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Review Article

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Gamma Knife Radiosurgery for Vestibular Schwannomas

Vestibular schwannoma (VS) is a benign tumor typically originated in the schwann cell of vestibular nerve and usually accompany hearing symptom. Microsurgical removal and radiosurgery have a great role for the treatment of VS. Recently radiosurgery has been considered as an alternative or primary treatment for VS with the tremendous increase of patients who were treated with gamma knife radiosurgery (GKS) though microsurgery still takes the premier. By many published results, it is proved that GKS is a effective and noninvasive technique for VS, especially small sized tumors with satisfactory tumor control rate. The authors assumed that GKS can be expected to achieve satisfactory tumor control rate for small VS under 5 cc in volume. A major interest regarding radiosurgery nowadays is to determine the optimal radiation dose for hearing preservation to improve the quality of life of patients. The more high radiation dose are used for effective tumor growth control, the more radiation-related complications like as hearing deficit, the impairment of other cranial nerve function are increased. Since 1990's the mean radiation dose for tumor margin was more than 18 Gy, but there were high complication rate in spite of good tumor growth control. After the year of 2000, under the influence of advanced neuro-imaging techniques and radiosurgical planning system which enable clinicians to do more precise planning, marginal dose for VS has been decreased to 12-13 Gy and the radiation-related complications has been reduced. But because there may be a unexpected radiation-induced complications as time goes by after the latency period, optimal radiation dose for VS should be established on the basis of more long term follow-up observation.

KEY WORDS : Gamma knife radiosurgery · Vestibular schwannoma · Hearing preservation.

INTRODUCTION

Vestibular schwannoma (VS) is a histopathologically benign tumor which typically originates from the lining schwann cell of vestibular branch of the 8th cranial nerve. It sometimes grows in a malignant fashion and erodes the internal auditory canal. VS can compress V, VII, VIII, IX, X nerves and the nucleus of brain stem; this may lead to hydrocephalus or death in serious cases. The most frequent initial clinical symptom is unilateral hearing loss, and major symptoms are tinnitus and episodes of vertigo[3,43].

The goal of treatment for VS is tumor removal or tumor growth control and functional preservation like as hearing, facial nerve and other cranial nerves[40,48]. VS has been treated mainly by microsurgical procedure, and mass has been removed by three surgical approaches : the suboccipital approach, the translabyrinthine approach, and the middle fossa approach. The choice of surgical approach may be variable according to the tumor size, the erosion of the internal acoustic canal, and hearing loss. Recently radiosurgery, which is known for a noninvasive treatment, has emerged as a useful technique for treatment of VS, especially on the point of hearing preservation, reducing the rate of facial nerve injury and various complications related with open surgery[8,16,24].

The treatment of VS by microsurgery has developed tremendously for several decades. Pollock et al[54] asserted that the gamma knife radiosurgery (GKS) for treatment of VS was applied for only in 20% of all VS cases in 1998, but they expected that the percentage will increase to 50% in 2005-2010 and 2/3 of all by 2020. Until 2006, about 120,000 cases of benign brain tumor were treated in 207 gamma knife centers around the world; among them radiosurgery for VS accounted for about 30,000 cases, and it is expected that this number will rise as time goes by. The mortality rate of microsurgery is reported to be lower than 1% and the recurrence rate, lower than 3%. However, the hearing preservation rate and the rate of cranial nerve complications which are important in the treatment of VS have not yet reached a satisfactory level[33,57].

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Since 1951, when radiosurgery was first introduced by Professor Lars Leksell from the Karolinska Institute in Sweden, its technical aspects and clinical applications have been steadily researched. It has been widely used as one of the advanced treatment tools for intracranial lesions with the rapid development of neuroimaging techniques after 1990's. Since results of GKS for VS have been proved to be successful, their uses have been increased worldwide. The principle of GKS is to apply high-intensity ionizing radiation to the lesion for maximum destruction of the lesion with minimal injury to the surrounding tissues. The radiosurgery of VS focuses on maximizing tumor control while minimizing the radiation induced complications on important surrounding structures such as facial nerves, auditory nerves, trigeminal nerves, brain stem, and cerebellum[44,45,48].

