Gamma Knife surgery and trigeminal schwannoma: is it possible to preserve cranial nerve function?

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Object. The current study was undertaken to evaluate the tumor control rate and functional outcome after Gamma Knife surgery (GKS) in patients with a trigeminal schwannoma. The conditions associated with the development of cranial neuropathies after radiosurgery were scrutinized.

Methods. The authors reviewed the clinical records and radiological data in 22 consecutive patients who received GKS for a trigeminal schwannoma. The median tumor volume was 4.1 ml (0.2–12.0 ml), and the mean tumor margin dose was 13.3 ± 1.3 Gy at an isodose line of 49.9 ± 0.6% (mean ± standard deviation). The median clinical follow-up period was 46 months (range 24–89 months), and the median length of imaging follow-up was 37 months (range 24–79 months).

Results. Tumor growth control was achieved in 21 (95%) of the 22 patients. Facial pain responded best to radiosurgery, with two thirds of patients showing improvement. However, only one third of patients with facial hypesthesia improved. Six patients (27%) experienced new or worsening cranial neuropathies after GKS. Ten patients (46%) showed tumor expansion after radiosurgery, and nine of these also showed central enhancement loss. Loss of central enhancement, tumor expansion, and a tumor in a cavernous sinus were found to be significantly related to the emergence of cranial neuropathies.

Conclusions. The use of GKS to treat trigeminal schwannoma resulted in a high rate of tumor control and functional improvement. Cranial neuropathies are bothersome complications of radiosurgery, and tumor expansion in a cavernous sinus after radiosurgery appears to be the proximate cause of the complication. Loss of central enhancement could be used as a warning sign of cranial neuropathies, and for this vigilant patient monitoring is required.

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Key Words • cranial neuropathy • Gamma Knife surgery • trigeminal schwannoma

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VER the last few decades, the importance of noninvasive modalities for the treatment of intracranial lesions has been emphasized, and they are now widely accepted in clinical practice. Gamma Knife surgery is one such example. Many types of tumors in the skull base, which usually denies easy surgical access, are now being actively treated with GKS. Moreover, the treatment outcomes after radiosurgery for skull base meningiomas and schwannomas, which are the two major tumors found in the skull base, are compatible with these changing treatment trends.4,8,9,25

Long-term follow-up data on vestibular schwannomas after GKS show that the tumor control rate is comparable to that of microsurgery and that the ability to preserve cranial nerve function by using radiosurgery may exceed that made possible by using microsurgery.25,10,13,21

Trigeminal schwannoma is an uncommon tumor that arises from the sheaths of the trigeminal root, ganglion, or nerves. It usually grows in the Meckel cave, the posterior fossa, or in a cavernous sinus, and frequently straddles multiple cranial fossae. Once considered formidable tumors with a high rate of surgery-related mortality and morbidity, trigeminal schwannomas now can be totally removed using a combination of skull base approaches and microsurgery. Nevertheless, cranial nerve deficits are common after such radical tumor resections, in addition to other surgical complications.1–3,12,22,23

Several reports are available about stereotactic radiosurgery for trigeminal schwannomas, including GKS,7,11,15,20 and the tumor control rates and functional outcomes disclosed so far are promising and warrant further investigation. In this study, the treatment outcomes in 22 patients with a trigeminal schwannoma treated by GKS were analyzed, with a focus on improvements and deteriorations in cranial nerve functions.

Clinical Material and Methods

Patient Population

Inclusion criteria were as follows: 1) a radiological and/or pathological diagnosis of trigeminal schwannoma; 2) the absence of a diagnosis of neurofibromatosis; and 3) a clinical and radiological follow-up period of at least 2
gamma knife radiosurgery (GKS) was performed with a mean dose of 14.4 Gy (standard deviation 1.5) and a mean margin dose of 13.0 Gy (standard deviation 2.2). The median number of treatments was 2 (range 1–5). No other active medical treatment was used during the follow-up period.

Follow-Up Protocol and Data Analysis

A regular clinical follow-up schedule was offered to all patients, beginning 1 month after GKS. Brain MR images were obtained at the 6-month and 1-year follow-up visits, and thereafter annually scheduled MR imaging was recommended. When a patient complained of aggravating symptoms or showed clinical deterioration, MR imaging was indicated regardless of the schedule. The MR images were reviewed independently by a neuroradiologist for clinical follow-up, and review and volume measurement were performed by the authors. Tumor volumes were calculated using Osiris 3.0 (University Hospital of Geneva).

