An evidence-based treatment algorithm for the management of WHO Grade II and III meningiomas

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The management of WHO Grade II “atypical” meningiomas (AMs) and Grade III “malignant” meningiomas (MMs) remains controversial and under-investigated in prospective studies. The roles of surgery, radiation therapy, radiosurgery, and chemotherapy have been incompletely delineated. This has left physicians to decipher how they should treat patients on a case-by-case basis. In this study, the authors review the English-language literature on the management and clinical outcomes associated with AMs and MMs diagnosed using the WHO 2000/2007 grading criteria. Twenty-two studies for AMs and 7 studies for MMs were examined in detail. The authors examined clinical decision points using the literature and concepts from evidence-based medicine. Acknowledging the retrospective nature of the studies concerning AM and MM, the authors did find evidence for the following clinical strategies: 1) maximal safe resection of AM and MM; 2) active surveillance after gross-total resection of AM; 3) adjuvant radiation therapy after subtotal resection of AM, especially in the absence of putative radioresistant features; and 4) adjuvant radiation therapy after resection of MM.

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KEY WORDS meningioma; atypical meningioma; anaplastic meningioma; malignant meningioma

Abbreviations AM = Grade II meningioma (atypical meningioma); EBM = evidence-based medicine; EBRT = external beam radiation therapy; EGFR = epidermal growth factor receptor; EOR = extent of resection; GTR = gross-total resection; LC = local control; MM = Grade III meningioma (malignant meningioma); NTR = near-total resection; OS = overall survival; PDGFR = platelet-derived growth factor receptor; PFS = progression-free survival; RTK = receptor tyrosine kinase; SRS = stereotactic radiosurgery STR = subtotal resection; VGFR = vascular endothelial growth factor receptor.

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* Mr. Sun and Dr. Hawasli contributed equally to this work.
with the term meningioma/meningiomas. To meet the inclusion criteria for this study, each article must have reported separate outcomes for Grade II versus Grade III meningiomas and have referenced the WHO 2000 or 2007 classification scheme for meningiomas. Importantly, only articles that included meningiomas graded according to the WHO 2000/2007 system were included in this study. The WHO 2000 and WHO 2007 systems for Grade II and III meningiomas are identical, except that in the latter, “brain invasion” is an independent criterion for the Grade II designation. Twenty-two studies for AMs and 7 studies for MMs met the final inclusion criteria.

**Article Analysis**

Local control (LC) and progression-free survival (PFS) values were obtained from each article where available. If LC and PFS were not in the text, they were extracted from survival curves using DigitizeIt software (http://www.digitizeit.de/). Published data were summarized into levels of evidence and grades of recommendation based on evidence-based medicine (EBM) systems. In brief, the grade of recommendation (1 or 2) refers to the clarity of risk/benefit, whereas the level of evidence (A–E) refers to the study design that a given recommendation is based on. Recommendations were aggregated to create a complete treatment algorithm for AM and MM.

**Results**

**WHO Grade II Meningiomas**

**Surgical Management**

Studies of WHO Grade II or AMs often report outcomes following surgery, since WHO histological grading is not possible without biopsy or resection. However, we recognize that observation in the appropriate clinical context is a reasonable strategy for dural-based tumors of unknown grade that are small and asymptomatic and do not show evidence of growth on repeat imaging.

For biopsy-proven AMs, maximal extent of resection (EOR) has been associated with improved long-term outcomes (Table 2). Recent retrospective studies corroborate the importance of gross-total resection (GTR) or Simpson Grade I–III resection for AMs. The 5-year PFS after GTR is 59%–90% but the 5-year PFS after subtotal resection (STR) is only 30%–70% (Table 2). For each of these studies, GTR shows a significant benefit over STR or Simpson Grade IV resection for AMs (EBM Level 3, Grade 1C recommendation). However, “maximal safe resection” may be a more appropriate strategy than GTR, given the surgical morbidity associated with resection in certain locations (e.g., cavernous sinus). Hence, while GTR is the goal, STR may be considered in select patients through traditional open surgery or minimally invasive techniques. It is unknown whether STR improves outcomes compared with biopsy alone.

