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Case Study

Glomus tumors treated with stereotactic radiosurgery: A retrospective study

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ABSTRACT

Background: Glomus tumors are difficult to manage surgically because they are vascular tumors that are topographically associated with important vascular and neuronal structures. Hence, there is a strong risk of incomplete resection and a high morbidity rate. In addition, they grow slowly. Recent treatments have increasingly involved a combination of surgical resection and radiosurgery. We present our experience in treating glomus tumors of the skull base with stereotactic radiosurgery as an upfront therapy.

Methods: We analyzed data from 13 consecutive patients with glomus tumors that were initially treated with stereotactic radiosurgery in our institute from February 2010 to April 2012. The tumor control rate, resolution of symptoms, and the complication rate were tabulated.

Results: All patients were female with a median age of 63 (mean 62.7+/-14.6 years). The median treatment dose was 25.8 Gy (27.6 Gy +/- 9.5 Gy) and the median tumor volume 10.4 mL (9.2 +/- 6.5). The median follow-up was 47.4 months (51.8+/-11.2 months, range 31-74). The tumor control rate was 92.3%; 46.7% of the patients had noticeable tumor shrinkage. This happened at a median interval of 17 months (18.7+/-6.8) after treatment. Most patients with tinnitus had resolution of their symptoms (87.5%). Four patients presented with new symptoms and four patients with worsening of pre-existing symptoms. The time course of symptomatic improvement followed that of tumor size reduction. However, there was no statistical correlation between the amount of tumor reduction and symptomatic relief.

Conclusion: Stereotactic radiosurgery (SRS) is an effective upfront treatment option in the management of glomus tumors.

Keywords: Stereotactic radiosurgery, glomus tumors, outcome study, case series

INTRODUCTION

Glomus tumors of the skull base are a group of hypervascular tumors that arise from the paraganglia within the temporal bone and in the proximity of the jugular foramen, including the glomus jugulare and glomus tympanicum. They grow slowly and are most common in females in their fifth and sixth decades [1,2].

The traditional treatment for glomus tumors is embolization followed by surgical resection. The complexity of the surgical approach is well documented [3]. Even in the hands of experienced surgeons, gross total resection may not be achievable, and the post-operative morbidity rate is higher than acceptable [4].

For over three decades, radiation therapy has played the role of an adjuvant therapy to treat residual tumors, while also employed as an upfront therapy, but that too has its short comings. Since the late 1990s, stereotactic radiosurgery has been used to treat residual tumors [5,6]; in recent years, SRS has increasingly been a substitute for craniotomy. We present our single institutional experience in treating this group of tumors with stereotactic radiosurgery as an upfront treatment modality, and compared our outcome to those reported in literature. Our results show that radiosurgery has a high success rate in growth control, with fewer complications and a high degree of certainty in abolishing pulsatile tinnitus.

METHODS

Data Collection

We retrospectively reviewed the charts of patients with glomus tumors that were treated with radiosurgery between 2009 and 2012.Thirteen patients with glomus tumors were treated upfront by radiosurgery. These patients were diagnosed with a glomus tumor on the bases of anatomical location, imaging features (including MRA), and clinical presentations. None of these patient have tissue diagnosis or more specific imaging studies such as PET scan with 11C-methionine.

The demographic data of the patients, the pre- and post-treatment symptoms, time to respond, and the tumor volume before and after treatment were assessed. To classify the anatomical involvement of the tumors, we used the Fisch grading system. We did not segregate these tumors ino jugulare and tympanicum.The study was approved by the Institutional Review Board and waived patient informed consent based on the retrospective study design (CN-15-2233-H).

Radiosurgery Treatment

All the patients were treated with X-band 6MV photons from a LINAC System, Cyberknife®. Using the Accuray Multiplan system, non-contrasted enhanced CT scans (1.25 mm slice thickness) were fused with axial T1 post gadolinium-enhanced FSE MRI scans (2mm thickness) without any skipped. The target volume was defined using Multiplan contouring software without target expansion. The median treatment dose was 25 Gy (15-30 Gy), prescribed to the 80% iodose line (79.61+/- 1.85%). The tumor volume was 10.4 mL (9.2 +/- 6.5) and the mean dose 27.6 Gy (+/- 9.5Gy, see Table 2). We treated tumors larger than 12 ml in five fractions, while using one session for tumors of less than 3 ml. The inner ear apparatus was contoured; the cochlea maximum dose was constrained to below 8, 24, and 27.5 Gy in a single fraction, three fractions, and five fractions respectively.

