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Vestibular schwannoma

Long-term follow-up reveals low toxicity of radiosurgery for vestibular schwannoma☆

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Abstract

***Aim*: The long-term effects of radiosurgery of vestibular schwannomas were investigated in a group of consecutively treated patients.**

***Methods and materials*: Between 1995 and 2001, 26 patients (median age: 67, range: 30—82) with a vestibular schwannoma were treated by Linac-based stereotactic radiosurgery (SRS). The median follow-up was 49 months (16—85 months). Only progressive tumours were treated. The median size of tumours was 18 mm (range 9—30 mm). Before SRS, 11 patients had a useful hearing (Gardner—Robertson classes 1 and 2). Single doses of 10—14 Gy were prescribed at the 80% isodose at the tumour margin. The follow-up consisted of regular imaging with MRI the first 3—6 months after the intervention, followed by additional yearly MRIs, a hearing test and a neurological examination.**

***Result*: The 5-year-probability of tumour control (defined as stabilization or decrease in size) was 95%. Five-year-probability of preservation of hearing and facial nerve function was 96% and 100%, respectively. Hearing was preserved in 10 out of 11 patients who had a normal or useful hearing at the time of treatment. Mild and transient trigeminal toxicity occurred in 2 (8%) patients. It appeared to be significantly correlated to the dose used ($p = 0.044$). However, only a tendency to significance could be demonstrated in the relationship between the two factors when using the Cox analysis (hazard ratio = 1.7; 95% CI: 0.7—3.9; $p = 0.23$).**

***Conclusions*: With the doses used, our study demonstrates that SRS provides an equivalent tumour control rate when compared to surgery, as well as on a long-term basis, an excellent preservation of the facial and the acoustic nerves. Although no permanent trigeminal toxicity was observed, our data confirm that doses below 14 Gy can avoid transient dysesthesias.**

Keywords: Radiosurgery; Vestibular schwannomas; Cranial nerve toxicity

Vestibular schwannomas (VS) have an incidence of ±1/100.000 and account for 6—10% of primary intracranial tumours [6]. They arise from the Schwann cells lining the vestibular branch of the VIIIth cranial nerve. Although these tumours are histologically benign, their behaviour is often unpredictable. Some do not grow or even involute [17,30]. However, some others may locally erode the auditory canal and compress adjacent structures, such as the auditory portion of the VIIIth nerve and the facial nerve. Hearing loss can occur even with tiny tumoral volumes, which can now be diagnosed earlier with special sequences of MRI. These tumours produce hearing loss, tinnitus and vestibular dysfunction and symptoms worsen as the tumour grows.

Two forms of VS can be distinguished. The sporadic form, which makes up for 95% of the cases, is usually unilateral and mainly occurs at the age of 60. The other 5% are associated with type 2 neurofibromatosis (NF2). They are typically bilateral and observed in younger patients, around the age of 30 years.

In the past, surgery was the recommended treatment for patients with VS, because it produces a high rate of local control, up to 90—95% according to published series [26,29,34]. However, even with the more recent technical advances, surgery is not always devoid of side-effects, which include facial palsy and numbness, complete hearing

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loss, dizziness, ataxia, brainstem compression and leak of cerebro-spinal fluid [10,15].

Stereotactic radiosurgery (SRS) [31] and fractionated stereotactic radiotherapy (fSRT) [4,9,24,25] of VS have been extensively studied and have shown to reduce or arrest tumour growth. There was some scepticism in the early 1990s about the real efficacy of these techniques (because of the variable evolution of the lesion). Moreover, this question is still discussed [30]. However, a study comparing fSRT and simple observation of the patients clearly demonstrated that radiotherapy induces a significant tumour control, and markedly decreases the need for salvage therapy, without worsening hearing [28]. Local control rates similar to those of surgery were found, in addition to a lower incidence of complications [13,33].