Although the benefit of GTR versus STR is well established for AMs, the benefit of obtaining Simpson Grade I versus Grade II–III resection is less clear. Indeed, this is even a controversy for benign meningiomas (WHO Grade I). For benign meningiomas, some authors reported that Simpson Grade I–III resection yielded equivalent results, while others have advocated for Simpson Grade I or even more radical resection. This issue becomes even more ambiguous for AMs. Hammouche et al. reported a 5-year PFS of 74% after Simpson Grade I resection of AMs but only 34% after Simpson Grade II resection. These data are in opposition to 2 of the largest

<table>
<thead>
<tr>
<th>Year of WHO Classification</th>
<th>AMs</th>
<th>MMs</th>
</tr>
</thead>
</table>
| 1993                       | Several of:  
  - Frequent mitoses  
  - Increased cellularity  
  - Small cell change  
  - Prominent nucleoli  
  - Patternless or sheet-like growth | Histological features of frank malignancy far in excess of the abnormalities noted in atypical meningiomas, or Brain invasive |
| 2000                       | ≥4 mitoses per 10 hpf, or  
  ≥3 of:  
  - Increased cellularity  
  - Small cell change  
  - Prominent nucleoli  
  - Patternless or sheet-like growth  
  - Foci of “spontaneous” or “geographic” necrosis | ≥20 mitoses per 10 hpf, or Anaplastic (malignant) cytology resembling that of carcinoma, melanoma, or high-grade sarcoma |
| 2007                       | ≥4 mitoses per 10 hpf, or  
  ≥3 of:  
  - Increased cellularity  
  - Small cell change  
  - Prominent nucleoli  
  - Patternless or sheet-like growth  
  - Foci of “spontaneous” or “geographic” necrosis, or Brain invasive, or Predominant chordoid or clear cell morphology | ≥20 mitoses per 10 high-power fields (HPFs), or Anaplastic (malignant) cytology resembling that of carcinoma, melanoma, or high-grade sarcoma, or Predominant papillary or rhabdoid morphology |
Management of WHO Grade II and III meningiomas

studies on AMs that reported 5-year PFS rates of 85% and 89% after Simpson Grade I–II or I–III resection for AMs, respectively,26,78 suggesting that complete excision of dura may be less important than complete excision of tumor alone for AMs. Most surgeons, however, including the senior authors of this study, would favor Simpson Grade I resection, if surgically feasible with little to no additional morbidity.

Adjuvant EBRT After GTR

The use of adjuvant external beam radiation therapy (EBRT) following GTR for AM is the subject of considerable debate.34,41,49 Three retrospective studies advocated the use of adjuvant EBRT after GTR of AM (Table 3).2,3,45 These studies reported improved LC or a trend toward improved LC with adjuvant EBRT and GTR versus GTR alone (p = 0.04, p = 0.09, and p = 0.10; Table 3), although none reported PFS outcomes. These studies have 2 limitations. First, they include to varying degrees AMs diagnosed according to the 1993 WHO system, which have been shown to respond differently to EBRT compared with AMs diagnosed according to the 2000/2007 WHO system.3,17 Second, in 2 of these studies, no patient with an AM undergoing EBRT has a follow-up time longer than 7.5 years.2,45 Hardesty et al. and Sun et al. reported that AMs can recur over 10 years after initial treatment with or without adjuvant EBRT.26,78 Therefore, it is possible that these studies may not capture late recurrences for patients treated with adjuvant EBRT.

