Significance of Simpson grading system in modern meningioma surgery: integration of the grade with MIB-1 labeling index as a key to predict the recurrence of WHO Grade I meningiomas

Clinical article

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Object. Techniques for the surgical treatment of meningioma have undergone many improvements since Simpson established the neurosurgical dogma for meningioma surgery in his seminal paper published in 1957. This study aims to assess the clinical significance and limitations of the Simpson grading system in relation to modern surgery for WHO Grade I benign meningiomas and to explore the potential of the cell proliferation index to complement the limitations in predicting their recurrence.

Methods. The surgical records of patients who underwent resection of intracranial meningiomas at the University of Tokyo Hospital between January 1995 and August 2010 were retrospectively analyzed. The authors investigated the relationships between recurrence-free survival (RFS) and Simpson grade or MIB-1 labeling index value.

Results. A total of 240 patients harboring 248 benign meningiomas were included in this study. Simpson Grade IV resection was associated with a significantly shorter RFS than Simpson Grade I, II, or III resection (p < 0.001), while no statistically significant difference was noted in RFS between Simpson Grades I, II, and III. Among meningiomas treated by Simpson Grade II and III resections, however, multivariate analysis revealed that an MIB-1 index of 3% or higher was associated with a significantly shorter time to recurrence.

Conclusions. The clinical significance of the different management strategies related to Simpson Grade I–III resection may have been diluted in the modern surgical era. The MIB-1 index can differentiate tumors with a high risk of recurrence, which could be beneficial for planning tailored optimal follow-up strategies. The results of this study appear to provide a significant backing for the recent shift in meningioma surgery from attempting aggressive resection to valuing the quality of the patient’s life.

Abbreviations used in this paper: LI = labeling index; RFS = recurrence-free survival.

Abstract

Most meningiomas are slow-growing lesions and are usually benign in nature. It has been a widespread belief that extensive resection is beneficial for minimizing the risk of tumor recurrence. In 1957, Simpson classified the extent of resection of meningiomas into 5 subdivisions and demonstrated that the postoperative recurrence rates of these tumors were correlated with the extent of resection. In his report, the risks of eventual recurrence after Simpson Grade I, II, III, and IV resections were 9%, 16%, 29%, and 39%, respectively, when the patients survived for 6 months or longer after surgery. Since then, various attempts have been made to achieve better Simpson grades in the surgical treatment of meningiomas. Therefore, the Simpson grading system has been the important and irreplaceable standard for determining the extent of resection, predicting the recurrence of meningiomas, and comparing the results of different surgical approaches. However, surgical technologies and devices related to neurosurgery have undergone many improvements since the 1950s. The quality of surgical instruments such as bipolar forceps and drilling equipment has improved dramatically. Monitoring devices and techniques are now commonly used for tumors in the vicinity of cranial nerves. Current radiological diagnostic tests can detect very small tumor components in complicated skull base structures such as the optic canal, internal auditory meatus, jugular foramen, and other similar structures.

With the aid of advances in diagnostic radiology, most contemporary research on the operative results of meningiomas target radiological recurrence or regrowth. However, the Simpson grading system was based on clinical events, including development or worsening of symptoms.
or death that could presumably be attributed to tumor recurrence. Innovations in postoperative radiation therapy are another critical improvement from the viewpoint of total patient management. However, the optimal management approach for postoperative radiation treatment, especially for WHO Grade I meningiomas, remains to be elucidated.\textsuperscript{32-38} The Simpson grading system alone appears to be inconclusive with respect to this issue because the immediate necessity of radiation therapy for benign meningiomas after Simpson Grade I, II, or III resection is usually minimal. Several studies have advocated the use of proliferation markers such as the MIB-1 LI for anticipating tumor recurrence based on follow-up data from a relatively small number of patients.\textsuperscript{2,3,4,13,14,23,26,40} whereas other studies have reported the limitations of such markers.\textsuperscript{1,12,30,31,39} To plan an adequate follow-up and decide the optimal timing of postoperative radiation for each patient, we need to know the most appropriate role of the Simpson grading system in the modern surgical era, and we need to determine whether the MIB-1 LI can compensate for the shortfall in information that results from relying solely on Simpson grades. In this study, we retrospectively analyzed the operative outcomes in patients with WHO Grade I meningiomas treated by Simpson Grade I, II, III, or IV resection between 1995 and August 2010. We emphasize the importance of the integration of the Simpson grading system and the MIB-1 LI for postoperative management of benign meningiomas.

