Vestibular schwannoma treatment : patients' perceptions and outcomes

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Chapter 4

Quality of life and clinical outcome after radiosurgery for vestibular schwannoma

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Abstract

Objective: To assess quality of life and clinical outcome in vestibular schwannoma patients after radiosurgery with marginal tumor doses of 12 Gy.

Study Design: Retrospective study conducted in a university-based referral centre.

Patients and Methods: Seventy-two consecutive, newly-diagnosed patients with a solitary vestibular schwannoma underwent linear accelerator-based radiosurgery between 2001 and 2007, all with marginal tumor doses of 1 x 12 Gy prescribed to the 80% isodose-line. A total of 66 patients were included in the study and 64 patients (97%) filled out the SF-36. The SF-36 scores of the patients were compared with SF-36 scores of healthy controls. Local tumor control and symptoms were also studied. The median follow up between treatment and quality of life assessment measured 34 months (mean, 35 mo; range, 3-78 mo). The median imaging follow-up was 31 months (mean, 34 mo; range, 4-64 mo).

Main outcome measures: Quality of life and clinical results.

Results: The median tumor diameter was 17 mm (mean, 17 mm; range, 4-28 mm). The clinical tumor control rate was 100% after a median follow-up of 31 months (mean, 34 mo; range, 4-64 mo). The imaging control rate was 98%. None of the patients had serviceable hearing before the radiosurgery. Dizziness and tinnitus were present in 45 (70%) and 46 (72%) patients before treatment, respectively. None of the patients developed dizziness or tinnitus after treatment, but dizziness worsened in 2 (3%) and tinnitus in 3 (5%) patients. Facial nerve and trigeminal symptoms developed after treatment in 2 (3%) and 4 (6%) patients, respectively. In one patient (2%) hydrocephalus occurred. The SF-36 scores for social functioning and general health were statistically significantly lower when compared to healthy controls ($p = 0.01$ and $p = 0.001$, respectively). There was no significant correlation of the SF-36 scores and tumor size, dizziness, facial or trigeminal nerve symptoms or co-morbidity. Tinnitus inversely correlated with physical-role functioning ($p = 0.01$).

Conclusion: Vestibular schwannoma patients experience impaired quality of life after radiosurgery when compared to healthy controls. However, radiosurgical treatment for vestibular schwannoma offers good tumor control and favorable clinical outcome similar to earlier reports. There is no significant correlation between quality of life outcome and disease-related symptoms, tumor size or comorbidity.

Introduction

Over the past decades, radiosurgery has become a well-established treatment for vestibular schwannoma (VS) (1-7). The two main goals of treatment are long term tumor control and preservation of quality of life (QoL), including neurological functions. Recent studies have reported long term clinical tumor control rates up to 97-99% with low marginal doses (12-14 Gy) (3-5). Despite these advances, radiosurgical treatment of vestibular schwannoma may induce or worsen complaints such as hearing loss, tinnitus, facial nerve dysfunction, facial pain and dysbalance. Another sequelae of treatment is hydrocephalus, which may require a ventriculo-peritoneal shunt (8,9).

In VS literature, the frequency and impact of these symptoms vary considerably, but an increased awareness of QoL issues has drawn more attention to these outcomes. Most radiosurgical reports, however, mainly focus on tumor control and objective neurological deficit. More subjective effects of radiosurgery on for instance tinnitus, dizziness or balance problems are scarcely reported (3). Especially imbalance and vertigo have shown to result in an impaired QoL (10,11).

So far, little is known from the patients' perspective of what constitutes a radiosurgical success. In order to increase knowledge of the patient's perception of radiosurgical treatment of VS, we assess QoL and clinical outcome in newly-diagnosed patients with solitary VS after linear accelerator-based (LINAC) radiosurgery.

