



# DEGRO practical guideline for central nervous system radiation necrosis part 2: treatment

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Received: 11 June 2022 / Accepted: 15 June 2022  
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## Abstract

**Purpose** The Working Group for Neurooncology of the German Society for Radiation Oncology (DEGRO; AG NRO) in cooperation with members of the Neurooncological Working Group of the German Cancer Society (DKG-NOA) aimed to define a practical guideline for the diagnosis and treatment of radiation-induced necrosis (RN) of the central nervous system (CNS).

**Methods** Panel members of the DEGRO working group invited experts, participated in a series of conferences, supplemented their clinical experience, performed a literature review, and formulated recommendations for medical treatment of RN, including bevacizumab, in clinical routine.

**Conclusion** Diagnosis and treatment of RN requires multidisciplinary structures of care and defined processes. Diagnosis has to be made on an interdisciplinary level with the joint knowledge of a neuroradiologist, radiation oncologist, neurosurgeon, neuropathologist, and neurooncologist. If the diagnosis of blood–brain barrier disruptions (BBD) or RN is likely, treatment should be initiated depending on the symptoms, location, and dynamic of the lesion. Multiple treatment options are available (such as observation, surgery, steroids, and bevacizumab) and the optimal approach should be discussed in an interdisciplinary setting. In this practice guideline, we offer detailed treatment strategies for various scenarios.

**Keywords** Radiation necrosis · Stereotactic radiotherapy · Bevacizumab · Steroids · Brain metastases · Glioma · Blood–brain barrier disruptions

**Disclaimer** Our recommendations are a resource for professionals involved in the management of RN. The implementation of this guideline requires multidisciplinary structures of care and defined processes of diagnosis and treatment. These recommendations are a guide and not meant to be prescriptive; ultimately, each physician will need to make treatment decisions based on discussions with the patient and the potential local reimbursement situation. Adherence to this practical guideline will not ensure successful treatment in every situation. This guideline was prepared on the basis of information available at the time the panel conducted its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may develop over time.

**Availability of data and material** All references are cited in the manuscript. There are no additional data or material involved.

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## Introduction

Brain metastases (BM) are frequent in cancer patients and diagnosed in approximately 20 to 30% of all cancer patients during the course of their disease [1–3]. In the past decade, several innovations in cancer therapy have led to an improvement in outcomes. By prolonged survival, the absolute risk of developing BM as well as RN rises. Pseudoprogression and RN are frequent in glioma patients following radiotherapy and often the differentiation between true RN and pseudoprogression is challenging. RN is considered as a dose-limiting toxicity for radiotherapy (RT), especially in areas with critical structure involvement, such as the brainstem [4, 5]. Currently, there is no defined guideline for the treatment and diagnosis of RN. Several guidelines already recommend the use of steroids and bevacizumab in the treatment of RN, although there are no defined treatment algo-

rhythms [6, 7]. This lack of consensus was identified by the DEGRO and, therefore, the DEGRO board mandated the DEGRO Working Group for Neurooncology (AG NRO) to establish a practice guideline. In 2020, a position paper about the use of bevacizumab and the treatment of RN was already established and published by the DEGRO society. A detailed nomenclature of treatment-related changes and a multistep approach for their diagnosis was presented in part I of the DEGRO practice guideline. In this practice guideline, we have integrated the limited results from contemporary clinical trials and the available retrospective data. The guideline aims to provide guidance for treatment decisions. The implementation of this guideline requires multidisciplinary structures of care and defined processes of diagnosis and treatment of RN.

## Methods

This guideline was prepared by an expert panel of the DEGRO AG NRO in cooperation with members of the Neurooncological Working Group of the DKG-NOA. The guidelines' subcommittee recruited a panel of recognized experts from the field of neurosurgery, neuroradiology, neuropathology, and neurooncology/neurology. This task force represents all disciplines involved in the diagnosis and care of patients with CNS RN/BBD. We retrieved references published in English on PubMed with the search terms "radiation necrosis" alone and in combination with "avastin," "bevacizumab," "steroids," "radiosurgery," "stereotactic," "re-irradiation," "vascular endothelial growth factor (VEGF)," "immunotherapy," and "dexamethasone" from January 1, 2000, to November 1, 2021. We also identified publications through searches of the authors' own files. Screening and initial eligibility were addressed by six authors (DB, SC, AG, SR, SK, and LK), consulting others for disagreement resolution. Panel members of DEGRO and experts participated in a series of virtual conferences, circular emails, supplemented their clinical experience, and formulated recommendations for the treatment and diagnosis of RN in clinical routine. The treatment recommendations were formed by full consensus of the participating experts.

