

Editorial

Malignant meningiomas

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The article by Sughrue and colleagues¹ in this issue of the *Journal of Neurosurgery* is important for several reasons: it is the largest published series of patients with malignant meningiomas treated at a single institution (63 patients); the follow-up is relatively long (median follow-up time 5 years; range 1–22 years); and the survival results are well described using Kaplan-Meier analysis. The most interesting result is that patients with subtotal resection (STR) followed by fractionated radiotherapy actually did better than patients in whom the operation consisted of gross-total resection (GTR) followed by radiotherapy. Although this unexpected result deserves some analysis and discussion, it should not obscure the fact that there are other important findings in this paper. I will proceed to discuss the latter ones before commenting on the issue of STR versus GTR.

In my opinion, the most important finding in this study is that radical surgery (gross-total or subtotal excision) is an effective treatment for recurring malignant meningiomas that were initially treated with surgery and postoperative fractionated radiotherapy. Patients who underwent a second operation on recurrence (37 patients) had a median survival of 53 months after the operation, whereas those who were not treated with surgery at the time of first recurrence (8 patients) had a median survival of only 25 months. Clearly, there was a significant selection bias and, as the authors admit, older patients and those with significant neurological impairment were less likely to undergo a repeat operation. However, when the authors corrected for age and Karnofsky Performance Scale (KPS) score on Cox regression analysis, there was still a major survival advantage with repeat surgery. Importantly, such repeat operations did not appear to result in significantly increased morbidity as compared to primary operations. The fact that a second operation is of significant value for recurrent malignant meningiomas is particularly important because it is well known that other forms of salvage therapy, particularly chemotherapy, are of little value under these circumstances.

This study confirms that patients with malignant men-

ingiomas do much better after radical surgery and postoperative fractionated radiotherapy than do patients with more common intracranial malignancies such as primary brain tumors and metastasis. In this particular series, the 2-, 5-, and 10-year survival rates were 82, 61, and 40%, respectively. Although the fact that malignant meningiomas have a much better prognosis than other intracranial malignancies is well known, it is nice to have that confirmed in the largest series of such tumors reported.

In this particular series, the addition of focal radiotherapy, either with stereotactic radiosurgery (SRS; 13 patients) or with ¹²⁵I interstitial brachytherapy (13 patients) after repeat operation on recurrence, did not seem to add a significant survival advantage. It appears to me, however, that with these relatively small numbers and with the retrospective nature of the study, this question remains unanswered. Incidentally, another important question that remains unanswered is whether focal radiosurgery at recurrence, in those tumors that are small enough to be treated with this modality, could be as effective as resection. Likewise, because all patients were treated with fractionated radiotherapy after the initial operation, we do not know if patients in whom gross-total excision was achieved would have done as well without radiotherapy, or if SRS for the small residual tumor in patients with subtotal excision would have been as satisfactory.

In this series, the location of the tumor appears to have made no difference in terms of postoperative morbidity or survival. This is a bit surprising, because one would naturally expect patients with tumors in more critical and surgically difficult locations such as the skull base to do worse. The authors address this issue well in their discussion, and their explanation is that the operations for tumors of the skull base were likely to have been less aggressive. Why the individuals in this subgroup lived as long as patients with meningiomas in more accessible locations, whose tumors were probably removed more radically, relates to what I consider the most interesting finding of this study, and that is that patients with STR did as well as (actually better than) those with GTR in terms of survival.

There were 34 patients who underwent primary resection at the authors' institution (University of California at San Francisco [UCSF]). Of these, 23 patients had what the authors estimated at surgery and on postoperative studies to have been a GTR, and 11 patients underwent STR (which the authors prefer to call "near-

total” resection, because in their estimate, these patients had at least 90% of their tumor removed). It is important to emphasize that all of these patients received postoperative fractionated radiotherapy. Clearly, the finding that the patients who had STR had a longer median survival than those who underwent GTR (107 vs 50 months) is counterintuitive. Similar but less robust findings applied to the group of patients who underwent a second operation at UCSF. The authors discuss the plausible explanations for these findings well, and admit that they could not come up with a good explanation. Both patient groups had similar KPS scores before surgery. There was no difference between the times of initiation of radiotherapy in the 2 groups. It is not clear from my reading of the paper whether the authors looked for other variables such as age, preoperative comorbidities, size and/or location of the tumor, and so on, which may have played a role in the difference in survival in the 2 groups; however, I suspect that they would have commented on this if they had seen any gross differences in these factors in the 2 groups. I admit that after carefully analyzing their data and looking for a reasonable explanation for this unexpected finding, I can do no better than the authors.