Materials and Methods

Patients

Between June 2001 and December 2007, 72 consecutive newly-diagnosed patients with unilateral VS underwent linear accelerator-based (LINAC), low-dose radiosurgery at the Erasmus University Medical Centre in Rotterdam with marginal doses of 12 Gy. Retrospective analysis of the clinical charts showed that of the 72 patients, 6 patients were deceased. It were all disease unrelated deaths: four patients died because of a primary malignancy or metastasis of a malignant tumor, one patient died of a glioblastoma and one patient passed away as a result of old age. No patients were lost to follow up. This resulted in 66 eligible patients for our study. To obtain the QoL data, all these patients received a questionnaire accompanied by a letter informing them

of the purpose of the study and instructions on how to complete the questionnaires. A total of 64 patients completed and returned the questionnaire (97%). Two patients were unwilling to participate and did not fill out the questionnaire. The patient data were obtained from the patients' clinical charts and our VS database; they are summarized in Table 1. The median age of the 64 patients was 65 years (mean, 66 yr; range, 36-84 yr) when they filled out the questionnaire. Thirty two patients (50%) were male. Follow-up was defined by the time interval between treatment and the most recent MRI scan and neurological examination. The median follow-up of the 64 patients was 31 months (mean, 34 mo; range, 4-64 mo).

Table 1. Patient characteristics (n = 64).

No. of patients	64
Age, yr (median, range)	66 (65, 36-84)
Male/female	32:32
Follow-up, mo	34 (31, 4-64)
Initial tumor size, mm	17 (17, 4-28)

Tumor characteristics

All tumor diameters were measured and volumes were calculated using the planning magnetic resonance imaging (MRI) scan. The median tumor diameter was 17 mm (mean, 17 mm; range, 4-28 mm) and the median tumor volume was 2.2 cm^3 (mean, 2.2 cm^3; range, 0.1-11.4 cm^3).

Local tumor control was assessed in two ways. First, by imaging; radiological tumor control was defined as an increase in tumor diameter of less than 2 mm in any direction. A 2 mm difference seems appropriate because of the variation in voxel size and scan angle/head position during MRI. Second, by final clinical outcome; local control was defined as freedom from surgical resection.

Radiosurgical treatment

Patient immobilization was provided by the Brown-Robert-Wells stereotactic coordinate headframe from Radionics (Radionics Inc., Burlington, MA, USA). Stereotactic planning computed tomography (CT) scans were performed and co-registered with 1-2 mm slice thickness MRIs. The XKnife™ RT software from Radionics was used for image fusion, contouring and planning. Tumor and organs

at risk delineation was carried out on T1-weighted MRI sequences. A dose of 12 Gy was delivered at the 80% isodose by means of a Varian 2300 LINAC (Varian Medical Systems, Palo Alto, CA, USA).

Symptoms

Pretreatment and posttreatment trigeminal nerve symptoms were defined as subjective or objective decrease in facial sensation or facial pain documented either by patient interview or physical examination. Pretreatment and posttreatment facial nerve symptoms were defined as any decrease in facial nerve function as documented by a decrease in House-Brackmann Grades (H-B Grades I-VI) (12). Guidelines of the AAO-HNS Committee on Hearing and Equilibrium were used to classify patients' preoperative hearing status (13). Cochleovestibular symptoms such as dizziness and tinnitus were also recorded together with the patients' comorbidity and neurological complications.

Quality of life

The median follow-up between treatment and QoL assessment was 34 months (mean, 35 mo; range, 3-78 mo). QoL was measured using the SF-36, which is the most widely used generic questionnaire to assess QoL and has been validated and proven to be a reliable instrument to measure general QoL (14). It consists of 36 items comprising 8 subscales of QoL. These subscales are 1) physical functioning and 2) social functioning, that is, the degree of limitations experienced in daily life physically and socially, respectively; 3) physical role limitations and 4) emotional role limitations, that is, limitations in work or other daily activities due to physical and emotional problems, respectively; 5) mental health, the degree of depression and anxiety; 6) vitality, the degree of energy and exhaustion; 7) bodily pain and 8) general health which quantifies the subjective evaluation of the patient's own health status and pain. Higher scores indicate better perceived QoL. Data on patients' responses were scored according to the instructions on scoring syntax in the SF-36 manual and Dutch population norms are available for reference (15).

