Meningiomas are the second most common primary brain tumor and the most common extraaxial intracranial neoplasm. The World Health Organization (WHO) grading scheme classifies tumors based on histology, and it is the most powerful predictor of tumor recurrence following treatment and of overall survival. The vast majority of meningiomas are benign, or WHO Grade I. Following the WHO’s 2007 update of the diagnostic criteria for meningioma grading, the proportion of intracranial meningiomas histologically defined as atypical, or WHO Grade II, increased from 5% to 20%–35%. Anaplastic meningiomas, which are WHO Grade III, remain rare and comprise only 1%–2% of all meningiomas. Because Grade II and III meningiomas possess an intrinsically higher proliferation rate than Grade I meningiomas, their rate of recurrence following single or multimodality therapies is much higher.

The current WHO criteria, last updated in 2007, for atypical meningiomas are at least 4 mitotic figures per 10 high-powered fields (hpf) or at least 3 of the following histological characteristics: loss of lobular architecture (for example, sheeting), hypercellularity, prominent nucleoli, or small cells with high nucleus-to-cytoplasm ratios, foci of spontaneous necrosis, and brain invasion. The WHO criteria for anaplastic meningiomas are at least 20 mitotic figures per 10 hpf or focal or diffuse dedifferentiation resulting in carcinoma-, sarcoma-, or melanoma-like appearance.

Radiosurgery has been shown to be an effective primary or adjunctive treatment for Grade I meningiomas, especially for those located in regions where aggressive resection carries an especially high risk of operative morbidity, such as the skull base. However, the role of radiosurgery in the treatment of Grade II and III meningiomas is not well established, and the literature describing the radiosurgical outcomes for this uncommon subset of meningiomas is relatively sparse.

We review the radiosurgery literature for WHO Grade II and III intracranial meningiomas with an emphasis on predictors of recurrence and survival.

Methods

Utilizing PubMed, we performed a comprehensive
literature search for all radiosurgery series reporting treatment outcomes for WHO Grade II and III intracranial meningiomas using the search terms “radiosurgery,” “Gamma Knife,” “CyberKnife,” meningioma,” “WHO Grade II,” “WHO Grade III,” “atypical,” and “anaplastic.” Single case reports and case series comprising fewer than 10 cases of Grade II or III lesions were excluded. We identified 19 intracranial meningioma radiosurgery series that were published between 1998 and 2013 and included at least 10 cases of WHO Grade II or III lesions. All studies were single-center, retrospective chart reviews and therefore presented Class III evidence. Six of the meningioma radiosurgery series included treatment results for WHO Grade I tumors as well.11,18,20,24,25,40

The median number of patients per series was 22 (range 12–50 patients). A total of 647 Grade II and III tumors were treated, with a median of 30 tumors per series (range 12–87 tumors). Most patients underwent resection prior to radiosurgery. The proportion of meningiomas that were treated with radiation therapy prior to radiosurgery ranged from 0% to 80% (median 37%). The median tumor volume was 2.2–14.6 cm³, the median radiosurgical margin dose range was 14–21 Gy, and the median reported range of radiological follow-up duration was 22–72 months. The type of radiosurgery (Gamma Knife, CyberKnife, or linear accelerator), number of patients and tumors, preradiosurgery treatment with external beam radiation therapy (EBRT), tumor volume, radiosurgical margin dose, follow-up duration, progression-free survival (PFS), and complication rates were noted. Additionally, we noted any predictors of radiosurgical tumor control as determined by univariate or multivariate statistical analysis.

**Results**

The radiosurgery outcomes for WHO Grade II and III meningiomas are summarized in Table 1.3,5,8,11–15,17,18,20,24,25,27,28,33,40,43,45

**Tumor Control**

The 5-year PFS was reported separately for Grade II meningiomas in 4 series and was 25%–83% (median 59%).3,13,24,40 Similarly, 5-year PFS was reported separately for Grade III meningiomas in 4 series and was 0%–72% (median 13%).13,24,28,40 Rates of PFS were reported for Grade II and III tumors without distinction between grades in 6 series and were 37%–73% at 2 years (median 50%) and 40%–67% at 5 years (median 48%).8,15,17,27,35,45 In most series, tumor control afforded by stereotactic radiosurgery (SRS) was generally better for Grade II meningiomas than for Grade III ones.