Methods

Patient Population

This study was approved by the University of Tokyo Institutional Review Board. We retrospectively analyzed the data of patients who underwent resection of intracranial meningiomas at the University of Tokyo Hospital between January 1995 and August 2010. Surgical treatment of all patients was performed by 8 brain tumor specialists or senior residents under the supervision of these specialists. When the patient underwent multiple surgeries, only data from the first surgery were used. We only dealt with the data of patients with WHO Grade I meningiomas who underwent postoperative radiological follow-up for 6 months or longer. Patients with neurofibromatosis or those with radiation treatment prior to or immediately after surgery were eliminated from the study. We included patients with recurrent meningiomas whose initial surgery was performed at another facility if they had never previously undergone any type of radiation therapy.

Data Collection

We reviewed the operative records regarding tumor location and Simpson grade reported by the surgeons. Information relating to time to recurrence, regrowth, and last follow-up was collected from outpatient charts. Pathological diagnosis was made in the Department of Pathology at our institution based on 1993 or 2000 editions of the WHO Classification of Tumors of the Central Nervous System.\textsuperscript{15,16} Three angiomatous meningiomas were included in this study. Since we have experienced a few cases of some angioblastic or angiomatous meningiomas that turned out to be meningeal hemangiopericytomas at the second surgery, we carefully reexamined these 3 cases and confirmed that they were WHO Grade I meningiomas. If any sign of brain invasion was noted, we excluded these tumors because they could be classified as WHO Grade II meningiomas according to the current diagnostic criteria. The MIB-1 LI was calculated using the highest LI method in areas of their maximum density as identified by visual analysis.\textsuperscript{29}

The first postoperative MRI studies were usually obtained before discharge from the hospital. If no residual tumor was observed on these images, radiological follow-up was planned on a yearly basis at our institution. More frequent radiological studies at an interval of 3–6 months were conducted for small residual tumors. Recurrence or regrowth was evaluated on MRI scans by neuroradiologists in a blinded fashion. In this report, we defined RFS as the time from the date of surgery to the date of the last MRI study for tumors without any radiological change, or as the time from surgery to the date when recurrence or regrowth was observed on an MRI study (Fig. 1). In addition, follow-up was censored if the tumor was treated with radiation therapy because of changes in the treatment strategy despite the tumor size being stable.

Statistical Analysis

The comparison of continuous variables was performed using ANOVA. The Pearson chi-square test was used to compare groups. The RFS was assessed by Kaplan-Meier curves, followed by log-rank tests. A Bonferroni correction was applied for comparison of multiple curves. All analyses were performed with JMP version 7.0.2 (SAS Institute, Inc.). A p value < 0.05 was considered statistically significant.

Results

The Relationship Between Simpson Grade and RFS

Between January 1995 and August 2010, 685 meningiomas were surgically treated. After applying the inclusion and exclusion criteria, 240 patients (64 men and 176 women) harboring 248 meningiomas were included. The mean patient age was 55.2 years (range 12–80 years). Table 1 summarizes the characteristics of the patients and tumors according to Simpson grade. While no significant differences were observed between Simpson grade and age, sex, or MIB-1 LI value, tumor location was, as expected, related to the extent of resection. The relationship between RFS and Simpson grade in all patients is shown in Fig. 2. Five-year RFSs after Simpson Grade I, II, III, and IV resections were 97.6\%, 87.7\%, 84.1\%, and 56.8\%, respectively. Patients with meningiomas treated by Simpson Grade IV resection had a significantly shorter RFS than those treated by Simpson Grade I, II, or III resection (p < 0.001). If we excluded tumors treated by Simpson Grade IV resection, there was no statistically significant difference between the RFSs of patients treated by Simpson Grade I, II, or III resection (p = 0.07). On examination of 126 tumors that had been followed up for 3 years or longer, the results were the same; that is, Simpson grade had
no impact on the RFS of patients treated by Grade I, II, or III resection, while tumors treated by Simpson Grade IV resection recurred significantly sooner than those treated by Simpson Grade I, II, or III resection (data not shown).