## Treatment options

Several therapeutic approaches have been suggested in the past, including drug therapy, surgery, hyperbaric oxygen, heparin, warfarin, pentoxifylline, and vitamin E [8].

## Corticosteroids

Corticosteroids, such as dexamethasone, have long been the gold standard of RN treatment. For symptomatic patients, corticosteroids are the first-line treatment due to their anti-inflammatory potential and reduction of BBB leakage [9]. Improvement can often be seen rapidly due to the reduction of edema in RN patients with symptoms associated with the edema. Corticosteroids are potent, but offer only symptomatic relief from RN. Corticosteroids can be a double-edged sword, with a significant benefit and a low incidence of adverse effects for a limited treatment duration, but unmindful withdrawal or prolonged administration can have serious side effects [10]. Adverse effects of corticosteroids are both dose and time dependent, whereas other adverse effects follow a linear dose response, with an incidence increase with higher dose. Other adverse effects may follow a threshold dose–response pattern [11]. Benefits of corticosteroid use include their general and fast availability in most countries and the relative inexpensiveness compared to bevacizumab use or surgery. Since there are no studies regarding dose, we prefer to use dexamethasone with an initially high starting dose of 20–40 mg intravenous dexamethasone or 8 mg (1-0-0 up to 1-1-1) in symptomatic patients for 3 to 5 days, followed by a gradual reduction. We recommend a short-course maintenance dose of 1.5–2 mg, until the first follow-up (FU) MRI (6–8 weeks after initial diagnosis of blood–brain barrier disruptions [BBD]/RN) is performed to prevent a rebound effect. For immediate symptom relief, an attempt with high-dose dexamethasone (e.g., 20 mg i.v.) can be reasonable. In general, the lowest possible dose for the shortest possible duration is recommended. Patient education is vital in recognizing the adverse effects early. Furthermore, communication with other health professionals, especially in post-hospital treatment, is necessary to ensure that the patient is adequately monitored and the corticosteroid dose is reduced. With multimodal oncological treatments, it is often necessary to combine dexamethasone with other ongoing systemic therapies. In the era of immunotherapy, this becomes challenging, posing the question of whether the immunosuppressive effects of corticosteroids may lower the efficacy of immune- or targeted therapies [12].

## Bevacizumab

Bevacizumab is a potent mediator in inhibiting the vicious cycle of RN development, and the efficacy of bevacizumab is supported by class IIb evidence. A double-blind, placebo-controlled phase II study evaluated bevacizumab for the treatment of symptomatic and progressive CNS radiation necrosis [13]. Eligible bevacizumab-naïve patients had undergone cranial radiation for grade 2–3 primary brain neoplasm, meningioma, or head and neck carcinoma and had

progressive neurological symptoms with radiographic evidence of radiation necrosis. Patients were randomized to receive bevacizumab 7.5 mg/kg every 3 weeks ( $n=5$ ) or placebo ( $n=7$ ). At week 6, a median increase of 14% in T2-weighted FLAIR volume was observed in placebo-treated patients vs. a median decline of 59% for bevacizumab-treated patients ( $p=0.0149$ ). In addition, a median increase of 17% in T1-weighted contrast-enhanced volume was observed in placebo-treated patients vs. a median decrease of 63% in bevacizumab-treated patients ( $p=0.0058$ ). Xu et al. investigated, in a multicenter open-label study, patients with RN who were randomly assigned to a bevacizumab group (5 mg/kg intravenously every 2 weeks, 4 cycles) or a corticosteroid group: 38 patients in the bevacizumab group showed a response, which was significantly higher proportion than in the corticosteroid group (65.5% vs. 31.5%,  $p<0.001$ ). Furthermore, radiographic response was improved in the bevacizumab group [14]. Several additional studies reported excellent response rates for the treatment of RN with bevacizumab. The recurrence rate for RN after bevacizumab treatment is unclear and studies have reported recurrence rates between 10 and 39%, mainly independent of the primary disease [15]. Li et al. indicated that the duration from RN diagnosis to start of bevacizumab is a predictive factor for RN recurrence [16]. In general, RN diagnosis is difficult, even more so in the recurrent setting. Therefore, accurate recurrence rates are rare because physicians are often unable to distinguish between RN and tumor progression. In addition to diagnostic response, bevacizumab offers clinical improvement in the majority of patients suffering from RN with minimal toxicity [15]. The dose in the literature varies, but lower doses of 5.0–7.5 mg/kg every 2 weeks seem sufficient under regular control of blood pressure or thrombotic events to prevent typical side effects. The obvious broad therapeutic range shows that studies are needed to establish a minimum dose requirement for achieving the maximum clinical benefit and to make the bevacizumab treatment more cost effective. In a prospective clinical trial, patients were even treated with ultra-low doses of 1 mg/kg and radiographic responses were observed in 20 of the 21 patients [17], suggesting that efficacy is associated with its anti-angiogenic effects rather than dose [14, 18]. Several studies reported that side effects were mild and reported mostly low-grade adverse events [13, 17, 19]. Side effects included vascular events, hypertension, fatigue, proteinuria, anemia, leukopenia, neutropenia, and lymphocytopenia. In a prospective trial, Levin et al. reported that 6 (55%) patients experienced serious adverse events, including aspiration pneumonia, pulmonary embolism, and superior sagittal sinus thrombosis [13]. Another prospective trial by Xu et al. reported 40 grade 1 or 2 adverse events experienced by 58 patients but only one grade 3 adverse event of ischemic stroke. In-

