DIAGNOSIS AND TREATMENT OF ATYPICAL AND ANAPLASTIC MENINGIOMAS: A REVIEW

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ATYPICAL AND ANAPLASTIC meningiomas are uncommon tumors with a poorer prognosis than benign meningiomas. We reviewed the current literature and attempted to integrate and summarize available information to determine a logical approach to these tumors. Both tumors are rare and are often integrated with benign meningiomas when treatments are evaluated. In addition, because there has not been one histopathological classification scheme for atypical and anaplastic meningiomas in the past, there are numerous inconsistencies in the literature. Malignant progression with accumulation of mutations in a benign meningioma can result in an atypical and/or anaplastic meningioma. Both tumors are difficult to manage and have high recurrence and poor survival rates. The extent of tumor resection and histological grade are the key determinants for recurrence. In addition, metastases are unusual, but they do occur. We also review the evidence available that has resulted in the current World Health Organization classification. Radiation therapy can be used as an adjunctive treatment after both total and subtotal resection. In addition, the role of stereotactic radiosurgery is increasing, along with a possible role for brachytherapy. There are no effective chemotherapeutic agents available. A treatment algorithm is suggested.

KEY WORDS: Atypical meningiomas, Anaplastic meningiomas, Stereotactic radiosurgery, Brachytherapy

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Atypical and anaplastic meningiomas are uncommon intracranial tumors. They have a poorer prognosis than benign meningiomas. Because they are rare, there is very limited information about these tumors. Both tumors are often integrated with benign meningiomas when treatments are evaluated. In addition, because there has not been one histopathological classification scheme for atypical and anaplastic meningiomas in the past, there are numerous inconsistencies in the literature. We review the literature to date and attempt to integrate and summarize available information to determine a logical means to approach these tumors.

INCIDENCE AND PREVALENCE

Between 13 and 26% of all intracranial tumors are meningiomas (9, 12, 24, 29, 48). Meningiomas occur mostly in middle-aged or elderly patients, but they can also occur in younger patients with dysgenetic syndromes such as neurofibromatosis Type 2 (NF2). The annual incidence rate is approximately 6 per 100,000 (19) but some tumors are only discovered during autopsy. Often, they are diagnosed incidentally on brain imaging for unrelated complaints. A minority of these tumors demonstrate histopathological and clinical features suggesting an aggressive potential. These are the atypical and anaplastic meningiomas. The former constitute between 4.7 and 7.2% of meningiomas, whereas the latter account for 1.0 to 2.8% (9, 12, 24, 48). Some series have shown that up to 2% of all benign meningiomas transform into malignant forms (2, 51), whereas up to 28.5% of all recurrent benign meningiomas will be found to be atypical or anaplastic (2, 18, 19). Hug et al. (17) reported that the annual incidence of these tumors in the United States is approximately 150 to 225. There is a wide range in the prevalence data for these malignant forms because variable pathological criteria exist for their classification. Benign meningiomas are more prevalent in women, but atypical and anaplastic forms seem to be more common in

men (29). The atypical and anaplastic forms are also more common in the cerebral convexities (29).

Atypical meningiomas have been reported to occur after cranial irradiation for other tumors or conditions. These are usually found in younger patients (3). This complication was first reported in 1953, in a child receiving radiation therapy for an optic glioma (17). Subsequently, children undergoing cranial radiation for medulloblastomas, astrocytomas, leukemia, and lymphoma have all been reported to develop meningiomas (17). These tumors have also been noted in patients who received low doses of irradiation for *tinea capitis* or after experimental radiation treatments during World War II (17). Dental x-rays have also been implicated (17). Often, multiple meningiomas are found in patients with these risk factors (3).

GENETICS

Loss of genetic material at chromosome 22q12, between the myoglobin and the c-sis proto-oncogene loci, has been reported to lead to the initiation of a meningioma (24, 62). This area represents a tumor suppressor gene. Both alleles must be affected before an arachnoid cap cell might turn into a meningioma. The protein encoded by this gene (known as merlin or schwannomin) is a structural protein located in plasma membranes that links the cytoskeleton to the cytoplasmic membrane (26). This is the same genetic locus that is abnormal in NF2. Loss of merlin leads to a loss in cell polarity, increased motility and invasiveness, and reduced contact inhibition, but the mechanism by which it exerts a tumor suppressive effect is not completely understood. Benign meningiomas are monoclonal; up to 70% can have the 22q12 mutation. Other mutations at 18p11 and 1p35 are also found in benign meningiomas (5). With accumulation of further mutations, they can become atypical and then anaplastic. Loss or increase of alleles results in this malignant progression. This can take place de novo in a meningioma, or it can occur during recurrence. In 1997, Weber et al. (61) analyzed the genomic alterations in meningiomas. Using the World Health Organization (WHO) criteria, this group of investigators classified meningiomas into benign (Grade I), atypical (Grade II), or anaplastic (Grade III). They then determined a stepwise change in the genetic characteristic of benign tumors, as these become anaplastic. The loss on 22q, a gain on 1q, 9q, 12q, 15q, 17q, and 20 and a loss on 1p, 6q, 10, 14q, and 18q resulted in an atypical meningioma. Further mutation with amplification on 17q and a loss on 9p (the CDKN2A, CDKN2B, and ARF genes) resulted in an anaplastic tumor (5, 41, 61). The only specific abnormal known genes are the NF2 gene and the CDKN2A, CDKN2B, and ARF genes (5, 61). The latter three on 9p are involved in the G1/S phase cell cycle checkpoint. It is not known what genes are abnormal on the other chromosomes that have mutated.

This theory of malignant progression is supported by the fact that benign meningiomas can recur with atypical or anaplastic pathology. Other tumors, such as gliomas, have been shown to mutate into malignant forms from an originally "low-grade" lesion after accumulating genetic abnormalities. However, Al-Mefty et al. (2) attempted to follow pathological malignant progression in recurrent meningiomas and found that the genetic alterations in the tumor cells were already apparent in the benign meningioma state. Thus, their results contradict the stepwise progression of genetic alterations described previously, but they only studied four specimens, and only three chromosomes were analyzed: chromosome 1, 14, and 22.

Cytogenetic analysis of radiation-induced tumors does not reveal these typical chromosomal changes; these tumors can have multiple complex chromosomal aberrations. Abnormalities in the NF2 gene or chromosome 22 are less consistent (3).

PATHOLOGY

The grading of meningiomas has been a topic of much debate, and a consensus classification has not been accepted. Several classification schemes exist, and the literature varies with respect to the grading system used. Evaluation of reported treatment results for these rare tumors has thus been rendered difficult.

In the 1977 edition of the classic Russell and Rubinstein textbook, Pathology of Tumors of the Nervous System, no designation for atypical meningioma was included (51). However, the authors did state that meningiomas that invaded the brain and/or metastasized were likely to be malignant. In 1979, the WHO grouped meningiomas as either benign or anaplastic/malignant (66). The latter included all meningiomas that displayed "anaplastic features" but that had not developed into a sarcoma. This definition was vague and largely unhelpful, and it did not distinguish between the atypical and anaplastic forms.