Follow-up

After treatment, our regional skull base clinic followed the patients. Pre- and post-treatment symptoms were recorded and updated either by phone follow-ups or in-person clinic visits. All patients underwent scheduled serial surveillance MRI studies at 3-, 8-, 12-, and 18-month time points, and then biennially.

The surveillance scans were done with the aforementioned scanning protocol, in addition to pre-gadolinium axial T2 FSE (2mm, no skip), coronal T1-post contrast, and sagittal T1 post con FSE. The MIM software was used to perform volumetric analysis of the tumor.

The pre-treatment diagnostic MRI scan and the most recent follow-up MRI scan were transferred to MIM Vista image registration program (MIM Vista 6.5, MIM Software, Cleveland, OH, USA). They were registered using a rigid registration algorithm. The tumors were contoured on both scans.

Statistical Analysis

Following is a list of methods used for statistical analysis. A description of patient characteristics (categorical, nominal and ordinal) before and after stereotactic radiosurgery treatment was provided and assigned a numerical value for dichotomous data analysis. We used the Fisher test to evaluate the significance of changes in the categorical data. Regression analysis addressed the correlation between changes in tumor volume and treatment parameters. The time to response was estimated using the Kaplan-Meier method. Statistical analysis was performed with Prism Statistical Software (GraphPad Software, Inc. San Diego, USA). A non-parametric test, ANOVA, determined the difference between the group of patients whose tumors responded to Stereotactic radiosurgery and those whose tumors did not. Effect Size analysis was carried out using open-source software and Forest plots generated with GraphPad.

RESULTS

Kaiser Patient Characteristics

Thirteen patients treated consecutively with Stereotactic radiosurgery for a glomus tumor between 2009 and 2016 were identified. Table 1 summarizes the demographics of these patients. All patients were female. Their age at the time of treatment ranged from 32 to 81 years, with a median age of 63 (62.7+/-14.6). One patient presented with Fisch stage B tumor; six patients had Stage C tumor, and six had Stage D tumors. The majority had a tumor on the right side.

The most common presenting symptoms were noticeable hearing loss and pulsatile tinnitus (eight patients). These were followed by balance issues, congestion of

Table 1. The demographic, Fisch grade, and symptomology of the reported patients. There was symptomatic relief in some of these patients.

Age (years)	63 (32-81)				
Gender	MALE	FEMALE			
	0	13			
Laterality	Right	Left			
	8	5			
Tumor volume	10.4 ml (1.19-11.46)				
Fisch grade	N (%)				
B	1 (7)				
C	6 (46)				
D	6 (46)				
Symptoms	N (%)				
	Pre SRS		Post -SRS		
		Stable or no change	Improved	Worse	New symptom
Hoariness	3 (23)	2	0	1	1
Swallowing difficulty	5 (38)	2	1	1	1
Facial weakness	1 (7)	0	1	0	0
Hearing loss	8 (62)	4	3	1	0
Tinnitus*	8 (62)	1	7	0	0
Subjective tongue weakness	3 (23)	0	3	0	0
Headache	1 (7)	0	0	1	1
Congestion of the ear**	5 (38)	1	4	0	0
Balance	7 (54)	5	2	0	0
Facial spasm	3 (23)	3	0	0	1

Note: Not all symptoms were alleviated statistically with this treatment; the ones for which the improvement was statistically significant are annotated with a *(p= 0.0015) and **(p=0.034).

the ear, tongue weakness, facial spasm, and hoarseness (Table 1). Nine patients experienced hypertension, five had thyroid problems, and one had a parathyroid issue. However, there was no autonomic dysfunction in any of our patients to suggest secretory tumors. It is noteworthy that there is no significant correlation between Fisch grade of the tumor and presenting symptoms (p=0.2).

Clinical Outcome

The time between diagnosis and treatment ranged between 2 and 60 months. Most of the patients were treated 4-6 months after the initial clinic visit. All patients in this study had symptoms at the time of presentation (Table 1). After treatment, the regional skull base clinic followed the patients with the abovementioned clinic visits and imaging studies. The median follow-up was 47.4 months (51.8+/-11.2 months, range 31-74 months). One patient experienced an increased tumor size and presented with bleeding and drainage from her ear six months after treatment. She was seen by a neuro-otologist, who discovered that the tumor had extended through the inner ear to the external auditory canal. The patient was treated with surgery.

