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CRITICAL REVIEW

A Systematic Review Informing the Management of Symptomatic Brain Radiation Necrosis After Stereotactic Radiosurgery and International Stereotactic Radiosurgery Society Recommendations

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Disclaimer: These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Stereotactic Radiosurgery Society assume no liability for the information, conclusions, and recommendations contained in this report.

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Abstract: Radiation necrosis (RN) secondary to stereotactic radiosurgery is a significant cause of morbidity. The optimal management of corticosteroid-refractory brain RN remains unclear. Our objective was to summarize the literature specific to efficacy and toxicity of treatment paradigms for patients with symptomatic corticosteroid-refractory RN and to provide consensus guidelines for grading and management of RN on behalf of the International Stereotactic Radiosurgery Society. A systematic review of articles pertaining to treatment of RN with bevacizumab, laser interstitial thermal therapy (LITT), surgical resection, or hyperbaric oxygen therapy was performed. The primary composite outcome was clinical and/or radiologic stability/improvement (ie, proportion of patients achieving improvement or stability with the given intervention). Proportions of patients achieving the primary outcome were pooled using random weighted-effects analysis but not directly compared between interventions. Twenty-one articles were included, of which only 2 were prospective studies. Thirteen reports were relevant for bevacizumab, 5 for LITT, 5 for surgical resection and 1 for hyperbaric oxygen therapy. Weighted effects analysis revealed that bevacizumab had a pooled symptom improvement/stability rate of 86% (95% CI 77%-92%), pooled T2 imaging improvement/stability rate of 93% (95% CI 87%-98%), and pooled T1 postcontrast improvement/stability rate of 94% (95% CI 87%-98%). Subgroup analysis showed a statistically significant improvement favoring treatment with low-dose (below median, ≤7.5 mg/kg every 3 weeks) versus high-dose bevacizumab with regards to symptom improvement/stability rate (P = .02) but not for radiologic T1 or T2 changes. The pooled T1 postcontrast improvement/stability rate for LITT was 88% (95% CI 82%-93%), and pooled symptom improvement/stability rate for surgery was 89% (95% CI 81%-96%). Toxicity was inconsistently reported but was generally low for all treatment paradigms. Corticosteroid-refractory RN that does not require urgent surgical intervention, with sufficient noninvasive diagnostic testing that favors RN, can be treated medically with bevacizumab in carefully selected patients as a strong recommendation. The role of LITT is evolving as a less invasive image guided surgical modality; however, the overall evidence for each modality is of low quality. Prospective head-to-head comparisons are needed to evaluate the relative efficacy and toxicity profile among treatment approaches.

Introduction

The use of stereotactic radiosurgery (SRS) for patients with brain metastases has been increasing, while whole-brain radiation therapy (WBRT) has been on the decline.[1,2] This stems from the increasing evidence regarding the neurocognitive adverse effect of WBRT and the improved access and availability of stereotactic-capable technology throughout the world.[3,4] SRS is able to deliver conformal doses to the target with a convenient schedule typically spanning between 1 to 5 fractions.[5] As a noninvasive therapy associated with high rates of local control the main drawback of SRS is the risk of adverse radiation effects, the most consequential being radiation necrosis (RN) which is defined by the Common Terminology Criteria for Adverse Events version 5 as "a necrotic process occurring in the brain."[6]

The pathophysiology of RN is not entirely clear and likely involves vascular changes resulting from endothelial injury[7] within both normal and tumor tissue mediated by proinflammatory cytokines such as vascular-endothelial growth factor (VEGF), hypoxia-inducible factor 1, and tumor necrosis factor-α.[8-10] The eventual manifestation of RN is secondary to fibrinoid necrosis of small vessels causing ischemia and brain parenchymal necrosis.[11] RN is considered to be a late complication of radiation and typically manifests months to even years after exposure (median ~7-8 months post-SRS).[12]

The incidence of RN post-SRS is highly variable and depends on many factors such as the prescribed dose and fractionation, prior or concurrent WBRT exposure, concurrent systemic chemotherapy, targeted therapy, underlying primary cancer subtype and lastly, the size and/or volume of target.[12-14] One of the largest series, assessing 1650 patients with 2843 brain metastases treated with SRS, reported RN incidence rate of 8% (with approximately half being symptomatic).[15] The risk of RN with concurrent immunotherapy is unclear, and the data are evolving such that recent analyses suggest the risk of RN is acceptable when immunotherapy is delivered within 4 weeks of SRS while respecting dosimetric parameters to guide dose-selection.[16,17] However, the definition of RN has an effect on the reported incidence − with some studies requiring pathologic confirmation and hence reporting a lower incidence of RN.[18] The symptoms related to RN are also highly dependent on the area where the lesion is present − these may include persistent headache associated with increased intracranial pressure, seizures or focal neurologic deficits.[19]

The radiologic interpretation of RN remains a diagnostic dilemma − particularly to differentiate it from recurrent tumor. Both of these entities occur within the high-dose treatment volume and exhibit overlapping magnetic resonance imaging features that may evolve over time. Characteristic enhancement patterns (including the "Swiss-cheese" and/or "soap-bubble" appearance) have a low positive predictive value for RN,[20] prompting the development of more advanced sequences such as perfusion, spectroscopy, chemical exchange saturation transfer, T1/T2 mismatch, treatment response assessment maps, diffusion-weighted imaging and machine-learning techniques involving radiomics.[21-27] The additional use of functional imaging techniques such as fluorodeoxyglucose-positron emission tomography, amino acid positron emission tomography and

thallium 201 single-photon emission computed tomography have also been reported to be useful to differentiate the 2 entities.[28-30] Although these methods may add to the interpretation of RN versus tumor progression, ultimately histopathologic confirmation is considered the gold standard.

The management of asymptomatic, or small volume, RN is generally close observation. Some may consider a combination of oral pentoxifylline and vitamin E.[14,31,32] In patients who present with progressive worsening or new symptoms associated with radiologic RN, a course of corticosteroids (i.e., dexamethasone at the dose of 4-8 mg per day) is the typical first-line treatment strategy.[33] Symptomatic response to corticosteroids is typically observed rapidly in RN in contrast to tumor progression. However, in some patients the pathophysiology is chronic and requires a prolonged course of corticosteroids which can lead to a host of accompanying toxicities and is therefore not regarded as a sustainable option.[34] Moreover, many of these patients may be on immunotherapy for systemic disease which may be hampered by the use of long-term corticosteroids and, thus, more definitive therapy in the early phases of symptomatic RN may be warranted.[35]

In corticosteroid-refractory patients, or those intolerant of corticosteroid therapy, several treatment strategies have been attempted to treat RN. These include bevacizumab (a humanized monoclonal antibody against VEGF), laser interstitial thermal therapy (LITT), surgery and hyperbaric oxygen therapy (HBOT). Although there are multiple case reports, case series and single-institutional reports supporting the efficacy of each of the aforementioned modalities, there is a lack of data to support a systematic evidence-based treatment algorithm.