On the other hand, 10 retrospective studies consisting only of AMs diagnosed according to WHO 2000/2007 guidelines recommended active surveillance without rou-

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Median Follow-Up Time (mos)</th>
<th>Adjuvant EBRT Patients</th>
<th>Outcomes After GTR Only</th>
<th>Outcomes After GTR+EBRT</th>
<th>Effect of Adjuvant EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al., 2008</td>
<td>24</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>None (PFS)†</td>
</tr>
<tr>
<td>Jo et al., 2010‡</td>
<td>11</td>
<td>40</td>
<td>5 (45)</td>
<td>100% 3-yr PFS</td>
<td>100% 3-yr PFS</td>
<td>None†</td>
</tr>
<tr>
<td>Mair et al., 2011</td>
<td>66</td>
<td>NR</td>
<td>15 (23)</td>
<td>NR</td>
<td>NR</td>
<td>None (PFS)†</td>
</tr>
<tr>
<td>Lee et al., 2013</td>
<td>71</td>
<td>49</td>
<td>17 (24)</td>
<td>65% 5-yr PFS</td>
<td>74% 5-yr PFS</td>
<td>None, p = 1.00</td>
</tr>
<tr>
<td>Park et al., 2013</td>
<td>55</td>
<td>43</td>
<td>17 (31)</td>
<td>65% 5-yr PFS</td>
<td>52% 5-yr PFS</td>
<td>None, p = 0.86</td>
</tr>
<tr>
<td>Hardesty et al., 2013</td>
<td>149</td>
<td>52</td>
<td>15 (10)</td>
<td>96% 5-yr PFS</td>
<td>100% 5-yr PFS</td>
<td>None†</td>
</tr>
<tr>
<td>Hammouche et al., 2014</td>
<td>34</td>
<td>50</td>
<td>9 (26)</td>
<td>67% 5-yr PFS</td>
<td>100% 5-yr PFS</td>
<td>None, p = 0.13</td>
</tr>
<tr>
<td>Choi et al., 2014‡</td>
<td>53</td>
<td>56</td>
<td>42 (79)</td>
<td>NR</td>
<td>NR</td>
<td>None, p = 0.28 (LC)</td>
</tr>
<tr>
<td>Sun et al., 2014778</td>
<td>151</td>
<td>45</td>
<td>37 (25)</td>
<td>91% 5-yr LC</td>
<td>100% 5-yr LC</td>
<td>None, p = 0.53</td>
</tr>
<tr>
<td>Wang et al., 2015</td>
<td>14</td>
<td>57</td>
<td>3 (21)</td>
<td>87% 3-yr LC</td>
<td>100% 3-yr PFS</td>
<td>None, p = 0.18</td>
</tr>
<tr>
<td>Aghai et al., 2009</td>
<td>108</td>
<td>39</td>
<td>8 (7)</td>
<td>57% 5-yr LC</td>
<td>100% 5-yr LC</td>
<td>Trend to benefit, p = 0.10</td>
</tr>
<tr>
<td>Komotar et al., 2012</td>
<td>45</td>
<td>44</td>
<td>13 (29)</td>
<td>47% 5-yr LC</td>
<td>78% 5-yr LC</td>
<td>Trend to benefit, p = 0.09</td>
</tr>
<tr>
<td>Aizer et al., 2014</td>
<td>68</td>
<td>59</td>
<td>18 (26)</td>
<td>68% 5-yr LC</td>
<td>83% 5-yr LC</td>
<td>Benefit, p = 0.04</td>
</tr>
</tbody>
</table>

NR = not reported.
* Shaded studies included patients who were diagnosed using pre-2000 WHO guidelines. Studies that did not use the 2000/2007 WHO guidelines were excluded.
† p value not explicitly reported.
‡ Data reported from the same institution.
tine adjuvant EBRT after GTR (Table 3). Eight of these 10 studies did not detect any significant improvement in PFS with adjuvant EBRT, and the remaining 2 studies did not detect any significant improvement in LC. The discrepancy between these and the aforementioned 3 studies may in part be due to the categorization of less intrinsically aggressive or more radiation-resistant meningiomas as 2000/2007 WHO AMs compared with the 1993 WHO criteria. Together, although these 13 studies are limited by their retrospective nature, sample sizes, and nonrandom treatment assignments, the current literature overall does not favor the addition of adjuvant EBRT for AMs after GTR.

