Approximately 20% of all primary intracranial tumors are meningiomas, and historically the majority of these are considered benign.\textsuperscript{6,9,12,18,23} Pathological grading of meningiomas prior to 2000 varied widely, with many highly subjective classification systems in place and little uniformity for the definition of an atypical meningioma.\textsuperscript{1,7,8,10,15–17,19,21,28,31} Most of these systems relied heavily on mitotic rates but remained subjective even with regard to the mitotic rate needed to classify a tumor as atypical. The not widely used 1993 WHO criteria describe atypical meningiomas as “meningiomas in which several of the following features are evident: frequent mitoses, increased cellularity, small cells with high nuclear to cytoplasmic ratios and/or prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of ‘spontaneous’ or geographic necrosis.”\textsuperscript{10} In 2000, the WHO reclassified meningiomas and created diagnostic criteria that became the standard for grading meningiomas in the years following their publication.\textsuperscript{13} Clarified subclasses of WHO Grade II meningiomas include clear cell, chordoid, and atypical meningiomas. Atypical meningiomas according to the WHO 2000 classification have at least 4 mitoses in 10 hpf or 3 of the following criteria: increased cellularity, high nuclear-to-cytoplasmic ratios, prominent nucleoli, uninterrupted patternless or sheet-like growth, or necrosis.\textsuperscript{13} Notably, neither elevated MIB-1 labeling nor brain invasion are part of these WHO criteria despite recognized predisposition for tumor recurrence when these factors are present.
noted. Although the criteria clarification has benefitted the evaluation of meningiomas by making interobserver and intraintitutional comparisons more valid, the change has required most institutions to adopt new and substantially different criteria for the grading of meningiomas.

In the years following the WHO reclassification, many institutions began to record different rates of atypical meningiomas than they had in the past. Some investigators perceived a decline in the diagnosis, while other institutions, including ours, placed more meningiomas in the atypical WHO Grade II category than were diagnosed as atypical before 2000.

Whereas the overall effect of a better-defined classification scheme is clearly positive, pathologists must become acquainted with the new grading system and develop a consensus on the components of diagnosis that remain subjective. Clinicians must also recognize and adapt to changes in the subtleties of this pathological diagnosis. In addition, new research and experience must be compiled to better guide future treatment of these neoplasms.

The focus of this study is to evaluate the pathological and clinical transition period for atypical meningiomas following the WHO 2000 grading system implementation, and to reevaluate our postoperative treatment for atypical meningiomas.

Clinical Materials and Methods

We retrospectively reviewed our surgical pathology database for meningiomas that had been resected or biopsied at our institution between January 1994 and November 2006 (Fig. 1). This search revealed 471 surgical cases in 440 patients (25 patients had 2 resections and 3 patients had 3 resections). The pathology specimens were categorized based on the year of resection and pathological diagnosis. Diagnostic groups included: WHO Grade I, benign or typical meningiomas (337 cases); WHO Grade II, atypical, clear cell, or chordoid meningiomas (77 cases); WHO Grade III, anaplastic or malignant meningiomas (41 cases); and typical meningiomas with aggressive features, such as necrosis, elevated MIB-1/mitotic rate, or brain invasion (16 cases). Table 1 lists the number of diagnoses per year, and Figs. 2 and 3 depict the annual percentages of each grade around the time of adoption of WHO 2000 grading criteria.

The 93 samples that were designated atypical (WHO Grade II) or typical meningiomas with aggressive features were selected for chart review to determine patterns of diagnosis, review of pathology records, and initial adjunctive treatments. In this chart review, meningioma with necrosis was diagnosed in 3 patients who were found to have had preoperative embolization and were therefore reclassified to the benign/WHO Grade I group. Tumor sites in the remaining 92 patients in either the typical meningioma

<table>
<thead>
<tr>
<th>Year</th>
<th>WHO Grade I</th>
<th>Aggressive Features</th>
<th>WHO Grade II</th>
<th>WHO Grade III</th>
<th>Yearly Totals</th>
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<td>1994</td>
<td>31</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>36</td>
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<td>43</td>
</tr>
<tr>
<td>Total</td>
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<td>16</td>
<td>77</td>
<td>41</td>
<td>471</td>
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</table>

* Average cases/year = 36.2 ± 11.8
Evolution of a treatment paradigm for atypical meningiomas

The Simpson resection grade\(^2\) was able to be determined in 74 of the atypical WHO Grade II meningiomas and in the 16 typical meningiomas with aggressive features. In atypical WHO Grade II cases, Simpson grades included Grade 1 (29 cases), Grade 2 (19 cases), Grade 3 (24 cases), and Grade 4 (2 cases) resections (Table 2). In typical meningiomas with aggressive features, Simpson grades included Grade 1 (5 cases), Grade 2 (4 cases), and Grade 3 (7 cases), with no Grade 4 resections.

