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The impact of stereotactic radiosurgery in the management of neurofibromatosis type 2-related vestibular schwannomas

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Abstract

Although there is an ongoing debate about the ideal management of vestibular schwannomas, radiosurgical treatment has become popular in the past decade with good to excellent results reported. Given the young age at presentation, the bilateral nature of vestibular schwanomas, the presence of other associated central nervous system tumors, patients with neurofibromatosis Type 2 (NF2) are very complex and present significant management challenges. Although results do not seem to be as good as for patients with sporadic unilateral tumors, stereotactic radiosurgery has proven a safe, attractive, and effective management modality for NF2 vestibular schwannomas. An overview of the impact stereotactic radiosurgery has had in the management of these tumors is discussed.

Key Words: Hearing preservation, local tumor control, neurofibromatosis type 2, stereotactic radiosurgery gamma knife, vestibular schwanomas

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INTRODUCTION

Medical advances and the availability of high technology have revolutionized the way we practice medicine today, and are indispensable for people's health and better quality of life. Given that we use a wide variety of technologies in assessing, diagnosing, and treating patients, our practice is inherently dependent upon health technology. The decision to implement a new medical technology requires that it not only increases survival and/or quality of life, but also be economically sound. Despite the fact that neurosurgeons in general welcome new technologies all the time, this is naturally accompanied with some degree of skepticism, as any change that might modify our traditional standard practice tend to shake our "comfort zone" and therefore generate anxiety. This was even more so at the beginnings of the stereotactic radiosurgical era for brain lesions as the results and success of the technique were not immediately evident.

The management of vestibular schwannomas has suffered an interesting evolution from traditional microsurgery to less invasive "technological" procedures, namely, cerebral stereotactic radiosurgery. Ever since the first patient with an acoustic schwannoma was treated with gammaknife in 1969, no one probably imagined the real impact stereotactic radiosurgery would have in the management of central nervous system (CNS) tumors. From that moment on, and after decades and hundreds of thousands of patients treated, neurosurgeons have debated as to which treatment, radiosurgery or microsurgery is most convenient for a patient with a tumor that is accessible to both procedures. For many years, only those tumors critically located and therefore surgically inaccessible were considered ideal candidates for radiosurgery. As

experience and knowledge in this field have grown and long-term results have been published, the trend for radiosurgical procedures has also grown and our practice has been changed accordingly.

Almost three decades later, in 1998, and already witnessing the power of the technology and potential success of this procedure, Pollock *et al.*[20] collected their available data since 1987 in order to predict the number of patients who would undergo radiosurgery in the future. According to their mathematical models and guided by the exponential growth curve of the technique, they assumed that stereotactic radiosurgery would replace surgical resection as the preferred management strategy for the majority of patients with vestibular schwannomas. Even though most of the literature dealt essentially with sporadic cases, the implications of this trend became rather obvious and found an excellent window of opportunity for patients with neurofibromatosis type 2 (NF2).

NEUROFIBROMATOSIS TYPE 2

This is an autosomal dominant genetic disorder caused by mutations on chromosome 22.[5] Patients usually harbor multiple CNS tumors, however, the presence of bilateral vestibular schwannomas is the hallmark of the disease [Figure 1]. Histological findings in NF2 tumors have shown several important and distinct characteristics in this population. Depending on the severity of the underlying mutation, multiple other CNS tumors can also be found, notably meningiomas, schwannomas, and gliomas, some of them involving cranial nerves [Figure 2]. Pathologically, vestibular schwannomas in NF2 have been found to be more lobular, less vascularized, and have an increased growth rate. They also tend to engulf and even infiltrate the surrounding cochlear and facial nerves with poor cleavage planes, whereas sporadic schwannomas usually compress and displace the nerves. This is a technical surgical detail to be seriously considered as it is one of the various reasons why these tumors in the context of NF2 are more difficult to remove surgically and therefore impose higher risks of hearing loss leading to lower hearing preservation rates reported as compared with their sporadic counterparts.[11,30] Therefore, NF2 should be probably understood, not as a single clinical entity but as a condition with different variations and prognoses.

