Adjuvant Radiotherapy Versus Watchful Waiting for World Health Organization Grade II Atypical Meningioma: A Single-Institution Experience

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BACKGROUND: Atypical meningiomas (AMs) are meningiomas that have a higher rate of recurrence than grade I meningioma. Due to the higher risk of recurrence, adjuvant radiotherapy (RT) after resection of AM has been employed. At our institution, some neurosurgeons employ adjuvant RT on all primarily resected AMs, while others employ watchful waiting with serial imaging.

OBJECTIVE: To study the effect of adjuvant RT on newly resected AMs.

METHODS: A retrospective review of all AMs primarily resected at our institution from 1996 to 2018 was completed. Data on patient demographics, radiographic findings, use of adjuvant RT, time of follow-up, and recurrences were collected. Adjuvant RT was defined as RT that occurred within 6 mo of initial resection.

RESULTS: A total of 162 patients met the inclusion criteria. Gross total resection was achieved in 73% of cases. Average time until recurrence in the cohort was 37 mo. A total of 108 patients had adjuvant RT, while 54 patients did not. On multivariate survival analysis, sex, Simpson grade resection, and use of adjuvant RT were independent predictors of recurrence. Mean time to recurrence in patients who received adjuvant RT was 43.7 mo versus 34.7 mo for those who did not receive adjuvant RT.

CONCLUSION: This study includes the largest retrospective cohort of patients who have received adjuvant RT after primary resection of AM. Our results suggest that the use of adjuvant RT is independently associated with a lower chance of recurrence. These data suggest that practitioners can consider the use of adjuvant RT for newly resected AMs, regardless of Simpson grade resection.

KEY WORDS: Meningioma, Radiotherapy, Adjuvant

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Meningiomas constitute 37% of all newly diagnosed intracranial neoplasms, making them the most commonly diagnosed intracranial mass.[1] Of these newly diagnosed meningiomas, the majority are World Health Organization (WHO) grade I meningiomas. WHO grade II meningiomas, also known as atypical meningiomas (AMs), which were formerly thought to comprise 5% of newly diagnosed meningiomas, are now thought to represent up to 20% to 35% of meningiomas.[2-4] AMs were first identified by the WHO in 1993, and were defined as a class between benign and anaplastic meningiomas.[5] Recently, the WHO further clarified their definition of AMs as meningiomas that meet 1 grading criterion or 3 out of 5 staging criteria. Brain invasion was elevated to a grading criterion, along with increased mitotic activity (>4 per high-power field). Staging criteria include spontaneous necrosis, high cellularity, small cells, prominent nucleoli, and sheeting.[5] Changes in the definition of AM made by the WHO have increased the recognition of AM and relative proportion in diagnosis to grade I and III meningiomas.[3]

It is well established within the neurosurgery and radiation oncology disciplines

ABBREVIATIONS: AM, atypical meningioma; **CI,** confidence interval; **GTR,** gross total resection; **HR,** hazard ratio; **RT,** radiotherapy; **WHO,** World Health Organization

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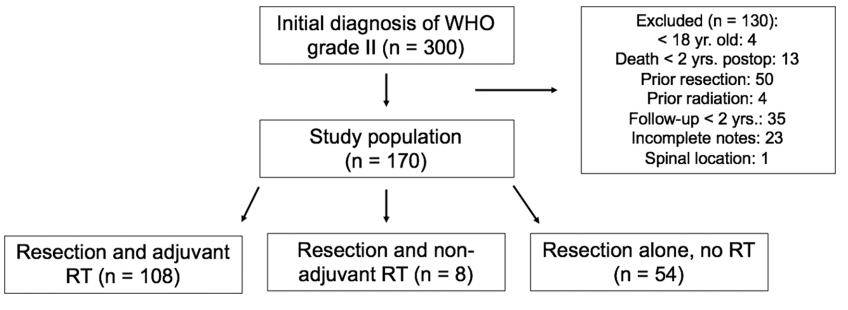