A major interest regarding radiosurgery nowadays is to determine the optimal radiation dose for hearing preservation to improve the quality of life of patients. Recent developments in diagnostic equipment have provided the accurate identification of anatomical structures around the auditory nerves, which has reduced the radiation dose to critical surrounding structures[13,32,38,39]. In additions, various studies about hearing preservation according to the location and size of tumor are now giving many helps to radiosurgical planning. Author intended to review the history, the roles, the treatment results, the optimal radiation dose, and the future development directions of radiosurgery for VS with the reviews of literatures.

HISTORICAL BACKGROUND OF GKS FOR VESTIBULAR SCHWANNOMA

The history of GKS began in 1968 when a prototype of the Leksell Gamma Knife® was first installed in Stockholm, Sweden. In 1986, the Leksell Gamma Knife® B type was introduced, which has spread worldwide, including in Korea, and GKS has been actively conducted since the early 1990s. After 2000, the Leksell Gamma Knife® C type with robotic automatic positioning system and automatic helmet changer was introduced, which allowed for more convenient and rapid treatment, and this is still being used now. In 2004, the Leksell Gamma Knife® 4C type was introduced. It features new Leksell GammaPlan® software, provides the ability to co-register non-stereotactic images, allows planning from various image sources such as computed tomography (CT), magnetic resonance image (MRI), and positron emission tomography (PET), and sharing the remote images from the center where gamma knife are not available. Most recently, radical developments have been made by the next-generation Gamma Knife Perfexion System® in the treatment of peripherally located brain tumor, and made it possible for precise planning according to the shape of the tumor (Fig. 1). Regis et al.[57] reported from their experience of treatment that they could plan more conveniently and accurately using the Perfexion System® and, above all, collision risk fell from 48.3% to 3.3%. It has been useful tool for treating brain tumors without affecting the accuracy which was merit of a conventional gamma knife.

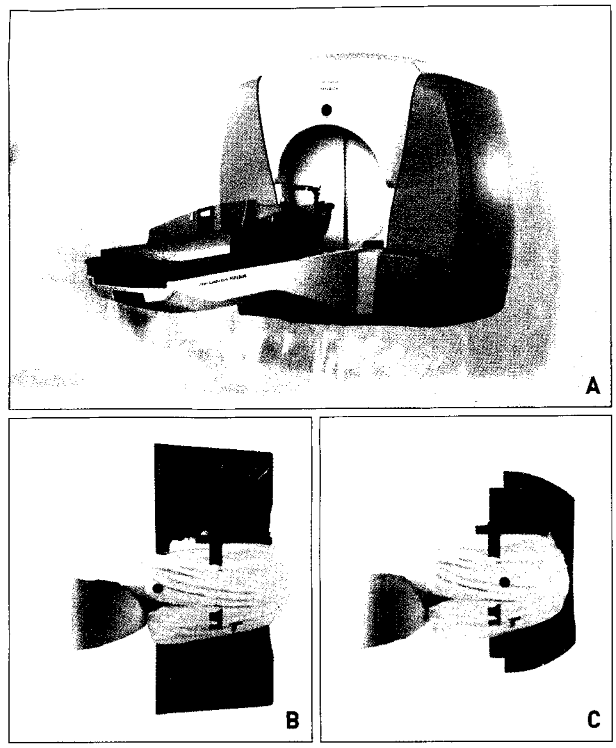

Fig. 1. The advanced gamma knife system 'the perfexion' (A) : three times larger than before previous gamma knife and it has fixed 1 collimator with division of 8 sectors controlled by the each servo drive to accurate and comfortable planning. By perfection system (B), peripheral or lower-lying brain lesions can be treated easily more than previous gamma knife system (C).

GKS for VS was first conducted by professor Leksell in Sweden in 1969[27]. Worldwide interest in GKS was roused when results of GKS for VS were reported at the first international conference on VS held in Copenhagen in 1991. GKS was spotlighted as an ideal treatment for patients with high risk for surgery, old patients, and patients who refused to undergo any operation[36]. Since then, many medical centers have reported good results of GKS for VS.

