Scientific Article

Vestibular Schwannoma: Results of Hypofractionated Stereotactic Radiation Therapy

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Abstract

Purpose: Our purpose was to study the outcomes of hypofractionated stereotactic radiation therapy (HSRT) in terms of hearing and radiologic response for vestibular schwannomas.

Methods and Materials: This was a longitudinal retrospective study at a referral center from 2011 to 2016. All treatments were performed on a Cyberknife device with a dose of 21 Gy (3 × 7 Gy) or 25 Gy (5 × 5 Gy). We assessed tumor response, neurologic outcomes (hearing and facial nerve function), and treatment toxicity.

Results: A total of 82 patients were included. Fifty-three patients were treated with the 3 × 7 Gy scheme and 29 with the 5 × 5 Gy. Sixteen patients (20%) had a previous surgery. The median follow-up was 48 months (range, 12-88 months). We noted 3 recurrences leading to a control rate of 96.3%. In our cohort, predictive factors of vestibular schwannoma growth were a tumor volume >2 mm^3 and a conformal index <1.1 ($P < .0001$). The treatment was well tolerated with only 5 grade III acute toxicities (4 vertigo and 1 headache) and no grade IV or V. As for late toxicity, we noticed 2 cases of mild peripheral facial palsy (House and Brackman grade II) in previously operated patients. There was 46.0% hearing preservation among patients with serviceable hearing after HSRT.

Conclusions: Our results suggest that HSRT using 3 or 5 fractions is a well-tolerated and effective regimen. These findings are in addition to the few previous hypofractionation studies and contribute to the validity of this treatment modality.

Introduction

Vestibular schwannomas (VSs) are benign tumors arising from Schwann cells of the vestibulocochlear nerve, with an incidence of about 20 per million.[1] This benign nerve tumor can remain perfectly asymptomatic or generate more or less important symptoms related to the compression of adjacent structures.[2] Despite their good prognosis, these lesions can cause disorders ranging from a simple vertigo or tinnitus to signs of cerebellar ataxia, facial palsy, or cophosis.

This tumor is easy to diagnose thanks to the advent of magnetic resonance imaging (MRI) and can be managed in different ways.[3] A wait-and-see attitude seems reasonable for nonsymptomatic lesions with low volumes and low potential growth patterns.[4] Without these criteria, active treatment by surgery or radiation therapy should be offered to the patient. The nonsurgical approach was initially performed via a single session layout (stereotactic radiosurgery [SRS]) using GammaKnife.[5]

In the context of this very good benign tumor prognostic, beyond the local control (LC) data, particular attention should be paid to potential toxicity, hearing function preservation, and quality of life. The results of the first retrospective studies of fractionated stereotactic radiation therapy protocols (FSRT)[6-11] are promising and seem to provide the same benefits as SRS in terms of LC. In this radiation oncologist approach, it is thought that fractionation could provide better healthy tissue sparing and thus improve treatment tolerance. After a local multidisciplinary team meeting, we chose not to practice SRS and to give priority to hypofractionnated stereotactic radiation therapy (HSRT) for eligible patients and to routinely treat these lesions in 3 or 5 fractions according to the volume or Koos stage. Radiation therapy was delivered with FSRT only for Koos stage 4 patients.

We therefore carried out a retrospective analysis of the patients treated in our center with HSRT looking at LC and toxicities as primary objectives, considering patient characteristics and dosimetric parameters.

Methods and Materials

Population

This single-center study was conducted retrospectively from data obtained for clinical purposes. The study was approved by the institutional review board and registered under the reference R201-003-051. All patients treated in our center with HSRT protocol, from 2011 to 2016, were analyzed. All treated patients were discussed in multidisciplinary meetings involving at least a surgeon, a radiologist, and a radiation oncologist. The treatment decision was based on tumor growth confirmed on MRI. In most cases, in the absence of a surgical contraindication, the patient affected by Koos stage 2 VS could choose between surgery and radiation therapy. If the patient chose radiation therapy, clear and loyal information was given. The therapeutic modality was systematically validated by the multidisciplinary team. We chose to exclude 2 patients with neurofibromatosis in this study.