terestingly, comparable side effects were seen in the corticosteroid-treated group, indicating that bevacizumab may not increase toxicity in the treatment of RN compared to dexamethasone [14]. The results of a randomized phase II study, which aims to investigate whether the addition of bevacizumab to standard corticosteroid therapy results in greater improvement in symptoms and less treatment-induced symptoms compared to standard corticosteroid therapy for patients with symptomatic RN following SRS are pending (NCT02490878) [20].

### Laser interstitial thermal therapy

Laser interstitial thermal therapy (LITT) is a potential treatment option, but direct comparative data are scarce, with only a few patients being treated with LITT, and the technique is not generally available [21, 22]. The advantage of LITT is its minimal invasiveness and ability to provide same-procedure pathologic confirmation of RN. Palmisciano summarized the available evidence in a recent review. Among the 18 studies included, 143 patients received bevacizumab and 148 underwent LITT. Both strategies were effective in providing post-treatment symptomatic improvement ( $p=0.187$ ), weaning off steroids ( $p=0.614$ ), and local lesion control ( $p=0.5$ ) [23].

### Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) demonstrated the ability to reduce edema and prospective studies report radiographic and symptomatic improvement of RN with HBOT [24–27]. Approximately 90% of the patients improved and 60% responded clinically during the course of HBOT after a median of 30 treatments. It has to be highlighted that in many reported cases, HBOT was administered with concomitant dexamethasone or bevacizumab, and studies evaluating hyperbaric oxygen therapy alone are rare and the available evidence is low. Common side effects of HBOT are usually low grade and can include ear barotrauma, dyspnea, ear pain requiring myringotomy, and sinusitis [24, 27, 28].

### Surgical removal of rapidly progressing cerebral radiation necrosis in brain metastases

Standard of care for rapidly progressing, symptomatic RN is considered to be surgical removal, depending on the location and estimated morbidity of the procedure. This approach is consistent with the tumor-like growth pattern of RN and can be achieved with low rates of morbidity if patients are selected carefully and discussed within an interdisciplinary setting [29]. The incidence of wound healing and surgical complications, including serious and fatal

complications, is increased in bevacizumab-treated patients; thus, at least 28 days of bevacizumab “wash-out” before elective surgery is recommended at present [30]. Currently, data on the benefit of surgical resection of RN are sparse. However, existing evidence shows that gross total resection leads to reduced edema and use of steroids during follow-up [31]. Preoperative symptoms, such as headache or seizures, only improved in 55% after surgery but were independent of the extent of resection. However, regarding BM data, symptom relief was reported by 55% of patients undergoing RN resection independently of the extent of surgical resection (EOR), while most effects of bevacizumab were only reported 3 months after treatment or later.

### **Surgical removal of rapidly progressing cerebral radiation necrosis in glioma**

GBM does not usually have extracranial disease necessitating systemic therapy but requires an evaluation of rather a purely local disease.

Surgery can potentially reduce the CNS tumor burden if RN is combined with residual tumor cells. Yet, at least for GBM, no difference was shown in overall survival for surgery or bevacizumab if RN consisted of necrosis only vs. residual tumor cells [32]. Thus, there seems to be no advantage of cytoreduction or RN resection in terms of survival. Considering the goal of maximizing quality of life (QOL) in tumor patients, the treatment of agonizing symptoms, such as seizures or headache, is a legitimate rationale for surgical treatment. The resection of RN is very similar to a glioma resection, with a continuous border between healthy tissue and necrosis. Thus, the same principles need to be applied by the neurosurgeon, including intraoperative neurophysiology via MRI to secure maximum safe resection. Since RN neighbors previous resection cavities, it can affect eloquent subcortical anatomy, necessitating the respective caution and measures, especially considering the usually closer location to eloquent tracts.