Complications of adjuvant EBRT should also be considered in clinical decision making. For example, Aghi et al. reported that although none of 8 patients receiving adjuvant EBRT suffered a recurrence, 1 patient developed radiation necrosis, which was subsequently treated with resection. In other studies on AMs, radiation necrosis occurred in 4.2% and 10.2% of patients. Without definitive evidence that EBRT reduces the risk of tumor recurrence and subsequent retreatment for all 2000/2007 WHO AMs, the risk of toxicity related to upfront EBRT needs to be carefully considered.

It is possible that some aggressive AMs may benefit from adjuvant EBRT. Independent prognostic factors for reduced time to recurrence after resection of 2000/2007 WHO AMs include elevated mitotic index (5 of 6 studies), elevated Ki 67 index (3 of 8 studies), brain invasion (2 of 4 studies), and histological features. The current recommendation of active surveillance overall does not favor the addition of adjuvant EBRT for AMs after GTR.

Results from studies (617 patients in total) relying solely on 2000/2007 WHO guidelines support active surveillance after GTR of AMs (EBM Level 3, Grade 1C recommendation). Multidisciplinary management is recommended for those AMs with particularly aggressive histological features. The current recommendation of active surveillance is certainly subject to revision pending results from the RTOG 0539/EORTC 1308 studies.

STR and Adjuvant EBRT

In contrast to gross-totally resected AMs, adjuvant radiation therapy after STR of these tumors is generally accepted in the field. Five of 8 studies using 2000/2007 WHO guidelines demonstrated improved PFS after adjuvant EBRT (Table 4). However, Grade II meningiomas represent a heterogeneous group of tumors, and not all patients may benefit equally from adjuvant EBRT. In particular, histological necrosis has been shown to be a strong predictor of radioresistance in a large study by Sun et al. such that the efficacy of adjuvant EBRT may be limited in AMs with necrosis (EBM Level 3, Grade 2C recommendation). If supported by additional validation studies, necrosis may become a valuable biomarker with which to tailor treatment for patients. In addition, Yang et al. reported that brain invasion correlates with decreased PFS and OS after STR and adjuvant EBRT but not after resection alone. This finding's applicability to clinical decision making after STR is confounded by these authors' pooling of outcomes after GTR and STR. Overall, adjuvant EBRT is reasonable after STR (EBM Level 3, Grade 1C recommendation), but the results of STR and EBRT remain suboptimal, with a 5-year PFS of 43%–91%. Therefore, dose escalation of EBRT or novel approaches using radiosensitization should be investigated, especially for AMs with necrosis.

Radiosurgery as an Adjuvant and Salvage Treatment

There is abundant evidence for the use of stereotactic radiosurgery (SRS) as an effective alternative to surgery for newly diagnosed meningiomas that are presumably benign. However, it is unclear what role SRS plays in the treatment of AMs. A review of modern literature on SRS suggests that this modality can be effective for biopsy-proven AMs (Table 5). In particular, adjuvant SRS following STR resulted in equivalent rates of long-term tumor control as adjuvant EBRT (EBM Level 3, Grade 2C recommendation), although SRS tended to be used for smaller residual tumors in a smaller resection bed. SRS is also used as a salvage measure for AMs for which surgery and EBRT have failed. Prior EBRT is known to be a negative predictor of outcome in patients undergoing SRS for AMs. Therefore, the true efficacy of SRS for AMs should be viewed in the context of radiation-naive versus nonradiation-naive AMs. Series that do not restrict analysis to radiation-naive AMs may therefore underestimate the LC and PFS afforded by SRS in the setting of radiation-naive AMs. Indeed, there is little to no difference between the 2 modalities for radiation-naive AMs as adjuvant therapy after STR or as salvage therapy after recurrence (S.Q. Sun and A.H. Kim, unpublished data). One caveat is that SRS would not be expected to affect microscopic disease in the entire resection bed, and therefore, treatment failures outside the radiosurgical target volume have been reported. In summary, EBRT and SRS are complementary strategies for management of AMs after STR or recurrence. One may be more appropriate depending on clinical circumstances, and, in particular, the volume of the residual or recurrent disease. Larger studies comparing these 2 radiation modalities are necessary.

