Glioblastoma multiforme as a secondary malignancy following stereotactic radiosurgery of a meningioma: case report

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The documentation and exact incidence of stereotactic radiosurgery (SRS)-induced neoplasia is not well understood, with most literature restricted to single case reports and single-center retrospective reviews. The authors present a rare case of radiosurgery-induced glioblastoma multiforme (GBM) following radiosurgical treatment of a meningioma. A 74-year-old patient with a sporadic meningioma underwent radiosurgery following surgical removal of a WHO grade II meningioma. Eighteen months later she presented with seizures, and MRI revealed an intraaxial tumor, which was resected and proven to be a glioblastoma. As far as the authors are aware, this case represents the third case of GBM following SRS for a meningioma. This report serves to increase the awareness of this possible complication following SRS. The possibility of this rare complication should be explained to patients when obtaining their consent for radiosurgery.

<https://thejns.org/doi/abs/10.3171/2019.3.FOCUS1948>

KEYWORDS malignant transformation; glioblastoma; meningioma; radiosurgery

THE indications for and use of radiotherapy in the management of benign and malignant intracranial neoplastic and nonneoplastic pathologies is increasing. The minimal upfront risks of focused radiotherapy are highly attractive—however, the potential long-term carcinogenic risk of secondary de novo malignant tumor induction or malignant conversion of a benign primary tumor needs to be considered. The concept of radiation oncogenesis is well established, and radiation-induced neoplasms after conventional fractionated radiotherapy are well documented.⁶⁷ The documentation of radiation-induced neoplasms following stereotactic radiosurgery (SRS), however, is not as well established, with very few cases reported in the literature.^{21,67} We report a case of an SRS-induced glioblastoma multiforme (GBM) following treatment for a meningioma.

Case Report

A 74-year-old previously healthy woman with no significant prior history or familial history of cancer presented with progressive left-sided weakness. She was diagnosed

with a 4.8 × 3 × 4.5-cm parafalx meningioma (Fig. 1). Preoperative digital subtraction angiography revealed a patent sagittal sinus. Preoperative embolization was not feasible. A craniotomy was performed for removal of the lesion. All gross tumor other than that invading the sagittal sinus was removed. Histological investigation revealed an atypical meningioma (WHO grade II). SRS was offered for treatment of the remaining dural/intrasinus segment, and SRS-Gamma Knife (SRS-GK) was performed. The maximum and marginal doses were 14 Gy and 28 Gy, respectively. A follow-up MRI study performed 6 months after the SRS was clear of recurrence. At 18 months after the surgery and SRS the patient presented with a seizure. Repeated MRI revealed a right-sided parietal lesion with inhomogeneous contrast enhancement, measuring 5 × 5.2 × 3.9 cm. Figure 2 demonstrates the GK treatment plan overlaid on the MR image demonstrating the GBM. The lesion had arisen in the low-dose, peripheral region of the SRS field. A craniotomy was performed for resection of the lesion. Histology revealed a glioblastoma, with the tumor displaying high cellularity and focal necrosis. Immunohistochemical investigation yielded a positive response

ABBREVIATIONS GBM = glioblastoma multiforme; GK = Gamma Knife; MPNST = malignant peripheral nerve sheath tumor; NF2 = neurofibromatosis type 2; SRS = stereotactic radiosurgery; VS = vestibular schwannoma.

SUBMITTED January 24, 2019. **ACCEPTED** March 18, 2019.

INCLUDE WHEN CITING DOI: 10.3171/2019.3.FOCUS1948.

FIG. 1. Presurgical axial MR image showing the meningioma in our patient.

to anti-GFAP, and the Ki-67 showed a high proliferation rate ($> 20\%$). As far as we are aware this is the 11th case of GBM following SRS and the third case following SRS for a meningioma.

Methods

We performed a detailed search of the PubMed/MEDLINE database, using the following key words: malignant transformation, radiation induced, radiation associated, stereotactic radiosurgery, gamma knife, cyber knife, secondary neoplasm, secondary tumor, and combinations thereof. There were no limitations on language or time of publication. We also manually reviewed all relevant citations for additional cases.

Results

We identified 16 reported cases of de novo secondary malignant tumor formation in patients with no genetic predisposition to neoplasia (Table 1), to which we added our present case. In addition, we identified an additional 5 cases of de novo secondary benign lesions (Table 2), and 17 cases of malignant progression/transformation in patients with no genetic predisposition to neoplasia (Table 3). An additional 3 cases of secondary malignant neoplasms developing following SRS in patients with an existing malignant CNS neoplasm were identified (Table 4).

In addition to this we identified 4 cases of de novo secondary malignant tumors and 9 cases of malignant progression of the primary lesion in patients with a genetic susceptibility to carcinogenesis (Tables 5 and 6, respectively).

