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# Radiosurgery in Comparison with Surgery for Treatment of Neurofibromatosis Type 2 (NF-2) Associated Acoustic Neuroma (AN)

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Abbreviations: AN: Acoustic Neuroma; CNS: Central Nervous System; VGEF: Vascular Endothelial Growth Factor; EGFR: Epidermal Growth Factor Receptor; mTOR: Mammalian Target of Rapamycin; SRS: Stereotactic Radiosurgery; FSRT: Fractionated Stereotactic Radiotherapy; HFSRT: Hypofractionated Stereotactic Radiotherapy; SABR: Stereotactic Ablative Body Radiotherapy

### **Abstract**

Acoustic neuroma (AN), also known as acoustic neurinoma or vestibular schwannoma is a primary intracranial tumor derived from Schwann cells of the myelin sheath surrounding the 8th cranial nerve. AN is typically located in the internal auricular canal or at the cerebellopontine angle in the vicinity of critical neurovascular structures, and compression due to the mass effect may lead to associated symptoms in affected patients with potential to deteriorate quality of life. NF-2 refers to a neurocutaneous tumor predisposition syndrome with autosomal dominant inheritance pattern, and presence of bilateral AN is considered as a hallmark. Management of NF-2 associated AN warrants thorough consideration of individual patient characteristics given that different cranial nerves may be involved in these patients. Advances in the discipline of radiation oncology coupled with improvements in neuroimaging have expanded the applications of radiosurgery to be used more frequently as a primary treatment modality for many intracranial disorders and tumors. In the context of AN management, safety and efficacy of radiosurgery is being increasingly evident with accumulating data from several centers worldwide. Nevertheless, utility of radiosurgery in treating NF-2 associated AN is less clear with less available data compared to unilateral sporadic AN. Both surgery and radiosurgery have their unique advantages and disadvantages in management. Radiosurgery has the inherent advantage of being a noninvasive treatment modality with improved normal tissue sparing capability due to steep dose gradients around the target volume. A direct comparison between surgery and radiosurgery is confounded by several factors. Herein, we provide a concise review of radiosurgery in comparison with surgery for treatment of neurofibromatosis type 2 (NF-2) associated AN.

Keywords: Neurofibromatosis Type 2 (NF-2); Acoustic Neuroma (AN); Radiosurgery

# Introduction

Acoustic neuroma (AN), also known as acoustic neurinoma or vestibular schwannoma is a primary intracranial tumor derived from Schwann cells of the myelin sheath surrounding the 8th cranial nerve which may be observed or treated by surgery, radiosurgery, or with a combined modality approach depending on individual patient and tumor characteristics [1-5]. The incidence of these benign and typically slow growing tumors is in an increasing trend given the substantial improvements in neuroimaging techniques and aging of the population [6-8]. Despite the indolent disease

course in an overwhelming majority of patients, symptomatology may include hearing impairment, tinnitus, vertigo, dizziness, headache, incoordination or instability, gait ataxia, cranial nerve symptoms due to involvement of facial and trigeminal nerves, facial dysesthesia or spasms, dysphagia, dysarthria, cerebellar seizures, symptoms of increased intracranial pressure and respiratory distress in some of the affected patients [1-5]. AN is typically located in the internal auricular canal or at the cerebellopontine angle in the vicinity of critical neurovascular structures, and compression

due to the mass effect may lead to associated symptoms in affected patients with potential to deteriorate quality of life. Several factors such as lesion size, location and association with critical structures, symptomatology, age, patient preferences, and logistical issues are taken into account in decision making for management of AN. Herein, we provide a concise review of radiosurgery in comparison with surgery for treatment of neurofibromatosis type 2 (NF-2) associated AN.

# Literature Review of Radiosurgery in Comparison with Surgery for Treatment of NF-2 AN

NF-2 refers to a neurocutaneous tumor predisposition syndrome with autosomal dominant inheritance pattern which is specified by multiple neoplasms and several central nervous system (CNS) manifestations [9-11]. There is mutation of the tumor supressor gene NF-2 located on chromosome 22, and presence of bilateral AN is considered as a hallmark [9-11]. A variety of molecularly targeted therapies focused on inhibition of angiogenesis, vascular endothelial growth factor (VGEF), epidermal growth factor receptor (EGFR), mammalian target of rapamycin (mTOR), tyrosine kinases and several other targets have been utilized for management of NF-2 [12-15]. Management of NF-2 associated AN warrants thorough consideration of individual patient characteristics given that different cranial nerves may be involved in these patients [16]. Most frequently involved cranial nerves include the facial and vestibulocochlear nerves, and management without further deterioration of quality of life is an important aspect in decision making for treatment. Radiosurgical management with stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (FSRT), hypofractionated stereotactic radiotherapy (HFSRT), and Stereotactic Ablative Body Radiotherapy (SABR) serves as a viable treatment approach for focused and accurate irradiation of many CNS disorders and tumors throughout the human body with encouraging therapeutic outcomes [17-53]. Rationale for radiosurgery is to provide focused and ablative treatment through vascular endothelial damage, and well defined and relatively smaller targets are well suited for radiosurgical applications given the high doses delivered in single or a few fractions under robust immobilization and image guidance.

