

Evaluation of brain edema formation defined by MRI after LINAC-based stereotactic radiosurgery

Maciej Harat¹, Andrzej Lebioda^{2,4}, Judyta Lasota³, Roman Makarewicz^{2,4}

¹ Department of Radiotherapy, The Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland

² Department of Oncology and Brachytherapy, Nicolaus Copernicus University, Ludwik Rydygier Collegium Medicum, Bydgoszcz, Poland

³ Department of Medical Physics, The Franciszek Lukaszczyk Oncology Centre, Bydgoszcz, Poland

⁴ Department of Oncology and Brachytherapy, The Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland

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Correspondence to: Maciej Harat, 85-796 Bydgoszcz, Romanowskiej 2 St., Poland. Phone: +48 52 374 3479; E-mail: haratm@co.bydgoszcz.pl

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Background. Peri-lesional edema is a serious and well-known complication of stereotactic radiosurgery (SRS). Here we evaluated edema risk after SRS and assessed its formation and resolution dynamics.

Patients and methods. 107 patients underwent SRS for heterogeneous diagnoses: 34 (29%) with arteriovenous malformations, 38 (35%) with meningiomas, 16 (15%) with metastatic tumors, 16 (15%) with acoustic neuromas, 3 with (3%) cavernomas, and 2 (2%) each with anaplastic astrocytomas and anaplastic oligoastrocytomas. Edema area was delineated in MRI T2-FLAIR sequences 0, 6, 12, 18, 24, 30, and 38 months after treatment. Lesion location was defined as either above ($n = 80$) or below ($n = 32$) the "Frankfurt modified line" (FML).

Results. 17% of patients developed or had worsening post-treatment edema. Edema volume was maximal at 6 months (mean 7.2, SD 1.2) post radiosurgery. Post-SRS edema was 5.1 (1.06 – 24.53) times more likely in patients with lesions above the FML. There was no association between edema development and age, PTV size, number of beams, and diagnosis ($p = 0.07$).

Conclusions. Radiosurgery-associated edema develops within 6 months of treatment and decreases over time. Edema occurrence is strongly related to lesion location, and its presence is much more likely when the treated lesions are situated above the Frankfurt line.

Key words: brain edema; LINAC; radiosurgery; stereotactic

Introduction

Intracranial stereotactic radiosurgery (SRS) is a radiotherapy technique used to treat patients unsuitable for surgery or after partial resection of meningiomas, neuromas, brain metastases, and vascular malformations. Typical eligibility criteria are patients with tumors not exceeding 3.5 cm and those who can cooperate during the procedure.^{1,2}

Brain edema is a common radiosurgery-related side effect³⁻⁷ that often requires symptomatic treat-

ment since untreated it can impair quality of life or even cause death. For many years, the most effective edema treatments have been corticosteroids (dexamethasone) and mannitol.

The exact pathophysiology of edema formation after radiotherapy remains unclear but may be related to cerebrovascular impairment, disruption of the blood-brain barrier, or radiation-induced damage to microglia and astrocytes.⁸ Aquaporin 4 and other mediators have been implicated in edema formation including inflammatory cytokines, an-

giogenesis factors (VEGF), hypoxia-related factors (HIF-1), cyclooxygenases, and markers of glial activation.^{5,9-11}

Current evidence suggests that radiosurgery-related brain edema is associated with tumor size, location of the lesion, the prescribed radiotherapy dose, and the presence of edema before treatment.^{12,13} Some data show that brain edema, even in homogenous clinical groups, is unrelated to the maximum dose or the surrounding conformity index.¹⁴ It should be noted that most existing research concerns edema related to meningioma radiosurgery.^{5,12,13}

We have observed edema after radiosurgery in patients with various clinical and histopathologic diagnoses in our practice, the significance of which remains uncertain. We therefore sought to identify factors that predispose to edema formation after SRS and assess edema formation and resolution dynamics.

Patients and methods

One hundred and three patients undergoing 111 SRS procedures were treated in the Oncology Centre in Bydgoszcz between January 2008 and October 2012. The study population had a heterogeneous set of histopathological diagnoses: 34 (29%) arteriovenous malformations (AVMs), 38 (35%) meningiomas, 16 (15%) metastatic tumors, 16 (15%) neuromas, 3 (3%) cavernous angiomas, 2 (2%) anaplastic astrocytomas, and 2 (2%) anaplastic oligoastrocytomas. The baseline patient characteristics are shown in Table 1.

Patients were treated with a 6 MV photon beam provided by a linear accelerator (Varian, USA) and a micromultileaf collimator with 3mm width leaves at the isocenter (Brainlab, Germany). The median prescribed doses at the lesion margin (isodose line) was 16 Gy for all lesions apart from for neuromas (12 Gy). Patient immobilization and target volume definition were achieved using a stereotactic frame or thermoplastic mask. After mask/frame fixation, three-dimensional computed tomography (3D-CT) was performed and then fused with non-stereotactic gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) sequences.

