Guest Editorial

Meningiomas: a quest for the optimum therapy

STEVEN A. NEWMAN, M.D.

Departments of Ophthalmology and Neurological Surgery, University of Virginia Health Sciences Center, Charlottesville, Virginia

It is not surprising that meningiomas, the most common benign intracranial tumor, have fascinated neurosurgeons since the inception of the subspecialty. As with other benign tumors of the central nervous system, surgical excision should be expected to cure the affected individual. This has not always been the case. Harvey Cushing, always alert to the deficiencies of his evolving subspecialty, discussed problems of recurrence in the greatest of his monographs. Why did surgical excision fail to cure these patients? Cushing noted a more rapid growth with angioblastic meningiomas compared with the more benign course of meningothelial or fibroblastic variants. Differences in histology, however, were only a small part of the answer. The most obvious reason for recurrent tumor was primary failure to completely excise the lesion. Published studies confirm the higher incidence of recurrence associated with incomplete excision. This could be attributed to three factors: 1) failure to appreciate the extent of the meningioma; 2) premature termination of surgery related to hemorrhage often obstructing visualization or even compromising the stability of the patient; and 3) involvement of critical neural, vascular, or paracranial structures.

Neuroimaging has made a dramatic impact on the first of these problems — our ability to recognize the extent of the tumor. It is sometimes difficult for those who finished training within the last 20 years to appreciate just how much of a change in clinical practice was produced by the introduction of computerized tomography (CT) scanning. Subsequent use of magnetic resonance (MR) imaging, especially with gadolinium enhancement, has even better outlined the true size of meningiomas. We can thus not only preoperatively outline the extent of the tumor but also recognize postoperative residual tumor or detect recurrence.

Improvement in hemostasis intraoperatively can be attributed to the use of bipolar coagulation and newer hemostatic agents. Preoperative angiography can define the tumor vascular supply. Adjunctive embolization can substantially reduce bleeding when performed prior to surgery.

The third problem, the involvement of critical structures, has been addressed by parallel improvements in surgical techniques. This has had its most dramatic effect in dealing with tumors of the sphenoid wing and parasellar region. While complete resection rates of 91% are claimed for tumors affecting the lateral aspect, only 47% of inner sphenoid meningiomas could be completely excised. Among the surgical trends has been the recognition of the advantages of a joint approach to lesions of the skull base. By combining the talents of head and neck surgeons, otologists, plastic surgeons, and ophthalmologists with those of the neurosurgeon, morbidity may be reduced and more extensive tumors addressed. Direct surgical approach to lesions of the cavernous sinus, an area previously considered sacrosanct, represents a second area of surgical advance. The use of the microscope, high-speed drills, laser, and ultrasound fragmentation have all contributed to better visualization, less tissue manipulation, and more selective protection of surrounding structures.

In spite of these advances, meningiomas continue to recur. The problem of involvement of adjacent critical vascular or neural structures, in particular, continues to be an issue. Even with surgery within the cavernous sinus, extension to the wall of the carotid artery limits complete microscopic resection without en bloc removal with or without reconstruction of the carotid artery itself. Aggressive excision in the medial sphenoid area can result in substantial problems with the major cranial vessels. Whether the risks and effort involved in this procedure are outweighed by the potential benefits remains to be seen.

Finally, even when complete excision is accomplished tumors may recur. While the recurrence rates vary among papers, applications of statistical analysis and life-table studies suggest that the long-term recurrence rates are much higher than suggested in earlier articles or even in more recent ones when the
length of follow-up monitoring is not taken into account.\textsuperscript{4} The lack of recurrence described by Maroon, et al.,\textsuperscript{26} in their series with a mean follow-up period of 40 months may be misleading in light of the slow-growing nature of these tumors and the difficulty of recognizing growth. Recurrence at the edge of the resection may possibly represent a local field effect or propensity that led to the development of the primary tumor in the first place.\textsuperscript{5,4} Even in patients without neurofibromatosis, the occurrence of multiple meningiomas suggests that a subpopulation of patients will lack a permanent cure. And in the best of hands, patients with Simpson Class 1 tumors\textsuperscript{26} cannot be guaranteed to be tumor-free using open-ended follow-up evaluation.

