JMRO
Journal of Medical and Radiation Oncology
Journal homepage: www.jmedradonc.org

Use of Boswellia Serrata for Cerebral Radiation Necrosis – A Case Report

Malina Ioschici[1], Elena Nagy[2], Claudiu Hopirtean[3]

[1] *Institute of Oncology "Prof. Dr. Ion Chiricuta", Cluj-Napoca, Romania*
[2] *OncoHelp Oncology Center, Timisoara, Romania*
[3] *Department of Radiation Oncology, RTC Amethyst, Cluj-Napoca, Romania*

doi: 10.53011/JMRO.2024.02.06
ISSN: 2784 – 0131

Received 16 November 2024
Revised 17 December 2024
Accepted 30 December 2024
Available online 31 December 2024
***Corresponding author:**
Malina Ioschici
Email: malina.ioschici@gmail.com

ABSTRACT
Radiation necrosis is a dose-limiting side effect of radiation therapy for brain lesions. Several treatment options are available. However, they offer limited symptomatic relief and have important side effects. Boswellia serrata extract shows promising results in reducing the associated cerebral edema and neurological symptoms.
We present the case of a 44-year-old male, diagnosed with an unspecified glioma, who received surgery, followed by concurrent Temozolomide and radiation therapy on the tumor bed (60 Gy/30 fr), followed by adjuvant Temozolomide (6 cycles). Two years later, the patient became symptomatic again and an MRI confirmed two recurrent lesions, that were treated with fSRS and 6 cycles of Temozolomide. Two months later, the patient developed headaches and balance impairment and was diagnosed by MRI spectroscopy with radiation necrosis. He started treatment with corticosteroids, which he inconsistently used due to side effects. After three months he was advised to add Bevacizumab, Hyperbaric Oxygen, and Boswellia serrata. At 2 months he showed impressive symptomatic benefit, concurrent with improvement on MRI imaging, despite the suboptimal use of corticosteroids and hyperbaric oxygen.
KEYWORDS: *Boswellia serrata, fSRS, late toxicity, radiation necrosis, radiation therapy*

1. Introduction

Radiation necrosis (RN) is a serious, late-onset complication of radiation therapy for either primary or metastatic brain tumors. It can manifest through various neurological symptoms, significantly impacting a patient's quality of life.

The risk and severity of radionecrosis depend on the administered radiation dose and the size of the target volume. Standard fractionation presents a 5% risk of radiation necrosis at a biologically effective dose (BED) greater than 120Gy (1). In the case of stereotactic radiosurgery (SRS), a tumor volume greater than 8.5 cc receiving more than 12Gy is indicative of a radiation necrosis risk higher than 10% (2). For brain metastasis treated with a course of stereotactic radiotherapy (the most common fractionation schedule was 25Gy/5 fractions) in patients who also received whole brain radiotherapy (WBRT), the incidence of symptomatic radionecrosis was 11.6% at 6 months and 17.4% at 12 months (3).

Several treatment options exist, with oral corticosteroids being an effective, first-line intervention. However, the well-known toxicity of long-term corticosteroid use and potential drug interactions, particularly with immunotherapy agents, highlight the need for a novel approach to the treatment of radiation necrosis (4).

Case Reports

Other second-line therapies include Bevacizumab for cases refractory to corticosteroids and surgery, for selected, rapidly progressive cases, or when there is compression of vital cerebral structures. (4)(7)

Alternative treatments have been studied with variable success. A promising option is a readily available supplement, Boswellia serrata (BS). Boswellia serrata is a tree with a resinous sap that contains several acids, namely Β-boswellic acid, acetyl-Β-boswellic acid, 11-keto-Β-boswellic acid, and acetyl-11-Β-boswellic acid with anti-inflammatory properties. Its use has been investigated in several inflammatory pathologies such as inflammatory bowel disease, asthma, and rheumatoid arthritis. Moreover, given that boswellic acids permeate the blood-brain barrier, BS shows promising anti-edematous effects in the brain (5).

One prospective, randomized, placebo-controlled trial has shown a decrease in radiation-induced cerebral edema by up to 75%, in more than half of the patients, compared to placebo (6).

Here, we present the case of a male patient reirradiated with fractionated stereotactic radiosurgery (fSRS) for a recurrent unspecified glioma, who subsequently developed radiation necrosis. We outline the various treatment strategies employed and the benefits shown in this case by adding Boswellia serrata to manage this condition.

