ORIGINAL ARTICLE

Non surgical Treatment of Vestibular Schwannoma

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KEYWORDS
Vestibular schwannoma; Acoustic neuroma; Radiosurgery; Fractionated stereotactic radiotherapy; Observation

Abstract

Introduction and objectives: To evaluate the results of local control and complications in the treatment of vestibular schwannoma treated with radiation.

Methods: A retrospective study of 194 patients diagnosed with vestibular schwannoma, treated consecutively with radiation (either stereotactic radiosurgery or fractionated radiotherapy) from 1997 to 2012. We analyse the local control of tumours, as well as secondary complications to treatment with radiation.

Results: A total of 132 (68%) tumours, 68% are grade I-II tumours of the Koos classification, 40 (19%) are grade III, and 22 (13%) are grade IV. The tumours associated with neurofibromatosis (NF2) are 3.6% (6 tumours in 4 patients). The tumour control for the overall series is 97% at 5 years, with a median follow-up of 80.4 months. For large tumours the local control is 91% at 5 years. Free survival of chronic complications is 89% at 5 years. Additionally, 50 tumours were subjected to regular follow-up with MRI without treatment, and 28 (58%) did not experience tumour growth.

Conclusions: Radiation and follow-up with MRI are alternatives to surgery in the treatment of vestibular schwannoma, with a low level of complications in a multidisciplinary approach.

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Introduction and Objectives

Vestibular schwannomas (VS) are benign extra-axial tumours, usually originating in the vestibular section of the eighth cranial nerve. The incidence of VS has increased in recent years, mainly owing to increased use of a cerebral magnetic resonance imaging (MRI) in diagnosis. It is estimated that annual incidence in the U.S.A. is 0.99–1 per 100,000 inhabitants per year. Treatment possibilities are observation, microsurgery or radiosurgery (RS). Radiosurgery is when a single dose of radiation is administered and fractionated stereotactic radiotherapy (FSRT) is the administration of several fractions (from 5 to 28). Treatment is selected according to tumour and patient characteristics.

Treatment must be administered by a multidisciplinary team who are experienced in all the above mentioned procedures. In 2006 a favourable recommendation was obtained (grade 2 of scientific evidence) for RS, compared with surgery in tumours under 25 mm, and there were better results for patients treated with RS with regard to facial and trigeminal nerve function, preservation of hearing, postoperative complications and hospital stay, as well as quality of life. The aim of this article is to describe the results of patients diagnosed with VS who were referred to a multidisciplinary unit for radiation treatment.

Method

A retrospective study of 194 patients diagnosed with VS who were treated with radiation or were under observation was performed. They were treated consecutively in the Radiation Oncology Department (ROD), Neurosurgery Department and ENT Department from February 1997 to May 2012. Initial radiation treatment was given to 144 patients (74%) and follow-up was indicated for 50 patients (26%). From this group either tumour growth or an increase in symptoms in 21 cases (42%) was detected, with the resulting indication for radiation treatment. The remaining 29 patients (58%) presented tumour stability and stability in audiometry. These patients were controlled but did not receive direct treatment. To the group of 144 patients treated from the beginning, we added the 21 patients treated after follow-up was indicated, with the total patients treated therefore numbering 165; as 2 of the patients presented with bilateral tumours, we obtained a total of 167 tumours treated with radiation.

Tumours were classified according to size using the Koos classification (Table 1). Large tumours were defined as those measuring ≥30 mm in any dimension, or those >8 cc.1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Intracanalicular tumour</td>
</tr>
<tr>
<td>II</td>
<td>Small tumour protruding at cerebellopontine angle, up to 2 cm</td>
</tr>
<tr>
<td>III</td>
<td>Tumour which occupies the cerebellopontine angle cistern, with no displacement of the cerebral trunk, up to 3 cm</td>
</tr>
<tr>
<td>IV</td>
<td>Large tumour, with displacement of the trunk or cranial nerves, &gt;3 cm</td>
</tr>
</tbody>
</table>

Source: Gonzalez-Darder et al.1
Hearing was assessed using the House and Brackman (HB) classification.9

Those patients with intracanalicular tumours or with a minimum extracanalicular component, i.e. Koos grade I–II, who were oligo- or pauci-symptomatic, were offered the option of surveillance, observation, or follow-up. Initial control 9 months after diagnosis included clinical examination, audiometry and MRI, with subsequent annual examinations up to year 5; thereafter examinations were to be performed every 2 years, or every 5 years depending on patient characteristics.