Therefore, on behalf of the International Stereotactic Radiosurgery Society (ISRS) guidelines committee, in this report we summarize the current evidence on efficacy and toxicity of available treatments for patients with symptomatic corticosteroid-refractory/intolerant RN. Furthermore, we propose a clinically relevant grading system and management recommendations for RN in this context.

Methods and Materials

Evidence acquisition

The Population, Intervention, Control, Outcomes, and Study Design (PICOS) method was used to define literature inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology reporting guideline methodologies were followed.[36] A comprehensive search was conducted in PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews between January 1989 and November 2021. The search strategy applied concepts of RN, SRS/radiation therapy, which was defined as the stereotactic delivery of conformal doses with 1 to 5 fractions, and treatments of RN, which included bevacizumab, LITT, surgery, and HBOT (with corticosteroids and/or anticoagulants being used as a control). The detailed search strategy is summarized in the Data Supplement 1. In addition, references within selected articles were hand-searched for relevant studies and included as appropriate. Search results were loaded into the web-based systematic review platform Rayyan and screened by the lead author.[37]

Inclusion criteria consisted of prospective or retrospective trials with adult patients who (1) were previously treated by SRS; (2) developed RN; and (3) underwent treatment with either bevacizumab, LITT, HBOT, surgery, or a combination of these modalities; and where (4) the primary outcome measured crude symptom improvement and/or radiologic response rates.

Exclusion criteria consisted of (1) case series with <10 patients; (2) studies presented in abstract form only; (3) non-English articles; (4) inclusion of a mixture of recurrent tumor and RN; (5) articles where our primary outcome of interest was not discernible; and (6) if treatment was delivered with nonstereotactic techniques such as 3-dimensional conformal radiation therapy.

Outcome measures and data extraction

The primary outcome measure was the proportion of patients with symptom improvement/symptom stability and/or radiologic improvement/stability postintervention. Secondary outcomes included: (1) proportion of patients with recurrent RN requiring salvage treatment; (2) overall survival (defined as time from RN intervention to death); (3) proportion of patients with severe intervention-related toxicity (grade 3 and above); and (4) proportion of patients who were able to reduce steroid use.

Data on study design, number of patients, number of lesions, details of intervention applied, primary and secondary outcomes, and median follow-up of the cohort were extracted. Individual study effect sizes were modelled as proportions in which the denominator was the total number of patients for which the outcome was available, and the numerator was the number of patients experiencing the particular outcome measure of interest. Crude rates were utilized and expressed as percentages.

Quality (risk of bias) assessment

There is no single recommended instrument to assess the risk of bias for systematic reviews that includes both prospective and retrospective observational studies. We chose to evaluate the risk of bias by using a previously published system based on a 9-item assessment (Data Supplement 2).[38,39] The system was developed to evaluate bias and completeness of information. In particular, items 1 to 2 assess selection bias, items 3 to 5 reporting bias, item 6 attrition bias, and items 7 to 10 assess the extensiveness of available information on intervention and reported outcomes. We used a 3-point scale where "yes"

indicates a low risk of bias, "no" indicates a high risk of bias, and "unclear" indicates uncertainty regarding the risk of bias.

Statistical analysis

Random-effects weighted-analysis of proportion was performed for all primary and secondary outcomes using the DerSimonian and Laird method, with a Freeman-Tukey double arcsine transformation. Heterogeneity between study effect size was assessed using the Higgins I^2 test. Studies with an I^2 test above 75% were considered to have high heterogeneity. A P value $< .05$ was considered statistically significant. Forest plots (with 95% CIs) were generated for the primary outcome for each modality, if 3 or more studies were available. Subgroup analysis was planned a priori for the studies investigating bevacizumab (to compare the pooled proportions between patients who were treated with bevacizumab above and below the median dose). Sensitivity analysis was done only including the prospective studies. Funnel plots were generated as a measure of publication bias for each of the reported outcomes. Statistical analysis was performed with R version 4.2.2 using meta package.

Summary of strength of the body of evidence

The standard of evidence assessments were combined into an overall rating of the strength of evidence according to the Agency for Healthcare Research and Quality for each intervention.[40] A clinically relevant grading scale of RN based on severity was defined by the authors to further provide grading-specific recommendations with the accompanying level of evidence.

Results

The PubMed, Embase, and CENTRAL searches identified 1668 potential studies. Six additional papers were obtained from searching the reference lists within selected papers. After removal of duplicates, 1323 papers remained; 1283 were excluded upon screening the title and abstract. Forty reports were sought for retrieval, and of these 6 were removed as they were meeting proceedings. After full text review of the remaining 34 studies, 21 were deemed to have met the inclusion criteria and were selected for this review. These are graphically represented in the PRISMA flowchart (Fig. 1), and the included study characteristics are summarized in Tables 1 through 4. Two studies were nonrandomized prospective studies, and the remainder were uncontrolled retrospective cohort studies.

Bevacizumab

Thirteen reports (involving 260 patients) described the use of bevacizumab for the treatment of symptomatic RN.[41-53] All were retrospective cohorts, except Furuse et al[45] and Zhuang et al,[53] and 3 were multicenter retrospective cohort studies.[43,45,47] The dosing strategy varied from 1 to 15 mg/kg every 2 to 3 weeks (median, 7.5 mg/kg every 3 weeks), and a median of 4 cycles (range, 1-27) was administered. Almost all patients were on baseline corticosteroids, and the majority had RN-related symptoms.

