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CLINICAL ARTICLE - BRAIN TUMORS

Glioblastoma after AVM radiosurgery. Case report and review of the literature

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Abstract
Background Stereotactic radiosurgery (SRS) is considered to be a relatively safe procedure in cerebral arteriovenous malformation management. There are very few reported cases of SRS-associated/induced malignancies.
Methods We show the case of a 21-year-old female who presented with a 21-mm^3 ruptured AVM in the right mesial frontocallosal region. Embolization and/or radiosurgery was proposed. She preferred radiosurgery. The AVM was treated with CyberKnife® SRS. Results: She presented behavior changes 6 years after SRS. MRI showed a right subcortical frontal lesion with increased perfusion, more consistent with high-grade glioma. The lesion's center was within the irradiated region of the previous SRS, having received an estimated radiation dose of 4 Gy. Pathological examination noted a hypercellular tumor showing astrocytic tumor cells with moderate pleomorphism in a fibrillary background, endothelial proliferation, and tumor necrosis surrounded by perinecrotic pseudopalisades. Numerous mitotic figures were seen. The appearances were those of glioblastoma, WHO grade IV, with neuronal differentiation. SRS-associated/-induced GBM after treatment of a large AM is exceptional. SRS-associated/-induced malignancies are mostly GBMs and occur on average after a latency of 9.4 years, within very low-dose peripheral regions as well as the full-dose regions; 33.3 % of patients were under 20 years at the time of SRS, and in 66 % the lesion treated was a vascular pathology.
Conclusion Although it is unlikely that the risk of radiation-induced cancer will change the current standard of practice, patients must be warned of this potential possibility before treatment.

Keywords CyberKnife · Radiosurgery · Radioinduced · Glioblastoma · Brain tumor · AVM

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Introduction

Arteriovenous malformations (AVMs) represent a relatively rare but complicated vascular pathology for which the treatment will always involve a multidisciplinary approach [12]. The management of larger volume (>10 cm³) symptomatic AVMs still remains a perplexing clinical challenge. In addition to observation, management options include resection, embolization, and radiosurgery (SRS), alone or in combination [11].

SRS is considered to be a relatively safe procedure in cerebral arteriovenous malformation management. There are very few reported cases of SRS-associated/induced malignancies. Most of the reported cases of radiation-associated tumors were related to conventional radiotherapy. However, malignant tumors after SRS of benign lesions have rarely been discussed.

In the present report, we relate a fatal case of glioblastoma multiforme (GBM) that appeared 6 years after radiosurgery for an AVM.

Case report

A 21-year-old female presented with a 2.7×4.0×3.0-cm (21-mm³) ruptured AVM in the right mesial fronto-callosal region. Embolization and/or radiosurgery was proposed. She preferred radiosurgery. The AVM was treated with CyberKnife® SRS with a prescription dose of 10 Gy to the 78 % isodose (Fig. 1). The minimal dose was 9.1 Gy, maximal dose 12.8 Gy, conformity index 1.52, and homogeneity index 1.28; coverage at the prescription dose was 96.29 %.

Magnetic resonance imaging (MRI) scans 2 years later showed persistent flow in the AVM and no other pathology (Fig. 2). She was lost to follow-up until she presented, 6 years after SRS, with behavior changes, apathy, disequilibrium, recent urinary incontinence, and memory disturbances. MRI showed the known unchanged AVM and a right subcortical frontal lesion behind and above it, which enhanced heterogeneously after contrast administration, as well as bifrontal edema and callosal infiltration. The perfusion MRI showed increased perfusion, more consistent with high-grade glioma (Fig. 3). The lesion's center was within the irradiated region