Meanwhile, new neuroimaging techniques are playing the role of contribution to develop GKS further. The recently introduced high Tesla MRI provides more accurately recognize the important structures around the VS through thin slice images and their compositions. Three-dimensional images, constructive interference in steady state (CISS) and fast imaging employing steady-state acquisition (FIESTA) images clarify the contrast between cerebrospinal fluid and the structures, making it easier for us to identify the surrounding structures[34,35,41].

RADIOBIOLOGY OF RADIOSURGERY

The effect of irradiation on tumor tissue is shrinkage of tumor cell by DNA damage and intratumoral vascular obliteration. Ionized irradiation causes DNA damage to cells, and the apoptosis of cells promotes early tumor shrinkage. In the case of late responding tissues, a long cell cycle time causes delayed tumor shrinkage. Meanwhile, the irradiations of the blood vessels of the tumor interrupt the blood flow through hyalinization of arterioles, myointimal cell injury, and endothelial proliferation, which slowly reached to ischemia, hypoxia of the tumor cells, and damage to the cells. This is similar to the treatment mechanism for arterio-vascular malformation[29,46].

INDICATIONS OF RADIOSURGICAL TREATMENT

Regarding the natural course or conservative management for VS, Yamakami et al.[68] reported on the natural course of 903 patients who underwent conservative treatment; in the average observation period of 3.1 years, 51% of the tumors had grown and the mean growth rate was 1.87 mm / year. In the end, 20% of the patients needed surgical treatment. The tumor size may not grow within a certain time, but surgical treatment becomes necessary at some point in a long-term follow-up observation for VS in a young patient. Considering this fact, treating the tumor when it is still small will help the patient and provide a better prognosis[35].

One advantage of microsurgery is that many surgical techniques are well known due to its long history, and good treatment results can be expected from skillful surgeons. Although better treatment results can be expected with the profound learning of surgical anatomy, a time interval of learning curve is still required. On the other hand, radiosurgery does not need stiff learning curve like microsurgery, and it is relatively accurate and much easier than microsurgery because the dose selection can be applied by already existing dosimetry data and treatment planning can be performed with use of neuroimaging anatomy. Radiosurgery has gained superiority in the treatment of brain lesions because it can achieve the similar results with 1/3 to 1/10 radiation dose of conventional radiotherapy.

VS has characteristics, appropriate for radiosurgery, such as relatively clear tumor margin, no infiltration into surrounding brain tissues, good identification by MRI with contrast enhancement, and adaptability in even irregular tumors by steep radiation fall-off[4].

Microsurgery and radiosurgery for treatment of VS have developed in their own ways, and have become established for their respective indications after making efforts to improve treatment indications and functional outcome. GKS can be conducted as the primary treatment for small and medium-sized VS, and for old patients and patients who have medical problems for surgical treatment. It can be conducted as a secondary treatment for a remained tumor or a recurred tumor. However, microsurgical treatment must be performed first for large tumors with cysts or brain stem compression.

The common indications for GKS are a lesion with a diameter less than 3cm, a small lesion limited to the internal acoustic canal, or a recurred lesion after microsurgery[51]. Moreover, in author's personal experience, better treatment effects can be expected from radiosurgery with a volume of less than 5 cc.

DOSE SELECTION OF VS RADIOSURGERY

Dose selection is most important thing in radiosurgical treatment for VS, however, there is still controversy over the proper dose selection.

The risk factors for cranial nerve damage during radiosurgery are reported to be total dose, total volume, prior resection, length of cranial nerve irradiated, and the maximal dose to brain stem[28,34,66]. Initially there was no MRI system for brain scans and the resolution of brain CTs was so low that accurate treatment planning was difficult. Besides, 18 Gy and higher irradiation brought about various complications, such as trigeminal neuropathy and facial paralysis, with low rate of hearing preservation[30,40]. However, recently 14 Gy was applied to small sized tumors, 12 Gy to medium sized tumors, and 10 Gy to large one. Now the trend is to decrease the dose to 12 Gy for small sized tumors (Fig. 2). Despite the decreased irradiation of 12 Gy, the tumor growth suppression rate is same as before, and the complications of