FIG. 2. Gamma Knife treatment plan superimposed on axial MR image demonstrating the GBM.

Discussion

The delayed risk of both benign and malignant neoplasm in tissue exposed to conventional radiation therapy is well known and has a cumulative risk of 1.3% at 10 years, and approximately 2% by 20 years posttreatment.^{9,10} The risk of SRS-induced neoplasia is unfortunately far less understood. In a literature review Patel and Chiang⁴³ estimated the risk of combined de novo tumor induction and malignant transformation to be 0.04% at 15 years, in contrast to the largest retrospective study to date, in which Wolf et al.⁶⁵ reviewed the results from 5 SRS-GK centers and included 4905 patients. The cumulative incidence of SRS-associated malignancy in Wolf et al. was only 0.00045%.

The criteria for radiation-induced neoplasia were established by Cahan et al.¹¹ in 1948, and are as follows: 1) the secondary tumor must appear within the irradiated field; 2) the secondary tumor must not be present before irradiation; 3) a sufficient latency period (usually 5 years) must elapse between the irradiation and the appearance of the tumor; 4) the patient must not have a genetic predisposition to a second malignancy; and 5) the histological findings must be distinct from those of the original irradiated lesion.

Adhering strictly to the original Cahan criteria eliminates a significant percentage of the reported cases of SRS-induced neoplasia. This arises for several reasons when treating with SRS: many cases do not have pre-SRS histological studies given that most patients are treated without a definite histological diagnosis; many of these patients do have a genetic predisposition toward neoplasia, in particular patients with neurofibromatosis type 2 (NF2); and a latency of 5 years may not be appropriate following SRS-in-

TABLE 1. De novo secondary malignant tumors in patients with no genetic predisposition

Authors & Year	Age (yrs), Sex	Primary Lesion	Modality	Dose	Latency	Second Malignancy
Yu et al., 2000	63, F	Meningioma	SRS-GK	20 Gy	7 yrs	GBM
Kaido et al., 2001	14, M	AVM	SRS-GK	20 Gy	6.25 yrs	GBM
Shamisa et al., 2001	57, M	VS	SRS-GK	11 Gy	7.5 yrs	GBM
Salvati et al., 2003	66, F	Cavernous angioma	SRS-GK	10 Gy	13 yrs	GBM
Muracciole et al., 2004	64, F	VS	SRS-GK	13 Gy	8.4 yrs	GBM
Sanno et al., 2004	53, F	Meningioma	SRS-GK	30 Gy	4 yrs	Sarcoma
Balasubramaniam et al., 2007	60, F	VS	SRT	Total dose 50 Gy	5 yrs	GBM
Berman et al., 2007	34, F	AVM	SRS	15 Gy	9 yrs	GBM
Rowe et al., 2007 ⁴⁹	NR, F	Cavernous angioma	SRS-GK	10 Gy	8 yrs	AA
Lee et al., 2012	47, F	Meningioma	SRS-GK	16 Gy	4.8 yrs	GBM
Sasagawa et al., 2013	24, F	PA	SRS-GK	16 Gy	15 yrs	Sarcoma
Starke et al., 2014	26, M	AVM	SRS-GK	12 Gy	25 yrs	AA
Yoshida et al., 2014	4, F	AVM	SRS-GK	16 Gy	5.8 yrs	GBM
Xhumari et al., 2015	21, F	AVM	SRS-GK	10 Gy	6 yrs	GBM
Kapurch et al., 2016	54, M	VS	SRS-GK	12.5 Gy	3 yrs	Gliosarcoma
Arán-Echabe et al., 2016	69, F	VS	SRS-GK	13 Gy	3.4 yrs	AA
Present study	74, F	Meningioma	SRS-GK	14 Gy	1.5 yrs	GBM

AA = anaplastic astrocytoma; AVM = arteriovenous malformation; CK = CyberKnife; PA = pituitary adenoma; SRT = stereotactic radiotherapy.

duced neoplasms.^{29,66} There has been a proposal to modify the criteria of Cahan et al.¹¹ to include cases with a shorter latency.^{13,39} For these reasons we have chosen to present all the cases described in the literature, with the caveat that they do not all meet the original Cahan criteria. We report the cases with a genetic predisposition separately from the remainder of the cases.