Statistical analysis

Statistical analysis was performed using SPSS version 14.0 for Windows. The one sample t-test was used for comparison between SF-36 scores of the radiosurgery patients and the healthy age matched control population. The independent samples

t-test was used for comparison between SF-36 scores of the radiosurgery patients using different patient or tumor variables. A 95% level of significance ($p < 0.05$) was used. Correlations between SF-36 scores and patient- or tumor variables were analyzed using the Pearson correlation coefficient.

Results

Clinical outcome

Tumor control is presented in Table 2. None of the 64 patients required a second treatment at a median follow-up of 31 months. The clinical tumor control rate was therefore 100%. In one patient increase of tumor diameter (2 mm) was observed on the first post-irradiation MRI due to tumor necrosis. A follow-up of more than 3 years showed no further tumor progression in this patient. This resulted in an imaging-defined tumor control rate of 98%.

Table 2. Tumor control after radiosurgery (n = 64).

Tumor arrest (%)	33 (52)
Tumor reduction (%)	30 (47)
Tumor progression (%)	1 (2)
Need for second treatment (%)	0 (0)

The clinical results are presented in Table 3. All 64 patients presented with non-serviceable hearing on the ipsilateral ear before treatment (Class C and D according to the AAO-HNS classification) (13). Dizziness was present in 45 of the 64 patients (70%) before radiosurgery. Tinnitus was initially present in 46 patients (72%). Before radiosurgery, two patients (3%) had H-B Grade II paresis and five patients (8%) experienced facial numbness or facial pain. As expected after treatment all the 64 patients retained non-serviceable hearing (Class C and D according to the AAO-HNS classification). Dizziness worsened in 2 patients (3%), and remained unchanged in 43 patients (67%). The patients who did not report dizziness before treatment (30%) did not develop dizziness after treatment. Tinnitus worsened in 3 patients (5%) and remained unchanged in 43 patients (67%). The patients who did

not report tinnitus before treatment (28%) did not develop tinnitus symptoms after treatment. Two patients (3%) developed facial nerve palsy H-B Grade III at 7 and 8 months after treatment. Facial nerve function did not deteriorate after treatment in the two patients with decreased facial nerve function prior to treatment. Trigeminal symptoms developed in four patients (6%) at 5, 6, 11, and 12 months posttreatment. There was no deterioration of symptoms in the five patients with trigeminal symptoms before treatment. In one patient trigeminal symptoms even resolved at 24 months after treatment.

Table 3. Clinical results after radiosurgery (n = 64).

	Pre-existing deficit (%)	Stable after treatment (%)	Worsened after treatment (%)	New after treatment (%)
Facial nerve	2 (3)	62 (97)	-	2 (3)
Trigeminal nerve	5 (8)	60 (94)*	-	4 (6)
Hydrocephalus	0 (0)	0 (0)	-	1 (2)
New neoplasia	-	-	-	0 (0)
Dizziness	45 (70)	62 (97)	2 (3)	0 (0)
Tinnitus	46 (72)	61 (95)	3 (5)	0 (0)

* in one patient pre-existing trigeminal symptoms improved and disappeared at 24 months after treatment.

One patient (2%) developed hydrocephalus at 4 months after radiosurgery, which was treated with a ventriculo-peritoneal drain and which resolved without permanent sequelae. There were 7 patients who suffered from pre-existing neurologic comorbidity: stroke (n = 5), meningioma (n = 1) and multiple sclerosis (n = 1). One patient was surgically and curatively treated for a small cell lung carcinoma, one patient was curatively irradiated for a prostate carcinoma and one patient was bound to a wheelchair due to orthopaedic problems.

