

Imaging Findings Post Stereotactic Radiosurgery for Vestibular Schwannoma: A Primer for the Radiologist

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ABSTRACT

Non-invasive tumor control of vestibular schwannomas through stereotactic radiosurgery allows for high rates of long-term tumor control and has been used primarily for small and medium-sized vestibular schwannomas. The post-treatment imaging appearance of the tumor, temporal patterns of growth and treatment response, as well as extra-tumoral complications can often be both subtle or confusing and should be appropriately recognized. Herein, the authors present an imaging-based review of expected changes, as well as associated complications related to radiosurgery for vestibular schwannomas.

ABBREVIATIONS: FSRT: Fractionated stereotactic radiotherapy, ISRS: international stereotactic radiosurgery, MPNST: Malignant peripheral nerve sheath tumor, SRS: Stereotactic radiosurgery, VS: Vestibular schwannoma.

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INTRODUCTION

Vestibular schwannomas (VS) are benign, slow-growing tumors that most often arise from the vestibular component of the eighth cranial nerve, commonly presenting clinically with unilateral hearing loss and tinnitus. Less commonly, disequilibrium, ipsilateral trigeminal hypoesthesia or neuralgia, or hydrocephalus may occur.(1, 2) Advances and wider availability of MR imaging have allowed for an earlier diagnosis of these lesions, at times when patients may have only minimal hearing loss or are asymptomatic.(3) This has led to an increasing role of minimally invasive management strategies such as stereotactic radiosurgery (SRS) in VS management.(2)

The international stereotactic radiosurgery (ISRS) practice guidelines consider both observation and SRS as reasonable treatment options for newly diagnosed VS without significant mass-effect.(4) On the other hand, microsurgical resection can be employed for any sized tumor, and is currently considered the treatment of choice for larger tumors.(5) In general, lesions up to 2.5 cm in maximal cerebellopontine angle diameter are considered appropriate for SRS treatment, although more recent studies have also explored SRS for larger lesions with acceptable results.(4, 6, 7) The ISRS practice guidelines recommend a dose of 11-14 Gy to the tumor margin for single-fraction SRS in VS.(4) Fractionated stereotactic radiotherapy (FSRT) may also be used, and provides a similar 5-year tumor control rate.(2) No randomized trials have evaluated the efficacy of SRS versus FSRT for tumor control in VS. Limited available data however does not suggest any definite advantage of one modality over the other.(8) Unlike SRS, which involves 1-5 fractions, FSRT delivers the prescribed radiation dose in 25-30 fractions to maximize targeting tumor cells during radiation-sensitive phase of cell-cycle.(8)

Acute radiation effects following SRS are not uncommon and have been reported in up to 22-24% of patients. These generally include vertigo, hemifacial spasm, gait disturbance and exacerbation of pre-existing hearing loss and may appear in the first few months. (9, 10) SRS however can also lead to a myriad of imaging appearances in VS, which may be more apparent over the ensuing months to years. Herein, we present an imaging-based review of both the common (and often expected) as well as atypical appearances in VS post SRS. An increased awareness of these findings may help avoid imaging pitfalls, as well as recognize complications at an earlier stage.

Pseudoprogession:

VS treated with SRS may show transient tumor enlargement in the first three years after SRS, often referred to as pseudoprogession (Fig 1).(5) In such cases, the tumor will develop early swelling or growth, but then stabilize or shrink in size. Contrastingly, true progression (i.e., radiation failure) implies sustained tumor growth over serial MRI studies. The incidence of pseudoprogession is variable, ranging between 5-74% in different studies.(11-13) This wide variability is due to considerable heterogeneity in imaging techniques, measurement methodology (2D versus 3D) and also due to the criteria used to define pseudoprogession which is variably considered as 10-20% increase in VS volume over baseline, with some studies even considering any increase in VS volume over baseline as pseudoprogession.(13) Regardless, findings are often accompanied by variable loss of central enhancement on MR imaging. Even though several studies have not shown any correlation between pseudoprogession and post-SRS clinical deterioration, a few others have noted higher incidence of cranial nerve impairment, increased risk of hydrocephalus requiring shunt placement and loss of serviceable hearing.(13-15)

During pseudoprogression, the increase in tumor volume can be quite impressive, with a reported median of 20-88% over baseline, and up to 800% in some cases.(13, 16) The underlying risk factors for pseudoprogression remain unclear, though one study noted higher probability with solid-VSs (OR: 2.79; p=0.017).(12)

