

# Transient Tumor Volume Increase in Vestibular Schwannomas after Radiotherapy

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## Abstract

**Background:** Transient tumor progression is difficult to diagnose and is challenging for the physician.

**Objectives:** To report and review the transient tumor progression rate and induced toxicities in patients treated for vestibular schwannomas (VS).

**Materials and Methods:** From January 2005 to February 2010, 43 patients with VS were consecutively treated at our institution. Twenty patients (46.5%) were treated with fractionated stereotactic radiation therapy (FSRT) using a LINAC or a CyberKnife technique with doses varying between 18 and 50.4 Gy. Radiosurgery (SRS) on a conventional LINAC and on a CyberKnife were performed in 13 patients (30%) (median dose of 12 Gy). Tumor volume increase was calculated from the first tumor volume increase until tumor stability or regression. A Fisher's exact test and Mann-Whitney U test were used for statistical analysis.

**Results:** Transient tumor volume increase occurred in 10 patients (25%) with a median time to tumor enlargement of 5.5 months (1-25 months). Prior surgical resection was significantly associated with transient tumor volume increase (Fisher exact,  $p=0.02$ ). Increased rates of facial and trigeminal neuropathies were associated with transient tumor volume increase ( $p=0.04$  and  $p=0.08$ , respectively). The pseudoprogression rate and the cranial nerve toxicity were not associated with any dosimetric factor.

**Conclusions:** Transient tumor volume increase is frequent (25%) after radiotherapy and significantly associated with previous resection possibly due to the surgical microvascular insult. Cranial nerve toxicities are significantly correlated with, and possibly caused by, transient tumor progression.

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**Categories:** Radiation Oncology, Neurosurgery

**Keywords:** cyberknife, vestibular schwannomas, surgical resection, linac, transient tumor progression

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## Introduction

Vestibular schwannomas (VS) are benign intracranial tumors, which represent 8% of adult intracranial tumors. With a growth rate approaching 2 mm per year [1], tumor progression can lead to progressive hearing loss, tinnitus and vestibular ataxia.

With the exception of large tumors with acute mass effect, management options can lead to controversy. Surgical resection is often proposed to medically fit patients [1] for whom it has a low mortality rate (0.3-0.6%) [2, 3], a high rate of complete tumor removal and a low probability of recurrence [4-7]. Hearing preservation is achieved in 32-50% of cases, while permanent facial neuropathy and postoperative CSF leak occur in 14-29% and 6-11%, respectively [2, 3, 8, 9].

Conservative management with serial MRIs is valid option in older patients with a short life expectancy, slow growing, small to medium-sized tumors, and a low symptomatic burden. Whether or not delayed treatment results in worse ultimate cranial nerve function is debatable. In observed patients, tumor growth will lead to further permanent hearing loss [10] in 29-54 % of patients. Sixteen to twenty-six percent of observed patients will eventually require tumor-directed treatment [2, 11-15].

New studies with Bevacizumab reported promising results in patients with type 2 Neurofibromatosis and evidence of progressive VSs that were considered poor candidates to surgery and radiation therapy [16].

Stereotactic radiosurgery (SRS) is a common alternative to surgical resection. It can be delivered using an isocentric linear accelerator (LINAC), a GammaKnife or a CyberKnife robotic radiosurgery device (CK). Patients with small (<2.5 cm) tumors without significant brainstem compression are eligible for stereotactic radiosurgery (12-13 Gy).

Fractionated stereotactic radiotherapy (FSRT) is a safe alternative for selected patients ill-suited to radiosurgery because of tumor size or mild brainstem compression. Controversy exists as to the relationship of fractionation and hearing preservation - most departments where FSRT is available will recommend fractionation to patients with serviceable hearing. Dose schedules vary considerably - 18-54 Gy in three to 30 fractions. Independent of the selected schedule, local control is expected in 90-98% [17-21]. The main advantage of CK over other radiation techniques is that there is no technical compromise when delivering a fractionated course of radiation.

Transient tumor progression following radiation is commonly reported, although the underlying physiopathology is poorly acknowledged. Such transient progression, which can last up to two years, has been well-described after single fraction SRS. There is limited data concerning transient progression following FSRT.

The objective of our study is first to report our transient tumor progression rate as well as the contributing factors in patients treated with stereotactic radiotherapy. Second, we will review the correlation between transient tumor progression and the adverse reactions observed after radiation.

