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 fractioned radiotherapy are well documented.67 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 intraxial 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

**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 for the presence of a glioblastoma.
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).

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. The risk of SRS-induced neoplasia is unfortunately far less understood. In a literature review Patel and Chiang 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. 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. 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-
duced neoplasms. There has been a proposal to modify the criteria of Cahan et al. to include cases with a shorter latency. 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. 3) The high single doses delivered during SRS would preferentially lead to cytotoxicity over mutagenicity. This may be an oversimplification, however. In fact, basic science and clinical studies instead support a biphasic response to radiation carcinogenesis; i.e., when cells are irradiated, the probability of malignancy increases with dose—with no dose too small to be causative—up to a dose of 3–10 Gy, followed by a subsequent increase in cell cytotoxicity and a fall in tumorigenicity. Importantly, the severity of the secondary tumor is not related to the dose of radiation.

The foregoing may account for the formation of secondary tumors in the low-dose peripheral regions of SRS fields. 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.

### 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), 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, which in a large retrospective study found 7 cases of malignant transformation in their patients with meningioma.

### 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              |
| Shamia 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 | 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-CK   | 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.

### 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.
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. 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, 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, 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. 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. 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 large studies 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’s original criteria, these patients with NF2 should be excluded from the population of SRS-induced neoplasia, and certain authors do choose to do so. However, progression to MPNST is extremely rare, but not zero, and thus these patients should potentially still

### 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.

### 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 |
|-------------------------|---------------|---------------------------|----------------|-------|---------|-------------------|
| McIver & 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               |
be included under the banner of radiation-induced neoplasia. In Maducdoc et al.'s 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. The highest degree of caution should therefore be exercised in this group of patients undergoing SRS.

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 benign but also for WHO grade II and II meningiomas.

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. 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 complication. 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).

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.

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.

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

| 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 |
| 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 |
| Tanbouzi Husseini et al., 2011 | 20, M | VS | SRS-GK | 13.5 Gy | 5 yrs | MPNST |
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**Disclosures**

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**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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