Pseudoprogression generally peaks around 6 months post SRS and resolves between 12-18 months. However, these timelines are approximate at best, and up to 17% of patients may show late pseudoprogression peaking around 3-4 years while some may show delayed resolution over the next 2-3 years.(11, 13) Given the wide variabilities in timelines for pseudoprogression and overlap with treatment failure, there are no well-defined timelines for adjudicating treatment failure. In general, pseudoprogression should be considered when tumor volumes increase in the first three years post SRS.(4) A recent systematic review of 300 patients who underwent microsurgical decompression post-SRS also noted that the mean time to surgery post SRS was 39.4 months, with the overwhelming indication (92%) being tumor growth post SRS.(17)

Loss of central lesion enhancement often follows a similar timeline, but likely has a different pathogenesis from pseudoprogression (Fig 2). Some authors believe it reflects an early effect of radiation and is not necessarily indicative of long-term tumor control. The reported prevalence varies between 45-93% in literature.(11, 13) In authors' personal experience, the loss of central enhancement can vary considerably in individual cases, reaching up to 50-60% of the tumor volume.

Treatment response and tumor growth:

SRS can achieve long-term tumor control in greater than 90% of cases with a relatively low risk of neurological deterioration or facial nerve palsy.(6, 8, 18, 19) Tumor control is broadly considered as lesion regression or stability, obviating need for additional intervention (Fig 3, 4).(2, 19) Kawashima et. al., in their cohort, noted tumor regression in 62%, stable tumor in 31% and enlargement in 7% of patients post-SRS.(18) Treatment failures may be more common with larger or fast-growing tumors at baseline (Fig 5).(7, 20)

As noted earlier, tumors may also occasionally show a delayed pseudoprogression and tumor enlargement within the first 3-4 years is generally not used as a sole criterion for salvage therapy. (16) Since differentiation between tumor regrowth and delayed pseudoprogression may be challenging on conventional MRI imaging, some authors recommend documented increase in tumor size over three consecutive annual scans before adjudicating treatment failure, except in cases with new symptoms or larger tumors.(11) Table 1 outlines the various forms of treatment outcomes that may be seen in VS post SRS.

Surrounding parenchymal changes:

Development of peritumoral edema post radiosurgery is well recognized with meningiomas and has been reported in 28-50% of cases.(21) Similar changes may also be observed along the pons and cerebellar peduncles in patients with VS treated with SRS, and have been reported in about 24% of patients, developing at a median of 6 months post radiosurgery (range 4-24 months).(9) These may be associated with contrast enhancement and generally resolve on follow-up imaging (Fig 6). The exact etiology is unclear, but presumably related to radiation effects, given the temporal association with SRS. Hayhurst et. al., noted that the development of edema was significantly associated with non-auditory complications such as hydrocephalus (6%), ataxia (12.5%), trigeminal (21%) or facial nerve dysfunction (3.75%) (p = 0.001, OR 7.27; 2.33-22.66).(9) Overall, there is scarce literature on these findings which may not always be clinically symptomatic but can nevertheless be mistaken for inflammation and or tumor extension into the inner ear structures.

Intra-cochlear hemorrhage secondary to SRS has been previously reported and is rare, generally presenting with acute onset hearing loss.(22) Additionally, increased dose to the cochlea is may be associated with post-SRS hearing loss, and it is generally recommended to keep the cochlear radiation dose below 4 Gy when possible.(23)

Development of cysts post SRS:

Intra- or peri-tumoral cysts may occur de novo, or enlarge post SRS, with the incidence of delayed cyst formation reported at about 2.3% (Suppl fig 1).(24-26) The thin-walled peri-tumoral cysts may histopathologically demonstrate arachnoid cells without any tumor cells. (26) Enlarging or symptomatic cysts (secondary to mass-effect) may require surgical decompression or may spontaneously regress over time.(27)

Contrast leakage:

Peripheral contrast leakage, manifesting as a 'peri-tumoral halo' may be seen in about 90% of treatment naïve VS patients. In such cases however, the contrast is only seen along the periphery of the VS. (28) In our experience, early or delayed intra-tumoral contrast leakage in VSs treated with SRS may also be seen in a large proportion of cases (Fig 7). The exact incidence or clinical relevance of the latter remains unclear, but the phenomenon is likely secondary to slow diffusion of the contrast into the necrotic/ extracellular spaces. Similar findings have also been described in metastatic brain lesions post SRS, as well as in cardiac imaging.(29) On imaging, this may manifest as increased signal within the tumor core on FLAIR images, as well as increased extra-cellular, extra-vascular gadolinium in the internal auditory canal and vicinity of tumor. Whether this can serve as a marker of increased tumor leakage or correlates with elevated CSF protein post SRS remains unclear.