All patients with radiological signs of brain edema during follow-up examinations were included. Edema volume was delineated on T2-weighted axial MRI/FLAIR scans with a 1 mm slice thickness using the Oncentra Brachy (Nucletron) treatment planning workstation. Edema analysis was performed on MRI scans prior to treatment and 3, 6, 9, 12, 18, 24, 30, and 36 months after treatment. An example is shown in Figure 1.

To analyze lesion location, lesions were separated into occurrence above ($n = 80$) and below ($n = 32$) a plane separating the top and bottom of the skull extending from frontal to parietal (protuberantia frontalis to protuberantia occipitalis) and situated 3 cm above the Frankfurt line¹⁴ (referred to here as the Frankfurt modified line (FML)) (Figure 2). All infratentorial tumors (number), lesions localized in the central brain structures (*e.g.*, hippocampus, caudate nucleus), lesions localized to the temporal and inferior parts of the frontal lobes, and meningiomas of the tentorium and sella turcica were regarded as “below” FML lesions and all others as “above” FML lesions. The study was performed in accordance with the principles of the Helsinki Declaration and was approved by the Ethics Committee of Collegium Medicum of Nicolaus Copernicus University.

TABLE 1. Baseline patient characteristics

Characteristic		Number of patients
Total number of lesions		111
Sex	Male	40
	Female	63
Age (mean)		51
Histopathological diagnosis	Arteriovenous malformation	34
	Meningioma	38
	Metastasis	16
	Neuroma	16
	Cavernous angioma	3
	Anaplastic astrocytoma	2
	Anaplastic Oligoastrocytoma	2
Lesion location	Ponto-cerebellar angle	24
	Cerebellum	7
	Parietal lobe	16
	Frontal lobe	17
	Subcortical nucleus/hippocampus	12
	Convexity	2
	Petroclival	1
	Temporal lobe	8
	Falx	13
	Tentorium	3
	Occipital lobe	4
More than one SRS treatment		8
Mean V_{12}		6.3 cm ³