### **Considerations for the treatment of radiation necrosis in the era of immunotherapy**

Corticosteroids are one of the principal treatments for immune-related adverse events of checkpoint inhibitors (CPIs) but also an exclusion criterion for CPI clinical trials [33–35]. In day-to-day clinical routine, corticosteroids are often used as part of the palliative treatment for cancer-related symptoms such as dyspnea and edema in symptomatic brain metastases [36, 37]. In a recent review, Petrelli et al. summarized the data of studies where the outcome of corticosteroid-using patients treated with immunotherapy were compared with those not assuming or using steroids at lower doses (less than 10mg equivalent of prednisone)

[38]. They found that patients taking steroids were at an increased risk of limited overall survival and progression compared to patients not using steroids ( $p=0.03$ ). Even though immune-related toxicities necessitate corticosteroid therapy for improvement, use of steroids in these cases seems not to reduce overall survival (OS) in cancer patients treated with CPIs and may be safely administered without compromising outcome [33, 39]. Conversely, more caution is needed for patients using higher doses of corticosteroids for a longer period of time, especially as palliative treatment. In analogy to this, short-course steroid use for immediate symptom relief in patients with symptomatic RN (e.g., 20mg dexamethasone i.v.) might not compromise CPI treatment, but long-term steroid use over a course of several weeks might be detrimental. In these cases, discussing different treatment options (e.g., bevacizumab or surgery) may avoid compromising treatment with CPIs. Dexamethasone, as the potentially cheaper treatment of RN compared to bevacizumab or surgery, might compromise not only the survival of patients undergoing a working CPI treatment but also might be rendered less cost effective by inhibiting the effect of cost-intensive CPIs. CPIs have significantly improved the prognosis of patients with various tumors. As part of their multidisciplinary treatment, many patients will be treated with high-dose radiotherapy (RT) to CNS metastases and receive CPIs either concurrently or within short time intervals both before or after RT; this combination has been observed to beneficially decrease the incidence of new CNS metastases [3]. On the contrary, CPIs and other targeted therapies have been demonstrated to enhance the risk for symptomatic RN [4]. Most RN occur within the first year after RT [40]. Despite the general notion of preferably no or low steroid doses while receiving CPI, most reported RN has been treated with steroids, while few authors have reported the efficacy of bevacizumab [41, 42]. A current clinical phase I study is investigating the effect of low-dose radiosurgery in combination with CPI on the occurrence and course of RN [43].

### **Reimbursement situation and consecutive workflow issues**

Despite clear data supporting bevacizumab's efficacy in the treatment of RN, it is still considered an off-label use. As a result, seeking insurance approvals can lead to treatment delays and, if ultimately not covered, the drug cost can be expensive for patients and treating physicians [44]. In order to avoid reimbursement claims following off-label use, physicians in Germany (and other European countries) can file an application for cost coverage with the patients' health insurance prior to treatment initiation [45]. In this context, the position paper of the European Society for Medical Oncology (ESMO) describes a number of ethical problems for

**Table 1** Proposed treatment algorithm for BBD and RN in glioma patients

Most likely radio-graphic and clinical diagnosis according to interdisciplinary decision	Symptom-atic	Dynamic/progressive	Localization	Treatment strategy
SCE	No	Fluctuating or no	Every location	Observation with regular FU
BBD	No	No	Uncritical	Observation (regular FU MRI, approximately 12 weeks)
BBD	No	No	Critical	MRI follow-up (8–12 weeks), short-course dexamethasone can be considered depending on the size and extent of edema to prevent symptoms in critical areas like brainstem
BBD	No	Yes	Uncritical	In smaller lesions, regular observation (FU MRI approximately 12 weeks) is reasonable. For larger lesions short-course dexamethasone can be considered if severe edema is present to prevent symptoms followed by shorter MRI follow-up (6–8 weeks). Diagnostic verification of RN with FET PET MRI in progressing glioma lesions can be discussed
BBD	Yes, but not severe	No or yes	Uncritical	Short-course dexamethasone if severe edema is present can be considered, MRI follow-up (6–8 weeks)
BBD	Severe	No or yes	Uncritical or critical	For immediate symptom relief an attempt with dexamethasone (e.g., 20 mg i.v.) can be reasonable, followed by short-course dexamethasone for a few days depending on the symptoms; if no symptom improvement occurs, surgical intervention or bevacizumab should be considered (→ <i>continue treatment as RN, diagnostic verification of RN with FET PET MRI in progressing glioma lesions</i> )
RN	No	No	Uncritical or critical	MRI follow-up (8–12 weeks), short-course dexamethasone can be considered depending on the size and extent of edema and the location of the lesion (e.g., critical brainstem lesions) followed by shorter MRI or for glioma FET PET MRI follow-up (6–8 weeks)
RN	No	Yes	Uncritical	Short-course dexamethasone if edema is present, MRI or FET PET MRI follow-up (6–8 weeks)
RN	Yes, but not severe	Yes	Uncritical	Consider diagnostic verification of RN with FET PET MRI in progressing lesions in glioma. Consider short-course dexamethasone depending on the symptoms; if no symptom improvement is seen, surgical intervention or bevacizumab should be considered
RN	Yes, but not severe	Yes	Critical	Consider diagnostic verification of RN with FET PET MRI in progressing lesions. Consider a short course of dexamethasone for a few days depending on the symptoms and extent of the edema; if no symptom improvement is seen, surgical intervention or bevacizumab should be considered. In patients with no or only small edema, surgery or bevacizumab without prior dexamethasone should be considered
RN	Severe	Yes (rapidly progressing)	Uncritical or critical	Consider diagnostic verification of RN with FET PET MRI in progressing lesions. Surgical intervention or bevacizumab should be considered. In patients with no or only small edema, surgery or bevacizumab without prior dexamethasone therapy should be considered. For immediate symptom relief, an attempt with high-dose dexamethasone (e.g., 20 mg i.v. can be reasonable)