Several other classification systems have been published subsequently. Jääskeläinen et al. (18, 19), Rohringer et al. (50), Maier et al. (30), and Mahmood et al. (29) all tried to develop a grading system using specific pathological features to assess the tumor. However, there was much potential subjectivity in criterion weighting from one pathologist to another. Furthermore, benign tumors such as microcystic and angiomatous meningiomas would have been classified as atypical because of the presence of degenerative atypia and pleomorphism. The drawbacks of the system proposed by Maier et al. (30) included a failure to address brain invasion or tumor architecture and to specify what is meant by hypercellularity or "high" mitotic rate. The classification scheme devised by Mahmood et al. (29) also had a degree of subjectivity, especially with regard to descriptions of hypercellularity and nuclear pleomorphism. Additionally, this classification gave importance to necrosis, a feature seen in all meningiomas.

Two studies from the Mayo clinic reported by Perry et al. (43, 44) merit particular attention because they attempted to design a simply applied and reproducible grading scheme for meningothelial neoplasms. In the first study (44), the authors analyzed meningiomas from 581 consecutively treated patients and provided grading recommendations based primarily on those cases in which a gross total resection (n = 463) was

accomplished. The histological features assessed included cellular pleomorphism, nuclear atypia, presence of macronuclei, small cell cytology, sheeting (patternless architecture), atypical mitoses, necrosis, maximal mitotic rate, level of cellularity, and brain invasion. All patients considered, brain invasion, sheeting, absence of nuclear atypia or cellular pleomorphism, and a maximal mitotic rate of ≥4 mitoses/10 high-power microscopic fields (HPF) (≥2.5/mm^2) were univariately associated with decreased recurrence-free survival. These factors, as well as necrosis and macronuclei, were statistically significant in the gross total resection subset, whereas hypercellularity (≥53 nuclei/HPF; ≥118/mm^2) alone proved significant in the subtotally resected cohort.

On multivariate analysis, microscopic brain invasion emerged as the most powerful predictor of reduced recurrence-free survival. In fact, no other histological variable contributed significantly to variation in recurrence-free survival time in the brain-invasive meningioma subset. Brain parenchyma was present for evaluation in 89 cases with only 23 exhibiting invasion. *Fig. 1* illustrates brain invasion by a benign meningioma. When brain invasion was removed from consideration, an independent and especially strong association of reduced recurrence-free survival with a maximal mitotic rate of ≥4/10 HPF (≥2.5/ mm^2) was noted. The absence of cellular pleomorphism, a far more subjective criterion, also remained independently significant, as did various histological features when found in combination. Of greatest statistical power, and prognostically significantly independent of mitotic rate, was the presence of at least three of the following four variables: sheeting, macronuclei, small cell formation, and hypercellularity. The authors recommended that "atypical" meningiomas be defined as those exhibiting the latter profile or a minimum of four mitoses per HPF. *Fig. 2* illustrates these features.

In their second study, Perry et al. (43) focused on the significance of brain invasion and other traditional indices of malignancy in meningiomas by assessing 116 cases that had been branded "malignant" on the basis of histologically confirmed brain infiltration, extracranial metastases, or frank morphological anaplasia (defined as having ≥20 mitotic figures/10 HPF or exhibiting a loss of meningothelial differentiation resulting in carcinoma-, sarcoma-, or melanoma-like

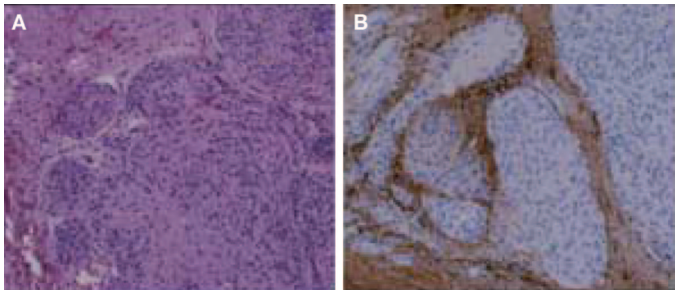

FIGURE 1. *Histopathological images of a benign meningioma illustrating invasion of the brain parenchyma.* A, *Hematoxylin and eosin stain.* B, *Glial fibrillary acidic protein stain.*

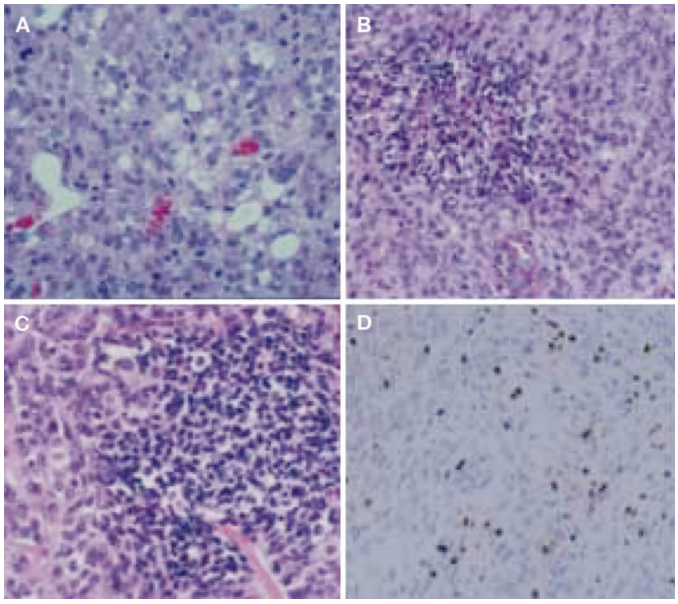

FIGURE 2. *Histopathological images (hematoxylin and eosin stain) of an atypical meningioma showing mitotic figures and macronuclei* (A)*, sheeting and hypercellularity (with an area of necrosis)* (B)*, small cell formation* (C)*, and MIB-1 labeling* (D).

histology). *Fig. 3* demonstrates these features in an anaplastic meningioma. In fact, only 17% of brain-invasive meningiomas exhibited frank anaplasia; 23% were otherwise benign in appearance, whereas the majority (61%) qualified as atypical by the criteria enumerated in the authors' previous analysis. Although brain invasion proved to be a powerful predictor of reduced recurrence-free survival, the worst prognosis was attached to meningiomas evidencing frank histological anaplasia as previously defined, whether invasive or not. By contrast, survival differences for "brain-invasive, otherwise benign" and "brain-invasive, otherwise atypical" meningiomas were not statistically significant, nor did these invasive but histologically non-anaplastic lesions as a group differ significantly from otherwise atypical meningiomas without brain invasion, in terms of overall or recurrence-free survival. Given these findings, Perry et al. (43) recommend that the designation of "atypical" be further extended to meningiomas of ostensibly benign morphological aspect that infiltrate the brain parenchyma. The final grading recommendations of the

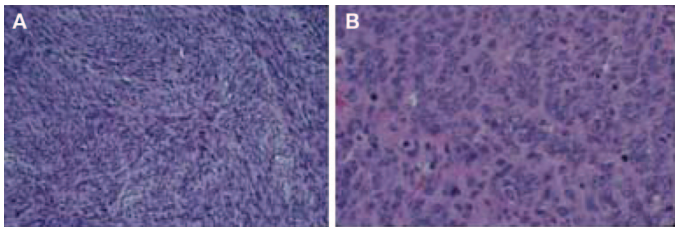

FIGURE 3. *Histopathological images (hematoxylin and eosin stain) of an anaplastic meningioma showing sarcoma-like morphology* (A) *and mitotic figures* (B).