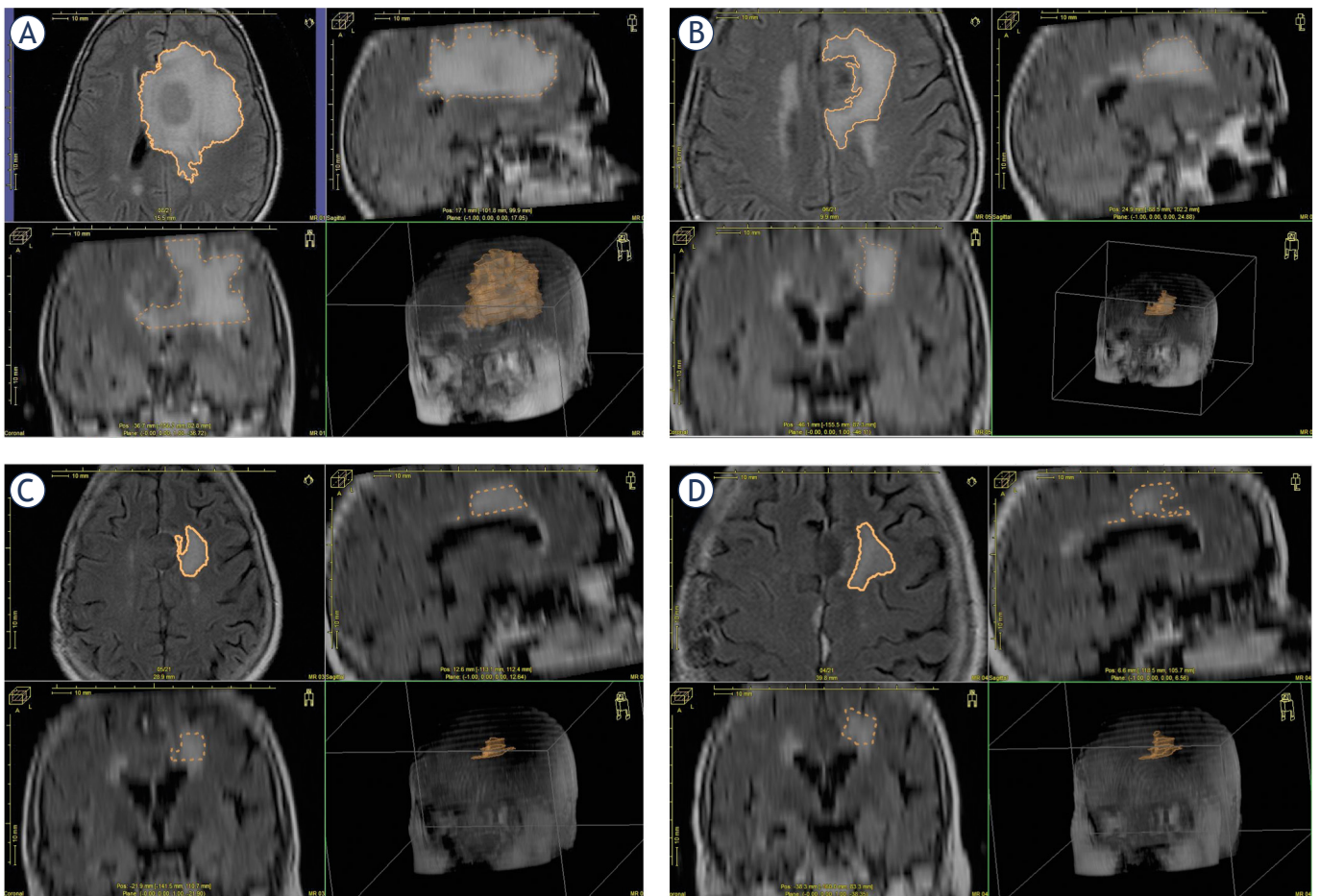


FIGURE 1. MRI scans performed after treatment showing delineation of area with decreasing edema. (A) 6 months; (B) 12 months; (C) 18 months; (D) 24 months.

All statistical analyses were performed using Statistica v.10 (Dell Inc., Austin, TX).

Results

Five patients did not attend for follow-up studies and were excluded from further analysis. SRS-associated edema occurred in 17 patients, of whom one patient was diagnosed with a meningioma located in the pontocerebellar angle with edema prior to SRS and that increased in volume in the six months after treatment. The initial MRI did not reveal edema in the other patients. SRS-related edema occurred in 2/16 (12.5%) metastatic tumors, 5/34 (14.7%) AVMs and 10/38 (26.3%) meningiomas.

The dynamics of edema formation over time (log-normal distribution) are shown in Figure 3. There were no associations between edema development and age, size of irradiated area, volume of

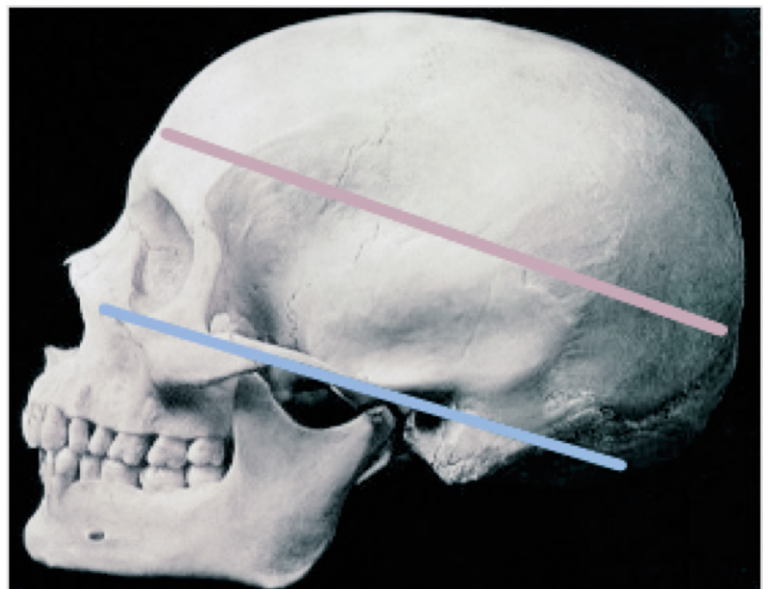


FIGURE 2. The Frankfurt Line (blue line) and the Frankfurt modified line (FML; red line).

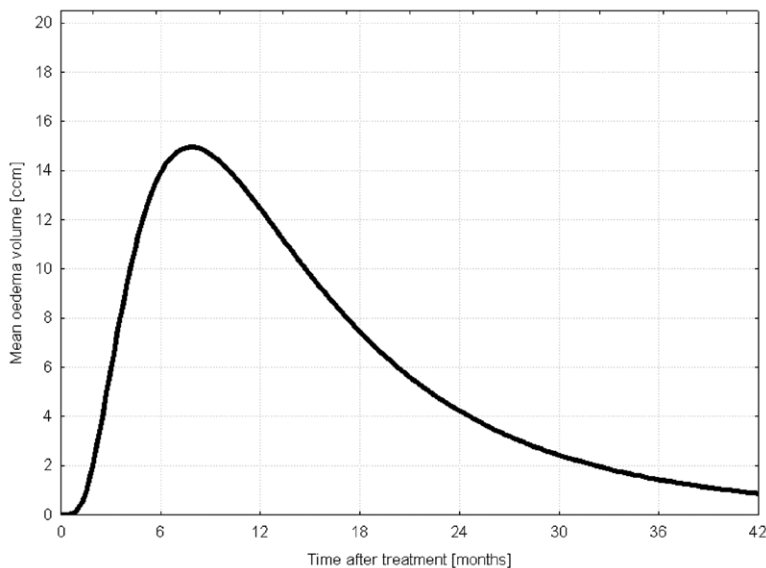


FIGURE 3. The largest volume of edema was observed at 6 months (mean 7.2 months, S.D. 1.2 months) after radiosurgery and decreased thereafter.