Early studies used a relatively high dose of 18–20 Gy [22]. However, a later large study showed that low dose treatment (12–13 Gy) effectively controls tumour growth while inducing less side-effects in terms of hearing loss and function of the trigeminal and facial nerves [7]. The reported median follow-up in this study was 24 months.

Based upon the data available in 1995, we started to treat VS with Linac-based SRS. Treatment indication was a proven tumour progression, as assessed by imaging and/or progressive worsening of the symptoms. We here report the results both on effectiveness and tolerance.

Patients and methods

General

Between 1995 and 2001, 26 patients (16 women and 10 men) received treatment for a VS. Indications for treatment were significant worsening of symptoms or tumour progression. All patients had a well-circumscribed tumour in the cerebello-pontine angle with imaging characteristics and clinical criteria of a schwannoma. The median age of the patients was 67 years (range: 30–82 yrs). Two had a neurofibromatosis type 2 (NF2), one of them had a bilateral hearing loss due to a bilateral VS. Two patients had undergone surgery previously. They underwent SRS for progressive residual tumours 11 and 30 months after subtotal resection. One patient had a NF1 and, in addition a neurinoma of the trigeminal nerve. One patient had an essential bilateral trigeminal neuralgia treated by thermocoagulation of both Gasserian ganglia. The neuralgia was probably unrelated to the VS because the latter was unilateral and no direct relation between the VS and the trigeminal nerve was seen on imaging.

Tumour characteristics

Tumour size was evaluated according to the largest diameter in any axis in the ponto-cerebellar angle and also according to the relation of the tumour to the brainstem and the cerebellum (classification of Koos). Two patients had a stage 1 (intracanalicular) lesion. The majority of patients had stage 2 (lesion in the angle, but without reaching the brainstem; $n = 18$) or 3 (lesion in the angle, reaching and possibly deforming the brainstem, but without a displacement of the fourth ventricle; $n = 5$) tumours. The median diameter of the lesions was 18 mm (range: 9–30 mm) (Table 1, Fig. 1).

Table 1
Characteristics of the study population

Variable	*n*	Mean ± SD (frequency in %)	Median	Minimum–maximum
Age at the time of SRS (years)	26	63 ± 13	67	30–82
Gender				
Men	26	10 (38%)		
Women		16 (62%)		
Tumour size (mm)	26	18 ± 5	18	9–30
Tumour				
Intracanalicular	26	2 (8%)		
1–10 mm		1 (4%)		
11–20 mm		18 (69%)		
21–30 mm		5 (19%)		
Hearing level at baseline (Gardner–Robertson scale)	26			
Class 1		4 (15%)		
Class 2		7 (27%)		
Class 3		5 (19%)		
Class 4		4 (16%)		
Class 5		6 (23%)		
Previous surgery	26	2 (8%)		
Treatment indication				
Increase in size of the schwannoma	26	10 (38%)		
Re-increase in size after surgery	26	2 (8%)		
Symptoms	26	16 (62%)		
Associated pathologies				
None	26	20 (77%)		
Precocious genetic deafness	26	1 (4%)		
Trigeminal neurinoma	26	2 (8%)		
Essential trigeminal neuropathy or zona	26	4 (15%)		
Dose (Gy) at the 80% isodose	26	12 ± 1	12	10–14
Neurofibromatosis	26	2 (8%)		
Duration of the symptoms (years)	22	5.4 ± 6.1	2.5	0–20

Radiosurgery

In all patients, the Brown–Robert–Wells° stereotactic coordinate headframe from Radionics was used. Stereotactic CT scans and MRIs were performed in order to define the shape of the schwannoma, to locate critical local structures and to obtain target coordinates. Contrast-enhanced CT (5000 model, Picker, Cleveland, OH, USA) was acquired with the headframe attached in the U-shaped fixation system of the couch, using a slice thickness of 1.5 mm. The planning MRI was performed with a Magnetom Symphony 1.5 T (Siemens, Erlangen, Germany). Slice thickness and voxel size were 1.5 mm and 0.97 mm^3, respectively. The planning target volume was defined as the area of contrast enhancement on T1 MRI. The maximal dose to the brainstem was kept below 10 Gy. For dose calculation, the X-knife treatment planning system (Radionics, Burlington, MA, USA) (Fig. 2A) was used. Patients received 10, 11, 12,