Chemotherapy

Chemotherapy for AMs has been an active area of research for decades. Most studies have had limited scope, lacking control-cohort data, and the studies rarely separate outcomes for Grade II and Grade III meningiomas. As a whole, chemotherapy for AMs has had limited success. In a recent review of surgery- and radiation-refractory AMs and MMs treated with medical therapies, the weighted average PFS at 6 months was 26% (95% CI 19.3%–32.7%); stratification by Grade II versus III was not available because most studies pooled AMs and MMs together. Pa-
Management of WHO Grade II and III meningiomas

Patients with these refractory tumors typically have a median overall survival of only 6–33 months.9,38,56 Modern trials have looked at the possible utility of receptor tyrosine kinase (RTK) inhibitors. Gefitinib, erlotinib, and imatinib, which target platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR), respectively, have generally been ineffective for AM and MM.56,66,82 Although imatinib in combination with hydroxyurea did achieve a modest effect in Grade II and III meningiomas with a 6-month PFS of 46%, the 12-month PFS was only 8%.66 Several authors have suggested antiangiogenic agents for the treatment of AM and MM.30,62,63 Agents that target vascular endothelial growth factor receptor (VEGFR) have had more success in recent Phase II trials. Vatalanib, an oral RTK inhibitor with activity against VEGFR1–3, achieved a 6-month PFS of 64% in AMs and 38% in Grade III meningiomas.65 Sunitinib, an oral RTK inhibitor against VEGFR, PDGFR, and KIT, achieved a 6-month PFS of 42% in Grade II and III meningiomas.39 Agents against VEGFR and VEGF, including RTK inhibitors and bevacizumab, respectively, have demonstrated 6-month PFS rates of 42%–64% against AM and MM.39,65 This relative success must be tempered, however, by the high rate of side effects and the low median overall survival (OS) with chemotherapy for these surgery- and radiation-refractory Grade II and III meningiomas, at approximately 24 months.39,55,56,65 Chemotherapy for AMs shows promise but should only be considered for select refractory tumors as salvage therapy.

Treatment Algorithm for AMs

Based on the evolving literature and our institutional data of the treatment of these lesions, we suggest an algorithm for AM management (Fig. 1). Importantly, treatment

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Patients w/ Adjuvant EBRT</th>
<th>5-Yr PFS After STR Only</th>
<th>5-Yr PFS After STR + EBRT</th>
<th>Improved PFS w/ Adjuvant EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo et al., 2010</td>
<td>23</td>
<td>16</td>
<td>34%</td>
<td>63%</td>
<td>Yes, p = 0.01</td>
</tr>
<tr>
<td>Mair et al., 2011</td>
<td>48</td>
<td>15</td>
<td>14%</td>
<td>43%</td>
<td>Yes, p = 0.04</td>
</tr>
<tr>
<td>Hardesty et al., 2013</td>
<td>79*</td>
<td>20</td>
<td>60%</td>
<td>80%</td>
<td>No, p = 0.55</td>
</tr>
<tr>
<td>Park et al., 2013</td>
<td>25</td>
<td>7</td>
<td>0%</td>
<td>68%</td>
<td>Yes, p &lt;0.001</td>
</tr>
<tr>
<td>Lee et al., 2013</td>
<td>19</td>
<td>5</td>
<td>20%</td>
<td>91%</td>
<td>Yes, p = 0.002</td>
</tr>
<tr>
<td>Hammouche et al., 2014</td>
<td>45</td>
<td>27</td>
<td>NR</td>
<td>NR</td>
<td>No, p &gt;0.34†</td>
</tr>
<tr>
<td>Sun et al., 201477</td>
<td>59</td>
<td>25</td>
<td>30%</td>
<td>65%</td>
<td>Yes, p = 0.03</td>
</tr>
<tr>
<td>Wang et al., 2015</td>
<td>14</td>
<td>9</td>
<td>0%</td>
<td>49%</td>
<td>No, p = 0.07</td>
</tr>
</tbody>
</table>