Bevacizumab-related severe toxicities were reported in 9 studies, ranging from 0% to 24.4%.[41,44−48,50,52] However, the toxicity scales used in each of the studies were not specified and not uniformly reported. The pooled proportion of patients (from 13 studies) with symptom improvement/stability was 86% (95% CI 77%-92%; I^2 = 60%). The pooled proportion of patients (from 10 studies) with improvement/stability of T2 changes (peri-lesional edema) was 93% (95% CI 87%-98%; I^2 = 48%). The pooled proportion of patients (from 8 studies) with improvement/stability of enhancing necrotic component (T1) was 94% (95% CI 87%-98%; I^2 = 36%). These results are presented in Fig. 2A-C. Subgroup analysis was performed to investigate the effect of bevacizumab dosing on the primary outcome, which may account for the heterogeneity seen in the results. There was a statistically significant difference in symptom control (P = .02), but not radiologic changes, when subgroups above and below (or at) the median doses (i.e., 7.5 mg/kg every 3 weeks, 2 doses) were compared (Data Supplement 3). Sensitivity analysis (limited to only the prospective studies) did not show any statistically significant differences for the above outcomes. Funnel plot analysis did not suggest a high risk of publication bias (not shown).

LITT

Five reports (involving 151 patients) described the use of LITT for the treatment of symptomatic RN, 4 were retrospective, and 1 study by Ahluwalia et al[54] was a multicenter prospective study.[50,55-57] Three of the 5 studies relied on histologic confirmation of RN.[54,56,57] Baseline steroid use was not uniformly high and ranged from 30% to 68%. Symptom improvement was only reported in 2 studies and therefore could not be pooled. Radiologic improvement/stability on the T1-enhancing necrotic component was analyzable with a pooled proportion of 88% (95% CI 82%-93%; I^2 = 0%; Fig. 3). Severe treatment-related complications were only reported in 2 studies, ranging from 0% to 3%.[55,62] However, the toxicity scales used were not specified and not uniformly reported. Funnel plot analysis did not suggest a high risk of publication bias (not shown).

Surgical resection

Information regarding outcomes of surgical resection was available from 5 reports (108 patients), all of which were single-institution retrospective series.[49,56,58−60] All patients were symptomatic at baseline. Data regarding radiologic control was not uniformly available, hence not pooled; however, the pooled proportion of patients reporting symptom

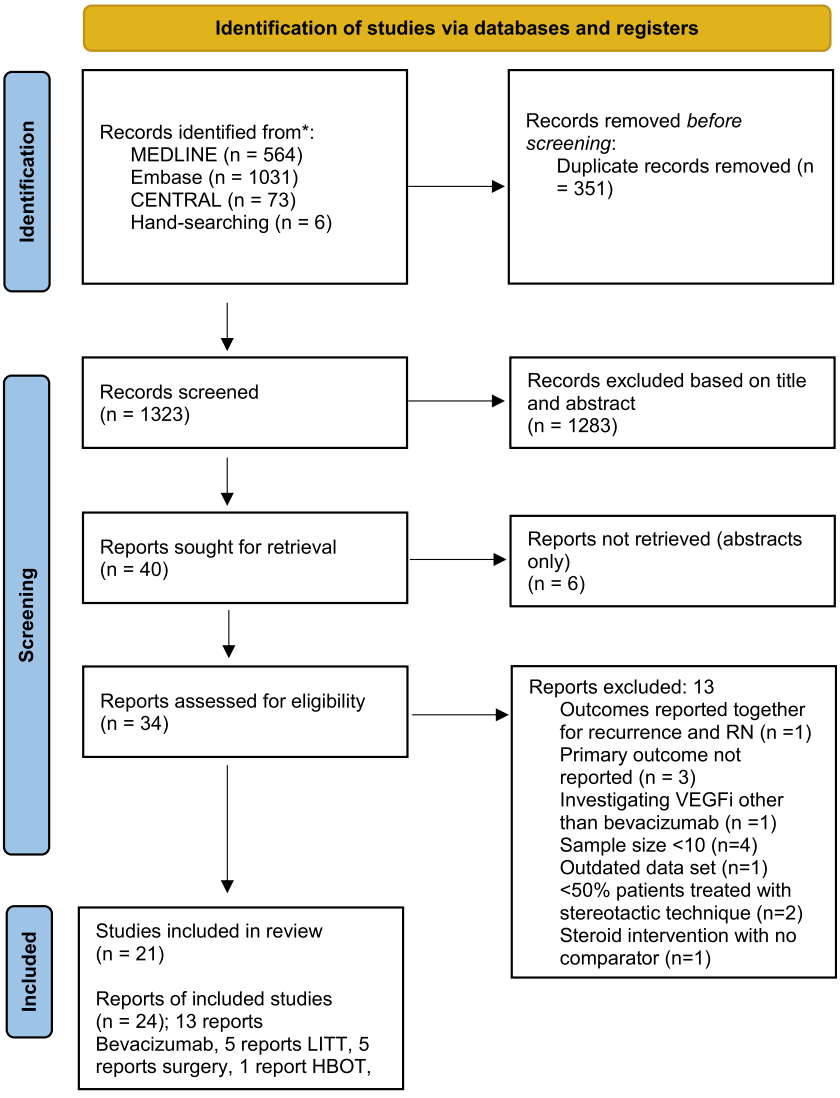

Fig. 1. PRISMA flowchart. *Abbreviations:* HBOT = hyperbaric oxygen therapy; LITT = laser interstitial thermal therapy; RN = radiation necrosis; VEGFi = vascular endothelial growth factor inhibitors.

improvement/stability was 89% (95% CI 81%-96%; I^2 = 14%; Fig. 4). Severe complications from surgery were only reported in 3 studies and ranged from 0% to 2%.[58–60] However, the toxicity scales used were not specified and not uniformly reported. Funnel plot analysis did not suggest a high risk of publication bias (not shown).

HBOT

Only 1 uncontrolled retrospective cohort study reported the use of HBOT for symptomatic RN (13 patients) and included 13 patients treated between 2008 and 2018.[61] The settings ranged from 2 to 2.4 atmospheric absolute at 14.7 to 20 pounds per square inch, for a median of 30 (range, 20-60) sessions each lasting 90 minutes. Twelve of 13 patients showed symptom improvement/stability. There was radiologic improvement in all 8 patients with available imaging follow-up. One patient experienced recurrence, requiring salvage treatment. There were no severe treatment-related complications reported.