## Materials And Methods

### Characteristics of the patients

From January 2005 to February 2010, 43 patients with VS were consecutively treated with FSRT or SRS at our institution with a minimum follow up of two years. Radiation was used as primary treatment in 23 patients (53.5%), as salvage treatment following surgery in nine patients (21%)

and at progression following observation in 11 patients (25.5%). Five patients with neurofibromatosis type 2 were included in our study. Median age at diagnosis was 56 years. Prior to RT, 16 patients (37.2%) had serviceable hearing - Gardner-Robertson Grade 1-2. Patient and tumor characteristics are detailed in Table 1.

Characteristics	Patients (%)
Neurofibromatosis type 2	5 (12%)
Tumor localisation	
Right	24 (56%)
Left	16 (37%)
Cranial nerve neuropathy at diagnosis	
CN V	8 (19%)
CN VII	5 (12%)
CN VIII	42 (98%)
CN IX, X and XII	8 (19%)
Tumor size	
< 2cm	28 (65%)
2-4 cm	11 (26%)
> 4cm	2 (5%)
Radiation therapy fractionation	
12-30 fraction FSRT	18 (42%)
3 fraction FSRT	10 (23%)
SRS	15 (35%)

**TABLE 1: Patients and treatments characteristics**

Surgical resection prior to radiotherapy had been performed in 9 patients (20.9%) for a total of 12 surgeries (3 patients had 2 surgeries prior to RT) of whom 3 had gross total resection and 9 had subtotal resection.

Tumor size was measured according to the cerebellopontine angle maximum method (CPA). The tumor including the extracanalicular component was measured in the maximum anteroposterior and medial-lateral diameters on axial MRI. . The majority of patients (28 patients, 65%) had maximum tumor diameter  $\leq$  20 mm, 11 (25.5%) patients had tumors 20-40 mm and 2 (4.6%) had tumors > 40 mm.

At diagnosis, 8 (18.6%) and 5 (11.6%) patients had a trigeminal or facial neuropathy, respectively. Toxicity was assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3). Facial nerve palsy was graded according to the House-Brackmann score.

## Radiotherapy techniques

All patients had a contrast-enhanced computed tomography (CT) and 3D Gradient Echo Ultrafast MRI with a slice thickness of 1 mm for treatment planning. Thin slice, contrast CT images in the treatment position were co-registered to the MRI. Later in the series, a True Fast Imaging with Steady state Precession (FISP, CISS or FIESTA) sequence was often co-registered to the CT and T1 contrast images.

Twenty patients (46.5%) were treated with isocentric LINAC-based FSRT using a micro multi-leaf delivery system (Brainlab, Feldkirchen, Germany). The prescription dose was 45-50.4 Gy in 25-28 fractions for 9 patients and 36 Gy in 12 fractions for 9 patients at the isodose line covering 98-100% of the PTV. The fractionation regimen of 36 Gy in 12 fractions was used in 2005 and 2006 in our institution as an equivalent biological dose [17] to 45-50 Gy in 25 fractions using an  $\alpha/\beta$  of 3. It was mainly used in older patients and in those who had a transportation limitation.

Radiosurgery using conical collimation on a conventional LINAC (Philips/Elekta) was performed in 7 patients (16.3%) using an invasive stereotactic localization frame and in 2 patients using a thermoplastic mask. The median dose delivered was 12 Gy (range 12-14.5 Gy) prescribed to the covering isodose surface and delivered through 3-5 noncoplanar arcs.

FSRT using a Cyberknife technique was performed in ten patients at a dose of 18 Gy in 3 fractions. Six patients received SRS (12-12.5 Gy) with the Cyberknife. The ultra-short course FSRT (associated with the misnomer "staged radiosurgery") was mainly used in patients with serviceable hearing and/or larger tumors in contact with the brainstem.

For each treatment approach, the dose, fractionation, prescription isodose line, maximal dose for the PTV, conformity index, homogeneity index, PTV and GTV volume were reported.

