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Analysis of the results of recurrent intracranial meningiomas treated with re-radiosurgery

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ABSTRACT

Objects: Meningioma is the most common intracranial neoplasm, comprising approximately 30% of all primary intracranial tumors (Claus et al., 2005) [1]. Treatment options include observation, microsurgical resection, stereotactic radiosurgery (SRS), and whole brain radiation therapy (WBRT). Gamma knife radiosurgery (GKRS) is a very effective treatment for intracranial meningiomas; previous studies showed the tumor control rate at 5–10 years of follow-up as 84.3%–100% in all cases (Feigl et al., 2005; Linskey et al., 2005; Malik et al., 2005; Aichholzer et al., 2000; Hakim et al., 1998; Chang and Adler 1997; Lunsford, 1994; Ganz et al., 1993) [2–9]. Many studies have discussed issues like optimal dose, conformal configurations, and adverse effects to improve the treatment result with GKRS (Malik et al., 2005; Kenai et al., 2005; Rowe et al., 2004; Shrieve et al., 2004) [4,10–12]. There are some cases in which the radiosurgery result is unfavorable and perhaps further treatment is needed. In these cases, re-radiosurgery can be an option. However, there have not been comprehensive studies discussing the issues of re-radiosurgery. Therefore, we analyzed the result of re-radiosurgery for recurrent meningiomas and their impact on clinical outcomes.

Methods: From 1995 to 2015, we retrospectively reviewed 1163 patients who underwent GKRS for intracranial meningioma at the Asan Medical Center. Patients with multiple meningiomas or a follow-up with a period of less than a year were excluded from this study. Finally, 865 patients were enrolled in this study. Clinical symptoms and brain magnetic resonance imaging (MRI) scans were assessed by neurosurgeons. When tumor size increased together with newly developed neurologic symptoms, further management, such as microsurgical resection or SRS, was considered. Histologic analysis of the resected tumors was performed by neuropathologists. Clinical data, including patient's sex, age, and tumor locations were recorded. Treatment data included tumor volume, tumor grade, radiation dose, and presence of edema. Final outcome data including follow-up period, time to progression, interval between first and second radiosurgery courses and interval between microsurgery and radiosurgery were obtained.

Results: Among 865 patients, tumor recurrence was found in 63 patients (7.28%). Seven patients showed transient tumor growth after GKRS. These patients have been under close observation without any further treatments. Fifty-six patients (6.47%) showed permanent tumor growth on follow-up MRI. Thirty-three patients from this group underwent repeated radiosurgery owing to tumor growth, resulting in a re-irradiation rate of 3.82% at our radiosurgery center. The other 23 patients were treated using methods other than re-radiosurgery. Among the 33 patients, 25 underwent microsurgical resection prior to their initial course of GKRS, and the other 8 were treated with re-radiosurgery only. An analysis was performed to determine factors that may have a role in treatment results. Of the many variables, tumor grade ($p = 0.004$, Fisher's exact test) was the only significant factor for progression-free survival (PFS). Thirteen patients with unbiopsied or benign meningioma showed stable tumor size, while there was tumor growth in 8 patients. Among high-grade meningioma patients, 3 and 9 showed stable disease and tumor growth, respectively. As a result of re-radiosurgery, 11 out of 17 patients showed tumor growth and needed further treatments; this involved a third GKRS for 4 patients, microsurgical resection for 6 patients, and cyber knife radiosurgery (CKRS) for 1 patient. Four patients from this group were also treated with WBRT.

Abbreviations: CKRS, cyber knife radiosurgery; GKRS, gamma knife radiosurgery; MR, magnetic resonance; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; WHO, World Health Organization.

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Conclusion: We analyzed the results of re-radiosurgery for recurrent meningiomas and observed that World Health Organization (WHO) grade II and III was significantly associated with a lower PFS rate compared with low-grade meningiomas (p = 0.004). Conversely, patients with benign meningioma or unbiopsied tumors had much better results. Hence, re-radiosurgery is recommended for patients with unknown or benign meningiomas if their first GKRS result is unsatisfactory. However, re-radiosurgery should be considered carefully for recurrent high-grade tumors. Owing to the small number of recurrent meningioma patients treated with re-radiosurgery, further studies are required to delineate the role of this treatment.