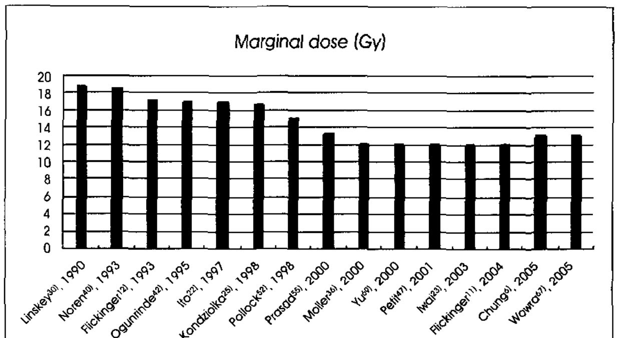

Fig. 2. Dose changes of gamma knife radiosurgery for vestibular schwannoma.

irradiation for auditory and facial nerves have decreased[23,47,69]. However there is no definitive proved result of radiosurgical treatment with 12 Gy as a marginal dose, yet. Although, in principle, higher radiation dose would results in higher tumor growth control rate, it is essential to choose the adequate radiation dose because of more complications related with a higher radiation dose. Although proper dose selection was not established, it must not exceed 14 Gy for VS radiosurgery.

TREATMENT RESULTS OF GKS

Tumor control rate

According to the results of GKS for VS reported by many gamma knife centers, tumor control rate ranges from 87 to 98% and hearing preservation rate from 40 to 87%[6,11,18,26,29,40,62]. After analysis of GKS for 669 VS patients from 1969 to 1997, Noren[40] reported that tumor control rate was 95%, complication rate on trigeminal nerves lower than 2%, and hearing preservation 70 to 74%. Lunsford et al.[31] reported the treatment results for 829 VS patients in 2005. From a six year follow-up after a mean marginal dose of 13 Gy, tumor control rate was 98.6%, hearing preservation rate 78.6%, the rate of facial nerve complications lower than 1%, and the rate of trigeminal nerve complications 3.2% or lower. Regis et al.[56] conducted 1,000 cases of GKS on 927 VS patients. The mean tumor size was 12.7 mm, which was relatively large, and the treatment results showed that the tumor control rate was 97%, the rate of facial nerve complications 1.3%, and the rate of trigeminal nerve complications 0.6%. From many studies, the results of tumor control rate of GKS for VS were found to be satisfactory.