Mayo Clinic group are summarized in *Table 1*. It should be noted that the increased risk of extracranial metastases attached to histologically anaplastic meningiomas was a rare event in the experience of these authors. Additionally, in one instance, a benign meningioma was found to be metastatic. This is a recognized, though most exceptional, phenomenon (benign metastasizing meningiomas) (*Figs. 4* and *5*).

In 2000, the WHO revised the grading of meningioma subtypes as shown in *Table 2* (24). The Mayo Clinic criteria for the designations of atypical and anaplastic meningioma are endorsed with little modification. The WHO does not specifically recommend terming atypical those otherwise benign lesions that invade brain but acknowledges that brain infiltration increases the risk of recurrence. Additionally, necrosis is enumerated as a criterion of atypical meningioma when found in combination with other features. Specifically, it is suggested that meningiomas not showing increased mitotic activity be termed atypical when exhibiting at least three of the following five features: increased cellularity, prominent nucleoli, small cell cytology, sheet-like or patternless growth, and spontaneous or geographic necrosis (i.e., zonal, as opposed to single-cell, necrosis in the absence of prior embolization). The WHO classification specifically recognizes the increased biological potential of clear cell, chordoid, rhabdoid, and papillary meningiomas while acknowledging that elevated proliferative indices, as defined most commonly by immunohistochemical detection of the Ki-67 antigen, may constitute evidence of aggressive capacity in meningiomas of any histological subtype or grade.

In meningiomas, a fairly good correlation exists between histological grading and Ki-67 antigen expression as determined by immunoreactivity with the MIB-1 monoclonal antibody (23). Although a poor prognosis may be associated with a high MIB-1 labeling index (i.e., the percentage of positively labeled tumor cell nuclei), significant overlap exists in the MIB-1 labeling ranges for benign, atypical, and anaplastic meningiomas (23). This warrants caution in interpreting an individual MIB-1 index (1). These conclusions stem from studies that used classification systems differing from WHO 2000 (24) or Perry et al. (43, 44) to grade their lesions. Therefore, Perry et al. (45) used their criteria to initially grade meningiomas pathologically, and then determined the MIB-1 labeling

TABLE 1. Meningioma grading: The Mayo Clinic scheme[a]

Pathological criteria for the diagnosis of atypical meningiomas
≥ 4 mitoses/10 HPF (≥ 2.5/mm²)
Or at least three of the following features:
Sheeting
Macronuclei
Small cell formation
Hypercellularity (≥53 nuclei/HPF; ≥118/mm²)
Brain invasion
Pathological criteria for the diagnosis of anaplastic meningiomas
≥20 mitotic figures/10 HPF (≥12.5 mm²)
Or
Focal or diffuse loss of meningothelial differentiation resulting in carcinoma-, sarcoma-, or melanoma-like appearance

[a] HPF, high power microscopic fields (43,44).

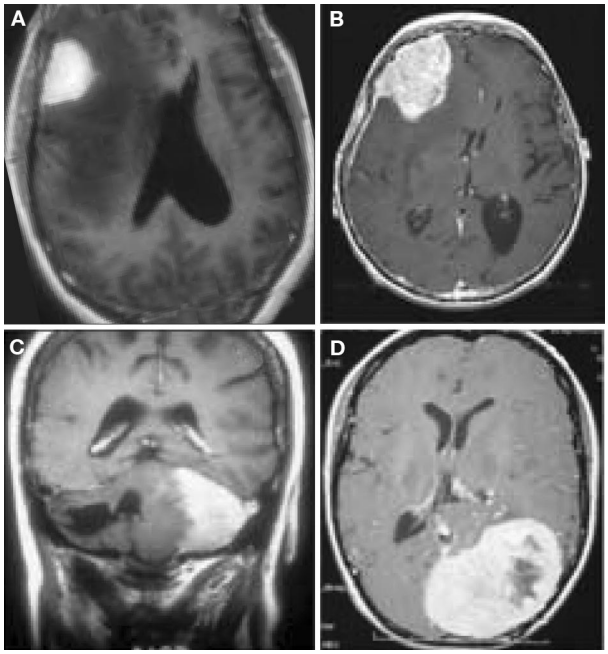

FIGURE 4. *T1-weighted images of the brain with contrast showing a variety of atypical meningiomas with associated radiographic features.* A, *Severe peritumoral edema with mass effect and midline shift.* B, *mushrooming.* C, *wisps of contrast enhancement within the brain parenchyma consistent with brain invasion.* D, *necrosis.*

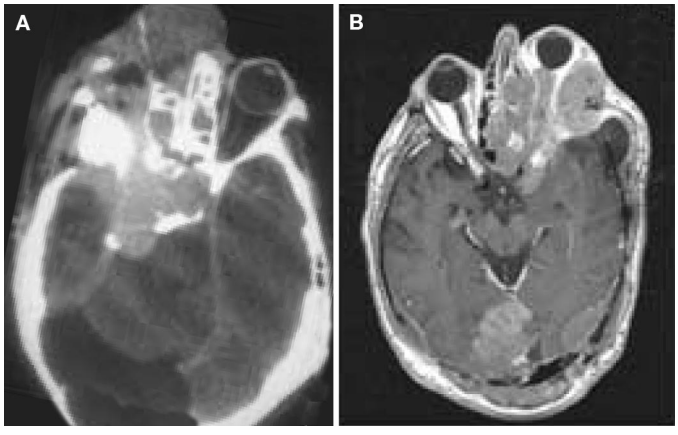

FIGURE 5. A, *axial computed tomographic scan of the brain with contrast showing an anaplastic meningioma causing extensive bony erosion and invasion.* B, *axial T1-weighted image with contrast showing a large anaplastic meningioma infiltrating the orbit and sinuses, causing severe exophthalmos.*

TABLE 2. Meningiomas grouped by likelihood of recurrence and World Health Organization classification[a]

Meningiomas with low risk of recurrence and aggressive growth	
Meningothelial meningioma	WHO Grade I
Fibrous (fibroblastic) meningioma	WHO Grade I
Transitional (mixed) meningioma	WHO Grade I
Psammomatous meningioma	WHO Grade I
Angiomatous meningioma	WHO Grade I
Microcystic meningioma	WHO Grade I
Secretory meningioma	WHO Grade I
Lymphoplasmacyte-rich meningioma	WHO Grade I
Metaplastic meningioma	WHO Grade I
Meningiomas with greater likelihood of recurrence and/or aggressive behavior	
Atypical meningioma	WHO Grade II
Clear cell meningioma (intracranial)	WHO Grade II
Chordoid meningioma	WHO Grade II
Rhabdoid meningioma	WHO Grade III
Papillary meningioma	WHO Grade III
Anaplastic (malignant) meningioma	WHO Grade III
Meningiomas of any subtype or grade exhibiting high proliferation indices or brain invasion	WHO Grade III

[a] WHO, World Health Organization.

indices. They found that the MIB-1 labeling index was only valuable when evaluating tumors with borderline atypia. In such a case, an index of ≥4.2% would classify the tumor as atypical. *Fig. 2D* shows MIB-1 labeling in an atypical meningioma. However, other studies have shown no correlation of clinical outcomes with this index (36, 58).