Treatment is shown in Table 2. 86% (145 tumours) were treated exclusively with radiation, 133 with RS and 12 with FSRT. The remaining 14% (22 tumours) received RS as rescue treatment after surgery.

We used RS in all tumours ≤25 mm; the procedure is currently outpatient. The dose used was 12 Gy at the margin of the lesion marked by the MRI imaging in the T1 sequence contrast enhancer and in CISS T2 sequence, with no additional margin; we applied several dose limits to the trigeminal nerve level of ≤9 Gy; the dose of both the cochlea and the encephalon trunk level had to be as low as possible, trying not to go above 5 Gy at the cochlear (marked in the CISS T2 sequence or the bony window) or above 10–12 Gy in the encephalon trunk (a volume below 0.1 cc). Initially we used the stereotactic frameworks of Prof. Barcia Salorio and Leksell; since 2005 we have been using the Brainlab AG (Feldkirchen, Germany) framework. In lesions over 25 mm we used FSRT, with a dose range between 30 and 50.4 Gy with fractionating of either 3 or 5 Gy per day if we administered 30 Gy or 1.8 Gy per fraction per day if we administered 50.4 Gy. This dose was administered to the marked lesion as it was with RS, increasing the irradiated volume between 2 and 3 mm to compensate for possible positioning errors. The procedure was performed with repositionable masks, made for each patient.

Until 2005, conical collimators and dynamic RS therapy were used; from then onwards we carried out the treatments with a multilamine microcollimator, BrainLAB AG plan, with dynamic conformal arc therapy technique. This plan creates automatic fusion of the cerebral MRI imaging of the gadolinium enhanced sequences in T1 and CISS T2 sequences with the brain CAT scan with the inserted stereotactic framework/repositionable mask on the patient.

Follow-up after treatment involved clinical examination of the fifth, seventh and eighth cranial homolateral nerve, audiometry, and MRI after 9 months. This examination was then annual for 5 years and bi-annual afterwards up to 10 years; after this period, follow-up was every 3–5 years, depending on patient characteristics.

The absence of the need to administer any other treatment was considered as the local clinical control (LCC). A criterion of local radiological failure was a >2 mm increase in any dimension, present in at least 2 cerebral MRIs. Severe complications were those appearing during the first 3 months after treatment. Chronic complications were those appearing from the 6th month after treatment.9

Estimation of survival was performed using the Kaplan–Meier method. For analysis of those factors which could potentially affect survival, the Cox Regression was used. A value of P<.05 was used as a statistically significant difference. For the creation of the database and statistical analysis, the STATA 12.0 statistical package was used. For the different survival analysis, multivariate studies were performed using the Cox model of proportional risks.

Results

Baseline patient characteristics are included in Table 3. Mean age is 58.4, with a range between 19 and 87 years. Median follow-up is 80.4 months (12–175 months). Median tumour volume is 0.98 cc. Using Koos classification, 17% are grade i, 51% grade ii, 21% grade iii and 12% grade iv. 22 patients (13%) with large tumours were treated. Neurofibromatosis (NF2) tumours represented 3.6% (6 tumours in 4 patients).

LCC is 97% at 5 years and 95% at 10 years. Local clinical failure is 3%. In large tumours, a 91% LCC is obtained at 5 and 10 years. Local control was obtained in 6 cases of VS related to NF2.

Of the 5 local failures, resection was performed in 2, and patients are currently tumour free. The other 3 patients were referred for treatment and received repeated cyst punctures, and died due to secondary surgical complications. They were all treated with RS. No Koos i patient relapsed; 2/84 (2.3%) with grade ii relapsed, 1/34 (2.9%) with grade iii relapsed, as did 2/22 (9%) with level iv (Table 4).

Of those patients who were under observation or follow-up (34 were Koos grade i and 14 grade ii), 14 from the first group had tumour growth and 7 from the second group, i.e. growth was 42% and 58% remained stable.

Severe complications appeared in 15 patients (9%). These included increased instability in 10 cases, facial and eyelid oedema the day after treatment, in one case, increased tinnitus with sudden deafness in another, homolateral trigeminal pain in 2 cases, and infection in a stereotactic frame attachment point, in another case. All cases were rapidly resolved with medical treatment.