The classical management of neurofibromatosis (NF)-related schwannomas has been standard microsurgical resection,[4] however, vestibular schwannomas in NF2 represent a very different clinical scenario. To begin with, the problem is already double from the time of diagnosis as the schwannomas are bilateral and tend to be more aggressive, so managing these patients is rather challenging, complex, and even controversial. Several biological behavior features of the disease are worth mentioning as need to be taken into account in the decision making process. The natural history of vestibular schwannomas and other tumors in patients with NF2 is somehow difficult to predict. It is perceived that the solution of NF2-associated acoustic neuroma (whether microsurgery or radiosurgery) is accompanied by greater risk than in the setting of sporadic cases. Cranial nerve paresis rates and loss of hearing are higher because, as explained before, there is a propensity of these lesions to diffusely infiltrate the nerve. The bilateral nature of this disease compounds the risk of profound deafness whether treatment is instituted or not. Furthermore, the risk of recurrence or progression is higher for NF2 tumors, regardless of which is chosen as the primary treatment. The tumors are commonly found at a younger age meaning that they have a significant cumulative risk

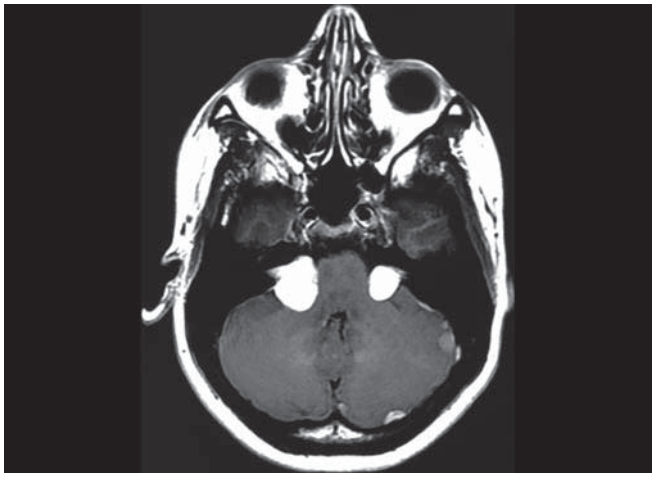

Figure 1: Axial magnetic resonance imaging slice with contrast enhancement of a typical patient with neurofibromatosis type 2 with bilateral vestibular schwanomas. There are two other small contrast enhancement lesions in the convexity of the left cerebellar hemisphere (meningiomas)

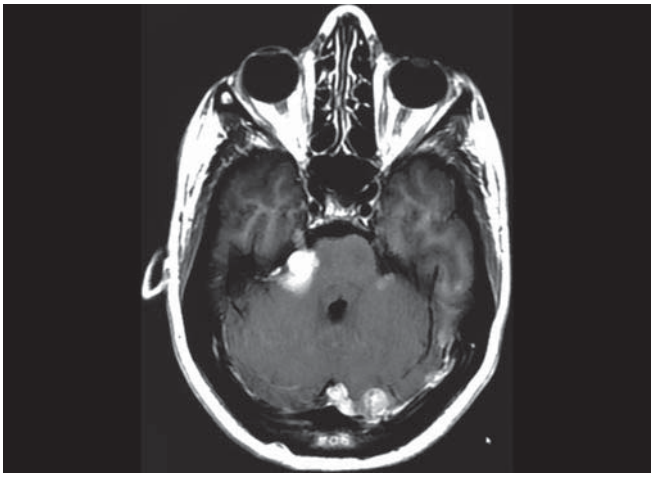

Figure 2: Axial magnetic resonance imaging with contrast enhancement of the same patient is a slice above the previous image showing other small contrast enhancement lesions (meningiomas) in the convexity of the left cerebellar hemisphere near the midline and torcula

of neurological complications. Symptoms might include bilateral deafness and facial paresis of several degrees, eventually hydrocephalus and even compromise of life expectancy.[2,17] It has also been noted that younger patients seem to belong to a population with more aggressive mutations and clinical course of the disease and therefore might have worse control rates.[13] Tumors seem to grow faster in these patients[2] and given their youth, this is precisely the same age group that will have more years to fail and more years to potentially develop radiation-induced malignancy, if radiosurgery is proposed.