Quality assessment

Based on the established risk-of-bias assessment method, only 1 study fulfilled the criteria for low risk of bias, according to the 4 sections (selection bias, reporting bias, attrition bias, extensiveness of information on interventions analyzed).[45] Two studies may be considered at low risk for selection bias, as they enrolled patients in a consecutive manner and reported the reasons for exclusion.[45,53] Four studies could be considered at low risk of reporting bias.[45,54,55,59] Two studies could be considered at low risk of attrition bias.[45,55] Three studies were considered to be at low risk of bias with respect to the reporting of the results.[45,47,55]

Table 1 Characteristics of included studies for bevacizumab

First author, ref	Retrospective (R)/prospective (P)	Single(S)/ multi center (M)	Year range	RN diagnosis: radiology (R)/pathology (P)	Number of patients	Number of lesions	Median age	Baseline steroid use	Baseline steroid dose mg/d (range)	Bevacizumab dose	Bevacizumab cycles	OS	% with severe treatment-related toxicity	% with steroid reduction	% requiring salvage treatment	Median follow-up in months (range)	% WBRT/ partial brain RT	Remarks
Bodensohn[41]	R	S	NR	R	21	NR	56 (31-82)	Y	NR	7.5 mg/kg q 3 wk	2 (1-4)	NR	0	NR	0	NR	NR	Malignant brain lesions
Boothe[42]	R	S	NR	R	11	14	63 (27-79)	Y	8 (0-24)	10 mg/kg q 2 wk	4 (1-8)	NR	NR	100	NR	NR	45	BM patients
Deibert[43]	R	M	NR	R	29	NR	NR	Y	NR	7.5 mg/kg q 3 wk	5 (1-13)	NR	NR	NR	38	NR	NR	Malignant and nonmalignant brain lesions
Furuse[44]	R	S	2009-2010	R	13	NR	55 (27-76)	NR	NR	5-10 mg/kg q 2 wk	4 (3-6)	NR	15.3	NR	18	14.4 (2.9-32.4)		Malignant brain lesions
Furuse[45]	P	M	2011-2013	R	38	NR	54 (17-73)	Y	NR	5 mg/kg q 2 wk	6	NR	24.4	76.3	21	13.1	55	Malignant brain lesions
Li[46]	R	S	2011-2019	R	40	40	55 (29-72)	Y (97.5%)	NR	5 mg/kg q 2 wk (5-10 mg/kg q 2-3 wk)	2	NR	NR	0	NR	NR	37.5	BM patients
Moore[47]	R	M	2017-2020	R	13	21	58 (49-70)	Y	8 (4-12)	7.5 mg/kg q 3 wk	2 (1-5)	21.9 m	15.3	77	7.6	11.9 (2-35.4)	NR	BM patients on concurrent immunotherapy
Sadraei[48]	R	S	2007-2012	R	24	NR	57 (31-67)	Y	NR	7.5 mg/kg q 3 wk (5-15 mg/kg q 2-3 wk)	6 (2-13)	NR	4.2	18	95	NR	54	Malignant brain lesions
Sayan[49]	R	S	2009-2018	R	6	NR	54 (35-81)	Y	NR	NR	NR	NR	NR	NR	NR	8.5 (3.2-96)	66	BM patients
Sujijantarat[50]	R	S	2011-2018	R	13	NR	63 (33-72)	Y (54%)	NR	15 mg/kg q 2 wk (7.5-15 mg/kg q 2 wk)	4 (1-7)	15.2 m	7.6	86	NR	12 (1.5-27.5)	15	BM patients
Tripathi[51]	R	S	2012-2017	R	17	NR	42 (19-61)	Y	16	5-10 mg/kg q 2 wk	7 (5-27)	NR	NR	17	NR	NR	0	Nonmalignant brain lesions
Zhuang[52]	R	S	2011-2013	R	14	NR	53 (31-70)	NR	NR	5 mg/kg q 3 wk	3 (3-10)	NR	0	NR	NR	NR	28.6	BM patients
Zhuang[53]	P	S	2016-2019	R	21	NR	55 (43-70)	NR	NR	1 mg/kg q 3 wk	3 (3-5)	NR	0	NR	NR	22.7 (6.1-38)	23.8	BM patients

Abbreviations: BM = brain metastases; NR = not reported; OS = overall survival; RN = radiation necrosis; RT = radiation therapy; WBRT = whole-brain RT.

Table 2 Characteristics of included studies for LITT

First author, ref	Retrospective (R)/ prospective (P)	Single (S)/multi center (M)	Year range	RN diagnosis: radiology (R)/ pathology (P)	Number of patients	Number of lesions	Median age	Baseline steroid use	Baseline steroid dose mg/d (range)	LITT system	OS	% with severe treatment-related toxicity	% with steroid reduction	% requiring salvage treatment	Median follow-up in months (range)	% WBRT/ partial brain RT	Remarks
Ahluwalia[54]	P	M	2012-2015	P	19	NR	58.5 (32-74)	Y (36.8%)	NR	Neuroblate	82.1% at 6 mo	NR	NR	NR	NR	NR	BM patients
Hernandez[55]	R	S	2010-2017	R	59	74	63 (35-90)	Y (30%)	NR	Visualase	NR	3.4	81	16.9	11 (2-62.7)	NR	BM patients
Hong[56]	R	S	2007-2016	P	18	NR	60 (49-71)	Y (68%)	NR	Neuroblate	94.4% at 6 mo	NR	NR	NR	NR	20	BM patients
Lanier[57]	R	S	2011-2018	P	30	NR	60 (50-71)	Y (40%)	NR	Neuroblate	Median 25 mo	3.3	77	6.7	NR	27	BM patients
Sujijantarat[50]	R	S	2011-2018	R	25	NR	62 (35-81)	Y (56%)	NR	Neuroblate	Median 24.8 mo	NR	71	20	27.5 (5.8-92.5)	16	BM patients

Abbreviations: BM = brain metastases; LITT = laser interstitial thermal therapy; NR = not reported; OS = overall survival; RN = radiation necrosis; RT = radiation therapy; WBRT = whole-brain RT.

Table 3 Characteristics of included studies for surgery

First author, ref	Retrospective (R)/ prospective (P)	Single (S)/multi center (M)	Year range	RN diagnosis: radiology (R) /pathology (P)	Number of patients	Number of lesions	Median age	Baseline steroid use (%)	Baseline steroid dose mg/d (range)	Type of surgery	OS	% with severe treatment-related toxicity	% with steroid reduction	% requiring salvage treatment	Median follow-up in months (range)	% WBRT/ partial brain RT	Remarks
Hong[56]	R	S	2007-2016	R	15	NR	60 (49-71)	Y (46%)	NR	Gross or near total removal	93.3% at 1 y	NR	NR	NR	NR	20	BM patients
Newman[58]	R	S	2003-2018	P	46	46	60 (35-83)	Y (54%)	NR	Gross total in 59%, partial removal in 41%	Median 86 mo	2.1	70	6.5	22	9	BM patients
Sayan[49]	R	S	2009-2018	R	8	NR	54 (35-81)	Y	NR	NR	NR	NR	NR	NR	8.5 (3.2-96)	66	BM patients
Shah[59]	R	S	2011-2016	P	24	NR	60 (50-70)	Y	8-16	Gross total removal	93.3% at 1 y	0	100	NR	13.3 (0.4-42)	NR	Malignant brain lesions
Telera[60]	R	S	2005-2011	R	15	NR	58 (35-72)	Y	NR	Gross total removal via microsurgery	Median 19 mo	0	100	NR	14 (6-38)	20	BM patients

Abbreviations: BM = brain metastases; NR = not reported; OS = overall survival; RN = radiation necrosis; RT = radiation therapy; WBRT = whole-brain RT.

