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Evaluation of Reported Malignant Transformation of Vestibular Schwannoma: De Novo and After Stereotactic Radiosurgery or Surgery

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Objective: To critically analyze each reported case of malignant transformation of vestibular schwannoma (VS) after either stereotactic radiosurgery (SRS) or microsurgery (MS).
Data Sources: We searched the Pubmed/Medline database using the relevant key words *vestibular schwannoma*, *acoustic neuroma*, *malignant*, *transformation*, *radiation*, *induced*, *stereotactic*, *radiosurgery*, *malignancy*, *GammaKnife*, and *CyberKnife* and combinations thereof.
Study Selection: Inclusion criteria for malignant transformation of VS after SRS included histopathology of initially benign VS, subsequent histopathology confirming malignant VS, reasonable latency period between malignancy and benign diagnoses.
Data Extraction: A neurotologist and a skull base neurosurgeon independently assessed each case report for quality, entry, exclusion criteria, and comparability of extracted data.
Data Synthesis: We calculated median age, latency times, and survival times for each case report.
Results: Malignant transformation has been documented to occur after either SRS or MS. Eight cases were included that showed histopathologic evidence of malignant transformation after SRS and MS. Four cases of malignant transformation were included that demonstrated malignant transformation after MS only. Malignant transformation of VS can also occur de novo, and de novo malignant VSs are also encountered, which can confound a causal inference from either SRS or MS. Eighteen cases of primary malignant VS were included. Studies that were identified but not included in the review are summarized and tabulated. We found 12 studies of malignant transformation associated with NF2.
Conclusion: The potential mechanism leading to malignant transformation of VS seems more obvious for SRS and is less understood for MS. Given a low incidence of de novo malignant schwannoma, the possibility that these are spontaneous events in either setting cannot be ruled out. Risk of malignant transformation of VS after either SRS or MS is not zero; however, the magnitude of this risk is probably minimal based on the evidence from eight histopathologically confirmed cases. **Key Words:** CyberKnife—GammaKnife—Malignant transformation—Microsurgery—Radiotherapy—Stereotactic radiosurgery—Vestibular schwannoma.

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Although malignant transformation of vestibular schwannoma (VS) after stereotactic radiosurgery (SRS) is rare, the increasing number of patients undergoing SRS makes it a potential concern. In 1998, Comey et al. (1) reported the first malignant transformation of VS after SRS. Additional cases of malignant transformation of VS attributed to SRS have been reported in subsequent years (2–7). These case reports suggest a greater number of malignant VS cases with the growing use of SRS (8). Neurotologists and neurosurgeons debate both the magnitude of the risk as well as the proposed mechanisms behind malignant transformations of VS. In addition, defining suspected or possibly confirmed malignant transformation is difficult.

Multiple reviews have investigated the association of fractionated radiotherapy (FRT) with the incidence of secondary neoplasms. Ron et al. (9) found a relative risk of 8.4% for head and neck neural tumors after low-dose radiation exposure of the scalp in a large population. A study on the use of external beam therapy on prostate

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cancer revealed significant increases in secondary malignancies (10). In addition, a study found that the odds ratio for subsequent gliomas in children treated by radiation for childhood cancers was 6.78 (11). Minniti et al. (12) demonstrated that the cumulative risk of secondary brain tumors increased after radiation exposure for pituitary adenomas. The study found that, at 10 and 20 years, the cumulative risk for secondary brain malignancy was 2.0% and 2.4%, respectively. Published studies report risks of overall radiation-induced secondary neoplasm at 1% to 3% (13). These studies support the ability of radiation to induce neoplasms of normal tissues from iterative low-dose high-volume radiotherapy; however, it offers scant information on malignant transformation induced by single or hypofractionated-dose radiosurgery for a benign tumor.

In 2000, Baser et al. (14) reviewed 106 neurofibromatosis type 2 (NF2) patients treated by SRS and found five radiation-induced malignant peripheral nerve sheath tumors (MPNSTs), suggesting an increased incidence in this population. In 2011, Husseini et al. (8) reviewed 26 cases of radiation-related malignancies of VS after SRS. In those cases, they cited 17 cases of malignant transformation of VS. However, in 2013, Patel and Chiang (13) reviewed the literature and found only 13 malignant transformations of VSs secondary to radiosurgery. Furthermore, Lunsford et al. (15) reported a long-term study on SRS of 829 patients and found no transformed or induced malignancy. Rowe et al. (16) reviewed 5,000 patients after SRS treatment and found no increased risk in malignancy. To date, no definitive evidence exists to suggest that radiosurgery causes increased malignant transformations of VS. In fact, there are also published reports describing malignant transformation of VS after microsurgery (MS) (17,18).