Other markers may also aid in the segregation of benign versus potentially aggressive meningiomas. Nagashima et al. (35) investigated the expression of c-myc protein and messenger ribonucleic acid (mRNA). In their series of 20 meningiomas, 10 benign tumors did not express this protein or mRNA, whereas all 10 atypical and anaplastic tumors did. Furthermore, they showed that the frequency of c-myc immunopositive cells positively correlated with Ki-67 proliferative indices (35).

There has been concern in the literature about the possibility of over-grading benign meningiomas that were embolized before surgical excision. Perry et al. (42) addressed this issue in a study of 64 embolized meningiomas. The Mayo Clinic scheme devised by this group was used to grade these tumors (as outlined above). Embolized atypical meningiomas made up a large proportion of the study group and were associated with a significantly increased recurrence and death rate. The reason outlined for the larger fraction of atypical tumors was that these were more likely to be selected for embolization. Embolization leads to necrosis, nuclear atypia, macronuclei, and increased proliferation (and therefore an increased mitotic index). Necrosis and nuclear atypia are not used as criteria for grading according to the Mayo Clinic scheme and therefore had no impact on grading. However, the presence of areas of necrosis associated with visible embolization material, the same stage of tumor degeneration in all areas, and nuclear pyknosis within these areas are consistent with changes caused by embolization. This provides a clue that successful embolization was achieved and grading must be carefully considered. Macronuclei alone in an embolized tumor have mild significance without the presence of sheeting, hypercellularity, or small cells and therefore have little impact on grading. If proliferation is noted in an embolized tumor, nonnecrotic regions are assessed for mitoses. If ≥4 mitoses/10 HPF are seen, the tumor is graded as atypical (42). Thus the conclusion was that although embolization causes changes in these tumors, they are rarely sufficient to lead to overgrading if the Perry et al. and Mayo Clinic scheme is used.

PATHOLOGICAL CHANGES AT PROGRESSION

In their initial study of grading criteria for meningiomas, Perry et al. (44) additionally reviewed pathology at recurrence. Slides from 35 patients were available for review: 29 remained at the same grade, two became atypical from benign, and four were classified as benign, but were initially atypical. Another review of 936 patients by Jääskeläinen et al. (19) revealed that 70 meningiomas that were initially benign recurred: 60 stayed benign, but 10 showed atypical or anaplastic changes. Additionally, 19 initially atypical lesions recurred; four were found to be anaplastic and one sarcomatous (19). Thus, all of these tumors can progress biologically. Others have also noted this malignant progression with recurrence (9, 17).

Metastases

Metastases are rare, even for anaplastic meningiomas. The lungs are the most common site for seeding, but lesions have been seen in the liver, bone, skin, and subcutaneous tissue (17, 34). Benign meningiomas can also spread to other locations, including within the craniospinal axis.

Imaging of Atypical and Anaplastic Meningiomas

An atypical or anaplastic meningioma can present with any of the following features on computed tomographic scanning: heterogeneous appearance, homogeneous dense contrast enhancement, nodular or irregular cerebral surface, mushrooming on the outer edge of the lesion, bone destruction, absence of calcification, and marked edema (18, 19, 29, 62, 64). However, none of these features is unique to these tumors and can also be seen in benign meningiomas. The presence and quality of enhancement, as well as the density, on unenhanced imaging are not consistent with higher grade lesions in all studies (64).

Several studies have shown that distinction between benign and anaplastic or atypical meningioma is not particularly reliable with magnetic resonance imaging (MRI) either (59, 65). Recently, diffusion weighted (DW) imaging has been used to image primary brain tumors. It has been determined that the apparent diffusion coefficient (ADC) value could correlate with tumor cellularity and grade (10). Highly cellular tumors have reduced extracellular water and space and have lower ADC values or average diffusion constants compared with normal brain tissue. In a small study of 17 patients with meningiomas, the four patients with WHO anaplastic or atypical meningiomas had lesions that were hyperintense on the DW image and hypointense on the ADC map (10). However, the remaining 13 benign meningiomas had variable intensity on DW imaging. Despite this, there was a significant difference in the average diffusion constant with benign tumors having a much higher value. Although this study was very small, patients were prospectively selected and assessed. More conclusive evidence supporting diagnosis of atypical or anaplastic meningiomas with MRI is needed.

There are, therefore, no hallmarks of aggressiveness, and one cannot use imaging to diagnose atypical or anaplastic meningiomas. To date, neither cerebral angiography nor positron emission tomography has been reported to reveal any specific characteristics of atypical or anaplastic meningiomas.

Magnetic resonance spectroscopy is another diagnostic modality that is gaining popularity in the diagnosis and differentiation between lesions seen on MRI. A number of studies have shown that alanine, glutamine/glutamate, and choline levels are elevated in meningiomas (7, 31, 56). Cho et al. (7) also tried to differentiate between subtypes of meningioma in a series of 19 meningiomas but could not conclusively define any specific spectral characteristics. However, Shino et al. (56) suggested that higher grade meningiomas have increased lactate and choline/creatine ratios and can also have a methylene signal. Obviously, larger studies are needed before any conclusive information can be determined.

Prognosis and Prognostic Factors of Atypical and Anaplastic Meningiomas

The histopathological prognostic factors have been discussed previously and have been used to grade atypical and anaplastic meningiomas. It has been shown that age less than 40 years, cranial base meningiomas, and male sex are associated with recurrence in benign meningiomas that have been subtotally excised (44). Although such data are not available for atypical and anaplastic meningiomas, it is generally agreed that these factors are probably similar for these tumors. Using the Perry et al. criteria (44), it was determined that 81% of the 581 meningioma specimens were benign, with a 12% 5-year recurrence rate; 15% were atypical with a 41% 5-year recurrence rate; and 4% were brain-invasive with a 56% 5-year recurrence rate after gross total resection. The high recurrence rate noted for brain-invasive lesions is likely the result of microscopic residual tumor tissue within the brain parenchyma or invasive tumor tissue that is not resected because of potential morbidity. Median survival time for the anaplastic lesions in the Perry et al. study was 1.5 years, with a 5-year mortality rate of 68% (43). For the brain-invasive anaplastic lesions in the Perry et al. study (43), the 5-year mortality rate was 83% and median survival duration was 1.4 years. Benign and atypical brain invasive lesions showed similar 5-year mortality rates of approximately 25% and between 10 and 14 years median survival.

Similar to benign meningiomas, gross total resection of an atypical meningioma is associated with lower recurrence rates than with subtotal resection (17% versus 87%) (9). Reduced recurrence and increased survival also followed total resection of anaplastic meningiomas (43). Similarly, Palma et al. (40) concluded that a Simpson Grade 1 resection for an atypical or anaplastic meningioma leads to improved survival time. Furthermore, when conducting a retrospective review, this group of investigators concluded that recurrence of atypical and anaplastic tumors was reduced when these tumors were located in the cranial convexity. However, the results of this review displayed a variable clinical course: 50% of 108 patients with atypical or anaplastic meningiomas responded just as well as those with benign tumors, 25% evolved slowly from an atypical pathology to anaplastic pathology to death, and 25% followed a steep downhill course. Dziuk et al. (9) reviewed recurrent atypical and anaplastic tumors. They found that the parasagittal-falcine lesions present with the highest recurrence rates. This is probably because residual tumor remains along the superior sagittal sinus. The authors of this study, along with numerous others in the literature, also concluded that total resection improves recurrence-free survival (9, 34). Once recurrence develops, prognosis is poor because of the high likelihood of treatment failure (9, 17).

