Current treatment strategy for vestibular schwannoma: image-guided robotic microradiosurgery

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Object. Gamma Knife surgery (GKS) is becoming a standard treatment for vestibular schwannoma (VS); it is ranked with microsurgery from the perspective of tumor control and facial nerve function preservation. A new treatment technique that will improve the tumor shrinkage ratio, shorten the patient’s recovery time, and even recover some cranial nerve function is described.

Methods. Along with advances in the GKS system, the authors have developed magnetic resonance imaging sequences specific to particular treatments. These newly developed sequences provide much clearer visualization of the distribution of the cranial nerves, especially in the area from the cisterns to the internal acoustic meatus. Magnetic resonance images have been fused with computed tomography scans to facilitate better delineation of the anatomical relationships. These dose-planning images allow for a higher isodose line (80%) inside the tumor. The aim is to shrink the tumor and not just to control it. To date, 130 patients have been treated with GKS in conjunction with this new technique. Of the 130, 91 patients were observed for more than 12 months. The tumor shrinkage rate was 65.9% (76% for patients with > 24 months of follow up), the facial nerve preservation rate was 98.9%, the hearing preservation rate was 92.3%, and four (4%) of 91 patients recovered hearing function. Transient tumor enlargement was observed in most cases, but no severe complications were found.

Conclusions. Although these results are preliminary, they would appear to represent a potential breakthrough in the treatment of VS. Longer follow-up periods and additional cases will firmly establish this method as an absolute treatment option for patients with a VS.

KEY WORDS • Gamma Knife surgery • vestibular schwannoma • internal acoustic meatus • automatic positioning system
and eighth cranial nerves. Moreover, Gd-enhanced CISS imaging demonstrates tumor clearly as well delineating the surrounding cranial nerves. Clearer visualization of the tumor and each nerve has made it possible to spare nerves from radiation damage during treatment.

In addition, we homogenize the internal dose to the tumor to allow for higher mean and integrated doses. We aim not only to control the tumor but also to shrink it. We believe that the purpose of performing GKS for acoustic tumors should include directly tumor control and preservation of current function but to increase the rate of tumor shrinkage and the rate of recovery of function.

Clinical Material and Methods

Patient Population

In December 2002, Gamma Knife model C APS was installed at our institute. From December 2002 to April 2006, 150 patients with acoustic tumors have been treated using GKS. According to the Koos classification, nine patients had Stage 1 tumors, 56 patients had Stage 2 tumors, 50 patients had Stage 3 tumors, and nine patients had Stage 4 tumors. Based on preoperative neurological findings and the House–Brackmann scale, facial nerve palsy was graded as follows: 97 patients with Grade I, 11 patients with Grade II, seven patients with Grade III, and five patients with Grades IV to V. Hearing levels were graded according to the Gardner–Robertson classification (Class I–V): 21 patients had Class I, 25 had Class II, 30 had Class III, 12 had Class IV, and 32 patients had Class V.

Treatment Planning

The Leksell G stereotactic headframe was attached to patient’s head after application of a local anesthetic. Gadolinium-enhanced axial T1-weighted MR images and CT scans were acquired in 1-mm slices images. All of the imaging data were then fused with 1-mm axial CT bone window scans and uploaded to GammaPlan for dose planning. Magnetic resonance CISS images provide excellent visualization of the structures in the pontocerebellar cistern and were particularly useful in allowing us to distinguish among the tumor, facial nerve, and acoustic nerve; however, those structures were still difficult to distinguish in the IAM. Gadolinium-enhanced CISS images, on the other hand, demonstrate tumor and peritumoral cranial nerves very clearly. Fusing the CT and CISS images provides an even clearer view of the anatomical structures of the fundus of the IAM. The modified time-of-flight images are advantageous because this sequence provides a three-dimensional view of the tumor as well as of peritumoral vessels.

Treatment planning proceeds as hundreds of MR and CT images are imported to GammaPlan. First, we expand the image views in GammaPlan and construct a three-dimensional workspace in which to examine the anatomical relationship of tumor and surrounding vital structures. Second, we delineate the tumor and facial and acoustic nerves. The treatment is carefully planned to cover the tumor conformally and selectively at the 50% isodose line. Delineation of the facial and acoustic nerves is often impossible in tumors that are Koos Stage 3 and higher, so we avoid drawing a contour dose and proceed at this stage. We believe that the purpose of performing GKS for acoustic tumors should include directly tumor control and preservation of current function but to increase the rate of tumor shrinkage and the rate of recovery of function.

