Radiation Therapy in Acoustic Neuroma

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Abstract

Neuromas or schwannomas of the eighth cranial nerve are benign slow-growing Schwann cell-derived tumors, called acoustic neuromas, or vestibular schwannomas. The incidence is approximately less than 1 per 100,000 persons/year. Acoustic neuroma has a clinical presentation related to cranial nerve involvement or brainstem and cerebellar compression due to tumor progression. When suspected, clinical diagnosed is confirmed by MRI. The management of vestibular schwannoma is still a quite controversial issue and can include wait and see policy, surgery, and radiotherapy. The treatment choice is based upon the balance between the expected morbidity of the tumor and of the therapy, taking into account also patient's preference.

Medium size (2–3 cm) and large tumors (>3 cm) need an active treatment (surgery or radiotherapy), while smaller tumors can undergo observation as an alternative to active treatment.

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Epidemiology, clinical presentation, diagnosis, and results of the current treatment options including observation, surgery, and radiotherapy will be presented and discussed.

Keywords
Acoustic neuroma · Observation · Surgery · Radiotherapy · Treatment outcome

Epidemiology

Neuromas or schwannomas are benign Schwann cell-derived tumors. When occurring in the vestibular portion of the eighth cranial nerve, they are called acoustic neuromas or vestibular schwannomas. This tumor is the most common of the cerebellopontine angle (90%) accounting for approximately 6% of all intracranial neoplasms. The incidence is approximately less than 1 per 100,000 persons/year (Lin et al. 2005). During the last decades, the incidence of acoustic neuroma seems to be growing. This is caused by improvement of audiology tests, increasing access to magnetic resonance imaging (MRI) and significant longer and healthier lifetime of the population. For these reasons, the tumor size at diagnosis has been decreased and treatments such as surgery and radiotherapy have improved the chance of hearing and facial nerve function preservation (Stangerup et al. 2010).

Acoustic neuromas occur more frequently unilaterally and only rarely bilaterally. For the unilateral presentation, the median age at diagnosis is 50 years, with a gender ratio (F:M) greater than 1. A bilateral vestibular schwannoma is pathognomonic of neurofibromatosis type 2 (NF2) and occurs in younger age, typically at 10–20 years (Chen et al. 2016).

Virtually in all schwannomas and in NF2 disease as well, tumor cell proliferation is caused by altered production of the tumor suppressor schwannomin due to inactivation of the NF2 gene (Schulz et al. 2016). The knowledge of the biological behavior of the sporadic tumor is currently poor, being the pattern of growth different and heterogeneous. The biomarkers involved in the cascade of benign cells proliferation by intratumor assessment of peptides YAP, TAZ, and Areg have been recently investigated. The aim of aforementioned research line is to find a correlation between tumor size and pattern of growth. The results of these studies are still preliminary but quite encouraging (Martini et al. 2017).

Possible risk factors associated to the development of acoustic neuroma are the followings:

- Childhood exposure to ionizing radiation due to medical treatment or extraordinary events (i.e., atomic explosions) (Schneider et al. 2008);
- Exposure to electromagnetic fields; a recent meta-analysis reported a significantly higher risk for any type of intracranial tumor after use of mobile phone over 10 years (odds ratio (OR) = 1.3, 95% confidence interval (CI): 1.028–1.704) (Bortkiewicz et al. 2017);
- Noise exposure; a meta-analysis published in 2016 suggests an elevated risk for acoustic neuroma in individuals who were ever exposed to leisure noise (OR = 1.3, 95%CI: 1.05–1.68), but not to occupational noise (OR = 1.2, 95% CI: 0.84–1.72) (Chen et al. 2016).

Symptomatology

Acoustic neuroma has a clinical presentation related to cranial nerve involvement or brainstem and cerebellar compression due to tumor progression.

Symptoms related to cochlear nerve are hearing loss and tinnitus. Unilateral hearing progressive or sudden abnormalities are present in the majority of patients, sometimes with complete recovery after onset of hearing loss and tinnitus. This clinical deficit may be progressive and chronic and patients are not always able to be fully aware of this symptom.

The finding of a small acoustic neuroma may also be incidental, which is today not so infrequent due to available imaging performed for other medical reasons.

The involvement of the vestibular nerve is clinically represented by vertigo. During the clinical examination, patients describe an unsteadiness while walking or sudden onset of vertigo during head movement, not relating to the most typical otologic forms of peripheral vertigo. Some patients do not usually describe acute symptomatology because of the slow-growing behavior of the acoustic neuroma, which allows the central vestibular system to develop a physiological compensation (Chen et al. 2016).

An accurate report of the clinical history and a greater attention on these kind of disease make easier to reach an early diagnosis at the beginning of such symptoms. Clinical examination may be normal in presence or absence of symptoms, but an accurate vestibular examination shows asymmetry of labyrinthine function, which is a high index of suspicion of unilateral peripheral disease. If symptoms are underestimated or the intrameatal portion of the tumor does not primarily affect hearing or balance, the tumor may grow in the cerebellopontine angle and the diagnosis becomes evident when signs of cerebellar and brainstem compression appear. When the expansion into the cerebellopontine angle is observed, sometimes as the consequence of an inadequate patient's follow-up if the tumor is observed, the tumor may lead to trigeminal nerve symptoms (i.e., paresthesia, hyperesthesia and pain) as well as facial nerve symptoms (i.e., facial nerve paralysis). The facial nerve may be subclinically affected although its clinical function is still normal. This is an event occurring also with small intrameatal tumors when growth expands the internal auditory canal, determining nerves compression between the bony walls and the tumor. Moreover, ataxia and impairment of IX, X, XI, and XII cranial nerve function are symptoms of large tumors compressing cerebellum and brainstem (Frisch et al. 2015).