Radiation-induced meningiomas are also more aggressive and can recur early after excision. They can also involve bone to a greater degree, preventing complete resection (3).

Molecular markers of prognosis have also been described. Perry et al. (41) determined that the CDKN2A deletion, along with a 9p21 deletion, is a predictor of malignant progression, worse survival rates, and increased recurrence. As mentioned in Pathology, an elevated MIB-1 index can correspond with increased malignancy.

Surgical Treatment of Atypical and Anaplastic Meningiomas

Surgery is the primary means of treating all types of meningiomas. Surgical resection of meningiomas allows definitive diagnosis, reduces mass effect, and alleviates signs and symptoms. The surgical principles are the same as those for benign meningiomas. Excision should be as complete as possible to allow a possible cure. If possible, a margin of duramater should be excised around the tumor. If bone is involved, it too must be completely resected. As previously mentioned, subtotal resection of atypical and anaplastic meningiomas may lead to a high recurrence rate. Cranial base lesions can be difficult to excise totally because of potential morbidity or technical and surgical reasons. Meningiomas that are densely adherent to the cortical surface may also be difficult to totally excise without significant morbidity. Such tumors often require adjuvant therapy and/or repeat surgery at recurrence. In our experience, anaplastic and/or invasive meningiomas are often adherent or intertwined with cortical vessels and therefore more difficult to excise. Thus there is an increased risk of postoperative complications such as infarction and edema and, therefore, neurological deficits.

Embolization of meningiomas with polyvinyl alcohol, alcohol, gelatin foam, coils/microcoils, and Avitene (Davol, Inc., Cranston, RI), among other agents, has been used as an adjunct to surgery for several decades (32). This procedure minimizes blood loss, can reduce tumor volume, and makes surgical excision easier. However, practice patterns vary widely and not all neurosurgeons consider this option. The decision to embolize is often made on a case-by-case basis. Both benign and malignant meningiomas have an equal propensity to bleed. Malignant tumors are not necessarily more vascular than benign tumors. Tumors that may respond positively to embolization are those that are hypervascular on angiography. Meningiomas supplied by branches of the internal carotid artery are usually not amenable to embolization because of the risk of stroke. Risks associated with tumors along the falx or convexities are minimal because distal branches of the middle meningeal branches supply these. Even so, particles may enter the ophthalmic artery, resulting in blindness. Other risks include carotid dissection, propagation of carotid emboli into the brain, and acute deterioration caused by bleeding within a necrotic meningioma (8, 22). For these reasons, some surgeons opt not to embolize these tumors preoperatively and disrupt blood supply intraoperatively before excising the tumor.

Radiation Therapy

Because of small numbers and variation in histopathological classification, the data for radiation therapy of atypical and anaplastic tumors are difficult to analyze. Interpretation of studies is further complicated by unknown factors such as the extent of surgical resection and the presence of brain invasion.

Conventional Fractionated Radiation Therapy

Goldsmith et al. (11) reviewed a series of 140 patients with meningiomas who underwent subtotal resections followed by fractionated radiation therapy (FRT). This group included 23 patients who had either atypical or anaplastic meningiomas. This subgroup had a 58% 5-year survival rate and a 48% 5-year progression-free survival rate. The authors recommended that patients receive at least 53 Gy to ensure a better outcome and noted a trend toward longer remission when radiotherapy was administered immediately after surgery. These investigators therefore advised adjuvant FRT after subtotal resection (in fact, they also came to the same conclusion for subtotally resected benign meningiomas).

Similarly, the authors of another review of 59 patients with atypical and anaplastic lesions concluded that immediate FRT improved outcome with increased progression-free survival, disease-free survival (DFS), and overall survival rates (34). These results resembled those from previously reported studies in which radiation was offered immediately. However, the minimal radiation dose was at least 50 Gy with a 3- to 4-cm margin of surrounding tissue within the radiation field.

Dziuk et al. (9) reported a 5-year DFS rate of 80% after FRT, immediately after initial resection, compared with 15% without radiation. The authors reviewed the records of 48 patients with atypical and anaplastic meningiomas. If recurrent atypical or anaplastic meningiomas were treated with radiation, the 2-year DFS improved from 50 to 89% (at 5 years all patients had disease). This group of authors concluded that early postoperative radiotherapy was an independent predictor for improved DFS. They recommended that at least 60 Gy should be administered, even after a total resection.

Pourel et al. (48) also recommended immediate FRT after surgery after reviewing their series of patients with atypical and anaplastic meningiomas. Thus the consensus favors administering FRT early to patients who have undergone both subtotal and total resections. However, there are no prospective controlled studies supporting this.

Stereotactic Radiosurgery

Recently, several investigators have attempted to define a role for stereotactic radiosurgery (SRS) as a treatment modality in the management of all grades of meningiomas. Certainly, benign meningiomas are encapsulated, usually noninvasive, easy to image, and have easily defined tumor margins. Hence, they are quite favorable for treatment with SRS. One could consider this modality for small or inoperable benign lesions and for recurrent or residual tumors after surgery. However, for atypical and anaplastic meningiomas, the situation is more complicated.

In 1998, Hakim et al. (15) published a review of 127 patients with all types of meningiomas treated with linear accelerator-based SRS. This study used 15 Gy as the median marginal tumor dosage (equivalent to 50 Gy of fractionated radiotherapy), which resulted in a tumor control rate of 89.3% at 5 years. Complications including blindness, hearing loss, hemi-

paresis, and death occurred in 4.7% of patients. Of the patients, 15% had tumors that showed progression. From these results, the investigators concluded that SRS was safe and effective. There were only 26 atypical and 18 anaplastic meningiomas in this series. For these tumors, the median PFS rates were 24.4 and 13.9 months, respectively, with 3-year survival rates of 83.3% and 43.1%, respectively.

The University of Pittsburgh group (25) also presented their results of 99 consecutive patients with benign meningiomas who were treated with SRS with a median marginal dose of 9–25 Gy. They reported an 88% rate of tumor reduction 8 to 10 years after treatment. The failure rate was approximately 5% at 53 to 120 months. This is the longest follow-up period in the literature so far and only pertains to benign meningiomas. Kondziolka et al. (25) therefore recommend radiosurgery as an effective means of treatment after subtotal resection, recurrent tumor, or for nonoperative or small asymptomatic lesions. However, they concur that lesions greater than 3 cm in size should receive conformal radiation therapy. Subsequently, in 2003, this group reported their treatment results for malignant meningiomas in 30 patients (18 atypical, 12 anaplastic tumors) who had previously undergone surgery (16). The average marginal dose was approximately 15 Gy, with an average maximum dose of approximately 30 Gy. They determined that early radiosurgery after surgery and small tumor volumes were associated with better PFS. Atypical meningiomas had 5- and 10-year survival rates of 59%, whereas anaplastic meningiomas had rates of 59 and 0%, respectively. PFS rates at 5 years were 83 and 72% for atypical and anaplastic meningiomas, respectively. Because of these very positive results, immediate radiosurgery was recommended for residual tumor after surgery and for any recurrence during follow-up. The authors also stated that it is difficult to define optimal management for these tumors because of the small number of patients and the lack of uniformity in patient population; they suggested a prospective multicenter trial.

