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Original article

Long-term outcome after highly advanced single-dose or fractionated radiotherapy in patients with vestibular schwannomas – Pooled results from 3 large German centers

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ABSTRACT

Purpose: To evaluate long-term clinical outcome and determine prognostic factors for local-control, hearing preservation and cranial nerve toxicity in 449 patients treated for 451 vestibular schwannomas (VS) with radiosurgery ($n = 169$; 38%) or fractionated stereotactic radiotherapy (FSRT; $n = 291$; 62%).

Methods and materials: 245 patients were male (55%), and 204 were female (45%). Median age was 60 years (range 17–88 years). Median tumor diameter was 15 mm. For FSRT, a median dose of 57.6 Gy in median single doses of 1.8 Gy was applied. For SRS, median dose was 13 Gy. The median follow-up time was 67 months.

Results: Local control was 97% at 36 months, 95% at 60 months, and 94% at 120 months with no difference between FSRT and SRS ($p = 0.39$).

"*Useful hearing*" was present 46%. After RT, "*useful hearing*" was preserved in 85% of the patients. Loss of useful hearing was observed in the FSRT group in 14%, and in the SRS group in 16% of the patients. For patients treated with SRS $\leqslant$13 Gy, useful hearing deterioration was 13%. For trigeminal and facial nerve toxicity, there was no difference between FSRT and SRS.

Conclusion: Supported by this large multicentric series, both SRS and FSRT can be recommended for the treatment of VS. SRS application is limited by tumor size, and is associated with a steep dose–response-curve. When chosen diligently based on tumor volume, pre-treatment characteristics and volume-dependent dose-prescription in SRS ($\leqslant$13 Gy), both treatments may be considered equally effective.

Treatment alternatives for patients with vestibular schwannoma (VS) include wait-and-scan, surgery and radiation therapy (RT). The discussion on treatment recommendations remains controversial, however, every alternative bears its own risk or safety profile, as well as benefits.

In general, growth rates for VS have been reported to be around 1–3 mm per year, and the majority of patients remain asymptomatic for many years [1–6]. In patients with typical imaging characteristics of VS without any clinical symptoms treatment may be withheld until progression is documented, or when clinical symptoms develop. During this time close clinical and imaging monitoring is required, and this strategy bears the risks of rapid tumor growth in some cases which cannot be predicted. Even in the "wait-and-see"-population hearing reduction between 40 and 60% can be observed over time [7].

Surgical alternatives are associated with a distinct risk profile due to the intricate anatomy of the cranial nerves [8–10]. Early reports have indicated significant morbidity and mortality rates, but improvement in surgical techniques such as implementation of microsurgical approaches has led to a reduction thereof. Usually preservation of serviceable hearing is between 30 and 50%, and permanent damage to the facial nerve is around 10–20% [3,11]. Preservation of hearing as well as cranial nerve function are a main advantage of highly conformal RT alternatives. With radiosurgery (RS), applying the dose in a single fraction, hearing preservation is commonly between 50 and 80% with modern RS techniques and marginal doses limited to 13 Gy [12–22]. Yet, single-dose approaches are limited by tumor size, with increasing rates of side effects not only with dose, but with volume. With fractionated RT

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the radiobiological properties of repair can be exploited providing a beneficial risk profile also for larger volume tumors. Local control is comparable to RS, i.e. between 80 and 100%, and hearing preservation is high also for larger tumor volumes [13,23–28].

To date, no randomized comparison of both radiation concepts exist. To further evaluate and compare individual risk factors and outcome after single-dose and fractionated stereotactic radiotherapy (FSRT), the current multicenter analysis was performed including 449 patients treated for 451 VS with RS ($n = 169$; 38%) or FSRT ($n = 291$; 62%).

Materials and methods

Patients' characteristics

245 patients were male (55%), and 204 were female (45%). Median age was 60 years (range 17–88 years). 291 patients (65%) were treated with FSRT, 160 (35%) with SRS. Median tumor diameter was 15 mm (range 3–58 mm). Clinical symptoms included tinnitus in 219 patients (49%), facial impairment in 61 patients (14%), trigeminal neuralgia in 67 patients (15%) and vertigo in 197 patients (44%). Taken together, for FSRT, a median dose of 57.6 Gy (range 25–66 Gy) in median single doses of 1.8 Gy was applied. For SRS, median dose was 13 Gy (range 10–20 Gy). In the following, site specific dosing, prescribing as well as treatment planning characteristics are described (Table 1).