RISK OF RADIOSURGERY-INDUCED MALIGNANCY

Published data on the different treatment alternatives for sporadic vestibular schwannomas and those NF2 related will support our understanding of why radiosurgery has become such a huge impact in the management of these patients. Even though the level of tumor control and hearing preservation is not quite the same as for their sporadic counterparts, gammaknife and Linear accelerator (LINAC-) based radiosurgery have proven to be excellent tools for the treatment for vestibular schwannomas in patients with NF2. In general, excellent local control rates have been achieved and reported in the vast majority of series with minimal facial and trigeminal nerve toxicity.[8,9,12-14,16,18,21,22,24-26,29,33]

Better functional outcomes after stereotactic radiosurgery as compared with surgical resection have been reported,[8,9,16,21,22,24,25] therefore, the sooner the diagnosis the better the likelihood of dealing with smaller volumes early in the course of their disease. Furthermore, the lack of need for additional treatments and the absence of developing radiosurgical-related malignancies (a point long considered of major concern) after many years of follow up seem to further substantiate this philosophy.[12] Rowe *et al.*[27] reported no increased risk of delayed malignancy in a very large population of patients after gammaknife radiosurgery during their study period, however, it is a known fact that this risk may well extend up to several decades.

TUMOR CONTROL RATES AND PRESERVATION OF CRANIAL NERVE FUNCTION

Tumor control rates for NF2 vestibular scwannomas have been reported to range roughly between 85% and 80% at 5-10, years respectively.[13,29] Even more, it has been shown that radiosurgery may alter the natural history of vestibular schwannomas by successfully preventing or reversing tumor growth.[33] Rowe *et al.*[28] nicely summarized their vast radiosurgical experience treating NF2 vestibular schwannomas, and estimated that 8 years after radiosurgery, 20% of patients will require further treatment, 50% will be well-controlled, and in 30% there will be some concern regarding control, but they will be managed conservatively. Even though they claim that their clinical results are worse than those of sporadic tumors, they also seem to be better than the results of surgery or observation.

The actuarial serviceable hearing preservation rate show a decline over time varying from around Radiosurgery for Neurofibromatosis type 2 vestibular schwanomas 50-70% at 1 year, 45-60% at 2 years, and 33-45% at 5 years after radiosurgery.[18] Better ipsilateral hearing at the time of radiosurgery was associated with significantly greater serviceable hearing preservation. Rowe *et al.*'s findings documented a very good overview of the natural history of hearing after radiosurgery showing that 40% of patients retained their hearing, 40% had worsened hearing but could still hear, and 20% became deaf.[28] The hearing preservation LINAC results are very similar and as good as gammaknife, depending on the initial hearing status of the reported patient groups.[14] A number of publications reported worse hearing preservation rates after radiosurgery for vestibular schwannomas in patients with NF2, compared with those for sporadic ones.[1,7,32]

The facial and trigeminal nerve function preservation rate in radiosurgery for NF2-related vestibular schwannomas seems to be as high as that in radiosurgery for sporadic cases with most published series reporting treatment-related toxicity in less than 10% of patients. Radiation dose and tumor volume were predictive of development of new deficits.[13,14]

After multivariate analysis, no evident factors have been identified as predictive of growth of vestibular schwannomas in NF2 patients,[10] however, tumor volume has been indeed considered to be a significant predictor of local control after the procedure. Additionally, a low marginal dose and a young age at radiosurgery were associated with poor tumor control.[18]