Pollock et al. reviewed 50 cases involving patients with Grade II (n = 37) and III (n = 13) meningiomas (71 tumors) who were treated with radiosurgery.33 The median tumor volume was 14.6 cm³ and the median margin dose was 15 Gy. Nine patients (18%) underwent repeat radiosurgery, including 2 patients who each underwent 2 repeat radiosurgical treatments (10%). At 1 and 5 years after radiosurgical treatment, the disease-specific survival rates were 90% and 62%, the local tumor control rates were 85% and 45%, and the PFS rates were 76% and 40%, respectively. Tamura et al. described the radiosurgical outcomes for 16 patients with atypical (n = 9) and anaplastic (n = 7) meningiomas and reported successful tumor control in 29% (mean follow-up 41 months) and failed tumor control in the remaining 71% (mean follow-up 31 months).33 We recently reported our results from the radiosurgical treatment of 13 patients with Grade II (n = 11) or III (n = 2) meningiomas.45 The PFS rates at 1, 2, 3, and 4 years were 92%, 73%, 63%, and 31%, respectively.

Most studies adequately powered to detect a difference in tumor control between Grade II and III meningiomas found significantly better tumor control in Grade II tumors. Harris et al. reviewed the radiosurgical outcomes for 30 patients with atypical (n = 18) or anaplastic (n = 12) meningiomas.13 The actuarial 5-year PFS was significantly higher in the patients with atypical meningioma than in those with anaplastic meningioma (83% vs 72%, p = 0.018). In a large study of 972 patients with 1045 intracranial meningiomas treated with radiosurgery, Kondziołka et al. treated 87 patients with WHO Grade II (n = 56) or III (n = 31) meningiomas.35 In contrast to Grade I meningiomas, which had a tumor control rate of 93%, Grade II and III meningiomas had tumor control rates of 50% and 17%, respectively. Kim et al. reported the radiosurgical outcomes for 35 patients with 49 atypical (n = 30) or anaplastic (n = 19) meningiomas and found that the atypical cohort had significantly longer overall survival (p = 0.038) and actuarial 2-year PFS than the anaplastic cohort (53% vs 10%, p < 0.001).17

Typically, the magnitude of the radiosurgical margin dose correlates with the tumor grade, although this can vary across institutions. Additionally, tumor location (for example, skull base lesions adjacent to radiosensitive structures such as the optic apparatus or brainstem), tumor volume, and prior treatment with EBRT or radiosurgery may affect the margin dose delivered to the lesion. Margin doses generally range from 16 to 20 Gy for Grade II meningiomas and from 18 to 22 Gy for Grade III meningiomas. In a study of 12 patients harboring 30 atypical (n = 25) or anaplastic (n = 5) meningiomas, Kano et al. reported significantly higher PFS (p = 0.014) for patients treated with a margin dose of 20 Gy (85%, 63%, 63% at 1, 2, and 5 years, respectively) compared with those treated with a margin dose less than 20 Gy (39%, 29%, 29% at 1, 2, and 5 years, respectively).15

Compared with EBRT, which may be used to irradiate a postsurgical resection cavity including a margin of normal brain parenchyma, radiosurgery is only used to target radiologically demonstrable tumor and relatively spares normal tissue due to its steep dose fall-off (gradient index). While this steep gradient index theoretically decreases the risk of radiation-induced toxicity associated with radiosurgery compared with EBRT, it may also predispose radiosurgically treated patients to tumor recurrences in regions adjacent to or at the margin. Attia et al. treated 24 patients with atypical meningiomas and reported 14 cases of treatment failure (58%) including 8 recurrences in the radiosurgical treatment field (33%), 4 recurrences adjacent to but outside the treatment field (17%), and 2 recurrences distant to the treatment field.
Radiosurgery for WHO Grade II and III meningiomas