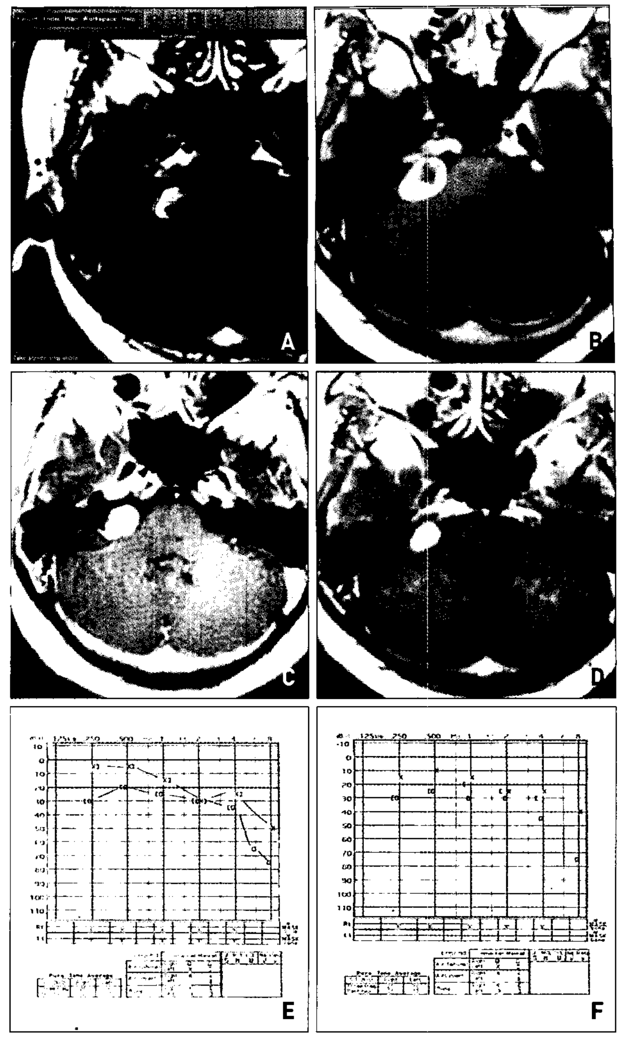

Fig. 3. A 56-year-old female was diagnosed with vestibular schwannoma with useful hearing (E). And the tumor was treated by gamma knife radiosurgery (GKS) with radiosurgical prescription of 16 Gy marginal dose on 1.6 cc volume (A). And at 16 months after GKS, the tumor size was enlarged with loss of enhancement in the tumor center but we observed (B). At 30 months (C) and 60 months (D) after GKS, the tumor decreased and her hearing was preserved (F).

Transient enlargement of the tumor

Tumor size may be increased firstly in clinical treatment due to necrosis of the tumor solid part by radiosurgery and formation of intratumoral cysts. This must not be regarded as a failure of the GKS, but follow-up observation is required as long as there is no new neurologic symptome[19,26]. Long-term follow-up observation reveals that in most cases the intratumoral cysts are absorbed and the tumor size decreases (Fig. 3).

Post-radiosurgical enlargement of tumor is a phenomenon that can happen within a certain period after treatment. Therefore, transient enlargement after radiosurgery must be differentiated from continuous enlargement, and must be observed carefully. If the central enhancement of the tumor on MRI after surgery is disappear, it is highly likely to indicate transient tumor growth after radiosurgery. This is regarded as a radiation effect on the tumor[33,38,62]. Many literatures reported that the central enhancement is disappear in about 80% of VS. Regarding this transient growth, it has been reported that swelling occurs in 5% of VS after GKS and surgical treatment was necessary for about 2%. However, there are many cases that require surgical treatment due to an accompanying cystic tumor[9,53,61]. Pollock et al.[49] reported that it occurred in 14% of the patients, and Delsanti et al.[7] in 15% of the patients. Kondziolka et al.[25] stated that five (3%) of 162 patients occurred transient tumor growth, but it was caused by central necrosis from radiation, and follow-up observation found tumor growth control in all cases. These results of study suggested that transient growth of VS after radiosurgery is a natural progress by the radiation effect on the tumor, and a follow-up observation for at least 2 years is required to determine whether the tumor size increases. A more caution is needed for surgical treatment due to transient tumor growth during this period. The tumor growth, hearing dysfunction, facial numbness, and weakness after radiosurgery are temporary phenomena that can appear with the transient tumor growth and most of them are cured. Two years seems to be too short for define the treatment effects of radiosurgery and observation more than three years is recommended[2,17].

Hearing preservation after GKS

The hearing preservation rate after radiosurgery for VS has been reported to be in the range of 40 to 78.6%[10,31,55,57,68]. It is not easy to simply compare the various reports on global hearing preservation because of the lack of uniformity in reporting results. Clinically, the most reasonable way to determine the hearing preservation rate after radiosurgery is to confirm the results after treatment for patients of Gardner-Robertson grade I and II (PTA>50 dB, SDS>50%) which is serviceable hearing[15].

However, the hearing preservation rate is gradually improving recently with the application of a lower radiation dose than the past. Flickinger et al.[11] reported 71% hearing preservation rate with 13 Gy on average. Niranjan et al.[39] reported that good tumor control and hearing preservation were achieved with using a 4 mm collimator and 13-14 Gy marginal dose. There are recent clinical results showing that a low dose of 12 Gy or lower could achieve good hearing preservation without affecting tumor control rate[23,69].

Recently there have been reports on hearing preservation after relatively long-term follow-up observation. Hempel et al.[20] have carried out GKS on 123 patients since 1994, and achieved a tumor control rate of 96.7%; the mean impairment of hearing was 18% for 8.2 years after GKS. Hasegawa et al.[19] conducted a follow-up observation for a relatively long term of 135 months, applied the mean marginal dose of 14.6 Gy, and hearing preservation rate was 37%. This data was relatively lower than other previous reports. During the early days of radiosurgery, they expected that hearing impairment would occur within one year after radiosurgery for VS and then a stable clinical course would be expected[21]. But more long term observation should be performed for the accurate estimation of the hearing function after GKS.