Steeper dose gradients around the target allows for improved normal tissue sparing, however, accurate target localization by use of advanced neuroimaging capabilities is an important aspect of radiosurgical management to avoid geographical misses [17-53]. There are currently different platforms for radiosurgery which all provide excellent delivery of focused irradiation to achieve satisfactory local control rates for AN. In the context of NF-2 associated AN, several studies have addressed the utility of radiosurgery for management [54-62]. In the study by Mathieu et al. assessing the outcomes of radiosurgery for NF-2 associated AN, 74 lesions of 62 patients were treated [54]. At a median follow up duration of 53 months, reported rates of actuarial local control

at 5, 10, and 15 years was 85%, 81%, and 81%, respectively [54]. The authors concluded that selected patients with NF-2 associated AN could be considered for primary radiosurgical management given the safety and efficacy of radiosurgery for treatment of these patients [54]. In the study by Meijer et al. addressing management of bilateral NF-2 associated AN with linear accelerator based radiosurgery, local control was provided for the 20 evaluable patients without treatment related trigeminal or facial nerve toxicity at a median follow up duration of 51 months [55]. The authors concluded that excellent local control rates were achieved with linear accelerator based radiosurgery for NF-2 associated AN [55]. In the study by Rowe et al., the authors suggested radiosurgery as a valuable minimally invasive therapeutic option for management of selected patients with NF-2 associated AN [56].

In the study by Phi et al. assessing the radiologically proven local control rates after radiosurgery of NF-2 associated AN, 36 lesions in 30 patients were analyzed with a median clinical follow up duration exceeding 4 years and median radiological follow up duration exceeding 3 years [57]. Actuarial tumor control rates at 1, 2 and 5 years was 81%, 74%, and 66%, respectively [57]. The authors concluded that radiosurgery could be included in management options for patients with NF-2 associated AN [57]. In the study by Sun and Liu evaluating long term clinical outcomes and the role of radiosurgery for NF-2 associated AN, total rate of tumor control for bilateral NF-2 associated AN was 84% [58]. The authors concluded that radiosurgery provided long term tumor control for small to medium sized lesions and other types of tumors despite the fact that unilateral sporadic AN had better response to radiosurgery compared to NF-2 associated AN [58]. In the study by Mallory et al. assessing optimal radiosurgery dose parameters and long term outcomes of radiosurgery for NF-2 associated AN, 32 lesions in 26 patients were treated [59]. At a median follow up duration of 7.6 years, no growth was observed in 27 lesions (84%) out of the total 32 lesions [59]. The authors concluded that higher marginal doses than frequently prescribed for sporadic AN radiosurgery were found to be in association with increased tumor control for NF-2 associated AN [59]. Also, the advantage of radiosurgery which is allowing an anatomically preserved cochlear nerve was emphasized along with the opportunity of hearing rehabilitation with cochlear implantation [59]. In the study by Kruyt et al., actuarial tumor control rates were 98%, 89%, 87%, and 87% after 1, 3, 5, and 8 years, respectively for NF-2 associated AN [60]. The authors concluded that the use of low margin doses for treating growing NF-2 associated AN with modern radiosurgical techniques yielded good long term tumor control rates and radiosurgery could serve as a valid treatment option for particularly small to medium size NF-2 associated AN [60].

In the study by Shinya et al. evaluating radiosurgical outcomes for AN, 30 lesions in 25 patients with NF-2 associated AN were analyzed with a mean follow up duration exceeding 10 years [61]. The authors concluded that excellent long term tumor control

coupled with the inherent advantage of being a noninvasive treatment modality rendered radiosurgery a favorable therapeutic option for small to medium sized NF-2 associated AN [61]. In the systematic review by Shinya et al. comparatively assessing radiosurgery versus surgery for NF-2 associated AN management, major databases were queried by using relevant search terms and retrospective studies focusing on outcomes of patients undergoing either radiosurgery or surgery for NF-2 associated AN were included with exclusion of single patient case reports [62]. A total of 974 patients 485 of whom received radiosurgery and 489 of whom underwent surgery were identified [62]. Mean 5 year local control rate was 75.1% for radiosurgery with the mean recurrence rate for surgery being 8.1% [62]. Hearing preservation rates were higher after surgery compared to radiosurgery, and facial nerve preservation rates were higher after radiosurgery compared to surgery [62]. Despite higher hearing preservation rates in surgery cohorts, radiosurgery was found to achieve high local control rates with significantly lower facial nerve complications [62]. The authors commented that selected patients with NF-2 associated AN could benefit more from radiosurgery than surgery [62].

# **Conclusion and Future Perspectives**

Recent years have witnessed many improvements in the radiation oncology discipline including, but not limited to, contemporary irradiation technologies such as Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), Breathing Adapted Radiation Therapy (BART), Adaptive Radiation Therapy (ART) as well as radiosurgical applications such as SRS, FSRT, HFST, and SABR [17-53,63-71]. These advances coupled with improvements in neuroimaging have expanded the applications of radiosurgery to be used more frequently as a primary treatment modality for many intracranial disorders and tumors. In the context of AN management, safety and efficacy of radiosurgery is being increasingly evident with accumulating data from several centers worldwide. Nevertheless, utility of radiosurgery in treating NF-2 associated AN is less clear with less available data compared to unilateral sporadic AN. Both surgery and radiosurgery have their unique advantages and disadvantages in management. Surgical techniques are in evolution towards improved sparing of functionality and quality of life although there is room for further improvements. Radiosurgery has the inherent advantage of being a noninvasive treatment modality with improved normal tissue sparing capability due to steep dose gradients around the target volume. A direct comparison between surgery and radiosurgery is confounded by several factors. In this context, future trials are needed to shed light on optimal management of NF-2 associated AN.

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