* May include patients with spinal meningiomas or syndromic meningiomas, as well as patients that had undergone previous tumor resection or EBRT at the site of the atypical meningiomas
† p value not explicitly reported.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Median Follow-Up Time (mos)</th>
<th>SRS Cases</th>
<th>Outcomes After SRS</th>
<th>EBRT Cases</th>
<th>Outcomes After EBRT</th>
<th>Difference After SRS vs. EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi et al., 2010</td>
<td>22</td>
<td>20</td>
<td>54% 3-yr LC</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pollock et al., 2012</td>
<td>38</td>
<td>18</td>
<td>50% 5-yr LC†</td>
<td>0</td>
<td>89% 5-yr DFS†</td>
<td>—</td>
</tr>
<tr>
<td>Hardesty et al., 2013</td>
<td>52</td>
<td>22</td>
<td>90% 5-yr PFS</td>
<td>20</td>
<td>80% PFS at 5 yrs</td>
<td>No, p = 0.52</td>
</tr>
<tr>
<td>Sun et al., 201477</td>
<td>67</td>
<td>7</td>
<td>67% 5-yr LC</td>
<td>25</td>
<td>64% LC at 5 yrs</td>
<td>No, p = 0.30</td>
</tr>
<tr>
<td>Harris et al., 2003</td>
<td>28</td>
<td>18</td>
<td>83% 5-yr PFS</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Matteo et al., 2007</td>
<td>42</td>
<td>19‡</td>
<td>100% 3-yr PFS</td>
<td>5</td>
<td>33% PFS at 3 yrs</td>
<td>NR</td>
</tr>
<tr>
<td>Kano et al., 2007</td>
<td>43</td>
<td>25§</td>
<td>48% 5-yr PFS¶</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Attia et al., 2012</td>
<td>43</td>
<td>24**</td>
<td>25% 5-yr PFS</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hanakata et al., 2013</td>
<td>24</td>
<td>28††</td>
<td>16% 5-yr LC</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; — = not applicable.
* Shaded studies included patients who were not uniformly radiation naive.
† Includes 1 case of Grade III meningioma.
‡ Three cases received prior EBRT.
§ Four cases received prior EBRT or SRS.
¶ Includes 5 cases of Grade III meningioma.
** Eleven cases received prior EBRT.
†† Nine cases received prior EBRT or SRS.
of neurooncology patients is a multidisciplinary endeavor and requires input from all teams involved, including but not limited to surgeons, radiation and medical oncologists, neuropathologists, and neuroradiologists. The algorithm attempts to summarize key findings in the literature while allowing considerable room for clinical decision making.

For recurrent AMs, fewer evidence-based recommendations can be made based on available literature. In particular, no studies of WHO 2000/2007 AMs compare outcomes of salvage resection against salvage EBRT or SRS for recurrent AMs; for these tumors, we recommend tailoring treatment to the specific clinical scenario. In our experience, salvage resection is considered if the recurrent AM is accessible, salvage SRS is considered if the recurrent AM is relatively small and localized, and salvage EBRT is considered if the recurrent AM is radiation-naïve and of a relatively larger volume such that SRS is not feasible.