Ojemann et al. (39) also reviewed 22 patients with atypical and anaplastic meningiomas who underwent gamma knife radiosurgery. Nineteen patients were treated after tumor recurrence. In this recurrent group, 37 lesions were treated with SRS with 2- and 5-year progression rates of 48 and 34%, respectively. A 23% rate of radiation necrosis occurred in the whole series, with a few patients requiring surgery. As expected, larger tumors did not respond as well as smaller tumors (volume < 8 cm^3 was found to be a significant factor). Younger patients had a better outcome than older patients.

Some data do not support SRS as favorably in the literature. For instance, a recent series of 13 patients with atypical and nine patients with anaplastic meningiomas who were treated with SRS revealed a 5-year local control rate of 68 and 0%, and a 5-year survival rate of 76 and 0%, respectively (57). This study did not specify whether SRS was administered immediately postoperatively for residual tumor, or after recurrence. Moreover, the anaplastic lesions did very poorly and did not benefit from SRS. This series included another 168 patients with benign tumors who were also treated with SRS and showed a higher risk of radiation-related complications among patients who had received conformal radiotherapy before SRS.

But, because most studies report few complications and fairly good results in the setting of easy therapeutic application and outpatient management, SRS has now become part of the armamentarium when treating atypical and anaplastic meningiomas. It could probably be offered to the patient as soon as possible postoperatively for any nodular residual tumor, along with FRT to the tumor bed. Certainly, the invasive nature of these tumors has to be considered, and SRS may not have any effect on infiltrative areas not appreciated during treatment planning. Its role after complete resection of an atypical or anaplastic meningioma is also less clear. Instead, FRT to the tumor bed should be administered, as suggested by the previously quoted data.

The Role of Proton Beam Therapy

Proton beam therapy has also been considered for primary and recurrent atypical and anaplastic meningiomas (11, 38). Proton beam therapy allows high dosages of radiation delivery to regions near critical structures. It also enables treatment of tumors with irregular shapes. Both Hug et al. (11) and Noel et al. (38) showed that a proton boost, combined with >60 Gy photon therapy, can improve survival and local control. The former study reported a 5-year survival rate of 89% for atypical tumors and 51% for anaplastic tumors. Although the results seem promising, proton beam therapy is not easily available, it is very expensive to set up, and there are implicit limits to the size of tumor that can be treated. This makes other modalities such as intensity modulated radiation therapy (IMRT) more practical.

Intensity Modulated Radiation Therapy

IMRT improves target conformality and coverage by 10 and 36%, respectively, when compared with conformal radiotherapy (46). IMRT can treat tumors of complex forms using variable beam shapes whose intensity can be modulated. Pirzkall et al. (46) used this novel means of therapy to treat recurrent, residual, or untreated skull-base benign meningiomas. After a median follow-up period of 36 months, no tumor growth was observed. This mode of treatment has not been included among other series in the treatment of atypical or anaplastic meningiomas but may definitely play a role, especially in lesions close to critical structures. IMRT can attain high doses, with reduced risks to adjacent structures, because it is very focused with a very rapid dose fall-off. This treatment modality has the unique characteristic that it can be used to treat meningiomas in spinal locations.

Brachytherapy

Ware et al. (60), from the University of California at San Francisco, reviewed a series of 22 patients with recurrent atypical or anaplastic meningiomas who were treated with surgery and brachytherapy. Recurrent tumor predicts a poor

outcome, thus warranting aggressive management. Therefore, after safely resecting all removable tumor tissue, I-125 was implanted into the tumor bed. This study comprised an equal distribution of atypical and anaplastic tumors, with similar survival rates in both groups. The median freedom from progression in 15 patients (who were followed closely) was 10.4 months, whereas the median survival was 2.4 years for patients with both recurrent atypical and anaplastic lesions after brachytherapy. Of the patients, 27% had wound breakdown problems and 13% required repeated resection for recurrence, eventually determined to be radiation necrosis. These complications are similar to those reported by Ojemann et al. after stereotactic radiosurgery (39). Thus, brachytherapy may play a role in therapy, but further study and larger numbers of patients are required. This form of therapy is for salvage purposes and should only be used when the patient is no longer a candidate for further externally delivered radiation therapy.

Chemotherapy

Several chemotherapeutic options have been used to treat atypical and anaplastic meningiomas. Mifepristone, an antiprogesterone agent, has been used to treat unresectable benign meningiomas (14). Grunberg et al. (13) reported the negative results of a Phase III double-blinded, randomized, placebo-controlled trial involving 193 patients for the treatment of unresectable meningiomas using mifepristone at the American Society of Clinical Oncology meeting in 2001. Interferon-α-2B was used in a small series of six patients with recurrent unresectable benign, atypical, and anaplastic meningiomas (21). Five patients showed a positive response, and tumor size apparently stabilized for 6 to 14 months.

Similarly, in another series of patients, combination chemotherapy with cyclophosphamide, adriamycin, and vincristine resulted in 11 of 14 patients having disease stabilization or reduction in tumor size (6). The median time to tumor progression was 4.8 years.

Recently, the role of hydroxyurea in the treatment of recurrent meningiomas has been explored (33, 53, 54). Schrell et al. (53) showed that hydroxyurea inhibits meningioma cell growth in vitro by causing apoptosis. Subsequently, the drug was used to treat four patients with recurrent, unresectable tumors (54). Three patients had benign lesions and one had a malignant tumor. The tumors shrank in all four patients within 6 to 24 months. Mason et al. (33) used the drug in a larger group of patients who had one anaplastic, three atypical, and 16 benign meningiomas. All tumors were recurrent or unresectable. The authors reported no change in 12 patients' tumors and clinical improvement in two (duration of follow-up was 8–151 wk). The anaplastic tumor progressed. Thus, one concludes from this limited study that benign meningiomas may respond to hydroxyurea, whereas anaplastic meningiomas may not. However, more recently, Loven et al. (28) published the results of a series of 12 patients with meningiomas (eight benign, four atypical) treated with hydroxyurea. They did not find any evidence that this agent was effective in treating meningiomas. Similarly, Newton et al. (37) reported no benefit from this agent.

In summary, until now, none of these chemotherapeutic drugs have shown any convincing effect on atypical or anaplastic meningiomas.

Currently, novel therapeutic drugs that act on growth factor receptors on meningiomas and other tumors are being manufactured and tested. Platelet-derived growth factor (PDGF) subunits and their receptors; specifically PDGF-A, PDGF-B, and PDGF-β-receptor are expressed in meningiomas (4). PDGF-BB and activated PDGF- β-receptor are overexpressed in meningiomas; this growth factor and its receptor augments c-fos levels via an autocrine or paracrine loop. This in turn causes increased cell division and tumor proliferation (4, 20, 55). Furthermore, Yang and Xu (63) reported significantly more PDGF-BB and PDGF- β-receptor in atypical and anaplastic meningiomas than in benign ones. Thus, increased interaction between these two molecules may contribute to more malignant meningiomas. An anti-PGDF compound could therefore be tested in the treatment of these tumors. At the moment, Gleevac (STI571), a PDGF antagonist, is being studied in a North American Brain Tumor Consortium phase one protocol.