normal brain covered by 12 Gy isodose (V_{12}), number of beams, type of tumor ($p = 0.07$), or the type of immobilization applied.

With respect to lesion location, edema occurred in 2/32 lesions below the FML and in 15/80 lesions above the FML, representing a 5.1-times (1.06 – 24.53) increased incidence of edema after radiosurgery for lesions above the FML.

There was no association between edema development after secondary radiosurgery in the same patients if no edema formed after the initial treatment.

Discussion

Radiosurgery-related peri-lesional edema is a well-known but rarely described complication of SRS. Here we present the relationship between edema occurrence and lesion location in a population of patients with heterogeneous diagnoses.

The incidence of edema in this cohort (17%) is consistent with the published literature, recognizing that most data relates to edema occurring after radiosurgery for meningiomas. Chang *et al.* observed edema in 26.3% of patients with meningiomas after radiosurgery, about 40% of whom presented with symptoms of increased intracranial pressure.¹⁵ Kobayashi *et al.* reported edema in 13.8% of patients with benign meningiomas after radiosurgery.¹⁶ With respect to radiosurgery-relat-

ed edema in patients with other histopathological diagnoses, Hallemeier *et al.* reported edema after radiosurgery in 44% of patients with astrocytoma, which was effectively treated with oral or intravenous steroid therapy¹⁷, while Williams *et al.* described a case of steroid-resistant edema treated with bevacizumab that developed 9 months after radiosurgery for a vascular malformation.¹⁸

Cai *et al.* found that the risk of edema increased with greater tumor-brain contact interface area, supporting the observed differing incidence of edema according to location: the decreased incidence of edema below the FML may be associated with the amount of brain surrounding the lesion, since the lesion-brain contact interface above the FML is greater than below the FML.¹⁹

We found no association between the presence of edema and lesion size, dose escalation, or histopathological diagnosis. Although this finding may be due to the small number of patients in each group, these parameters need to be taken into account when assessing edema risk after radiosurgery.²⁰

The lack of an association between the histopathological diagnosis and lesion size suggests a common pathway for post-SRS edema formation, most likely related to impaired blood flow surrounding the intracranial lesion and explaining why the incidence of edema is lower in locations with better blood supply. For instance, with respect to tumors occurring in the parasagittal region, a higher edema risk may be present due to an unfavorable location (above the FML) and a histopathological diagnosis of meningioma. In this area, numerous veins carry blood to the superior sagittal sinus and the lower and deep vein (Galena vein), and numerous vessels at the tumor border drain blood from the tumor to normal brain vessels. Radiosurgery may impair flow in these vessels, similar to the mechanism seen when vessels in an AVM are obliterated. This leads to regional impairment of venous drainage from the brain and, as a consequence, edema.

We observed an increase in edema volume over the first 6 – 9 months and a decrease thereafter. In one retrospective multi-center study, the average duration of edema after radiosurgery was estimated to be 15 months (range 5 – 18 months)²¹, with maximum accumulation after 6 – 8 months, consistent with the results presented here. Not all brain edema is symptomatic or requires treatment, but if edema is observed radiologically at follow-up 3 months after treatment even in the absence of symptoms, a short regimen of steroids may be ap-

propriate to avoid the natural dynamics of edema formation occurring.

Patients treated with multiple rounds of radiosurgery to more than one lesion are a valuable study group for assessing the prevalence of complications. Here, this patient subgroup did not develop edema at follow up after both the first and subsequent treatments. This may suggest that resistance to edema formation depends on host or individual factors, but this hypothesis would require further clinical validation.

The study has several limitations. The FML plane was arbitrarily selected by the investigators from personal observations and does not represent an anatomical border that may explain differences in edema formation. Due to the retrospective nature of the analysis, we were unable to examine steroid treatment and its influence on edema formation and resolution. Nevertheless, to our knowledge, this is one of the largest studies of SRS-related edema formation.

Conclusions

Peri-lesional cerebral edema is a temporary intracranial complication after radiosurgery. The most severe MRI changes can be observed in the first six to nine months after treatment. The occurrence of cerebral edema is dependent on the intracranial location. Localization of lesion above the FML is a strong predictor of the emergence of this treatment complication.

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