Quality of life

The results of the SF-36 are presented in Table 4. The mean SF-36 scores for the radiosurgically treated patients were lower (i.e., reflecting a poorer QoL) for all subscales except for bodily pain and physical functioning when compared to the mean SF-36 scores of the controls. The SF-36 scores for the dimensions social functioning and general health were statistically significantly lower when compared

to the controls (p = 0.01 and p = 0.001, respectively). The scores for bodily pain and physical functioning did not significantly differ from that of the controls (p = 0.4 and p = 0.9) (Table 4). SF-36 scores did not significantly correlate with tumor size, dizziness, trigeminal or facial nerve function, other sequelae such as hydrocephalus, or comorbidity (all p > 0.05). Physical-role functioning inversely correlated with presence of tinnitus (p = 0.01).

Table 4. SF-36 scores after radiosurgery (n = 64).

Short Form-36 scales	After treatment		Healthy controls	
	Mean	SD	Mean	SD
PF	73.0	27.9	66.7	26.0
SF	74.8*	25.7	83.2	23.7
RF	60.9	44.5	69.1	42.5
RE	76.7	40.4	82.9	33.8
MH	72.5	19.6	75.9	17.3
VT	63.2	25.5	64.2	22.0
BP	77.6	28.4	74.8	28.0
GH	53.6*	11.8	60.1	23.9

SD: standard deviation; * p < 0.05.

Discussion

This study reported on the outcome after radiosurgical treatment for VS from both a QoL and clinical perspective. As many other authors, we demonstrated that a marginal dose of 12 Gy is sufficient to control tumor growth of VS treated with radiosurgery. Our clinical tumor control rate was 100% after a follow-up of 31 months, which corresponded with earlier large series reporting control rates of 97-99% during a follow-up of 3-5.7 years (3-5). In our series, we found favorable facial and trigeminal outcome (97% and 94%, respectively), which is also in line with the results of the abovementioned studies. Hydrocephalus occurred in one patient (2%) at 4 months post-treatment, which was treated with a ventriculo-peritoneal drain and without permanent sequelae. Roche et al. recently reported that newly developed post-

radiosurgery hydrocephalus is generally of low incidence (1%) and that radiosurgery does not decompensate the majority of preexisting radiological hydrocephalus (8).

Dizziness and tinnitus were present in most of our patients before treatment, which was in line with other rates varying between 40-60% and 63-75%, respectively (16). After treatment dizziness and tinnitus worsened in only a fraction of our patients, and there were no patients reporting new dizziness or tinnitus. As reported earlier, dizziness may have serious impact on QoL (10). In this study, however, dizziness did not affect QoL outcomes. Development of tinnitus after VS treatment is generally thought to be unpredictable, but a slight overall increase has been reported. We found a significant inverse correlation between tinnitus and physical daily tasks. This outcome was somewhat surprising, because often patients with tinnitus experience emotional disability instead of physical disability.

We observed that social functioning and general health domains of our treated patients were significantly affected compared to the control sample. For the other 6 QoL domains, no significant difference was observed. Patients with trigeminal symptoms did not have significantly lower pain scores when compared to other patients or the healthy control sample. The 4 patients (2 post-radiosurgery) with H-B Grades II-III did have reduced scores on social and physical functioning domains; however, this observation failed to reach statistical significance.

A possible explanation for the abovementioned results might be that most of the symptoms were already present in most patients even before treatment and that patients adjusted to symptoms over time. This phenomenon is known as response shift (17).

It is now well recognized that microsurgical treatment may have a strong impact on the patients' QoL (18,19). In addition, stability in QoL has been reported following conservative treatment (20,21). We are aware of 5 studies reporting on QoL following radiosurgery (Table 5). Pollock et al. first described functional outcomes after radiosurgery and microsurgery. More recently, they prospectively compared QoL outcomes between these treatment modalities. They concluded that QoL was better after radiosurgery when compared to microsurgery using validated QoL questionnaires (22,23). Van Roijen et al. also investigated QoL for both modalities and emphasized that radiosurgery was more cost-effective than microsurgery (24). A recent study by Régis et al. described more favorable long term outcomes after radiosurgery regarding posttreatment complications and hospital stay using a custom made QoL questionnaire. Furthermore, they also found that most