Vascular endothelial growth factor (VEGF) and its receptor are also expressed in meningiomas (*Fig. 6*), where they play a role in angiogenesis (49, 52). VEGF expression is increased 10-fold in anaplastic and 2-fold in atypical meningiomas compared with benign meningiomas (27). Peritumoral edema and microvascular density correlate with VEGF expression (49). Both PDGF and epidermal growth factor (EGF) increase VEGF expression (49). Therefore, anti-VEGF, anti-EGF, or anti-PDGF compounds may help to control tumor proliferation by an anti-angiogenic property. Several angiogenesis inhibitors that inhibit VEGF or the VEGF receptor are available: ZD6474 (AstraZeneca, Wilmington, DE), PTK787 (Novartis Pharmaceuticals, East Hanover, NJ), AEE788 (Novartis), Avastin (Genentech, South San Francisco, CA), and IMC-1C11 (ImClone). All these drugs are currently being investigated. Two EGF receptor antagonists, Tarceva (OSI774) and Erlotinib

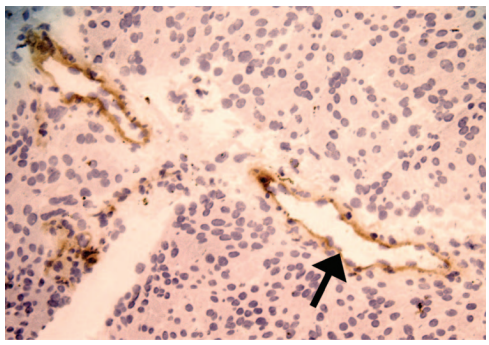

FIGURE 6. *Atypical meningioma with vessel endothelium (*arrow*) showing strong immunohistochemical expression of VEGFR2 receptor (hematoxylin and eosin stain).*

(ZD1839), are being studied by the North American Brain Tumor Consortium in phase one protocols.

After safety is established, both anti-PDGF and anti-EGF compounds could be used in Phase 2 protocols in patients with atypical or anaplastic meningiomas that are resistant to other therapy.

A Proposed Treatment Algorithm for Atypical and Anaplastic Meningiomas

Although anaplastic meningiomas are more straightforward to manage, it is difficult to design a treatment algorithm for an atypical meningioma, because it really is a spectrum of disease. Management of these tumors at our institution is based on the Mayo Clinic pathological classification and corresponding prognosis and prognostic factors determined by Perry et al. (43, 44). We usually adhere to the system outlined as follows (*Fig. 7*).

All anaplastic meningiomas should be treated by FRT soon after resection. If there are focal nodular residual lesions amenable to treatment with SRS, it should also be considered. If there is a recurrence, surgical resection should be offered if possible. Further SRS for residual tumor is also an option.

Atypical meningiomas that are subtotally resected should also be treated with early adjuvant FRT. Any focal nodular residual lesions could also be considered for SRS. If an atypical meningioma is completely excised but is found to be brain-invasive, postoperative FRT is prescribed because nearly 60% of brain-invasive tumors recur within 5 years with an approximate 25% mortality rate.

When there is no brain invasion in an otherwise atypical meningioma that has been completely excised, other factors such as the number of mitoses and MIB-1 index are taken into account. With the minimal 4 mitoses/10 HPF, approximately half of the patients who have undergone gross total resection of a tumor will have recurrence at 5 years. It would seem reasonable to follow these patients closely without irradiation if the surgeon felt that the resection was truly excellent. If there are many more than 4 mitoses/10 HPF, this atypical meningioma is probably more aggressive and further treatment is based on judgment. Certainly, the recurrence rate for atypical tumors with perhaps 10, 15, or 19 mitoses/10 HPF may be much greater than 50% at 5 years, and fractionated irradiation after gross total resection is therefore reasonable. It is uncommon for pathologists to report the number of mitoses/10 HPF; therefore, the MIB-1 index is also used as an aid in determining management. If it is at least 4.2%, postoperative FRT is also offered.

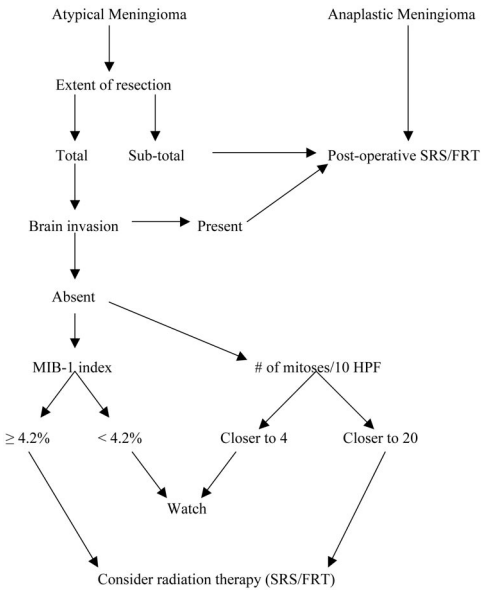

FIGURE 7. *Treatment algorithm for the management of atypical and anaplastic meningiomas at our institution.*

This leaves the gray zone of tumors that fall short of atypical meningioma criteria, those with bland histology and a MIB-1 index ≥4.2%, or those with perhaps a couple of histological features of atypia and, for example, 2 mitoses/10 HPF. If such tumors are gross totally resected, it seems reasonable to watch them closely as well, and administer radiation therapy only after the tumor recurs.

For the brain-invasive meningiomas that have no other characteristics of atypia and display pathological characteristics of chronic presence with gliosis (benign invasive meningiomas), further treatment may be based on the MIB-1 index after subtotal resection. If it is at least 4.2%, postoperative FRT is offered. If totally excised, observation is acceptable.

If meningiomas of any kind progress or recur after the above treatments, they are operated on again and excised if possible. Postoperatively, SRS can be used to treat any focal residual lesions. Patients who have not received before FRT can also be treated with this modality after surgery. Effective chemotherapy is currently not available.

CONCLUSION

The Perry et al. and Mayo Clinic (43, 44) scheme seems to be the most objective classification system to grade meningiomas. The WHO grading is based on this system. In the future, appropriate categorization can guide therapy and will allow further objective studies to assess therapeutic modalities. Atypical and anaplastic meningiomas are distinct entities whose prognosis is poor if left untreated. Surgery remains the main therapeutic option for these tumors. Subtotal resection has a high risk of recurrence. Adjuvant therapy is recommended with radiotherapy. Other modalities, such as SRS, IMRT, and brachytherapy, have all been used with some success. No role for chemotherapy currently exists, but a role for growth factor (PDGF, VEGF) inhibitors may be established in the future.

