Histopathological features predictive of local control of atypical meningioma after surgery and adjuvant radiotherapy

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OBJECTIVE The goal of this study was to investigate the impact of adjuvant radiotherapy (RT) on local recurrence and overall survival in patients undergoing primary resection of atypical meningioma, and to identify predictive factors to inform patient selection for adjuvant RT.

METHODS One hundred eighty-two patients who underwent primary resection of atypical meningioma at a single institution between 1993 and 2014 were retrospectively identified. Patient, meningioma, and treatment data were extracted from the medical record and compared using the Kaplan-Meier method, log-rank tests, multivariate analysis (MVA) Cox proportional hazards models with relative risk (RR), and recursive partitioning analysis.

RESULTS The median patient age and imaging follow-up were 57 years (interquartile range [IQR] 45–67 years) and 4.4 years (IQR 1.8–7.5 years), respectively. Gross-total resection (GTR) was achieved in 114 cases (63%), and 42 patients (23%) received adjuvant RT. On MVA, prognostic factors for death from any cause included GTR (RR 0.4, 95% CI 0.1–0.9, p = 0.02) and MIB1 labeling index (LI) ≤ 7% (RR 0.4, 95% CI 0.1–0.9, p = 0.04). Prognostic factors on MVA for local progression included GTR (RR 0.2, 95% CI 0.1–0.5, p = 0.002), adjuvant RT (RR 0.2, 95% CI 0.1–0.4, p < 0.001), MIB1 LI ≤ 7% (RR 0.2, 95% CI 0.1–0.5, p < 0.001), and a remote history of prior cranial RT (RR 5.7, 95% CI 1.3–18.8, p = 0.03). After GTR, adjuvant RT (0 of 10 meningiomas recurred, p = 0.01) and MIB1 LI ≤ 7% (RR 0.1, 95% CI 0.003–0.3, p < 0.001) were predictive for local progression on MVA. After subtotal resection, adjuvant RT (RR 0.2, 95% CI 0.04–0.7, p = 0.009) and ≤ 5 mitoses per 10 hpf (RR 0.1, 95% CI 0.03–0.4, p = 0.002) were predictive on MVA for local progression.

CONCLUSIONS Adjuvant RT improves local control of atypical meningioma irrespective of extent of resection. Although independent validation is required, the authors’ results suggest that MIB1 LI, the number of mitoses per 10 hpf, and brain or bone invasion may be useful guides to the selection of patients who are most likely to benefit from adjuvant RT after resection of atypical meningioma.

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KEYWORDS atypical meningioma; MIB1; radiation; radiotherapy; oncology

Meningiomas are the most common primary CNS neoplasm, and comprise 20%–35% of all primary brain tumors.9,26 Although most meningiomas are effectively treated with surgery, a subset follows an aggressive clinical course characterized by local recurrence and poor survival.8,26 Atypical meningiomas (WHO grade II) display intermediate aggressiveness between that of benign (WHO grade I) and anaplastic (WHO grade III) variants.8,23 Historically, maximal safe resection has been the primary treatment for atypical meningioma, but even

ABBREVIATIONS EBRT = external beam radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; GTR = gross-total resection; IQR = interquartile range; KPS = Karnofsky Performance Scale; LFFR = local freedom from recurrence; LI = labeling index; MVA = multivariate analysis; OS = overall survival; RPA = recursive partitioning analysis; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; STR = subtotal resection.


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after optimal resection, patients with atypical meningioma are at substantial risk of recurrence.3 Thus, some patients with atypical meningioma are treated with adjuvant radiotherapy (RT), but the indications for adjuvant RT, particularly after gross-total resection (GTR), have not been well established. Indeed, no prospective data are available to answer this question, although 3 clinical trials of adjuvant RT for atypical meningioma are currently ongoing (NCT03180268; ClinicalTrials.gov).16,32 As a result, criteria to guide adjuvant RT after resection of atypical meningioma is limited to data from retrospective studies with small sample sizes and mixed results that are confounded by differences in institutional practices. One histopathological factor that has been shown to have prognostic significance is the MIB1 labeling index (LI), which is a widely used marker of cellular proliferation across multiple tumor types,27,40 including atypical meningioma.11,26,29

Multiple studies have independently reported high rates of local control in patients receiving adjuvant RT following GTR of meningioma.1,2,5,14,21,34 Nevertheless, there is significant variability in treatment of atypical meningioma because limited data exist to identify patients who are most likely to benefit from adjuvant RT.35 The purpose of this study was to investigate the impact of adjuvant RT on local recurrence and overall survival (OS) in patients undergoing primary resection of atypical meningioma, and to identify predictive factors to guide patient selection for adjuvant RT.