In follow-up imaging studies, the overall tumor control rate was 92.3%. Only one patient in this study failed radiosurgery treatment and had to have surgery (as described above). Three patients had a slight, but insignificant increase, in the size of their treated tumor (median 10.8%), ranging from 1.3 to 18.9% (the mean increase in the tumor volume was 10.3+/- 8.8%). Conventionally, any volume changes of less than 20% after radiation treatment are considered insignificant. Our result showed that there was a reduction in volume ranged between 8 and 64%, with a mean of 32.5 +/- 16.5% (median 33.6%). Six of the patients (46.7%) had more than 20% reduction in tumor volume. The median volume change was -37.5% (mean -38.2+/-15.93); this was statistically significant as compared to the overall change in volume or a reduction of less than 20% after treatment within the duration of this study (p=0.042, p=0.001). These changes normally happened around 18 months after treatment (17.6 months, CI 10.59-24.74) (Figure 1). However, there were no identifiable predictors for tumor control. There was no correlation between the treatment dose and the target volume, or other parameters such as Dmax (maximum dose), CI (conformality index), HI (homogeneity index), or BED (biological equivalent dose).

Four patients developed new symptoms after the treatment. One patient experienced an intermittent facial spasm, which has not been resolved. Another developed a swallowing problem in addition to increased hoarseness, and still another suffered post-procedural hoarseness.

One patient had a problematic sigmoid sinus thrombosis with intracranial hypertension. She underwent repeated lumbar punctures and diuretic therapy, and more than 18 months passed before she experienced symptomatic relief.

Three patients developed new symptoms after the treatment. In this group of patients, one patient had a sigmoid sinus thrombosis with increase intracranial hypertension. She underwent repeated lumbar punctures and diuretic therapy, and more than 18 months passed before she experienced symptomatic relief. One patient developed new intermittent facial spasm, which has persisted to this day. This patient also developed new hoarseness; one patient developed new swallowing problem and worsening of his hoarseness. Additionally, one patient experienced increased hearing problems (resulting in deafness), one patient had increase headache, and one patient with worsening of swallowing.

Three patients reported improvements in their hearing. All three individuals demonstrated improved speech receptive threshold (SRT; 10 +/-5 dB) but with less than 20% increases in their speech discrimination. Interestingly, all three of these patients had complete resolution of the congestion of their ear. The latter might partly explain the improvement in their SRT.

For most of the patients, the onset of their new symptoms or worsening of pre-existing ones happened around 2.8 months (CI: 1.1-13.2 months) after the procedure. Seven out of eight patients had complete resolution of their pulsatile tinnitus (87.5%). Four out of five patients had found relief from the congestion in the affected ear (Figure 1). Collectively, this represents an 80.7% chance of having some symptomatic relief with an odd ratio of 0.0141 at 95% confidence level, p=0.001, see Table 3). Symptomatic relief often happened at around 16.5 months (CI:11.0-24.0).

None of our patients had autonomic dysfunction at or after treatment. No significant correlation was found between change in tumor volume and the worsening of symptoms or development of new symptoms, nor was there any relationship between the reduction of tumor volume and symptomatic relief (p= 0.0787, Figure 2). The timing of tumor volume changes and symptomatic relief after treatment is rather similar (Figure 1). A regression analysis with a Gehan-Breslow-Wilcoxon test for curve comparison showed that there is a close association between these two parameters (r^2=0.91).

