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 audiofacial 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

There are two possible treatment strategies for acoustic tumor: resection and radiosurgery. In general, resection has been recommended as the first treatment choice. Recently, there has been an increase in the use of radiosurgery as the first line treatment, especially in elderly patients and those with other comorbid conditions. The use of the Koos classification (Stages 1–5) provides an excellent indication for treatment. In particular patients with Stage 2 (tumor protruding into the posterior fossa from the IAM but not touching the brainstem) and Stage 3 (tumor touching the brainstem but not causing compression) tumors but in whom there is no neurological deficit are considered to be a good candidates for radiosurgical treatment. Recently, even tumors localized in the IAM (Koos Stage 1) are treated more often by radiosurgery, with the intention of preserving hearing function.

The primary aims in performing GKS for VS are control of the tumor and preservation of the surrounding nerve function. There have been many articles written about GKS for acoustic tumors in which tumor control rates of more than 95% has been reported. Compared with the results of resection, GKS produces higher preservation rates of facial nerve function and hearing function.

Many technological improvements and updates have been made to the Gamma Knife unit in recent years. The previously used manual procedure for targeting and administering radiation doses has been replaced with an automatic system assisted by computer robotics (the model C-APS), which guarantees accurate radiation placement to within 0.1 mm. Technical advances have also occurred in diagnostic imaging instrumentation. Thin-slice MR CISS imaging now provides clear visualization of the seventh
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 not be merely 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, 130 patients with acoustic tumors have been treated using GKS. According to the Koos classification, nine patients had Stage I tumors, 56 patients had Stage II tumors, 50 patients had Stage III tumors, and nine patients had Stage IV 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 as well as 1-mm axial bone windows scans and imported into GammaPlan (Elekta Instruments AB).

In addition, 0.5-mm axial CISS images, 0.5-mm axial Gd-enhanced CISS images, and 1-mm axial modified time-of-flight images were also obtained. All of the imaging data were then fused with 1-mm axial CT bone windows 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 and its involvement with 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 administering a radiation dose to anterior and posterior portions of the tumor. We carefully placed each isocenter within the tumor so as not to involve the anterior and inferior wall of the IAM. Once the treatment planning is complete, we review the points of all isocenters simultaneously; if part of one of the isocenters is involved in peritumoral cranial nerves, we adjust the position of the isocenter by 0.1 mm to ensure that the nerve will be spared. Finally, we confirm the location and the area of the 80% isodose line. If the the 80% isodose line occupies an area that is too small to see, we add another lower weight isocenter to expand the area within the tumor as wide as possible.

**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 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 mJ (range 1.8–126.4 mJ), and the mean energy unit was 16.8 mJ/cm³ (14–19.6 mJ/cm³).

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. After more than 2 years of follow up, 25 patients (27%) had a 100% tumor control rate and the tumor shrinkage rate was 76% (50% volume reduction in 28%). The facial nerve preservation rate was 100%, and improvement was seen in 4%. The hearing preservation rate was 88%, and improvement was seen in 4%.

At a median 6 months follow up MR imaging demonstrated loss of central enhancement in 94.5% of tumors. Significant transient enlargement of more than 2 mm was observed in 25.8% of tumors. By 12 months post-GKS the tumor had shrunk to its pretreatment size in all patients. Although some patients complained of slight vertigo during this time, no patient presented with significant complications. No patient experienced hydrocephalus or trigeminal neuropathy during the follow-up period. Although the follow-up period was short, there found no indication of malignant tumor transformation in any patient. Among a total of 130 patients, 91 patients were followed up for more than 1 year and 25 patients were followed up for more than 2 years.

**Illustrative Cases**

**Case 1**

This 58-year-old woman had developed sudden deafness and MR imaging demonstrated a right acoustic
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Case 1

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 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.

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.
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.

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%).1–5,8,13–15,18,22 The results derived from follow-up periods of 10 years or more also suggest a similar tumor control rate (range 91–97%).3,9 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.4,13 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.1,13 This loss of central enhancement is caused by subacute inflammatory changes in the tumor after GKS, and in most cases, the enhancement reverts to the pre-GKS state.12,22 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.15 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 (57%); 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.5,8,14,15,18

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 postoperatively 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.11 Tamura, et al.20 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%.3,5,8,10,14,18,22 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.,2 reported on 27 cases treated by linear accelerator–based radiosurgery.

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.

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.
The preservation rate of auditory nerve function was 55\% at the 9-year follow up. 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 excessive irradiation of the portion of the tumor within the IAM could cause hearing function worsen postoperatively. On the other hand, patients with tumors located in the IAM (Koos Stage 1) and those with serviceable hearing preoperatively (particularly patients with tinnitus) have excellent auditory nerve function rate postoperatively, which is over 90\%.3,4,8

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 homogeneous 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 enlargement was seen in 25\%. The actuarial preservation rate of facial nerve function was 98.9\% at the 1-year follow up (postoperatively one patient experienced the onset of hearing disturbance and facial nerve palsy; the patient had experienced some attacks of transient facial nerve palsy preoperatively), and 100\% at 2-year follow up. The actuarial auditory nerve function preservation rate was 92.3\% at the 1-year follow up and 88\% at the 2-year follow up. Transient trigeminal sensory neuropathy associated with transient VS enlargement was observed in 4.4\% of patients, but 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.

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 underlying 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. The preservation rates of facial and auditory function are much higher than those of microsurgery in our institute, which was reported by Maruyama.9 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 planning that aims not only at tumor control and preservation of current function but tumor shrinkage and recovery of function. Making full use of the latest technological advances, we do our best to visualize the facial and auditory nerves to spare them from the target volume. Moreover, we consider how to administer a well-collimated and localized radiation dose to the tumor and how to give more 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 homogeneity of the intratumoral dose distribution. By confirming 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 (milliJoules/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 using the conventional treatment method is approximately 15 mJ/cm³. With the current method, the unit energy is approximately 16.8 mJ/cm³. The tumor shrinkage rate exceeds 60% at 12 months and 75% at 24 months of follow up, which may be due to the increased unit energy. In 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 auditory nerve between the tumor and the IAM bone. 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 dysfunction. Based on experience, we will focus on sparing the surrounding nerves from the target irradiation field to reduce damage and increase sufficient intratumoral irradiation volume and energy volume as much as possible.

Recently, the number of reports on treatment using fractionated stereotactic radiotherapy has increased from the viewpoint of neurological function preservation. As for benign tumors, however, we strongly recommend radiosurgery 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.

References

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