Methods
Study Design and Patient Population

We performed a retrospective chart review of patients who underwent primary resection of atypical meningioma at a single institution between 1993 and 2014. Follow-up was monitored through May 2017. Study subjects were identified from institutional databases capturing all patients who underwent surgery for meningioma. Clinical and histopathological variables were collected from the electronic medical record, pathology databases, and radiology archives. This study was approved by the Institutional Review Board, Human Research Protection Program Committee.

Clinical and Histopathological Variables

Clinical variables assessed included age at the time of surgery, sex, meningioma location, extent of resection, preoperative Karnofsky Performance Scale (KPS) score, history of prior cranial RT, and receipt of adjuvant RT. Meningioma grade was based on the WHO criteria at the time of surgery, and all meningiomas included in subsequent analyses were WHO grade II. Retrospective review was performed for 67 cases (37%), and confirmed the diagnosis of atypical meningioma in all instances. Radiation modality, dose, and adverse events (Radiation Therapy Oncology Group [RTOG] grade > 1)90 were also collected from the medical record. Histopathological data collected from pathology archives included the following: 1) MIB1 LI; 2) the number of mitoses per 10 hpf; and reports of 3) sheeting or loss of architecture, 4) increased cellularity, 5) foci of spontaneous necrosis, 6) nuclear pleomorphism or atypia, 7) brain invasion, and 8) bone involvement. Gross-total resection (Simpson grade I–III) and subtotal resection (STR; Simpson grade > III) were defined radiographically based on postoperative imaging, in conjunction with Simpson grade as determined by the surgeon at the time of operation (52 patients, 29%). All postoperative scans occurred within 48 hours of surgery. If not explicitly stated, the KPS score was retrospectively determined based on the preoperative consultation records.

Results
Patient Characteristics and Clinical Outcomes

We identified 182 patients who underwent primary resection of atypical meningioma between 1993 and 2014 (Table 1). The median imaging follow-up was 4.4 years (interquartile range [IQR] 1.8–7.5 years), and the median survival status follow-up among all patients was 6.0 years (IQR 3.7–9.7 years). The median KPS score was 80 (IQR 60–80). A GTR was achieved in 114 cases (63%) and 42 patients (23%) received adjuvant RT. Adjuvant RT was more common after STR (p < 0.0001) and for skull base meningiomas (p = 0.02). Otherwise, there were no differences in patient age, sex, preoperative KPS score, history
of prior cranial RT, or histopathological features with and without adjuvant RT.

To account for changes in WHO grading criteria over the study period, we performed univariate analysis of demographic and tumor characteristics stratified by 3 time periods corresponding to WHO editions: 1993–2000, 2001–2007, and 2008–2014. There were no significant differences in patient age, sex, preoperative KPS score, skull base location, history of prior cranial RT, or extent of resection among the cases from these time periods, although there was a trend toward greater use of adjuvant RT over time (11%, 18%, and 30%, respectively; *p* = 0.06). In addition, there were no significant differences between MIB1 LI, mitoses/hpf, presence of brain invasion, recurrence (p = 0.13, log-rank test), or survival (p = 0.49, log-rank test) among the cases from these time periods.