Table 4 Characteristics of included studies for HBOT

First author, ref	Retrospective (R)/ prospective (P)	Single (S)/multi center (M)	Year range	RN diagnosis: radiology (R)/ pathology (P)	Number of patients	Number of lesions	Median age (range)	Baseline steroid use (%)	Baseline steroid dose mg/d (range)	HBOT details	OS	% with severe treatment-related toxicity	% with steroid reduction	% requiring salvage treatment	Median follow-up in months (range)	% WBRT/ partial brain RT	Remarks
Co[61]	R	S	2008-2018	R	13	NR	46 (21-63)	Y (85%)	NR	2-2.4 ATA at 14.7–20 PSI for 90 min daily, for 30 sessions (range, 20-60)	Median 15 mo	15.3	47%	NR	10 (1-60)	NR	Malignant and nonmalignant brain lesions

Abbreviations: ATA = atmospheric absolute; HBOT = hyperbaric oxygen therapy; NR = not reported; OS = overall survival; PSI = pounds per square inch; RN = radiation necrosis; RT = radiation therapy; WBRT = whole-brain RT.

The risk-of-bias assessments for the included studies are available in Data Supplement 2.

ISRS grading system for RN and summary of the strength of evidence

The proposed ISRS grading system (4-tier), which is based on the severity of RN symptoms and responsiveness to first-line corticosteroid therapy, is presented in Table 5. In addition, strength of evidence (for the 4 interventions) was assessed using Agency for Healthcare Research and Quality recommendations. As there were no randomized controlled trials included, strength of evidence ranged from insufficient to moderate. There was only 1 observational study for HBOT, and it was therefore classified as insufficient. LITT and surgery were assessed to be low because of the small number of observational studies and lack of prospective randomized data. Bevacizumab was judged to be moderate, as we found 13 reports including 2 single-arm prospective studies. Strength of recommendation (strong vs weak) for each intervention was based on author consensus (Table 5). Recommendations were developed in an iterative manner, building on author consensus. Authors rated their agreement with each recommendation on a 5-point scale (strongly agree, agree, disagree, strongly disagree, or uncertain). A threshold of 80% or more (agree or strongly agree responses) represented a strong consensus and scores below 80% were regarded as weak.

Discussion

The results of our systematic review indicate that the majority of the evidence for the treatment of steroid refractory RN is based on the use of bevacizumab. Invasive procedures such as surgery and LITT are established treatments of RN; however, the evidence was more limited both in terms of number of studies and quality. Although traditionally associated as a treatment for radiation injury, the evidence supporting HBOT was limited to 1 retrospective study, which highlights the overall lack of evidence surrounding this modality in the management of RN. However, in aggregate, symptom control (defined as improvement or stability) and/or radiologic control (defined as improvement or stability) rates generally ranged from 80% to 90%, supporting efficacy.

As an ISRS guideline committee of experts, our recommendations must be taken in context of the limitations of the reported literature. From our review, we have judged the quality of all the evidence to be overall low, given that the majority of the published studies were single institution retrospective cohort studies. Outcome reporting was also inconsistently defined among the studies and for consistency, we could only pool the proportion of patients who exhibited symptom and radiologic control. Moreover, there was inconsistent toxicity reporting for any of the proposed

