Malignant meningiomas constitute 10% to 15% of all meningiomas and limited information exists regarding adjuvant treatment of these aggressive primary brain tumors. Fourteen patients (eight men, six women), ranging in age from 28 to 61 years (median 51 years), were prospectively treated for primary malignant meningiomas according to an institutional protocol. All patients underwent surgery (gross-total in four and subtotal resection in 10 patients) followed in 2 to 4 weeks by involved-field radiotherapy (range 59–60 Gy, median dose 60 Gy). Two to 4 weeks after radiotherapy all patients were treated with adjuvant chemotherapy that included cyclophosphamide, adriamycin, and vincristine (CAV). Patients who underwent gross-total resection received three cycles, whereas those with subtotal resection received six cycles of CAV.

Four patients required CAV dose reduction due to myelosuppression, and in three patients, myelosuppression prevented administration of the planned course of CAV. Four patients required transfusions (four received red blood cells, three received platelets), and two developed neutropenic fever without bacteriological documentation. Neuroradiographic response included three partial responses and 11 with stable disease. The median time to tumor progression was 4.6 years (range 2.2–7.1 years) and median survival was 5.3 years (range 2.6–7.6 years). The author concludes that combined modality therapy for the treatment of malignant meningiomas is associated with acceptable toxicity and a modest improvement in survival when compared to patients treated with surgery alone.

Key Words • malignant meningioma • chemotherapy • radiotherapy
dextrose in 0.45% NaCl daily; 15 mg/m²/day Adriamycin on Days 1 through 3; and 1.4 mg/m² vincristine (2 mg maximum dose) on any day between Days 10 through 14.

Toxicity permitting, CA V was given monthly and repeat evaluation of disease status by means of cranial contrast-enhanced magnetic resonance (MR) imaging was performed bimonthly. Chemotherapy continued for a total of six 4-week cycles in patients with subtotally resected tumors and three 4-week cycles in patients with totally resected malignant meningiomas. Blood counts were obtained weekly. Hematological, gastrointestinal, and neurological toxicity were defined according to the expanded toxicity criteria of the Cancer and Leukemia Group B.

Modifications of the CA V dose were made at the initiation of a subsequent cycle of therapy and were as follows: 100% CA V when granulocyte levels were greater than or equal to 1500/μL and platelet counts were greater than or equal to 100,000/μL; 50% CA V with granulocyte levels 100 to 1499/μL and platelet counts 99,999 to 75,000/μL; and CA V discontinued when granulocytes were less than 100/μL and platelets were less than 75,000/μL.

### Imaging Modalities

Cranial MR images were obtained on a 1.5-tesla superconducting magnet (Signa; General Electric, Milwaukee, WI). Using a spin-echo pulse sequence, axial T₂-weighted images (repetition time (TR) 3000 msec/echo time (TE) 80 msec) proton density-weighted (TR 3000 msec/TE 30 msec) were initially acquired. Subsequently, both sagittal and axial or coronal T₁-weighted images (TR 600 msec/TE 25 msec) were acquired. Slice thickness was 5 mm, with a 2.5-mm interval between successive slices in all instances; a 256 × 256 pixel matrix was used. After intravenous administration of 0.1 mmol/kg gadolinium–diethylenetriamine pentaacetic acid contrast enhancement, coronal, axial, and sagittal T₁-weighted sequences (TR 600 msec/TE 25 msec) were obtained. All contrast images were obtained within 30 minutes of gadolinium infusion.

### Assessment of Response

Blood counts were obtained weekly, neurological examination was performed monthly, and contrast-enhanced cranial MR imaging was obtained every 8 weeks after two cycles of CA V and prior to initiating the next cycle. After CA V chemotherapy was terminated, contrast-enhanced cranial MR images were obtained every 4 months or more often if clinically indicated.

