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Analysis the causes of radiosurgical failure in intracranial meningiomas treated with radiosurgery

Moinay Kim[a], Young Hyun Cho[b], Jeong Hoon Kim[b], Chang Jin Kim[b], Do Hoon Kwon[b,*]

[a] Graduate School of Medicine, University of Ulsan, Seoul, 05505, Republic of Korea
[b] Department of Neurological Surgery, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, 05505, Republic of Korea

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ABSTRACT

Objectives: Surgical resection is a primary indication for intracranial meningioma. Radiosurgery is also an excellent treatment modality for postoperative residual tumors, or tumors in high-risk locations, such as the skull base. Despite multimodality treatments, there are some cases in which radiosurgery fails and surgical resection or re-radiosurgery is required. However, there has not been a comprehensive study focusing on the causes of secondary treatment for local recurrence or a new mass that develops outside the target area after radiosurgery. Hence, we analyzed the causes of radiosurgical failure in patients with meningioma.

Methods: From 2000 to 2015, we retrospectively reviewed 1086 patients who underwent gamma knife radiosurgery (GKRS) for intracranial meningioma at the Asan Medical Center. Multiple meningiomas or tumors with a volume greater than 7000 mm^3 were excluded. All patients had a minimum follow-up of 12 months. Finally, 771 patients were enrolled in this study. Clinical symptoms and brain MRI findings were assessed by neurosurgeons. When the tumor size increased and was accompanied by newly developed neurological symptoms, further management was considered (e.g. microsurgical resection and stereotactic radiosurgery). Histological analyses of the resected tumors were performed by neuropathologists.

Results: Among the 771 patients, tumor growth was observed in 60 patients (7.78%). Seven patients showed transient tumor growth after GKRS. These patients have been under close observation without any further treatment. Thirty patients (3.89%) underwent re-radiosurgery for tumor control. Another 23 patients underwent procedures other than re-radiosurgery; 8 underwent microsurgical resection, 3 underwent cyber knife radiosurgery (CKRS), 1 underwent radiation therapy, and 8 were closely followed-up. Three patients visited other clinics or were lost to follow-up. Of the remaining 30 patients, 22 (group 1) underwent microsurgical resection prior to their initial course of GKRS and the other 8 (group 2) were treated only with re-radiosurgery. In group 1, recurrence rates after radiosurgery were 2.47% (n = 19) and 0.39% (n = 3) for local and distant recurrence, respectively. In group 2, recurrence rates after radiosurgery were 0.52% (n = 4) and 0.52% (n = 4) for local and distant recurrence, respectively. An analysis was performed to determine the factors that may result in differences between the two groups. Of the many variables, local recurrence ($p = 0.0331$, Fisher's exact test) was the only significant factor.

Conclusion: We analyzed the causes of radiosurgical failure in meningioma patients and observed that microsurgery before radiosurgery was significantly associated with a high local recurrence rate compared with primary radiosurgery. Furthermore, the percentage of local recurrence cases that required secondary radiosurgery was as low as 2.98%. This result is comparable with that of microsurgical resection, which is the mainstay of treatment for meningioma.

Abbreviations: CKRS, cyber knife radiosurgery; GKRS, gamma knife radiosurgery; MR, magnetic resonance; SRS, Stereotactic Radiosurgery; WBRT, Whole Brain Radiation Therapy.

* Corresponding author at: Department of Neurological Surgery, Asan Medical Center, College of Medicine, University of Ulsan, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 05505, Republic of Korea.
E-mail address: ykwon@amc.seoul.kr (D.H. Kwon).

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1. Introduction

Meningioma is one of the most common tumors of the central nervous system, and accounts for approximately one-third of all intracranial tumors [1]. Treatment options include observation, microsurgical resection, and radiation therapy. Microsurgical resection is generally the mainstay of treatment in meningioma. However, complete resection is not always possible owing to its proximal location to critical structures, such as the optic apparatus and brainstem. Simpson grade 1 resection rates vary from 20% to 90%, depending on the location and size of the tumors [2,3]. Although the effectiveness of gamma knife radiosurgery (GKRS) is well known, there are some cases in which the result is unfavorable and further treatment is considered. Radiosurgery is an effective salvage treatment for disease recurrence after surgical resection [4–6]. However, in some cases, meningiomas that have recurred once can recur at shorter intervals. A previous study reported that 2- and 5-year progression-free survival rates after the first tumor recurrence improve from 50% to 80% when a patient undergoes microsurgery followed by additional radiation therapy [7]. However, studies describing the causes of radiosurgical failure after re-radiosurgery are scarce. Furthermore, clinicians tend to disregard the long-term outcome and progress of radiosurgery. An analysis of the causes of radiosurgical failure in the treatment of local or distant recurrence is required. In this study, we present a large single-institution retrospective review of re-radiosurgery in the treatment of meningioma. Analyzing the patterns of radiosurgical failure and evaluating the associated factors will have an impact upon the clinical outcomes.