The risk of radiosurgery-induced tumor formation has generally been thought to be quite low for several reasons. 1) The irradiated volume is very small compared with traditional radiotherapy techniques. 2) The volumes and doses of radiation along the entry and exit pathways are small, and therefore the likelihood of secondary tumors would be diminished.²⁸ 3) The high single doses delivered during SRS would preferentially lead to cytotoxicity over mutagenicity.⁴³

This may be an oversimplification, however. In fact, basic science and clinical studies instead support a biphasic response to radiation carcinogenesis;¹⁹ i.e., when cells are irradiated, the probability of malignancy increases with dose—with no dose too small to be causative²⁹—up to a dose of 3–10 Gy, followed by a subsequent increase in cell cytotoxicity and a fall in tumorigenicity.⁴⁰ Importantly, the

severity of the secondary tumor is not related to the dose of radiation.³⁸

The foregoing may account for the formation of secondary tumors in the low-dose peripheral regions of SRS fields.^{29,66} The presently reported case appears to support this. It may also explain why vestibular schwannomas (VSs), which are traditionally treated with lower SRS doses, are associated with greater rates of secondary neoplasms than would be expected.⁴³

SRS-Induced Malignant Transformation in Nonpredisposed Patients

We identified 17 reported cases of malignant progression of primary benign tumors exposed to SRS. All of these cases were VSs that de-differentiated into either a malignant peripheral nerve sheath tumor (MPNST, 12 cases), a triton (2 cases), an undifferentiated high-grade pleomorphic sarcoma (1 case), or a sarcoma (2 cases). The mean time to progression was 5.4 years. Not included in this case series are the results from the Mayo Clinic,⁴⁶ which in a large retrospective study found 7 cases of malignant transformation in their patients with meningioma

TABLE 2. De novo secondary benign tumors in patients with no genetic predisposition

Authors & Year	Age (yrs), Sex	Primary Lesion	Modality	Dose	Latency	Second Malignancy
Loeffler et al., 2003	41, M	PA	Proton beam	87 Gy peak dose	16 yrs	Meningioma
	53, M	PA	Proton beam	104 Gy peak dose	19 yrs	VS
Sheehan et al., 2006	7, M	AVM	SRS-GK	15 Gy	15 yrs	Meningioma
	12, F	AVM	SRS-GK	25 Gy	10 yrs	Meningioma
Copeland & Link, 2013	60, M	DAVF	SRS-GK	16 Gy	13 yrs	Meningioma

DAVF = dural arteriovenous fistula.

TABLE 3. Malignant progression of primary benign tumor in patients with no genetic predisposition

Authors & Year	Age (yrs), Sex	Primary Lesion	Modality	Dose	Latency	Second Malignancy
Comey et al., 1998	50, M	VS	SRS-GK	14.4 Gy	5 yrs	Triton
Hanabusa et al., 2001	51, F	VS	SRS-GK	15 Gy	6 mos	MPNST
Shin et al., 2002	26, F	VS	SRS-GK	17 Gy	6 yrs	MPNST
Kubo et al., 2005	51, M	VS	SRS-GK	14 Gy	8 mos	MPNST
Wilkinson et al., 2004	53, M	VS	SRT	NR	4 yrs	MPNST
Muracciole et al., 2004	61, F	VS	SRS-GK	10 Gy	4 yrs	Triton
Maire et al., 2006	45, F	VS	SRT	1.8-Gy fractions, total dose 54 Gy	8 yrs	MPNST
Chen et al., 2008	51, F	VS	SRS-GK	NR	8 mos	MPNST
Van Rompaey et al., 2009	53, F	VS	SRS-GK	12 Gy	8 yrs	MPNST
Akamatsu et al., 2010	67, F	VS	SRS-GK	12 Gy	7.5 yrs	MPNST
Demetriades et al., 2010	27, M	VS	SRS-GK	15 Gy	10 yrs	MPNST
Yang et al., 2010	74, M	VS	SRS-GK	12.5 Gy	6 yrs	Sarcoma
Schmitt et al., 2011	51, M	VS	SRS-GK	12 Gy	7.25 yrs	UHGPS
Puataweepong et al., 2012	34, F	VS	SRT	30 Gy in 6 fractions	6 yrs	MPNST
Yanamadala et al., 2013	46, F	VS	SRS-GK	14 Gy	6 yrs	MPNST
Seferis et al., 2014	46, F	VS	SRS-GK	12 Gy	6 yrs	MPNST
Se et al., 2017	49, F	VS	SRS-GK	12.5 Gy	6 yrs	Osteosarcoma

NR = not reported; UHGPS = undifferentiated high-grade pleomorphic sarcoma.

treated with SRS. In this series, meningioma patients were at the greatest risk of malignant transformation after SRS (2.2%). The median time to malignant transformation in this group was 4.6 years.

SRS-Induced Progression and New Malignancies in Patients With Known Genetic Mutations

There appears to be a marked bias toward treating these patients, in particular patients with NF2 and Von Hippel–Lindau disease, with SRS.⁵⁰ This reflects the limitations of surgery and the more aggressive natural history of tumors in these patients.