2. Case presentation

A 44-year-old male presented May 2022 with balance impairment, a decrease in visual acuity, and severe anxiety. His MRI showed a 33/27 mm right frontoparietal proliferative mass. The lesion had an irregular ring contrast enhancement, was associated with vasogenic cerebral edema, and exerted a mass effect, resulting in a leftward median shift of 8.6 mm. The patient had no significant risk factors or medical history.

Abdominal, pelvic, and thoracic CT scans were performed the same week the lesion was detected on the MRI and they all came back clear of any metastases.

Surgery was was performed the same month, with total resection of the lesion through a frontoparietal osteotomy.

The pathology report described a grade III anaplastic oligodendroglioma with predominantly epithelioid cells, numerous atypical mitoses, extended ischemic necrotic areas, vascular proliferations, including glomeruloid ones and vascular thrombosis. The cells were positive for glial fibrillary acidic protein (GFAP) and negative for synaptophysin. The Ki-67 marker was 20%. The margins were clear of tumoral cells. No molecular testing was performed to confirm this pathologic type, so we will consider it an unspecified glioma.

A few days later, a brain CT scan showed no post-operative complications.

In June 2022, adjuvant, external beam radiation therapy was administered every day to the tumor bed (Total Dose = 60 Gy in 30 fractions) by intensity-modulated radiation therapy (IMRT) by an Elekta linear accelerator (LINAC). No other planning details were available for this report. The treatment ended in July and was well tolerated with no immediate side effects. Concurrently with the radiotherapy, he received Temozolomide (75 mg per square meter of body-surface area per day, 7 days per week, followed by another 6 cycles of adjuvant Temozolomide (150 mg per square meter for 5 days during each 28-day cycle). During the administration of the adjuvant temozolomide, the patient presented with grade II neutropenia which was subsequently managed with granulocyte colony-stimulating factors (G-CSF).

A follow-up MRI in October, three months post-radiotherapy, showed no visible signs of residual tumor and in January 2023 the last Temozolomide cycle was administered.

No follow-up MRI was performed after that.

One year later, in January 2024, the patient presented headaches and additional narrowing of the visual field. The MRI made in February 2024 revealed a new 9/7/10 mm lesion in the right parietal lobe and a 10/7/4 mm occipital lesion in close contact with the lateral ventricle (Figure 1).

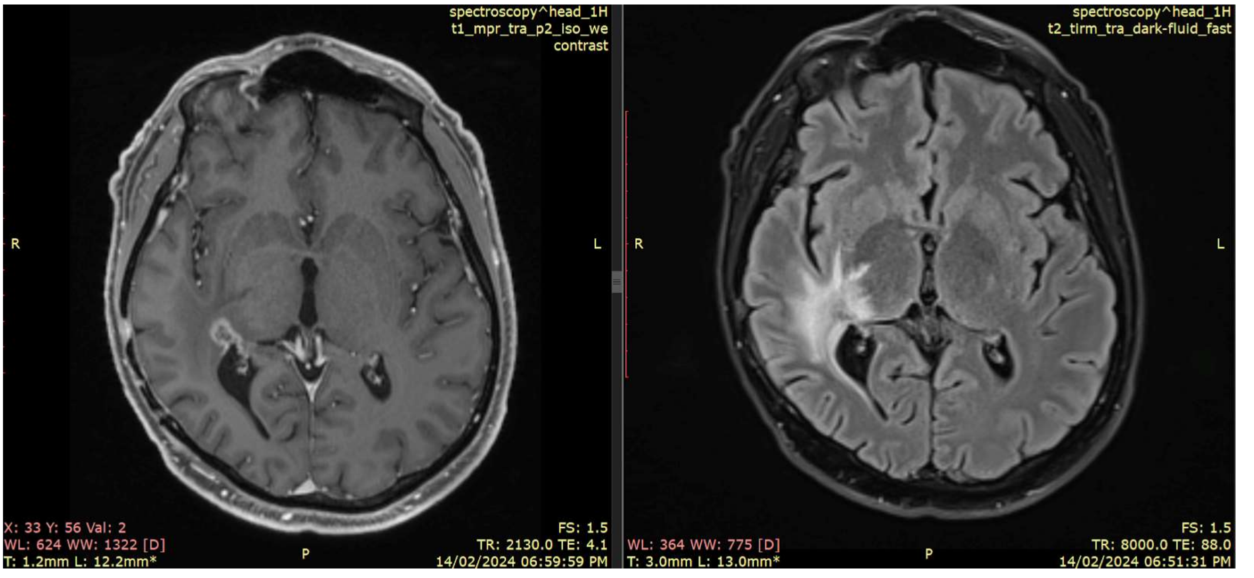


Figure 1. MRI from February 2024 showing an occipital lesion in close contact with the lateral ventricle. Left: T1 weighted image. Right: T2 weighted image