Hydrocephalus:

Even though hydrocephalus may be seen with untreated VS in about 3.7-18% of cases, it may additionally develop post SRS in 2-

3% of patients (Fig 8). (30-32) The precise causal relationship remains controversial and potential mechanisms include obstruction of the fourth ventricle, protein shedding from the tumor leading to plugging of arachnoid granulations as well as alterations in CSF flow dynamics in the basal cisterns.(30, 32, 33) Patients may develop communicating hydrocephalus 4-18 months post SRS and often show elevated CSF protein levels and may have normal opening pressure.(30, 33) Risk factors include larger tumor size and female gender. (34)

Patients may also present with signs of elevated intracranial pressure, or gait disturbances and urinary incontinence as seen with normal pressure hydrocephalus.(35) Surgical CSF diversion may be required in a majority of patients to alleviate symptoms. (31) Table 2 summarizes the various reported post-SRS complications in VS patients.

Tumors post SRS:

The risk of a secondary malignant CNS tumor developing post SRS is considered low, with the overall risk estimated at approximately 0.04% at 15 years.(36) However, these can nevertheless still occur and should be carefully considered especially in young patients and those with underlying tumor predisposition syndromes such as neurofibromatosis.(37)

Tumors reported post SRS include malignant gliomas (including astrocytoma, glioblastoma and ependymomas), sarcomas, meningiomas as well as dedifferentiation of primary VS into malignant nerve sheath tumor (MPNST). In the context of VSs, MPNST and glioblastoma appear to be overall more common (Fig 9, 10).(36, 37)

The mean latency period for stereotactic radiosurgery induced neoplasms is about 7.9 years and is generally shorter for malignant neoplasms (7.1 years) as compared to benign secondary neoplasms (14.25 years). Secondary neoplasms may occur either inside or outside the original lesion, as well as in regions receiving high- or low-dose radiation. The size of the original tumor often tends to be greater than 2 cm.(36, 37)

Conclusion:

Post-SRS vestibular schwannomas can present with a myriad of variable appearances, besides the rare occasional complications such as secondary tumor and hydrocephalus. Familiarity with the various imaging findings may be helpful so as to avoid incorrect interpretation and recognize early complications.

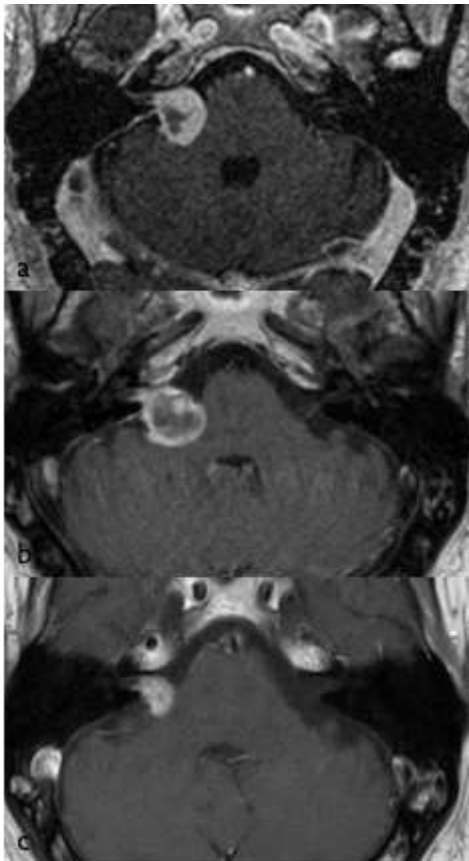


FIG 1 (a-c): Pseudoprogression in a VS treated with SRS. Tumor volume on the planning scan (a) was 3.9 cc which increased to 4.4 cc six months post treatment. Follow-up study at four years (c) showed tumor regression with volume of 0.6 cc.