89% of patients had chronic complication-free survival after 5 years, and 85% after 10 years. Neuropathy of the facial nerve appeared in 9 patients with a 5% probability to appear after 5 years and 7% after 10 years. 4 patients presented with sensory-motor impairment, and 5 with facial myokymias.11 Of these, 3 presented simultaneously with trigeminal neuropathy. Permanent paralysis (always Grade HB i–ii) occurred in 1.1%. They were more frequent in men, with a 2:1 ratio and if the dose was above 13 Gy, at a 2:2:1 proportion, they appeared with greater frequency between 60 and 69 years of age, and also increased with tumour size. None of these conditions were statistically significant.
Neuropathy of the trigeminal nerve presented in 11 patients (8% to 5 and 10 years). They were related to a dose >13 Gy (P=.05). They presented more frequently in women and with a ratio of 2.69:1. They may present with clinical symptoms which are sensitive to changes in facial sensitivity in the form of hypoesthesia, disestesias or parestesias, or as trigeminal neuralgia, mainly in V2-V3. All chronic complications appeared in patients treated with RS.

With regard to hearing preservation, only 19% of our patients had useful hearing prior to diagnosis, after RS hearing was preserved in 68.7% of the overall sample.

The rate of overall hydrocephalus was 5% after 5 and 10 years, and all the patients had tumours larger than 2 cm treated with RS.

We observed no radiation-induced secondary brain tumours. In 2 patients with NF2 standard meningiomas were associated and schwannomas of the trigeminal nerve, synchronous with VS.

Fourteen patients (8.3% of the sample) presented with an extracerebral cancer during their lives, synchronous in 3 cases and metachronic in 11 cases (over 6 months before or after VS was diagnosed). If the overall cancer rate is 241.1 cases per 100 000 inhabitants and year, for the mean follow-up of 6.7 years they should have presented 3.27 cases of cancer for the 165 patients of the sample treated, 10 which is why the incidence of presented extracerebral malignant tumours is 4.27 times higher.

**Discussion**

Regarding symptomology, as with other works, we found no relationship between the clinical symptoms presented by the patient and tumour size 14-17; thus intracanalicular tumours which maintain useful hearing below the mean were 16.8% compared with the 19% overall.

LCC of 97% after 5 years and 95% after 10 years is found between the rates of tumour control described, as between 93% and 100%. 14,12-17

Local clinical failure is 3%, similar to the rate of local clinical failure of published series for RS with Gamma knife, with linear accelerator (LA) or with FSRT, which ranges between 1.4% and 9%. 14-22 The 5 tumorigenes after RS of our series occurred during the first 2 years. The different authors state them as appearing within the first 3 years 14,23,24 although they are described sporadically 3, 4 and 18 years after treatment. 14,25,26

Local radiological control of the 167 tumours 5 years after treatment is 93%, descending to 90% after 10 years. These results are similar to those published which range from 85.4% 21 to 93%. 19,27-30

### Table 3 Base Patient Characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement</th>
<th>Total (n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Months</td>
<td>80.4 (12-175)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>93 (56%)</td>
</tr>
<tr>
<td>Side</td>
<td>Left</td>
<td>88 (53%)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean (years)</td>
<td>58.4 (19-87)</td>
</tr>
<tr>
<td></td>
<td>Median (years)</td>
<td>60</td>
</tr>
<tr>
<td>Image</td>
<td>Intracanalicular</td>
<td>30 (18%)</td>
</tr>
<tr>
<td></td>
<td>Extracanalicular</td>
<td>137 (82%)</td>
</tr>
<tr>
<td>Volume (cc)</td>
<td>Mean</td>
<td>2.76 cc</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.98 cc</td>
</tr>
<tr>
<td>Permissible dose D</td>
<td>Mean</td>
<td>12.4 Gy</td>
</tr>
<tr>
<td>(Gy)</td>
<td>Median</td>
<td>12.0 Gy</td>
</tr>
<tr>
<td>Hypoacusia prior to treatment</td>
<td>Useful (slight-moderate 0-50 db)</td>
<td>32 (19%)</td>
</tr>
<tr>
<td></td>
<td>Severe (55-80 db)</td>
<td>103 (61%)</td>
</tr>
<tr>
<td></td>
<td>Profound</td>
<td>32 (19%)</td>
</tr>
<tr>
<td>Clinical expressions prior to treatment</td>
<td>Duration of symptoms</td>
<td>34 months</td>
</tr>
<tr>
<td></td>
<td>Hypoacusia</td>
<td>159 (95%)</td>
</tr>
<tr>
<td></td>
<td>Changes in balance</td>
<td>97 (58%)</td>
</tr>
<tr>
<td></td>
<td>Tinnitus</td>
<td>90 (54%)</td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus</td>
<td>19 (11%)</td>
</tr>
<tr>
<td></td>
<td>Trigeminal nerve damage</td>
<td>17 (10%)</td>
</tr>
<tr>
<td></td>
<td>Facial nerve damage</td>
<td>12 (7%)</td>
</tr>
<tr>
<td></td>
<td>Sudden deafness</td>
<td>8 (5%)</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis</td>
<td>6 (3.6%)</td>
</tr>
</tbody>
</table>