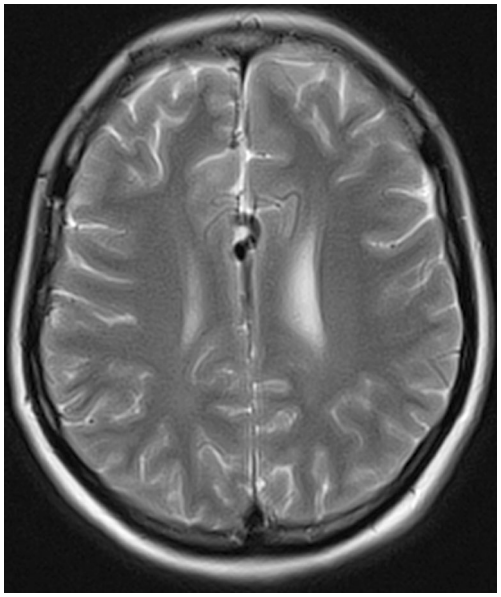

Fig. 2 T2-weighted axial magnetic resonance imaging scan at 2 years after SRS

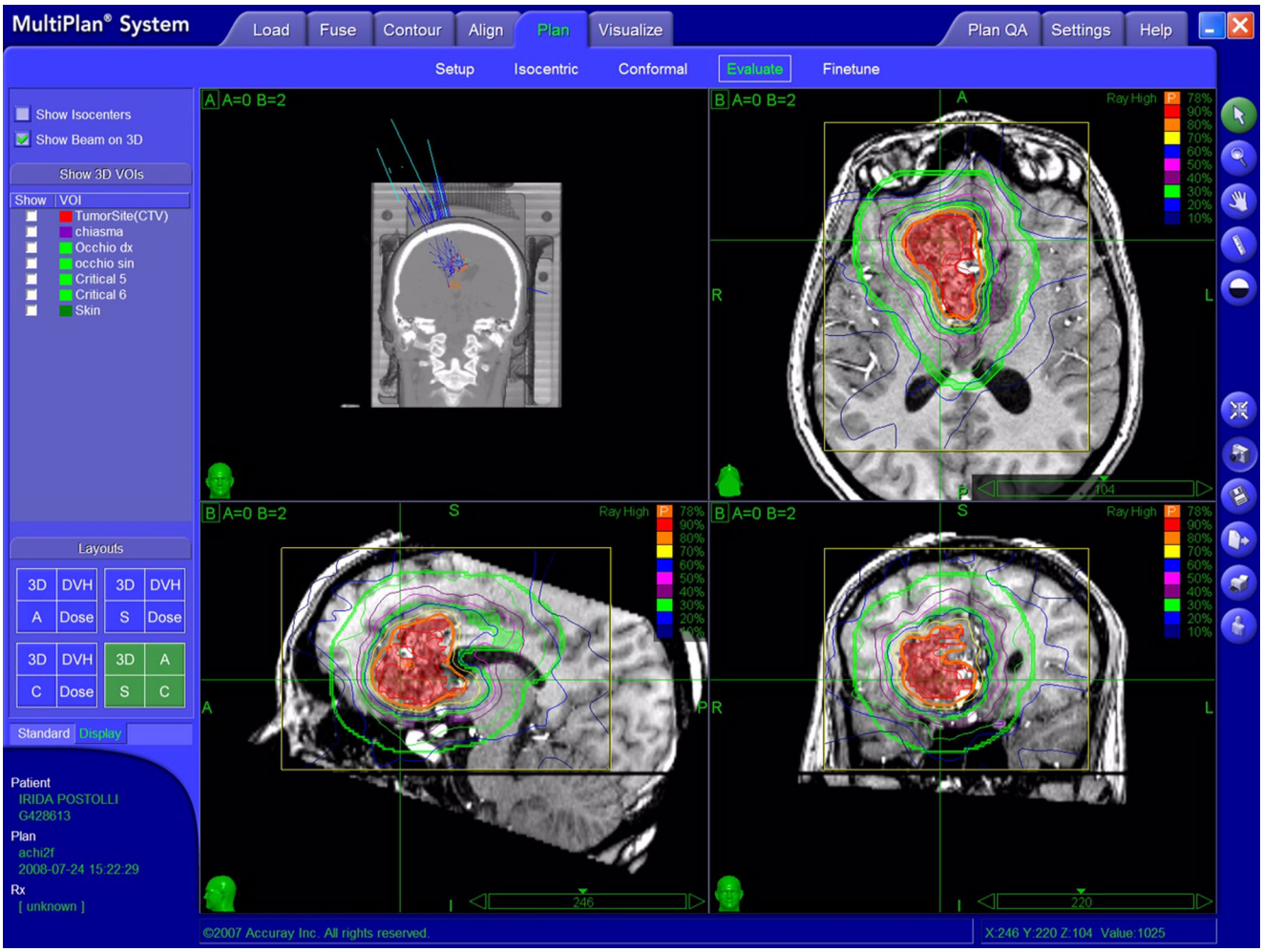

Fig. 1 Screenshot of CyberKnife® treatment planning

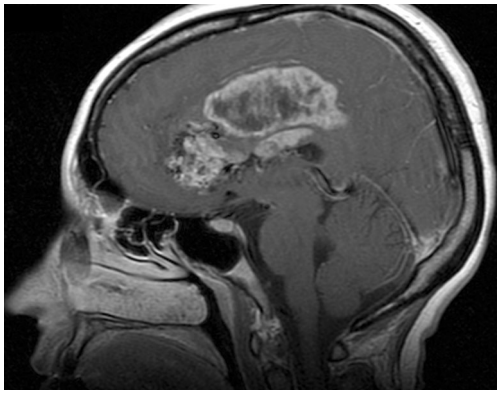

Fig. 3 T1-weighted post-gadolinium sagittal magnetic resonance imaging scan demonstrating a mass with peripheral enhancement and central necrosis involving the right mesial frontal lobe with extension into the corpus callosum

of the previous SRS, having received an estimated radiation dose of 4 Gy.

Maximal debulking was performed. Pathological examination noted a hypercellular tumor showing astrocytic tumor cells with moderate pleomorphism in a fibrillary background. There was an increased number of vessels, some of them with endothelial proliferation. Areas of tumor necrosis surrounded by perinecrotic pseudopalisades were also present. Numerous mitotic figures were seen. Using the Ventana BenchMark XT system for the immunostains, the cells were GFAP focally positive, P53 positive in 40–50 % of cells, IDH1 negative, SYN positive, EGFR negative, and Ki67 positive in 95–100 % of cells. The appearances were those of GBM, WHO grade IV, with neuronal differentiation (Fig. 4).

The patient was treated adjuvantly with concurrent temozolomide and radiotherapy.

Discussion

The appearance of GBM subsequent to radiosurgery of a large AVM is an extremely rare event. In a recent review the risk of developing an SRS-induced neoplasm is approximately 0.04 % at 15 years [18].