*IT* immunotherapy, *FU* follow-up, *RN* radiation necrosis, *SCEs* speckled contrast-enhancing lesions, *BBD* blood–brain barrier disruptions

treating physicians [46]. Where evidence is available, several clinical practice guidelines recommend off-label use of drugs but this is perceived by the ESMO as “outside existing regulatory boundaries” [46] and by prescribing off-label, the physician is asked to take a special responsibility. Although this off-label use of drugs is not unpermitted or illegal, there are some important differences in comparison with licensed pharmaceutical products within the approved indications [47–49]. The off-label issue can be as acute as

the symptoms of a patient with RN. For bevacizumab it is currently unlikely that pharmaceutical companies will support large-scale phase II/III trials. When the drug patent expires, there is limited financial interest in pursuing any label extension. In cases of acute RN, physicians have to decide between immediate start of a potentially curative therapy and risking reimbursement claims. Filing an off-label application often takes several weeks before reimbursement is granted. In patients with severe neurological



**Table 2** Proposed treatment algorithm for BBD and RN in patients with brain metastases

Most likely radio-graphic and clinical diagnosis according to interdisciplinary decision	Symptom-atic	Dynamic/progressive	Localization	Treatment strategy
BBD	No	No	Uncritical	Observation (regular FU MRI, approximately 12 weeks)
BBD	No	No	Critical	MRI follow-up (8–12 weeks), short-course dexamethasone can be considered depending on the size and extent of edema to prevent symptoms in critical areas like brainstem. In patients undergoing IT, MRI follow-up without dexamethasone should be considered
BBD	No	Yes	Uncritical	In smaller lesions regular observation (FU MRI approximately 12 weeks) is reasonable. For larger lesions, short-course dexamethasone can be considered if severe edema is present to prevent symptoms, followed by shorter MRI follow-up (6–8 weeks). In patients undergoing IT, MRI follow-up without dexamethasone should be considered
BBD	Yes, but not severe	No or yes	Uncritical	Short-course dexamethasone can be considered if edema is present with MRI follow-up (6–8 weeks). In patients undergoing IT, dexamethasone should be critically discussed. In rapidly progressing lesions, bevacizumab can be considered
BBD	Severe	No or yes	Uncritical or critical	For immediate symptom relief, an attempt with dexamethasone (e.g., 20 mg i.v.) can be reasonable, followed by short-course dexamethasone for a few days depending on the symptoms; if no symptom improvement occurs, surgical intervention or bevacizumab should be considered. In symptomatic patients with no or only small edema and in patients undergoing IT, surgery or bevacizumab without prior dexamethasone should be considered. (→ <i>continue treatment as RN</i> )
RN	No	No	Uncritical or critical	MRI follow-up (8–12 weeks), short-course dexamethasone can be considered depending on the size and extent of edema and the location of the lesion (e.g., critical brainstem lesions) followed by shorter MRI follow-up (6–8 weeks). In patients undergoing IT, only MRI follow-up is recommended
RN	No	Yes	Uncritical	Short-course dexamethasone if edema is present, MRI follow-up (6–8 weeks). In patients undergoing IT, only MRI follow-up should be discussed depending on the dynamic. In rapidly progressing lesions, bevacizumab can be considered
RN	Yes, but not severe	Yes	Uncritical	Consider short-course dexamethasone depending on the symptoms; if no symptom improvement is seen, surgical intervention or bevacizumab should be discussed. In patients undergoing IT, surgery or bevacizumab should be considered
RN	Yes, but not severe	Yes	Critical	Consider a short course of dexamethasone for a few days depending on the symptoms and extent of the edema; if no symptom improvement appears, surgical intervention or bevacizumab should be discussed. In symptomatic patients with no or only small edema and in patients undergoing IT, surgery or bevacizumab without prior dexamethasone should be considered
RN	Severe	Yes (rapidly progressing)	Uncritical or critical	For immediate symptom relief an attempt with high-dose dexamethasone (e.g., 20 mg i.v.) can be reasonable. Surgical intervention or bevacizumab should be considered. In symptomatic patients with no or only small edema and in patients undergoing IT, surgery or bevacizumab without prior dexamethasone should be considered