In order to compare our results to those reported in the literature, we selected three papers that described general symptomatic outcomes. We performed an effective size analysis using a fixed effect model on our own result and compared it to these studies. [7,8,1,] (Table 3, and a Forest plot). We found that SRS was useful in alleviating tinnitus and congestion of the ear with odds ratios of 0.0089

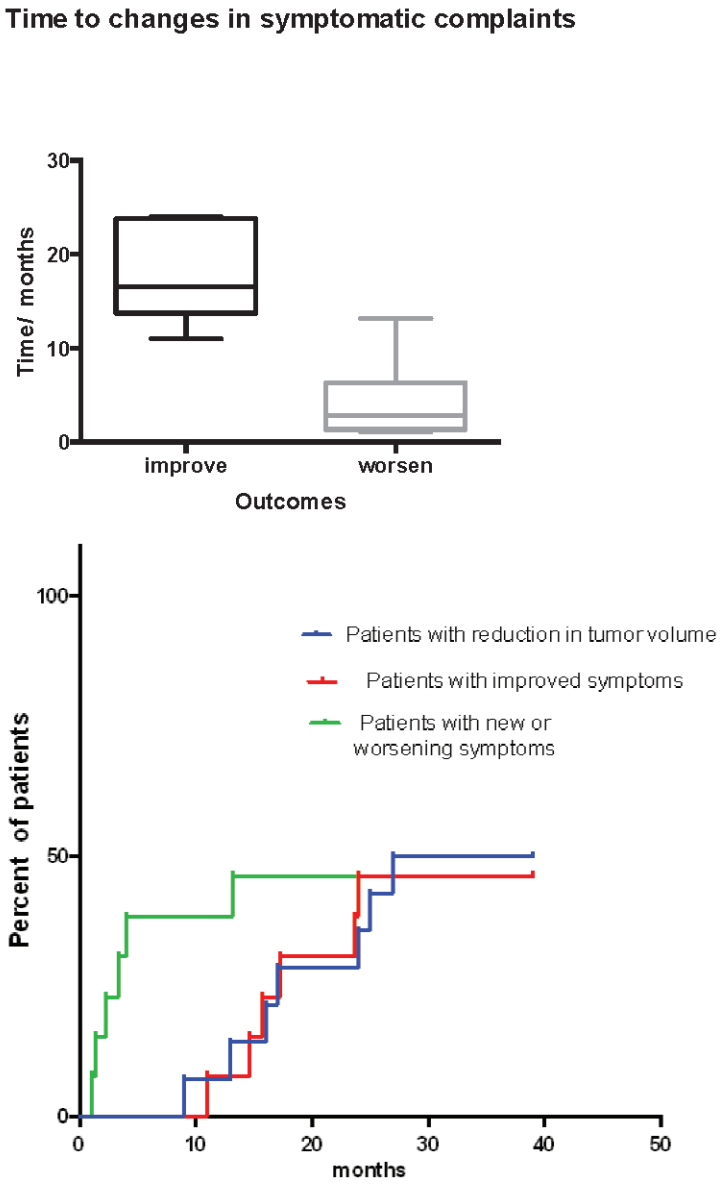


Figure 1. Evolution of tumor size and symptoms. A composite figure illustrating the time to symptom changes. The upper panel (box plot) shows the difference in the time to develop new or worsened symptoms. The lower panel illustrates the time to symptom improvement, and symptom worsening.

(p=0.0015) and 0.025 (p=0.034) respectively. Our result was closely compatible with those in the literature.

DISCUSSION

Glomus tumors are slow growing, so some of the patients in our series had been followed for over 3 to 5 years prior to treatment. Similarly, Cosetti reported a 33-year follow-up in some patients without a change in tumor volume [9].

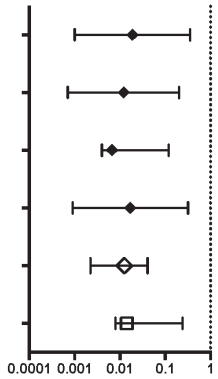
These tumors are highly vascular and are in difficult locations at the skull base, which makes gross total resection difficult. In the past, these tumors were treated by surgery followed by external beam radiation (EBRT) as adjuvant therapy or as an alternative to surgery, resulting in good tumor control (80-100%) [10-12] . However, the treatment carries a risk of complications such as xerostomia, dermatitis, osteoradionecrosis, cranial nerve neuropathy, otitis and the possibility of developing a secondary malignancy [13]. There is also some concern that glomus tumors are radio-resistant [14].

Table 2. The treatment characteristic of patients in this study. The median target coverage was 95.4% (95.02-95.77%), and the median prescribed isodose line was 80% (76-81%).