Diagnostics and Classification

An acoustic neuroma should be hypothesized in case of asymmetric hearing loss or other VIII cranial nerve deficits. In fact, the natural history of this benign tumor is related to the extension from the internal auditory canal into the cerebellopontine angle and then brainstem compression, if not treated.

The histopathologic appearance has a typical pattern and consists of two subtypes: Antoni A and Antoni B.

The Antoni histological subtype A is characterized by a dense cellularity, whereas the Antoni B is characterized by a sparse cellularity. At immunohistochemistry, acoustic neuroma expresses S-100 protein (Sriskandan and Conner 2011).

Complete medical history has to be investigated and physical examination should be reported with a great attention to the neurological symptoms and signs. The performance status should be scored according to the Karnofsky performance status (KPS) or the Eastern Cooperative Oncology Group (ECOG) scale. The neurological assessment should include the neurological function status (NFS). Pure tone and speech audiometry are the most useful screening tests for assessing hearing function. Selective loss of speech discrimination in excess of pure tone loss is particularly suggestive of acoustic neuroma. Hearing performance is assessed according to Gardner-Robertson grade hearing classification, where grade 1–2 are good and serviceable hearing function, while grade 3–4 are nonserviceable and poor hearing function. The facial nerve function should be evaluated according to House–Brackmann facial weakness scale, where grade 1 describes a normal symmetrical function in all areas; grade 2 a slight weakness; grade 3 an obvious weakness, but not disfiguring; grade 4 an obvious disfiguring weakness; grade 5 a motion barely perceptible; and grade 6 no movement, loss of tone (Persson et al. 2017).

Imaging studies are the standard for the diagnosis and differential diagnosis of acoustic neuroma. Size, location, and growth of the acoustic neuroma are defined by radiological imaging. Nowadays, MRI is the gold standard, although high resolution computed tomography (CT) scan with and without contrast enhancement is a good alternative in case of contraindication to MRI. An acoustic neuroma appears hypo-isointense at T1-weighted sequences, whereas it is

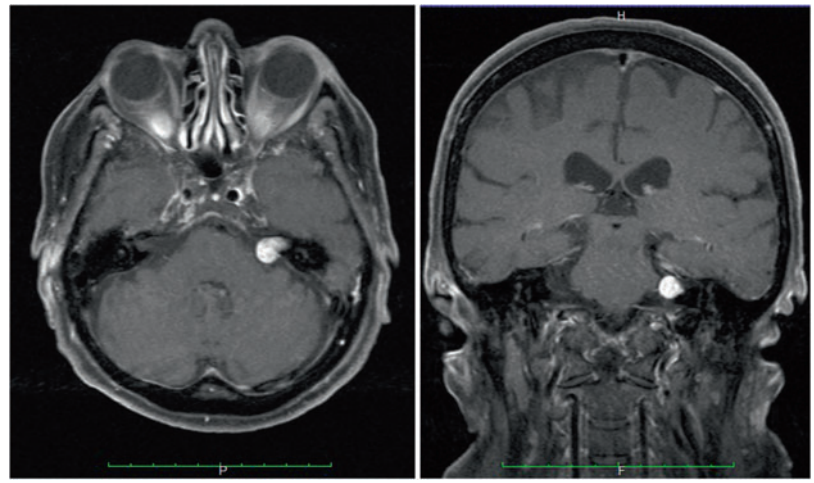

Fig. 1 Axial and coronal T1-weighted postcontrast MRI demonstrate a postcontrast enhancing small acoustic neuroma in the left cerebellopontine angle

T2-weighted hyperintense relative to the pons (Fig. 1). Although acoustic neuromas typically have a homogeneous contrast enhancement at postgadolinium T1-weighted sequences, heterogeneous and cystic appearances of the tumor tissue are also described. Entirely intracanalicular tumors with the typical trumpeted internal acoustic meatus (IAM) are usually round or oval, with a convex medial margin.

Any extrameatal component is usually spherical with a funnel-shaped component with respect to the IAM, often similar to an "ice cream cone" (Sriskandan and Conner 2011).

The two previously reported histological subtypes are responsible of the different MRI findings. Antoni histological subtype A tumors are smaller and enhance homogeneously; Antoni histological subtype B or mixed A and B tumors are larger with cystic components and heterogeneous enhancement (Sriskandan and Conner 2011).

Constructive interface in steady-state (CISS) T2-weighted sections may be performed for screening purpose, along with drive equilibrium (DRIVE) and fast imaging employing steady state with phase cycling (C-FIESTA). Contrast-enhanced sequences are added in case of a suspicious lesion.

Tumor size measurement should include intra and extra-canalicular dimensions, using at least linear measurement of both maximum axial and cranial-caudal directions (Committee on Hearing and Equilibrium 1995; Smouha et al. 2005).

In regard to tumor location and dimension, acoustic neuromas are staged according to Koos classification (Sriskandan and Conner 2011), as follows:

Stage I: purely intracanalicular lesions
Stage II: extrameatal tumor defined as those protruding into the cerebellopontine angle without contact with the brainstem; tumor <2 cm in diameter
Stage III: extrameatal tumor reaching, indenting, but not shifting the brainstem; tumor >2 cm in diameter
Stage IV: extrameatal tumor compressing the brainstem regardless of the size

To achieve a correct diagnosis and treatment approach, a good knowledge of the imaging characteristics of these tumors is crucial. Acoustic neuroma is in differential diagnosis with meningiomas, epidermoid cysts, nonacoustic schwannomas, vascular lesions, and last but not least lesions infiltrating from adjacent structures. Such lesions may arise from meninges, vascular tissue, bone, fat, and embryological elements (Sriskandan and Conner 2011).