Results

We used the Leksell Gamma Knife model CAPS (versions 1.1 and 1.2) for treatment of all patients. The mean maximal tumor diameter was 18.3 mm (range 8.2–33.7 mm) and the mean tumor volume was 1.6 cm³ (range 0.11–9 cm³). For dose planning, the mean margin dose was 11.9 Gy (range 11–12.4 Gy) and the mean target volume was 1.96 cm³ (range 0.14–12.9 cm³). The mean number of isocenters was 18.5 (range 2–50), the mean conformity rate was 0.94 (range 0.33–1), and the selectivity rate was 0.83 (range 0.26–1). The mean integrated dose to the tumor was 25.1 mGy (range 1.8–126.4 mGy), and the mean energy unit was 16.8 mJ/cm² (14.19–6.4 mJ/cm²).

In 91 patients with more than 1 year of follow-up review a 100% tumor control rate was achieved and the tumor shrinkage rate was 65.9% (> 50% volume reduction in 15.3%). The facial nerve preservation rate was 98.9% and improvement was observed in 2.2% of patients. The hearing preservation rate was 92.3%, and improvement was observed in 4.4% of patients. The mean conformity rate was 0.94 (range 0.33–1), and the selectivity rate was 0.83 (range 0.26–1). The mean integrated dose to the tumor was 25.1 mGy (range 1.8–126.4 mGy), and the mean energy unit was 16.8 mJ/cm² (14.19–6.4 mJ/cm²).

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Illustrative Cases

Case 1

This 58-year-old woman had developed sudden deafness and MR imaging demonstrated a right acoustic
tumor. She elected to undergo GKS. Preoperative evaluation suggested that the tumor was a Koos Stage 1, Gardner–Robertson Class II, and House–Brackmann Grade I.

The headframe was attached after application of a local anesthetic. Thin-slice MR and CT imaging was performed, and a total of 280 images were imported into GammaPlan. The dose planning is shown in Fig. 1. On the coronal views, the tumor was localized at a groove right under the horizontal bar. We determined that the tumor was an inferior VS. On axial views, the facial and acoustic nerves could be seen directly at the front of the tumor. We covered the tumor to the 50% isodose line conformally and selectively and spared the nerves from radiation damage.

Case 2

This 56-year-old woman presented with progressive hearing loss and disequilibrium. Magnetic resonance imaging demonstrated a right acoustic tumor. Preoperative evaluation suggested that the tumor was a Koos Stage 3, Gardner–Robertson Class III, and House–Brackmann Grade I.

The headframe was attached after application of a local anesthetic. Thin-slice MR and CT imaging was performed, and a total of 360 images were imported into GammaPlan. Figure 2 shows the dose planning. On axial views, visualization of the facial and acoustic nerves was difficult. Therefore, we carefully produced a dose plan that would allow us to avoid administering extreme amounts of radiation to the anteroinferior part of the tumor and would not involve isocenter placement directed to the anterior wall of the IAM. We covered the tumor at the 50% isodose line conformally and selectively. We devised the planning so that the 80% isodose line area was within the tumor as much as possible to increase the intratumoral radiation dose. As a result, the tumor had shrunk more than 50% 2 years later (Fig. 3).

Case 3

This 65-year-old woman presented with progressive hearing loss and disequilibrium. Magnetic resonance imaging demonstrated a right acoustic tumor. She had a history of myocardial infarction. After consultation, she elected to undergo GKS. Preoperative evaluation suggested that the tumor was a Koos Stage 4, Gardner–Robertson Class IV, and House–Brackmann Grade I.

The headframe was attached after application of a local anesthetic. Thin-slice MR and CT imaging was performed, and a total of 440 images were imported into GammaPlan. Dose planning was performed as shown in Fig. 4. We could not delineate facial and acoustic nerves on the axial CISS view; however, the use of Gd-enhanced CISS imaging demonstrated the tumor well. We were able to visualize the acoustic nerve under the tumor and facial nerve adhering to the anterior part of the tumor (Fig. 5). We successfully spared the facial nerve and acoustic nerve and covered the tumor to the 50% isodose line conformally and selectively (Fig. 6). We also devised the planning so that the 80% isodose line area was within the tumor as much as possible to increase the intratumoral radiation dose.