TABLE 1: Summary of radiosurgery series for WHO Grade II and III meningiomas*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Radiation System</th>
<th>No. of Pts/ Tumors</th>
<th>% of Pts w/ Prior RT</th>
<th>Tumor Vol (cm³)</th>
<th>Margin Dose (Gy)</th>
<th>Follow-Up (mos)</th>
<th>PFS</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hakim et al., 1998</td>
<td>LINAC</td>
<td>NR/44</td>
<td>NR</td>
<td>4.1†</td>
<td>15†</td>
<td>NR</td>
<td>5%†</td>
<td></td>
</tr>
<tr>
<td>Ojemann et al., 2000</td>
<td>GK</td>
<td>22/26</td>
<td>23</td>
<td>NR</td>
<td>16</td>
<td>29</td>
<td>32% at 2 yrs, 26% at 5 yrs</td>
<td>23%</td>
</tr>
<tr>
<td>Kobayashi et al., 2001</td>
<td>GK</td>
<td>12/12</td>
<td>0</td>
<td>NR</td>
<td>17</td>
<td>32</td>
<td>NR</td>
<td>14%‡</td>
</tr>
<tr>
<td>Stafford et al., 2001</td>
<td>GK</td>
<td>22/22</td>
<td>73</td>
<td>8.2§</td>
<td>16§</td>
<td>40§</td>
<td>68% at 5 yrs for Gr II, 0% at 5 yrs for Gr III</td>
<td>13%§</td>
</tr>
<tr>
<td>Harris et al., 2003</td>
<td>GK</td>
<td>30/36</td>
<td>80</td>
<td>13.5</td>
<td>15</td>
<td>28</td>
<td>83% at 5 yrs for Gr II, 72% at 5 yrs for Gr III</td>
<td>3%</td>
</tr>
<tr>
<td>Huffman et al., 2005</td>
<td>GK</td>
<td>15/21</td>
<td>7</td>
<td>5.0</td>
<td>16</td>
<td>35</td>
<td>NR</td>
<td>7%</td>
</tr>
<tr>
<td>Malik et al., 2005</td>
<td>GK</td>
<td>NR/23</td>
<td>NR</td>
<td>7.3¶</td>
<td>20/20¶</td>
<td>44¶</td>
<td>49% at 5 yrs for Grade II, 0% at 5 yrs for Grade III</td>
<td>3%¶</td>
</tr>
<tr>
<td>Kono et al., 2007</td>
<td>LINAC</td>
<td>12/30</td>
<td>17</td>
<td>2.9/4.4</td>
<td>20/18</td>
<td>44/43</td>
<td>48% at 2 yrs, 48% at 5 yrs</td>
<td>17%</td>
</tr>
<tr>
<td>Mattozo et al., 2007</td>
<td>LINAC</td>
<td>NR/35</td>
<td>NR</td>
<td>2.2**</td>
<td>16**</td>
<td>42**</td>
<td>100% at 3 yrs for Gr II, 0% at 1 yr for Gr III</td>
<td>0</td>
</tr>
<tr>
<td>Kondziolka et al., 2008</td>
<td>GK</td>
<td>NR/87</td>
<td>NR</td>
<td>7.4††</td>
<td>14††</td>
<td>48††</td>
<td>NR</td>
<td>8%††</td>
</tr>
<tr>
<td>Choi et al., 2010</td>
<td>GK</td>
<td>25/34</td>
<td>20</td>
<td>5.3</td>
<td>21</td>
<td>22</td>
<td>90% at 2 yrs, 47% at 3 yrs</td>
<td>8%</td>
</tr>
<tr>
<td>El-Khatib et al., 2011</td>
<td>LINAC</td>
<td>16/29</td>
<td>19</td>
<td>4.8</td>
<td>14</td>
<td>60</td>
<td>67% at 5 yrs, 58% at 10 yrs</td>
<td>6%</td>
</tr>
<tr>
<td>Attia et al., 2012</td>
<td>GK</td>
<td>24/24</td>
<td>46</td>
<td>5.5/7.9</td>
<td>14</td>
<td>43</td>
<td>40% at 2 yrs, 25% at 5 yrs</td>
<td>8%</td>
</tr>
<tr>
<td>Kim et al., 2012</td>
<td>GK</td>
<td>35/49</td>
<td>46</td>
<td>3.5</td>
<td>16</td>
<td>29</td>
<td>37% at 2 yrs, 25% at 3 yrs</td>
<td>7%</td>
</tr>
<tr>
<td>Pollock et al., 2012</td>
<td>GK</td>
<td>50/71</td>
<td>40</td>
<td>14.6</td>
<td>15</td>
<td>38</td>
<td>76% at 1 yr, 40% at 5 yrs</td>
<td>26%</td>
</tr>
<tr>
<td>Hardesty et al., 2013</td>
<td>GK/Ck</td>
<td>32/35</td>
<td>NR</td>
<td>11.4</td>
<td>14‡‡</td>
<td>72</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mori et al., 2013</td>
<td>GK</td>
<td>30/36</td>
<td>37</td>
<td>8.6</td>
<td>17</td>
<td>28</td>
<td>52% at 2 yrs, 34% at 3 yrs</td>
<td>NR</td>
</tr>
<tr>
<td>Tamura et al., 2013</td>
<td>GK</td>
<td>16/21</td>
<td>NR</td>
<td>7.1</td>
<td>19</td>
<td>37</td>
<td>29% at 41 mos</td>
<td>NR</td>
</tr>
<tr>
<td>Williams et al., 2013</td>
<td>GK</td>
<td>13/13</td>
<td>46</td>
<td>7.0</td>
<td>16</td>
<td>50</td>
<td>92% at 1 yr, 31% at 4 yrs</td>
<td>62%</td>
</tr>
</tbody>
</table>