Next, we investigated the relationship between tumor location and recurrence. Simpson grade was not statistically significant in relation to RFS for convexity meningiomas (Fig. 3). Since we were unable to exclude the

![Fig. 1. Images of meningiomas with (upper) and without (lower) recurrence during the follow-up period. A: Preoperative axial T1-weighted enhanced MRI study demonstrating a left temporal convexity meningioma. B: Postoperative MRI study obtained immediately after a Simpson Grade I resection. C: Axial MR image obtained 7 years after surgery showing no recurrence. D: Photomicrograph of this tumor with an MIB-1 staining index less than 1%. E: Preoperative coronal contrast-enhanced T1-weighted MRI study showing a left parasagittal meningioma. F: Postoperative MRI study obtained immediately after a Simpson Grade II resection. G: Coronal MRI study obtained 5 years after surgery, revealing a recurrent mass on the wall of the superior sagittal sinus. H: Photomicrograph of this meningioma with an MIB-1 staining index of 4%. Original magnification × 400 (D and H).]

### TABLE 1: Patient demographics for each Simpson grade*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simpson Grade</th>
<th>p Value</th>
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<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>no. of tumors</td>
<td>63</td>
<td>106</td>
</tr>
<tr>
<td>no. of patients</td>
<td>62</td>
<td>104</td>
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<td>34</td>
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<td>female</td>
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<td>72</td>
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<tr>
<td>MIB-1 labeling index (%)†</td>
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<td>skull base</td>
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<td>44</td>
</tr>
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</table>

* — = not performed.
† MIB-1 labeling index was studied for a total of 205 tumors with Simpson Grade I, II, and III resections.
‡ A total of 18 tentorial meningiomas, 5 ventricular meningiomas, and 2 intraorbital meningiomas were excluded.
possibility of statistical bias due to the small number of patients with convexity meningiomas treated by Simpson Grade III (n = 2) and IV (n = 2), we then compared Simpson Grade I and II resections. However, there was no significant difference noted in this comparison (p = 0.11). As for falcine and parasagittal meningiomas, although Simpson Grade IV resection was associated with a significantly higher recurrence rate than Grade I, II, and III resections, the recurrence rates of tumors treated by Simpson Grade I, II, and III resections were not significantly different (Fig. 4). Similarly, the analysis of tumors with a skull base location revealed a significant difference between the recurrence of tumors treated by Simpson Grade IV resection and that of tumors treated by Simpson Grade I, II, or III resection. However, no difference was noted between the recurrence rates of tumors treated by Simpson Grade I, II, or III resection (Fig. 5).

**The Relationship Between RFS and the MIB-1 LI**

Because we did not detect any substantial differ-

ence among Simpson Grade I, II, and III resections, we examined our cohort with respect to the significance of the MIB-1 LI for macroscopically total resections. The distribution of the results of the MIB-1 LI for these tumors is shown in Fig. 6. Only one tumor recurred after a Simpson Grade I resection in this study, indicating an extremely low risk of recurrence after Grade I resection. On the other hand, as Fig. 2 shows, the Kaplan-Meier curves of 142 Simpson Grade II and III resections were quite similar. Among these, however, tumors with an MIB-1 LI of 3% or higher showed significantly more rapid recurrence than tumors with an MIB-1 LI lower than 3% (Fig. 7, p = 0.0016). In addition, a multivariate analysis using a Cox proportional hazard model for Simpson Grade II and III resections demonstrated that the MIB-1 LI was the single significant predictor of recurrence (OR 4.65, 95% CI 1.59–14.0; p = 0.006 [Table 2]).

**Discussion**

**Limited Significance of the Simpson Grading System in the Modern Surgical Era**

It is a well-known fact that meningiomas can recur even after resection with no appreciable residual mass visible on postoperative images. Recently, we experienced a case of recurrent convexity meningioma that was resected 10 years previously (Fig. 8). A small portion affecting the wall of the superior sagittal sinus was coagulated to achieve a Simpson Grade II resection. Postoperative pathological examination revealed the tumor to be a WHO Grade I meningioma. MIB-1 staining was not a routine procedure at our institution at that time. After radiological follow-up for 3 years after surgery, the patient stopped visiting our hospital because no recurrence was observed on his MRI studies. However, when he presented to our hospital 7 years later with seizures, he was found to have a large recurrent tumor. The MIB-1 LI calculated using his initial surgical specimen showed that 15% of tumor cells were positive for MIB-1 staining. This case led us to reevaluate and refine our follow-up strategy.
for benign meningiomas on the basis of combined results of the Simpson grade and the MIB-1 LI value.