The main objective of this comprehensive review is to critically analyze each reported case of malignant transformation of VS. Currently, there is variability in defining evidence for post-SRS malignant transformation versus speculative cases of transformation. We aim to include malignant transformations of VS secondary to radiosurgery and malignant transformations of VS after MS and primary malignant VS or de novo transformations of VS. We recognize the difficulty in identifying true malignant transformation of VSs; however, we hope to offer an unbiased perspective on published case reports. Finally, we suggest possible mechanisms underlying the malignant transformation of VS to spur future research.

METHODS

We performed a search using the Pubmed/Medline database using the following key words: *vestibular schwannoma*, *acoustic neuroma*, *malignant*, *malignancy*, *transformation*, *radiation*, *induced*, *stereotactic*, *radiosurgery*, *GammaKnife*, and *CyberKnife* and combinations thereof. We have included international publications in the search. There were no limitations on language or time of publication. For case reports not in English, we obtained translated versions. Furthermore, we manually reviewed all relevant citations from each case report or case series for additional cases.

Our initial search yielded 53 possible cases of malignant transformation of VS secondary to SRS. Each case report was independently reviewed by the senior authors. Although malignant transformations of VSs do not strictly fit Cahan's criteria, we used it as the foundation of our inclusion criteria (19). One of the main problems with defining malignant transformation is differentiating between suspected versus confirmed change in the tumor. Thus, in an effort to remain as objective as possible, we settled on very strict criteria for inclusion into our analysis. Our inclusion criteria for malignant transformation of VS after radiosurgery include initial histopathologically confirmed benign VS tumor, histopathologically confirmed subsequent malignant VS, latency period between malignancy and benign disease, and evidence of malignant transformation or dedifferentiation of the original tumor. Most studies defined a reasonable latency period between malignancy and benign disease at 5 to 7 years (19). However, we included case reports with histopathologic evidence of transformation even without fulfilling a reasonable latency period because there may be no definitive time threshold for malignant transformation and because time thresholds for higher-dose single-session radiosurgery might conceivably be shorter than those established for multisession low-dose radiotherapy. We included reported cases that used radiosurgery as a treatment modality such as the modified linear-accelerator systems (CyberKnife; Accuray Inc., Sunnyvale, CA, U.S.A.) and the 60-cobalt–based systems (Leksell Gamma Knife, Stockholm, Sweden). We used the same inclusion criteria for malignant transformation of VS after MS. Our exclusion criteria included lack of histopathologic evidence of the benign tumor of the initial tumor, lack of histopathologic evidence of a transformed malignant tumor, or no evidence of malignant transformation of a benign tumor. We excluded all reports of NF2 patients with possible malignant transformation of VS. We provided a discussion of our inclusion and exclusion criteria later in the review. We divided the case reports into three different categories (Table 1).

We designed our review to have strict inclusion criteria to highlight case reports that show strong evidence of radiation-induced malignant transformation of VS. Our end goal was to separate case reports with speculative or presumed evidence of malignant transformation of VS. Our strict criteria imply that cases that were only treated with SRS can never be defined as a malignant transformation. The exclusion of studies does not imply that malignant transformation did not occur but indicates that the evidence for transformation remains speculative and weak.

RESULTS

In our review of the literature, eight case reports of malignant transformation of VS post-SRS qualified for

TABLE 1. *Categories of malignant transformations of VSs*

Histopathologically confirmed benign VS undergoing malignant transformation into histopathologically confirmed malignant VS after MS and SRS
Histopathologically confirmed benign VS undergoing malignant transformation into histopathologically confirmed malignant VS after microsurgery only
Primary malignant VS or de novo malignant transformation of VS with no history of SRS

MS indicates microsurgery; SRS, stereotactic radiosurgery; VS, vestibular schwannoma.