General Management Principles

The main management options for acoustic neuromas are observation, surgical resection, and radiation therapy. Each choice is a balance between the expected morbidity of the tumor and of the therapy.

Medium size (2–3 cm in the cerebellopontine angle) and large tumors (>3 cm) need active treatment (surgery or radiotherapy) and the matter knows no controversy.

The problem arises when small tumors are diagnosed and hearing is still present, which is rather a common event today due to early diagnosis. In this framework, an active therapy should be conceived only if gives better prognosis than observation.

The natural history of acoustic neuroma is slow growth, with unpredictable pattern, or no growth, and hearing decline, which takes place inexorably over the years in an unforeseeable manner and despite growth. Recent studies on observation showed that intrameatal tumors may stop growing in more than 70% of the cases (Kirchmann et al. 2017; Stangerup et al. 2010). Once the tumor develops in the cerebellopontine angle and growth is evident, it rarely stops although progression occurs in an unpredictable manner. Observation is an option in those non- or very slow-growing tumors, which remain small or within the size of 1.5 cm in the cerebellopontine angle (Brackmann et al. 1994; Falcioni et al. 2011). Waiting for a further growth is not advisable, since the facial nerve may become affected and the morbidity of the active therapy becomes higher. In elderly patients, observation may be proposed up to 2 cm tumor size, provided no compression or symptoms are evident. The limit for observation is also related to the expected morbidity of the treatment which is going to be proposed. By surgery, facial nerve preservation is inversely proportional to tumor size and excellent functional results on the facial nerve can be obtained with lesions up to 1.5 cm (Brackmann et al. 1994; Falcioni et al. 2011). By radiotherapy, the main issue is hearing preservation which correlates to the maximum dose to the cochlea, whereas facial nerve deficit rarely appears (Marks et al. 2010).

When observation is proposed in small tumors with good hearing at the diagnosis, hearing preservation rates are excellent at short term, but long-term results of the largest series show that at 10 years the rate of preservation is 17% and serviceable hearing around 35% (Kirchmann et al. 2017).

When this noninterventional approach is proposed to young and healthy patients, the debate is the hearing outcome at long term, since this affects the prognosis of hearing all life-long.

For each patient under observation, a clinical and imaging monitoring the size of the tumor should be performed at least annually. Two review studies analyzed the results of 2327 patients' natural history of acoustic neuromas and recommended a change from the "wait and see" approach to an active therapy in case of tumor growth >2.5 mm/year or hearing symptoms progression (Smouha et al. 2005; Sughrue et al. 2010). An active treatment should guarantee a high chance of local control, as well as preservation of cranial nerve function. The current results in terms of tumor control and functional outcome permit a tailored approach based on tumor presentation (size), growth, and patient's characteristics. The choice between surgery and radiotherapy depends on the planned goal of therapy and should be extensively discussed with the patient. Hearing preservation surgery, radiotherapy, or observation are equivalent options at short term, but the value of each choice on hearing function should be judged at long term (Apicella et al. 2016; Carlson et al. 2013; Gait et al. 2014; Mazzoni et al. 2011).

In medium-size tumors, where control of growth is the main goal, surgical resection, or radiotherapy gives good results in terms of disease control and functional nerve preservation (V, VII, IX, X, XI, XII cranial nerves): surgery is generally recommended for younger and healthy patients while radiotherapy for all the other cases (Zanoletti et al. 2016).

Large tumors, often with perilesional edema, brainstem compression, or cystic components, are probably better treated by surgery, although the predictable postoperative morbidity is high, mainly related to VII and IX-XII cranial nerve deficits.

The systemic treatment has a limited role in the management of acoustic neuroma. A few studies have explored the use of antiangiogenetic drugs such as bevacizumab in progressive bilateral acoustic neuromas associated with neurofibromatosis type-2 (NF-2). Temporary promising results have been obtained, but tumor re-growth is observed after stopping the treatment (Plotkin et al. 2009).

Given the variety and complexity of therapeutic approaches, a multidisciplinary team work with radiologist, pathologist, otolaryngologist, neurosurgeon, and radiation oncologist is essential in the management of acoustic neuroma, in order to discuss diagnostic and treatment aspects and offer the best and most appropriate management taking into account also patients' preferences.

Surgical Therapy

Historically, the first successful surgery was performed by Sir Charles Balance in 1894. Currently, the goals of the surgical treatment are the cure of the disease with complete resection and the lowest morbidity, with the preservation of facial nerve and, when feasible, of hearing function. When hearing preservation is required, surgery can be performed with three standard operative approaches, summarized as: standard retrosigmoid, retrosigmoid with retrolabyrinthine meatotomy, and middle cranial fossa approach (Angeli 2012; Brackmann et al. 1994; Friedman et al. 2011; Samii et al. 2006; Zanoletti et al. 2016). All of them are microsurgical approaches and can benefit from the use of the endoscope to better visualize the nerves at the fundus of the internal auditory canal. The preoperative selection of patients is a key point in the therapy planning and can be based on predefined decision criteria (Martini et al. 2017):

- If hearing is still preserved, the retrosigmoid approach and retrolabyrinthine meatotomy (Mazzoni et al. 2017) are the surgical options of choice; the middle cranial fossa approach can also be adopted, especially for intrameatal tumors with very limited extension in the cerebellopontine angle (Figs. 2 and 3). The institution experience and surgeon preference can influence the choice, but the risk of worse functional result on facial nerve by using the middle cranial fossa compared to the retrosigmoid approach should be carefully considered.
- If hearing function is severely impaired or definitively lost, or the preoperative conditions are too poor for attempting hearing preservation surgery, the goal should be control of the disease possibly with good functional results on the facial nerve. In general, the translabyrinthine approach is preferred, because it allows a transpetrous corridor to the cerebellopontine angle, with no cerebellar retraction and easy identification of the facial nerve in all its tract (Fig. 4). The long bony work which is required is made at the expense of hearing loss. The translabyrinthine approach provides an extradural corridor to the internal auditory canal, allowing for a good exposure of the cerebellopontine angle with the possibility of a radical removal of the tumor with nerves and vessels under direct control, for any size of tumors. In these conditions, the retrosigmoid approach is also feasible and, in the majority of the cases, the surgeon's expertise guides the preference for the approach (Zanoletti et al. 2016).