The median duration of clinical follow-up was 46 months (24–89 months), and the median duration of imaging follow-up was 37 months (24–79 months). Treatment outcomes were evaluated 3 years after GKS in 22 (95.6%) of the 23 patients. The median follow-up period was 37 months (24–79 months).

GammaPlan (Elekta Instruments AB). Multiple-isocenter planning was applied to minimize the radiation exposure of adjacent structures.

The median tumor volume was 4.1 ml (0.2–12.0 ml). The mean tumor margin dose was 13.3 ± 1.3 Gy at an isodose line of 49.9 ± 0.6%, and the maximal dose administered was 26.9 ± 2.7 Gy (mean ± standard deviation). The median number of shots was 11 (5–19).

Patients received 10 mg of dexamethasone intravenously before GKS, and 4 mg every 8 hours thereafter, and all were discharged on the day of or 1 day after treatment. Oral prednisolone was prescribed on a tapering schedule over 1 week.

### TABLE 1

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<th>Case No.</th>
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<th>Sex</th>
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<th>Margin Dose (Gy)</th>
<th>CE Loss</th>
<th>Tumor Expansion</th>
<th>FU (mos)</th>
<th>Tumor Outcome</th>
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<td>45</td>
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<td>no preop symptoms</td>
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</table>

* CE = central enhancement; CNP = cranial nerve palsy; ES = extracranial space; Fdys = facial dysesthesia; Fhyp = facial hypesthesia; FU = follow-up; HA = headache; MF = middle fossa; MW = masseter weakness; PF = posterior fossa; res = residual; TP = trigeminal pain; + = present; – = absent.
comes were measured based on three aspects: oncological outcome (tumor growth control), functional outcome (symptomatic improvement), and GKS complications (new or worsening cranial neuropathy). Symptomatic improvement and cranial neuropathy were assessed during the clinical examination. All statistical analyses were performed using SPSS version 12.0 statistical software (SPSS, Inc.).

Results

Oncological Outcomes

Based on serial follow-up MR imaging studies and volumetric analyses, tumor growth was found to be controlled in 21 (95%) of the 22 patients, after a median imaging follow-up period of 37 months (range 24–79 months). Final tumor volumes decreased in 16 patients (73%), were stationary in five (23%), and increased in 1 (4%). After GKS, 11 patients (50%) showed continuous tumor volume reduction, 10 patients (46%) had tumor expansion, and one patient showed virtually no volume change. After an initial tumor expansion in the 10 patients, tumor shrinkage followed in five (Fig. 1), tumor volumes became stationary in four, and one patient experienced shrinkage and later regrowth, leading to treatment failure.

Transient tumor volume expansion was significantly more frequent in larger tumors. The initial tumor volume (mean ± standard deviation) was 6.8 ± 3.7 ml in patients with transient volume expansion, whereas it was 2.7 ± 2.4 ml in those without volume expansion (p = 0.01, Student t-test). Nine of the 10 patients with tumor expansion showed central enhancement loss between 6 and 18 months after GKS, which coincided with or preceded tumor expansion (p < 0.001, Fisher exact test).

In the only case of tumor control failure, marked tumor enlargement with a central enhancement loss was noted at 6 months after GKS, and this caused multiple cranial neuropathies, some of which became permanent. Subsequently, tumor shrinkage followed over 3 years, only to be followed by tumor regrowth at 4 years after GKS. Resection was recommended, but the patient refused because the chief symptom, facial dysesthesia, was well tolerated while the patient continued oral medication.

Functional Outcome

Trigeminal pain responded best to GKS; eight (73%) of 11 patients experienced pain remission. Headaches also responded, and were relieved in five patients (63%). Oculomotor and abducent nerve palsy disappeared in two (67%) of three patients. However, there appears to be little chance of regaining facial sensory function; only three (27%) of 11 patients improved, and trigeminal motor dysfunction, once established with masseter atrophy, did not improve at all. Functional outcomes are summarized in Fig. 2.

New or Worsening Cranial Neuropathies

New or worsening cranial nerve deficits were observed in six patients (27%); three had permanent and three had transient deficits after radiosurgery. Only one patient with permanent deficits experienced tumor control failure, and tumor volume was eventually reduced or stationary in the other two. Trigeminal pain and abducent nerve palsy were invariably transient, whereas new-onset facial hypesthesia and dysesthesia remained permanent.