The total number of cases per year and the ratio of atypical meningiomas to total cases were plotted and evaluated using chi-square analysis, and by determination of the 95% CIs\(^4\) for each year of treatment. To achieve a valid result using chi-square analysis and to create easier to interpret CIs, the period from 1994 to 1999 in which there were 7 atypical meningiomas out of 169 total cases was combined and compared with subsequent years (Fig. 2).

Of the 77 atypical/WHO Grade II meningiomas evaluated, 59 had MIB-1 staining, 30 had mitotic counts \(\geq 4/10\) hpf, and 47 cases were diagnosed based on cellular morphology with lower mitotic counts (both formal counts and designations of rare, occasional, scattered, and infrequent were included). The rate at which atypical meningiomas demonstrated increased mitotic activity was analyzed using the Fisher exact test from before and after 2002, when the WHO guidelines were adopted at our institution.

The rate of radiotherapy given was analyzed using the chi-square test for both the year of diagnosis and the Simpson resection grade. Groupings for radiotherapy administration rates for the periods 1994–2002 and 2003–2006 were established to test for significant variation over time (Fig. 4). Likewise, Simpson resection Grades I and II (no gross residual tumor) were paired as were Grades III and IV (gross residual tumor) to allow statistical analysis of the role of resection grade in deciding whether or not to use radiation therapy. Patients were considered not eligible for radiation therapy if they had had prior treatment, suffered perioperative complications that precluded treatment, or if they had another documented contraindication to treatment.

From clinic notes and using the consensus views of the treating clinicians, we created a general treatment paradigm upon which the decision of whether or not to use adjuvant radiation therapy or radiosurgery was generally based. The criteria used to create the treatment paradigm were compared with data from patients treated between 2004 and 2006 to evaluate how closely the paradigm actually mirrored our treatment patterns.

![Figure 2](image-url) Line graph showing the percentage of total meningiomas designated as atypical (WHO Grade II) per year. Data points are the total percentage in each calendar year (2006 does not include December). Bars represent the 95% CI. *\(p < .001\) compared with the 1994–99 group.

<table>
<thead>
<tr>
<th>Simpson Grade</th>
<th>No. of Patients</th>
<th>Not Eligible or Declined</th>
<th>Conformal/Beam Radiotherapy</th>
<th>Radiosurgery</th>
<th>Eligible</th>
<th>Patients Treated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>27</td>
<td>7 (26)</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>17</td>
<td>4 (24)</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>15</td>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2 (100)</td>
</tr>
</tbody>
</table>

TABLE 2
Treatment summary of patients with atypical/WHO grade II meningiomas classified according to Simpson resection grade

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Results

Arrival at a Diagnostic Steady State

In 2002, the new WHO criteria began to be cited by the neuropathologists at our institution as the basis by which pathological diagnoses for meningiomas were reported. Prior to this change, the percentage of atypical meningiomas reported had been stable at approximately 4.6% for many years. Between 1994 and 2006 we averaged 36.2 meningioma surgeries/year (Fig. 1). Between 1994 and 2000 the rate of atypical meningiomas ranged from 0 to 3/year, or 4.4% of the total reported for the entire period. Following 2002, the annual percentage of atypical meningiomas rose over a 2-year period, leveling off at between 32.7 and 35.5% between 2004 and 2006. Fifty-four atypical meningiomas were resected in those 3 years. When compared with the rate in 1994–1999, both measurement of CIs and chi-square analysis demonstrate the statistical significance (p < 0.001) of the increased diagnostic rate for atypical meningiomas during all years after 2002. The change in 2002 did not reach statistical significance. It took approximately 1.5–2 years for the new diagnostic criteria to

Fig. 3. Graph showing the cumulative percentage of pathological diagnosis grades by year. There was a slight reduction in the number of malignant meningiomas, but most of the change in atypical meningioma frequency was accounted for by a decrease in benign disease.

Fig. 4. Bar graph showing that the rate of adjunctive radiotherapy for atypical meningiomas in the form of either formal radiation therapy or radiosurgery has remained similar over the study period (p = 0.506).
During the transition period (2002 and 2003), 69 meningiomas were resected at our institution, of which 11 were diagnosed as WHO Grade II. In addition to patients undergoing operations at our institution, during this transition period 23 meningioma specimens were referred for review from outside our institution. A total of 2 years passed and 92 meningiomas were reviewed before the diagnostic transition period was complete.