FIGURE 1. *Patient flow diagram.*

that safe, gross total resection (GTR) of any progressing, symptomatic, or large meningioma is the standard of care.[6,7] However, there is a lack of consensus regarding the postoperative management of newly diagnosed AMs. Studies have suggested an AM recurrence rate of 29% to 52% at 5 to 10 yr.[2,8-10] This has led the neurosurgery community to consider the benefit of adjuvant radiotherapy (RT) in the postoperative management of newly diagnosed AMs. Indeed, several studies have hinted toward improved outcomes/recurrence rates after adjuvant RT in AM, but studies report low numbers of patients receiving adjuvant RT.[2,5-7]

An evidence-based approach to the postoperative management of AM is sorely needed. Within our institution, neurosurgeons have employed both adjuvant RT and watchful waiting in AM after maximal safe surgical resection. We offer a retrospective analysis of every AM treated at our institution from 1996 to 2018.

METHODS

Population

All patients with WHO grade II meningioma noted on pathology who were operated upon at Emory University Hospital Medical Center from 1996 until 2018 were retrospectively entered into a database. Patients included within this analysis were those who were >18 yr at the time of surgery, had complete pathology reports, and had time of follow-up of 2 yr or more with neuroimaging (Figure 1). Adjuvant RT was defined as any RT that was applied to the tumor resection cavity or residual mass. In those patients who underwent RT, all patients (except for 3 who received stereotactic RT) received fractionated external beam RT with doses ranging from 18 to 60 Gy. Tumor recurrence was defined as a new enhancing mass or any increase in growth of residual mass on repeat imaging. This study was approved by the institutional review board at our institution. This was a retrospective review including deidentified patient data, so informed patient consent was not required.

A Note on WHO Meningioma Classification

Prior to 2007, WHO classified "brain invasion" as a staging feature, rather than a grading feature for grade II meningioma. Grade I meningiomas with brain invasion were noted to have similar recurrence rates to AM.[11] For this reason, in 2007, brain invasion was elevated to a grading feature, which it shares with >4 mitoses per high-power field.[5] The neuropathologists at Emory University Hospital Medical Center used the current classification schema of WHO guidelines for the diagnosis and grading of meningiomas during the duration of our study period. Therefore, the pathology classification for AM during our study period is fitting with the current WHO guidelines.

Variables

Baseline patient data including age at diagnosis, age at surgery, sex, pre- and postoperative Karnofsky Performance Status, date of death (where applicable), and date of last follow-up were collected. We noted Simpson grade after resection by operative note and/or immediate postoperative imaging.[12] Data were collected for variables regarding preoperative and intraoperative tumor morphology including tumor size (largest dimension in cm), approach to tumor (endoscopic or craniotomy), brain involvement (preoperative imaging or intraoperative observation), bone involvement (preoperative imaging or intraoperative observation), and whether or not GTR was achieved. Specifically, both operative note and postoperative magnetic resonance imaging (MRI) were employed to confirm GTR. Additionally, tumors were further described by 1 of 12 typical meningioma sites of origin: convexity, parasagittal/parafalcine, sphenoid wing/clinoidal∗, cavernous sinus∗, planum/olfactory groove, tuberculum sella/parasellar∗, tentorial/torcular, temporal/middle fossa, petroclival∗, cerebellopontine angle∗, posterior fossa∗, or orbital. Sites of origin with asterisks were defined as "skull base location." We collected postoperative variables, including recurrence, date of recurrence, surgical complications (where applicable), and whether or not RT was undertaken. Variables regarding RT included the date when RT was initiated, radiation dose, whether or not the dose was fractionated, presence of radiation necrosis on follow-up, and whether there were adverse effects from radiation. Last, pathology variables noted included presence of brain invasion, mitotic figures per high-power field, and MIB-1 labeling index.

Statistical Analysis

All statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, North Carolina). In the descriptive analysis, *P*-value was calculated by *t*-test or Fisher's exact test. The Cox proportional hazard model was used for the univariate and multivariate survival analyses. The hazard ratio (HR) with 95% CI is presented along with the log-rank test *P*-value for univariate survival analyses and chi-square *P*-value for multivariate analyses.