## Post-treatment clinical assessment

Most of the patients were seen 6 weeks after their treatment and thereafter at 3 to 6 months interval for the first 2 years and then annually. With the approval of the local ethics review board, all patients were contacted according to a pre-defined telephone protocol. Serial MRIs were requested every 6 months for the first 2 years then once a year or in accordance to clinical findings. Local control was measured from the end of radiation. As described by Flickinger [22], we defined tumor volume increase as tumor growth of 1 mm in any two directions or 2 mm in one direction. Tumor enlargement due to treatment failure usually occurs several months after radiation and tends to persist for a greater period than two years whereas transient tumor volume increase occurs in a relatively acute setting and stabilizes within two years. Therefore, local control was calculated using the last follow up MRI and transient tumor volume increase was calculated from the first tumor volume increase until stability or regression of the tumor. Patients who had systematic tumor volume increase without stability or regression were considered to have treatment failure. Tumor stability was defined as no change in tumor size on serial MRIs.

## Statistical analysis

The Kaplan Meier method was used to estimate local control. A Fisher's exact test was

performed to validate statistical correlation and Mann-Whitney U test was performed to compare the different treatment technique. All tests were two-tailed. SPSS 17.0 was used (IBM, Armonk, New York).

Results

Transient tumor volume increase

In order to estimate the transient tumor volume increase rate, we excluded the three out of the 43 patients who did not have a control MRI after radiation. Transient tumor volume increase occurred in 10 patients (25%) with a median time to tumor enlargement of 5.5 months (one-25 months). Prior surgical resection was significantly associated with transient tumor volume increase (Fisher exact,  $p=0.02$ ). Indeed, among the 10 patients with transient tumor volume increase, five patients had prior surgery. The median and mean time-length of transient tumor volume increase were 14 (5-45 months) and 17 months (5-29 months) respectively. Two patients had further surgery after radiotherapy because of increased symptoms or significant brainstem compression. The pathological findings were consistent with residual vestibular schwannoma for both patients without evidence of tumor necrosis.

Prescription dose, GTV volume, PTV volume, maximum dose to PTV, BED, gender, age at treatment and the presence of neurofibromatosis type 2 did not significantly influence the rate of pseudoprogression by Mann-Whitney analysis (Table 2).

Factors evaluated	Transient tumor progression
Prescription dose	P=0.35
GTV volume	P=0.55
Maximum dose to PTV	P=0.24
BED	P=0.71
Age at treatment	P=0.59
NF 2	P=0.96
Gender	P=0.7
Previous surgery	P=0.01
Facial nerve toxicity	P=0.04
Trigeminal nerve toxicity	P=0.08

TABLE 2: Factors associated with transient tumor volume increase

Cranial nerve toxicities

Among the 16 (37.2%) patients who had a serviceable hearing prior to RT, seven patients (47%) preserved a serviceable hearing and nine patients (53%) presented with hearing loss (Gardner-Robertson grade 3-5) at a mean clinical follow-up of 32 months.

Transient trigeminal neuropathy grade 1-2 according to the CTCAE was observed in four

patients (9%) at two years. Patients with prior trigeminal neuropathy did not experience a worsening of their symptoms after RT. No grade 3-4 trigeminal neuropathy was observed.

Among our cohort of patients, three (7%) developed transient facial neuropathy (grade 2-3) after treatment according to the House-Brackmann score. No grade 4 facial neuropathy was reported. All the patients with radiation-induced cranial nerve toxicities had transient neuropathy, and therefore no medical treatment was needed.

Transient tumor volume increase was statistically associated with an increased rate of facial neuropathy ( $p=0.04$ ). There was a trend for increased trigeminal neuropathy with transient tumor volume increase ( $p=0.08$ ) but no association was found with serviceable hearing loss. The prescription dose, homogeneity index, conformity index, isodose line and maximum dose received by the PTV were not correlated with any cranial nerve toxicity.

## Discussion

Discriminating transient tumor volume increase from local failure is difficult but important if one is to avoid unnecessary surgery. In a large series of 452 patients treated over a 10-year period, 13 patients (3%) underwent surgery after radiosurgery of whom 10 patients (77%) had postoperative House Brackmann grade III to VI facial neuropathy [23]. In our study, two patients (4.7%) had further surgery following radiotherapy.

Transient increase in tumor volume occurred in 10 patients (25%) of whom five were treated with FSRT (18%) and five with SRS (33%). Previous studies reported transient tumor volume increase rates varying between 5-74% among patients treated with SRS [24-31] and a 48% rate among patients treated with FSRT [32]. A recent study showed that transient tumor progression after FRST can occur up to three years and is more frequent in larger tumors ( $> 3$  cm) [33]. Some studies found a correlation between tumor enlargement and initial tumor volume after SRS [28], others did not [26,29,31]. In our study, GTV volumes were not associated with transient tumor volume increase ( $p=0.5$ ) after SRS or FSRT.