Pathological Characteristics

Prior to the acceptance of the WHO 2000 criteria, the diagnosis of atypical meningioma was made most frequently in the presence of increased mitotic activity. No universally accepted quantified criteria to diagnose atypical meningiomas existed at the time. Prior to 2002, the majority of atypical meningiomas at our institution displayed increased mitotic activity, with 59% having \( \geq 4 \) mitoses/10 hpf; after 2002, this rate decreased to 36%. The increase in atypical meningiomas with lower mitotic rates is due to the inclusion of other quantified pathological features in the WHO 2000 diagnostic criteria. Although this difference did not reach statistical significance (\( p = 0.12 \)), it does suggest that the WHO criteria for diagnosis of atypical meningiomas now rely more heavily on features other than mitotic activity.

Rate of Radiation Treatment

Radiation was delivered in the form of conformal/beam radiotherapy and/or stereotactic radiosurgery (Gamma Knife surgery at our institution) to 24 of 77 patients with atypical WHO Grade II tumors and to 3 of 16 patients with typical meningiomas with aggressive features. For both groups, 23 patients received formal radiation therapy and 5 patients were treated with radiosurgery (1 patient was treated with both). As would be expected, the Simpson resection grade correlated much more substantially (\( p = 0.0027 \)) with a propensity to give or withhold radiation therapy than did the year of resection (\( p = 0.228 \)). In patients with WHO Grade II tumors, 11 (25%) of 44 eligible candidates with Grade I or II resections (no gross residual tumor) received formal radiation therapy with no patients receiving radiosurgery, whereas 13 (76%) of 17 patients with Grade III or IV resections were treated (9 with formal radiation therapy and 4 with radiosurgery). Despite a lack of statistical significance, there is a recent trend toward more aggressive radiation treatment of incompletely resected atypical meningiomas; 18.7% were so treated prior to 2003 and 34.4% were so treated during and after 2003.

A chart review to determine changes in practice patterns associated with changing frequency of atypical meningiomas revealed that the most prolific surgeons for treating meningioma (4 surgeons accounted for 85% of cases) have tended to develop similar treatment paradigms. Surgeons who found lower volumes of meningiomas tended not to change their preexisting thinking regarding postoperative radiation therapy, and showed less sensitivity to the change in the diagnostic criteria. The most prolific surgeons were more reluctant to administer radiation for fear that the potential detrimental effects of cranial irradiation outweighed the benefits of reduced tumor recurrence, which was particularly the case with complete resection. Most commonly in cases of incomplete resection, patients were monitored closely using serial imaging ~ every 3 months for the first year to note an early tumor recurrence and then underwent imaging with reduced frequency.

In cases of incomplete resection, radiation therapy is almost uniformly recommended. In cases with a radiosurgery target, Gamma Knife surgery has become our preferred treatment modality. In patients with residual disease but no clear radiosurgery target, the benefits of fractionated
radiation therapy are considered by a multidisciplinary board. 

Thirty of the 54 patients with atypical meningiomas who underwent operations since the beginning of 2004 were treated without radiotherapy. The average Simpson resection grade for expectantly managed (closely monitored) patients was 1.61 (excluding the 4 Grade III resections in which formal radiation therapy or radiosurgery was recommended but the patient declined). The average follow-up period for the patients receiving no adjuvant radiation therapy was 28.2 months.

Six patients who did not receive radiation therapy had tumor recurrence, with an average time to recurrence of 17.7 months. Two of these patients had recurrence within the 1st year. Both of these patients had incomplete resections, and their initial treatment plans included radiation therapy. One patient was offered radiosurgery but declined, and in the other, planned radiation therapy was delayed because of the patient’s poor functional status and chronic pressure sores. These patients were both eventually treated with radiosurgery with no further evidence of progression. The remaining 4 patients averaged 22.5 months before tumor recurrence with expectant management. One patient required repeat resection and showed tumor progression to a malignant meningioma. She continues to do well 2 years after her repeat resection was augmented with radiosurgery and formal radiation therapy. Two recurrences were treated successfully with radiosurgery, leading to tumor regression. One patient with multifocal progression and involvement of the optic nerve received conventional radiation and had a radiographic response in the size of the tumor but not a return of vision.

A general consensus treatment paradigm for atypical meningiomas is demonstrated in Fig. 5. This paradigm is the product of combined experience and current data and reflects our current multidisciplinary practice based on chart review. For patients who underwent resection of atypical meningiomas at our institution between 2004 and 2006, 83.3% have been treated according to the paradigm. The failures to follow the paradigm included 6 patients (11.3%) who had complete resections but received formal radiation therapy and 3 patients (5.6%) who had radiosurgery targets but did not receive treatment. All 3 patients who had radiosurgery targets but did not get treatment were offered treatment but declined. Excluding cases in which radiation therapy was recommended but not completed, our recurrence rate for expectantly managed atypical meningiomas was 9% over 28.2 months.