* Tumor volume, margin dose, and follow-up are reported as median or mean values. CK = CyberKnife; GK = Gamma Knife; Gr = WHO grade; LINAC = linear accelerator; NR = not reported; pts = patients; RT = radiotherapy.
† This series included 106 patients with WHO Grade I meningiomas and 5 patients with meningiomatosis.
‡ This series included 87 patients with WHO Grade I meningiomas.
§ This series included 168 patients with WHO Grade I meningiomas.
¶ This series included 286 WHO Grade I meningiomas.
** This series included 5 patients with WHO Grade I meningiomas and 12 WHO Grade II and III meningiomas treated with fractionated radiotherapy.
†† This series included 424 WHO Grade I meningiomas and 536 tumors without histological diagnosis.
‡‡ This was the median margin dose for patients treated with Gamma Knife (n = 19). Some patients treated with CyberKnife (n = 13) received hypofractionated radiosurgery.

(8%). In our series, 5 (45%) of the 11 cases of recurrence were out-of-field recurrences.45

Prior treatment with fractionated radiotherapy may reduce the efficacy of radiosurgery, although whether this is due to desensitization to radiosurgery or a selection bias toward inherently more aggressive tumors is unknown. Choi et al. treated 25 patients with 34 atypical meningiomas with CyberKnife radiosurgery and showed that patients who did not receive prior radiotherapy (80%) had locoregional tumor control rates of 93% and 54%, respectively, at 2 and 3 years after radiosurgery.3 Despite the available literature, the benefit of radiosurgery to patients with nonbenign meningiomas remains a subject of debate. In a large series of 228 patients with atypical meningioma treated with resection, Hardesty et al. did not find a difference in PFS between the 32 patients treated with adjuvant radiosurgery and those whose cases were managed expectantly.15

