Simpson Grade and MIB-1

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The paper by Oya and colleagues in the Journal of Neurosurgery is timely and important. These authors from the University of Tokyo have retrospectively, but very carefully, analyzed a series of 240 patients with 248 benign (WHO Grade I) intracranial meningiomas that were resected at the University of Tokyo Hospital between January 1995 and August 2010. The authors included only patients who had undergone radiological follow-up for at least 6 months, and they calculated the 5-year recurrence-free survival (RFS) by Kaplan-Meir analysis and correlated that with the Simpson grade and the MIB-1 labeling index (LI). All patients underwent yearly radiographic follow-up unless there was residual tumor after surgery, in which case they underwent more frequent imaging; follow-up was censored if the tumor was treated with radiation. In brief, the authors found no statistically significant difference in RFS between Simpson Grade I, II, and III resections, and when they reanalyzed the data excluding patients who had a follow-up shorter than 3 years, there was still no statistically significant difference between Grade I, II, and III resections. As expected, subtotal or partial resections (Simpson Grade IV) led to a significantly higher recurrence rate (56.8% 5-year RFS for Simpson Grade IV resections compared with 97.6%, 87.7%, and 84.1% for Grade I, II, and III resections, respectively).

The most interesting and relatively novel aspect of this study is that the proliferation index (MIB-1 LI) emerged as a very significant factor influencing the frequency of recurrence in this group of benign meningiomas that underwent grossly complete resection (Simpson Grade I, II, and III resections). The authors established a cutoff point of 3% for the MIB-1 LI and found that tumors with an index of 3% or higher had an odds ratio of 4.65% for recurrence compared with those tumors that had an index of less than 3%. This difference was highly statistically significant. It should be noted that there was only 1 recurrence in the group of patients who underwent a Simpson Grade I resection, so that essentially the authors’ analysis pertains to patients with Simpson Grades II and III resections.

On the basis of their findings, these authors question the significance of the Simpson grading system in modern meningioma surgery. In this respect, they join the authors of a very recent paper published in the Journal of Neurosurgery by Sughrue and colleagues from University of California, San Francisco, for which I had the privilege of writing an editorial comment. Similar to the findings of Oya and colleagues, the San Francisco group found no statistically significant difference in recurrence between Simpson Grade I, II, and III resections. However, as opposed to the findings in the Tokyo group where Grade IV resections led to a significantly higher recurrence rate, there was no statistically significant difference in Grade IV resections in the San Francisco series. Importantly, however, the San Francisco group excluded tumors that involved the cavernous sinus, and undoubtedly this was a very important factor in allowing them to leave only minimal amounts of residual tumor in their Grade IV resections, which therefore could essentially be called “near-total” resections. I assume that the Tokyo group included tumors that involved the cavernous sinus in the 114 skull base meningiomas in their series. Of that group, they were able to achieve only a Simpson Grade IV resection in 30 patients, and I presume that in many of these cases, this was due to the fact that the tumor involved the cavernous sinus and a significant amount of tumor had to be left behind, accounting for their considerably greater recurrence rate. This difference notwithstanding, these 2 large and well-studied series offer considerable evidence in support of the notion that there is very little difference in 5-year RFS between Simpson Grade I, II, and III resections. It should be kept in mind that the follow-up in the original Simpson series was much longer, which may partially account for the differences in recurrence rates between the different grades of resection in that series, as discussed in my previous editorial. Undoubtedly, many in the neurosurgical community must have gradually become aware of the lack of important differences between these 3 Simpson resection grades and have begun using the loose terms “grossly complete resection” or “macroscopic complete resection” to refer to Grade I, II, and III resections.