Only the presence of a tumor involving the cavernous sinus was found to be related to the emergence of cranial neuropathies, and tumors confined to the posterior or temporal fossae were not associated with the development of cranial neuropathy after GKS (six of 14 compared with 0 of eight cases; p = 0.034, Fisher exact test).

Patients who developed new or worsening cranial nerve deficits were given oral steroids to alleviate symptoms and MR imaging was recommended to evaluate tumor status. Five of these six patients showed a loss of central enhancement and tumor expansion, and central enhancement loss

Fig. 1. Axial MR images demonstrating a medium-sized, dumbbell-shaped trigeminal schwannoma (5.2 ml) in the right Meckel cave and posterior fossa. An initial dose of 14 Gy was given at an isodose line of 50% (A). Transient tumor expansion (10.9 ml) was noted at 6 months after GKS (B). Thereafter, the tumor volume gradually decreased; follow-up MR images obtained 12 (C) and 24 months (D) after GKS demonstrated lower tumor volume (5.6 and 2.1 ml, respectively).
preceded volume expansion in two cases and coincided with it in three cases. Tumor expansion proved transient and was followed by shrinkage in four patients, but was continuous in one, in whom it led to control failure. Both central enhancement loss and tumor expansion on follow-up MR images were significantly related to the emergence of cranial neuropathies ($p = 0.033$ for each factor, Fisher exact test); Fig. 3 illustrates an exemplary case. The initial tumor volume and prescribed radiation dose showed no significant correlation with cranial nerve deficits after GKS.

**Discussion**

Direct comparisons of the outcomes of microsurgery and radiosurgery are usually hampered by some limitations. One major problem is that, generally, larger tumors are involved in surgical series than in radiosurgical series. Moreover, most reports on radiosurgery of trigeminal schwannomas, including ours, have only a short- or medium-length follow-up. Because the effects and complications of microsurgery are immediate, whereas those of radiosurgery come insidiously over the following years, long-term results of tumor control and adverse radiation effects should be evaluated. Nevertheless, considering the fact that no controlled studies on the treatment of trigeminal schwannomas have been performed, continuation of the comparative analysis in spite of such limitations is worthwhile.

Trigeminal schwannoma is an overwhelmingly benign neoplasm that can be cured by complete surgical removal. The advancements in microsurgical techniques have made it possible to remove this tumor totally, despite its strategic location at the skull base and its involvement of important neurovascular structures. When McCormick et al. reported that total resection was possible in six of 14 cases of trigeminal schwannoma, although it was a great achievement at the time, they also made it clear that this was not achieved without cost; 12 patients in their series (86%) experienced new-onset permanent cranial neuropathies. Sim-
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ilarly, in a series by Samii et al., half of the patients had postoperative complications, such as tetraparesis or facial nerve palsies, and three quarters of their patients also experienced loss of or an impaired trigeminal nerve function. Day and Fukushima reported total trigeminal schwannoma resection in 30 of 38 patients, and again loss of trigeminal nerve function was not uncommon; six had new-onset trigeminal hypesthesia, five had trigeminal anesthesia, and 20 had trigeminal motor weakness. Yoshida and Kawase observed that 93% of patients with tumor underwent total resection, but that 20 had postoperative complications, mainly cranial neuropathies. Moreover, all 25 patients in a series by Al-Mefty et al. underwent total resection, but surgical complications occurred in 12 patients, and three of these had permanent cranial neuropathies. Thus, surgical complications, especially cranial neuropathies, remain the main obstacle to the radical resection of trigeminal schwannomas, despite improved tumor control outcomes.

Several reports are available on stereotactic radiosurgery for trigeminal schwannomas. Huang et al. described treatment outcomes for GKS in trigeminal schwannoma for 16 patients. After an average follow-up period of 44 months, 100% tumor control and no complications were observed. Mabanta et al. described the outcomes of linear accelerator stereotactic radiosurgery in a series of nonacoustic schwannomas, which included seven patients with trigeminal schwannoma. After an average follow-up period of 32 months the tumor control rate was 100%, but one sixth of patients developed cranial neuropathies in that series. Pollock et al. performed a detailed analysis of treatment outcomes of nonacoustic schwannomas treated with GKS, which included 10 patients with trigeminal schwannoma. All trigeminal schwannomas were controlled after a mean of 43 months, except in one case with malignant histological findings. However, permanent cranial nerve deficits developed in three patients. Nettel et al. extended the series of Huang et al., and reported a tumor control rate of 91% after a median follow-up period of 40 months, and noted that 9% of the patients developed new or worsening cranial neuropathies.