While radiosurgery may afford definitive treatment for Grade I meningiomas, it is not usually adequate for long-term control of Grade II and III tumors.20,38 Therefore, patients frequently require additional treatment for tumor recurrence; the modality depends on the patient’s age, comorbidities, the size and pattern of recurrence, and prior treatments. Of 13 patients with Grade II or III meningioma treated at our institution, 11 underwent further treatment after radiosurgery (85%). Ten patients had repeat resections, 8 had repeat radiosurgery, 3 had EBRT, and 2 had chemotherapy following initial radiosurgical treatment. Of the 20 radiation-naïve patients treated with SRS in another series, 5 (25%) underwent additional treatment for tumor recurrence after SRS, including surgery in 3 cases, single-session radiosurgery in 2 cases (scheduled in a third case at the time of writing), EBRT in 2 cases, and multisession radiosurgery in 1 case.3 In a large series of 50 cases of Grade II or III meningioma treated with SRS, tumor progression was noted in 15 (30%) of 50 patients; 12 of these patients underwent further treatment—resection in 9 cases, repeat radiosurgery in 9 cases, and EBRT in 3 cases.35
Prognostic Factors

By identifying patient-specific, tumor-specific, and treatment characteristics that are associated with favorable and unfavorable radiosurgical outcomes, we may improve the future selection and counseling of patients harboring Grade II and III meningiomas. A number of factors have been identified through statistical analysis to be associated with successful or failed tumor control. Due to the relatively small number of lesions in most series, statistically analyses may have been underpowered and therefore unable to identify potentially significant predictors of radiosurgical outcome.45

Ojemann et al. reported the first distinct cohort of patients (n = 22) with nonbenign meningiomas who were treated with radiosurgery.28 Age less than 50 years and tumor volume less than 8 cm³ were determined to be independent predictors of improved PFS and overall survival. In the study by Harris et al., early radiosurgery and smaller tumor volume were significant predictors of improved PFS, and younger age was a significant predictor of improved overall survival as determined by multivariate analysis.43 Multivariate analysis by Kondziolka et al. determined higher WHO grade to be a significant predictor of decreased overall survival, disease-specific survival, and local tumor control.30 Choi et al. used univariate analysis to identify number of recurrences prior to radiosurgery (p = 0.046), radiosurgical treatment within 6 months of resection (p = 0.03), and lower age (p = 0.01) to be associated with tumor control.5

From the series by Attia et al., multivariate analysis determined conformity index, defined as the ratio of the prescription isodose volume to the tumor volume, to be a predictor of recurrence in or adjacent to the treatment field (p = 0.04).1 Additionally, radiosurgical dose greater than 14 Gy was significantly associated with increased PFS (p = 0.01) in the same study. Multivariate analysis by Kim et al. determined that a mitotic index of greater than 8 per 10 hpf (p = 0.014) and MIB-1 labeling index greater than 8% (p = 0.012) were independent predictors of worse local tumor control.13 Another multivariate analysis by Pollock et al. identified prior EBRT and increased tumor volume to be independent predictors of worse disease-specific survival and local tumor control.39 Prior EBRT was also independently associated with decreased PFS (p = 0.002). Recently, Tamura et al. found lower tumor volume (p = 0.02), increased margin dose (p = 0.04), and increased maximum dose (p = 0.02) to be predictors of tumor control.43 WHO grade was not associated with tumor control (p = 0.42) although the number of tumors in each cohort was relatively low.

Complications

Due to overlapping time course of radiosurgery-induced complications, which invariably present in a delayed fashion, and clinical decline due to tumor progression, it may, at times, be difficult to distinguish between the two phenomena. The radiosurgery-related complication rates for Grade II and III meningiomas varied significantly from 0% to 62% (median 8%). Harris et al. reported a median time to neurological deterioration of 48 months without a difference between the atypical and anaplastic cohorts.13 In a large study of over 1000 meningiomas, which included meningiomas of all grade, Kondziolka et al. also did not find that tumor grade was significantly associated with radiosurgery-induced complications.56 Pollock et al. found that radiosurgery-related complications developed in 26% of patients (major complications in 18% and minor in 8%).31 Although the preradiosurgery Karnofsky Performance Status (KPS) score was not reported by Tamura et al., the study reported postradiosurgery KPS scores of least 80 in 19%, and less than 80 in 81% of patients including a 31% mortality rate secondary to tumor progression.43 Williams et al. reported a median postradiosurgery KPS score of 80 (range 40–100), which was decreased from the median preradiosurgery KPS of 90 (range 60–100).45 The rate of neurological decline following radiosurgery was 62%, and the decline occurred at a median interval of 6 months after treatment (range 2–16 months). In that series, new or worsening visual dysfunction developed in 5 patients (38%, tumors located at the anterior clinoid process, posterior parasagittal region adjacent to the occipital lobe, and cavernous sinus), new-onset seizures in 3 (23%), ataxia in 2 (15%, both with tumors located at the tentorium), and hypopituitarism in 1 (8%, tumor located in the cavernous sinus).