TABLE 1. Summary of Patients Characteristics (Excluding Nonadjuvant RT Group, N = 162)

Covariate	Level	Radiotherapy (RT)		*P* value
		No RT (N = 54)	Adjuvant RT (N = 108)	
Age of surgery (mean ± SD)		54.98 (14.97)	55.30 (12.68)	.89
Tumor size (mean ± SD)		4.57 (1.62)	4.84 (1.60)	.31
Sex	Male	21	46	.65
	Female	33	62	
Type of meningioma	Convexity/lobar	10	18	.55
	Parasagittal/parafalcine	15	33	
	Sphenoid wing/clinoidal	13	31	
	Planum/olfactory groove/anterior skull base	5	14	
	Others	11	12	
Osseous involvement	No	30	63	.74
	Yes	24	45	
Brain invasion	No	18	37	.91
	Yes	36	71	
Brain involvement	No	28	36	.02
	Yes	26	72	
Simpson grade	1	21	33	.12
	2	15	34	
	3	8	7	
	4	10	34	
Adapted Simpson grade	Gross total resection	44	74	.08
	Subtotal resection	10	34	

RESULTS

A total of 300 patients were diagnosed with grade II AM from 1996 to 2015 at our institution. Of these, 170 patients met the inclusion criteria for retrospective analysis. Females comprised 101 (59%) of the patients studied. The length of follow-up after surgery ranged from 24 to 221 mo with the mean follow-up of 58.6 mo. A total of 54 (32%) patients received no RT, 8 (5%) patients received nonadjuvant RT, and 108 (63%) patients received adjuvant RT. Only the distribution of the tumor size upon presentation was different between these 3 groups ($P = .01$) (**Supplemental Digital Content 1**, **Table**). Of patients who received adjuvant RT, 89% (n = 96) of patients received greater than 59 Gy. Of those patients who received less than 59 Gy, 1 had 57 Gy, 5 had 54 Gy, 4 had 50 Gy, and 2 had 18 Gy cumulative radiation doses.

We attempted to control for bias from surgeon-to-surgeon variability in rate of GTR and use of adjuvant RT. An analysis demonstrated that the distribution of no RT, RT, and adjuvant RT cases (**Supplemental Digital Contents 2 and 3**, **Tables**), Simpson grade resection status (**Supplemental Digital Content 4**, **Table**), and rate of recurrence (**Supplemental Digital Content 5**, **Table**) among our surgeons was not adequately powered to detect statistically significant differences.

Patients who received no RT and those who received adjuvant RT were compared (Table 1). GTR (Simpson grade 1-3) was achieved in 72.8% of cases. This analysis revealed that the only difference between the groups was observation of brain involvement/invasion ($P = .02$). On univariate recurrence survival analysis, female sex (hazard ratio [HR] = 2.40) and lower Simpson grade (HR G1: ref G2: 1.34 [$P = .085$], G3: 4.93 [$P = .0005$], G4: 1.64 [$P = .0082$]) were significantly associated with lower tumor recurrence rate (Table 2). Additionally, participation in adjuvant RT was associated with lower tumor recurrence rate (HR = 0.10) (Table 2). Multivariate recurrence survival analysis confirmed that female sex and presence of adjuvant RT remained significantly associated with reduced rate of recurrence after controlling for other variables (Tables 3 and 4, and Figure 2). Patients undergoing adjuvant RT after Simpson grades I, III, and IV resections had significantly lower rates of recurrence than those who did not receive adjuvant RT. While statistically significant on univariate analysis, on multivariate analysis, patients who received a Simpson grade II resection did not have a statistically significant recurrence rate reduction with adjuvant RT, but the *P*-value did approach significance (.085) (Figure 3).

Recurrence-free survival rate comparisons between no RT and adjuvant RT at 24 mo (80.7% vs 99.0%), 36 mo (71.8% vs 97.8%), and 60 mo (49.4% vs 93.7%) were significantly different. Mean time to recurrence was longer in patients who received adjuvant RT (43.71 vs 34.71 mo) (Tables 4 and 5). Of note, 8 (7.4%) patients who received adjuvant RT had complications related to RT. Of these patients, 4 had radiation necrosis, 1 had intractable fatigue, 1 had delayed wound breakdown requiring reoperation, 1 had delayed cerebral edema necessitating high-dose steroids and hospital admission for observation, and 1 had post-RT seizures.