When a radical resection is achieved, the tumor recurrence rate is near to 3% after hearing preservation surgery with the retrosigmoid approach; this rate grows to 21–22% in case of subtotal resection (Zanoletti et al. 2016).

The reported surgery-related death and severe complication rates are lower than 0.5% in the more recent series (Mazzoni et al. 2011; Samii et al. 2006). It should be underlined that surgery can be considered a low-morbidity treatment, with

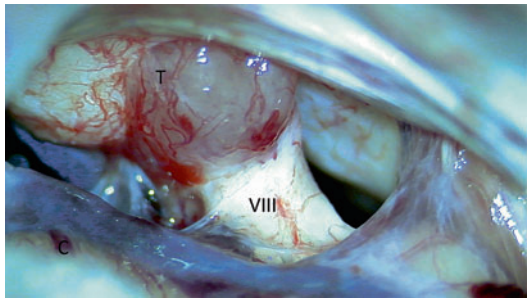

Fig. 2 Right small vestibular schwannoma with few millimeters extension in the cerebellopontine angle. Retrosigmoid approach. The petrous bone has not yet been drilled. *T* tumor, *VIII* eight cranial nerve, *C* cerebellum

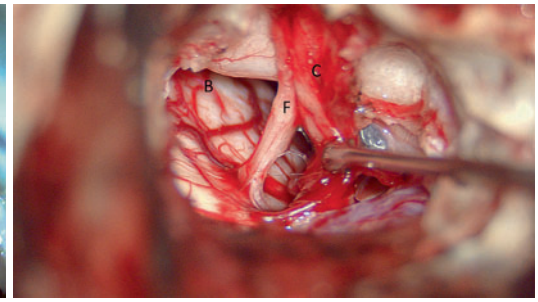

Fig. 4 Right side exposure of the cerebellopontine angle after removal of acoustic neuroma with translabyrinthine approach. The internal auditory canal is drilled, and the whole course of facial nerve (*F*) and cochlear (*C*) nerve is exposed, from the roots to the fundus. Tumor has been completely excised with preservation of the nerves. A large view of brainstem (*B*) and of the cerebellopontine angle is allowed by this approach

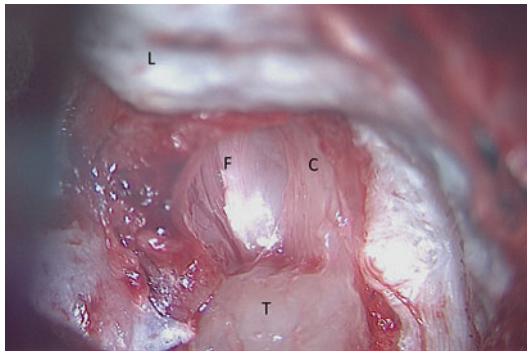

Fig. 3 Right side removal of the intracanalicular portion of the small acoustic neuroma with retrosigmoid approach and retrolabyrinthine meatotomy. The internal auditory canal has been drilled up to the fundus. *F* facial nerve, *C* cochlear nerve, *T* tumor, after removal from the fundus of the internal auditory canal; *L* labyrinth

very few major or minor complications if it is performed in centers with numerous cases by experienced hands. In this regard, small and medium-sized tumors do not differ in terms of the associated major complications. On the other hand, looking at long-term facial nerve and hearing preservation outcomes, tumor size is a crucial factor. The postsurgical rate of normal facial nerve preservation is 83–96% for patients with tumors up to 1.5 cm in size, while the rate falls down to 70% in tumors over 2.5 cm and to 50% in those over 3.5 cm (Falcioni et al. 2011).

Considering the aforementioned data, 1.5 cm should be considered the cut-off tumor size for a treatment that can guarantee a better outcome. In this tumor setting, preservation of useful hearing typically ranges from 51% to 74%, but there are also some reports in the literature of only 5% (Mazzoni et al. 2011; Myrseth et al. 2009; Samii et al. 2006). The variability of these results, which is the main problem of the conservative microsurgical approaches, relates not only to the surgeon's experience, but also to the preoperative selection of patients, which influences prognostically the outcome: again, better results are reported in series with small tumor with good preoperative hearing.

Radiation Therapy

The first radiation treatment for acoustic neuroma was conducted by Leksell in 1969. Nowadays, radiotherapy is used in case of radical treatment or in case of planned subtotal resection for large lesion (>3 cm) at excessive risk of neurological impairment or in case of disease recurrence after surgery (Apicella et al. 2016).