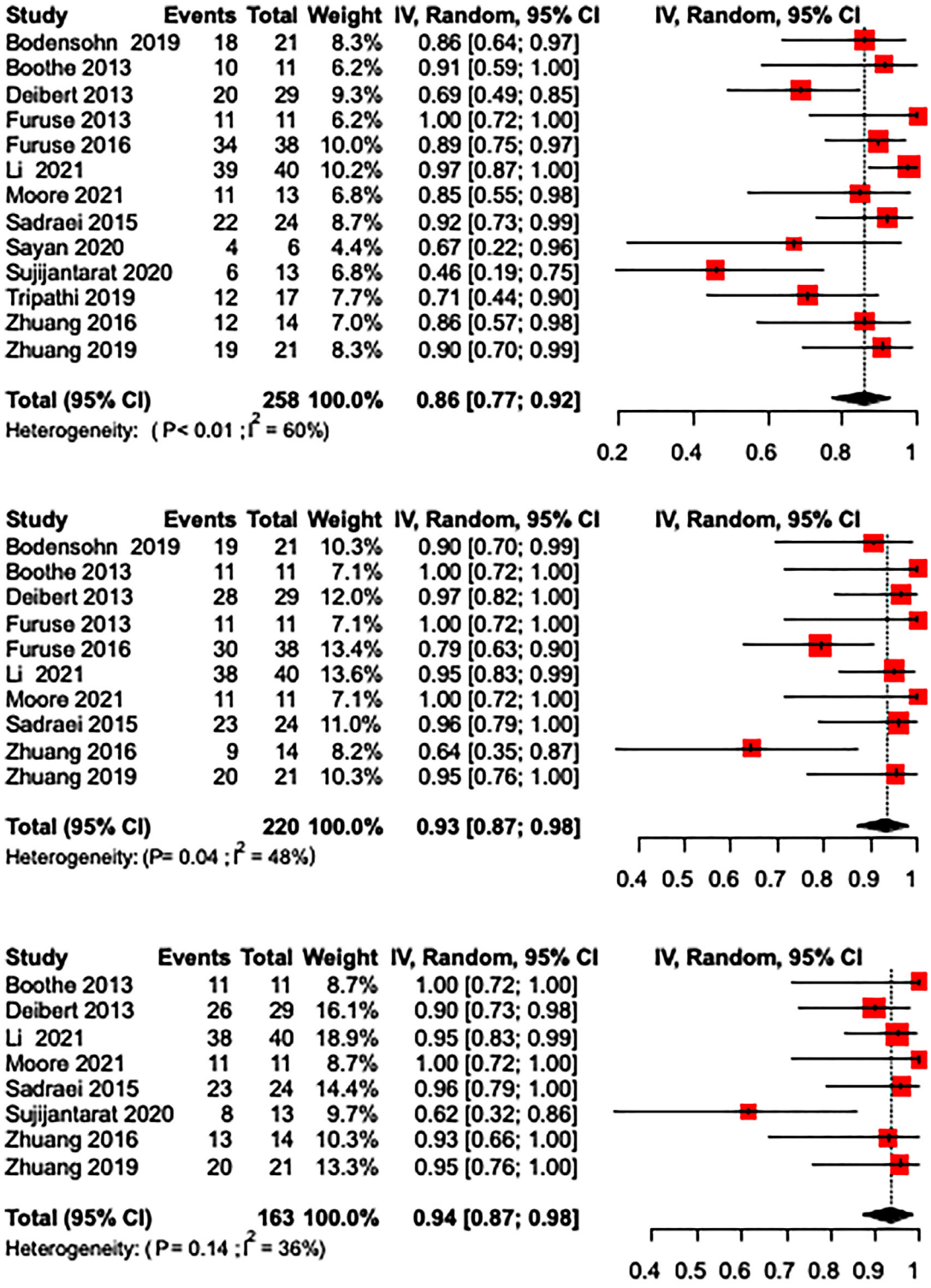

Fig. 2. Pooled proportion of symptom or radiological improvement/stability with bevacizumab. (A) Pooled proportion of symptom improvement/stability with bevacizumab. (B) Pooled proportion of radiological T2 improvement/stability with bevacizumab. (C) Pooled proportion of radiological T1 (contrast enhanced) improvement/stability with bevacizumab.

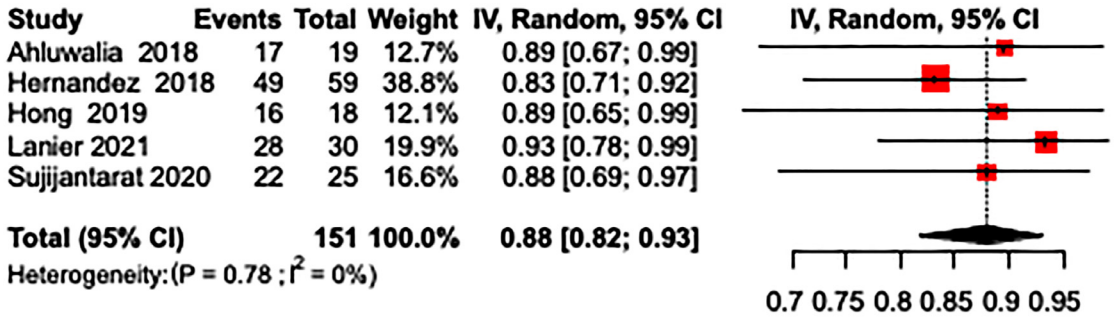

Fig. 3. Pooled proportion of radiological T1 (contrast enhanced) improvement/stability with laser interstitial thermal therapy.

RN treatments. The duration of control is an important consideration in decision-making; however, we were unable to draw firm conclusions and our recommendations relied primarily on the expert opinion of the committee (Table 5).

Our analyses and committee discussion have resulted in a strong recommendation based on moderate evidence supporting the use of bevacizumab for patients with symptomatic and steroid-refractory RN (Table 5). However, this should be utilized in select patients after multidisciplinary assessment to minimize potential toxicity. Bevacizumab is an intravenously administered humanized monoclonal antibody against VEGF used as an antineoplastic agent in a variety of cancer conditions. The approved dosing regimen varies from 5 mg/kg every 2 weeks to 15 mg/kg every 3 weeks.[63] In comparison, the recommended dosing as monotherapy in recurrent glioblastoma is 10 mg/kg every 2 weeks.[64] Toxicities from bevacizumab include, but are not limited to, wound dehiscence, intra- or extracranial hemorrhage, uncontrolled hypertension, thromboembolic events, other cardiovascular complications, and bowel perforation.[63] The optimal dosing for RN is unclear and may be lower than that used for anticancer therapy. A number of studies have used low and ultralow doses (e.g., 1 mg/kg every 3 weeks) of bevacizumab for RN and did not demonstrate any significant difference in efficacy.[29,45,53,52] Our subgroup analysis comparing low and high bevacizumab dosing (using the median dose as a cut-off, 7.5 mg/kg every 3 weeks) suggested that low doses may be sufficient for symptom control. This should be considered as hypothesis-generating and an area of future research, as low doses could reduce treatment-related toxicity and costs for the health system. The number of cycles required to treat RN also remains unclear, with most studies using 3 to 6 cycles. The prospective study by Furuse et al[45] utilized 3 cycles, with an interim response assessment, and continued a further 3 cycles depending on patient tolerability and response. Bevacizumab may be particularly useful for steroid-weaning and in patients where RN is multifocal or in deep or eloquent areas inaccessible to LITT or surgical resection.

Levin et al conducted a small, randomized, double-blind, placebo-controlled trial involving 14 patients with RN.[65] This seminal study did not fall under our inclusion criteria (as the majority of patients were treated with conventionally fractionated radiation therapy for glioma and head/neck cancer) but deserves special mention as it is heavily referenced and preferentially used in neuro-oncology practice. In this study, patients were randomized to saline or bevacizumab (7.5 mg/kg every 3 weeks for 2 cycles). Crossover was allowed for patients who progressed on the placebo arm and all patients who responded were given 2 more infusions of the same assigned treatment. All 12 patients (including those who crossed over) treated with bevacizumab showed radiologic improvement (on T2- and T1-contrast sequences) and symptomatic improvement, thereby supporting the use of bevacizumab for patients with symptomatic RN. Another similar study, conducted by Xu et al,[66] randomized

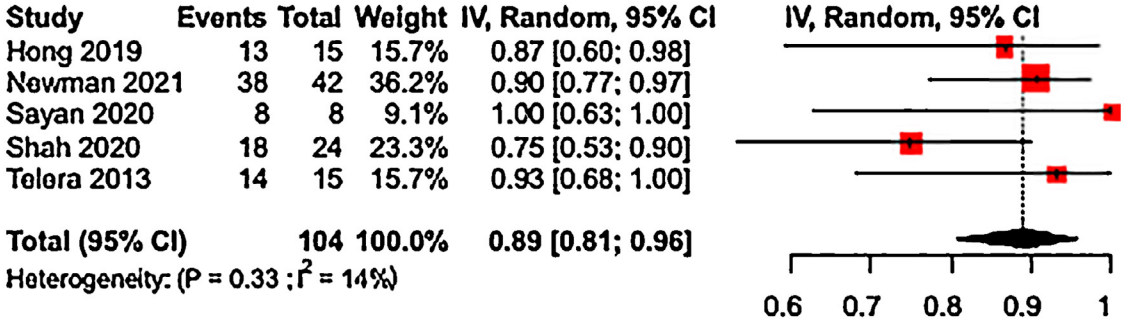

Fig. 4. Pooled proportion of symptom improvement/stability with surgical resection.