It is simply and intuitively understandable that the amount of residual mass affects the recurrence rate. Simpson\textsuperscript{33} embodied this notion by defining the extent of resection in his famous 5 grades. This grading system created a widely accepted central dogma that a cure from meningioma could be obtained by total resection, which comprises a wide resection of the affected dura and the underlying bone.\textsuperscript{5,10,36} These are determining factors for selecting Simpson grades, especially Grades I, II, and III. Since the 1950s, however, there have been numerous advances in terms of surgical technique, perioperative management, and monitoring technique. Needless to say, developments in radiation therapy have also altered the goal of resection. This has brought about a significant change, particularly for skull base meningiomas.\textsuperscript{9,21,42} These factors have changed the significance of the Simpson grading system in the modern era.

It should also be mentioned that the quality of current MRI has a huge impact on the definition of recurrence. A brief summary of the literature on surgical outcome before 1990 indicates that the recurrence-free rates of benign meningiomas treated with gross-total resection ranged from 86% to 100% at 5 years and from 75% to 91% at 10 years, while those of tumors treated by subtotal resection were around 50% at 5 or 10 years after surgery.\textsuperscript{2,10,22,36} However, these relatively old data were either not based on radiological examinations or were based on CT findings. In contrast, wider clinical availability of MRI in the last 2 decades has led to improved detection of small masses. However, the literature after the 1990s clearly demonstrates that the effect of enhanced detection of recurrence has been countered by multiple advances in neurosurgery. For example, Strassner et al.\textsuperscript{37} reviewed 463 patients with an intracranial meningioma treated between 1991 and 2002. In their report, the recurrence rates after Simpson Grade I, II, III, and IV resections were 14.2%, 13.6%, 1.9%, and 30%, respectively. Pollock and colleagues\textsuperscript{28} reported 7-year progression-free survival rates of 96% and 82% after Simpson Grade I and II resections, respectively. The tumor control rates reported in these recent studies do not differ largely from those reported in Simpson’s era despite the better detection rates of small residual tumors. On the other hand, Sughrue et al.\textsuperscript{38} recently published valuable data on the relationship between Simpson grade and tumor control rates. These authors achieved excellent tumor control rates of 95%, 85%, 88%, and 81% 5 years after Simpson Grade I, II, III, and IV resections, respectively. They did not observe any significant difference between progression-free survival rates in Simpson Grade I, II, III, and IV groups. Our data are quite similar to those of their study except for the regrowth rate of tumors treated by Grade IV resections. In the literature, 5-year RFS rates after Simpson Grade IV resection have been reported to be 25%–45% even after the 1990s,\textsuperscript{8,17,19} despite the heterogeneity of each study protocol. Sughrue et al.\textsuperscript{38} attributed their extremely
high tumor control rate in Simpson Grade IV resections to technological advances in imaging, microscope use, surgical instruments, and alteration in the WHO classification, as well as to the study design, which excluded meningiomas with cavernous sinus extension. However, we would still have to assume that the definition of Simpson Grade IV resection may vary widely from institution to institution, indicating that we should be careful when comparing data on Simpson Grade IV resection from different studies. Sughrue et al. also referred to possible long-term effects of frequent preoperative embolization as a reason for the better results from Grade IV resection in their series. Although this is an intriguing idea, it led to skepticism because the effect of embolization should be more discernible in the early period of follow-up. Given the mechanism of embolization, the preventive effect on regrowth should fade with the development of new blood vessels. According to their data, however, the possible differences in tumor regrowth after Simpson Grade IV resection between tumors with and without embolization were not observed for approximately 5 years after surgery.