An additional deficiency in our quest for improved results relates to problems with recognition of tumor growth. This of course has been substantially improved by CT\textsuperscript{4} and more recently by MR imaging. There has, unfortunately, been a tendency to rely completely on imaging with deprivation of the clinical examination.\textsuperscript{40} This is particularly true in the retrospective studies published. In the case of basilar skull meningiomas this may limit recognition of growth. Because of the very slow-growing nature of most of these tumors, it is common for imaging studies to show no appreciable change over years.\textsuperscript{21} Progression of clinical symptoms can reveal growth in spite of image stability. This is probably most true for those lesions involving the optic nerve sheath or the medial sphenoid wing or tuberculum. In these locations, imaging studies (even with fat suppression and gadolinium enhancement) frequently fail to demonstrate change. At the same time, quantitative assessment of the afferent and efferent visual system function can indicate subtle progression. These techniques, including refraction for best corrected visual acuity, measurement of afferent pupillary defect with neutral density filters, and automated static perimetry, are not difficult and can detect minute changes in lesions that affect the optic nerve and chiasm. Similarly, somewhat less common techniques, such as measurement of ductions with the Goldmann apparatus, assessment of versions (Hess screen), and binocular single vision fields, provide quantitative assessment of third, fourth, and sixth cranial nerve function. Anesthesiometer rapidly quantitates corneal sensitivity and thus trigeminal nerve involvement. Other cranial nerve dysfunction can also be quantitated in patients with tumors involving the posterior cranial fossa and brain stem. The clinical examination is thus supplementary to and has not been replaced by sophisticated, carefully ordered, imaging studies.

If these advances in diagnosis and surgery still leave us with a substantial recurrence or residual rate (even some more recent series suggest that 100% cures are probably not obtainable\textsuperscript{26}), then consideration must be given to adjunctive therapy. Goldsmith and colleagues,\textsuperscript{16} from the radiation therapy group at the University of California, San Francisco, have presented their most recent results in this, the third of a series of articles\textsuperscript{4,41} reporting effectiveness of radiation therapy in the treatment of meningiomas. This group and Carculla, et al.,\textsuperscript{27} at the New York University Medical Center have pioneered the use of radiation therapy in treating meningiomas. As with their previous articles, the series of Goldsmith, et al., does suffer from its retrospective nature. Nonetheless, the authors have gone a long way to successfully challenging earlier skepticism about the effectiveness of radiation therapy.\textsuperscript{24} Their statistics set a standard that, presuming confirmation, will need to be bettered by other proposed treatments. They add further evidence to the growing number of series that report a beneficial effect of fractionated radiation therapy.\textsuperscript{4,21,24,25} More recently, preliminary reports of focused radiation therapy (for example, using the gamma knife or linear accelerator) suggest similar effectiveness in treating meningiomas;\textsuperscript{22} Morbidity, however, seems to be substantially greater than with fractionated therapy.\textsuperscript{21} While early reports of hormonal therapy suggest some additional benefit,\textsuperscript{16} too little data exist to date. The presence of hormonal receptors on meningiomas\textsuperscript{42} and the in vitro response to hormonal agents\textsuperscript{53,22} certainly does suggest future therapeutic approaches. Standard chemotherapeutic agents do not seem to offer much potential.

If radiation therapy or some other form of treatment can substantially alter the natural history of meningiomas, then these treatments need to be considered not only as adjunctive but also as alternative primary therapy.\textsuperscript{7,21} Their use, however, is predicated on knowledge of the natural history of meningiomas plus the absence of significant morbidity of alternative therapy. Unfortunately, in spite of almost a century of studying meningiomas, the natural history of individual tumors still cannot be accurately predicted. In addition, radiation therapy has not been entirely without side effects. Risk of radiation complications with fractionated irradiation has ranged from 3% to 38%.\textsuperscript{2,16} The most feared effect has been the development of radiation optic neuropathy. Fortunately, this is unlikely with doses less than 53 Gy,\textsuperscript{46} although reports exist of damage with doses as low as 40 or 45 Gy.\textsuperscript{2,25} The risk seems to increase with the fractional dose, with the total dose at risk dropping to less than 48 Gy when the fraction is greater than 2 Gy.\textsuperscript{21,25} When combined with chemotherapy, much lower doses of radiation may damage optic nerve function,\textsuperscript{16} although these earlier cases did not profit from imaging analysis to detect optic nerve pathology. Magnetic resonance imaging with gadolinium usually reveals enhancement of the optic nerve associated with the radiation-induced vasculopathy.\textsuperscript{12,26} While these cases are uncommon, they are poorly responsive to therapy, if they respond at all.\textsuperscript{35} There is little evidence that radiation therapy has a potential deleterious side effect on oculumotor function.\textsuperscript{25} Radiation therapy to posterior fossa tumors can potentially injure the lower cranial nerves including the auditory nerve.\textsuperscript{15,25} Memory difficulties and paraplegia have been reported following radiation therapy for meningioma.\textsuperscript{16} Nonspecific white matter changes are not uncommon following irradiation;\textsuperscript{21} their significance is less clear. Focused radiation therapy is designed to cre-