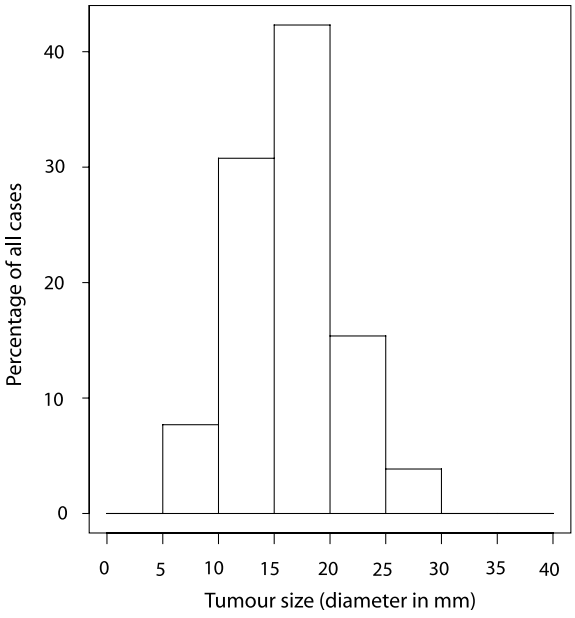

Fig. 1. Histogram of the maximal tumour diameters in our sample.

13 or 14 Gy (2 [in the NF2 patients], 1, 15, 6 and 2 patients, respectively), prescribed to the 80th isodose at the tumour margin (mean dose ± SD: 12 ± 1 Gy). Treatment was performed by using 4 or 5 arcs at a 6 MV Linac (Orion, GCR, Buc, France). Neither jaws nor a multileaf collimator was used. Sizes of circular collimators ranged from 10 to 30 mm. One isocenter was used.

After SRS, all patients were discharged from the hospital within 24 h. Corticosteroids were not routinely prescribed.

Follow-up

All patients were seen at the outpatient clinic by a neurosurgeon and an otorhinolaryngologist. Indications for SRS were discussed in a multidisciplinary team which also included a radiation oncologist.

Before treatment, evaluation included an interview and a neurological examination that focused on cranial nerve function. Facial nerve function was assessed and scored using the House–Brackmann facial nerve grading system which comprises of 6 grades (normal function, slight dysfunction, moderate dysfunction, frank dysfunction, severe dysfunction, complete loss of function). Trigeminal nerve dysfunction was noted as hypoesthesia, dysesthesias, or trigeminal pain. It was rated as grade 0 (absent), 1 (present and amenable to medical treatment) or 2 (resistant to medical treatment). Hearing assessment included tonal and vocal audiometry, classified according to the Gardner–Robertson scale (class 1: less than 30 dB audiometric tonal loss and vocal discrimination >70%; class 2: 30–50 dB tonal loss and vocal discrimination >50%; class 3: >50 dB tonal loss and <50% vocal discrimination; class 4: 80–100 dB tonal loss and <20% vocal discrimination; class 5: non-measurable hearing). Hearing was considered useful if the Gardner–Robertson class was 1 or 2.

The planned follow-up consisted of a MRI at 3, 6 and 12 months after SRS and yearly thereafter. Cranial nerve function was assessed in the same manner as pre-operatively and at the same frequency as the MRIs.

Tumour control was defined radiologically as one of the two following conditions: arrest of growth or decrease in the size, and, clinically, as no need for further treatment (i.e. no increase in symptoms).