TABLE 2. *Histopathologically proven malignant transformation after MS and SRS of sporadic VS*

Year	Author	Age (yr)	Sex	Side	Initial Tumor Size (cm)	ST Pathology	Months From MS to RS	Months From RS to ST	Survival Months from ST
2001	Hanabusa et al.	51	F	R	NR	MPNST	56	7	25
2002	Shin et al.	26	F	R	3	MPNST	1	72	10
2004	Kubo et al.	51	M	L	NR	MPNST	19	8	NR, >4
2009	Van Rompaey et al.	53	F	R	6	MPNST	3	96	0
2010	Yang et al.	74	M	L	2.5	UHGS	96	72	1
2010	Demetriades et al.	27	M	L	4.5	MPNST	NR	120	1
2010	Akamatsu et al.	67	F	R	NR	MPNST	72	96	NR
2013	Yanamadala et al.	46	F	R	2.9	MPNST	8	59	11

NF2 VS tumors are excluded.

F, indicates female; L, left; M, male; MPNST, malignant peripheral nerve sheath tumor; MS, microsurgery; NF2, neurofibromatosis type 2; NR, not reported; R, right; RS, radiosurgery; SRS, stereotactic radiosurgery; ST, second tumor; UHGS, undifferentiated high-grade sarcoma; VS, vestibular schwannoma.

inclusion (Table 2) (2,4–7,20–22). The median age of the patients was 51 years. The median time between the initial surgery and the SRS was 19 months. Reported peripheral (minimum) doses ranged from 11 Gy to 18 Gy. The median time between SRS and diagnosis of the second malignant tumor averaged 72 months. The median time between the initial MS and the second malignant tumor was 86 months. Median survival from the diagnosis of the malignant tumor was 4 months.

We excluded three case reports of malignant transformation of VS post-FRT (Table 3) (23–25). The median age of the patients is 45 years. Median time between MS and radiotherapy is 12 months. Median time between FRT and second malignant tumor is 144 months. The median survival time after the second tumor is 7 months.

We found four case reports showing malignant transformation of VS after MS only (Table 4) (17,18,26). The median age of the patients was 61.5 years. Median time between initial MS and diagnosis of a second malignant tumor was 10 months. Average survival time from the diagnosis of malignant tumor was 2 months.

We found 18 primary malignant VSs or de novo malignant transformation of VSs (Table 5) (27–41). The median age of the patients was 45 years. After review of those 18 cases, two reported cases demonstrated both benign and malignant features within the same tumor at the time of resection. Median survival time is 5 months after diagnosis.

In our review, we excluded 12 cases of radiation-associated malignant tumors in the setting of NF2 (Table 6) (1,3,14,42–47). For all the excluded NF2 patients, the median age of the patients was 21 years. Median time between SRS/FRT and diagnosis of a second malignant tumor is 36 months. Median survival time from the diagnosis of malignant tumor was 3 months.

We excluded eight case reports for not providing histopathologic evidence of a benign tumor or lacking evidence of malignant transformation of the VS (Table 7) (1,4,48–52).

DISCUSSION

Investigation of malignant transformations of VS treated by radiation is relevant because at least 42% of neurotologists use SRS to treat VS (53). However, malignant transformation of VS secondary to SRS is difficult to define. Other reviews typically report second neoplasms post-SRS and malignant transformations of VS post-SRS together (13,25). However, Hanabusa et al. (2) argued that most malignant transformations of VS are caused by de novo transformations and not radiation induced. Thus, differentiating between malignant transformations of VS from other radiation-induced secondary neoplasms is important (54). Even though the clinical presentations of malignant transformation of VS and secondary tumors are similar, the theoretic incidence rate of malignant transformation probably differs from the background incidence of secondary tumors. Therefore, differentiating the two disease processes may yield information applicable in the clinical context. If we determine that there is minimal risk for malignant transformation, then the management of younger patients who are reluctant to undergo SRS may be affected by the result of this review. Our

TABLE 3. *Excluded cases of histopathologically proven malignant transformation after FRT and MS of sporadic VS*

Year	Author	Age (yr)	Sex	Side	Initial Tumor Size (cm)	ST Pathology	Months From MS to RT	Months From RT to ST	Survival Months from ST
2004	Wilkinson et al.	53	M	L	NR	MPNST	NR	NR	8
2006	Maire et al.	45	F	L	2	MPNST	12	216	NR
2012	Puataweepong et al.	34	F	L	NR	MPNST	12	72	6

NF2 VS tumors are excluded.