IT immunotherapy, FU follow-up, RN radiation necrosis, BBD blood–brain barrier disruptions

symptoms and no surgical treatment options, any treatment delay can cause irreversible neurological brain damage or even be lethal. Additionally, in centers with high volumes of stereotactic RT or re-irradiation cases, reimbursement applications become a time-consuming and staff-intensive task which is not financially compensated for.

## Proposed treatment strategy

Treatment of BBD and RN is similar, although it should be performed more straightforwardly in RN due to the more aggressive and tumor-like clinical behavior. Treatment should be initiated based on symptomatology and the anatomical region of the CEL. Observation (on a regular basis every 3 months) is a viable option in asymptomatic patients with classical BBD that occur as a side effect af-

ter RT, since they are mostly self-limiting and temporary. Also, patients who have been treated with SRS sometimes experience an increase in size during FU. In patients receiving immunotherapy, delayed CEL is possible, an effect that is already well known and considered in the iRECIST and RANO criteria [5, 50]. However, it is recommended to more closely monitor patients clinically and radiologically (e.g., every 2–3 months). Of further importance is the fact that once there is a progressive RN detected, this damage can be irreversible, underlining the importance of prompt treatment induction with bevacizumab after diagnosis. Since bevacizumab is effective in reduction of edema, corticosteroids should be reduced as soon as possible. A FU-MRI scan should be scheduled after four cycles to evaluate further treatment with bevacizumab. Bevacizumab dose is typically 5–10 mg/kg, q2–4w, and patients receive at least two doses. Due to the half-time of bevacizumab of 3 weeks, treatment with only one application is not recommended, since it can cause rebound effects. Because the treatment goal is symptom oriented and not prolongation of survival, we suggest that patients should be treated until symptoms are relieved and imaging improves; the treatment should then be discontinued. The decision on whether to use bevacizumab or perform surgery should be discussed within tumor boards and put into the context of the underlying primary disease, especially in patients with extracranial tumor progression requiring immediate systemic therapy. The possible morbidity of each strategy and necessary perioperative systemic treatment interruptions should be weighed against the potential benefit. On the other hand, if bevacizumab is used, the further need of surgical interventions can be complicated. Detailed treatment strategies for glioma patients and patients with brain metastases are explained in Table 1 and 2, respectively.

## Conclusion

Due to the increasing use of SRS and Re-RT, high-dose treatment at the skull base, and other dose-escalating radiotherapy approaches, detection of new or progressing CEL is encountered more frequently. Since BBD may be self-limiting and reversible, treatment is not always mandatory and clinical symptoms as well as radiographic features should be taken into consideration. On the other hand, the rapid progression and tumor-like growth patterns of RN as well as the accompanying clinical symptoms often require prompt initiation of treatment with corticosteroids, bevacizumab, or surgery. High-dose radiotherapy provides a curative treatment option in many situations, and RN may be an accepted side effect in this context. This practice guideline offers a multistep approach to improve treatment of radiation-induced injuries, helping us to treat unwanted side ef-

fects effectively, and offering a balanced recommendation for anticipated side effects associated with curative high-dose treatments.