Statistical evaluation

Data were expressed as means and standard deviations for continuous data and as counts and frequencies for categorical data. Local control and cranial nerve (V, VII and VIII) function probabilities were calculated using the Kaplan–Meier method. Survival was calculated from the date of SRS until a change in tumour size or an event of toxicity occurred. For comparison between useful and non-useful hearing, the log-rank test was applied. Cox's proportional hazards regression was used to assess the effect of the dose on the risk of development of trigeminal neuropathy. Results were considered significant at the 5% level ($p < 0.05$). All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA) and S-PLUS 6.2 (Insightful Corp., Seattle WA, USA).

Results

Patients were treated by SRS 1–104 months after diagnosis (median value: 11.3 months). From the time of SRS treatment, the median durations of follow-up concerning tumour size, trigeminal, facial and acoustic nerve function were 49 months (range: 16–85 months), 46 months (range: 9–89 months), 46 months (range: 9–74 months) and 45 months (range: 9–73 months), respectively.

Patient characteristics are given in Table 1.

Initial evaluation of cranial nerve function

The function of the trigeminal nerve was normal in 22 patients (85%). Four patients had trigeminal neuropathy (grade 1 [$N = 3$] or grade 2 [$N = 1$]).

Facial nerve function before treatment was as follows: 23 patients (89%) had a normal function (grade 1). The 3 other patients had a grade 2, 3 and 5, respectively. The patients with a grade 2 and 5 function were those who had undergone surgery prior to SRS.

Four patients (15%) had a class 1 hearing according to the Gardner–Robertson scale (normal hearing) and seven patients (27%) had a class 2 hearing (functional hearing) (Table 1). Thus, 11 patients (42%) had a preserved auditory function. The remainder (15 patients) had a function between classes 3 and 5. Six patients had a non-measurable function according to the scale (one of these patients had a small intracanalicular VS).

Tumour control

Twenty-three tumours (88%) decreased in size (median: −4 mm in diameter) and 2 tumours (8%) were stabilized. One tumour (4%) increased in size after 3 months and remained stable thereafter up to 42 months of observation. This patient had received 14 Gy to the margin of the target. No salvage treatment was used because of her age (73 yrs) and because the symptoms were stable.