In March 2024 the patient underwent fractionated stereotactic radiosurgery (fSRS) on both lesions. A CT simulation was performed in a supine position and the patient was immobilized with a Klarity Stereotactic Mask. The target coverage was 100% of the prescribed dose to 98% of the planning target volume (PTV). The quality assurance (QA) was performed via the SRS QA MapCHECK by Sun Nuclear. Thirty-five Gy were delivered every day in 5 fractions by an Elekta linear accelerator (LINAC) with a 6 MV flattening filter-free photons configuration. There were no immediate side effects of the radiotherapy.

Adjuvant Temozolomide (320 mg/day, days 1 to 5) was started in April, a total of six cycles being given.

In May 2024, two months after the reirradiation, he presented with severe headaches and impaired balance. By this point, the underlying anxiety had turned into panic attacks. The patient was promptly admitted to the hospital and started on high-doses corticosteroids and mannitol. This alleviated only the headache, while the rest of the symptoms remained unchanged. After discharge, the patient was prescribed 2 mg/day of Dexamethasone.

Given the timing of the symptoms and the history of fSRS, there was a high clinical suspicion of radiation necrosis. Therefore, a contrast MRI with both perfusion and spectroscopy sequences was performed in May 2024, which described a 30/24 mm lesion in the right temporal lobe adjacent to the right lateral ventricle. The lesion had irregular ring contrast enhancement, marked central diffusion restriction, and perilesional vasogenic edema which exerted a mass effect on the lateral ventricle. A leftward 7 mm midline shift could be observed. Perfusion MRI identified a predominantly hypovascular appearance of the lesion (maximal rCBV value 2.3). The spectroscopy sequences revealed low choline, creatine, and N-acetylasparate (NAA) peaks and high amounts of lactate and lipids, all suggesting radiation-induced necrosis. However, there were also areas of moderately high choline and low NAA meaning that residual disease could not be excluded. Further radiological follow-up was advised.

In July 2024, another MRI spectroscopy confirmed the suspicion of radiation necrosis, with low choline, creatine, and NAA peaks and markedly high lactate and lipids within the lesion. At this time, the MRI also revealed that the size of the contrast-enhanced lesion was slightly larger: 33/28 mm compared to 30/24 mm in May. The growth was based on the progression of the central necrosis. The edema had also extended to the internal and external capsules, the thalamus, the midbrain, and the right optic tract including the right half of the optic chiasm. These findings were consistent with a grade 2 radiation injury, according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