![Image 1](image1.jpg)

*Fig. 1. Case 1. Dose planning images obtained for GKS of a Koos Stage 1 acoustic tumor.*

![Image 2](image2.jpg)

*Fig. 2. Case 2. Dose planning images obtained for GKS of a Koos Stage 3 acoustic tumor.*

![Image 3](image3.jpg)

*Fig. 3. Case 2. Magnetic resonance images obtained 2 years after GKS, demonstrating tumor shrinkage of more than 50%.*
Discussion

Comparison With Other GKS Series

To date, many results of GKS for VS have been reported. A dose to the tumor margin of 12 to 13 Gy (50% isodose line) to achieve tumor control and to preserve facial and hearing function is a well-established protocol. Despite some slight differences, authors of recent reports indicate that the average tumor control rate has reached 93% (range 87–97%) \(^{3,5,13–15,18,22}\). The results derived from follow-up periods of 10 years or more also suggest a similar tumor control rate (range 91–97%). \(^{3,5}\) It has been reported that if a tumor shows no regrowth within 3 years after treatment, the possibility of longer-term control of the tumor is very high. \(^{4,11}\) As for the postoperative tumor volume change, loss of central enhancement has been observed in 70 to 84% of cases at 6 to 9 months post-GKS. \(^{9,11}\) This loss of central enhancement is caused by subacute inflamma-

Fig. 4. Case 3. Dose planning CISS images obtained for GKS of a Koos Stage 4 acoustic tumor. The peritumoral cranial nerves could not be identified.

Fig. 6. Case 3. Three-dimensional dose planning images for a Koos Stage 4 acoustic tumor. The peritumoral cranial nerves will be totally spared from the 50% isodose area.

Fig. 5. Case 3. Dose planning images obtained after addition of Gd for a Koos Stage 4 acoustic tumor. The peritumoral cranial nerves are now identifiable because of the transparency of the tumor.

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GKS enhancement changes in the tumor after GKS, and in most cases, the enhancement reverts to the pre-GKS state. \(^{9,13–15}\) During the same time period (6–9 months), transient enlargement was reportedly observed in 14.4 to 41% of tumors. \(^{13,15,22}\) Pollock, et al. \(^{18}\) reported on a series of patients with transiently enlarged tumors, and loss of central enhancement was observed in 93%. They reported that there are three patterns in tumor enlargement: 1) transient enlargement (37%); 2) remains stable in size after treatment (29%); and 3) continues to enlarge (14%). Koos Stage 3 or 4 tumors are the primary cause of new neurological deficits, one of which is trigeminal neuropathy. However, it is notable that the morbidity rate of 2 to 5% in the group with transient enlargement seems to be very low considering the number of patients. It gives us the impression that it is fewer in comparison with the rate of transient enlargement. \(^{3,5,14,15,22}\)

When the results of GKS are compared with those of microsurgery, the postoperative complication rates related to facial and auditory nerve dysfunction are always mentioned. When performing GKS with margin doses of 12 to 13 Gy, the facial nerve function (including transient facial palsy) preservation rate is very high: over 99% in most reports. This rate is equivalent to that produced by microsurgery and the result is superior.