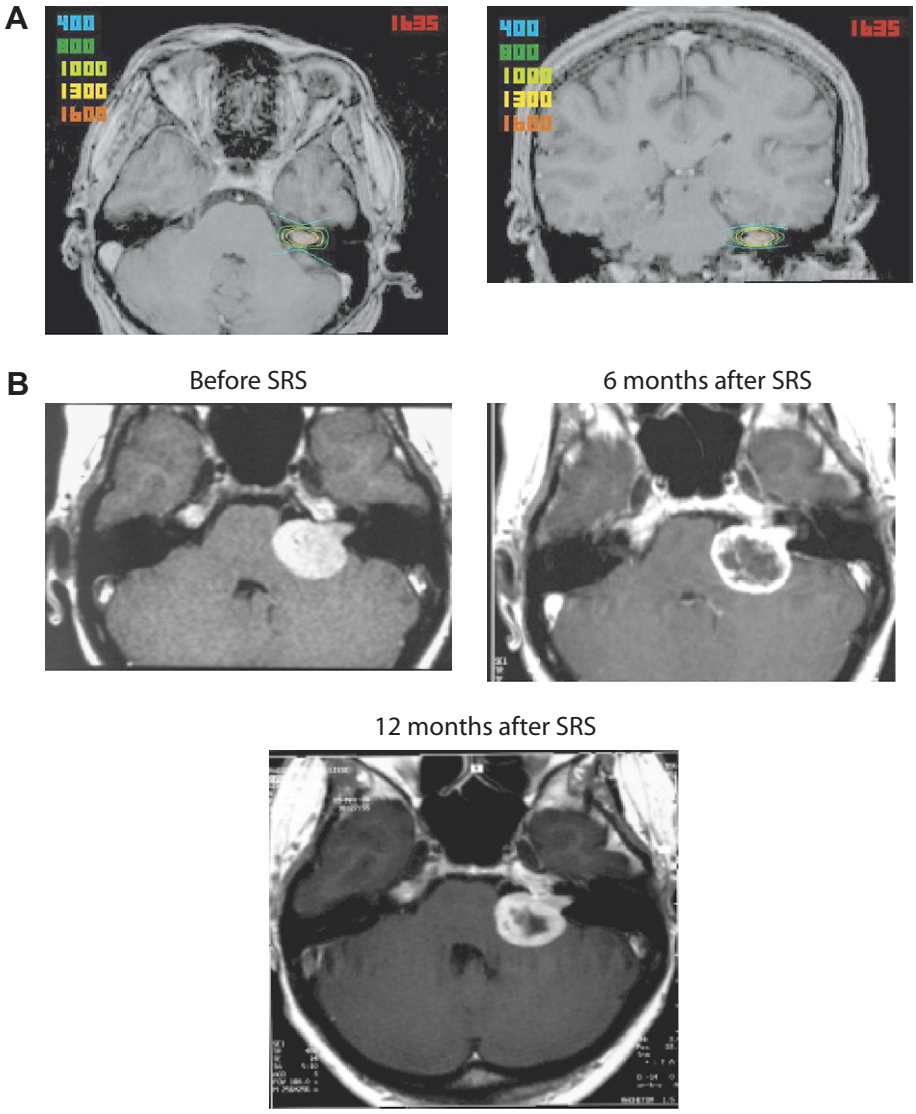

Fig. 2. (A) Isodose lines of a radiosurgery plan. (B) Evolution of the size of the vestibular schwannoma of one patient as a function of time. Note the transient slight increase in size at six months which appears to be due to edema surrounding the central necrosis.

The evolution of each tumour and the general trend are shown in Fig. 3A. There was no significant difference between the size at the time of SRS and at the end of the follow-up ($r = -0.35$, $p = 0.076$). The probability of tumour control was 94.7% at 5 years. According to the morphological classification of Koos, 19 tumours (73%) remained in the same class, six (23%) were staged one class down and one (4%) was staged one class up.

Interestingly, a transient increase in tumour size was observed in several cases, as shown in Figs. 2B and 3A. This increase regressed after 12—20 months (Fig. 3A).

Effect of the treatment on cranial nerve function

In 25 patients (96%), the class of the Gardner—Robertson scale was unchanged. One class 2 patient had a one class increase. Thus, the latter patient had a clinically significant worsening of his auditory function. The probability of preservation of acoustic nerve function was 90% when considering only patients who had a usable hearing before radiosurgery. It was not significantly different from that in patients with not-useful hearing ($p = 0.221$, log-rank test). These results are summarized in Fig. 3B.

Facial nerve function according to the House—Brackmann scale was unchanged in all patients. Thus, the probability of preservation of the facial nerve was 100% at 5 years.

Trigeminal function was unchanged in 92% (24 out of 26 patients) after SRS. The two patients whose function worsened had a normal trigeminal function before treatment and developed paresthesias that could be ameliorated by medical treatment. This worsening was reversible after 6 months and 3 years, respectively.

Influence of the initial tumour size and dose on various parameters

In our population, there was no influence of the initial tumoral size on any parameter investigated (evolution of