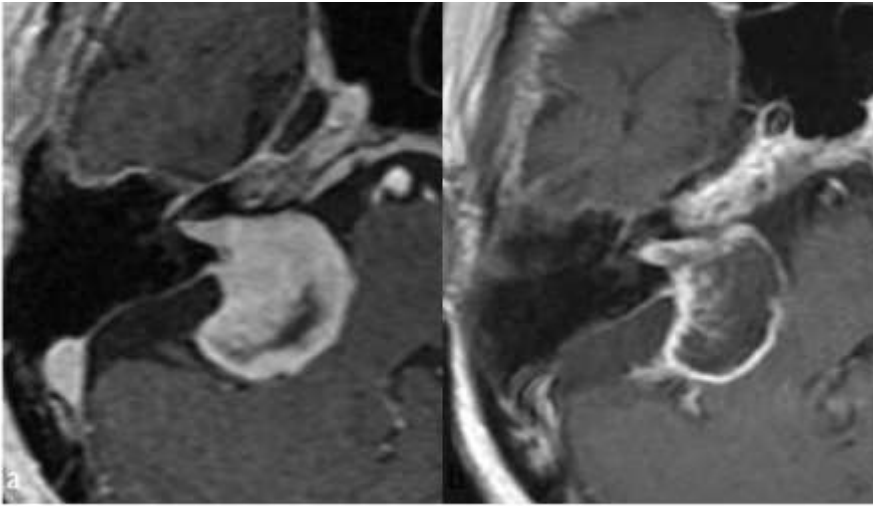


FIG 2 (a, b): Loss of central enhancement. Post-contrast images obtained pre-(a) and six months post-SRS (b), showing near complete loss of central enhancement in the right VS.

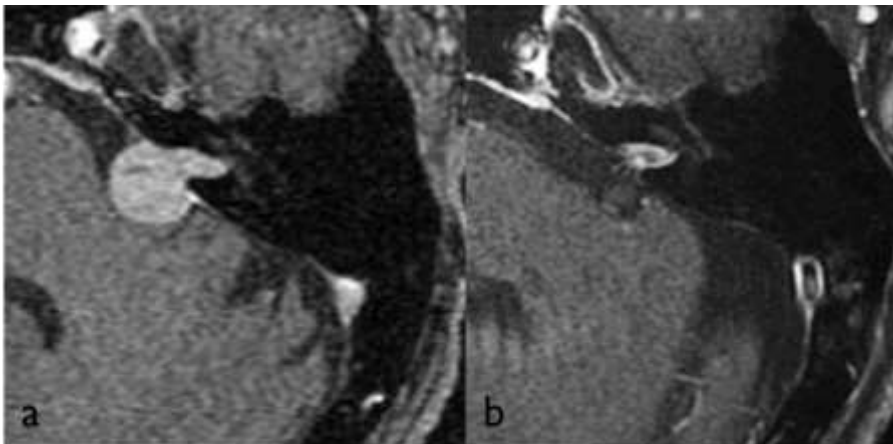


FIG 3: Favorable treatment response post-SRS. Axial post-contrast images obtained pre-SRS (a) and at eight years post-SRS (b) show considerable lesion regression, consistent with response.

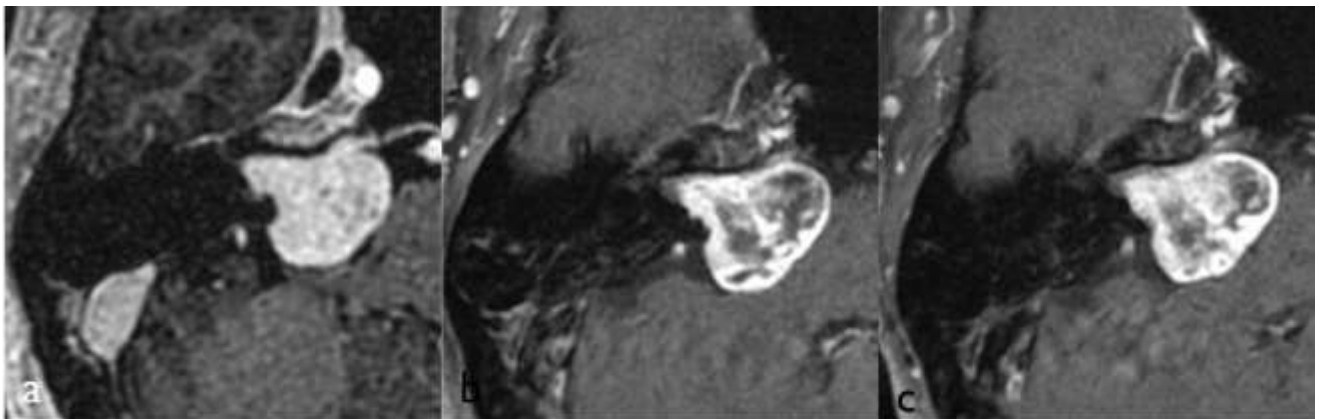


FIG 4: Tumor control post-SRS. Axial post-contrast images obtained pre-SRS (a), at one (b) and three years (c) post-SRS showing stable tumor size, despite considerable loss of central enhancement in the post-SRS period.