In terms of technical aspects, SRS can be performed with Gamma Knife (Elekta AB, Stockholm, Sweden) and also with linear accelerators (LINACs) equipped with micromultileaf collimators and high dose rate for stereotactic radiation

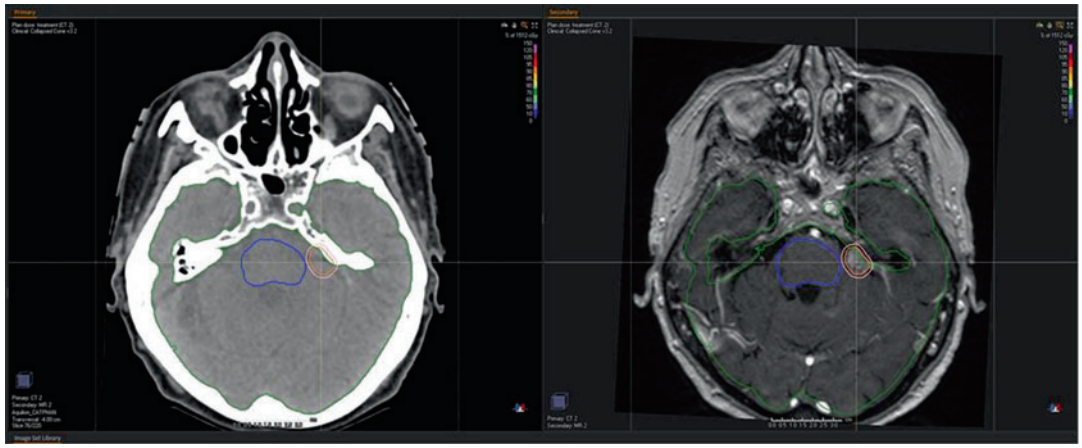

Fig. 5 CT simulation and co-registered MRI for a patient with a left-sided acoustic neuroma. The gross tumor volume (*GTV*) is outlined in orange (internal contour) and the planning target volume (*PTV*) in pink (external contour); the brainstem is outlined in blue

therapy or with CyberKnife (Accuray, Sunnyvale, CA, USA), a LINAC mounted on a robotic arm. LINACs can also be used for fractionated treatments (Persson et al. 2017).

For radiotherapy simulation purpose, the patient is in supine position and a stereotactic frame can be applied to the patient's head using local anesthesia for Gamma Knife SRS. A modified stereotactic frame or a 3-point thermoplastic fixation mask is often used for LINAC-based systems.

A contrast-enhanced CT scan is acquired at a thickness of 1 to 3 mm from the vertex of the head to the mid-cervical spine. Co-registration and fusion with a gadolinium-enhanced T1-weighted MRI with 1 to 2 mm slices allows for the identification of tumor volume and organs at risk (Fig. 5).

The gross tumor volume (GTV) should be delineated by the T1-weighted MRI with gadolinium. In case of thermoplastic fixation mask, planning target volume (PTV) is based on the set-up error and patient's position reproducibility. Organs at risks, including brain, brainstem, chiasm, optic nerves, and cochlea have to be also outlined. A planning at-risk volume based on set-up of 2–3 mm is generally applied around the critical structures (Fig. 6) (Persson et al. 2017). Suggested treatment volumes and doses are reported in Table 1.

Image guided radiotherapy (IGRT) depends on the type of treatment machine. In case of treatments performed on a linear accelerator, a cone-beam CT should be the standard of care for the daily IGRT. In case of dedicated machine such as Gamma Knife and CyberKnife, orthogonal kV x-rays are performed.

General planning strategies are 3-dimensional-conformal radiotherapy, intensity-modulated radiotherapy (IMRT), and volumetric-modulated arc therapy (VMAT) with circular or micro-multileaf collimator. Treatments are mainly performed by using one to multiple isocenters, in particular in case of Gamma Knife radiosurgery (Persson et al. 2017). Ideally, at least 95% of the PTV should receive the prescription dose in case of FSRT. For SRS, planning is evaluated according to conformality index, heterogeneity index, and gradient index. Dose identification to organs at risk is integral part of the quality control before approving the treatment plan. Suggested dose constraints are reported in Table 2.

Stereotactic radiotherapy (SRT) can be performed in single fraction (stereotactic radiosurgery, SRS) or in multiple fractions (fractionated stereotactic radiotherapy, FSRT), with standard fractionation or hypofractionation.

Stereotactic radiosurgery for acoustic neuroma, usually prescribed to median marginal dose of 12–13 Gy, provides a good local control, with a progression-free survival rate of 95% after