Number of Patients (%)	Median Dose (range)	Number of Fractions	Mean Target volume (+/-SD)
8 (62)	30 Gy (25-30)	5	12.4 (6.9)
4 (31)	23.25 Gy (21-24)	3	8.27 (4.6)
1 (7)	15 Gy	1	2.9

Table 3. Impact of radiosurgery on symptoms: An effect-size analysis consisted of extracting data from the aforementioned studies. The cumulative symptoms were from selected studies. Studies by Sheehan [7] and Chun [8] addressed the effect of radiosurgery on tinnitus explicitly. The black diamonds are the effect sizes of these studies. The large open diamond is the summary effect using a fixed effect model. The open square is effect size from our institutional data. The individual Odds ratio, their relative weight, and their p-valves were included.

Impact of SRS on Symptomatic Relief				
Study	Odds Ratio	Relative Weight		P value
Hefez	0.0189	24		0.005
Sheehan	0.0120	26		0.001
Sheehan	0.0067	26		0.001
Chun	0.0016	24		0.001
Summary effect	0.0125	100		0.013
current study	0.0141			0.001



In recent years, stereotactic radiosurgery (SRS) has increasingly been used to treat glomus tumors, given their slow proliferation and need for a larger radiation dose, with a steep dose gradient to minimize damage to the neighboring cranial nerves. [15]. Patients treated with SRS upfront have at least as good a control rate as those who have SRS as an adjuvant therapy to surgery. Importantly, patients suffer less lower cranial nerve neuropathy when treated with SRS alone [3]. The overall tumor control rate in the literature is quite good, ranging from 65-100% [16, 17]. Tumor shrinkage has also been reported [18, 19].

In this study, we did not find any correlation between tumor response to SRS and the marginal dose, initial target volume, Fisch grade, HI, CI, mean dose, and Dmax. The dose range used in this series is extrapolated from external beam radiation and that reported in the literature. Our results are compatible with those reported in the literature when treatment schedules of 45-55 Gy given in 20-25 fractions [11, 12, 20, 21], 12.5-18 Gy in a single session [15, 22-30] and 18-25 Gy in three sessions [19], providing a tumor control rate ranging from 85-100%. Our data showed that this treatment scheme confers 93% growth control and 46% tumor shrinkage rate. However, we could not be certain that stable tumors or tumors that shrank in size will not progress in a long-term follow-up. In fact, Chen [31] reported tumor progression three years after radiosurgery in a patient who showed tumor regression at the initial follow-up imaging study. Long-term follow-up is thus necessary.

EBRT ameliorated clinical symptoms in 71% of the cases [32]. Patients treated with SRS experienced reported clinical improvement in 36% of the cases, while 21% of patients suffered a worsening of hearing [14]. In a meta-analysis performed by Guss [5], 95% achieved clinical control. On the whole, symptomatic relief results from treating glomus tumors with radiosurgery (summary odds ratio of 0.0139). In this study, we estimated that there is an 80% chance that patients will experience some degree of symptomatic relief. Congestion of the ear and pulsatile tinnitus are the two symptoms that responded most favorably to treatment It seems that new or worsening symptoms come early in the course after treatment as compared to symptomatic relief. The latter take months to materialize.

LIMITATIONS OF THE PRESENT STUDY

There are limitations to a case series of this kind because the number of patients is unusually small (13 patients in a two-year period), and the duration