F indicates female; FRT, fractionated radiotherapy; L, left; M, male; MPNST, malignant peripheral nerve sheath tumor; MS, microsurgery; NF2, neurofibromatosis type 2; NR, not reported; RT, radiotherapy; ST, second tumor; VS, vestibular schwannoma.

TABLE 4. *Histopathologically proven malignant transformation of sporadic VS after MS only*

Year	Author	Age (yr)	Sex	Side	Initial Tumor Size (cm)	ST Pathology	Months From MS to ST	Survival Months from ST
1990	McLean et al.	75	F	R	NR	MPNST	11	2
2001	Son et al.	33	F	L	4.5	MPNST	2	NR
2009	Scheithauer et al.	67	M	R	2	MPNST	10	1
2009	Scheithauer et al.	56	M	R	NR	MPNST	7	2

F indicates female; L, left; M, male; MPNST, malignant peripheral nerve sheath tumor; MS, microsurgery; NR, not reported; R, right; ST, second tumor; VS, vestibular schwannoma.

main focus is to elucidate the role of radiosurgery in malignant tumors. In addition, we admit that malignant transformation of VS cannot be truly attributed to SRS. We would define them as post-SRS malignant transformation without assuming causality.

Researchers typically use Cahan's criteria to determine if secondary neoplasms are radiation induced (13,22,46,47). However, malignant transformations of VSs do not strictly qualify in Cahan's criteria for radiation-induced secondary neoplasms (55). Thus, we modified Cahan's criteria to include only post-SRS malignant transformations of VS. Many reported cases of malignant transformations of VS fail to provide histopathologic evidence of an initially benign tumor (1,14). The benign nature of the tumor is inferred from serial radiologic monitoring spanning a number of years. However, radiobiologic effects of radiosurgery of VS may mask the aggressive nature of a presumed benign tumor, delaying definitive treatment for the patient. Radiographic imaging may not be sufficient evidence for determining the benign nature of the initial tumor. For example, Schmitt et al. (52) reported a case of sarcoma in a patient 7 years after radiosurgery for a presumed VS. A review of the article by our team found a clear dural tail in the initial imaging. This would significantly reduce the likelihood of VS as the primary histopathology of the tumor. In addition, the histopathology of the subsequent tumor cells lacked evidence of immunostaining with S-100 and no foci of schwannoma were found. Therefore, without initial histopathology showing benign schwannoma, it would be difficult to assume that the initial tumor was VS.

Following our strict criteria, only eight case reports qualified for inclusion. This is a lower number than what is typically reported by other reviews of malignant transformation (13,46,47). Reasons for exclusion were the following: history of NF2 (n = 12), lack of histopathologic evidence of benign tumor (n = 4), and no evidence of malignant transformation of VS (n = 5). A recent review calculated a theoretic risk of 0.04% for all radiation-associated secondary neoplasms after SRS (13). Patel and Chiang (13) estimated the denominator for the calculation of the theoretic risk at 80,000 cases of treated VSs. The number is a conservative estimate because there are data indicating that 70,000 patients have been treated by a 60-cobalt–based radiosurgical system. However, we admit that an estimate of an appropriate denominator is difficult, if not impossible. As both of the numerator and denominator are estimates based on incomplete data and

TABLE 5. *Primary malignant VSs/de novo malignant transformations of sporadic VSs*

Year	Author	Age (yr)	Sex	Side	Initial Tumor Size (cm)	Initial Tumor Pathology	Survival Months from Tumor
1983	Kudo et al.	54	F	R	NR	MPNST	6
1986	Hernanz-Schulman et al.	1.6	F	L	2.2	MPNST	NR, >12
1986	Miller et al.	74	M	R	NR	Melanotic schwannoma	NR, >12
1987	Best	24	F	R	3.5	Triton	4
1990	Matsumoto et al.*	54	M	R	NR	Triton	NR
1992	Han et al.	47	F	R	4	Triton	13
1993	Maeda et al.	38	M	R	3	MPNST	1.2
1994	Gruber et al.	61	F	R	NR	MPNST	NR, >24
1994	Mrak et al.	40	F	L	3	MPNST	NR, >7
1994	Earls et al.	77	M	R	NR	Melanotic schwannoma	NR
2007	Gonzalez et al.	43	F	L	5.4	MPNST	12
2008	Muracciole and Régis	61	F	L	2.5	Triton	NR
2008	Chen et al.	62	F	L	2	MPNST	4
2009	Scheithauer et al.	32	M	L	NR	MPNST	3
2009	Scheithauer et al.	5	M	L	4.6	MPNST	NR
2011	Karami et al.	23	F	L	NR	MPNST	27
2012	Wei et al.	41	F	R	2.7	MPNST	NR
2012	Gong et al.	55	F	L	NR	Triton	NR, >5