Discussion

Current management of atypical and malignant meningiomas includes initial resection with or without adjuvant radiation therapy in the form of EBRT or stereotactic radiosurgery, depending on the preferences and experience of the treating physician and institution as well as the patient. While WHO Grade I meningiomas may be successfully managed by gross-total resection (GTR) alone, Grade II and III meningiomas are significantly more difficult to control without adjuvant radiation therapy.26,39 Multimodality management, including surgery, radiation therapy, radiosurgery, and chemotherapy, may be required for patients with atypical and malignant meningiomas.

Resection of WHO Grade II and III Meningiomas

The primary treatment for most Grade II and III meningiomas remains resection. The goals of surgery are to achieve maximal safe cytoreduction, decrease local mass effect, decompress critical neural structures, and obtain tissue for histopathological diagnosis. Since the WHO classification is based on histology, some degree of surgical debulking is necessary to confirm the diagnosis of a nonbenign meningioma regardless of neuroimaging characteristics. Additionally, even subtotal resection of the portions of tumor abutting radiosensitive structures, such as cranial nerves and the brainstem, may allow delivery of an increased adjuvant radiation dose to the remainder of the lesion by increasing the distance between the residual tumor and high-risk structures. Repeat resection carries a higher risk of operative morbidity and mortality than the initial resection due to scarring, poorly demarcated anatomy, frail neovascularized tissue, and increased risk of surgical site infection.32 Goyal et al. reported a substantially higher rate of local
tumor control for patients with atypical meningioma who underwent GTR compared with those who had subtotal resection (87% vs 17% at 10 years, \( p = 0.02 \)). Sughrue et al. analyzed the surgical outcomes for 63 patients with WHO Grade II or III meningiomas, including 34 patients undergoing initial resection and 29 patients who had undergone previous resection and presented with recurrent intracranial disease.\(^5\) For the patients undergoing initial resection, the rates of recurrence-free survival at 5 and 10 years were 57% and 40%, respectively. In a statistical analysis controlling for age and KPS score, patients who underwent repeat surgery at the time of recurrence had significantly better survival than those who did not (\( p = 0.02 \)). The rates of postoperative surgical morbidity, surgical mortality, and medical morbidity were 21%, 2% and 10%, respectively.

Palma et al. evaluated the surgical outcomes for 42 patients with Grade II and 29 patients with Grade III meningioma.\(^9\) The 10-year survival for patients with Grade II meningioma was significantly higher than for those with Grade III meningioma (79% vs 35%, \( p = 0.001 \)). Of the 23 meningiomas that had initially been Grade II and had recurred, 26% underwent malignant transformation to Grade III lesions. Simpson Grade I resection was associated with better survival than Simpson Grade II or III resection (\( p < 0.0003 \)). As is the case for benign meningiomas, safely maximizing the extent of resection for Grade II and III meningiomas correlates with improved overall survival and PFS.\(^2\)\(^9\)\(^3\)\(^9\) Therefore, every effort should be made to optimize surgical intervention for these lesions at the outset of treatment. However, we caution against overly aggressive resection with the goal of obtaining a Simpson Grade I outcome.\(^42\) It may be preferable to control residual tumor with EBRT or radiosurgery rather than risk afflicting the patient with significant operative morbidity.