Should we conclude from these 2 studies that resection of the involved dura and underlying abnormal bone (Simpson Grade I resection) is useless, and we should not waste time with this maneuver? I do not think so. It is important to remember that a difference that is not statistically significant does not mean that the difference is not significant. In the San Francisco and the Tokyo series, Grade I resections were associated with a very low recurrence rate compared with Simpson Grade II and III resections. True, these differences did not reach statistical significance in either series, but there was a strong trend in favor of Grade I resections in both series. The 5-year RFS in the San Fran-
cisco series was 95% for Grade I resection versus 85% and 88% for Grade II and III resections, respectively. Similarly, in the Tokyo series, the 5-year RFS for Grade I resections was 97.6% versus 87.7% and 84.1% for Grades II and III resections, respectively. As alluded to above, it is possible that over a longer follow-up period these trends may reach statistical significance. These results, as well as common sense, tell me that whenever possible, if it can be done with minimal or no risk of additional morbidity, it is prudent to remove the involved dura and the abnormal bone at the attachment of benign meningiomas. This, of course, can be consistently achieved with convexity meningiomas, but it is much more difficult to achieve, without additional morbidity, with many skull base and parasagittal meningiomas. On the other hand, the fact that the differences in recurrence rates between Grade I, II, and III resections are small indicates that the surgeon should avoid any maneuvers that endanger the patient to any significant degree in order to achieve the ideal Simpson Grade I resection. The authors of the Tokyo paper put it very well in their statement, “We believe that the pursuit of better Simpson Grades is still important, provided that it does not carry significant risk.” I could not agree more.

Finally, how could we use the important information gained from the Tokyo series on the MIB-1 LI? Although many neuropathologists routinely include this index in their neuropathological reports, I suspect that most of us have not used this to change our treatment paradigm on benign (WHO Grade I) meningiomas. Clearly, what we do at surgery cannot be changed by this information, which usually takes a few days to obtain in most neuropathological laboratories. However, this information may be valuable in terms of postoperative treatment and follow-up of these patients. I do not believe that many neurosurgeons would recommend routine postoperative radiation therapy for benign meningiomas that have been grossly completely resected (Simpson Grades I, II, and III) on the basis of an MIB-1 index of 3% or higher. However, should radiation therapy be considered in cases of incomplete resection when the MIB-1 index is 3% or higher? A definitive answer to this question can only be obtained in prospective studies, but I personally will pay increased attention to this index in the future and will probably be inclined to recommend either radiosurgery or external-beam radiation therapy to patients with residual tumor even if the pathology is otherwise typical of a benign meningioma, when the MIB-1 index is 3% or higher. Additionally, in patients who have undergone a grossly complete resection, I will be inclined to request a closer follow-up, perhaps every 6 months for the first few years instead of just yearly, if the patient has a high MIB-1 index.

One interesting question that this study raises is whether the high MIB-1 index should be one of the factors considered in classifying a meningioma as “atypical” (WHO Grade II). It would be interesting to compare the recurrence rate of grossly completely removed benign (WHO Grade I) meningiomas with a high (3% or higher) MIB-1 LI with the recurrence rate of atypical meningiomas (WHO Grade II) that have been grossly completely removed. Although I have not searched the literature carefully in this respect, it is my impression that the recurrence rate found in this study for patients with benign meningiomas with an MIB-1 LI of 3% or higher approximates the recurrence rates quoted in the literature for WHO Grade II meningiomas. Perhaps the authors of the current paper can comment on this. Have they reviewed the histopathological slides of some of their benign meningiomas with a high MIB-1 LI to see if they showed some other “atypical” features? I congratulate the authors on an excellent study. (http://thejns.org/doi/abs/10.3171/2012.1.JNS112319)

Disclosure

The author reports no conflict of interest.

References


Response

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First, we would like to thank Dr. Heros for his thoughtful commentary on our study. There has been a concerted effort to develop surgical techniques and devices over the past several decades that have influenced current conceptions regarding what types of meningioma patients should be treated surgically and how aggressive the surgeon should be. In this study, we specifically focused on the relationship between Simpson grades and RFS after resection to reflect on the classification system’s meaning in modern neurosurgical technology.

Our fundamental findings are that there were no statistical differences between RFSs of Simpson Grade I, II, and III resections, and that the value of the MIB-1 LI could differentiate tumors with the potential to grow rapidly after gross-total resection from truly “benign” meningiomas. However, we are also aware of the limitations of our study. As Dr. Heros mentioned, the minimal differences discussed in this study would eventually become statistically significant with a much longer follow-up period, which has important implications for the management of benign tumors, such as vestibular schwannomas and meningiomas.