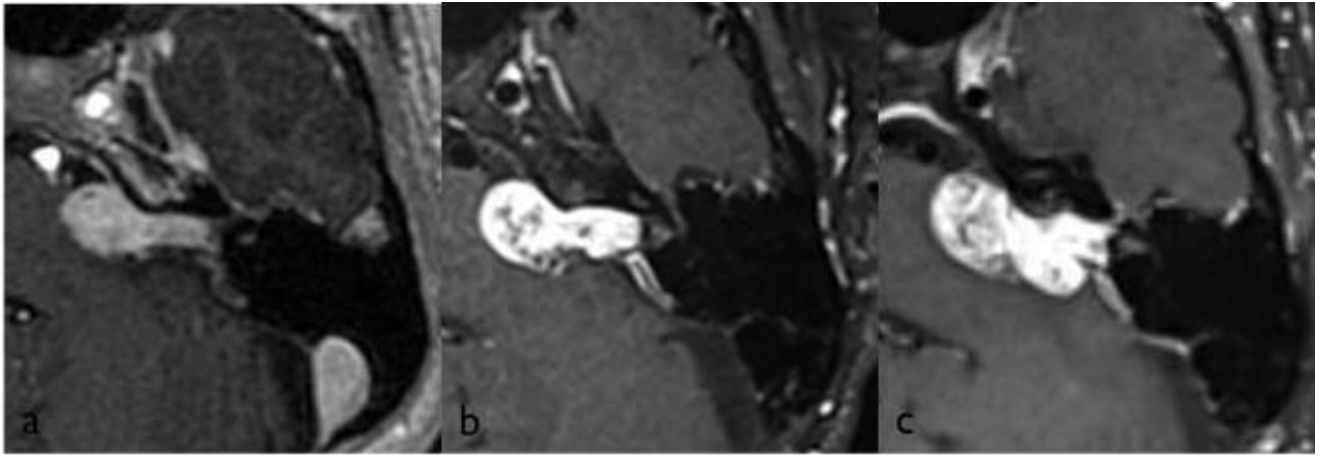


FIG 5: Treatment failure post-SRS. Axial post-contrast images obtained pre-SRS (a), and at one (b) and two (c) years post therapy showing progressive increase in tumor volume from 1.9 cc at baseline to 3.2 cc at two years, accompanied by worsening disequilibrium clinically.

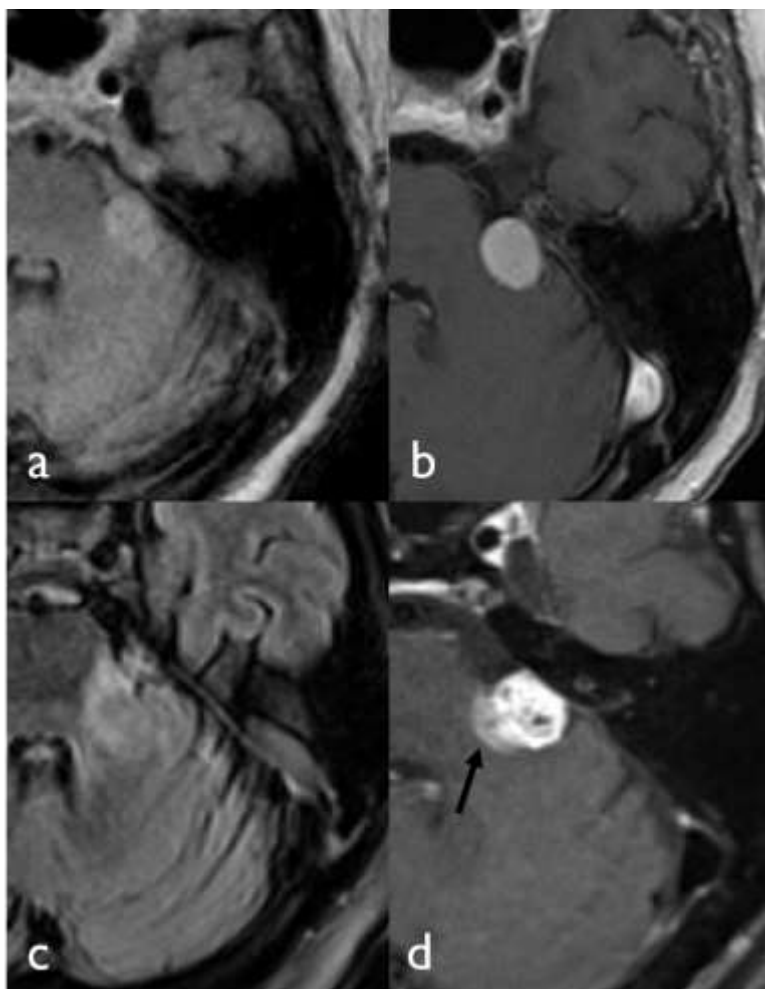


FIG 6: Parenchymal edema and enhancement post-SRS. Axial FLAIR (a) and post-contrast (b) images show a left-sided VS abutting the left brachium pontis without edema. Post-SRS, axial FLAIR (c) and post-contrast T1WI (d) reveal parenchymal edema (c) and enhancement (arrow, d).