The predominant radiation modality was external beam RT (EBRT) (86%, median dose 59.4 Gy, range 36–60 Gy); a minority of patients received adjuvant stereotactic radiosurgery (SRS) (14%). One patient with a history of prior craniospinal radiation for medulloblastoma received a reduced EBRT dose of 36 Gy. The median time to radiation treatment was 10.6 weeks, to allow for adequate postoperative healing. Grade 2+ adverse effects of RT occurred in 5 patients (12%). Two patients (5%) experienced radiation necrosis, 1 patient experienced progressive spastic lower-extremity paresis attributed to radiation, 1 patient experienced short-term visual blurring that improved with steroids, and 1 patient experienced transient radiation-induced encephalopathy that responded to steroids. One patient (3%) who experienced radiation necrosis developed intracranial hemorrhage following craniotomy for the necrosis, and died several months later.

The study design and Kaplan-Meier curves detailing clinical outcomes for patients based on extent of resection and adjuvant RT are shown in Figs. 1–3. During the study period, 51 patients experienced local recurrence (28%) and 45 died (25%). The LFFR at 5 years was 69% overall (95% CI 61%–77%), 72% with GTR versus 64% with STR (p = 0.03) (Fig. 2A), and 82% with RT versus 65% without RT (p = 0.08) (Table 1). The OS at 5 years was 86% overall (95% CI 81%–92%); 91% with GTR versus 81% with STR (p = 0.02) (Fig. 2B); and 85% with RT versus 87% without (p = 0.64). Cause of death was identified for 30 patients who died (67%). After censoring patients with an unknown cause of death, the disease-specific survival at 5 years was 93% overall (95% CI 89%–97%), 95% with GTR versus 92% with STR (p = 0.14, log-rank test), and 95% with RT versus 93% without (p = 0.86, log-rank test).

Clinical and histopathological factors associated with LFFR and OS on Kaplan-Meier analysis are summarized in Table 2. Prognostic factors on MVA (Table 3) for local progression included GTR (RR 0.19, 95% CI 0.06–0.54, *p* = 0.0018); adjuvant RT (RR 0.15, 95% CI 0.05–0.43, *p* = 0.0004); MIB1 LI ≤ 7% (RR 0.21, 95% CI 0.07–0.53, *p* = 0.0009); and a remote history of prior cranial RT (RR...
5.65, 95% CI 1.25–18.78, p = 0.03). With respect to the latter, 5 patients had a remote history of prior cranial RT for childhood leukemia, 6 for childhood nonmeningioma brain tumors, 1 for adult optic glioma, and 1 for vestibular schwannoma (Table 1). Prognostic factors on MVA for death from any cause included GTR (RR 0.35, 95% CI 0.14–0.86, p = 0.02); MIB1 LI ≤ 7% (RR 0.38, 95% CI 0.14–0.94, p = 0.04); and age at the time of surgery (RR 1.08 per year increase, 95% CI 1.05–1.12, p < 0.0001). No other clinical or histopathological features reached statistical significance for LFFR or OS on multivariate analysis.

### Adjuvant RT After GTR

There were 26 local recurrences after GTR (23%), none of which received adjuvant RT. After GTR, an MIB1 LI ≤ 7% was associated with improved LFFR on MVA (RR 0.06, 95% CI 0.003–0.32, p = 0.0004). There was a trend toward improved LFFR with adjuvant RT on univariate Kaplan-Meier analysis (p = 0.10) that reached statistical significance after adjusting for covariates on MVA (p = 0.01). Indeed, there were no recurrences in the 10 patients treated with GTR and adjuvant RT (Fig. 3A). The mean MIB1 LI for the 10 meningiomas treated with GTR and adjuvant RT was 9.5% ± 5.7% (range 3.6%–19.1%), which was not significantly different from the meningiomas treated with GTR alone (7.7% ± 5.6%, range 1.0%–30.0%). There was no significant difference in OS after GTR with or without adjuvant RT (Fig. 3B).