Radiation therapy technique

All patients were treated with a CyberKnife device (Accuray, Sunnyvale, CA). Before the planning, contrast-enhanced 3-dimensional T1-weighted MRI with a millimetric slice thickness and high-resolution T2-weighted axial MRI were systematically acquired and fused to the dosimetric computed tomography. Computed tomography was performed as well with a millimetric slice thickness. At first, the clinical target volume (CTV) was defined as an abnormal contrast-enhanced lesion on T1-weighted MRI. Then, this CTV was corrected using the T2 axial fusion to exclude vessels and nerves from the CTV. The planning target volume (PTV) was defined as CTV increased by a margin of 2 mm. In some cases for which the organs at risk (brain stem and cochlea) were in the immediate vicinity of the PTV, or overlapping with the PTV, a margin of 0 mm in the direction of the organs at risk was used to generate the PTV from the CTV. At the discretion of the patient's physician, 3×7 Gy or 5×5 Gy was prescribed on the 80% isodose. The 5-fractions protocol was preferred for large volume lesions with brain stem proximity (Koos stage 3). All treatments were delivered with 1 day off between each fraction. The dosimetry was then carried out using the multiplan software. All dosimetric parameters were subsequently recorded, such as cochlear, vestibular, and trigeminal nerve doses, and with a particular attention given to the conformity index (CI), homogeneity index (HI), and new conformity index (nCI).

$CI = V_{RI}/TV$ where V_{RI} = reference isodose volume and TV = target volume.

$HI = I_{max}/RI$ where I_{max} = maximum isodose in the target and RI = reference isodose. $nCI = (TV \times PIV)/(TV_{PIV})^2$ where PIV = prescription isodose volume.

Follow-up

Patients were initially followed up with an MRI at 6 months, which showed necrosis and swelling. These findings interfered with our study observations and therefore we decided to perform MRIs yearly instead. The therapeutic response was monitored according to the diameter length of the tumor in the cerebellopontine angle. All MRI images were discussed by several senior radiologists during multidisciplinary team meetings and then interpreted by the same senior blinded to the patient's history and clinical characteristics for the study purpose. LC is defined as the absence of progression on 2 MRI scans done 6 months apart. Clinical follow-up was also carried out annually and alternately between the surgical and radiation oncologist teams to assess potential toxicities. Audiograms were performed before and every 12 months after the end of HSRT. Hearing results were reported according to level 1 of the guidelines published by the American Academy of Otolaryngology. Pure-tone average air conduction was computed as the average thresholds at 0.5, 1, 2, and 3 kHz. Audiometric data analysis of pure-tone average was performed according to Gardner Robertson's scale (GR) based on each patient's assessment audiograms. Hearing function was then assessed according to the persistence or loss of serviceable hearing (GR I and II). Cranial nerve toxicities were recorded if there was a new symptom or progression of a pre-existing symptom. Facial nerve dysfunction (FND) that was

treatment-related was defined by an increase in House-Brackman score. Treatment-related trigeminal nerve dysfunction (TND) included masticatory weakness, numbness, pain, and/or paresthesia.

Statistical analysis

A descriptive analysis of the population, VS characteristics, and follow-up, was first carried out based on data collection. Kaplan-Meier method was used to measure the LC. LC rate was defined as no sign of VS growth. For LC or toxicity, these factors were evaluated: tumor volume, Koos stage, prior surgery, nCI, PTV marginal dose and maximum dose, number of fractions (3 or 5), diabetes, gender, initial symptoms (FND, TND, tinnitus, hearing loss as GR), cochlea mean and maximal dose, brain stem mean and maximal dose, TN mean and maximal dose.

To analyze factors that affected LC, a log-rank test was used for categorical variables and a receiver operating characteristic analysis for continuous variables; censoring was considered noninformative for the statistical analysis. The SPSS software version 20 (IBM, Armonk, NY) was used for statistical analysis with a significance threshold of 5%.