The NF2 population poses a unique group. The initial mutation in NF2 results in an inherited loss of one *NF2* gene on chromosome 22, resulting in the loss of an important tumor suppressor gene. According to the “two-hit” hypothesis of oncogenesis,⁴⁵ radiation might induce a second “hit” and predispose these patients to secondary malignancies, both in the existing VS and the surrounding region. Our literature review identified 4 cases of de novo secondary malignant tumors and 9 cases of malignant progression of the primary lesion, all in patients with NF2 treated for VS (Tables 5 and 6). We identified 39 plus the present

case of secondary tumor in nonpredisposed individuals. If you consider that the NF2 population probably accounts for only approximately 5% of the VS SRS-treated population,⁴ it appears that the NF2 population is overrepresented. Whether this reflects a true increase in SRS-induced malignancies is an open question. In a large survey of SRS in patients with NF2 who were treated for VS, Baser et al.⁶ estimated the incidence of MPNST in nonirradiated NF2 VSs to be less than 0.5%, compared to a 6% incidence in NF2 VSs that had received SRS, suggesting a 12-fold increase. Likewise, Seferis et al.,⁵⁵ using population incidences and reported cases, concluded that the risk of developing an MPNST following SRS was 9 to 14 times greater than in a nonirradiated VS population. In contrast to this are 4 large studies^{26,34,48,59} that demonstrated no increased risk of SRS-induced neoplasia. However, none of these aforementioned studies are large enough to detect very infrequent events such as malignant transformation.

According to Cahan's¹¹ original criteria, these patients with NF2 should be excluded from the population of SRS-induced neoplasia, and certain authors do choose to do so.⁴⁰ However, progression to MPNST is extremely rare, but not zero, and thus these patients should potentially still

TABLE 4. De novo secondary tumor in patients with a primary malignant tumor

Authors & Year	Age (yrs), Sex	Primary Lesion	Modality	Dose	Latency	Second Malignancy
Mclver & Pollock, 2004	37, F	Metastatic melanoma	SRS-GK	15 Gy	5.3 yrs	AA
Abedalthagafi & Bakhshwin, 2012	43, F	Metastatic renal cell carcinoma	SRS-CK	NR	4.5 yrs	GBM
Nukaga et al., 2018	66, F	Metastatic non-small cell lung carcinoma	SRS-GK	NR	5.7 yrs	GBM

TABLE 5. De novo secondary malignant tumors in patients with a genetic predisposition

Authors & Year	Age (yrs), Sex	Primary Lesion	Modality	Dose	Latency	Second Malignancy
Baser et al., 2000	NR	VS	SRS-NR	NR	NR	Malignant meningioma
	NR	VS	SRS-NR	NR	NR	Malignant ependymoma
Rowe et al., 2007 ⁴⁸	NR, F	VS	SRS-GK	14 Gy	3 yrs	Glioblastoma
Carlson et al., 2010	25, F	VS	SRT	50 Gy	10 yrs	Rhabdomyosarcoma

TABLE 6. Malignant progression of primary benign tumor in patients with a genetic predisposition

Authors & Year	Age (yrs), Sex	Primary Lesion	Modality	Dose	Latency	Histological Findings
Norén, 1998	18, F	VS	SRS-GK	20 Gy	5 yrs	Triton
Thomsen et al., 2000	19, F	VS	SRS-GK	12 Gy	6 yrs	Meningiosarcoma
Baser et al., 2000	NR	VS	SRS-NR	NR	NR	MPNST
	NR	VS	SRS-NR	NR	NR	MPNST
	NR	VS	SRS-NR	NR	NR	MPNST
Ho & Kveton, 2002	14, F	VS	SRT	18 Gy	7 mos	NR (rapid growth)
Bari et al., 2002	28, F	VS	SRS-GK	15 Gy	3.5 yrs	MPNST
McEvoy & Kitchen, 2003	22, M	VS	SRS-GK	15 Gy	2 yrs	NR (rapid growth)
Tanbouzi Hussein et al., 2011	20, M	VS	SRS-GK	13.5 Gy	5 yrs	MPNST

be included under the banner of radiation-induced neoplasia.⁴ In Maducdoc et al.'s³² review of the literature they identified 18 cases of primary malignant VS and 4 cases of "microsurgery-induced" VS transformation. These authors speculate that inflammation due to microsurgery or the effects of electrocoagulation may induce malignant transformation.