microsurgically treated patients experienced significantly more psychobehavioral problems such as tiredness, depression and anxiety compared to radiosurgically treated patients. However, there was no significant difference between treatment modalities regarding tinnitus, vertigo or imbalance (25). Myrseth et al. used the SF-36 and found that general QoL, facial nerve function and complications rates were all significantly in favor of radiosurgery when compared to microsurgery. However, QoL of both groups was reduced when compared to the healthy controls. In addition, no clear relationship was found between QoL and facial nerve function, tumor size or cochleo-vestibular symptoms (26). Sandooram et al. recently investigated QoL following radiosurgery, microsurgery and conservative management for vestibular schwannoma using the Glasgow Benefit Inventory (GBI). They found poorer QoL after microsurgery when compared to radiosurgery (27). From these studies it appears that QoL after radiosurgery is generally better when compared to microsurgery. However, when compared to the control populations, impaired QoL still exists for both the treatment modalities.

We acknowledge that the retrospective design is a limitation of the study. By using this kind of approach, it remains unclear whether the QoL outcome is affected by either the radiosurgery or by suffering from the tumor itself. Still, there is evidence to suggest that retrospective measurement of QoL is at least as clinically relevant and scientifically sound as prospective assessment (28). However, when compared to other published results from our center, in which QoL was measured in a sample of untreated VS patients, our radiosurgically treated patients displayed improved QoL (29). From this point of view, it appears that QoL was positively influenced by the radiosurgery and the QoL impairment may probably be caused by suffering from the disease itself. A possible explanation might be that the radiosurgically treated VS patients experienced their illness as being controlled without serious morbidity. In contrast, the untreated patients did not receive treatment yet.

Another limitation of the study might be the use of a generic questionnaire (SF-36) for QoL assessment. It would have been more preferable to combine generic with disease-specific QoL measures. Until now no validated questionnaire is available for assessing VS-specific QoL. This implies that developing a VS-specific QoL questionnaire for this specific category of patients is one research implication of our study.

Table 5. Overview of quality of life results in relation to radiosurgery.

First author	Study design	Sample (n)	Treatment	Questionnaire used for QoL assessment	QoL results
Pollock et al. (23)	prospective	82	RS; MS	HSQ*, DHI	RS significantly better than MS; less dizziness after RS compared to MS; no comparison with healthy sample
Van Roijen et al. (24)	retrospective	145	RS; MS	SF-36	RS better than MS; no comparison with healthy sample; RS more cost-effective than MS; disease-specific symptoms were not evaluated
Régis et al. (25)	prospective	210	RS; MS	Custom made, disease-specific	RS better than MS; no comparison with healthy sample;disease-related symptoms were evaluated
Myrseth et al. (26)	retrospective	189	RS; MS	SF-36	RS significantly better than MS; RS and MS impaired compared to healthy sample;disease-related symptoms were not evaluated
Sandooram et al. (27)	retrospective	165	RS;MS;WS	GBI	RS better than MS; disease-related symptoms were not evaluated
present study	retrospective	64	RS	SF-36	RS impaired when compared to healthy sample; disease-related symptoms were evaluated

QoL: quality of life; Treatment: RS: radiosurgery; MS: microsurgery; WS: wait and scan; Quality of life questionnaires: SF-36: Short Form-36 Health Survey; GBI: Glasgow Benefit Inventory; DHI: Dizziness Handicap Inventory; * short version of the SF-36.

Conclusion

Radiosurgery has become a well-established treatment option for VS. Previous studies have reported long term clinical tumor control rates up to 99% and favorable cranial nerve outcome with low marginal doses. Our study also shows that low dose radiosurgery for VS offered good tumor control and comparable clinical outcome. We found that QoL after treatment was impaired when compared to the age-matched healthy controls, which is also in line with existing literature. There was no significant correlation between the QoL outcome and disease-related symptoms, tumor size or comorbidity.

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