Benign and aggressive intracranial meningiomas, as the authors state, are seemingly simple tumors (even with benign histology) that can behave in a clinically malignant fashion solely by location. Clinicians with experience in the management of patients with aggressive, recurrent, or malignant meningiomas are all too well aware of the difficulties of recommending effective therapy beyond surgery and radiation therapy. Clearly, there is much room for improvement in the treatment of recurrent or malignant meningiomas with local or systemic chemotherapy and/or biologic therapies.

A key to the uniform reporting and analysis of the results of the treatment of meningiomas is a standard classification system based on histopathologic features. Although many different schemes have been proposed since the time of Cushing and Eisenhardt [1], the scheme by Russell and Rubenstein [2], and the World Health Organization Classification of Tumors, Second Edition (WHO-2) [3], seem to be the most widely used. As the authors point out, these descriptors of pathologic type may be supplemented by the Helsinki grading system, which attributes either 0 or 3 points for the absence or presence of six features of anaplasia [4]. These features include loss of cell architecture, increased cellularity, nuclear pleomorphism, mitotic figures, focal necrosis, and brain infiltration. The sum of these points is then used to assign a grade from I to IV corresponding to descriptions of benign, atypical, anaplastic, and sarcomatous forms of meningiomas.

Although bromodeoxyuridine labeling indices (developed by Dr. Takao Hoshino at the Brain Tumor Research Center at the University of California, San Francisco) were used in the past, we have now turned to ex vivo labeling studies, including the use of Ki-67 and MIB-1 [5]. MIB-1 is commercially available and can be used on paraffin-embedded tumor sections; these sections can be recovered in such a fashion as to reactivate an epitope of Ki-67, which stains for the expression of several proliferation-associated nuclear proteins, and a proliferating cell index can be derived. Typically, with this technique, the labeling index is 2.4 to 1.8 times higher than it is with the bromodeoxyuridine labeling index. There is, however, a strong correlation among the bromodeoxyuridine, MIB-1, and Ki-67 proliferating cell indices [5]. These indices correlate with the proliferative potential of a tumor more accurately than do other tissue descriptive assessments. The results of the combination of histopathologic information, tumor grade, labeling index information, and the Simpson surgical grade, as discussed by the authors, should be available from future clinical series reporting on the treatment of meningiomas [6].

**Surgical Treatment Options**

Although surgical resection remains an important part of the treatment of both benign and malignant meningiomas, not all patients with intracranial meningiomas require surgery, especially elderly patients [7]. Now, for a variety of reasons, small dura-based tumors with imaging characteristics compatible with meningiomas are more often detected via imaging of the central nervous system. Beyond the determination of whether or not a meningioma is responsible for any signs or symptoms, patient and tumor factors must be weighed to determine the appropriateness, and benefit, of any recommended surgical procedure. It is not uncommon to see a patient with a heavily calcified meningioma that does grow appreciably for a considerable period. Clearly, if a decision is made not to intervene, the patient should agree with this approach and be available for regular clinical and radiologic follow-up, so if new symptoms or signs develop, or there is objective...
evidence of tumor growth, the situation can be reevaluated. Preoperative medical therapy for patients with meningiomas does not necessarily have to include embolization, as the authors indicated. With a convexity meningioma, the dural blood supply can be exposed easily and interrupted during the exposure necessary for resection of the tumor. Furthermore, in certain locations, such as the olfactory groove, embolization may present too high a risk. In the case of a small falk meningioma, for which preoperative angiography is not necessary, we have found magnetic resonance venography to be an important adjunct in surgical decision-making regarding the side from which to approach the tumor, given the pattern of veins draining into the superior sagittal sinus. Any additional information that may reduce the potentially devastating consequences of interrupting a "safe" parasagittal draining vein should be considered.

There is no question that during the mid-to-late 1980s, the development of skull-base approaches allowed surgeons to remove tumors previously thought to be unapproachable. However, by their very nature, these procedures are complex and lengthy and may be associated with significant morbidity. In a recent seminal article, Larson et al pointed out the pathologic findings of infiltration of cranial nerves within the cavernous sinus by benign meningiomas, excluding any realistic possibility of "surgical cure" while maintaining extraocular muscle function and an acceptable rate of operative morbidity. Some impressive surgical results have been reported by surgeons accomplished in skull-base approaches; however, 5-year and 10-year rates of recurrence-free survival will be necessary to evaluate the efficacy of this complex surgical procedure.

Radiotherapy and Chemotherapy

It seems somewhat paradoxical that radiation therapy would be recommended as an adjuvant therapy for incompletely resected, recurrent, or malignant meningiomas when both low- and high-dose irradiation to large volumes of the scalp have been implicated in the development of meningiomas. Beyond the experience of Israeli children treated for tinea capitis with meningiomas, a recent review of the literature has revealed that the higher the dose and the younger the patient undergoing irradiation, the shorter the latency period for tumor development [9]. It must be understood that with conventional external-beam irradiation techniques and three-dimensional treatment planning, the volume of normal tissue irradiated to a significant dose has been greatly limited.