In addition to their possible genetic predisposition to transformation, VSs occur earlier in this group and they thus receive SRS at an earlier age. These patients therefore have a longer time to develop secondary malignancies because they accumulate radiation carcinogenic risks over a longer period of time. Several studies, in particular those involving breast carcinoma and radiation, have clearly demonstrated that young age at exposure is a particular risk factor for radiation-induced secondary cancer formation.¹⁹ The highest degree of caution should therefore be exercised in this group of patients undergoing SRS.⁴

Another important population group to consider is the patients with NF2 presenting with single or multiple meningiomas. In recent years SRS has been shown to be a safe and effective, definitive adjuvant treatment, not only for benign⁴⁴ but also for WHO grade II and II meningiomas.¹⁸

The same concerns regarding an increased risk of malignant transformation and secondary de novo neoplasia for VS in patients with NF2 have been raised for SRS treatment of meningiomas in patients with NF2.²⁰ The research, however, does not support an increased risk in these patients. In our review of the case reports, none of the meningiomas that were complicated by secondary malignancies were found in patients with NF, and no case reports of secondary degeneration in this group were identified. Additionally, 3 studies specifically looking at SRS-induced neoplasia in this group found no increased risk of this com-

plication.^{8,30,48} Intuitively, NF2 cannot be protective against neoplasia; therefore the risk of malignant transformation in this group should be assumed to be at least that reported from the Mayo group in patients without NF2 (2.2% at a mean follow-up duration of 4.9 years).⁴⁶

The above evidence clearly indicates that there is a risk of malignant transformation following SRS, and the genetically predisposed group may be specifically at risk. This risk, although unknown, is thought to be very low. The number of reported cases of malignant transformation is already increasing and, as the numbers of cases treated with SRS increase and the latency period following SRS treatment lengthens, we can expect to see a further increase in these cases.^{31,55}

Conclusions

The real risks of SRS-induced neoplasia remain very low, and in general should not deter one from offering radiotherapy to suitable patients. The risks are intuitively higher in the genetically predisposed group, but given the wide variance in reported risks in the literature, the true risks remain largely unknown in these patients. In particular, the patients with NF2 who have VS should be well counseled as to the risks of secondary neoplasia, and they should undergo long-term tumor surveillance given their unique predisposition.

Acknowledgments

We thank Dr. S. Taylor for the help in the preparation of this manuscript.