Discussion

During the study period we saw a significant change in the proportion of meningiomas that were designated as atypical. Although the magnitude of the change was impressive, changes in the rates of diagnosis have been previously noted. Recent reports on atypical meningiomas using the WHO 2000 grading system have shown rates that are similar to our 34% WHO Grade II diagnosis rate noted over the last 3 years.11,15,25,30 Our data, however, demonstrate the novel and interesting observation of a transition period following the introduction of new guidelines for these diseases.

The theory that there is a gradual progression to a steady state in the rate of diagnosis with any substantial change in the definition of a disease (in this case atypical meningiomas) has implications both in the research community and in clinical practice. When evaluating recent clinical publications on atypical meningiomas, the study group must be evaluated for homogeneity. Studies performed during the diagnostic transition could lead to incorrect conclusions if patients are categorized according to changing pathological criteria.

The effect that a transition period has on clinical practice is most likely to involve smaller practices. The 1–2 years that it took us to complete the transition and reach a steady state was likely influenced by a relatively high volume of cases. The length of time required for most pathology groups, especially those outside academic practice, to evaluate the 92 tumors reviewed at our institution between 2002 and 2003 would be substantially longer than 2 years. This duration could create a prolonged transition period for institutions without routine access to high tumor volumes or academic neuropathology departments.

It is important to recognize that the gradual change that occurs during a transition period does not reflect misdiagnosis and does not adversely affect patient care within a relatively high volume institution. The transition is, of course, a shift between 2 valid clinical frameworks, and therefore would not represent a diagnosis different from the standard of care. Furthermore, in the early period following the introduction of a new grading system there are (as in this case) no clear data on how a grading system should be used to guide patient care.

The transition in clinical practice for atypical meningiomas has been more difficult to assess than the diagnostic transition, probably because the clinical changes are more subtle and are currently ongoing. Prior to the WHO 2000 classification of meningiomas, a consensus for treatment paradigms for atypical meningiomas could not exist because the diagnostic criteria used at different institutions and in different publications varied widely. We are only now entering a stage in which evidence-based treatment schemes can be created and reliably tested across institutions.

At the University of Alabama at Birmingham, we have tended to be on the conservative end of the spectrum for the use of radiation therapy. We are aware of the reported 37% recurrence rate for “nonbenign meningiomas” without formal radiation therapy,2 and at our institution the radiation oncologists frequently favor more aggressive radiation treatment than neurosurgeons. In our experience, however, the potential cognitive effects of radiation therapy often outweigh the benefit of a reduction in tumor recurrence. Expectantly managing these tumors by monitoring them closely using serial imaging and immediately treating any recurrence is especially appropriate for tumors in areas that are easily accessible to open or radiosurgery. Our sentiments are similar to those reported by Simon and colleagues in 2006.25

An important aspect in the evolution of our treatment paradigm involves a multidisciplinary approach to these tumors. Treatment decisions are reached at a weekly neurooncology conference attended by neurosurgeons, neurooncologists, neuropathologists, and radiation oncologists and have tended to follow the proposed algorithm (Fig. 5). The algorithm does not provide hard and fast rules for how
to treat all patients, nor is it intended to. The algorithm is a product analysis of early success with expectant management and an attempt to do what is best for the patient on an individual basis. Despite good early results, the long-term outcome of patients treated according to our algorithm will not be known for many years. Therefore, it cannot be over-emphasized that the most important process in determining individualized treatment in the current changing environment is the pooling of experience and knowledge in a multidisciplinary fashion. Also, close follow-up of patients with atypical meningiomas is a necessity to allow rapid identification and aggressive treatment of any recurrence.

Although the 2000 WHO guidelines have provided relatively uniform standards that will now allow more widespread application of collected experience, this must be done with careful attention to minimizing bias from the transition period following a widespread change in diagnostic criteria. Twenty-three of the atypical meningiomas that were treated in this study are from before the evolution of a treatment paradigm to a steady state in 2004. Including these patients in long-term outcome analysis, without reclassification based on current pathological criteria, could lead to erroneous conclusions because they may not represent the same group that is now labeled Grade II meningiomas. We included these cases because they were helpful in understanding the progression toward a consensus treatment protocol. For long-term outcome analysis at our institution, meningiomas observed prior to 2004 would need to be reclassified. Eventually, the careful accumulation of data based on widely used diagnostic criteria will lead to well-evaluated and broadly accepted treatment plans for atypical meningiomas. For now, the treatment algorithm is included as our recommendation based on recent experience, but this manner of treatment requires longer follow-up for proper evaluation.

Conclusions

The WHO publication of clear diagnostic criteria for atypical meningiomas in 2000 resulted in a significant increase in our population of atypical meningiomas. In response to the unexpected increase in atypical meningiomas we reevaluated our treatment protocols and have developed an algorithm for the treatment of this population.

References

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