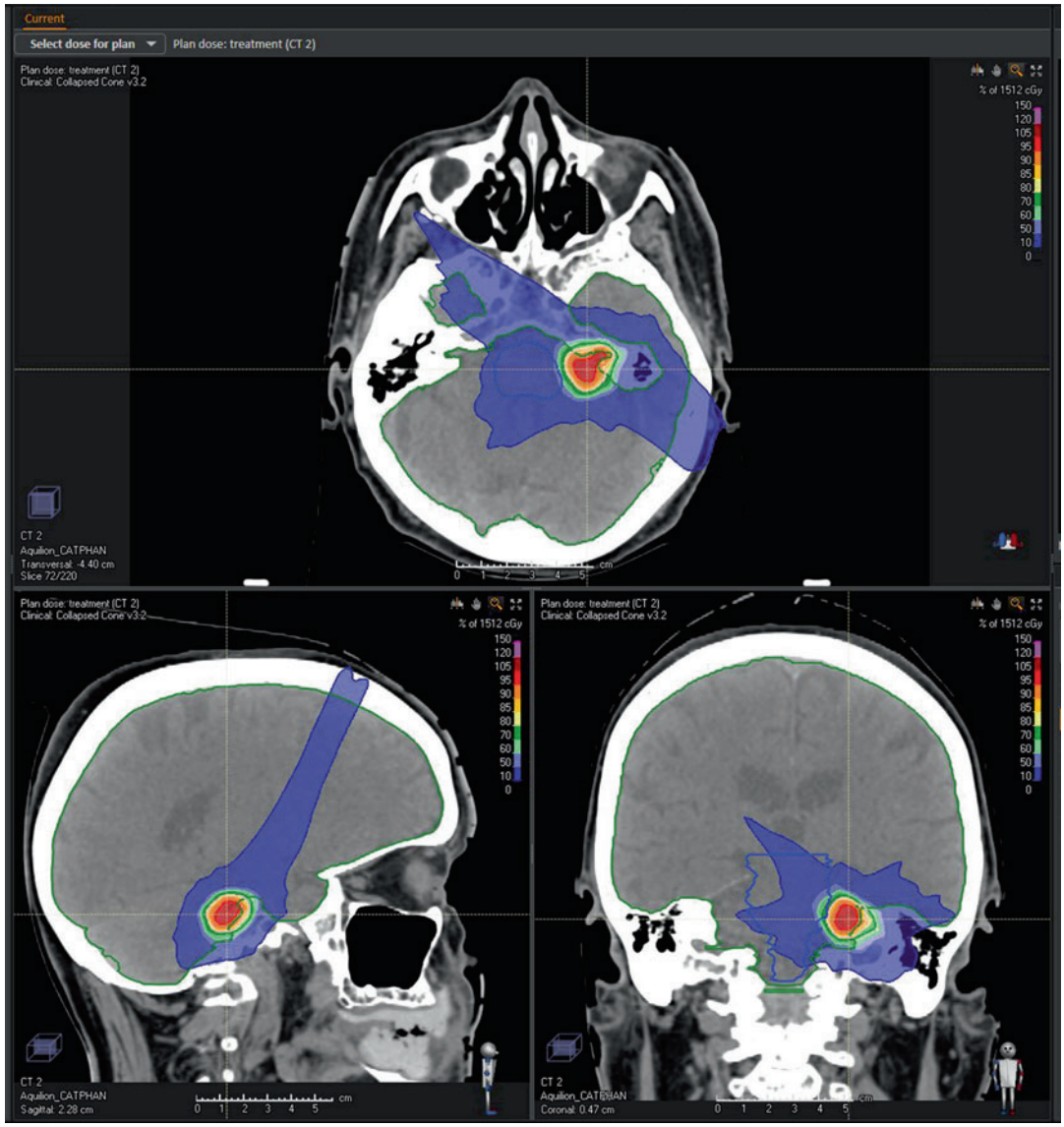

Fig. 6 Radiosurgery treatment plan with volumetric-modulated arc therapy (VMAT). The red color wash volume is encompassed by the isodose of 95% (dose prescription to 13 Gy)

median follow-up of 5–10 years. The average hearing deterioration rate after treatment is 49% when scored with Gardner-Robertson classification. In the majority of studies, facial and trigeminal nerve deterioration according to House–Brackmann scale is 3.6% and 6%, respectively, as reported in a recent systematic review (Persson et al. 2017).

Recent literature large series reported quite detailed data in terms of local control, hearing preservation, and side effects. Boari et al. reported a local control of 97.1% with a tumor volume downsizing of 82.7% at 6.5 years follow-up in 523 patients treated with Gamma Knife SRS to a median margin dose of 13 Gy. Treatment-related complications were only a transient worsening of pre-existing symptoms. The overall rate of serviceable hearing was 49% (Boari et al. 2014). Hasegawa reviewed the results of 347 patients treated by Gamma Knife. The actuarial 10-year

Table 1 Suggested target volumes and radiation doses for acoustic neuroma

Target volume	Definition	Dose
GTV	Tumor volume defined as the outer edge on postcontrast T1-w MRI	
CTV	CTV = GTV	
PTV	CTV + no margin in case of GK-SRS	GK-SRS: 12–13 Gy to the tumor volume in a single session prescribed to the 50% isodose (40–100%)
	CTV + 0.5–2.0 mm depending on setup system in case of SRS	LINAC-based SRS: 12–13 Gy to the 80–90% isodose
	CTV + 1.5–2.0 mm depending on setup system and reproducibility of patient positioning in case of FSRT	LINAC-based FSRT: 45–54 Gy, 1.8 Gy/fx to the 95% isodose (or hypofractionation)

GTV, gross tumor volume; *CTV*, clinical target volume; *PTV*, planning target volume; *GK-SRS*, Gamma Knife stereotactic radiosurgery; *LINAC*, linear accelerator; *fx*, fraction; *FSRT*, fractionated stereotactic radiotherapy

Table 2 Normal tissue dose constraints for conventional fractionation and stereotactic radiosurgery (SRS) (Marks et al. 2010)

Critical Structures	Conventional fractionation	SRS	Event
Spinal cord	Dose max <50 Gy	Dose max 13 Gy	Myelopathy
Brainstem	Dose max <55 Gy	Dose max 12.5 Gy	Permanent cranial neuropathy or necrosis
Cochlea	Dose max 55 Gy Mean dose <45 Gy	Dose max 12–14 Gy	Sensory neural hearing loss
Ventral cochlear nucleus Modiolus and the basal turn of the cochlea		≤ 9 Gy Ideally <4–5.3 Gy	

progression-free survival rate was 92%. The actuarial 10-year rate for preservation of VII nerve function was 97% in the marginal dose group (>13 Gy) and 100% in the marginal dose group (≤13 Gy) (Hasegawa et al. 2013). Kim et al. reported on their series of 60 patients treated with Gamma Knife to 12 Gy and observed that tumor growth of more than 20% from the pretreatment tumor size was a statistically significant risk factor for hearing deterioration. In addition, they identified a mean cochlear dose threshold of 4 Gy for the loss of serviceable hearing. The mean maximal and mean radiation doses to the ipsilateral cochlea were 8.2 ± 0.4 Gy (range, 2.7–16.6 Gy) and 4.2 ± 0.2 Gy (range, 1.6–8.9 Gy), respectively (Kim et al. 2013).