All patients did not initially receive any radiation before malignant change of the tumor.
F indicates female; L, left; M, male; MPNST, malignant peripheral nerve sheath tumor; NR, not reported; R, right; VS, vestibular schwannoma.
*Clinical course before malignancy suggested an apparently benign course.

TABLE 6. *Excluded cases of radiation-associated malignant transformation of NF2 patients*

Year	Author	Age (yr)	Sex	Side	Initial Tumor Size (cm)	Initial Pathology	ST Pathology	Type of Radiation	Months from RS to ST	Survival Months from ST
1998	Noren et al.	18	F	BLT	R:1.9, L:5	NR	Triton	SRS	72	NR
2000	Baser et al.	NR	NR	NR	NR	NR	MPNST	SRS	NR	NR
2000	Baser et al.	NR	NR	NR	NR	NR	MPNST	SRS	NR	NR
2000	Baser et al.	NR	NR	NR	NR	NR	MPNST	SRS	NR	NR
2000	Baser et al.	NR	NR	NR	NR	NR	Malignant meningioma	SRS	NR	NR
2000	Baser et al.	NR	NR	NR	NR	NR	Malignant ependymoma	SRS	NR	NR
2000	Thomsen et al.	19	F	BLT	R:1.5, L:5	R: NR, L: VS	GBM	SRS	7.5	NR
2002	Bari et al.	28	F	BLT	NR	R: VS, L: NR	MPNST	SRS	48	3
2003	McEvoy et al.	22	M	BLT	NR	R: NR, L: VS	NR	SRS	24	3
2008	Rowe et al.	NR	F	NR	NR	NR	Malignant glioma	SRS	36	6
2010	Carlson et al.	25	F	BLT	R: 2.5	R: VS	Rhabdomyosarcoma	FRT	10	3
2011	Tanbouzi Husseini et al.	20	M	BLT	L:2.2, R:1.8	NR	MPNST	SRS	60	2

All patients initially received radiation by radiosurgery without histopathologic confirmation of the benign nature of the tumor.

BLT indicates bilateral; F, female; FRT, fractionated radiotherapy; GBM, glioblastoma multiforme; M, male; MPNST, malignant peripheral nerve sheath tumor; MS, microsurgery; NF2, neurofibromatosis type 2; NR, not reported; RS, radiosurgery; SRS, stereotactic radiosurgery; ST, second tumor; VS, vestibular schwannoma.

literature, we cannot guarantee that it is the true theoretic rate; however, it represents a rate that may be the best approximation malignant transformation rate after SRS from the current data available. The high single doses of radiation given to a small target volume may have led to cytotoxicity instead of mutagenicity in most patients. Thus, less malignant transformations of VSs are observed. In addition, the extremely small number supports published long-term studies of VS patients treated with SRS that found no malignant transformation (15,16,56,57). In our literature search, we reviewed three cases of histopathologic-supported malignant transformation of FRT cases. The effects of multiple potentially mutagenic exposures through fractionation and lower doses per session may affect both the likelihood and the mechanism of transformation. Thus, FRT cases are excluded from the review; however, they still represent malignant transformation of VS postradiation and warranted special consideration.