Neuroradiographic response criteria were as follows: a complete response required disappearance of all lesion(s), a partial response required at least a 51% decrease in the largest area in cross-section of each measurable lesion on contrast-enhanced cranial MR imaging. In addition, the steroid dose, if any, must have been stable or decreased, and the neurological examination must have been stable or improved to warrant a designation of complete or partial response. Criteria for stable disease included a decrease of less than 50% in the largest area in cross-section of each measurable lesion or no significant change on contrast-enhanced cranial MR imaging. Progressive disease required a 25% increase in the greatest cross-sectional area of any measurable lesion, the appearance of a new lesion, or deterioration of the neurological examination not explained by other causes. The time to tumor progression was measured as the interval from entry in the study until documentation of progression. Patients with progressive disease were removed from the study.

### Results

All patients underwent surgery; of these, four had gross-total and 10 had subtotal tumor resection as assessed by contrast-enhanced postoperative cranial MR images obtained 24 to 48 hours postsurgery (Table 1). Two patients had transient worsening of preexisting hemiparesis...
Malignant meningiomas

post-surgery, but no other morbidity occurred as a consequence of surgery. All patients successfully discontinued oral steroids that had been initiated at the time of surgery within 1 to 2 weeks post-surgery.

Two to 4 weeks post-surgery, all patients were treated with involved-field radiotherapy, for which the tumor plus a 3-cm area surrounding it, as defined by the preoperative contrast-enhanced MR image, were irradiated with 59 to 60 Gy (median dose 60 Gy) in 1.8- to 2.0-Gy fractions once a day. Localized alopecia occurred in all patients as a consequence of radiotherapy. No other side effects were seen during radiotherapy.

Two to 4 weeks after radiotherapy, all patients began systemic chemotherapy in which four patients who had gross-total tumor resection were treated with three cycles, and seven patients who had subtotally resected tumors received six cycles of CAV. Three patients with subtotally resected tumors received only five of six planned cycles of CAV due to prolonged chemotherapy-related myelosuppression. All patients were treated with a single cycle of CAV every 4 weeks; however, four patients, all with subtotally resected tumors, required dose reductions during the final (sixth) cycle of CAV. Additional chemotherapy-related toxicity included: transient alopecia (14 patients); anemia (seven patients, of whom four required packed red blood cell transfusion); thrombocytopenia (six patients, of whom three required platelet transfusion); and neutropenic fever without bacteriological documentation (two patients). No bladder or cardiac toxicity occurred, and no patient died as a result of chemotherapy-related complications. At the completion of chemotherapy, Karnofsky performance scale scores ranged from 60 to 100, with a median of 90.

After radiotherapy, 10 patients had disease that could be evaluated and measured on contrast-enhanced cranial MR imaging. In nine patients (90%) neurorsurgical contrast-enhanced MR imaging, and one patient (10%) had a partial radiographic response.13 After chemotherapy, 10 patients had radiographic disease that could be evaluated; eight (80%) of these had stable disease and two (20%) had partial radiographic responses compared to preradiotherapy, prechemotherapy contrast-enhanced cranial MR images.13 In total, three (21%) of 14 patients demonstrated a partial response and 11 (79%) of 14 patients demonstrated stable disease after adjuvant radiochemistry. The median time to tumor progression as determined by serial contrast-enhanced cranial MR imaging was 4.6 years, with a range of 2.2 to 7.1 years. The median patient survival was 5.3 years, with a range of 2.6 to 7.6 years. Twelve of 14 patients have died of progressive tumor, all with local–regional recurrences. Two patients (15%) are alive and free of disease with a median follow-up time of 6.1 years (range 5.5–6.8 years).

Discussion

The World Health Organization (WHO) classifies meningiomas into four types: 1) classic (meningotheliomatous, fibroblastic, and transitional subtypes); 2) angio- blastic (hemangiopericytoma); 3) aggressive (papillary subtype); and 4) malignant.14,22 Malignant meningiomas are defined by the WHO as tumors demonstrating histological anaplasia, invasion of brain parenchyma, or metastases.1,2,6,7,10,16,17,21 The Helsinki group1 has proposed a grading system based on microscopic cytological features including loss of architecture, increased cellularity, nuclear pleomorphism, mitotic figures, focal necrosis, and brain infiltration.1,8,10 Tumors are graded I through IV based on the sum of microscopic features present on histopathological evaluation. Grade III meningiomas are designated as anaplastic meningiomas (an alternative term used by the WHO for malignant meningiomas) and have a 78% recurrence risk by 5 years.8,9