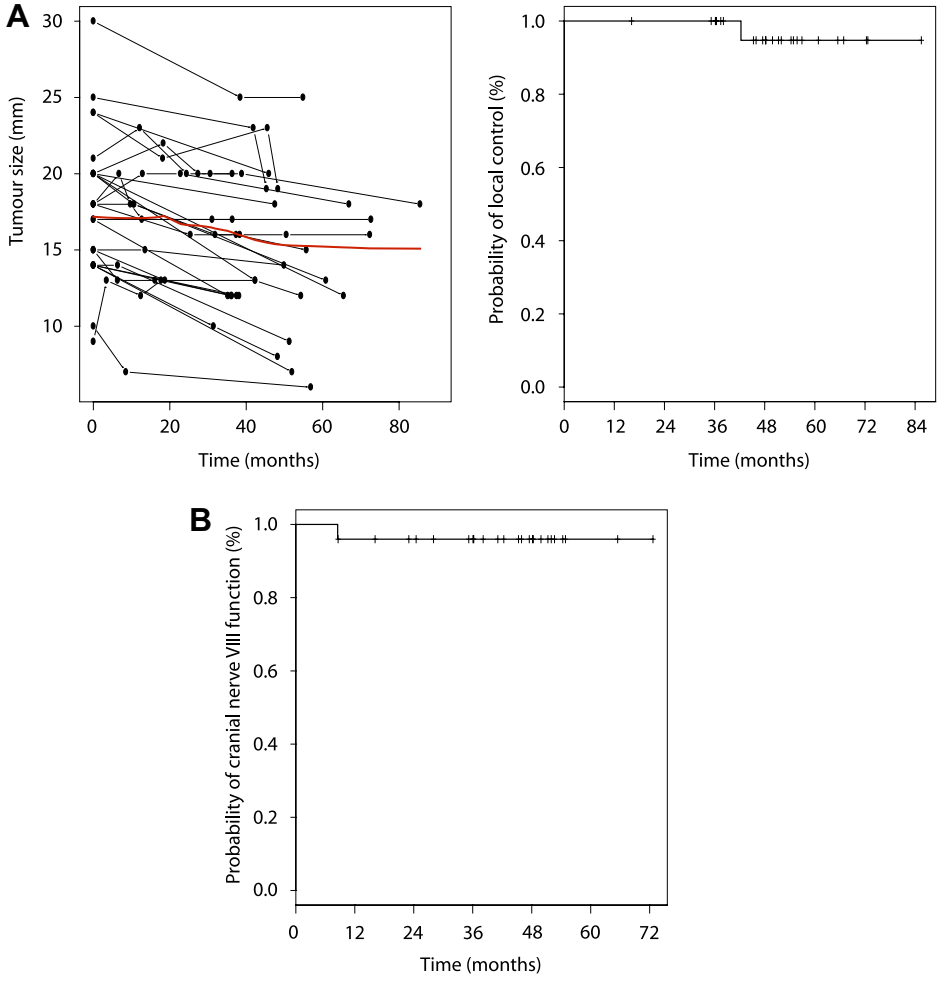

Fig. 3. Clinical results achieved after radiosurgery of vestibular schwannomas. (A) Plot of the size of the individual tumours as a function of time. The red line represents the mean evolution of the sizes. The Kaplan–Meier plot is shown on the right. (B) Kaplan–Meier plot of the preservation of nerve VIII.

the size and of the function of the cranial nerves). There appeared to be a significant correlation between the dose and the risk of transient trigeminal dysesthesia ($p = 0.044$, Kruskal–Wallis test). However, this correlation was weak because there was only a trend in the relationship between the two parameters using the Cox regression (hazard ratio = 1.7; 95% CI: 0.7–3.9; $p = 0.23$). No significant relationship was found between the dose and other parameters.

No secondary tumours have been observed within the irradiated area.

Discussion

In the past decade, stereotactic irradiation has become an important treatment option for VS besides microsurgery. Indeed, several studies have shown that SRS is effective in VS [13,19–21,32], but the follow-up was relatively short in some of them (34 months on the mean) whereas an actuarial follow-up of at least 3 years is considered to be meaningful [16].

The results presented here are consistent with those of previous large studies [1,7,8,11] which demonstrated that low dose SRS has a very interesting efficacy/toxicity ratio as compared to higher doses [16,21]. The median duration of our follow-up ($\sim$ 4 years) is sufficient to exclude the possibility of a later increase in tumour growth (except on the very long term) or worsening of neurological symptoms [16].