After reviewing all published literature on malignant transformations of VS and dividing the cases into three categories, we calculated median age, median latency time, and survival time. Median ages of patients in all sporadic VS groups are similar. The median latency time to formation of secondary malignant VSs of patients treated with SRS is longer than that of patients treated with MS. In addition, the median latency times between the SRS and MS group differ at 72 and 8.5 months, respectively. This suggests that malignant transformations of VSs after MS may have a different etiology than SRS-associated transformations. An alternative possibility is that most malignant tumor stem cells may die as a result of the initial SRS. With a small number of surviving stem cells (the cells that actually divide), the regrowth of the tumor may take years. After MS, however, a portion of the tumor will remain and the surviving malignant stem cells regrow at a much faster rate. Within the group treated by SRS, Hanabusa et al. (2) reported the shortest latency time between SRS and diagnosis of MPNST at 7 months. The short duration may indicate that the tumor was in the process of transforming before SRS.

Niranjan et al. (54) argued that malignant transformation of these VSs may simply represent the natural progression of the benign tumor. Indeed, our review of the literature found 18 published cases of primary malignant VS or possible de novo transformation. Furthermore, cases treated by SRS/MS and reported cases of primary malignant VS or de novo malignant transformation of VS yielded comparable survival times at 8 and 6 months, respectively. It is difficult to differentiate between malignant transformations of VS by SRS and primary malignant VS/de novo malignant transformation. However, our review suggests that reports of malignant transformation after SRS/MS may potentially represent the natural progression of

TABLE 7. *Excluded reports of malignant transformation of sporadic or NF2 VS*

Year	Author	Reason for Exclusion
1967	Dastur et al.	Not malignant transformation of a benign tumor
1998	Comey et al.*	No histopathology for benign tumor
2000	Harada et al.	Not malignant transformation of a benign tumor
2001	Shamisa et al.	Not malignant transformation of a benign tumor
2002	Ho and Kveton	Not malignant transformation of a benign tumor NF2 patient
2004	Yoshimoto et al.	No histopathology for benign tumor
2007	Balasubramaniam et al.	Not malignant transformation of a benign tumor
2008	Murraciole et al.	Not malignant transformation of a benign tumor
2011	Schmitt et al.	No histopathology for benign tumor

NF2 indicates neurofibromatosis type 2; SRS, stereotactic radiosurgery; VS, vestibular schwannoma.

*Clinical course may suggest post-SRS malignant transformation.

these tumors and indicates an overlap between the two categories. It is vital to recognize that malignant transformations of VSs may represent a natural progression of the disease. Indeed, there are no studies that definitively prove that radiation can induce malignant transformation of VSs (22,27). Physicians should use caution when determining the exact cause of malignant transformation even after treatment with SRS.

Our review found four cases of malignant transformation after MS (17,18,26). These cases may represent the natural progression of VSs into malignancy as we described before in the review. In these four cases, we are limited by a lack of access to the original pathologic material for re-review and must take it on faith that the pathologists involved, as well as the reviewers of the articles before publication, did not misidentify originally malignant tumors as ''benign.'' These four cases suggest that malignant transformation may occur after MS. The pathogenesis leading to malignant transformation of tumors by MS is difficult to determine based on the available case reports. Yanamadala et al. (22) entertained electrocautery as a possible cause of malignant transformation after MS. Muracciole and Régis (51) postulated that inflammation post-MS might promote proliferative changes in the tumor, transforming it into a malignancy. Hong et al. (57) discovered that cyclooxygenase-2 plays a significant role in the growth of sporadic and NF2-associated VSs. De Vries et al. (58) found that there is an association between the number of M2-type macrophages in VS with angiogenesis and volumetric tumor growth. Furthermore, Kandathil et al. (59) found that long-term aspirin intake might halt sporadic VS growth. These studies might explain how VSs treated by MS can transform into malignancy. Indeed, Marjolin ulcer, Barrett's esophagus, Crohn's disease, and ulcerative colitis are classic examples of malignancies induced by inflammation from normal tissue. However, the acute duration of inflammation in MS pales in comparison with the chronic inflammation of those diseases. Malignant transformation may be caused by edema and inflammation in both SRS and MS. Inflammatory factors may change the tumor's environment to trigger progression of a benign tumor into malignancy.

The scant reports of malignant transformation secondary to MS may be caused by physicians failing to recognize the true cause of the complication. Physicians may more easily recognize the possible association between malignant transformation of VS and radiosurgery; thus, these cases are more likely to be reported, thus representing a form of publication bias. Because all of our included cases for malignant transformations of VS after SRS had a history of at least one resection because of our requirement for histopathologic evidence of a benign tumor, it is also possible that the prior MS may have contributed to the induction of malignant transformation of these patients. Indeed, three of the eight cases of malignant transformation of VS after SRS had histories of multiple MS (7,21,22). We must recognize that there is a possibility of malignant transformation after MS just as we do after SRS. However, there is no definitive evidence of absolute causality. Thus, no conclusions must be made regarding the association between MS and malignant transformation based on these four case reports.