Table 5 Four-tier ISRS grading system based on the severity of RN, diagnosed by radiology or pathology, with the proposed management and follow-up recommendations

ISRS grade	Description of severity	Recommended management and follow-up	Supporting level of evidence/strength of recommendation based on author consensus
1	Asymptomatic and no prior corticosteroid administration	• Close surveillance with repeat imaging at 6-12 wk intervals • Consider a short-course of corticosteroids (e.g. dexamethasone). • Surgical resection can be considered first line if a pathologic diagnosis is urgently required to guide further management.	Not assessable based on this review
2	Symptomatic and no prior corticosteroid administration	• Dexamethasone can be started as 4-8 mg/d, with or without an initial bolus, and tapered gradually. Generally, a 3-6 wk course of steroids may be required. • Repeat imaging should be considered at 6-12 wk intervals. • Surgical resection can be considered first line if a pathologic diagnosis is urgently required to guide further management.	Not assessable based on this review
3	Symptomatic and corticosteroid-refractory	• Bevacizumab at doses ranging between 5-10 mg/kg every 2-3 wk for 2-4 cycles • Repeat imaging after 2 cycles and after the 4th cycle for response assessment and to guide corticosteroid tapering as required. • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Moderate/strong
		• LITT/surgery • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Low/weak
		• HBOT • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Insufficient/weak
4	Symptomatic with neurologic impairment, progressive RN despite a trial of noninvasive treatments, dependency on high doses of corticosteroid	• Surgical resection • Repeat imaging should be considered at 2-3 mo intervals to ensure improvement and/or stability.	Low/strong

Abbreviations: HBOT = hyperbaric oxygen therapy; ISRS = International Stereotactic Radiosurgery Society; LITT = laser interstitial thermal therapy; RN = radiation necrosis.

112 patients with nasopharyngeal carcinoma with RN to bevacizumab (5 mg/kg every 2 weeks for 4 cycles) versus corticosteroids (methylprednisolone 500 mg/d intravenously for 3 days, followed by prednisone 10 mg/d for 2 months). This study was not included in our review as it involved only patients with nasopharyngeal carcinoma who were commonly treated with fractionated chemo-radiation therapy. Nevertheless, their results are supportive of bevacizumab use as patients had a statistically significant radiologic treatment response rate (65.1% vs 31.5%; $P < .001$).

The RN recurrence was not different between the 2 arms, where a quarter of patients experienced recurrence during the 6-month follow-up. The conclusions from these 2 randomized studies can likely be extrapolated to the patient population evaluated in this review.

With respect to LITT, our analyses and committee discussion have resulted in a weak recommendation, based on low level of supporting evidence, for patients with symptomatic corticosteroid-refractory RN (Table 5). LITT is a minimally invasive technique that uses image guided thermal coagulation.[67] LITT was developed as a treatment option for brain neoplasms in the early 1990s.[68] One advantage of LITT is that it is able to obtain tissue confirmation during the same procedure. It is important to be mindful that transient worsening of peri-lesional edema may occur post-LITT, due to lack of decompression.[67,69] LITT is also a resource-intense and invasive procedure that requires specialized equipment and a trained team. Access to LITT in resource-constrained countries limits the utility in RN. Moreover, certain locations − such as those near the dura and cerebral vessels − can be challenging for LITT because of the heat-sink effect. Finally, in patients with a mixture of RN and residual viable disease, additional radiation therapy may be required.[56]

It is noteworthy that Palmisciano et al[70] conducted an indirect meta-analysis comparing bevacizumab to LITT in patients with RN secondary to brain metastases. They reported both modalities to be equally effective in symptom improvement (73.3% bevacizumab vs 60.8% LITT; P = .187). In terms of radiologic response (complete and partial response), bevacizumab was superior to LITT (83.2% vs 37.7%). However, when including patients with stable disease, both groups were similar (89.8% vs 86.9%). Our findings are congruent with this study and are numerically higher, as we defined our primary outcome as clinical, and/or radiologic improvement, and/or stability.

With respect to surgical management of RN, our analyses and committee discussion have resulted in a strong recommendation, despite being based on a low level of supporting evidence, for patients symptomatic with neurologic impairment and/or progressive RN despite a trial of noninvasive treatments (including high doses of corticosteroids; Table 5). Surgical resection is usually considered for lesions, which are easily accessible and located in noneloquent areas, particularly when less invasive options have failed. Considerations of surgery include potential neurosurgical complications, delays in oncologic therapy due to time for recovery and wound healing, and the nature of the patient population, who often have a limited life expectancy and lesions deep in the brain that may put the patient at risk of surgical morbidities and mortality. However, when there is mass effect not responding to steroid therapy, acute neurologic compromise, when diagnosis is critical to guide further management in an asymptomatic patient, or when noninvasive diagnostic testing is inconclusive and a tissue diagnosis needed, surgical resection is often considered first line. In commonly encountered situations when both recurrent tumor and RN are present within the pathologic specimen, the proportions of each can provide guidance on further treatment options, although criteria are unclear. Mechanistically, it is thought by surgically removing the necrotic nidus the inflammatory cycle is broken and, therefore, surgical resection is both therapeutic and diagnostic.

Although HBOT has been described as a potential therapeutic in other forms of radiation injury, we could not find much specific supporting evidence for brain RN. Access to HBOT requires specialized facilities and requires multiple sessions over a prolonged period. An updated Cochrane meta-analysis by Bennett et al[71] did not find HBOT to be beneficial for late radiation injury to neural tissues. The only randomized trial comparing HBOT to steroid therapy for RN is currently inactive with no reported results (NCT00087815). Therefore, we conclude that there is insufficient evidence to recommend this modality for RN but acknowledge the historic use of this treatment for late radiation injury. Ultimately, proper evidence is needed to inform the role of HBOT in the care pathway (Table 5).