Stereotactic radiosurgery with single doses of 13–14 Gy can be used to treat also postsurgery residual and recurrent acoustic neuromas, reporting a local control rate >90%, with a worsening of hearing function observed in up to 42% of the patients (Krengli et al. 2015).

Stereotactic fractionated radiotherapy was firstly used as an adjuvant treatment for non-radically removed acoustic neuromas. A fractionated schedule is currently employed in case of large tumors compressing and displacing the nervous structures when surgery is not feasible for local or general patient condition or for patient refusal. In this regard, fractionation can reduce the risk of late damage to brainstem and cerebellum in relation with the low alpha/beta value of the nervous tissue which is estimated of about 3 Gy.

A total dose of 45–55 Gy in 20–30 fraction with 5 fractions per week or an equivalent dose with hypofractionation is recommended in case of FSRT. In the last case, the most frequently dose prescription applied is 18 Gy in 3 fractions (Apicella et al. 2016). In this regard, the linear quadratic model showed an alpha/beta value for acoustic neuroma of 2.4 Gy (Vernimmen and Slabbert 2010). Fractionated stereotactic RT provides a high local control grade, with only 4.8%

loss of tumor control in long-term follow-up series. The risk of neurological deterioration in terms of hearing quality and facial deficit is similar to that of SRS (Persson et al. 2017).

Hansasuta reviewed the results in 383 patients treated with CyberKnife at the Stanford University Medical Centre between 1999 and 2007. A total dose of 18 Gy in 3 fractions was prescribed to a median tumor volume of 1.1 cc (range 0.02–19.8 cc). Local control rate at 5 years was 96% with a serviceable hearing preservation rate of 76%. Two percent of the patients developed trigeminal dysfunction, while no case of post-FSRT facial weakness was reported (Hansasuta et al. 2011).

A recent French experience reported outcomes in 158 acoustic neuromas treated with conventional fractionation. Patients received a dose of 50.4 Gy in five daily fractions of 1.8 Gy per week. Local tumor control rate was 95.2% after 7 years follow-up. Tinnitus and facial nerve impairment were observed in 2.1% and 2.5% of patients, respectively (Litre 2013). A reduction in total dose for FSRT to 46.8 Gy was explored by Champ et al. in 154 patients with acoustic neuroma. The 5-year tumor control rate was 93% with a hearing preservation of 54% (Champ et al. 2013).

Proton therapy may be an option for the treatment of acoustic neuroma since the proximity of radiosensitive organs at risk. The rapid fall of the dose to zero beyond the Bragg peak offers a theoretical advantage in this tumor setting (Fossati et al. 2016). Protons were used to a total dose of 26 Gy (RBE) in 3 fractions with mean minimum tumor dose of 21.4 Gy (RBE) at iThemba LABS, South Africa. Vernimmen et al. in a series of 51 patients, most of them with unresectable or recurrent acoustic neuroma, reported 98% of local control rate with a hearing preservation of 42%, facial nerve preservation of 90.5%, and trigeminal nerve preservation of 93% after mean follow-up of 60 months (Vernimmen et al. 2009).

Systemic Treatment

A standard systemic treatment does not exist for acoustic neuroma. Current research is moving on targeted therapy.

In case of neurofibromatosis type 2 with bilateral acoustic neuroma, where the standard treatment, based on surgery and radiotherapy, is encumbered with a high risk of side effects, patient's quality of life with the best preservation of bilateral hearing function should be the primary aim of the treatment. In such patients, antiangiogenetic treatment has been investigated with bevacizumab that binds the vascular epithelial growth factor (VEGF). Vascular endothelial growth factor (VEGF) and its receptor (VEGFR-1) have been detected in schwannomas, and increased levels of these factors correlate with increased rates of tumor growth (Plotkin et al. 2009). The first experience was reported by Plotkin et al. in patients who were poor candidates to standard treatments because of bilateral growing and compressing neuromas. After bevacizumab, 60% of patients had an imaging response. Furthermore, the median best response was a volumetric shrinkage of 26%. Currently other target molecules, such as everolimus, trastuzumab, and erlotinib, are under investigation (Ouerdani et al. 2016).

Outcome and Prognosis: Comparative Studies

The optimal modality for evaluating patient outcome is still matter of debate. Since acoustic neuroma is a slow-growing tumor, a prolonged follow-up time should be recommended. A follow-up regimen, with a first assessment within 6 months after surgery or radiotherapy and yearly thereafter, is usually adopted. The follow-up schedule includes contrast-enhanced MRI, hearing examination, and both facial and trigeminal nerve assessment as performed before treatment. The clinical outcome recorded on the medical report should include the assessment of tumor control defined as tumor growth arrest or tumor-shrinkage as well as tumor progression, stated by any radiological change of >2 mm in tumor

diameters, tumor 10–20% larger than the pretreatment tumor volume, or the necessity of a new treatment (Persson et al. 2017).

In this regard, the precise evaluation of tumor response or progression is not always easy to achieve. A possible radiotherapy effect is a transient increase in volume that mimic tumor progression, the so-called "pseudoprogression," related to edema or even necrosis of the tumor tissue. Such finding has been reported by MRI in one-fourth of patients treated for acoustic neuromas, occurring early after treatment. Therefore, repeated imaging and clinical follow-up should be performed for quite a long-time (Régis et al. 2017).

With the same attention, hearing deterioration as well as facial and trigeminal nerve deterioration should be checked during follow-up. In general, late side effects are observed within the first year after treatment, but the percentage of patients who can develop such symptoms after many years is not negligible.