Results

Population

A retrospective analysis was carried out on 82 patients (Table 1). The median age was 65 years (24-91). Sixteen (20%) patients had at least 1 previous surgery. All patients were treated unilaterally for tumors presenting a median volume of 1.01 cc (0.16-8.66). At the time of treatment, 41 patients (50%) had a grade 2 and 34 patients (41%) a grade 3 according to the Koos staging system. The initial symptoms were balance disorders and vertigo (61%; 50 of 82), hearing loss (48%; 25 of 52), and tinnitus (46%; 38 of 82). Baseline cranial nerve dysfunctions were observed: TND (5%, 4 of 82) and FND (2%, 2 of 82). All patients were alive at the date of the last follow-up.

Two fractionations were available: 3 fractions (3 × 7 Gy) were performed on 53 patients (65%) and 5 fractions (5 × 5 Gy) on 29 (35%) patients. Three fraction protocol was mainly chosen for grade 2 or less VS (79%, 35 of 53) and a 5 fraction protocol for grade 3 (79.3%, 23 of 29).

Local control

With a median follow-up of 48 months (12-88 months), there were 3 cases of recurrence observed,

Table 1 Baseline patient, tumor, and treatment characteristics

Variable	No. of patients (%)
Sex:	
Male	42 (51)
Female	40 (49)
Side:	
Right	41 (50)
Left	41 (50)
Age:	
Range	24-91
Median	65
Surgery:	
Previous surgery	16 (20)
Primary treatment	66 (80)
Koos stage:	
I	7 (9)
II	41 (50)
III	34 (41)
Max length (mm):	
Range	6-31
Median	17
Gardner-Robertson scale:	Total evaluable = 43 (100)
I	15 (35)
II	13 (30)
III	7 (16)
IV	2 (5)
V	6 (14)
Treatment protocol:	
3 × 7 Gy	53 (65)
5 × 5 Gy	29 (35)

resulting in a crude LC rate of 96.3% and a 5-year LC of 95% (95% confidence interval, 92.1-97.9). They occurred after a follow-up of 15, 29, and 41 months, in Koos stage 3 lesions treated in a primary setting, with a tumor volume of 2.14, 2.68, and 4.13 cm^3 and a dosimetric analysis showing CIs of 1.08, 1.09, and 1.38, respectively, for a median overall CI of 1.27 (1.08-2.29). Considering clinical characteristics like patient gender, diabetes, number of fractions, and Koos stage, the only significant association found with LC was Koos stage 3 ($P = .04$).

The gross tumor volume (GTV) showed a significant area under the curve (r = 0.985; 95% confidence interval, 0.87-1.0). The CI index also showed a significant association with the occurrence of these recurrences (r = 0.93; 95% confidence interval, 0.83-0.98). The best cut-off values were a GTV of 2 cc and an IC value of 1.1. An univariate Kaplan-Meier analysis with a GTV of more than 2 cc ($P = .001$) and a nCI of less than 1.1 ($P < .0001$) showed a significant association with LC.

Throughout the surveillance, more than 50% of patients developed radiologic signs of intratumor radionecrosis within a median posttherapeutic time of 7 months (3-17). This was unrelated to better LC, as 2

recurrences also exhibited signs of necrosis (P = .49). For all 3 cases of recurrence, the salvage treatment was a surgical procedure via translabyrinthine approach. Since then, these 3 patients have shown no signs of recurrence.

Acute toxicities

In terms of tolerance, there were 5 patients (6%) with grade III acute toxicities (appearing immediately after treatment <3 months). Four vestibular worsening syndromes and 1 case of headache were observed, all requiring the use of corticosteroids. The symptoms later improved but required several months of vestibular rehabilitation for vertiginous syndromes.

Late toxicities

There were 2 cases (2.4%, 2 of 82) of treatment-related FND, occurring in a postoperative context, after radiation therapy consisting of a permanent grade II FND. Less significantly, 8 patients (9.7%, 8 of 82) complained of hemifacial spasms, homolateral to the treated lesion, with sporadic manifestations. No correlation was found with dosimetric data.