References

1. Abedalthagafi M, Bakhshwin A: Radiation-induced glioma

- following CyberKnife® treatment of metastatic renal cell carcinoma: a case report. **J Med Case Reports** 6:271, 2012
2. Akamatsu Y, Murakami K, Watanabe M, Jokura H, Tomimaga T: Malignant peripheral nerve sheath tumor arising from benign vestibular schwannoma treated by gamma knife radiosurgery after two previous surgeries: a case report with surgical and pathological observations. **World Neurosurg** 73:751–754, 2010
 3. Arán-Echabe E, Cascallar Caneda L, Lobato Busto R, Reyes Santías RM, Varela Pazo A, Gelabert-González M: [High-grade glioma after stereotactic radiosurgery for vestibular schwannoma.] **Neurocirugía (Astur)** 27:33–37, 2016 (Spanish)
 4. Balasubramaniam A, Shannon P, Hodaie M, Laperriere N, Michaels H, Guha A: Glioblastoma multiforme after stereotactic radiotherapy for acoustic neuroma: case report and review of the literature. **Neuro Oncol** 9:447–453, 2007
 5. Bari ME, Forster DMC, Kemeny AA, Walton L, Hardy D, Anderson JR: Malignancy in a vestibular schwannoma. Report of a case with central neurofibromatosis, treated by both stereotactic radiosurgery and surgical excision, with a review of the literature. **Br J Neurosurg** 16:284–289, 2002
 6. Baser ME, Evans DG, Jackler RK, Sujansky E, Rubenstein A: Neurofibromatosis 2, radiosurgery and malignant nervous system tumours. **Br J Cancer** 82:998, 2000
 7. Berman EL, Eade TN, Brown D, Weaver M, Glass J, Zorman G, et al: Radiation-induced tumor after stereotactic radiosurgery for an arteriovenous malformation: case report. **Neurosurgery** 61:E1099, 2007
 8. Birkhead B, Sio TT, Pollock BE, Link MJ, Laack NN: Gamma Knife radiosurgery for neurofibromatosis type 2-associated meningiomas: a 22-year patient series. **J Neurooncol** 130:553–560, 2016
 9. Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellors PJ, Nussey S, et al: The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. **Clin Endocrinol (Oxf)** 38:571–578, 1993
 10. Breen P, Flickinger JC, Kondziolka D, Martinez AJ: Radiotherapy for nonfunctional pituitary adenoma: analysis of long-term tumor control. **J Neurosurg** 89:933–938, 1998
 11. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL: Sarcoma arising in irradiated bone; report of 11 cases. **Cancer** 1:3–29, 1948
 12. Carlson ML, Babovic-Vuksanovic D, Messiaen L, Scheithauer BW, Neff BA, Link MJ: Radiation-induced rhabdomyosarcoma of the brainstem in a patient with neurofibromatosis type 2. **J Neurosurg** 112:81–87, 2010 (Erratum in **J Neurosurg** 112:209, 2010)
 13. Carlson ML, Glasgow AE, Jacob JT, Habermann EB, Link MJ: The short-term and intermediate-term risk of second neoplasms after diagnosis and treatment of unilateral vestibular schwannoma: analysis of 9460 cases. **Int J Radiat Oncol Biol Phys** 95:1149–1157, 2016
 14. Chen L, Mao Y, Chen H, Zhou LF: Diagnosis and management of intracranial malignant peripheral nerve sheath tumors. **Neurosurgery** 62:825–832, 2008
 15. Comey CH, McLaughlin MR, Jho HD, Martinez AJ, Lunsford LD: Death from a malignant cerebellopontine angle triton tumor despite stereotactic radiosurgery. Case report. **J Neurosurg** 89:653–658, 1998
 16. Copeland WR, Link MJ: A radiation-induced meningioma “cures” a complex dural arteriovenous fistula. **J Neurol Surg A Cent Eur Neurosurg** 74 (Suppl 1):e215–e220, 2013
 17. Demetriades AK, Saunders N, Rose P, Fisher C, Rowe J, Tranter R, et al: Malignant transformation of acoustic neuroma/vestibular schwannoma 10 years after gamma knife stereotactic radiosurgery. **Skull Base** 20:381–387, 2010