**WHO Grade III Meningiomas**

Prior to the 2000/2007 WHO grading changes, MMs
TABLE 6. Literature review of studies assessing the role of surgery and radiation therapy for WHO 2000/2007 Grade III meningiomas*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Treatments</th>
<th>Outcomes</th>
<th>Improved Outcomes With Adjuvant EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durand et al., 2009</td>
<td>33</td>
<td>GTR/STR ± Adjuvant EBRT</td>
<td>8% 5-yr PFS</td>
<td>Benefit: p = 0.18 for PFS; p = 0.036 for OS</td>
</tr>
<tr>
<td>Rosenberg et al., 2009</td>
<td>13</td>
<td>GTR/STR ± Adjuvant EBRT</td>
<td>9% 3-yr PFS; 47% 5-yr OS</td>
<td>Trend to benefit; p values NR</td>
</tr>
<tr>
<td>Sughrue et al., 2010*</td>
<td>34</td>
<td>GTR/STR+Adjuvant EBRT</td>
<td>57% 5-yr PFS; 61% 5-yr OS</td>
<td></td>
</tr>
<tr>
<td>Adeberg et al., 2012</td>
<td>23</td>
<td>GTR/STR+Adjuvant EBRT</td>
<td>15% 5-yr PFS; 53% 5-yr OS</td>
<td></td>
</tr>
<tr>
<td>Pollock et al., 2012</td>
<td>13</td>
<td>Salvage SRS</td>
<td>27% 5-yr DFS</td>
<td></td>
</tr>
<tr>
<td>Ferraro et al., 2014</td>
<td>4</td>
<td>GTR/STR+SRS</td>
<td>0% 3-yr PFS; 33% 3-yr OS</td>
<td></td>
</tr>
<tr>
<td>Zhao et al., 2015</td>
<td>37</td>
<td>GTR/STR ± Adjuvant EBRT</td>
<td>12% 5-yr PFS</td>
<td>Benefit: p = 0.039 for PFS; p = 0.006 for OS</td>
</tr>
</tbody>
</table>

± = with or without.
* Shaded region indicates uncontrolled case series.

Surgery

Sughrue et al. performed a retrospective review of 34 patients with primary WHO Grade III meningiomas that were treated with resection (GTR, near-total resection [NTR]) and EBRT.46 Forty-seven percent of patients experienced recurrence at a mean follow-up of 6.9 years. Their 2-, 5-, and 10-year PFS rates after primary surgery were 80%, 57%, and 40%, respectively. Some patients with recurrence elected against repeat surgery, allowing the authors to compare repeat surgery versus no surgery. Their analysis demonstrated a significant survival benefit with repeat surgery compared with no repeat surgery for recurrent MMs (EBM Level 3, Grade IC recommendation).

The important question underlying these observations is whether EOR for MMs significantly affects outcome. Durand et al. and Adeberg et al. independently demonstrated no association between EOR and outcome.21,22 MMs are often brain invasive and difficult to resect completely from the adjacent brain. Indeed, Sughrue et al. actually suggested that for both primary surgery and repeat surgery, NTR may carry survival benefit over GTR.46 Taken together, despite a clear benefit of EOR per se, retrospective data on Grade III meningiomas support a maximal but cautious resection strategy and consideration of even repeat surgery for recurrence.

Radiotherapy

Only a handful of retrospective studies on MMs compared adjuvant radiotherapy versus resection alone (Table 6). Durand et al. reported that radiotherapy was associated with increased OS in MMs, and Zhao et al. reported that radiotherapy was associated with increased PFS and OS in MMs.21,22 With WHO 2000/2007 Grade III tumors constituting only 1.6% of meningiomas and the preponderance of expert opinion in favor of radiotherapy for MMs,63 the true efficacy of radiotherapy on WHO Grade III meningiomas is not likely to be evaluated in a randomized fashion even with multiinstitutional efforts. However, several reports have shown a benefit with dose-escalation of radiotherapy.23,33,52 Hug et al. reviewed 16 malignant meningiomas to show that conformal, high-dose radiotherapy resulted in significant improvement of local control and a survival benefit for malignant meningiomas.33 Limited studies have also reported improved outcomes with dose escalation using proton or carbon ion radiotherapy.11,16 Interpretation of the data on EBRT must be taken with some caution because the majority of dose-response studies were performed prior to the WHO 2000/2007 classification. Nonetheless, together with modern studies,1,13,21,22,61,68,76 evidence supports the use of radiotherapy for Grade III meningiomas (EBM Level 3, Grade IC recommendation).