TABLE 2. Univariate Recurrence Survival Analysis (n = 162)

Covariate	Level	N	Recurrence survival	
			Hazard ratio (95% CI)	Log-rank *P* value
Age	≤Median	83	Ref	.986
	>Median	76	1.01 (0.48-2.10)	
Tumor diameter	≤Median	94	Ref	.383
	>Median	64	1.38 (0.67-2.87)	
Sex	Female	95	Ref	.017
	Male	67	2.40 (1.14-5.05)	
MIB	<Median	42	Ref	.560
	≥Median	58	1.28 (0.56-2.90)	
Osseous involvement	No	93	Ref	.662
	Yes	69	1.18 (0.57-2.42)	
Brain invasion	No	55	Ref	.022
	Yes	107	0.42 (0.20-0.88)	
Brain involvement	No	64	Ref	.110
	Yes	98	0.56 (0.28-1.15)	
Type of meningioma	Convexity/lobar	48	Ref	.267
	Parasagittal/parafalcine	44	2.87 (0.99-8.36)	
	Sphenoid wing/clinoidal	19	2.67 (0.77 -9.25)	
	Planum/olfactory groove/anterior skull base	23	1.26 (0.30-5.29)	
	Others	28	2.00 (0.61-6.55)	
Simpson grade	1	54	Ref	.005
	2	49	1.34 (0.47-3.85)	
	3	15	4.93 (1.75-13.90)	
	4	44	1.64 (0.58-4.64)	
Adapted Simpson grade	Gross total resection	118	Ref	.982
	Subtotal resection	44	1.01 (0.44-2.30)	
Radiotherapy (RT)	No RT	54	Ref	<.0001
	Adjuvant RT	108	0.10 (0.04-0.25)	

TABLE 3. Multivariate Recurrence Survival Analysis (n = 162)

Covariate	Level	Recurrence survival	
		Hazard ratio (95% CI)	*P* value
Sex	Female	Ref	.023
	Male	2.53 (1.14-5.64)	
Simpson grade	1	Ref	
	2	2.63 (0.88-7.88)	.085
	3	6.78 (2.30-20.02)	.0005
	4	4.90 (1.51-15.88)	.0082
Radiotherapy (RT)	No RT	Ref	<.0001
	Adjuvant RT	0.27 (0.17-0.44)	
Brain involvement	No	Ref	
	Yes	0.51(0.217-1.205)	.125

DISCUSSION

Key Results

In this study, we have observed that adjuvant RT reduces the risk of recurrence in newly resected AMs. This is the largest retrospective review concerning the use of adjuvant RT in patients with AM. On univariate analysis, we observed lower recurrence rates in patients who received adjuvant RT, regardless of Simpson grade resection. On multivariate analysis, recurrence rate in each Simpson grade resection was significant, except for in grade II resections, which approached significance. Strengths of this study include the large retrospective cohort, the length of follow-up, and consistent pathological analysis.

Limitations

Some weaknesses of this study include the retrospective analysis and that it was performed at a single institution.

Interpretation

The gold-standard treatment for any meningioma is attempted safe GTR. It is well established that GTR in newly diagnosed AMs portends a lower recurrence rate.[2,10,13-17] The recurrence rate of AMs after resection, regardless of Simpson grade, is 3 to 4 times greater than grade I meningioma.[18,19] For this reason, many neurosurgeons and radiation oncologists advocate for adjuvant RT in an attempt to combat the higher recurrence rate observed in this population. However, the management of AMs still varies considerably from institution to institution. A survey of practicing neurosurgeons in the United Kingdom and Ireland revealed that

TABLE 4. Recurrence Survival Between No RT and Adjuvant RT Groups

RT	No. of subject	Event	Censored	24 M survival	36 M survival	60 M survival
No RT	54	24 (44.44%)	30 (55.56%)	80.7% (67.0%, 89.2%)	71.8% (56.8%, 82.3%)	48.4% (30.9%, 63.9%)
Adjuvant RT	108	6 (5.56%)	102 (94.44%)	99.0% (93.0%, 99.9%)	97.8% (91.3%, 99.4%)	93.7% (83.5%, 97.7%)