Throughout the follow-up we reported 3 cases of TND (3.6%, 3 of 82), 2 degradations of previously known TND and 1 new TND. These 3 patients showed nondisabling dysesthesias of the V3 or V2 territory, which was spontaneously resolved for 2 patients and that presented a fluctuating evolution for the third patient. There was a correlation between a brain stem mean dose of more than 5 Gy and the TND, P = .02. No clinical variables (age, gender, diabetes, Koos stage, fractionation) were associated with the TND or FND occurrence.

Hearing function

Out of the 82 patients studied, only 43 patients could be assessed on their hearing due to missing data (Table 2).

Median audiometric follow-up was 24 months (6-81). Out of the 15 patients with GR I, 7 (46.7%) reported equivalent audiometric scores, and out of the 13 patients with GR II, 3 (23%) reported equivalent audiometric scores. Regarding the 28 patients with functional hearing function (GR I and II), 46% (n = 13) maintained a GR audiometric score of I or II. The cochlea dosimetric analysis didn't find a statistical link between dosimetric analyze and audiometric degradation. For these patients, the actuarial hearing preservation rate were 75.6% at 1 year and 64.3% at 2 years with a mean time to hearing degradation of 29.4 months (95% confidence interval, 23.5-35 months).

Signs and symptoms

Excluding hearing loss, symptoms that initially presented before the completion of radiation therapy were vestibular dysfunction and tinnitus. During the long-term follow-up, these signs decreased, with 39% of patients complaining of dizziness (vs 61% initially) and 26.8% with tinnitus complaints (vs 46% initially).

Discussion

SRS is the first radiation therapy technique to have emerged as an alternative to surgery. Initially performed at a dose of 20 Gy in 1 fraction, significant rates of complications were reported, with approximately 15% FND and 15% TND.[5] At the beginning of the 2000s, 2 studies showed the results of reducing the treatment dose to 12 Gy (7.5-14 Gy).[12,13] They showed similar LC rates (>95%) while having a lower rate of TND and FND. These results were confirmed by Hasegawa et al,[14] who analyzed the treatment of 440 patients with VS by radiosurgery. With a significant median follow-up of 12.5 years, the authors showed an excellent control rate of 93% and 92% at 5 and 10 years, respectively. One of the major prognostic criteria found seems to be tumor

Table 2   Hearing function according to GR scale for 40 evaluable patients: Baseline and on follow-up.

GR grade	Initial total number	Protocol	Posttreatment total number	Protocol
I	15	11 (3 fractions)	7	7 (3 fractions)
		4 (5 fractions)		0 (5 fractions)
II	13	7 (3 fractions)	6	1 (3 fractions)
		6 (5 fractions)		5 (5 fractions)
III	7	5 (3 fractions)	18	12 (3 fractions)
		2 (5 fractions)		6 (5 fractions)
IV-V	8	6 (3 fractions)	12	9 (3 fractions)
		2 (5 fractions)		3 (5 fractions)

Abbreviation: GR = Gardner-Robertson.

volume (hazard ratio, 1.122/cm^3; P = .0001). In addition, tolerance to SRS was acceptable, with less than 5% facial palsy and 3 cases of TND (2 required surgical management and 1 required a new SRS).[14] Hearing evaluations were more difficult to assess, especially because dose levels studied have changed over time. The same team analyzed audiometric results from 117 patients with functional hearing (GR I or II) treated with SRS (median marginal dose of 12 Gy).[15] The authors described, with a median follow-up of 38 months, a hearing preservation rate of 55%, 43%, and 34% at 3, 5, and 8 years, respectively, after treatment. The absence of initial hearing impairment and the average dose to the cochlea (<6 Gy) appeared to reduce the risk of homolateral functional hearing loss. However, these results should be highlighted with the persistent risk of hearing loss even if treatment is not provided. Indeed, 2 studies[16,17] compared early SRS and a wait-and-see attitude. These 2 studies[16,17] found that hearing loss was generally similar in both situations, with a similar quality of life. Sughrue et al,[4] who followed 59 patients in a surveillance study, also found that the vast majority of patients reaching 10 years surveillance no longer had functional hearing regardless of the rate of tumor growth. This indicates that even in the absence of treatment, hearing function worsening prematurely is expected on the pathologic side. SRS treatment of these lesions seems more acceptable, because a recent study has shown that there is no risk, compared with the general population, of radiation-induced central nervous system malignancy after SRS treatment for benign diseases.[18]