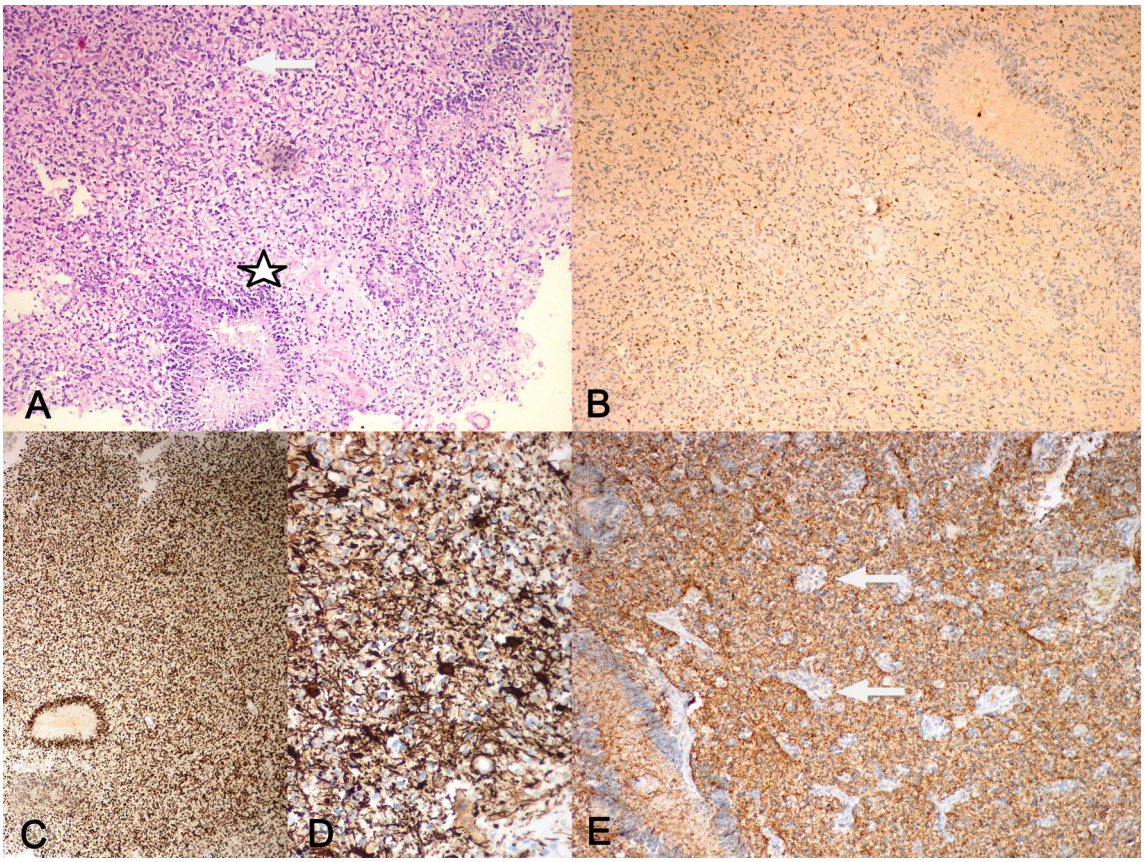

Fig. 4 Photomicrographs of tumor sections showing histopathological and immunohistochemical findings. **a** Paraffin sections (6 μm) stained with H&E demonstrating astrocytic tumor cells with moderate pleomorphism in a fibrillary background. Focal endothelial proliferation (*arrow*) and necrosis with pseudopalisading cells (*star*) were also seen. Numerous mitotic figures were seen. **b** Staining of the tumor with P53 demonstrating a labeling index of 40 to 50 %. **c** Staining of the tumor with KI-67 demonstrating a labeling index of 95–100 %, highlighting the pseudopalisading necrosis. **d** Staining of the tumor with GFAP demonstrating focal expression, especially in the upper left side. **e** Staining of the tumor with synaptophysine consistent with neuronal differentiation, highlighting the glomeruloid pattern of vascular proliferation (*arrow*). Original magnification×200

We might argue that the apparent association of radiosurgery with GBM formation may simply reflect the statistical intersection of the frequent use of this therapeutic modality with the not so uncommon development of a GBM, as Hoa et al. [9] also reported the association of a cerebellar GBM 2 years after microsurgery for vestibular schwannoma in the same side, without radiotherapy.

Radiation oncogenesis has been a topic of active investigation for almost a century [17]. Cahan et al. [6] defined the following criteria by which a tumor could be considered radiation-induced:

- There is a latency between the delivery of the radiation and the development of the tumor.
- The tumor arises in the irradiated region.
- The tumor is histologically distinct from the original irradiated tumor.
- Imaging indicates that the tumor in question was not present before radiation delivery.
- The patient has no genetic predisposition to cancer.

Even though our case clearly meets the conditions necessary to be considered "radiation induced," a stochastic coincidence cannot be excluded, and one must be careful not to confuse an association with causality.

Reported lesions associated with SRS can be divided into (1) de novo benign tumors (cavernous hemangioma [26], meningioma [14]) or (2) malignant tumors, which might be (a) a malignant progression of primary tumor [20, 31] or (b) a de novo malignant tumor (GBM [3, 10, 13, 24, 27, 33, 34], astrocytoma [23], anaplastic astrocytoma [16, 29], high-grade sarcoma [32], or osteosarcoma [25]).

Searching the literature for reported cases of SRS (excluding FSRT) associated malignant tumors, discounting malignant progression of the primary tumor as well as NF 2 patients, fulfilling all Cahan criteria, yielded 13 cases. The cases reported by Sanno et al. [24] and Yang et al. [30] might represent malignant transformation of the primary irradiated tumor. The cases reported by McIver et al. [16] and Abedalthagafi et al. [1] involve whole-brain radiotherapy and SRS, thus making it impossible to define the association with SRS certainly, because experiments on primates given therapeutic doses of fractionated whole-brain radiation have resulted in high rates of induction of glioblastoma multiforme [15]. The case described by Rowe et al. [23] should not be considered SRS-associated since they concluded that in the patient cohort of 5,000 patients with 30,000 patient-years of follow-up after SRS, no increased risk of malignancies was detectable. Only 1 astrocytoma was detected when in fact 2.47 cases should have been detected.