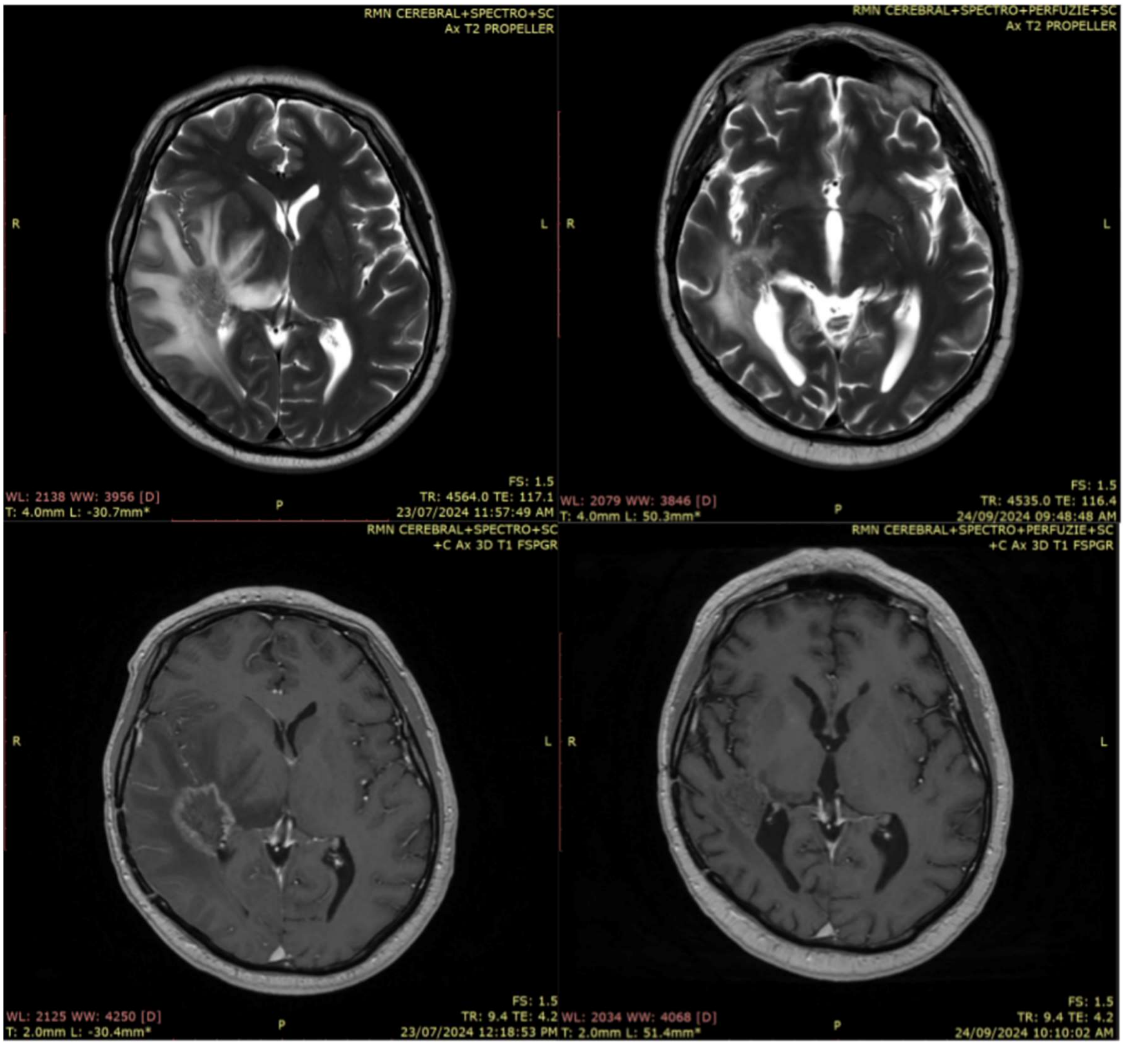
At this point, in mid-July 2024, he declared he was not constantly using Dexamethasone, due to side effects as insomnia, restlessness, worsened anxiety and Cushing Syndrome appearance. He started over-the-counter Boswellia serrata (GNC brand) 3600 mg daily in divided doses: 8 capsules/day with 450 mg standardized extract/capsule. The supplement was continued daily until his follow-up MRI, which was scheduled for September. No important side effects were noted.

At the end of July, he also began Hyperbaric Oxygen Therapy (HBOT), with a total of six sessions. The patient stopped attending the remaining four sessions he had booked, because of his anxiety disorder which was aggravated by the enclosed space in the HBOT chamber.

A month later, in August, he started to receive Bevacizumab, 5mg/kg, every two weeks amounting to four cycles. No side effects were reported.

At the end of September, a new MRI was performed. Compared with the MRI from July, there was a significant improvement in both the temporal periventricular radiation necrosis and the perilesional edema. The diameter of the lesion was now 30 mm. It maintained its central diffusion restriction and low rCBV. The midline shift present on the examination from July was no longer observed (Figure 2). At this point, we classified his radiation injury as a grade 1 according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Around the same time, the patient had completely stopped taking oral corticosteroids by his own will, with a subsequent improvement of the previously mentioned side effects.



July 2024 September 2024

Figure 2. Comparative MRI images showing improvement of radiation necrosis.
Top – T2 weighted images; Bottom – T1 weighted images. Left – July 2024; Right – September 2024.

In November 2024 the patient declared that he no longer experienced headaches or any sort of balance impairment. The bilateral narrowing of the visual field, documented by an ophthalmologist, was not modified. He was under medication for recurrent panic attacks (Zoloft, 2 ml in the morning and 1 ml at night, and Alprazolam, 0.5 mg).