Very limited information is available on the best approach for treatment of malignant meningiomas. Notwithstanding the controversy regarding the role of radiotherapy for classic meningiomas,14,15,19,20 there is universal agreement as to its application in malignant meningiomas irrespective of the extent of surgery.1,7,10,14,16,17,19,21 Unfortunately, outcome following adjuvant therapy (either radiation alone or radiation plus CAV chemotherapy) is difficult to interpret from these reports. In patients treated with adjuvant therapy after initial diagnosis, median survival time was 5 years and the degree of tumor resection did not predict recurrence. Because malignant meningiomas are uncommon tumors, a cooperative group study would be required to assess covariants such as extent of surgical resection that affect patient survival.

The largest group of patients treated for malignant meningiomas, in which 60 patients received various therapies, was reported from the University of California, San Francisco (UCSF).10,22 Forty-seven of 60 patients had malignant meningiomas at initial diagnosis and first surgery, and the remaining 13 had recurrent meningiomas found on reoperation to be malignant. Twenty-four patients treated with surgery only had a median survival time of 2 years. Of the remaining 36 patients, 26 received radiotherapy after surgery and 10 received radiotherapy and chemotherapy (CAV). Eight of the 10 patients with primary malignant meningiomas treated at UCSF with adjuvant radiotherapy and chemotherapy have no evidence of recurrence after a mean of 5 years of follow-up review.16,22 Survival data for patients with primary malignant meningiomas treated with adjuvant radiotherapy and no chemotherapy are not clearly stated in these reports.16,22

In the brief report by Rodriguez, et al.,16 regarding the experience at UCSF with malignant meningiomas, 35 patients were analyzed, of whom 12 (34%) were initially treated with surgery plus radiotherapy, 15 (43%) with surgery alone, six (17%) with surgery plus radiotherapy and chemotherapy, and two (6%) with no further treatment after initial diagnosis. Unfortunately this report does not specify how many patients had primary versus secondary malignant meningiomas, a lack of data that clearly confounds interpretation of outcome. Notwithstanding this limitation, 67% of patients experienced recurrence at 5 years and the 5-year survival rate was estimated at 64%. The 3-year recurrence probability was 27% for patients who received adjuvant radiotherapy versus 69% for patients treated solely with surgical resection. These data are compelling evidence for the role of adjuvant radiotherapy in patients with malignant meningiomas. Less clear, however, is the role of adjuvant chemotherapy. In the above-mentioned report by Rodriguez, et al., all six patients
treated adjuvantly with combined radiochemotherapy were free of recurrence at a median follow-up period of 4 years.

Our experience with primary malignant meningiomas is similar to that reported from UCSF, in which median survival exceeds 5 years with combined radiochemotherapy. Whether similar results are achievable with adjuvant radiotherapy alone is unknown and would require a multinstitutional study comparing surgery plus radiotherapy versus surgery plus radiochemotherapy in patients with malignant meningiomas. An aggressive treatment approach is warranted in patients with these tumors because prolonged palliation is possible. The role of adjuvant brachytherapy or radiosurgery is unknown, although these modalities may permit further improvement in patient survival given the present limitations of conventional radiotherapy and chemotherapy.12 Alternatively, other chemotherapeutics (for example, a platinum/VP-16 regimen such as ifosphamide, cisplatin, and VP-16 or mifepristone) may further improve patient survival.3 Chemotherapy using CAV was selected because of its activity in malignant brain tumors and soft-tissue sarcomas, systemic cancers that bear some affinity to malignant meningiomas, and because of limited prior experience with its use in patients with malignant meningiomas.11,16,22 The value of adjuvant chemotherapy in this prospective study is not clear given the confounding and probably more beneficial effects of adjuvant radiotherapy administered to these patients. In conclusion, in this small cohort of patients with primary malignant meningiomas, adjuvant external radiotherapy and CAV chemotherapy appear to improve median survival when compared to patients treated with surgery only and are associated with acceptable toxicity.

References