This means that, including our case, there are nine reported cases of "pure" SRS-associated malignancy (Table 1), which is remarkably few associated malignancies reported considering that radiosurgery is widely used via Gamma Knife and linear accelerator-based delivery worldwide.

Only two patients were male, and 3/9 (33.3 %) were younger than 20 years of age at the time. Since SRS is performed mostly in the adult population (mean age 45 ± 17 years in the report of Rowe et al. [23]) with an approximately equal sex distribution [23], these findings might suggest that in young female patients SRS could more easily induce a malignancy and raise the question whether patients under 20 years should really undergo SRS.

The length of time between radiation exposure and tumor formation is the major Cahan and Woodard [6] criterion, which has been modified by most investigators. It was recently suggested by the sarcoma team at Memorial Sloan Kettering Cancer Center that a latency of 6 months is sufficient to affirm the diagnosis of radiation-induced sarcoma [8], which contrasts with the generally accepted time frame of several years. In the reviewed literature, the average latency is 9.4 years, range 4.8–25 years (Table 1).

Table 1 Clinical characteristics of the reported SRS-associated malignancies

Reference	Age (years)/sex	Primary	Modality	Dose (Gy)	Second malignancy	Latency (years)	Midpoint solid tumor dose [a]
Yu [32], 2000	69/F	Meningioma	GK	20	GBM	7	High
Shamisa [26] 2001	49/F	Vestibular schwannoma	GK	11	GBM	7.5	Low
Kaido [10], 2001	14/M	AVM	GK	20	GBM	6.25	High
Salvati [23], 2003	66/F	Cavernoma	GK	10	GBM	13	NS
Berman [3], 2007	34/F	AVM	LINAC	15 (2)	GBM	9	Low
Lee [13], 2012	48/F	Meningioma	GK ×3	16, 13, 15	GBM	4.8	Low
Yoshida [31], 2014	5/F	AVM	GK	16	GBM	5.8	Low
Starke, [29] 2014	21/M	AVM	PB, GK	8.5, 12	AA	25, 19	High
Present case	19/F	AVM	CK	10	GBM	6	Low

[a] Estimated dose: >4 Gy, high dose; <4 Gy, low dose

GK Gamma Knife, *NS* not specified, *PB* proton beam radiosurgery, *CK* CyberKnife

The general form of the dose-response curve for radiation-associated tumors is not clear, but several experiments on small animals suggest that the incidence increases with dose up to a maximum usually occurring between 3 and 10 Gy, followed by a subsequent monotonic decrease [4]. There are also studies reporting that the highest incidence of radiation-associated tumors occurs at field peripheries, where the dose is less than at the field center [7]. In the reviewed literature, in one cases the dose in the region where the malignancy arose was not available, in three other cases it was a high dose, and in five (including this case) the dose was low (<4 Gy). These numbers do not permit drawing a conclusion, but raise the question of the appropriateness of the Cahan criteria when radiosurgery is considered. The high treating dose and steep fall in dose very near the target are dosimetric conditions very much different from the radiotherapy setting where those criteria have their place. Do we need to define new criteria for radiation-induced radiosurgery-related malignancies?

In the literature all but one of the reported associated malignancies are GBMs, and in six cases the lesion treated was AVM or cavernous malformation. It is interesting to note that both pathologies might result from a common pathway since in both cerebral AVMs and glioblastomas angiogenesis factors such as bFGF, VEGF in AVMs [22] and VEGF, TGF-β in gliomas [19] have been found, whereas they are absent in most normal adult vascular beds, including the cerebral vasculature. These finding are supported by the coexistence of a cerebral AVM and a brain tumor, mostly a glioma, which has been reported in several cases [21].

The precise mechanisms by which radiation may induce malignancy are unclear. There has been substantive speculation about radiation-induced genomic instability [2, 28, 30], although no studies have definitively shown this instability in human cancers.

There have been no radiographic or histopathological features identified to differentiate between spontaneous and radiation-induced gliomas, which is confirmed in our case, as well as in the reported cases (Table 2). It has been postulated that radiation may result in genetic alterations that differ from those seen in spontaneous tumors. Genetic alterations that have been described include a three-base pair homozygous deletion in exon 7 of the p53 gene, activating K-ras mutations [5], epidermal growth factor receptor amplification, p16 deletions, pentaerythritol tetranitrate mutations, and p53 mutations. It is possible that the radiation-induced damage in our patient mimicked the spontaneous accumulation of genetic defects observed in the transformation of a low-grade glioma but at an accelerated rate.