**Funding** Open Access funding enabled and organized by Projekt DEAL.

## Declarations

**Conflict of interest** D. Bernhardt reports personal fees and honoraria from Accuray Inc., AstraZeneca, and Novocure GmbH outside the submitted work. DB's spouse is employed at Gilead Science. L. König reports grants from Ruprecht-Karls Universität Heidelberg, and personal fees from Accuray Inc. and Novocure GmbH outside the submitted work. J. Debus: institution received research grants from Merck Serono, institution received consultation honoraria from Merck serono, JD received travel reimbursement from Merck Serono, institution received research grants from Siemens Healthineers and Accuray. S. Rieken is consultant for Brainlab AG (Munich, Germany) and Ulrich Medical (Ulm, Germany). S.K. received honoraria from Nexstim Plc (Helsinki, Finland), Spineart Deutschland GmbH (Frankfurt, Germany), Medtronic (Meerbusch, Germany), and Carl Zeiss Meditec (Oberkochen, Germany). M. Thomas reports personal fees, honoraria for advisory boards, and research funding from AstraZeneca, Beigene, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Daiichi Sankyo, GlaxoSmithKline, Janssen Oncology, Lilly, Merck, MSD, Novartis, Pfizer, Roche, Sanofi, and Takeda. F. Giordano reports research grants, honoraria, and travel expenses from Carl Zeiss Meditec AG and NOXXON Pharma AG, personal fees from MVZ Venusberg GmbH, and consulting/speaker honoraria from Bristol Myers Squibb, Medac GmbH, Merck Sharp & Dohme, Elsevier, AstraZeneca, and Guerbet SA. A.-L. Grosu, S.M. Krieg, W. Wick, B. Wiestler, F. Schmidt-Graf, F. Sahm, J. Gempt, B. Meyer, B.J. Krause, C. Petersen, R. Fietkau, A. Wittig-Sauerwein, G. Tabatabai, P. Hau, J. Steinbach, S.E. Combs, and the Expert Panel of the German Society of Radiation Oncology (DEGRO) declare that they have no competing interests.

**Ethical standards** Ethics approval was not necessary for the comprehensive review article. All co-authors have agreed to participate. *Consent for publication:* All co-authors have approved the final manuscript.

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## References


1. Barnholtz-Sloan JS et al (2004) Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 22:2865–2872
2. Langer CJ, Mehta MP (2005) Current management of brain metastases, with a focus on systemic options. *J Clin Oncol* 23:6207–6219