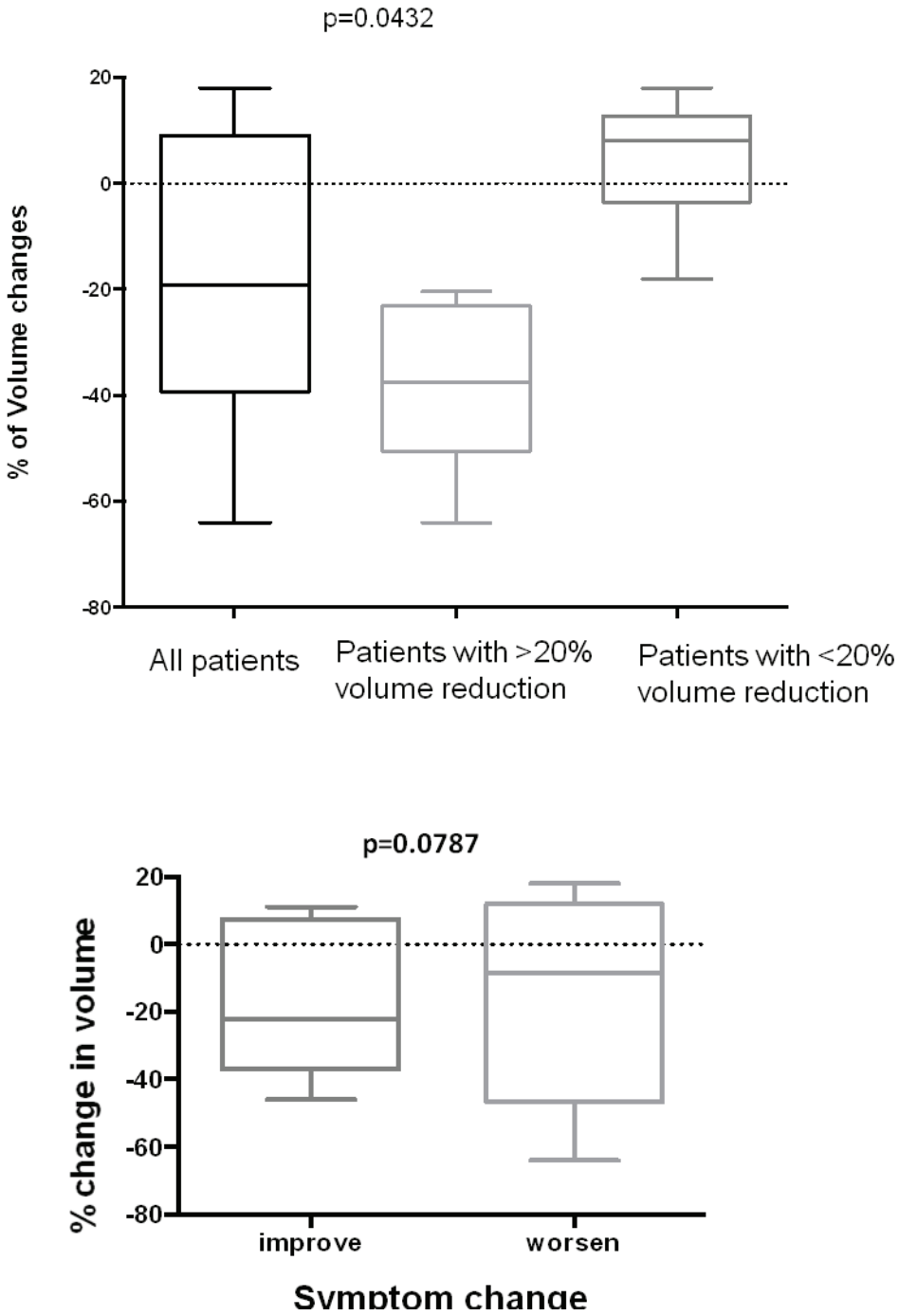


Figure 2. Symptoms and Change in Tumor Volume: The percentage of tumor volume changes after treatment and the corresponding symptomatic relief. The upper panel (box plot) illustrates the change in tumor volume after treatment in all patients, patients with more than 20% volume change and less than 20% volume change . The lower panel (box plot) shows there is no significant correlation between tumor volume changes and patients.

of follow-up is relatively short (50 months). Although we have demonstrated that a 20 % reduction of tumor volume in some tumors that have been treated with Cyberknife, we do not know whether we can directly compare our result to that of tumors that are partially treated by microsurgery. It has been shown that near total resection or even subtotal resection of the tumor afford tumor growth control.

CONCLUSION

Stereotactic radiosurgery is an effective, non-invasive treatment option in the management of glomus tumor which have a significant surgical risk.

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JS and VT contributed equally to this study in term of preparing the manuscript and the final statistical analysis. VT and AM did the clinical data extraction and review. JS and XF helped in the imaging analysis. AM, AG, LM, WS, and WS provided the needed clinical inputs. MT presented the preliminary results of this study at the International Stereotactic Radiosurgery Society (ISRS) 2015 Congress, 7-11 July 2015, Yokohama, Japan.

Authors' disclosure of potential conflicts of interest
The authors reported no conflict of interest.

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Conception and design: Victor Tse
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Data analysis and interpretation: Victor Tse, Xiaoyan Fu, Jussi Silanpaa
Manuscript writing: Victor Tse, Jussi Silanpaa, Ming Teng
Final approval of manuscript: Victor Tse, Jussi Silanpaa

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