The aim of FSRT is to improve the tolerance of healthy tissues by fractionation. Litre et al[19] evaluated a fractionated treatment by delivering 50.4 Gy in 28 fractions of 1.8 Gy in 155 patients, with a median follow-up of 60 months. The authors found LC comparable to SRS treatments with an LC of 99.3%, 97.5%, and 95.2% at 3, 5, and 7 years, respectively. Moreover, the treatment seemed to be well tolerated, with 2.5% of grade II FND, the absence of severe TND, and a high hearing preservation rate of 54%.[19] As for SRS, these good results in terms of LC have made it possible to reduce the dose level delivered. Champ et al[20] treated 154 patients at 46.8 Gy in 26 fractions of 1.8 Gy. Results seem to confirm a comparable efficacy, with a 99% and 93% LC rate at 3 and 5 years. There too, the treatment seemed to be very well tolerated, without toxicity of grade III or higher associated with a facial and trigeminal preservation rate of 99% and 98% at 3 and 5 years. The preservation of hearing function is estimated at 66% and 54% at 3 and 5 years.[20]

Several studies have attempted to retrospectively compare the outcomes between SRS and fractionated treatments (FSRT and HSRT).[5-7,10,21,22] Kopp et al[9] attempted to compare 68 patients treated with SRS at 12 Gy (median follow-up, 30.1 months) and 47 patients

treated with FSRT in 30 fractions of 1.8 Gy (median follow-up, 32.1 months). Despite significantly higher treatment volumes in the FSRT group (median PTV, 3.95 cm^3) than in the SRS group (median PTV, 1.02 cm^3) (P < .001), a similar LC rate was found between the 2 groups (97.9% and 98.5%, respectively). In addition, the preservation of functional hearing was similar in both groups, with 85% preservation for SRS versus 79% for FSRT.[8] Although higher than the literature data, the rate of TND remained higher in the SRS group (13%) compared with 0% in the FSRT group. These results are all the more interesting as the 54 Gy dose level is higher than actual standards. The largest multicentric study was conducted by Coombs et al.[10] Four hundred forty-nine patients were treated in 3 German centers, either with SRS (median dose of 13 Gy for a median PTV of 1.2 mL) or FSRT (median dose of 57.6 Gy in 32 fractions of 1.8 Gy for a median PTV of 2.4 mL). With a substantial median follow-up of 67 months, there was no significant difference in terms of LC, hearing preservation, FND, or TND. These results have to be balanced by the tumor volumes doubled in the FSRT group, an inappropriate dose level in the FSRT group, and the exclusion of SRS treatment higher than 13 Gy. One of the authors' conclusions is that FSRT offers a larger therapeutic window given the radiobiological effect of fractionation. The idea of HSRT is to benefit from this advantage while offering a treatment with low fractionation. This attitude seems encouraging when analyzing the 15 studies, evaluating a 3- or 5-fraction treatment (Tables 3 and 4).[23] In a recent review of the literature,[36] there does not seem to be any significant difference between SRS, FSRT, and HSRT. However, it may be necessary to pay attention to the dose level to obtain satisfactory LC, and above all, to preserve the function of the neighboring organs.

A recent study analyzed all data from studies carried out with SRS and HSRT (1, 3, or 5 fractions).[37] First, there is a clear difference between SRS and HSRT in the number of studies published (80 vs 15, respectively). This difference in favor of SRS shows that SRS remains the reference treatment for small lesions. While considering certain radiobiological unknowns, it would appear that both treatments are equally effective, although there seems to be a dose effect, with a probability of tumor control greater than 91% at 3 and 5 years with 1 fraction of 12 Gy, 3 fractions of 6 Gy, and 5 fractions of 5 Gy.