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Acknowledgments

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COMMENTS

This is a well-written, comprehensive review of a group of tumors that are often frustrating to treat. The authors begin by describing the sometimes confusing pathological criteria used to establish histological diagnosis. I agree with the authors' treatment algorithm after surgery and the need for an aggressive approach. Radiation therapy is indicated for incompletely resected atypical meningiomas and all anaplastic meningiomas regardless of degree of resection. The indications for radiation of a completely resected atypical meningioma are less obvious, and although the risk of recurrence is higher, it may be reasonable to follow these patients up closely and delay radiation until signs of recurrence appear. Alternatively, it may be reasonable to treat these patients with radiosurgery at recurrence. In general, radiosurgery seems reasonable for incompletely resected tumors; however, outcome studies are not definitive.

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In this comprehensive and thoughtful review, Modha and Gutin summarize current knowledge about meningiomas that are not histologically benign. One thing about these tumors is very clear: patients are likely to die as a result of them, and relatively soon after diagnosis. The authors quote a 5-year survival for anaplastic meningiomas of 32%, and even atypical lesions have substantial mortality. The second important fact that emerges is that we do not really know the best treatment for these tumors. This goes beyond a simple lack of surgical or radiological curability or effective chemotherapy: for many common clinical scenarios, we do not know the proper role of the therapies we already have. For example, after gross total resection of an atypical meningioma, probably the single simplest and most common scenario in the treatment of these lesions, we lack solid, prospective evidence for the value of adjuvant fractionated radiotherapy, despite its long history of availability and good reasons to believe it might work.

One reason for this situation is the rarity of histologically aggressive meningiomas. The authors quote an estimated incidence in the United States of 225 or fewer cases annually, but the true incidence of histologically aggressive meningiomas, using modern classification schemes, is not really known: the incidence of atypical tumors could be as high as 7.2% of all newly diagnosed meningiomas. Few neurosurgeons see more than a few of these tumors each year, limiting the ability of single institutions to conduct meaningful prospective trials for this disease. In contrast, much more is known about treatment of medulloblastoma, a malignant tumor with an annual incidence of cases not much greater than that of atypical and anaplastic meningioma, because of broad-based recruitment to multicenter trials.

To date, meningioma protocols have not been a priority for the National Cancer Institute-funded cancer cooperative groups. Because

the way forward for this disease so clearly lies in multi-institutional efforts, neurosurgeons should learn how to work better through existing clinical trial networks or create our own to foster real progress in this important disease.

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Aggressive meningiomas remain a vexing problem to neurological surgeons and their patients. Most meningiomas behave in a proper and predictable way, and long-term success can be predicated on the nature of the tumor and whether surgery, if feasible, completely removes the tumor. The location of the tumor predicates whether such an aggressive surgery is feasible or reasonable. It is likely that most cranial base meningiomas need to be treated by multimodality strategies, which include microsurgery and radiosurgery. For those tumors that have aggressive histological features, recur, or are intimately involved with critical brainstem or structures, fractionated radiation therapy seems to play a role. Radiation therapy seems to reduce the overall risk and time to recurrence in patients who have had incomplete resection. The evidence is not terribly strong, and for those patients who have a defined target that is residual after initial surgery or recurrent after a prior "gross total removal," radiosurgery may be a better option. Radiosurgery provides a focused radiation dose limiting the adverse radiation effects on the surrounding brain and allowing the effect of the radiation to be delivered in a single treatment session. This facilitates the patients' moving on with their lives and reduces risks related to frequent fractionated external beam radiation exposures.

The real rub is in the ability to treat those patients for whom surgery, radiosurgery, and/or radiation therapy fails. These patients include those with aggressive meningiomas with extensive local as well as regional dural spread, those with extracranial metastases, and those with locally infiltrative tumors in critical areas of the brain or brainstem. The present article provides a nice summary of the current state of the art. The vision for the future, especially for these aggressive tumors, requires additional thought, new clinical trials, and some out-of-the-box thinking. None of us remember all of the meningioma patients who have done well. None of us will forget the patients who continue to sustain recurrence and progression and who die despite our best efforts.

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The authors of this review address a problem that many of us frequently face in our clinical practices, namely, how can we treat patients with atypical and anaplastic meningiomas? Modha and Gutin searched the medical literature and found many relevant articles relating to the above-mentioned theme.

This article provides a comprehensive review of the topics "pathology" and "pathological changes at progression" concerning atypical and anaplastic meningiomas. In particular, it discusses and clarifies contradictory results published in this field. The identification of genetic markers and pathologically relevant features may also be a predictor for surgical outcome.

With respect to the part "chemotherapy," especially with hydroxyurea, we are observing 34 patients whom we have treated for 5 years with this compound. Our results (unpublished data) have been similar to those of Newton et al. (1) published recently: "about 80 to 90% of the patients (n=18/20) responded with stable disease ranging from 20 to 328+ weeks (median TTP 176 weeks, 11 patients censored)." Five of the stabilized patients progressed later, and 2 patients had early progressive disease. Although we know that meningiomas may progress in cycles, we have evidence that long-term treatment with hydroxyurea controls meningioma growth. If growth factor antagonists or angiogenesis inhibitors may solve the problem of uncontrolled growth, this may be a goal for the future. In summary, we think that this is a timely review, because it opens our eyes to the problematic treatment of atypical and anaplastic meningiomas.

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1. Newton HB, Scott SR, Volpi C: Hydroxyurea chemotherapy for meningiomas: Enlarged cohort with extended follow-up. **Br J Neurosurg** 18:495–499, 2004.

Treatment of patients with atypical and anaplastic meningiomas is a continued source of disappointment and frustration. Many people erroneously consider all meningiomas to be benign lesions, leading to unrealistic expectations as well as many inconsistencies in treatment. This review is welcome in the literature, because it brings to our attention the challenging surgical and management issues posed by these tumors. Modha and Gutin present a comprehensive review of the diagnosis, genetics, pathology, treatment options, and prognosis of atypical and anaplastic meningiomas, and they propose a treatment algorithm in the management of these lesions.

Some of the points discussed in the article warrant further emphasis and discussion. First, as the authors stated, extensive surgical resection is an important part of the management of World Health Organization Grade II and III tumors. However, surgical resection alone is often not enough. We think that it is in this subset of meningiomas that radiation therapy, as well as other adjuvant therapies, plays a critical role in patient management, because the tumor biology has made them more than a surgical disease.

The genetics of meningioma progression from benign to atypical and anaplastic forms is not fully understood and warrants further study. The finding of our group, that chromosomal abnormalities present in tumors that have progressed to malignancy may be present in their benign forms, introduces the possibility of identifying the "bad-acting" tumors before their histopathological progression. This may some day lead to genetic grading of histopathologically benign meningiomas, allowing adjuvant treatment to be given to those patients with tumors with a high likelihood of progression. Further study is required to look into the genetics and gene products associated with progression, which may open the door for the use of growth factor inhibitors as novel treatment options.

There continues to be a dilemma regarding the treatment of atypical meningiomas after complete surgical resection. The treatment algorithm proposed for the management of these tumors is reasonable and with basis. Early adjuvant radiotherapy should be considered in all cases of atypical meningioma despite complete surgical resection and should definitely be given to patients harboring tumors with higher proliferation rates and frequent mitoses. We would caution, however, that atypical meningiomas with complete resection that do not undergo adjuvant radiation therapy should be observed extremely closely with radiographic follow-up.

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