Ischemia of the cochlea auditory nerve fiber and the stretch injury of transitional Obersteiner-Redlich zone of the cochlea nerve are causes of the postoperative hearing loss[60]. By contrast, early hearing loss by radiosurgery is rare and typically occurs at 3 to 24 months by neural edema or demyelination, if it occurs at all[5,39,64]. The causes of delayed hearing loss have not yet been fully revealed, but are presumed to be gradual obliteration or direct radiation axonal injury of microvessels. Blood flow to the cochlea or cochlear nerve is blocked by endothelial proliferation and hyalinization of small to medium sized arteries with radiation[5,6,30,59]. Besides, it is said that the transient volume expansion of the tumor after radiosurgery can also compress the auditory nerves in the internal auditory canal, and the hypothesis has also been proposed that the adhesion between the perineural sheath of cochlear nerve and the tumor is the cause of hearing impairment[26,38,69].

On the anatomical view, an intracanalicular vestibular schwannoma is a higher risk for hearing impairment by irradiation, despite its small size. Furthermore, the longer the length of the irradiated nerve, the higher the risk of hearing impairment. The reason why an intracanalicular tumor is higher risk for hearing impairment is that the transitional Obersteiner-Redlich zone, which is extremely radiosensitive, is close to the internal auditory canal,

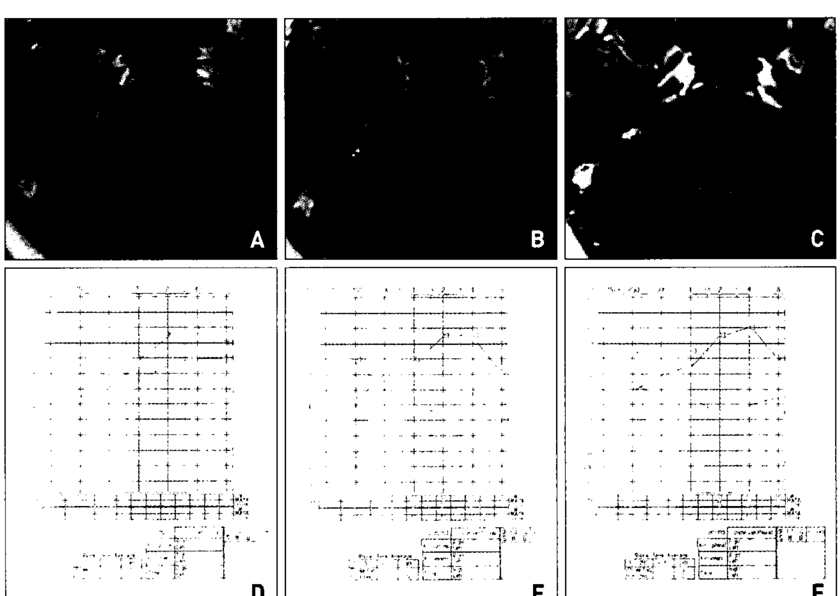

Fig. 4. A 44 year-old female patient was admitted with symptom of headache and dizziness. She had small enhancing mass in the right cerebellopontine angle and her hearing function was estimated as Gadner-Robertson grade II (40 dB) (A, D). Gamma knife radiosurgery (GKS) was done with radiosurgical prescription of 16.3 Gy marginal dose on tumor. At 16months (B, E) and 38 months (C, F) after GKS, the tumor was decreased but her hearing was decreased.