The results of a quality-of-life questionnaire given post-operatively to patients reveal that GKS is apparently superior to microsurgery (94.8% of patients reported improved function after GKS compared with only 79.8% after microsurgery) from the perspective of preservation of facial nerve function. \(^{15}\) Tamura, et al. \(^{22}\) reported that GKS preserves lacrimal function better than microsurgery, which indicates that GKS is more advantageous in that it can be used to preserve more sensitive functions. Although the preservation rate of auditory nerve function varies among institutes (63–84%), the mean rate is reportedly approximately 75% \(^{3,5,14,18,22}\). Van Eck, et al. \(^{22}\) reported that they were able to improve the preservation rate of auditory nerve function from the conventional rate of 70 to 84% by lowering the maximum dose from 26 to 20 Gy without changing tumor control rate. Combs, et al. \(^{7}\) reported on 27 cases treated by linear accelerator–based radiosurgery.
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The preservation rate of auditory nerve function was 55% and 90%, respectively. Based on a detailed evaluation of treatment planning, Masseger, et al., reported that the larger the tumor volume in the IAM or the higher the integrated dose to the tumor, the worse the preservation rate of auditory nerve function becomes. In addition, Paek, et al., reported that hearing deterioration is found more often in patients in whom a higher dose has been administered to the cochlear nucleus, strongly indicating that effective irradiation of the tumor within the IAM could cause hearing function worsen postoperatively. On the other hand, patients with tumors located in the lateral thalamus (Stage I) and those with nerves very close to the hearing preoperatively (particularly patients with innu- tias) have excellent auditory nerve function rate postoperatively, which is over 90%.13

We have come to understand that meticulous dose planning, including dose selection, tumor coverage, conformity, selectivity, homogeneous intratumoral dose administration, and prevention of excessive irradiation, is directly connected to improved therapeutic results.

Although we present a preliminary report involving a small number of patients with a short follow-up period, this newest treatment protocol—high-resolution MR imaging–guided GKS with the APS and a high integrated energy dose for homogenous intratumoral dose distribution—resulted in a perfect actuarial tumor control rate at 1 and 2 years of follow up. Loss of central enhancement was observed in 88% of patients, and transient enhancement was seen in 25%. The actuarial preservation rate of facial nerve function was 98.9% at the 1-year follow up and 90.0% at the 2-year follow up. Patients experienced some attacks of transient facial nerve palsy (peripherally), and 100% at 2 years follow up. The actuarial auditory nerve function preservation rate was 92.3% at the 1-year follow up and 88.6% at the 2-year follow up.

Transient trigeminal sensory nevralgia associated with transient VS enlargement was observed in 4.4% of patients every patient showed improvement at the 1-year follow up. No hydrocephalus or malignant transformation has been observed. We believe that our therapeutic results are good and our treatment strategy is practical, even at the present stage. This time we succeeded in achieving sharp delineation of the facial and acoustic nerve by using thin-slice CISS and Gd-enhanced CISS by MR imaging. Avoiding direct irradiation to the nerves must have been a good reason for decreased complication cases. But we need more cases and longer follow-up to evaluate final treatment results because this study was based on only cases with immediate effect.

**Advances in Equipment and Imaging Technology**

Installation of a new model Gamma Knife unit at our institute took place in 2002, which for the first time had an APS to make procedures precise and robotic. Unlike in the conventional manual positioning, human error is almost completely avoidable, which is a great advantage for medical safety.14,15

Imaging technology has advanced alongside equi- pment technology. MR imaging with sequences are essential to support the 0.1-mm level of current Gamma Knife unit capability. Conventional Gd-enhanced T1-weighted imaging provided approximate anatomical information and, therefore, were at least GKS imaging with the tumor and avoid the brainstem and cerebellum. Visual- ization of the facial and auditory nerves was impossible, meaning that the nerves would possibly be included in the radiation field. To spare the nerves from radiation damage, we set the margin dose to 13 Gy, which is still in use widely as the safe prescription dose.

More recently, CISS imaging has been reported to be a very effective adjunct in GKS of VS.16-20 It is par- ticularly useful in Koos Stage 1 and 2 tumors in which cerebrospinal fluid between tumor and brainstem helps in visualizing the facial and auditory nerves. Using 1.5-tesla MR imaging it is possible to visualize the auditory nerve as it separates into the cochlear nerve and the superoinferior vestibular nerve. Furthermore, after the images are uploaded into GammaPlan, the nerve running from the side of brainstem to the periphery of the tumor can be visualized three dimensionally.

If the IAM is almost completely occupied by the tu- mor, the visualization of each nerve could be limited at the entrance, in which case the addition of Gd enhancement makes the tumor transparent. Gadolinium enhance- ment makes it possible to track the nerves even to the periphery of the tumor, especially using high-performance 1.5-tesla MR imaging, which highlights the peritumoral cranial nerves.16 Moreover, by fusing the images with CT bone windows images in GammaPlan, we clearly see the facial notch that runs from the IAM to the geniculate gan- glia for use as a landmark. More often than not, the tumor extends down to the fundus. To avoid excessive irradia- tion of the fundus, we also added the CISS imaging with- out Gd enhancement to visualize the cerebrospinal fluid very clearly. On the other hand, Gd-enhanced T1-weighted MRI may cause some overlap between the IAM, and this we do not recommend for dose planning.