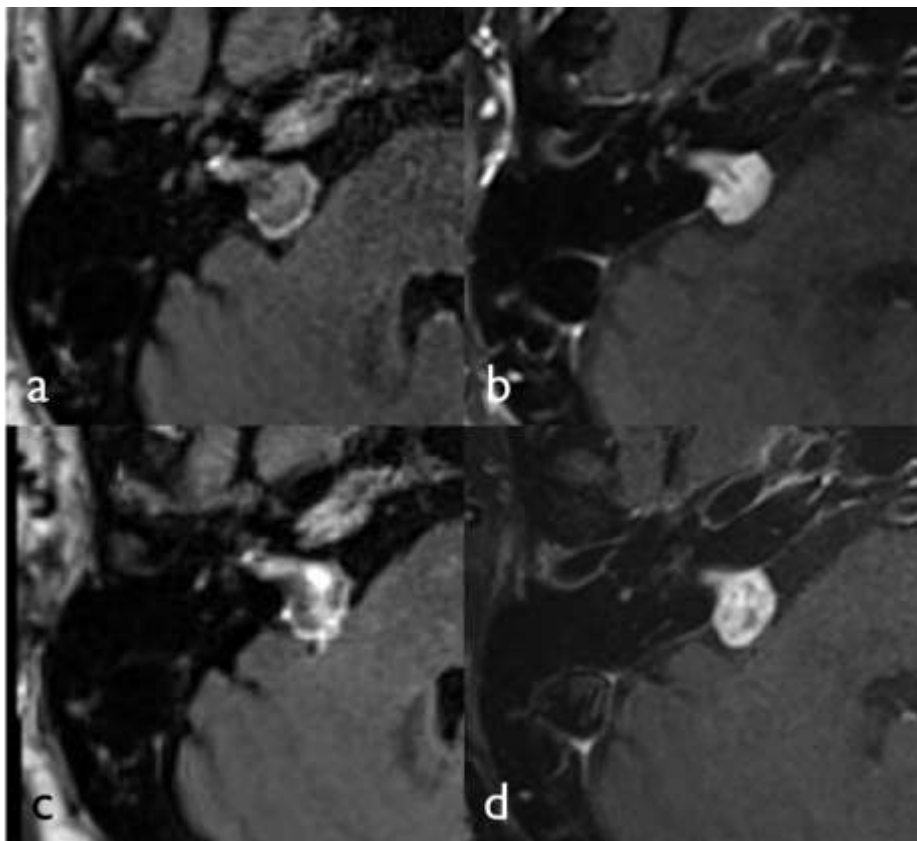


FIG 7: Contrast leakage post-SRS. Axial post-contrast FLAIR (a, c) and T1WI (b, d) obtained pre- (a, b) and one-year post-SRS (c, d). On the pre-SRS images, there is a thin 'peri-tumoral halo' on the FLAIR imaging (a) without any contrast leakage centrally. Post-SRS FLAIR (c) shows contrast leakage within the VS more centrally.