We excluded 12 cases of potential malignant transformation or radiation-associated secondary malignancy of VSs in NF2 patients. Traditionally, there is a known association of MPNST and NF1 (59,61). These patients already have a germ line loss of one tumor suppressor gene. The possibility of losing the second after SRS or even FRT is statistically more likely than SRS or FRT inducing the loss of two tumor suppressor genes in patients with unilateral VSs. Given the germ line suppressor gene loss predisposition, as well as recent reviews suggesting a possible correlation between NF2 and malignant transformation (14,46,47), we would caution in treating NF2 patients with radiosurgery.

Review of the excluded cases yielded an average survival time for NF2 patients after SRS/FRT of 3.4 months. Because NF2 can predispose patients to further malignancies, it is imperative to compare the incidence of malignant transformation between irradiated and nonirradiated NF2 patients. In a large retrospective study, Baser et al. (14) calculated that nonirradiated NF2 patients had an incidence of 725 per 100,000 persons for malignant nervous system tumors. Subsequently, they then calculated that irradiated NF2 patients had an incidence of 4,717 per 100,000 persons for radiation-associated malignant transformations. However, Mathieu et al. (55) observed no malignant transformations following up on 62 NF2 patients treated with SRS. In addition, a review of 118 cases of NF2 patients after radiosurgery only found two cases of intracranial malignancies that were not necessarily radiation induced (56). Radiosurgery may allow NF2 patients to live longer, allowing their VSs to naturally transform to malignancy. The association of NF2 and radiation-induced neoplasms is complex. We may be observing survivorship bias as NF2 patients in the past would have died before manifestation of their malignant transformation. In addition, the observed malignancies may have been induced by NF2 instead of the radiation. Thus, the natural progression of these tumors and the background incidence of malignant neoplasms need further consideration. Radiosurgery remains an attractive option for NF2 patients because of the decreased operative risk and fast recovery times (62). We conclude that the risk for malignant transformation of VSs in NF2 patients remains an area of contention and recommend careful selection of NF2 patients considered for radiosurgery. Ideally, very few NF2 patients should undergo SRS for their VSs because the theoretic risk of radiation-induced malignancy is higher in this patient group.

Limitations of this study include the limited information on malignant transformation of VS secondary to SRS. Quality of the review depended on the accuracy and comprehensiveness of each case report. The small number of case reports and lack of randomized control trials also make it difficult to derive any definitive conclusions. The calculation of the theoretic risk for

malignant transformation is subject to significant selection bias and does not reflect the true risk for malignant transformation. The range of denominators used in the theoretic risk calculation represents an estimate of the overall cases of SRS-treated VSs. However, determining the malignant transformation risk is impossible, and our review offers the closest estimate of the theoretic risk of malignant transformation. In addition, reports are sometimes incomplete and may not describe each case in full detail. There are also no published criteria to determine malignant transformation of VSs. However, our review emphasizes the complexities and controversies of malignant transformations of VSs secondary to SRS.

CONCLUSION

Only eight published case reports definitively demonstrated malignant transformation post-SRS with histopathologic evidence of both benign and malignant tumors. These cases represent the best support for induction of malignant transformation in VS by SRS. Three published case reports demonstrated histopathologic evidence of malignant transformation after FRT. We identified four cases of malignant transformations of VS after MS treatment only. In addition, we identified 18 cases of either primary malignant VS or de novo transformation to malignancy without surgical intervention of any type. Thus, it remains possible that the association of malignant transformation of VS after either SRS or MS represents the natural history of rare unfortunate patients experiencing this event. Potential mechanisms underlying malignant transformation after SRS seem plausible from prior radiation exposure experience. Mechanisms underlying malignant transformation after MS seem more opaque but may center on postsurgical inflammatory responses. NF2 may increase the risk of an individual for malignant transformation. Risk of malignant transformation of VS after either SRS or MS is not zero; however, the magnitude of this risk is minimal.

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