### Table 4 Recurrence According to Tumour Size (Koos Classification).

<table>
<thead>
<tr>
<th>Koos Classification</th>
<th>Recurrences, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koos I intracanalicular (27/167) 17%</td>
<td>0</td>
</tr>
<tr>
<td>Koos I ≤ 2 cm (84/167) 51%</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Koos II ≤ 3 cm (34/167) 21%</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Koos III &gt; 3 cm (22/167) 13%</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Total 167 patients</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>
In the surgical series the probability of incomplete excision ranges between 2.4% and 6%,13 the possibility of local recurrence between 0.7%,32 6.2%31 and 10%,45 with a surgical mortality of between 0 and 1.3%.7,31,32,34,35

The LC obtained in large tumours of 91% after 5 years, with follow-up of 9.3 years, is similar to that presented by other authors with RS between 87%6 and 82%.36 The complication level in this subgroup is lower than the rest of the series; we only found one patient with a transitory trigeminal disease 6 months after RS (4.5%), with no facial nerve damage or postural hydrocephalus after treatment, compared with 2% of facial damage, 6% of trigeminal nerve damage and 5% of hydrocephalus from the Yang et al.6 series, and 29% facial nerve damage and 13% of trigeminal nerve damage from the Mandl et al.36 series. Complications or recurrence appeared with a mean of 16 months.

Surgery on these tumours achieved complete resection which ranges between 100%6 and 87%,34 with morbidity of the facial nerve between 27% and 72%, LCR fistulas between 5.5% and 14%, a meningitis rate of between 5.5% and 9.5%, and no deaths during surgery.7,34,37

Although we have controlled the 6 tumours related to NF2, local control in this situation is not normally as good as in sporadic cases,29,38,39 with a need for additional treatment in 21% of patients treated with RS with a marginal dose of 13.4 Gy.

Regarding patients for whom follow-up was indicated, we observed that the number of patients who continued in follow-up was 58%, which is within published findings ranging between 50% and 68%.40-45 It is of note that the growth of these tumours is not affected by the tumour stage at diagnosis, since the percentage of patients with growth is the same in Grade i (41%) as in Grade ii (43%) tumours.

Severe complications, such as sudden deafness and trigeminal pain, are usually reversed with steroid treatment according to published works.3,9,22

Facial neuropathy incidence falls between the ranges described by different authors, between 4.5% and 8%.18,46-48 The rate of permanent facial paralysis (1.2%) ranges between 1% and 1.5%.22,48 Occasional spasms of the side of the face, with little clinical repercussions are present in 8%. In other series this is between 2%-4%22 and 8%.49 This low rate of permanent facial nerve damage is due to the mean dose of 12 Gy administered.12 In the surgical series facial damage (≥ HB iii) ranges between 10% and 40%,3,31,32 depending on the tumour size, the surgical approach route31 and the experience of the medical teams.

The 8% neuropathy of the trigeminal nerve is similar to other series where it ranges between 4%-5%17,48 and 8%-18%.30 Permanent dysfunction in our series is 2.3%, identical to that described by La Roche et al.48

68.7% of patients maintained their hearing levels prior to treatment. At present, it is stated that between 33% and 90% of hearing has been preserved4,25,51 in patients with previous useful hearing.

In the 3 cases who underwent surgery after RS failure, surgery presented greater difficulty, similar to that suggested by other authors.4,52

With regard to a higher incidence of extracerebral cancer being diagnosed, we must remember that the appearance of VS is associated with an alteration of the NF2 tumour suppressor gene and that the majority of diseases linked to the inactivation of the tumour suppressor gene lead to the development of malignant tumours, with this point being the possible focus of connection.44

Conclusions

We would suggest that follow-up is offered for Koos Grade −ii tumours when non-surgical treatment of VS is indicated, since almost 60% of them will not grow, nor will the patient be clinically compromised.

The lower aggressiveness of the technique and low level of complications of both RS and FSRT, compared with surgery, makes radiation a clear alternative to the surgical option which up until now was considered the standard treatment in small and intermediate sized tumours. In large tumours where there are surgical contraindications, FSRT may be an alternative, provided there are no neurological symptoms of compression of the encephalon trunk or cranial nerves, nor hydrocephalus, where surgery should continue being first line treatment.

Conflict of Interest

The authors have no conflicts of interest to declare.

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