Recursive partitioning analysis was performed to identify variables associated with an elevated risk of local progression after GTR of atypical meningioma (Fig. 4). Consistent with MVA, the first partition was based on the MIB1 LI, with a cutoff of 7%: 2.2% of meningiomas with MIB1 LI ≤ 7% recurred (1 of 45), as opposed to 36% of meningiomas with MIB1 LI > 7% (25 of 69). Next, RPA partitioned meningiomas with MIB1 LI > 7% based on adjuvant RT, which again was consistent with MVA: none

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**TABLE 2. Univariate analysis of outcomes of atypical meningioma according to clinical and histopathological features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>LFFR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 yrs</td>
<td>0.8</td>
<td>0.24</td>
</tr>
<tr>
<td>Female</td>
<td>0.55</td>
<td>0.55</td>
</tr>
<tr>
<td>Skull base</td>
<td>0.68</td>
<td>0.97</td>
</tr>
<tr>
<td>KPS score &gt;70</td>
<td>0.17</td>
<td>0.77</td>
</tr>
<tr>
<td>GTR</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>RT</td>
<td>0.08</td>
<td>0.1</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIB1 LI ≤7%</td>
<td>&lt;0.0001</td>
<td>0.01</td>
</tr>
<tr>
<td>Mitoses/hpf ≤5</td>
<td>&lt;0.0001</td>
<td>0.29</td>
</tr>
<tr>
<td>Sheetings/loss of architecture</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Increased cellularity</td>
<td>0.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Small cell change</td>
<td>0.59</td>
<td>0.41</td>
</tr>
<tr>
<td>Foci of spontaneous necrosis</td>
<td>0.42</td>
<td>0.78</td>
</tr>
<tr>
<td>Nuclear pleomorphism/atrophy</td>
<td>0.31</td>
<td>0.82</td>
</tr>
<tr>
<td>Brain invasion</td>
<td>0.22</td>
<td>0.03</td>
</tr>
<tr>
<td>Bone involvement</td>
<td>0.38</td>
<td>0.51</td>
</tr>
<tr>
<td>Prior cranial RT</td>
<td>0.06</td>
<td>0.03</td>
</tr>
</tbody>
</table>

The p values were calculated by Kaplan-Meier analysis and log-rank tests. Boldface type indicates statistical significance. Covariates with p values ≤ 0.10 were included in subsequent MVAs and RPA.
of the tumors with MIB1 LI > 7% treated with GTR and adjuvant RT recurred (0 of 6), as opposed to 40% of tumors with MIB1 LI > 7% treated with GTR alone (25 of 63). Finally, RPA partitioned meningiomas with MIB1 LI > 7% that did not receive adjuvant RT based on brain or bone invasion: 33% of tumors with MIB1 LI > 7% but no brain or bone invasion treated with GTR alone recurred (13 of 40), as opposed to 52% of tumors with MIB1 LI > 7% and brain or bone invasion treated with GTR alone (12 of 23).

Adjuvant RT After STR
Sixty-eight patients underwent STR (37%), after which 32 received adjuvant RT (47%) and 25 tumors recurred (37%) (Table 1). Twenty-five percent of patients who received RT experienced recurrence (8 of 32) compared with 47% of those who did not receive RT (17 of 36). After adjusting for covariates on MVA, adjuvant RT (RR 0.18, 95% CI 0.04–0.66, p = 0.009) (Fig. 3C) and ≤ 5 mitoses per 10 hpf (RR 0.12, 95% CI 0.03–0.44, p = 0.0018) were predictive for local progression. There was no significant difference in OS after STR with or without adjuvant RT (Fig. 3D), and RPA failed to identify any robust variables associated with an elevated risk of local progression after STR of atypical meningioma.

Salvage Treatment at Recurrence
Of 51 patients in whom lesions recurred, 8 (16%) underwent repeat surgery (5 with adjuvant RT), 20 (39%) underwent SRS, 10 (20%) underwent EBRT, 1 (2%) was observed, and 12 (23%) were lost to follow-up. Tumors in 17 of 38 (45%) patients who underwent salvage treatment subsequently re-recurred, and the median time to recurrence was 3.1 years. Kaplan-Meier analysis did not reveal a significant difference in LFFR between patients treated with EBRT versus SRS at recurrence (p = 0.95, log-rank test), although there was a significant difference between patients treated at recurrence with RT versus surgery (p = 0.0006, log-rank test). In that regard, patients treated with surgery at recurrence were more likely to experience tumor re-recurrence (7 of 8 patients, 88%), with a median time to re-recurrence of 1.1 years.