Interestingly, women might have a higher rate of transient tumor volume increase [28]. Seven female patients (32%) and four male patients (27%) had transient tumor volume increase ( $p=0.7$  for the correlation of gender and transient tumor increase).

On a Mann Whitney analysis, the prescribed dose, the biological effective dose [17], neurofibromatosis type 2, and age at treatment were not correlated to transient tumor volume increase. The lack of correlation may be due to the size of our cohort and the heterogeneity of treatments.

In our series, prior surgical resection was significantly associated with transient tumor progression ( $p=0.01$ ). This is a new finding. Transient progression may be due to vascular injury. In autopsies of patients dying within weeks of radiation, peri-vascular edema is seen along with thickening of arterial walls. These arterial walls are rich in fibrin, and platelet-fibrin thrombi may be found [34]. These pathologic changes might be exacerbated by previous surgical insult to capillaries and their endothelium.

Another hypothesis as to the pathogenesis of transient post-radiation progression is that radiation injury to tumor cells leads to necrosis and the subsequent release of thrombosis promoting cytokines, cytokines that may also lead to blood-brain barrier disruption. With increased resistance to intravascular outflow, tumors may become congested with blood and increased in size [35]. Indeed, surgical resection of tumors that had tumor volume increase after SRS showed hyalinised thrombosis, thickening of the vascular wall, vascular obstruction,

and granulomatous changes [24, 36, 37]. Patients that had initial surgery and needed further treatment had either incomplete tumor resection or tumor recurrence. Such "aggressive tumors" with higher cell turnover may suffer greater necrosis and inflammation following radiation.

In our cohort, the median time to transient tumor volume increase after SRS and FSRT was 5.5 months with subsequent tumor shrinkage occurring at a median of 14 months (range: 5-45 months). Similar results have been reported in the literature; the median time to tumor enlargement after SRS varying between six and 13 months [24, 26, 29, 31, 38] with a peak at four to six months [24, 31, 39, 40] followed by tumor shrinkage occurring within two to three years [24, 28, 29]. Therefore, it is reasonable to delay surgery for two years or more [23] in clinically stable and asymptomatic patients.

Little is known about transient tumor volume increase and cranial nerve toxicities. The hearing preservation rate was 47% at 2 years among patients treated with FSRT and SRS. Hearing preservation rates ranged between 53 and 94% [19, 41-44] and between 44 and 96% [43, 45-50] in patients treated with FSRT and SRS, respectively. Although many factors have been analyzed, no statistical association with hearing loss was found. Some studies have associated hearing loss and transient tumor progression [33], other studies did not report a correlation [31]. Predictors of hearing loss after SRS were significant hearing loss before SRS, tumor recurrence and the prescription isodose line, according to a recent study by Wowra et al. [51].

In our study, cranial nerve toxicities rates were low and transient with no permanent facial or trigeminal nerve toxicity. A statistically significant correlation and a trend towards association were found between transient tumor volume increase and increased facial neuropathy ( $p=0.04$ ) and trigeminal neuropathy, respectively ( $p=0.08$ ). Nagano et al. [31] reported a strong trigeminal and facial nerve dysfunction with transient tumor expansion ( $p=0.018$  and  $p=0.035$ , respectively). On the other hand, Hayhurst et al. [52] did not find an association between tumor pseudoprogression and cranial nerve toxicities. It would seem logical that transient tumor volume increase can cause local compression leading to temporary or permanent cranial neuropathy. Further larger studies are needed to confirm the correlation between transient tumor volume increase and cranial nerve toxicity.

## Conclusions

Transient tumor volume increase is frequent after both SRS and FSRT in VS (25%). The median time to transient tumor progression was 5.5 months. Transient tumor volume increase was significantly correlated with previous surgery and an increased rate of facial and trigeminal nerve toxicity. The main challenge to the treating physician is to discriminate tumor progression from transient tumor volume increase after radiotherapy in order to avoid unnecessary brain surgery. Conservative management with serial MRIs is recommended for clinically stable patients.

## Additional Information

### Disclosures

**Human subjects:** Consent was obtained by all participants in this study. The Ethics Committee of the Centre Hospitalier de l'Université de Montréal issued approval # 10.053. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the



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**Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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