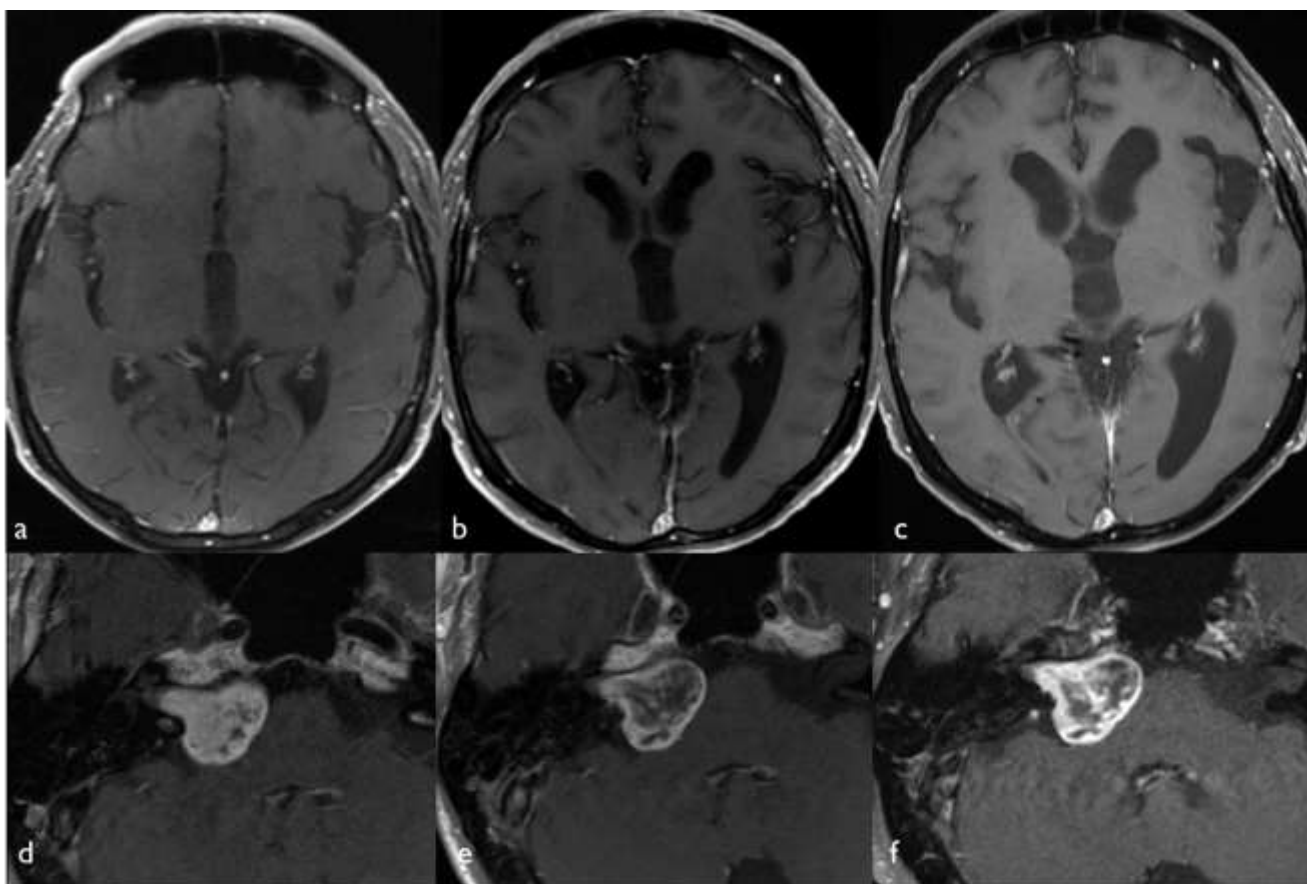


FIG 8: Hydrocephalus post-SRS. Axial post-contrast images at the level of third ventricle (a-c) and VS (d-f) obtained at baseline (a, d), at

one (b, e) and two years (c, f) post-SRS show progressive enlargement in ventricular dimensions and disproportionate enlargement of left sylvian fissure. The underlying VS (d-f) remained stable in size and showed loss of central enhancement. The patient was diagnosed with normal pressure hydrocephalus and underwent ventricular shunting.

