Ellenbogen declares that there is no conflict of interest. Andrew E. Sloan declares that there is no conflict of interest. Samuel T. Chao declares that there is no conflict of interest. John H. Suh declares that there is no conflict of interest. Eric L. Chang declares that there is no conflict of interest. Arjun Sahgal declares that there is no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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Large retrospective study from Cleveland Clinic looking at the association between RN and the use of various systemic therapeutic agents.

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