The authors have rightly assessed the utility of modern-day radiotherapy for subtotally resected and recurrent meningiomas. Series published since 1990 document 5-year progression-free survival rates for benign meningiomas of 84% to 89% [6]. In the University of California at San Francisco series published by Goldsmith et al, treatment complications, occurred in 5 patients (3.6%), 3 of whom had a sudden onset of blindness 20 to 22 months after treatment [10]. Others have reported such complications as hearing loss, memory impairment, pituitary dysfunction, and chronic otitis media. For surgeons and radiotherapists, information about microscopic rests of meningothelial cells at up to 3 cm from the margin of the original tumor in 57% of specimens is essential for treatment planning [11].

Although radiosurgery is a relatively new treatment for meningiomas, at least 2 series reported a median follow-up of at least 40 months. In the two series, tumor control rates were 76% and 80%, respectively [12,13]. As mentioned by the authors, reduction in tumor size is not the only end point in evaluating therapy, and no increase in tumor size is also an acceptable result. In our experience, only about 30% of meningiomas will become smaller after radiosurgery. Radiosurgery can be used for small, focal occurrences of benign meningiomas or as a boost for residual disease in malignant meningiomas. In their discussion of interstitial brachytherapy, the authors refer to two series by the same author, who reported remarkable radiologic response rates without complications. Our experience is encouraging but not nearly as dramatic! In an evaluation of 21 patients with recurrent or malignant meningiomas treated with iodine-125, low-activity permanent implants at the time of reoperation, the median time to tumor progression was 96 weeks and the median survival was 124 weeks from the time of implantation [14]. Complications occurred in a significant number of patients (38%). These implants are usually reserved for patients with a significant mass of recurrent tumor and for patients in whom other treatment modalities have failed. Obviously, these patients still must be strong enough for an open surgical procedure.

Conventional chemotherapy for recurrent or malignant meningiomas has certainly been disappointing. We have not found a regimen of cyclophosphamide (Cytoxan, Neosar), doxorubicin, and vincristine to be of any significant benefit, given the side effects; in 11 patients, our failure rate was 73% at 1 year and 100% at 2 years after the start of treatment [15]. Clearly, some other approach is warranted, given these poor results.
Experimental Therapies

Experimental studies have demonstrated a number of receptors present in meningioma cells, including progestins, androgens, glucocorticoids, dopamine (DA1), interferon alpha, epidermal growth factor, and platelet-derived growth factor, to mention a few [6]. Experimental evidence in animal models does exist for the use of some receptor antagonists against these different receptors in controlling tumor growth. In one study, trapidil, a drug with antiplatelet-derived growth factor activity, was combined with bromocriptine (Parlodel), a DA1-dopamine receptor blocker; this combination of drugs inhibited tumor growth more than either agent alone [16]. Obviously, the clinical applications of such experiments require further study. Although the antiprogestational agent mifepristone has generated much excitement, the small amount of objective data documenting tumor control requires further investigation. Although high doses of tamoxifen may, in fact, act against meningioma cells by inhibiting protein kinase C activity, rather than by any effect on estrogen receptors, few as they are.

A potentially exciting area of current laboratory investigation is the use of novel biologic therapies for the treatment of meningiomas. In this regard, options include using modified attenuated live virus and infecting the proliferating tumor; the enzyme activity of these proliferating cells is directed toward replication of the virus, and cell death occurs through the normal mechanisms of virus-induced cell lysis [17]. As well, the introduction of a specific gene, such as herpes simplex virus I thymidine kinase, with a retroviral vector may permit the incorporation of a small amount of this gene in actively proliferating cells [18]. The administration of a prodrug such as ganciclovir (Cytovene) permits the phosphorylation of the drug through the activity of thymidine kinase; the triphosphate form of ganciclovir is toxic to the tumor cells. According to Fick et al, current research now indicates that the bystander effect is likely related to the passage of phosphorylated forms of ganciclovir between tumor cells, and it appears that the efficiency of this bystander effect relates to the density of gap junctions that exist on the tumor cell surface [19]. Conveniently, meningioma cells happen to have abundant gap junctions. Therefore, these tumors may be well suited to this form of therapy. Obviously, if laboratory studies continue to indicate the effectiveness of this treatment, it will be some time before this therapy is brought to the clinical sphere.

Although it is true that the mainstay of therapy for meningiomas is surgery, clearly there are a significant number of patients for whom this option does not provide a cure, and other adjuvant therapies are necessary. Neurosurgeons, radiation oncologists, and medical oncologists with a special interest in these tumors have long been frustrated by their tenacity to resist conventional treatment. Advanced surgical techniques, improved radiotherapy using three-dimensional conformal treatment planning, and radiosurgery units have nearly reached their technical limits. Clearly, it is necessary to identify the most effective form of adjuvant chemotherapy, immunotherapy, or viral/genetic therapy for recurrent, aggressive, or malignant meningiomas.

References:

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