In December 2024 a new spectroscopy MRI showed an increased edema compared to September, but no clinical symptoms were present. The patient was advised to start again corticostroids. He did not accept continuous administration, but an intermittent one, to be started at the moment when he would become symptomatic. A timeline of the case is presented in Figure 3.

Figure 3. Timeline of disease and received therapy

IMRT – Intensity modulated Radiation Therapy; fSRS – fractionated Stereotactic Radiosurgery; MRI – Magnetic Resonance Imaging; HBOT – Hyperbaric Oxygen Therapy

3. Discussion

We presented the case of middle-aged man diagnosed with an unspecified glioma, for which he underwent total excision, followed by adjuvant external beam radiotherapy with temozolomide. One year later, an MRI showed a recurrence, for which he was treated with fSRS and temozolomide. Three months after the radiotherapy, he presented with neurological symptoms, and an MRI spectroscopy was performed, showing radiation necrosis. The radiation necrosis was managed with low-dose corticosteroids, hyperbaric oxygen therapy, Bevacizumab and Boswellia serrata.

This case is notable in that, despite the inconsistent use of dexamethasone, a substantial reduction in radiation necrosis was achieved, as evidenced by MRI spectroscopy. Additionally, there was a marked decrease in surrounding edema and the adjacent mass effect. Although the patient also underwent hyperbaric oxygen therapy, the limited number of sessions was unlikely to have influenced the outcomes significantly.

Several factors determine the choice in the management of radiation necrosis. The DEGRO Guideline advises that the location and progression rate of the lesion as well as the clinical presentation should all be taken into account when choosing a treatment option. Corticosteroids remain the first line of therapy, providing rapid symptomatic relief through their potent anti-edema effects. However, their long-term use is associated with important adverse effects. Additionally, given the frequent use of immunotherapy in various cancer treatments, concurrent administration of corticosteroids may undermine the efficacy of these agents and potentially be detrimental (7).

Another therapeutic agent used in radiation necrosis is Bevacizumab with a proven effect on both the symptomatic and the radiographical aspects of radiation necrosis. Nevertheless, no optimal dose has been established in order to assure both symptomatic control and minimal toxicities, with an average of 5.0–7.5mg/kg every 2 weeks being the current DEGRO guideline recommendation. Recurrence rates of radiation necrosis after bevacizumab therapy are not well documented in the literature, with studies showing rates between 10% and 39%. This is due to the diagnostic difficulty of radiation-related necrosis (7). A systematic review on the use of Bevacizumab for radiation necrosis which included 12 studies concluded that 84.7% of patients had a radiographic response, with a median volume reduction of 50% (range: 26%–80%) on T1 gadolinium enhanced and/or median: 59% (range: 48%–74%) on T2 FLAIR MRI (8).

The guideline also suggests the possible added benefit of Hyperbaric Oxygen Therapy (HBOT). While HBOT has not been established as a stand-alone approach in the management of RN, an added benefit after 30-60 sessions has been documented in the literature (7,9).

The first randomized, placebo-controlled trial to use Boswellia serrata in the setting of radiotherapy-related cerebral edema was conducted by S. Kirste et al. and published in 2011. They showed that compared to placebo, more than half of the patients treated with 4200mg/day of BS had more than 75% reduction in edema, based on T2-weighted MRI sequences. Moreover, no severe adverse effects were reported in the group that had taken the supplement (6).

In 2019 F. Di Pierro et al. evaluated the benefits of adding 4500 mg/day to treat cerebral edema in patients with confirmed glioblastoma treated with surgery, standard fractionated radiotherapy, and chemotherapy. They concluded that the use of corticosteroids in most patients either remained the same, was diminished, or in some cases, they were not at all utilized (10).

The most recent study by R. Upadhyay et al. published in 2023 used between 4200- 4500 mg of Boswellia Serrata in patients with radiation necrosis after stereotactic SRS for brain metastases. Compared to the baseline MRI, more than 50% of the patients had a reduction in edema greater than 25% on T2-weighted sequences (11).