Table 1. Published results of gamma knife radiosurgery for vestibular schwannoma

Author, year	Number of patients	Mean tumor volume, size	Mean maxiamal / marginal dose	Mean follow-up period	Tumor control rate (%)	Hearing preservation rate (%)	facial palsy (%)	Trigeminal neuropathy (%)
Kondziolka[25] 1998	162	diameter 22 mm (8-39)	32.7 (24-50) / 16.6 (12-20)	5-10 years	97	47 (G-R* I,II)	15	16
Moller[36] 2000	111	-	40 / 12	0.25-10 years	96	80	14	4
Prasad[55] 2000	200	0.02-18.3 cc	34 (17-53) /13 (9-20)	4.3 years	92	58	2	4
Regis[56] 2004	1000	12.7 mm^3	- / -	-	97	77.8 (G-R I) 47.6 (G-R II)	1.3	0.6
Flickinger[11] 2004	313	1.1 ml (0.04-21.4)	26 (20-26) / 13 (12-13)	24 months	93.5	78.6 (G-R I,II)	0	4.3
Hasegawa[18] 2005	73	6.3 cm^3	28.4 (16-36) / 14.6 (10-18)	135 months	87	37 (G-R I,II)	-	-
Chung[6] 2005	195	4.1 cm^3 (0.04-23)	21.9 (17.1-34.0) / 13 (11-18.2)	36 month (1-110)	93.6	60 (G-R I,II)	1.4	1.1
Lunsford[31] 2005	829	-	- / 13 (10-20)	6 years	98.6	78.60	<1	<3.1

*G-R : Gardner-Robertson grade

and it can receive higher pressure from the transient expansion of the tumor after radiosurgery[13,30,39,65] (Fig. 4).

Post-radiosurgical complications

There have been many reports on postradiosurgical complications such as cranial neuropathy, cerebellar infarction and edema, cyst enlargement, malignant transformations, intratumoral hemorrhage, and hemifacial spasm in relatively large VS, though, their incidence is not high[14,61,63]. Regarding trigeminal and facial nerve dysfunctions after radiosurgery for VS, Kondziolka et al.[25] reported in 1998 that the application of 16.6 Gy marginal dose on average resulted in facial dysfunction 15% and trigeminal dysfunction 16%. However, many authors reported lower incidence of complication (<4%) with low dose radiosurgery, recently (Table 1).

In cases of residual or recurred mass after microsurgery, the repeated operation was recommended generally, however, recently radiosurgery is considered as a secondary treatment instead of reoperation. On the other side, in case of increased tumor size due to failed radiosurgery, microsurgery is indispensable (Fig. 5). However, many authors reported that it may be difficult to remove the tumor due to fibrosis after radiosurgery[53].

Radiosurgery vs Microsurgery

Samii[58] and Noren[40] have both reported results of surgical treatment and GKS for VS respectively. Sammi reported 97.9% complete tumor removal, 8-12% trigeminal nerve dysfunction, 1.7% facial palsy, 39-50% hearing preservation rate, and 9.2% CSF leakage from his 1,000 cases experience of microsurgery for VS. Noren, reported 95% tumor control rate, 70-75% hearing preservation rate, 2% or lower facial dysfunction, and 2% or lower trigeminal dysfunction in the treatment of GKS for 669 VS patients. There were similar results in tumor control and tumor removal, but the radiosurgery showed better results of hearing preservation rate and cranial nerve complication. Further, Pollock[51] studied 40 patients who underwent microsurgery and 47 who underwent GKS in the same institution, and reported the advantages of GKS for the functional outcome. A comparison of the above results found better results of the GKS in hearing preservation and complications.

Based on previously reported papers, Yamakami et al.[68] divided subjects into a GKS group of 1475 patients, a microsurgery group of 5005 patients, and an observation group of 903 patients, and compared with each groups for the clinical progress and treatment results. For 3.8 years of mean follow-up observation after GKS for VS, tumor control rate was 92%, microsurgery was necessary in 4.6% of the patients after radiourgery, and 57% of them showed hearing preservation of useful hearing. In the microsurgery group, complete tumor removal was 96%, tumor recurrence 1.8%, mortality 0.63%, and hearing preservation of useful hearing 36%. As for complications after treatment of the GKS group, facial palsy or tinnitus occurred in 8% of the patients whereas 13% of the patients in the microsurgery group showed some facial dysfunction.