It has been suggested that there is a slightly higher rate of cranial nerve toxicity after SRS than after fSRT [4,5]. One possible reason for this is the dose inhomogeneity within the target volume when using SRS [27]. This is also probably dependent on the dose used and on the size of the tumour. However, we found no toxicity to the facial nerve in our study. This may be due to the low dose used. Moreover, the use of an invasive frame allowed us to carefully limit the dose at the anterior edge of the tumour.

Five-year probability of hearing was 96% in our study. However, the small size of our sample does not allow us to compare this result with those of much larger studies. Two recent large gamma knife studies (195 and 317 patients, respectively) with median follow-ups of 36 and 93 months examined the effectiveness and safety of this technique for the treatment of small-to-moderate size VS. The 5-year tumour control rate was $\sim$95%, with little toxicity

(1—2%) to the trigeminal and facial nerves, but a worsening of hearing in 40 and 32% of the patients, respectively [3,11]. Some authors suggest to treat the patients early in order to reduce the risk of toxicity to the VIIIth nerve [18].

We observed a rather high incidence of trigeminal neuropathy as compared to other studies. Again, this may be due to our small sample. This toxicity tended to be correlated to the dose, as already described [14], again emphasizing the need to use doses in the low range ($\leqslant$13 Gy) for SRS. However, the correlation between dose and trigeminal toxicity was weak in our study. On the other hand, this toxicity was transient and may have been due to a reversible edema within the brainstem nuclei of the nerve. With regard to this, the maximum brainstem dose was found to be the most important predictor of facial and trigeminal toxicity in a study using fSRT [2].

A significant number of tumours increased in size over 1—2 years before shrinking again to their original size or even to a smaller size. This has also been observed very recently in a large study in 17% of the cases [12]. These authors propose to subdivide these increases according to their putative nature, i.e. central necrosis (observed in our sample), solid expansion and cyst enlargement or formation. They recommend an observation policy, except in case of developing cysts. Our results are consistent with this proposal (Fig. 1B). Thus, in our sample, only aspects of central necrosis were observed and they were found to spontaneously regress. Interestingly, the development of cysts was apparently more frequent in the previous large study, possibly because of the use of multiple isocenters [12].

In our opinion, the large body of literature on the management of small-to-moderate size VS, as well as our results, allow us to draw the following conclusions (see also [5,23]). For small and paucisymptomatic lesions in elderly patients, an observation policy can be followed. In the case of growing or symptomatic small-to-moderate size ($\leqslant$30 mm) VS, surgery, if feasible, SRS and fSRT give similar tumour control rates of 90—100%. Preservation of useful hearing is quite variable (between 15 and 88%) for surgery. fSRT allows a hearing preservation in a higher percentage of patients (61%, 79% and 94% according to [4,7,19]). These values are $\sim$65% for SRS [18]. However, our results suggest that a high rate of hearing preservation can be obtained with SRS, although the small size of our sample is an obvious limitation. After microsurgery, fSRT and SRS, facial neuropathies are observed in 0—24%, 0—3% and 0—23% of the cases, respectively. The numbers are 17%, 0—13% and 4—27%, respectively, for trigeminal toxicity [4,5]. Taken together, these results suggest that SRS is as effective and less toxic than microsurgery. fSRT may be more protective to cranial nerves and the brainstem than SRS, particularly when the VS is in contact with the brainstem or very close to it. In other cases, SRS can be recommended as a safe and efficient treatment.

In summary, our study confirms in a small sample of patients that, using 12—14 Gy in most patients, SRS both provides excellent tumour control rate at 4 years with a low toxicity on the long term and preserves the facial and the acoustic nerves. Transient trigeminal toxicity may be dependent on the dose and may be more prevalent than in fractionated schedules.

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