1. Introduction

Meningioma accounts for 14–27% of all intracranial tumors, and is the most common benign intracranial neoplasm [13]. The World Health Organization (WHO) grading classifies meningioma into 3 categories based on histology; this classification is the most powerful predictor of tumor recurrence and overall survival [14]. Regardless of pathology subtypes, microsurgery has been the primary treatment option for meningiomas [15]. The 5-year recurrence-free survival rate after complete resection of meningioma is 95% for WHO grade I, 30–50% for WHO grade II, and 38–78% for WHO grade III tumors [16]. However, Simpson grade 1 resection rates vary between 20 and 90%, depending on the location and size of the tumors; hence, tumor recurrence is inevitable [17,18]. Although the effectiveness of gamma knife radiosurgery (GKRS) is well known, there are some cases in which recurrent meningiomas develop and further treatment is mandatory. Radiosurgery is also an effective salvage treatment for disease recurrence after surgical resection [19–21]. However, meningiomas that have recurred once tend to recur again at shorter intervals [15]. Therefore, re-radiosurgery for recurrent meningioma is essential in many cases. Few studies have analyzed the results of re-radiosurgery for recurrent meningiomas, and hence many clinicians tend to not realize the significance of these tumors. In this study, we present a large, single-institution, retrospective review of re-radiosurgery in treating recurrent meningiomas. We assessed the degree of tumor control and correlated variables that predict the outcomes of re-radiosurgery.

2. Materials and methods

2.1. Patient selection

This study was approved by our institutional review board. Between 1995 and 2015, a total of 1163 patients with meningioma were treated with GKRS at the Asan Medical Center. Among 1163 patients, those with multiple tumors (105 patients), a follow-up period of less than a year, or who visited other clinics (189 patients) were excluded. Four patients with trigeminal neuralgia caused by meningioma were excluded because their tumor size had not changed, but they required repeated radiosurgery owing to uncontrolled pain. Re-radiosurgery was indicated for patients whom their tumor was not favorable to treat with surgery or other radiation therapy. Surgery was recommended in cases where patients present neurologic symptoms with tumors in accessible locations. WBRT was recommended if there was an evidence of leptomeningeal seeding or multiple metastases. Also, small-sized meningiomas with no clinical symptoms were recommended for GKRS. Finally, 865 patients were enrolled in this study.

2.2. Stereotactic radiosurgery (SRS) and radiosurgical parameters

The Leksell model G stereotactic frame (Elekta Instruments Inc., Sweden) was used in patients with meningiomas. Treatment plans were generated using the Elekta Gamma Plan system based on gadolinium-enhanced axial 3-dimensional T1-magnetization-prepared rapid acquisition gradient echo magnetic resonance (MR) images (1.25 mm slice thickness). The optimal plan was created by adjusting the collimator and sectors so that optimal dose coverage of the target could be achieved while minimizing the dose to the surrounding normal tissues. The Leksell Gamma Knife Unit Model B type was used until June 2005, when it was replaced by the C type from July 2005 to January 2011. The Gamma Knife Perfexion unit has been used to treat patients since February 2011. The initial tumor volume was measured using Kula or Gamma Plan software. Serial volume changes after GKRS were measured by delineation of 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 MR imaging (MRI) were performed after GKRS at 6-month intervals during the first year of follow-up, then annually for 2 years, and biennially thereafter. If patients experienced any related symptoms, more regular follow-up was recommended.

Volumetric datasets for tumors on serial MRIs were obtained using 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. The tumor margin was delineated on radiological images (T1WI with enhancement) and merged, followed by volumetric calculations using Image J (NIH) to calculate the tumor volume. To evaluate the outcome (treatment failure) after radiosurgery, volumetric analysis and linear growth rates were used. Peritumoral edema was evaluated on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images. Patients with increased tumor volume or perilesional edema on follow-up MRI who showed clinical symptoms were managed with further treatments.

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

2.4. Statistical analysis

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 analysis of variance (ANOVA). 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.