The rate of serious neurological complications was higher in patients who underwent GTR (25 vs 11%), and it is possible that this difference, although not statistically significant, influenced the results. That is, patients with serious neurological morbidities may have been more prone to the development of life-ending medical complications, and/or were treated less aggressively for their complications than the patients who were doing well neurologically after surgery. This explanation is reinforced by a quick glance at the Kaplan-Meier graph, which indicates that the deaths in the group with GTR occurred gradually over the first few years, whereas most of the deaths in the STR group occurred later on, at the time of recurrence. Still, even though this factor may at least partially account for the better survival of patients with STR, it certainly does not explain why GTR did not result in a significantly delayed time of recurrence, and therefore longer survival.

From the practical point of view, the best lesson to take from these results is, to quote the authors, that “aggressive attempts at GTR in cases without a clear plane of resection do not seem to be significantly beneficial in these patients, and may be harmful in some cases.” Additionally, I think the authors’ data allow us to conclude that with these malignant meningiomas, to leave a small amount of residual tumor does not seem to worsen survival, provided that the patient is treated with postoperative radiotherapy. It would not be prudent and it may be harmful for neurosurgeons to conclude from these data that STR is preferable, even in cases in which GTR could be achieved with little likelihood of additional morbidity. Although the statistical analysis of these data indicates that STR is better than GTR, I submit (at the risk of sounding heretical to some of my colleagues) that this is a case where common sense should trump statistics.

In summary, this article provides substantial support for aggressive resection, both as primary therapy and at the time of recurrence, for malignant meningiomas. The

data suggest that attempts to remove the last bit of tumor stuck to eloquent brain or to cranial nerves or major vascular structures result in higher morbidity, and are not necessary, because survival seems to be at least no worse in patients with subtotal excision when surgery is followed by fractionated radiotherapy. This study also confirms, in a large series of patients, that with aggressive surgery followed by fractionated radiotherapy, these tumors are associated with much longer progression- and tumor-free survival times than other types of intracranial malignancies. This study also clearly shows that an aggressive repeat operation is effective in treating recurrences of these tumors. However, the study does not address the important question of whether such recurrences, when small enough, can be treated as effectively with radiosurgery. It also does not address the possible role of radiosurgery after subtotal excision, or simple observation without radiotherapy after gross-total excision. It is unlikely that these questions will be answered with randomized studies, because I suspect that neurosurgeons, including myself, will prefer to resect recurrences in accessible areas and use radiosurgery only for inaccessible tumor recurrences, and will continue to use fractionated radiotherapy preferentially after primary total or incomplete excision of these malignant tumors. This policy is supported by the excellent results obtained by the authors adhering to these principles.

The authors of this study ought to be congratulated on an excellent analysis of this large series of patients with malignant meningiomas.

Reference

1. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW: Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. Clinical article. *J Neurosurg* [epub ahead of print March 12, 2010. DOI: 10.3171/2010.1.JNS091114]

Response

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We thank Dr. Heros for his detailed and attentive analysis of our work. Our interpretations of these results are similar to the views he puts forward in his editorial. Importantly, we agree with his assessment that there remain a number of unanswered questions regarding the management of the disease in patients with malignant meningiomas.

Although our experience supports the treatment paradigm of aggressive resection and external-beam radiotherapy as initial treatment, followed by repeat resection at the time of first recurrence, the question of what to do after this remains unresolved. Are additional adjuvant treatments, such as SRS or 3D conformal radiotherapy

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helpful? This is an especially important question given the frequent need to leave behind small portions of tumor to prevent serious neurological injury. Although we did not note a survival effect for the small number of patients receiving radiosurgery or brachytherapy, as Dr. Heros notes, these data are hardly definitive, and more rigorous studies are warranted.

Another important remaining question is this: "What is the appropriate course of action to take upon second recurrence?" Given the apparent benefit of repeat resection, one approach would be to perform a third operation, if possible, and in the absence of more clearly defined, better options, this might be the best approach. It should be noted, however, that experience with 3 operations is limited, and the analysis of the effect of this approach is

complicated by small numbers and heterogeneous patient populations. There remains a realistic possibility that a doubly recurrent tumor is biologically distinct from the original lesion, and might be more aggressive, especially after having been subjected to the selective pressures of 1 or even 2 rounds of radiation treatment. Thus, although it seems reasonable to perform resection of a second recurrence in patients with good performance status, further data to support or refute this idea are needed.

Again, we appreciate Dr. Heros' interest in our work.

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