Many investigators have advocated gross-total resection over subtotal resection. As far as Simpson Grade I–III resections are concerned, however, statistically significant correlations between Simpson grade and the duration of RFS have not actually been proven. Kunishio et al. reported that Simpson Grade I resections were associated with a significantly better recurrence-free rate when compared with Grade II or III resection when the follow-up was for 20 years. Adegbite et al. also observed a significant difference between the RFS of patients treated by Simpson Grade I or II resection and that of patients treated by Grade IV resection, but they mentioned that the RFS of patients treated by Grade I or II resection was not significantly different. Most other studies, however, have failed to show a statistically significant correlation between Simpson Grade I, II, and III resections. Our data confirmed that Simpson Grade I resection can guarantee excellent tumor control, showing a nonsignificant but favorable trend for Grade I resection to be better than Grade II or III resection. On the other hand, our data revealed no significant difference between Simpson Grade II and III resections, indicating that the benefit of achieving a Grade II rather than Grade III resection may be more limited than those anticipated by us. The necessity to improve Simpson grades leads to practices such as aggressive coagulation of attachments near nerves and vessels or the peeling of small pieces of tumor off these critical structures, and these have to be judiciously evaluated before actually being performed. Although it should be remembered that statistical data are not all important when we discuss the postoperative outcome, the differences between Simpson Grade I, II, and III resections may be much smaller than we have thought. Our data indicate that it is at least not statistically significant based on the analysis from only a few hundred cases.

Although Simpson introduced the doctrine that the operative outcome of meningioma surgery could be best improved by maximal resection, current surgeons are also required to develop the ability to weigh the risks and benefits of aggressive resection. The requirement of this skill will become more important with the development of stereotactic radiotherapy. At the same time, the effort for maximal resection should not be abandoned because the operative outcomes reported here as well as those by other researchers have been achieved under the principle of aiming for better Simpson grades. We believe that the pursuit of better Simpson grades is still important, provided that it does not carry significant risks.

**Integration of the Simpson Grading System and the MIB-1 LI**

While our data showed some limitations of the Simp-
Simpson grading system in modern meningioma surgery

son grading system in terms of predicting tumor recurrence, the MIB-1 LI has been reported to be largely useful for evaluating the possibility of recurrence. Although several studies have debated its effectiveness, our data indicated that an MIB-1 LI value of 3% or higher was associated with a greater recurrence rate of WHO Grade I meningiomas surgically treated by Simpson Grade II or III resection. The optimal cutoff MIB-1 LI value for predicting recurrence of meningioma has not yet been determined. Previous studies limited to benign meningiomas have adopted the MIB-1 LI cutoff lines of 2%, 2.6%, and 3%, despite some variety of measurements. Given the difficulty of accurate quantification of the MIB-1 LI, it appears reasonable and simple enough to adopt 3% as a routine cutoff level, as we did in our study. One of the drawbacks of the MIB-1 LI is that we are unable to determine whether the tumor will exhibit a high index during surgery, thus enabling modification of our surgical strategy. However, if we combine the intraoperative findings from the Simpson grading system with postoperative results of the MIB-1 LI, we may be able to offer the most favorable treatment plan for patients with WHO Grade I meningiomas. Based on our results, we believe that patients with meningiomas with an MIB-1 LI value of 3% or higher should be properly informed of the necessity of long-term follow-up. It is probably common to integrate the results of the Simpson grading system with those of the MIB-1 LI in daily practice, and our data clearly support this approach. The results will need to be evaluated in a prospective protocol to further prove the validity of this approach.

Conclusions

We reviewed the surgical outcomes of WHO Grade I meningiomas treated by Simpson Grade I, II, III, or IV resection. Tumors treated by Simpson Grade IV resection were associated with a statistically significantly shorter RFS than tumors treated by Simpson Grade I, II, or III resection; this would advocate aiming for an extent of resection better than Simpson Grade IV. On the other hand, we did not observe any significant difference in tumor control rates between Simpson Grade I, II, and III resections, and this was irrespective of tumor location. An MIB-1 LI value of 3% or higher, however, was associated with shorter RFS, even for benign meningiomas treated by Simpson Grade II or III resection. Our data indicated that routine studies using MIB-1 LI data could differentiate meningiomas with high growth potential from those with a relatively low risk of recurrence and also complement the advantages of the Simpson grading system. The Simpson grade and MIB-1 LI results should be carefully integrated to provide an optimal follow-up strategy for patients with WHO Grade I meningiomas.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Oya. Acquisition of data: Oya. Analysis and interpretation of data: Oya. Drafting the article: Oya. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Oya. Statistical analysis: Oya. Administrative/technical/material support: Kawai, Saito. Study supervision: Nakatomi, Saito.

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