Our study addresses an unmet need in assessing the evidence for the treatment of RN. We chose to further refine this analysis by focusing on studies where patients had a brain neoplasm treated with SRS techniques. Unlike other similar meta-analysis on bevacizumab, we excluded case reports and case series with fewer than 10 patients given the concern for selection bias. The major limitation of our study is that most of the included studies were single-arm in nature, which severely limits any comparative analysis on efficacy as RN has been reported to wax and wane in a minority of patients.[72] In addition, only 2 reports were prospective, and the remaining retrospective studies were subject to unmeasured confounders and biases such as selection bias, lost to follow-up and reporting bias. We acknowledge that retrospective studies may overestimate the treatment effect.[73] Another limitation of our selected primary endpoint is that it provides information on improvement/stability but does not address duration of control and the need/incidence for salvage treatments given the lack in clarity of the data preventing summary statistic generation.

Key areas for future investigation

The optimal management of steroid-refractory RN has yet to be defined. Randomized phase 2 or 3 trials should be conducted to better assess the relative efficacy, toxicity, and durability of available treatment options. In the absence of randomized evidence, well-curated prospective registries for patients who underwent SRS and developed RN should include a better grading approach to categorize the severity of RN, a predefined follow-up schedule incorporating standardized imaging approaches, clearly defined endpoints for both imaging and clinical response, and treatment details including dosimetry parameters. Bevacizumab dosing, and specifically the efficacy of low-dose short-course regimens, should be investigated in a prospective manner as these may

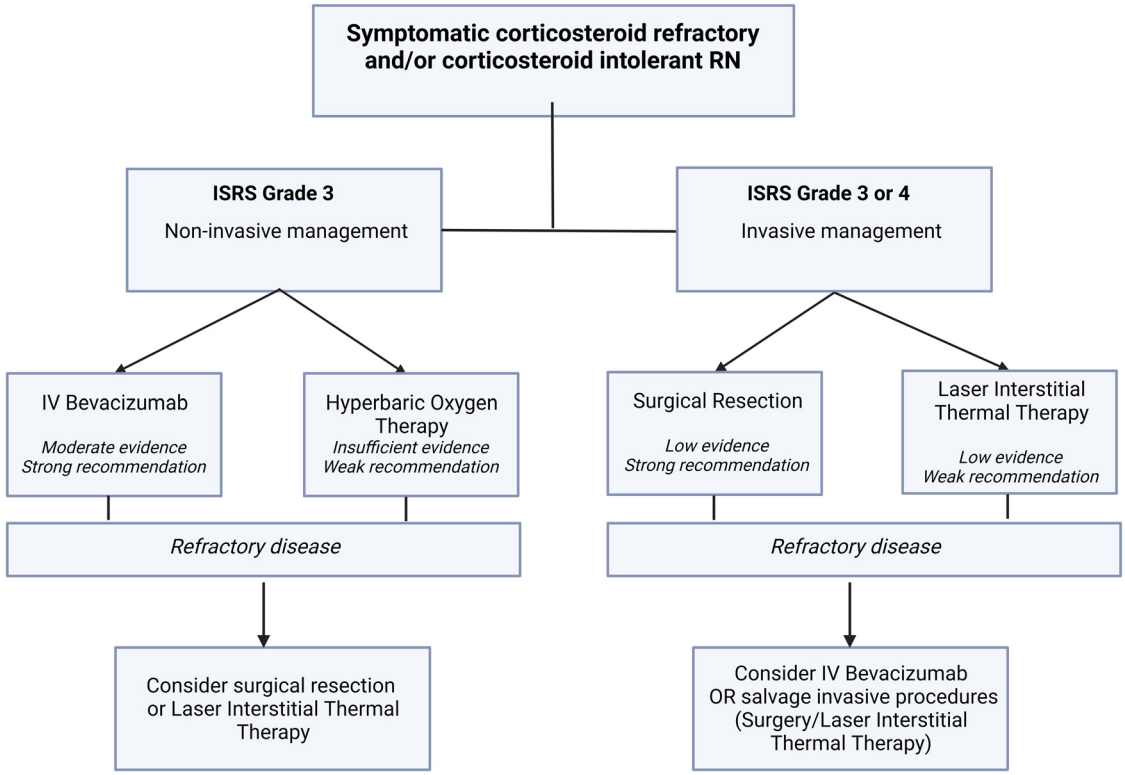

Fig. 5. Suggested management flowchart for symptomatic corticosteroid-refractory and/or corticosteroid-intolerant radiation necrosis.

reduce treatment toxicities and associated costs and increase availability. Lastly, one of the major limitations in comparing treatment efficacy for RN is that there is no uniform scale to judge the extent and severity of radiation-related changes. With a homogenously defined group of patients classified by severity, treatment strategies specific to RN can be compared more objectively.

ISRS recommendation/guidelines

Prevention/mitigation of RN

Upfront mitigation is the best strategy to prevent RN. In situations in which the risk of RN is deemed high (eg, large lesion, reirradiation), strategies such as using highly conformal planning, adherence to recommended dose-volume constraints, and fractionated treatment can be considered.[74–78]

Diagnosis of RN

Diagnosis of RN may require multimodal imaging (such as contrast-enhanced magnetic resonance imaging, perfusion, chemical exchange saturation transfer, spectroscopy, and functional imaging). In cases where uncertainty exists, pathologic confirmation or serial imaging should be considered.

Management of RN

Asymptomatic RN is typically observed with close clinical and radiologic follow-up. For those with symptomatic RN, initial treatment typically consists of a trial of oral corticosteroids. Further management options, particularly when steroid refractory, can include bevacizumab, surgery, LITT, or HBOT. The choice between these modalities should take into context patient-, treatment-, and disease-related factors, including the urgency of the patient's clinical situation. Surgical resection may be considered in patients with large surgically accessible lesions in noneloquent areas and can be lifesaving. Bevacizumab should be strongly considered in patients not requiring up-front surgical management given that it is relatively noninvasive, efficacious, and well-tolerated in select patients deemed to be at lower risk for toxicities.

We propose a 4-tier grading system based on the severity of RN, diagnosed by radiology or pathology, which incorporates proposed management and follow-up recommendations (Table 5). A flowchart for the management of symptomatic corticosteroid refractory RN is proposed in Fig 5.

Conclusion

The ISRS summary recommendations suggest high rates of symptom and radiologic control rates after either

bevacizumab, surgery, or LITT. However, it must be noted that this is based on low-level evidence from noncomparative studies. Randomized trials and a universally adopted grading system are in need to determine superiority, with respect to efficacy and treatment-related toxicity, before definitive recommendations can be made.

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