**Fractionated EBRT for WHO Grade II and III Meningiomas**

Resection alone is unable to provide long-term control of Grade II and III meningiomas in the majority of cases. Fractionated EBRT has been demonstrated to decrease local tumor recurrence and improve survival of patients with Grade II and III meningiomas, but it is not without adverse effects.\(^16\) In a large series of 108 patients with atypical meningiomas who underwent GTR, Aghi et al. reported a 30% recurrence rate in the 100 patients who did not receive postoperative EBRT (mean follow-up 3.2 years) compared with 0% in the 8 patients who received postoperative EBRT (mean follow-up 3.1 years).\(^2\) Due to the small size of the EBRT cohort, the difference in recurrence rates did not reach statistical significance (\( p = 0.10 \)).

Pasquier et al. analyzed the outcomes for 119 patients with Grade II (\( n = 82 \)) and III meningiomas (\( n = 37 \)) who underwent postoperative EBRT with a mean total dose of 54.6 Gy delivered in 1.8- or 2-Gy fractions.\(^36\) The extent of resection was Simpson Grade I–III in 71% of tumors, and EBRT was delivered after the initial resection in 79% of cases. Overall survival was 65% at 5 years and 51% at 10 years, and it was significantly affected by age greater than 60 years (\( p = 0.001 \)) and high mitotic rate (\( p = 0.02 \)) based on multivariate analysis. Of note, extent of resection and EBRT dose were not significant prognostic factors in this study, and the rates of overall survival and disease-specific survival were not significantly different for Grade II compared with Grade III tumors. Delayed radiation-induced toxicity was observed in 13% of patients. By contrast, Adeberg et al. treated 85 patients with Grade II (\( n = 62 \)) and III (\( n = 23 \)) meningiomas with fractionated radiotherapy (mean dose 57.6 Gy in 1.8- to 3-Gy fractions) and noted a significant difference between Grade II and III tumors with respect to both overall survival (81% vs 53% at 5 years, respectively; \( p = 0.022 \)) and PFS (50% vs 13% at 5 years, respectively; \( p = 0.017 \)).\(^1\)

In a study of 13 patients with Grade III meningiomas, the 3 patients who received adjuvant EBRT had a median survival of 5.4 years compared with 2.5 years in the 10 patients who did not undergo postoperative EBRT.\(^3\) As in the aforementioned study by Aghi et al., the difference was not statistically significant (\( p = 0.10 \)) due to the few number of patients receiving EBRT.\(^2\)\(^36\) Mair et al. evaluated the effect of postoperative EBRT on 114 patients who underwent first-time resection of atypical meningiomas.\(^23\) GTR, defined as Simpson Grade I or II, was achieved in 58% of cases, and postoperative radiotherapy was delivered to 26% of patients (mean dose 51.8 Gy in 28 fractions). GTR was significantly associated with improved PFS (\( p = 0.018 \)) but EBRT was not (\( p = 0.086 \)). In the subgroup of patients with subtotal resection, EBRT demonstrated a significant benefit to increased PFS (\( p = 0.043 \)). Currently, postoperative EBRT for Grade II and III meningiomas remains a subject of debate, especially for patients who have undergone GTR, but is an important part of treatment for those who have undergone a subtotal resection. While most data have shown some degree of benefit from postoperative EBRT, all of the studies are retrospective and many are statistically underpowered.

**The Role of Radiosurgery for WHO Grade II and III Meningiomas**

In our literature review of approximately 600 Grade II and III meningiomas treated with radiosurgery, we found a wide variation in outcomes. The PFS rates at 5 years were 25%–83% for Grade II tumors (median 59%) and 0%–72% for Grade III tumors (median 13%). The median radiosurgery-related complication rate was 8% (range 0%–62%). The relatively small number of patients (median 22) and tumors (median 30) in most of the studies resulted in significant limitations on the power of the statistical analyses. Nevertheless, a myriad of factors were shown to be associated with PFS, disease specific survival, or overall survival including patient age, tumor volume, WHO grade, mitotic index, radiosurgical margin and maximum dose, conformity index, timing of treatment, prior EBRT, and number of tumor recurrences prior to treatment.\(^1\)\(^2\)\(^3\)\(^5\)\(^13\)\(^15\)\(^17\)\(^18\)\(^28\)\(^43\)