3. Chen L et al (2018) Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 100:916–925
4. Martin AM et al (2018) Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. *JAMA Oncol* 4:1123–1124
5. Okada H et al (2015) Immunotherapy Response Assessment in Neuro-Oncology (iRANO): A report of the RANO working group. *Lancet Oncol* 16:e534
6. Leitlinienprogramm Onkologie (2020) S3-Leitlinie Supportive Therapie
7. Nabors LB et al (2020) Central nervous system cancers, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 18:1537–1570
8. Chao ST et al (2013) Challenges with the diagnosis and treatment of cerebral radiation necrosis. *Int J Radiat Oncol Biol Phys* 87:449–457
9. Kotsarini C, Griffiths PD, Wilkinson ID, Hoggard N (2010) A systematic review of the literature on the effects of dexamethasone on the brain from in vivo human-based studies: implications for physiological brain imaging of patients with intracranial tumors. *Neurosurgery* 67:1799–1815
10. Yasir M, Goyal A, Bansal P, Sonthalia S (2021) Corticosteroid adverse effects. *StatPearls*
11. Huscher D et al (2009) Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 68:1119–1124
12. Aldea M et al (2020) How to manage patients with corticosteroids in oncology in the era of immunotherapy? *Eur J Cancer* 141:239–251
13. Levin VA et al (2011) Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys* 79:1487–1495
14. Xu Y et al (2018) Bevacizumab monotherapy reduces radiation-induced brain necrosis in nasopharyngeal carcinoma patients: a randomized controlled trial. *Int J Radiat Oncol Biol Phys* 101:1087–1095
15. Khan M, Zhao Z, Arooj S, Liao G (2021) Bevacizumab for radiation necrosis following radiotherapy of brain metastatic disease: a systematic review & meta-analysis. *BMC Cancer*. <https://doi.org/10.1186/s12885-021-07889-3>
16. Li Y et al (2018) Clinical variables for prediction of the therapeutic effects of bevacizumab monotherapy in nasopharyngeal carcinoma patients with radiation-induced brain necrosis. *Int J Radiat Oncol Biol Phys* 100:621–629
17. Zhuang H, Zhuang H, Shi S, Wang Y (2019) Ultra-low-dose bevacizumab for cerebral radiation necrosis: a prospective phase II clinical study. *Onco Targets Ther* 12:8447–8453
18. Zhuang H, Shi S, Yuan Z, Chang JY (2019) Bevacizumab treatment for radiation brain necrosis: Mechanism, efficacy and issues. *Mol Cancer*. <https://doi.org/10.1186/s12943-019-0950-1>
19. Sadraei NH et al (2015) Treatment of cerebral radiation necrosis with bevacizumab: the Cleveland clinic experience. *Am J Clin Oncol* 38:304–310
20. ClinicalTrials.gov Corticosteroids + Bevacizumab vs. Corticosteroids + placebo (BEST) for radionecrosis after radiosurgery for brain metastases—Full text view. <https://clinicaltrials.gov/ct2/show/NCT02490878>. Accessed 02.05.2022
21. Amsbaugh MJ et al (2019) Laser-interstitial thermal therapy as a novel and effective treatment in radiation necrosis following stereotactic radiosurgery to the brain. *Int J Radiat Oncol Biol Phys* 105:S140–S141
22. Bastos DCA et al (2020) Laser interstitial thermal therapy in the treatment of brain metastases and radiation necrosis. *Cancer Lett* 489:9–18
23. Palmisciano P et al (2021) Bevacizumab vs laser interstitial thermal therapy in cerebral radiation necrosis from brain metastases: a systematic review and meta-analysis. *J Neurooncol* 154:13–23
24. Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C (2016) Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2016:4
25. Cihan YB, Uzun G, Yildiz Ş, Dönmez H (2009) Hyperbaric oxygen therapy for radiation-induced brain necrosis in a patient with primary central nervous system lymphoma. *J Surg Oncol* 100:732–735
26. Ohguri T et al (2007) Effect of prophylactic hyperbaric oxygen treatment for radiation-induced brain injury after stereotactic radiosurgery of brain metastases. *Int J Radiat Oncol Biol Phys* 67:248–255
27. Kohshi K et al (2003) Successful treatment of radiation-induced brain necrosis by hyperbaric oxygen therapy. *J Neurol Sci* 209: 115–117
28. Aghajani Y, Grover I, Gorski H, Tumblin M, Crawford JR (2019) Use of hyperbaric oxygen therapy in pediatric neuro-oncology: a single institutional experience. *J Neurooncol* 141:151–158
29. Campos B et al (2020) Analysis of a surgical series of 21 cerebral radiation necroses. *World Neurosurg* 137:e462–e469
30. fda & cder (2009) Label information Avastin FDA
31. Newman WC et al (2021) The effect of surgery on radiation necrosis in irradiated brain metastases: extent of resection and long-term clinical and radiographic outcomes. *J Neurooncol* 153:507–518
32. Cook TA et al (2021) Redo craniotomy or bevacizumab for symptomatic steroid-refractory true or pseudoprogression following IMRT for glioblastoma. *Neurooncol Pract* 8:601–608
33. Haanen JBAG et al (2017) Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 28:iv119–iv142
34. Carbone DP et al (2017) First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med* 376:2415–2426
35. Reck M et al (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 375: 1823–1833
36. Paulsen Ø et al (2014) Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. *J Clin Oncol* 32:3221–3228
37. Ryken TC et al (2010) The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 96:103–114
38. Petrelli F et al (2020) Association of steroids use with survival in patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. *Cancers (Basel)* 12:546
39. Brahmer JR et al (2018) Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 36:1714–1768
40. Kim PH et al (2021) Immune checkpoint inhibitor therapy may increase the incidence of treatment-related necrosis after stereotactic radiosurgery for brain metastases: a systematic review and meta-analysis. *Eur Radiol* 31:4114–4129
41. Moore A et al (2021) Bevacizumab for stereotactic radiosurgery-induced radiation necrosis in patients with non-small cell lung cancer treated with immune check-point inhibitors. *J Neurol Sci* 427:117556
42. Glitza IC et al (2017) Bevacizumab as an effective treatment for radiation necrosis after radiotherapy for melanoma brain metastases. *Melanoma Res* 27:580–584
43. McClelland S et al (2020) Radiosurgery dose reduction for brain metastases on immunotherapy (RADREMI): A prospective phase I study protocol. *Rep Pract Oncol Radiother* 25:500–506



44. Sharma A, Low J, Mrugala MM (2019) Neuro-oncologists have spoken—the role of bevacizumab in the inpatient setting. A clinical and economic conundrum. *Neurooncol Pract* 6:30–36
45. Seidenschur KEK, Dressler C, Weller K, Nast A, Werner RN (2017) Off-label prescriptions and decisions on reimbursement requests in Germany—A retrospective analysis. *J Dtsch Dermatol Ges* 15:1103–1109
46. Casali PG (2007) The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO). *Ann Oncol* 18:1923–1925
47. Lenk C, Duttge G (2014) Ethical and legal framework and regulation for off-label use: European perspective. *Ther Clin Risk Manag* 10:537–546
48. American Society of Clinical Oncology (2006) Reimbursement for cancer treatment: coverage of off-label drug indications. *J Clin Oncol* 24:3206–3208
49. Poole SG, Dooley MJ (2004) Off-label prescribing in oncology. *Support Care Cancer* 12:302–305
50. Seymour L et al (2017) iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 18:e143

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