Chemotherapy

The use of chemotherapy for MMs has mainly been limited to recurrent disease. As mentioned earlier, the population treated with chemotherapy has been a mix of patients with WHO Grade II and III meningiomas. As with AMs, the majority of case series using chemotherapy for MMs have studied the effects of hydroxyurea, imatinib, somatostatin analogs, and angiogenesis inhibitors. Hydroxyurea and imatinib have shown limited efficacy. Conversely, select trials have suggested that angiogenesis inhibitors may play a role in salvage therapy for recurrent or refractory MMs (EBM Level 2, Grade 2B recommendation).30,55,56,63 Clearly, additional studies are needed for these formidable meningiomas.

Treatment Algorithm for MMs

Based on the available literature, we suggest an algorithm for MM management (Fig. 2). The limited number of decision points and treatment options in the algorithm reflects the paucity of literature on MMs as well as the lack of effective therapies after multiple recurrences. New approaches are needed for this rare malignancy.

Discussion

Here, we have reviewed the modern literature on AMs and MMs through the lens of key clinical decision points in meningioma management, extracted outcome measures for relevant cohorts, and classified recommendations using EBM. In summary, we make EBM Level 3, Grade IC
recommendations for the following strategies: 1) maximal safe resection of AMs and MMs; 2) active surveillance after GTR of AMs; 3) adjuvant radiation therapy after subtotal resection of AMs; and 4) adjuvant radiation therapy after resection of MMs. We have also found EBM Level 3, Grade 2C recommendations for 2 intriguing strategies that require further corroboration in future studies: 1) selective radiation therapy for AMs based on the absence of histopathological necrosis; and 2) adjuvant SRS for small residual AMs after STR. It must be noted, however, that the entire body of AM and MM literature upon which this study rests is limited on multiple fronts. Notably, many studies consist of small numbers of patients with limited follow-up. Furthermore, given their retrospective nature, these studies all suffer from inhomogeneous data sets, nonrandom assignment to different management strategies, and inconsistent follow-up. As a result, the findings of this study are subject to revision pending results from ongoing prospective interventional studies.

We would like to particularly emphasize a key limitation of the existing data: a lack of long-term follow-up. The average age of a patient with newly diagnosed meningioma is in the 50s,\textsuperscript{76,78} and the average life expectancy in English-speaking countries is currently in the late 70s. However, the literature primarily consists of outcomes reported at 5 years. Patients with AM and MM continue to develop problems from their disease or sequelae from treatment at 10 or 20 years following initial surgery. A true understanding of the long-term, natural history of AM and MM will likely not be elucidated by recently initiated prospective, randomized studies in the near term. Instead, in the meantime, multicenter, retrospective cohort studies pooling individual patient data may be useful in the determination of effective treatment strategies. This study design has been used effectively in cardiology to determine the differential effects of treatment on subsets of patients,\textsuperscript{32} an approach that may be useful since recent AM literature suggests that subsets of tumors may respond differently to radiotherapy.\textsuperscript{77} In this regard, clinical correlation with the rapidly accumulating genetic data on meningiomas will certainly also help to tailor treatment recommendations for Grade II and III meningiomas.\textsuperscript{7,14,15}

Conclusions

This study reviews reported management strategies and outcomes for patients with WHO Grade II and III meningiomas in an effort to develop a logical algorithm for evidence-based treatment recommendations. The evidence primarily supports safe GTR of AMs or, if GTR is not feasible, STR with adjuvant radiotherapy. A safe maximal resection should be attempted for Grade III meningiomas followed by radiotherapy, with consideration for additional surgeries following recurrence. Additional treatments may be considered in select circumstances. The treatment algorithm and recommendations regarding therapies following surgery can serve as a current guide to practicing.
neurosurgeons until prospective data from RTOG (Radiation Therapy Oncology Group) 0539 (clinical trial no. NCT00895622) becomes available.

References


Author Contributions
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