**A New Goal and Challenge for GKS of VSs**

The original purpose of Gamma Knife treatment for VSs was to control tumor progression and preserve under- lying facial and auditory nerve function. Because treating VSs without transient enlargement is impossible, it is considered best to examine the tumor size and then irradiate the tumor with high conformity and selectivity.

So far, authors of reports on GKS for tumor control have put the tumor regression rate at 5 years follow up at approximately 60% and 70% at 10 years of follow up.21 The preservation rates of facial and auditory function are much higher than those of microsurgery in our institute, which was reported by Maryama.2 There has not, however, been a published report on how much pretreatment function was recovered.

We have had a therapeutic goal since the Gamma Knife system upgrade in December 2002. It is a treatment plan- ning that aims not only at tumor control and preserva- tion of current function but tumor shrinkage and recovery of function. Making full use of the latest technological advances, we do our utmost to visualize the facia- l and auditory nerves to spare them from the target volume. Mor- eover, we consider how to administer a well-collimated and localized radiation dose. Imaging sequences and MR imaging, especially high-performance CISS, provide extensive information on intratumoral radiation. We make it a rule to indicate not only the 50%, but also the 80% isodose area before the
completion of treatment planning so as to confirm homogene-
ity of the intratumoral dose distribution. By con-
firming intratumoral dose distribution, we are able to
place smaller isocenters to make radiation homogeneous
and make the higher isodose area occupy the maximum
amount of tumor. This would maximize the integrated
dose to provide maximum tumor shrinkage.

We have established a new parameter with which to set
a new evaluation standard. Intratumoral energy volume is
proportional to tumor volume. Therefore, energy volume
per unit volume, that is, unit energy (milli/joules/cubic
centimeter), is calculated in all cases and recorded in our
database. We think that the unit energy is linearly related
to the mean intratumoral dose and homogeneity. In other
words, even though the margin dose may be the same,
the difference in the unit energy should make a difference
in the irradiation of the tumor. We have not yet conducted
a precise evaluation of the treatment with the concept of
unit energy. The energy volume per unit volume when us-
ing the conventional treatment method is approximately
15 mJ/cm². With the current method, the unit energy is
approximately 16.8 mJ/cm². The tumor shrinkage rate ex-
ceeds 60% at 12 months and 75% at 24 months of follow
up, which may be due to the increased unit energy.
 Addition, greater than 50% of tumor volume reduction is
considered to be clinically significant; this was observed
in more than half of all cases. If the the tumor is a Koos
Stage 1 or 2 lesion and there is a short period from tumor
onset to GKS, there may be a possibility that the auditory
nerve function will recover after the treatment. Tumor
shrinkage at an early phase will decrease the compression
of the surrounding auditory nerve to the tumor and the IAMone. Some such cases at our institute may exemplify our
idea. We will continue our effort to achieve better results
by Gamma Knife treatment.

Conclusions

This time we made full use of the upgraded Gamma
Knife system model C-APS to present a new treatment
strategy for VS and its treatment results, even though we
only have a short-term follow up to see the advantage of
our treatment method. Previously, the primary goal of
Gamma Knife treatment for benign tumors was control of
tumor volume and preservation of underlying nerve
function. Now we seek more. We aim at achieving tumor
shrinkage at the early phase and recovery of nerve dys-
function. Based on experience, we will focus on sparing
the surrounding nerves from the target irradiation field
to reduce damage and increase sufficient intratumoral irra-
diation volume and energy volume as much as possible.

Recently, the number of reports on treatment using frac-
tioned stereotactic radiotherapy has increased from the
viewpoint of neurological function preservation. As for
benign tumors, however, we strongly recommend radio-
surgery from a microsurgical point of view because it
provides higher conformity, selectivity, and homogeneous
intratumoral dose distribution. We are determined to make
a relentless effort to complete optimal dose planning for
all patients in the near future.

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