Considering that the carcinogenetic potential is not necessarily dose-dependent and sublethal damage and repair errors are required for the development of secondary tumors, single-session radiosurgery may be relatively safer than fractionated radiotherapy with repeated chances for sublethal damage.

Table 2 Histopathological features reported

Reference	Histological description
Yu [32], 2000	NS
Shamisa [26] 2001	Large numbers of oval spindle-shaped pleomorphic glial fibrillary acidic protein-positive cells interspersed with neoplastic gemistocytes and multinucleated giant cells. Abundant mitotic nuclei were present, with a high Ki-67 labeling index of 10 to 15 %. Large areas of nearby necrosis with pseudopalisading tumor cells and increased staining with deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling were present. Typical of GBMs, there was increased tumor vascularity (marked by factor VIII-positive endothelial cells), with increased expression of vascular endothelial growth factor by the neoplastic astrocytes
Kaido [10], 2001	High cellularity and focal necrosis thickening of the wall of the vessels that had constituted the AVM positive to anti-GFAP within the cytoplasm of the cells
Salvati [23], 2003	NS
Berman [3], 2007	Infiltrating glial neoplasm comprised of highly atypical cells with pleomorphic angular nuclei and modest eosinophilic cytoplasm consistent with astrocytic lineage. Numerous mitoses were present, as were conspicuous areas of vascular proliferation and necrosis consistent with a glioblastoma multiforme. Immunohistochemistry revealed strong staining for vimentin and glial fibrillary acidic protein confirming glial lineage. Additional immunohistochemistry for Ki-67 revealed a high proliferative index. There was no staining for epidermal growth factor receptor. Greater than 75 % of nuclei stained positively with p53
Lee [13], 2012	Infiltrating glial neoplasm comprised of highly atypical cells with pleomorphic angular nuclei and modest eosinophilic cytoplasm consistent with astrocytic lineage. Numerous mitoses and tumoral necrosis are present
Yoshida [31], 2014	Microscopic examination revealed dense growth of spindle-shaped, glial fibrillary acidic protein-positive neoplastic cells and microvascular proliferation. Pseudopalisading necrosis was seen in the tumor. The MIB-1 index, which was very high, was up to 50 %
Starke [29], 2014	Tumor cells were pleomorphic with irregular hyperchromatic nuclei and high nucleus-to-cytoplasm ratios. Rare mitotic figures were present. Necrosis and microvascular proliferation were not identified. The Ki-67 proliferation index was markedly elevated. Immunohistochemical studies showed tumor cells were strongly positive for glial fibrillary acidic protein, vimentin, S100, and epidermal growth factor receptor and were negative for epithelial membrane antigen, cytokeratin, and CD99
Present case	Hypercellular tumor showing tumor cells with moderate pleomorphism. There were areas of tumor necrosis surrounded by perinecrotic pseudopalisades. Numerous mitotic figures were seen. Focal microvascular proliferation is noted. Cells were GFAP focally positive, P53 positive in 40–50 % of cells, IDH1 negative, SYN positive, EGFR negative, Ki67 positive in 95–100 % of cells

However, it seems that radiation-induced malignancy can occur within very low-dose peripheral regions as well as the full-dose regions. Because the number of patients who underwent radiosurgery and long-term follow-up is much smaller than that treated with fractionated radiotherapy, the relative safety of radiosurgery needs to be proven by further accumulation of clinical data.

Conclusion

SRS-associated/induced GBM after treatment of a large AVM is exceptional. SRS-associated/induced malignancies are GBMs and occur on average after a latency of 9.4 years, within very low-dose peripheral regions as well as the full-dose regions; 33.3 % of patients were under 20 years at the time of SRS, and in 66 % the primary treated was a vascular pathology.

Although it is unlikely that the risk of radiation-induced cancer will change the current standard of practice, patients must be warned of this potential possibility before treatment.

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Patient consent The next of kin has consented to the submission of the case report for submission to the journal.

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