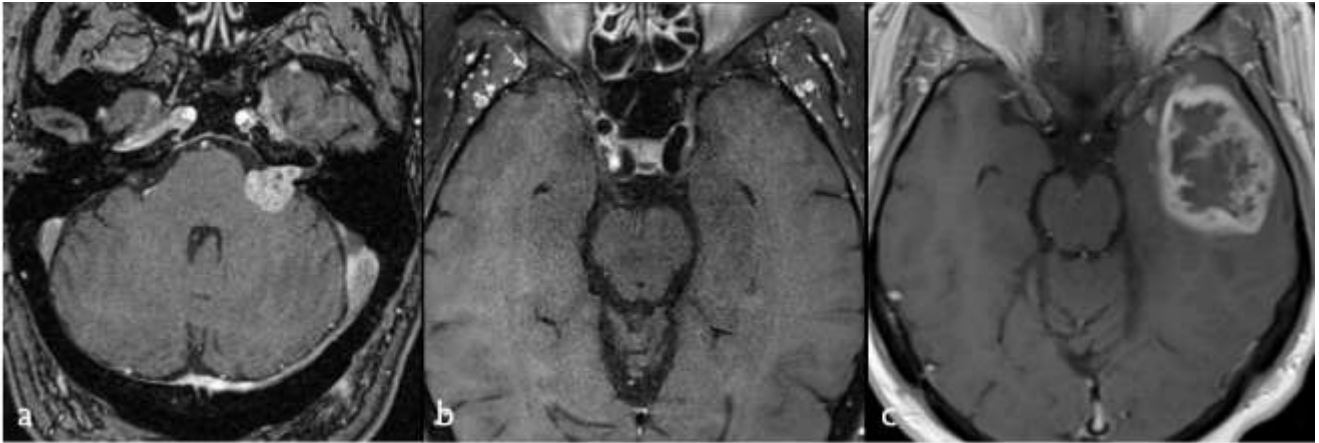


FIG 9: Glioblastoma post-SRS. Axial post-contrast, pre-treatment images reveal a left VS (a). Post SRS left temporal lobe at two-years (b) is without any lesions. Patient subsequently presented with seizures three years post-SRS with a new left temporal intra-axial mass on imaging (c) which was subsequently resected and diagnosed as a glioblastoma.

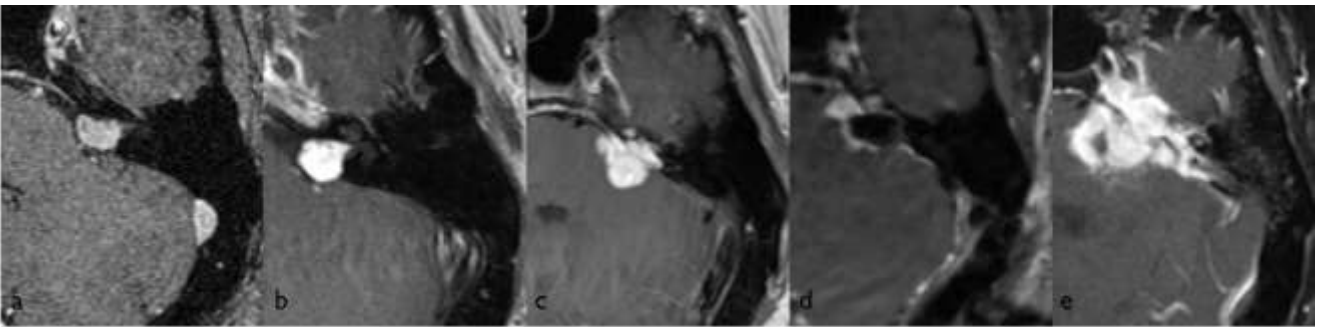


FIG 10: Malignant transformation of VS post-SRS. Pre-SRS (a) contrast-enhanced image shows a left-sided VS. Post-SRS image after 5 years (b) shows mild overall increase in tumor size. However, the tumor showed increased growth at 7 years post-SRS (c). A sub-total resection was performed (d) and pathology revealed a malignant peripheral nerve sheath tumor. Follow-up imaging after 4 months (e) shows considerable recurrent tumor burden with involvement of adjacent structures.

Table 1: Treatment outcomes in VS post-SRS.

Entity	Criteria	Reported incidence	New symptoms clinical	Approximate timeline
Tumor control	Lesion regression or stability	>90%	No	NA
Pseudoprogression	Transient increase in tumor volume over baseline	5-74%	No	5-18 months
Delayed pseudoprogression	Transient increase in tumor volume over baseline	6-17%	No	36-48 months
Tumor growth	Progressive increase in tumor size/ volume over three consecutive scans, or 40% over baseline by some authors	<10%	Yes	Generally, not considered till 3 yrs post SRS unless new symptoms

Table 2: Post-SRS complications in VS patients.

Post SRS Complication/ adverse effects	Reported incidence	Risk/ prognostic factors
Vertigo and disequilibrium	1-2%	Marginal dose < 13Gy; larger tumors; female gender associated with worse outcomes
Facial nerve dysfunction	<1%	Younger patients, smaller tumors <1.5 cm ³ and radiation dose< 13 Gy associated with better outcomes
Trigeminal nerve dysfunction	3% at 5 yrs	Total dose > 13 Gy; Brainstem dose > 10 Gy; larger tumor volume associated with worse outcomes
Worsening hearing loss	21-59% at 5 yrs	Cochlear dose> 4 Gy; Marginal dose > 13 Gy associated with worse outcomes
Hydrocephalus	2-3%	Age > 60; female gender; larger tumors associated with worse outcomes
Malignant transformation	<0.04% at 15 years	Underlying Neurofibromatosis associated with increased incidence

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SUPPLEMENTAL FILES

Suppl fig 1: Post-contrast images obtained at the level of tumor (a-c), and along the superior pole (d-f) at baseline (a, d), at one year (b, e) and five years (c, f). Intratumoral cyst along the superior pole of tumor enlarged post-SRS (e), but subsequently regressed (f), along with regression of VS (c).