Our data show that after a median imaging follow-up period of 37 months (± 2 years in all patients), 95% tumor control was achieved, and after a median clinical follow-up period of 46 months, two thirds of patients with preexisting facial pain and one third with trigeminal hypesthesia improved. This is a satisfactory outcome, even compared with those of recent surgical series. Nevertheless, new or worsening cranial neuropathies developed in 27% of patients. Although it is a relatively smaller figure compared with the outcomes of earlier surgical series, it is actually not a small percentage.

Ostensibly, tumor expansion in the cavernous sinus was the proximate cause of cranial neuropathies, and a loss of central contrast enhancement heralded or coincided with tumor expansion and the emergence of cranial neuropathies. Central enhancement loss and transient tumor expansion are typical responses of schwannomas to stereotactic radiosurgery. Studies on the stereotactic radiosurgery of vestibular schwannomas have revealed that as many as 72 to 88% of patients show central enhancement loss and 14 to 64% have tumor expansion. REGIS et al. interpreted these two phenomena as favorable signs for radiosurgical efficacy. Yu et al. also found that central enhancement loss and tumor expansion were closely related and that they were usually followed by tumor shrinkage. Pollock observed that 93% of patients with tumor expansion after vestibular schwannoma radiosurgery also showed central enhancement loss and that tumor expansion rarely denoted a failed treatment, because the majority of the tumors (86%) eventually regressed or stopped growing. These authors recommended a conservative approach to this situation, and stressed that if cranial nerve deficits develop they are usually transient. However, in 20% of their patients with tumor expansion, cranial neuropathies developed after the time of initial expansion, and half of the patients required repeated operation.

Our data indicate that the risk of cranial neuropathies at the time of tumor expansion is higher for trigeminal than vestibular schwannomas. Ten patients in our study showed tumor expansion after radiosurgery, and in five of them (50%) cranial neuropathies developed. Why then are cranial nerves more vulnerable to tumor expansion after trigeminal schwannoma radiosurgery? The cavernous sinus is a confined space and cranial nerve entrapment is more likely there than in the posterior fossa when tumor expansion occurs. Actually, no tumor outside the cavernous sinus (posterior fossa or temporal fossa) caused cranial neuropathies in our study, even though tumor expansion occurred in such cases.

In the series published by Pollock et al., who found a similar rate of cranial neuropathies (30%) to ours, they prescribed a relatively high marginal dose (18 Gy). Nettel et al. suggested that, according to their initial experiences, a higher marginal dose (15 Gy) led to two cases of cranial neuropathy, and accordingly, they recommended the application of a lower dose (13 Gy), as is recommended for vestibular schwannomas. We applied a relatively low marginal dose in this series (13.3 ± 1.3 Gy), but no correlation was observed between the prescribed dose and the emergence of cranial neuropathies. Although it is well established for vestibular schwannomas that a low-dose (12–13 Gy) radiosurgical strategy improves hearing preservation, it is uncertain at present whether dose reduction also favors cranial nerve preservation in trigeminal schwannoma radiosurgery.

It is possible that the development of cranial neuropathies after radiosurgery depends on a complex interaction of factors, such as the sizes of the cavernous sinus and Meckel cave, the susceptibilities of individual nerves, initial tumor volume, and prescription dose. Further study is warranted to elucidate more precisely the causes of cranial nerve deficits and to prevent complications.

Conclusions

Although microsurgical resection is mandatory for large tumors, GKS is an effective treatment for small- to medium-sized trigeminal schwannomas. The tumor control rate achieved using GKS was more than 90% after medium-length follow-up, and improvements in preexisting symptoms, especially trigeminal pain, were remarkable. Nevertheless, the development of cranial neuropathies after radiosurgery remains a problem, and thus every effort should be made to prevent and reduce such adverse effects.
and to maximize functional outcomes. Tumor expansion in the cavernous sinus after radiosurgery appears to be the proximate cause of cranial neuropathies. Moreover, because central enhancement loss was frequently found to herald or coincide with tumor expansion and the development of cranial neuropathies, it could be used as a warning sign of potential adverse effects. Vigilant patient monitoring and the prompt use of steroids are required if this sign is observed. Further studies with longer follow-up periods are required to define optimal radiosurgical strategies and to evaluate long-term outcomes.

References