A series of three case reports presented patients treated for brain tumors by stereotactic radiosurgery (SRS), who developed radiation-related adverse effects. In all cases, if the first-line therapy, consisting of a combination of corticosteroids, pentoxifylline, and vitamin E failed, a Boswellia extract (300 mg daily) was added to the treatment plan, The dose is apparently significantly lower compared to other studies, since the concentration of acetyl-11-keto-b-boswellic acid was higher (30%). At follow-up, MRI studies showed a significant reduction of the radiation-induced edema, and all patients were able to stop corticoid use. No adverse effects of BS were noted (12).

A case report, also from 2023 described a 59-year-old woman with metastatic, clear-cell renal cell carcinoma. A frontal lobe metastasis was treated using fSRS (24 Gy in 3 fractions). Her follow-up MRI 2 months after the treatment showed increasing edema surrounding the irradiated volume, which was categorized as a grade 1 radiation injury. She was started on 4500 mg of Boswellia serrata daily in 3 divided doses and it was well-tolerated. Her follow-up MRIs at 5- and 8-months post-treatment both demonstrated a considerable decrease in the size of the edema (13).

In some of the published data, the supplement was administered together with a fatty meal. The effect this has on the pharmacokinetics of BS has been shown by a randomized, open, single-dose trial. The trial demonstrated improved bioavailability of boswellic acids when administered concomitantly with a high-fat meal (14).

The supplement is generally well-tolerated, with only mild gastrointestinal effects being reported in some of the cited studies or case studies. In the setting of different inflammatory diseases, BS was tested on larger populations, and even though lower doses were used, no dose-related toxicity was observed (15).

The authors acknowledge the limitations of this case report, that cannot allow establishing a direct causality between the use of Boswellia and the significant imaging and symptomatic improvements. Firstly, combining the different therapeutic approaches such as corticosteroids, bevacizumab, and hyperbaric oxygen therapy makes it difficult to properly evaluate the effect of Boswellia serrata. Secondly, given the lack of regulations regarding supplements, without a plasma measurement of boswellic acids, it is impossible to quantify whether the therapeutic dosage was indeed achieved.

Our patient received a slightly lower dose (3600 mg/day) than previously reported in most of the studies (4200-4500 mg/day) (6, 10, 11, 13). However, Boswellia seems to be effective even at lower doses (300 mg/day) (12). This case shows spectacular improvement of radiation necrosis and the perilesional edema in the context of 4 cycles of Bevacizumab, but inconsistent use of corticosteroids and suboptimal use of HBOT.

Small parts of the brain receive high doses in case of SBRT and SRS for primary cerebral tumors or metastases. These regions can be larger or the total dose higher, in case of reirradiation, increasing the risk of radiation necrosis. Current treatment options have unsatisfactory results and potentially significant toxicities. Identifying new effective and safe therapies represents a long process in which scattered data such as case reports are the first step. Our report documents therapeutic results that are in line with previous studies, but to author's knowledge it is the first in this setting of multimodal treatment. The use of Boswellia Serrata could be an option to increase effectiveness of the standard of care or allowing reducing the doses of corticosteroids. Details on effective doses and timing needs to be further investigated in the setting of randomized clinical trials or large observational prospective studies.

4. Conclusion

Radiation necrosis developed after reirradiation for an unspecified glioma had a spectacular response after adding Boswellia serrata extract to a patient who received Bevacizumab, and who had inconsistent use of corticosteroids and suboptimal Hyperbaric Oxygen Therapy.

ABBREVIATIONS

BED – Biologically Effective Dose
BS – Boswellia Serrata
fSRS – Fractionated Stereotactic Radiosurgery
G-CSF – Granulocyte Colony-Stimulating Factors
GFAP – Glial Fibrillary Acidic Protein
HBOT – Hyperbaric Oxygen Therapy
MRI – Magnetic Resonance Imaging
NAA – N-acetylasparate
SBRT – Stereotactic Body Radiation Therapy
SRS – Stereotactic Radiosurgery
TD – Total Dose

STATEMENTS

Author's contributions: MI wrote the paper, CH provided the technical details, EN and CH provided the history of the patient, CH reviewed the paper, MI reviewed and approved the final version.

Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all co-authors.

Conflicts of interest: All authors declare having no competing interests associated with this publication.

Funding resources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Informed Consent: The informed consent was obtained from the patient(s) for publication and any accompanying images.

Statement of Ethics: The accompanying manuscript does not contain any studies carried out by the authors on humans or animals.

Ethical Approval: The treatment strategy was approved by the local tumor board in the clinics where the patient was treated.

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