 18. Ding D, Starke RM, Hantzmon J, Yen CP, Williams BJ, Sheehan JP: The role of radiosurgery in the management of WHO Grade II and III intracranial meningiomas. **Neurosurg Focus** 35(6):E16, 2013
 19. Epstein R, Hanham I, Dale R: Radiotherapy-induced second cancers: are we doing enough to protect young patients? **Eur J Cancer** 33:526–530, 1997
 20. Evans DGR, Birch JM, Ramsden RT, Sharif S, Baser ME: Malignant transformation and new primary tumours after therapeutic radiation for benign disease: substantial risks in certain tumour prone syndromes. **J Med Genet** 43:289–294, 2006
 21. Ganz JC: Gamma knife radiosurgery and its possible relationship to malignancy: a review. **J Neurosurg** 97 (5 Suppl):644–652, 2002
 22. Hanabusa K, Morikawa A, Murata T, Taki W: Acoustic neuroma with malignant transformation. Case report. **J Neurosurg** 95:518–521, 2001
 23. Ho SY, Kveton JF: Rapid growth of acoustic neuromas after stereotactic radiotherapy in type 2 neurofibromatosis. **Ear Nose Throat J** 81:831–833, 2002
 24. Kaido T, Hoshida T, Uranishi R, Akita N, Kotani A, Nishi N, et al: Radiosurgery-induced brain tumor. Case report. **J Neurosurg** 95:710–713, 2001
 25. Kapurch JR, Jacob JT, Carlson ML, Atkinson JL, Raghunathan A, Link MJ: Temporal lobe gliosarcoma after Gamma Knife radiosurgery for vestibular schwannoma. **Otol Neurotol** 37:1143–1147, 2016
 26. Kida Y, Kobayashi T, Tanaka T, Mori Y: Radiosurgery for bilateral neurinomas associated with neurofibromatosis type 2. **Surg Neurol** 53:383–390, 2000
 27. Kubo O, Chernov M, Izawa M, Hayashi M, Muragaki Y, Maruyama T, et al: Malignant progression of benign brain tumors after gamma knife radiosurgery: is it really caused by irradiation? **Minim Invasive Neurosurg** 48:334–339, 2005
 28. Larson DA, Flickinger JC, Loeffler JS: The radiobiology of radiosurgery. **Int J Radiat Oncol Biol Phys** 25:557–561, 1993
 29. Lee HS, Kim JH, Lee JI: Glioblastoma following radiosurgery for meningioma. **J Korean Neurosurg Soc** 51:98–101, 2012
 30. Liu A, Kuhn EN, Lucas JT Jr, Laxton AW, Tatter SB, Chan MD: Gamma Knife radiosurgery for meningiomas in patients with neurofibromatosis Type 2. **J Neurosurg** 122:536–542, 2015
 31. Loeffler JS, Niemierko A, Chapman PH: Second tumors after radiosurgery: tip of the iceberg or a bump in the road? **Neurosurgery** 52:1436–1442, 2003
 32. Maducdoc MM, Ghavami Y, Linskey ME, Djalilian HR: Evaluation of reported malignant transformation of vestibular schwannoma: de novo and after stereotactic radiosurgery or surgery. **Otol Neurotol** 36:1301–1308, 2015
 33. Maire JP, Huchet A, Milbeo Y, Darrouzet V, Causse N, Célérier D, et al: Twenty years’ experience in the treatment of acoustic neuromas with fractionated radiotherapy: a review of 45 cases. **Int J Radiat Oncol Biol Phys** 66:170–178, 2006
 34. Mathieu D, Kondziolka D, Flickinger JC, Niranjan A, Williamson R, Martin JJ, et al: Stereotactic radiosurgery for vestibular schwannomas in patients with neurofibromatosis type 2: an analysis of tumor control, complications, and hearing preservation rates. **Neurosurgery** 60:460–470, 2007
 35. McEvoy AW, Kitchen ND: Rapid enlargement of a vestibular schwannoma following gamma knife treatment. **Minim Invasive Neurosurg** 46:254–256, 2003
 36. McIver JI, Pollock BE: Radiation-induced tumor after stereotactic radiosurgery and whole brain radiotherapy: case report and literature review. **J Neurooncol** 66:301–305, 2004
 37. Muracciole X, Cowen D, Régis J: [Radiosurgery and brain radio-induced carcinogenesis: update.] **Neurochirurgie** 50:414–420, 2004 (French)
 38. Muracciole X, Régis J: Radiosurgery and carcinogenesis risk. **Prog Neurol Surg** 21:207–213, 2008