80% of practitioners would not pursue adjuvant RT in patients who had a completely excised AM.[20]

Changes in the WHO histological definition of AM may influence the discrepancies in the postoperative management of newly resected AMs. As previously mentioned, more precise histological definitions in AM as well as the inclusion of "brain invasion" as diagnostic criteria for AM have increased the overall incidence of AMs.[4,9,21] Incidence of AM has increased from 4% to 20% to 35% over the last 20 yr. AMs now comprise a more heterogeneous diagnosis. Other histological criteria have been studied in an attempt to further differentiate AMs, including MIB-1 labeling indices, genetic markers, and molecular alterations in the tumors.[22-24] The observation of spontaneous necrosis upon histopathological analysis of resected AMs has predicted less effective treatment with postoperative RT.[25] Over the last 20 yr, neurosurgeons have encountered more AMs than ever before, yet there is no consensus on ideal postoperative management.

Some institutions have advocated for watchful waiting after GTR. Hardesty et al[14] reviewed 228 patients who underwent resection of AM, and found that those patients who received adjuvant RT did not have a lower recurrence rate than patients who were watched with serial imaging. A weakness of this study was the very low number of patients who underwent adjuvant RT, only 32 in the cohort, which was less than 15% of the studied population. Graffeo et al[26] found no benefit of adjuvant RT in terms of lower recurrence rate in patients with resected AMs. Likewise, only 8 of 69 patients in this cohort underwent adjuvant RT. Lee et al[27] studied 90 patients with AM and found that adjuvant RT was associated with a lower recurrence rate in patients who received subtotal resections. Sun et al[28] observed only 8% recurrence rate after GTR of AM, and therefore advocated for watchful waiting after resection of AM. Other studies have recorded similar conclusions.[29] Pollock et al[30,31] advocated for withholding adjuvant RT in patients with postoperative MRI-confirmed GTR; if recurrence does occur,