In terms of treatment or no-treatment choice the debate is still open. To date, no prospective comparative randomized trials have been conducted in order to clarify the best approach for small, medium size, and large acoustic neuromas. However, quite large nonrandomized comparative studies are reported in the literature.

Breivik et al. reported on tumor growth rate, hearing loss, and quality of life of 237 patients with unilateral acoustic neuroma receiving either Gamma Knife SRS (12 Gy) or just observation. No significant difference in hearing preservation was observed between the two approaches: hearing was lost in 76% of conservative management patients and 64% of SRS patients. Of note, a highly significant percentage of patient needed for treatment following initial observation ($p < 0.001$) (Breivik et al. 2013). At present, based on literature data, the wait and see policy is considered the best initial option with regard to quality of life for not growing acoustic neuroma smaller than 1.5 cm.

In case of acoustic neuromas larger than 1.5–2 cm, microsurgery and SRS have comparable results in terms of tumor control. As a matter of fact, the available data suggest that local control rates higher than 80% can be achieved either with surgical resection or stereotactic radiotherapy. The main difference between surgery and radiotherapy is the onset of neurological deterioration which occurs immediately after surgery and usually 6–12 months or even later after radiotherapy. Microsurgery can be performed with low mortality, but it is still associated in some cases with a significant risk of neurological deficit in particular correlated to facial mimic. Furthermore, the bias of heterogeneity of microsurgical series is far to be solved. On the other hand, after a few decades experience, many centers adopted SRS for treatment of primary acoustic neuromas as a valid alternative to surgery. The center experience and the patients selection make difficult comparing outcome between the two procedures. In this regard, since no randomized studies have been conducted in order to compare the two treatment approaches, there is insufficient evidence to recommend either surgery or radiation therapy in the treatment of acoustic neuroma (Muzevic et al. 2014). In this regard, Maniakas's recent metanalysis reported a significant lower risk of neurological deterioration (serviceable hearing of 70.2% vs. 50.3%, $p < 0.001$) in favor of radiotherapy with similar tumor control rates (96.2% vs. 98.7%, $p = 0.122$) for acoustic neuromas <3 cm (Maniakas and Saliba 2012).

As far as radiation therapy is concerned, no randomized controlled studies comparing the safety and efficacy of SRS and FSRT have been published; however, studies comparing patients with similar tumor characteristics show that results are very similar in terms of local control and peripheral nerve toxicity (Table 3). Based on long-term results a lower number of experiences are reported after FSRT than after SRS. Such more solid data support the use of SRS for favorable long-term tumor control. The risk of facial and trigeminal nerve deterioration was less for patients treated in the SRS series compared to patients receiving FSRT, while the chance of preserved hearing showed no difference between the two treatment groups (Kessel et al. 2017).

In patients affected by acoustic neuromas, one more possible issue to take into account for the choice of the management is represented by the

Table 3 Selected series of acoustic neuroma comparing stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT)

Author	Year	N. of pts	Median follow-up (months)	Median dose	Mean/Median volume (cc)	Local control	Hearing preservation	Toxicity		
								VII c. n.	V c.n.	Others
(Collen et al. 2011)	2011	78	56	SRS 12.5 Gy	1.7	95%	82% 4 y	16%	6%	5% hydrocephalus
		41	73	FSRT 50 Gy, 25 fxs 40–30 Gy, 10 fxs	6.3		59% 4 y	3%	3%	
(Kopp et al. 2011)	2011	68	30	SRS 12 Gy	1.24	98.5%	85%	4.4%	13%	NA
		47	32	FSRT 54 Gy, 30 fxs	5.7	98%	79%	2.1%	4%	NA
(Puataweepong et al. 2013)	2013	39	61	SRS 12 Gy	0.9	95% 5 y	75% 5 y	<1%	0%	<1% hydrocephalus
		79	61	FSRT 25 Gy (range, 18–30), 5 fxs (range, 3–10)	3.9	100%, 5 y	87% 5 y	<1%	0%	<1% hydrocephalus
		28		45–50 Gy, 20–25 fxs	9.5	95%, 5 y	63% 5 y			
(Anderson et al. 2014)	2014	48	83.6	SRS 12.5 Gy	0.66	97%, 5 y 85%, 10 y	60%	2.1% 5 y	10.5% 5 y	2% tinnitus
		19	53.6	FSRT 45–50.4 Gy, 25–28 fxs	2.94	100%, 5 y	44%	0%	5%	6% vertigo 0% tinnitus
		37	43.1	20 Gy, 5 fxs, once a week	0.89	90.5%, 5 y	63%	2.1%	20.5%	3% vertigo 3% tinnitus
(Combs et al. 2015)	2015	158	67	SRS 13 Gy	1	95%, 5 y 94%, 10 y	86%	< 1%	2%	3% gait uncertainty
		291	67	FSRT 57.6 Gy, 32 fxs	3.5	95%, 5 y 94%, 10 y	84%	1%	14%	

pts, patients; *SRS*, radiosurgery (marginal dose); *FSRT*, fractionated stereotactic radiotherapy; *fxs*, fractions; *y*, years; *NA*, not available

cost-effectiveness analysis. A few studies analyzed the cost-effectiveness issue by comparing observation and active treatment with surgery or radiotherapy in case of acoustic neuromas up to 1.5 cm (Gait et al. 2014; Morrison 2010). In these analyses, an observational management resulted more effective and cheaper than an active treatment approach. In case of active treatment, SRS has a higher cost-effectiveness than surgery both for treatment and follow-up costs, based on Markov's decision analysis model (Gait et al. 2014). Analogous findings were shown by another recent study, where the cost of SRS by Gamma-Knife resulted on average 44% of the surgical cost (Caruso et al. 2015).

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