A corollary of the previous paragraphs is that surgical resection is commonly thought to carry a greater risk of functional deterioration, and, even though the level of tumor control and hearing preservation is not the same as for sporadic cases, stereotactic radiosurgery is a less invasive option that provides comparable, if not superior outcomes to resection providing satisfactory tumor control and hearing preservation in these patients.[26,29]

EVOLUTION OF MANAGEMENT

A few decades ago, when faced with a young patient with NF2 with demonstrable growing tumor(s), microsurgery was recommended for the bilateral vestibular schwannomas. It was a relatively common but unfortunate event to see these young patients with bilateral scars related to their suboccipital craniectomies and facial disfigurements as a result of surgery and cranial

nerve deficits. Needless to say, a natural consensus among all patients and specially the younger ones was their concern about functional preservation of both hearing and facial nerve function. The quality and performance of their personal and professional lives depend on both and the consequences of either dysfunction could be catastrophic. Tumor control and cranial neuropathy are thus crucial goals to achieve, the first one easily be done at the expense of damaging the latter. Before the availability of our current published data on the efficacy of radiosurgery, the decision in a way relied either on observation or microsurgery. Then radiosurgery came along and the procedure created such a dramatic impact that has essentially replaced surgery as the standard of care, especially for NF2 patients. Apart from patient satisfaction, an interesting fact supporting this notion is how most recently published series on NF2-related vestibular schwannomas deal only with radiosurgery as their treatment of choice for this population.

The management of NF2 vestibular schwannomas require a fine and delicate balance between growth control against preservation of hearing and other cranial nerves function. It is therefore very important to know how efficient the treatment will be and how much damage it is capable of producing while maintaining the primary aim of achieving the best possible patient's quality of life. Unfortunately these patients are complex and there are no established guidelines to give recommendations that could cover all situations, leaving experience and perhaps most importantly, common sense, to dictate management. There are, however, numerous factors to consider when deciding the best management options for NF2 patients. The decision between observation and either surgical or radiosurgical intervention, as well as the choice of surgical or radiation procedure to be offered, boils down to patient factors and preferences and on the experience of the treating center.

Current available studies on radiosurgery and stereotactic radiation therapy for sporadic vestibular schwannoma sare abundant with excellent performance[1,6,7,15,23,31] and the same has been happening with the published experience for patients with NF2, and, despite being more limited, has been expanding rapidly as well.[10,13,14,17-19,26,28,29,32,33] Additionally, as expected, other nonsurgical treatments for this population are being published, such as the antiangiogenic drug bevacizumab, which has shown some promising results,[19] and could become a future clinical approach, but needs to transcend more clinical trials and the barrier of time.

Truth is, we can actually find evidence in the literature to support anything we wish to hear or tell our patients backing up either treatment alternative we prefer. The real fact is that when NF2 patients are offered different treatment alternatives (with sufficient information on all of them), the vast majority, if not all, will choose the less invasive, less expensive, and less time consuming procedure, especially if treatment final results are similar, and also bearing in mind that these treatments will need to be bilateral. Nowadays, there are no significant differences in treatment results including the long-term growth control rate, hearing preservation rate, and incidence of postoperative cranial nerve disturbance between radiosurgery and microsurgery.

CONCLUSION

Radiosurgery has become so precise and accurate that the results have even exceeded our best surgical skills.[3] From being just an alternative treatment in the past, it has become the treatment of choice for several neurosurgical conditions. The real impact of radiosurgery, in particular for this population, is the way it has changed our perspective and has driven our decision making and also managed to replace a traditional and well established form of treatment (microsurgery) with a procedure harboring sub millimetric accuracy and minimal invasion to the brain. Neurosurgeons have been dealing for decades with complex neurosurgical pathologies such as NF2-related vestibular schwannomas, demanding our best and most delicate trained surgical skills, however, at the end of the day, there is nothing more attractive to patients than a minimally invasive procedure.

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