As mentioned above, two groups showed similar results regarding tumor removal and tumor control, but overall, the GKS group revealed lower complication rate. But there is still controversy over whether we should apply equal standards of interpretation to their treatment results,

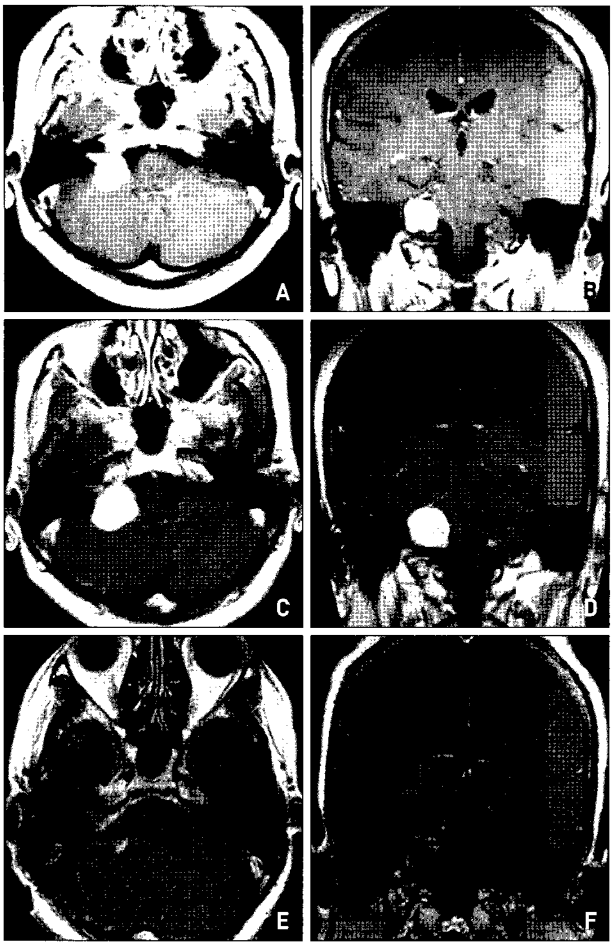

Fig. 5. A 35 year-old female patient was diagnosed with vestibular schwannoma. Magnetic resonance images showed well enhanced mass at at right cerebellopontine angle (A, B). The tumor volume was 5 cc and treated by gamma knife radiosurgery (GKS) with 12 Gy marginal dose. At 4 years after GKS, the tumor size was increased with decreased hearing (C, D) and then the mass was removed by microsurgery. Post-microsurgical magnetic resonance images (E, F).

because microsurgery is usually conducted for large tumors whereas radiosurgery more often deals with relatively small sized VS[37].

Radiosurgery for neurofibromatosis type II and bilateral VS

The results of GKS for VS in neurofibromatosis type II (NFII) are worse than in unilateral VS, because VS in NFII has the characteristic of infiltrating to surrounding cranial nerves[1]. Radiosurgery for NFII can be applied to both lesions simultaneously if patient suffer form bilateral hearing loss. Otherwise, however, it is recommended to perform staged radiosurgery as in microsurgery : first on the lesion with hearing loss and then on the other lesion when the tumor grows or hearing loss appears during follow-up observation[32].

For bilateral VS, a different method of radiosurgical treatment must be applied to NFII due to difference of radiosensitivity. Staged radiosurgery is recommended in this case : symptomatic site is treated first and the other site is treated in case of size growth or hearing declines.

CONCLUSION

Gamma Knife Radiosurgery is a effective and safe treatment modality for VS though microsurgery still takes the premier place. We are now in the new phase of GKS in the treatment VS. Although 40 years have been passed and 30,000 cases have been experienced in worldwide since first radiosurgery for VS by Leksell, there are still the unsettled question about some parts of VS radiosurgery, in spite of the development of radiosurgical tools and skills

It has been proven that radiosurgery for VS can achieve very satisfactory results with proper indication and sophisticated treatment planning. In the future, interest will be focused on how to keep hearing and minimize cranial nerve dysfunction while maintaining such excellent treatment effects. Recently, reports that even a low dose of 12 Gy could increase tumor control rate and hearing preservation have been increased. A low radiation dose of 12 Gy can be expected to achieve satisfactory tumor control rate for small VS under 5 cc in volume. Evolution of more accurate and convenient radiosurgical tools, development of planning techniques, and the advancement in neuron-imaging techniques will provide the key roles in implementing the basic principle of radiosurgery.

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