Our retrospective HSRT series of 82 patients, mainly treated with 3 fractions of 7 Gy, shows an equivalent efficacy with a crude LC rate of 96.3% at the end of the follow-up. Our results are consistent with the previously published HSRT studies in 3 to 5 fractions (Tables 3 and 4). LC varies among studies between 83% and 100%, with a median tumor volume varying between 0.81 and 4.74 cm^3. As described in the literature,[14,31] tumor volume significantly influences the risk of recurrence, especially for tumors larger than 2 cm^3. In our study, the CI

Table 3   Previous studies evaluating HSRT in 5 sessions

Study (first author)	No. of patients	Total dose	No. of fractions	Median tumor volume cm^3 (min-max)	Median follow-up (months)	Local control
Song[24]	31	25	5	1.1 (0.1-8.74)	NA	100.00%
Williams[25]	131	25	5	1.5 (0.05-8.8)	23	100.00%
Meijer[7]	80	20 (n = 12) 25 (n = 68)	5	2.5	35	94%/5 y
Anderson[22]	37	20	5	0.89	43.1	90.5%/5 y
Wong[26]	31	25	5	3.12	40.6	97.00%
Kapoor[27]	376	25 (n = 340) 30 (n = 36)	5 10	0.89 (0.01-26.30)	56	97.00%
Karam[28]	37	25 (n = 35) 21 (n = 2)	5 3	1.03 (0.14-7.60)	51	91%/3 y
Patel[29]	383	25	5	NA	72	97.70%
Our study	29	25	5	1.47 (0.56-4.13)	48	96.30%

Abbreviation: HSRT = hypofractionated stereotactic radiation therapy.

Table 4   Previous studies evaluating HSRT in 3 sessions

Study	No. of patients	Total dose	No. of fractions	Median tumor volume cm^3 (min-max)	Median follow-up (months)	Local control
Chang[30]	61	21 (n = 14) 18 (n = 47)	3	NA	48	98.00%
Hansasuta[31]	383	18	3	1.1 (0.02-19.8)	43.2	99%/3 y 96%/5 y
Tsai[32]	117	18	3	4.74 (0.02-19.87)	61.1	99.10%
Hayden Gephart[33]	94	18	3	NA	42	100%/2 y 96%/4 y
Vivas[34]	73	18	3	0.81	40	83.00%
Feng[35]	41	18	3	4.8 (0.2-19.9)	56.6	82.50%
Our study	53	21	3	0.66 (0.16-8.66)	48	96.30%

Abbreviation: HSRT = hypofractionated stereotactic radiation therapy.

significantly affected the LC, and 2 recurrences occurred in patients with the 2 worst CI values. This factor, not reported in the literature, shows the importance of adequate coverage of the volume. Strangely, 6% of grade III acute toxicity was recorded, all reported to be vestibular disorder. This toxicity does not seem to be well documented through previously published studies. As for late toxicities, tolerance of healthy tissues was good, with only 2 grade II FND (2.4%) in patients who had previously been treated (recurrent after surgery) and 3 TND (3.6%), 1 of which was unresolved but not permanent. We found a correlation between a brain stem mean dose of more than 5 Gy and the TND. It confirms the results of Senova et al,[38] showing that the dose received by the Vth nerve nucleus contributes as much as the dose received by the cyternal portion of the nerve, to the occurrence of

TND. These results also seem to be consistent with previous studies. Hansasuta et al[31] published a retrospective analysis of 383 patients treated mainly in 3 fractions of 6 Gy. With a median follow-up of 3.6 years, the authors found an LC rate at 3 and 5 years of 99% and 96%, respectively. These good results should be highlighted with the absence of FND, 2% of TND, and 76% of useful hearing preservation.

A large proportion of audiometric data are lacking in our study. Nonetheless, the audiometric outcomes seem to be below the expected results, with 46% preservation of hearing function at the end of the follow-up. To better assess this point, a prospective analysis is in progress in our institutions to analyze more precisely the effect of radiation therapy on vestibular and auditory functions.

Conclusions

Our study confirms the good LC obtained with HSRT treatment on Koos stage 1 to 3 VS with a satisfying follow-up. A significant relationship was found between the lesion volume and the dosimetric CI with LC. This good LC rate was obtained with few long-term toxicities. The relationship between clinical or dosimetric variables and the occurrence of toxicity is difficult to assess and is still a work in progress. Particular attention is warranted for the audiometric long-term results.

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