Heidelberg treatment planning

Details for the Heidelberg Center have been published previously [28]. Patients included were treated between 1990 and 2011. Generally, the use of FSRT is considered the treatment standard. SRS was performed after individual decision making and counseling of the patients. For SRS, patients were fixed using a minimally invasive head fixation with a stereotactic frame attached to the patient's head as reported previously, which was put in place by an experienced radiation oncologist. For treatment planning, the three-dimensional treatment planning system STP (Stryker Leibinger, Germany), or the Precisis Software was used. The Planning Target Volume (PTV) was defined as the Gross Tumor Volume (GTV) visible as contrast enhancement on T1-weighted MR-imaging adding a safety margin of 1–2 mm. Dose was delivered using predefined circular collimators and for irregularly shaped VS, with a micro-multileaf-collimator. Generally, 9–14 noncoplanar fields were applied. A median single dose of 13 Gy/80% isodose (range 10–20 Gy) was applied. The median PTV was 1.2 ml (range 0.2–3.3 ml).

For FSRT, patients were fixed in a head mask individually crafted for each patient attached to a stereotactic base frame. Target volume definition and treatment planning were performed using the three-dimensional treatment planning software Voxelplan (Voxelplan, DKFZ, Heidelberg, Germany) or STP (Stryker Leibinger, Germany), as well as the Siemens Oncologist Software (Siemens, Erlangen Germany) in combination with the Precisis Software. The gross tumor volume (GTV) was defined as the macroscopically visible contrast-enhancing lesion visible on T1-weighted MRI; the planning target volume (PTV) included the GTV with a safety margin of 1–2 mm. The median size of the PTV was 2.4 ml (range 0.4–33.4 ml). A median dose of 57.6 Gy/isocenter (range 25–66 Gy) was applied in a median single fractionation of 1.8 Gy/isocenter (range 1.8–5 Gy) in 5 fractions per week. Treatment planning was aimed for coverage of the 90% isodose around the PTV.

Munich treatment planning

At the Munich center, treatment decision for SRS or FSRT was mainly based on tumor size and hearing function of the contralateral ear between 1997 and 2012. Details have been published previously [29]. For SRS, single doses of 12 Gy/100% isodose covering the tumor margins were applied. Treatment planning and SRS were performed using the BrainLAB stereotactic frame system (BrainLAB, Feldkirchen, Germany) adapted individually for each patient. With this ring system an overall accuracy of 0.5 mm can be obtained. For target volume definition contrast-enhanced CT and T1-weighted MRI-scans with a slice thickness of 1.5–2 mm were used. The GTV was defined as the macroscopic tumor visible adding a safety margin for the PTV of 0.5–1 mm. The median PTV was 1.0 ml (range 0.1–5.4 ml). Treatment plan calculation was performed using the Brainscan planning system from BrainLAB.

For FSRT, a median dose of 54 Gy/100% isodose (range 30–54 Gy) in single fractions of 1.8 Gy (range 1.8–5 Gy) was applied. Treatment planning was identical to SRS, however individually manufactured Aquaplast-masks were used for immobilization, and the GTV-PTV margins were 1.5–2 mm. The median PTV for FSRT was 3.5 ml (0.1–19.3 ml). Both SRS and FSRT were performed with a 6 MeV LINAC adapted for stereotactic treatment with a leaf width of 3 mm at isocenter (Siemens, Erlangen, Germany).

All patients were included in a follow-up program including clinical assessment with special focus on hearing evaluation as published previously [29].

Freiburg treatment planning

Patients treated between 1998 and 2012 were included. For the SRS was used a commercial 3D planning system (Stereoplan STP and VIRTUOSO; Stryker-Leibinger, Freiburg, Germany) with 6–12 non-coplanar beams. The patients were fixed in a stereotactical ring (Leibinger, Freiburg, Germany). Irradiation was performed using mMLC with a leaf width of 1.6 mm at the isocenter or circular collimators. The GTV and PTV were delineated based on MRI/CT image co-registration. PTV was outlined with 1.5 mm margin to GTV. A median single dose of 13 Gy/95% isodose (range 12–15 Gy) was applied on the 95% isodose encompassing the PTV.

For fractionated treatments, patients were fixed minimally invasive with an in-house made stereotactic mask. The GTV was delineated based on CT/MRI image fusion. The PTV was defined with 2 mm margin to GTV. The treatment planning was performed in Helax TMS (Sweden) and Oncentra Masterplan (Elekta, Sweden) using 12–14 non-coplanar beams. A median total dose of

Table 1
Patients' characteristics regarding radiation therapy details per center.

	Heidelberg	Munich	Freiburg
Total patients	246 (248 VS)	124 (124 VS)	79 (79 VS)
Female	102 (41%)	61 (49%)	41 (52%)
Male	144 (59%)	63 (51%)	38 (48%)
FSRT, Pat.	216 (87%)	68 (55%)	60 (76%)
Dose FSRT median (range)	57.6 Gy/isocenter (25–66 Gy/isocenter)	54 Gy (30/3–54/1.8 Gy) 100% isodose	54 Gy (39/3–54/1.8 Gy) 95% isodose
SRS, Pat.	32 (13%)	56 (45%)	19 (24%)
Dose SRS median (range)	13 Gy/80% isodose (10–20 Gy)	12 Gy/100% isodose	13 Gy/95% isodose (12–15 Gy)

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