2. Materials and methods

2.1. Patient selection

This study was approved by our institutional review board. Between 2000 and 2015, 1086 patients with meningioma underwent GKRS at the Asan Medical Center. Among these patients, 116 with an initial tumor volume greater than 7000 mm^3, 69 with multiple tumors, and 126 who were followed up for less than a year or who visited other clinics were excluded. Many studies have reported that large volume meningiomas are less responsive to radiosurgery [8,9]. Large volume tumors were excluded to clarify the role of GKRS without volume-dependent complications. In addition, 4 patients with trigeminal neuralgia caused by meningioma were excluded because although their tumor sizes had not changed, they had undergone repeated radiosurgery owing to uncontrolled pain. Finally, 771 patients were enrolled in this study to analyze radiosurgical failure and tumor recurrence or progression (Fig. 1).

2.2. Stereotactic radiosurgery and radiosurgical parameters

The Leksell model G stereotactic frame (ELEKTA Instruments INC., Sweden) was used in patients with meningioma. Treatment plans were generated using the Elekta Gamma Plan system based on gadolinium-enhanced axial 3-dimensional T1-magnetization-prepared rapid acquisition gradient echo MR(Magnetic Resonance) images (1.25 mm slice thickness). The optimal plan was created by adjustment of the collimator and sectors so that the optimal dose coverage of the target can be achieved while minimizing the dose to the surrounding normal tissues. Until June 2005, the Leksell gamma knife unit model B type was used, replaced by the C type from July 2005 to January 2011. The gamma knife Perfexion unit has been adopted to treat patients from February 2011 onwards. Initial tumor volume was measured using Kula or Gamma Plan software. Serial volume changes after GKRS were measured by delineation of the tumor contours, followed by merging the images based on the ellipsoidal method.

2.3. Follow-up examination and serial volumetric analysis of MRI

Routine clinical examination and MRI were performed after GKRS at 6-month intervals during the first year of follow-up, then annually for two years, and biennially thereafter. If patients experienced any related symptoms, more regular follow-up was recommended.

Volumetric data sets for tumors on serial MRIs were obtained using the in-house software based on ImageJ, a java-based image processing program developed by the National Institutes of Health (http://rsbweb.nih.gov/ij/). Follow-up schedules were shortened in cases in which an increased tumor volume was identified using brain MRI.

Tumor response was evaluated by both a neurosurgeon and a neuroradiologist. To calculate the tumor volume, the tumor margin was delineated on radiological images (T1-weighted with enhancement) and merged, followed by volumetric calculations using ImageJ (NIH). Volumetric analysis and the linear growth rate were used for evaluating treatment failure after radiosurgery. Local recurrence was defined as a tumor size increase either within the radiosurgical prescription volume or just outside the prescription margin. Distant recurrence was defined as a new tumor that developed anywhere except the local recurrence area. Peritumoral edema was evaluated on T2-weighted or FLAIR (Fluid-attenuated inversion recovery) images. Patients with increased tumor volume or perilesional edema detected on follow-up MRI and who showed clinical symptoms were managed with further treatment.

Clinical data, including patient's sex, age, and tumor locations were recorded. Treatment data recorded included tumor volume, radiation dose, and presence of edema. Final outcome data including follow-up length, time to progression, and type of recurrence were obtained. Time to progression was measured from completion of the second radiosurgery course.

2.4. Statistical analysis

The values were reported as the mean ± standard deviation (SD) and the range was also provided. Statistical significance for continuous variables was evaluated using a two-tailed Student-Newman-Keuls test or a one-way ANOVA (Analysis of Variance). All statistical analyses were performed using the SPSS (PASW statistics v18.0) and R programs. A P value of less than 0.05 was considered significant.

3. Results

3.1. Patient demographic and treatment parameters

From 2000 to 2015, our institutional database included 771 meningioma patients who underwent radiosurgery. After radiosurgery, the tumor volume had not changed in 574 patients (74.45%) and had decreased in 137 patients (17.77%). If a stable or decreased tumor volume after radiosurgery is defined as a favorable result, the tumor control rate was 92.22%. If the size of meningioma does not alter after radiosurgery, administering corticosteroid can be considered depending on patient's clinical symptoms. If there is a neurological symptom related to tumor, corticosteroid could be administered. Of the 60 patients (7.78%) with tumor growth, there were 7 with a small transient increase in tumor size after GKRS. These patients have been under close observation without any further treatment. Hence, the other 53 patients (6.87%) showed persistent tumor growth on follow-up MRI. Thirty patients from