Discussion
Key Findings
Adjuvant RT improved LFFR of atypical meningioma irrespective of the extent of resection in this single-institution cohort with intermediate to long-term follow-up. An MIB1 LI ≤ 7% was a strong predictive factor for longer LFFR and longer OS after GTR. Consistently, RPA identified a subset of atypical meningiomas with MIB1 LI > 7% treated with GTR that appeared to benefit most from ad-
Adjuvant RT After GTR of Atypical Meningioma

The literature arguing for or against adjuvant RT after GTR of atypical meningioma is controversial. Studies have shown questionable or no benefit, and some have suggested that brain invasion, bone invasion, and higher Simpson grade are associated with increased risk of recurrence, consistent with prior studies. Conversely, brain invasion was associated with increased recurrence, consistent with prior studies. Thus, after GTR, atypical meningiomas with a high MIB1 LI and brain or bone invasion may benefit most from adjuvant RT. Future studies identifying and validating risk factors for recurrence in atypical meningioma, as well as expanding on recently identified molecular and methylation-based markers of meningioma subtypes, are warranted.

Strengths and Limitations

The results of this study should be interpreted in the context of several strengths and limitations. With respect to strengths, our study included a relatively large number of patients with nearly 5 years of imaging follow-up, allowing for multivariate Cox modeling and investigation of multiple histopathological features in relation to LFFR and OS.

With respect to limitations, the retrospective nature of our study introduces the potential for selection bias among patients who received adjuvant RT. Patients with and without adjuvant RT did not differ in age, sex, KPS score, and preoperative risk factors. The significance of the difference in meningioma location to our findings is not clear. In addition, our finding of a benefit in LFFR with adjuvant RT after GTR, although concordant with other recent reports, should be interpreted in the context of our very small sample size of 10 patients.

Our finding that the small subset of patients who underwent repeat surgery at recurrence had a high rate of recurrence should be interpreted with caution, because it most likely represents a selection bias toward aggressively recurrent tumors, which were not amenable to radiosurgery or EBRT. Further studies examining outcomes among different salvage treatment modalities are warranted.

Determination of extent of resection in our study was based on postoperative imaging in conjunction with Simpson grade as reported by the surgeon. Although this definition of GTR mirrors clinical practice at our institution, questions remain with regard to the potential impact of the timing of postoperative scans, differences in institutional practices, and experience with the determination of resection extent, all of which may limit the generalizability of our results.

Another possible limitation of this study relates to the changes in WHO grading criteria for atypical meningioma in 2000 and 2007, which have had the reported effect of increasing the proportion of atypical versus benign meningiomas diagnosed, potentially changing the
characteristics of tumors diagnosed in different eras. We attempted to account for these changes in grading criteria by stratifying by WHO era, and found no significant differences in patient demographics or tumor characteristics, although there was a trend toward greater use of adjuvant RT over time.

Finally, the various cutoffs identified in our study should be interpreted with caution. For instance, it is well recognized that interlaboratory variations of technique and interpretation make it difficult to establish MIB1 LI cutoffs that can be universally applied; as such, each laboratory must determine its own cutoff for an elevated LI locally.

Conclusions

Adjuvant RT reduces local progression of atypical meningioma irrespective of extent of resection, and is well tolerated. Although independent validation is required, our results suggest that the MIB1 LI, the number of mitoses per 10 hpf, and brain or bone invasion may be useful guides to the selection of patients who are most likely to benefit from adjuvant RT after resection of atypical meningioma.

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Disclosures
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
Conception and design: Raleigh, Braunstein. Acquisition of data: Raleigh, Chen, Magill, Wu, Braunstein. Analysis and interpretation of data: Raleigh, Chen, Magill, Morin, Braunstein. Drafting the article: Raleigh, Chen, Magill, Morin, Aghi, Theodosopoulos, Perry, McDermott, Sneed, Braunstein. Critically revising the article: Raleigh, Chen, Magill, Vaseudevan, Morin, Braunstein. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Raleigh. Statistical analysis: Raleigh, Chen, Braunstein. Administrative/technical/material support: Raleigh, Chen. Study supervision: Raleigh, Braunstein.

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