39. Murray EM, Werner D, Greeff EA, Taylor DA: Postradiation sarcomas: 20 cases and a literature review. *Int J Radiat Oncol Biol Phys* **45**:951–961, 1999
40. Niranjana A, Kondziolka D, Lunsford LD: Neoplastic transformation after radiosurgery or radiotherapy: risk and realities. *Otolaryngol Clin North Am* **42**:717–729, 2009
41. Norén G: Long-term complications following gamma knife radiosurgery of vestibular schwannomas. *Stereotact Funct Neurosurg* **70** (Suppl 1):65–73, 1998
42. Nukaga S, Naoki K, Yasuda H, Kawada I, Ohara K, Soejima K, et al: Secondary brain neoplasm after stereotactic radiosurgery in patients with metastatic non-small cell lung cancer. *Intern Med* **57**:2383–2387, 2018
43. Patel TR, Chiang VLS: Secondary neoplasms after stereotactic radiosurgery. *World Neurosurg* **81**:594–599, 2014
44. Pinzi V, Biagioli E, Roberto A, Galli F, Rizzi M, Chiappa F, et al: Radiosurgery for intracranial meningiomas: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* **113**:122–134, 2017
45. Plowman PN, Evans DGR: Stereotactic radiosurgery XI. Acoustic neuroma therapy and radiation oncogenesis. *Br J Neurosurg* **14**:93–95, 2000
46. Pollock BE, Link MJ, Stafford SL, Parney IF, Garces YI, Foote RL: The risk of radiation-induced tumors or malignant transformation after single-fraction intracranial radiosurgery: results based on a 25-year experience. *Int J Radiat Oncol Biol Phys* **97**:919–923, 2017
47. Puataweepong P, Janwityanujit T, Larbcharoensub N, Dhana-chai M: Radiation-induced peripheral malignant nerve sheath tumor arising from vestibular schwannoma after linac-based stereotactic radiation therapy: a case report and review of literatures. *Case Rep Med* **2012**:648191, 2012
48. Rowe J, Grainger A, Walton L, Radatz M, Kemeny A: Safety of radiosurgery applied to conditions with abnormal tumor suppressor genes. *Neurosurgery* **60**:860–864, 2007
49. Rowe J, Grainger A, Walton L, Silcocks P, Radatz M, Kemeny A: Risk of malignancy after gamma knife stereotactic radiosurgery. *Neurosurgery* **60**:60–66, 2007
50. Salvati M, Frati A, Russo N, Caroli E, Polli FM, Minniti G, et al: Radiation-induced gliomas: report of 10 cases and review of the literature. *Surg Neurol* **60**:60–67, 2003
51. Sanno N, Hayashi S, Shimura T, Maeda S, Teramoto A: Intracranial osteosarcoma after radiosurgery—case report. *Neurol Med Chir (Tokyo)* **44**:29–32, 2004
52. Sasagawa Y, Tachibana O, Iizuka H: Undifferentiated sarcoma of the cavernous sinus after gamma knife radiosurgery for pituitary adenoma. *J Clin Neurosci* **20**:1152–1154, 2013
53. Schmitt WR, Carlson ML, Giannini C, Driscoll CLW, Link MJ: Radiation-induced sarcoma in a large vestibular schwannoma following stereotactic radiosurgery: case report. *Neurosurgery* **68**:E840–E846, 2011
54. Se YB, Kim DG, Park SH, Chung HT: Radiation-induced osteosarcoma after Gamma Knife surgery for vestibular schwannoma: a case report and literature review. *Acta Neurochir (Wien)* **159**:385–391, 2017
55. Seferis C, Torrens M, Paraskevopoulou C, Psichidis G: Malignant transformation in vestibular schwannoma: report of a single case, literature search, and debate. *J Neurosurg* **121** (Suppl):160–166, 2014
56. Shamisa A, Bance M, Nag S, Tator C, Wong S, Norén G, et al: Glioblastoma multiforme occurring in a patient treated with gamma knife surgery. Case report and review of the literature. *J Neurosurg* **94**:816–821, 2001
57. Sheehan J, Yen CP, Steiner L: Gamma knife surgery-induced meningioma. Report of two cases and review of the literature. *J Neurosurg* **105**:325–329, 2006
58. Shin M, Ueki K, Kurita H, Kirino T: Malignant transformation of a vestibular schwannoma after gamma knife radiosurgery. *Lancet* **360**:309–310, 2002
59. Spatola G, Carron R, Delsanti C, Thomassin JM, Roche PH, Régis J: Long-term results of Gamma-knife stereotactic radiosurgery for vestibular schwannomas in patients with type 2 neurofibromatosis. *Neurochirurgie* **64**:355–363, 2018
60. Starke RM, Yen CP, Chen CJ, Ding D, Mohila CA, Jensen ME, et al: An updated assessment of the risk of radiation-induced neoplasia after radiosurgery of arteriovenous malformations. *World Neurosurg* **82**:395–401, 2014
61. Tanbouzi Hussein S, Piccirillo E, Taibah A, Paties CT, Rizzoli R, Sanna M: Malignancy in vestibular schwannoma after stereotactic radiotherapy: a case report and review of the literature. *Laryngoscope* **121**:923–928, 2011
62. Thomsen J, Mirz F, Wetke R, Astrup J, Bojsen-Møller M, Nielsen E: Intracranial sarcoma in a patient with neurofibromatosis type 2 treated with gamma knife radiosurgery for vestibular schwannoma. *Am J Otol* **21**:364–370, 2000
63. Van Rompaey K, Michotte A, Ampe B, Moens M, Ates R, Chaskis C, et al: Malignant transformation of a vestibular schwannoma after radiosurgery. *Surg Neurol* **71**:145, 2009 (Poster)
64. Wilkinson JS, Reid H, Armstrong GR: Malignant transformation of a recurrent vestibular schwannoma. *J Clin Pathol* **57**:109–110, 2004
65. Wolf A, Naylor K, Tam M, Habib A, Novotny J, Liscak R, et al: Risk of radiation-associated intracranial malignant after stereotactic radiosurgery: a retrospective, multicenter, cohort study. *Lancet* **20**:159–164, 2019
66. Xhumari A, Rroji A, Enesi E, Bushati T, Sallabanda Diaz K, Petrela M: Glioblastoma after AVM radiosurgery. Case report and review of the literature. *Acta Neurochir (Wien)* **157**:889–895, 2015
67. Yamanaka R, Hayano A, Kanayama T: Radiation-induced gliomas: a comprehensive review and meta-analysis. *Neurosurg Rev* **41**:719–731, 2018
68. Yanamadala V, Williamson RW, Fusco DJ, Eschbacher J, Weisskopf P, Porter RW: Malignant transformation of a vestibular schwannoma after gamma knife radiosurgery. *World Neurosurg* **79**:593.e1–593.e8, 2013
69. Yang T, Rockhill J, Born DE, Sekhar LN: A case of high-grade undifferentiated sarcoma after surgical resection and stereotactic radiosurgery of a vestibular schwannoma. *Skull Base* **20**:179–183, 2010
70. Yoshida K, Ichikawa T, Kurozumi K, Yanai H, Onoda K, Date I: Fatal glioblastoma after Gamma Knife radiosurgery for arteriovenous malformation in a child. *J Clin Neurosci* **21**:1453–1455, 2014
71. Yu JS, Yong WH, Wilson D, Black KL: Glioblastoma induction after radiosurgery for meningioma. *Lancet* **356**:1576–1577, 2000

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Labuschagne. Acquisition of data: Labuschagne. Analysis and interpretation of data: Chetty. Drafting the article: Labuschagne. Critically revising the article: Chetty. Reviewed submitted version of manuscript: Labuschagne.

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