Due to variance in patient populations, tumor characteristics, and outcome measures, it remains difficult to delineate the specific efficacy of radiosurgery for Grade II and III meningiomas. Authors of some series combined Grade I tumors with Grade II and III tumors without reporting the outcomes separately by grade.\(^1\)\(^11\)\(^20\)\(^25\)\(^40\) Others did not report the proportion of patients who received prior EBRT, which has been shown to predict poorer radiosur-
gical tumor control. Further complicating any comparison across different meningioma radiosurgery series is the 2007 change in the WHO diagnostic criteria for Grade II meningiomas, which drastically increase the proportion of meningiomas classified as atypical. Therefore, the Grade II meningiomas defined by the previous WHO criteria may represent lesions that are histologically and biologically different from those defined by the current criteria.

In many cases, when patients present for radiosurgery, EBRT has already failed (median 39%). These tumors may have acquired a degree of radioresistance following previous irradiation or they may represent more inherently aggressive lesions. Also, patients who have previously been treated with EBRT frequently require a reduction in SRS dose. Additionally the optimal timing of postoperative radiosurgery is unknown. Patients with significant residual tumor after subtotal resection may be offered upfront radiosurgical treatment. While some have suggested that EBRT to the tumor cavity after GTR may delay recurrence, there is currently no indication that radiosurgery should be considered following complete or near-complete macroscopic resection.

Despite the multitude of uncertainties that plague our understanding of radiosurgery outcomes for patients with Grade II and III meningiomas, it is clear from the current literature that radiosurgery does provide some degree of tumor control for the majority of patients, but this control is not always long term. Therefore, continued basic science, translational, and clinical research efforts are necessary to improve outcomes for this subset of aggressive tumors. Prospective clinical trials evaluating the risk-benefit profile of conservative management, EBRT, and radiosurgery in the setting of residual and recurrent disease are necessary. However, due to the relatively low prevalence of Grade II and III meningiomas compared with Grade I tumors, it is unlikely that a prospective trial will be able to accrue a statistically adequate number of patients.

Radiosensitizing agents may potentiate lower margin doses of EBRT or radiosurgery, thereby better sparing normal brain tissue and minimizing radiation-induced adverse effects. Improved understanding of the molecular biology of meningiomas and promoters of tumor progression may provide avenues for developing effective targeted agents or immunotherapies. Currently, there are no chemotherapeutic regimens that effectively treat meningiomas, but agents such as bevacizumab are being evaluated for the treatment of Grade II and III meningiomas. Finally, hypofractionated radiosurgery delivery systems, such as the Gamma Knife Extend (Elekta Instruments AB) may expand the versatility of radiosurgical treatment and ultimately result in better outcomes for patients harboring Grade II and III meningiomas.

Conclusions

WHO Grade II and III meningiomas are difficult to treat successfully. Despite multimodality management, including resection, EBRT, and radiosurgery, the long-term survival for patients harboring these lesions remains relatively poor, especially for those harboring Grade III lesions. Furthermore, the combined neurological morbidity from multiple treatment regimens accumulates over time. Radiosurgery appears to enhance tumor control and overall survival in this patient population, but the specific role for radiosurgery in Grade II and III meningiomas is not fully defined. Additional high-quality studies are required to improve our understanding of radiosurgery’s safety, efficacy, and optimal timing in relation to resection and fractionated radiation therapy.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sheehan, Ding, Starke. Acquisition of data: Ding, Hantzmon, Williams, Yen. Analysis and interpretation of data: Sheehan, Ding, Starke. Drafting the article: Ding. Critically revising the article: Sheehan, Ding, Starke, Williams, Yen. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Ding.

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Radiosurgery for WHO Grade II and III meningiomas.

Neurosurgery 42:446–454, 1998


Accepted September 4, 2013.
Please include this information when citing this paper: DOI: 10.3171/2013.9.FOCUS13364.