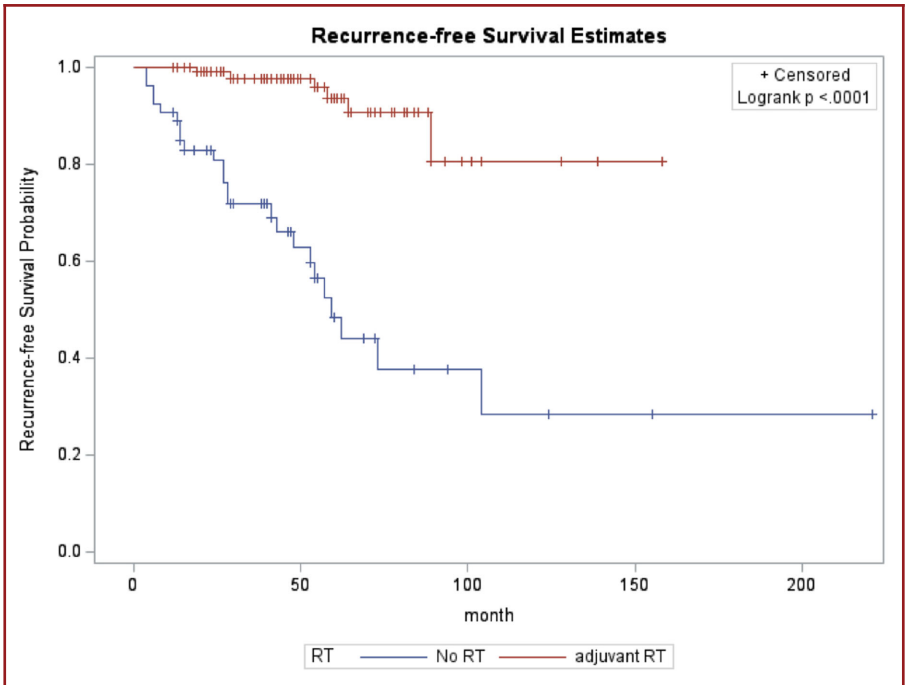

FIGURE 2. *Kaplan-Meier survival curve of recurrence by RT.*

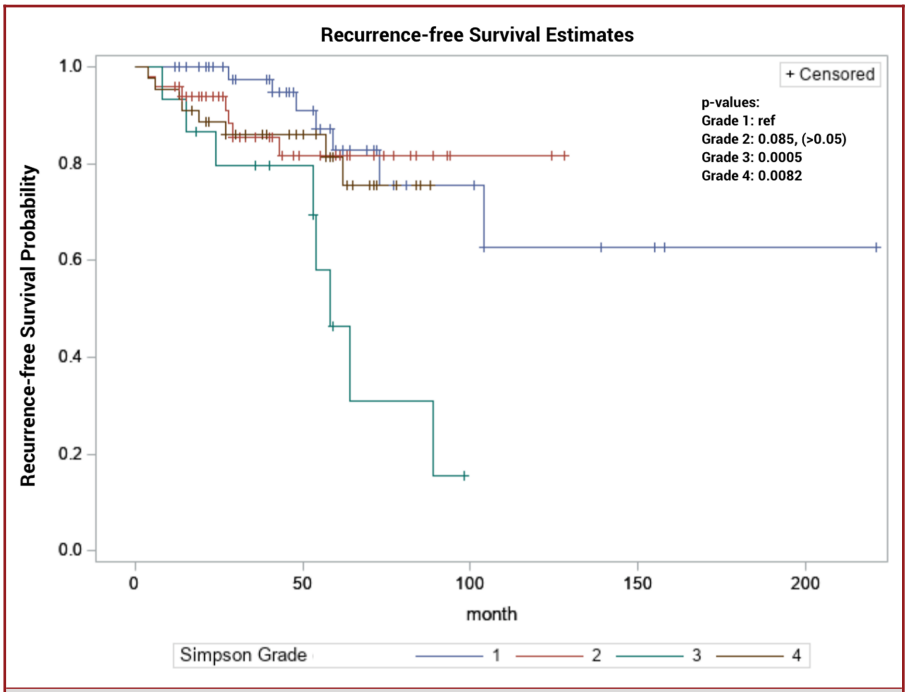

FIGURE 3. *Recurrence-free survival estimates.*

TABLE 5. Time to Recurrence

	Radiotherapy (RT)	
Time to recurrence	**No RT (n = 54)**	**Adjuvant RT (n = 108)**
Mean	34.71	43.71
Median	27.50	42.00

single-dose stereotactic radiosurgery (SRS) is employed for local control.

It is unclear what the meaning of recurrence of AM means for patients who have previously received surgical resection and/or RT treatment. Advocates for watchful waiting after GTR argue that durable local control can be achieved with SRS or delayed fractionated RT. Shakir et al[32] 2018 reported on residual AM growth rate after both adjuvant RT and no RT. They found a significantly higher growth rates in patients who did not receive postoperative RT than those who received postoperative RT (4.8 cm^3/yr vs –0.09 cm^3/yr, respectively). The growth rate of residual AM is significantly higher than the growth rate of their grade I counterparts.[33] With the high growth rate observed in AM, it is feasible that recurrent tumor can quickly result in neurological deficit for patients.

Other institutions recommend adjuvant RT after resection of AM, regardless of Simpson grade or postoperative MRI results. Aghi et al[8] reviewed AMs resected at Massachusetts General Hospital, and found that 8 patients who received adjuvant RT had no recurrence at latest follow-up. Bagshaw et al,[34] Hoffmann et al,[35] and Zhi et al[36] have added to the growing number of studies that suggest benefit of adjuvant RT for AMs in terms of better local control and lower recurrence rates. Multiple prospective trials are underway to further elucidate the role of adjuvant RT after GTR for AMs. The phase II Radiation Therapy Oncology Group 0539 trial, which randomized newly resected AMs and recurrent grade I meningiomas to adjuvant RT of 54 Gy dose to watchful waiting, recently reported their 3-yr data. They found no significant difference in progression-free survival between the 2 groups.[37] The European Organisation for Research and Treatment of Cancer 22042-26024 is a prospective observational trial prescribing 60 Gy adjuvant RT for resected AMs and grade III meningiomas. They have observed 3-yr progression-free survival of AMs to be 88.7%.[38] Other prospective trials are ongoing at the time of this publication.[39]

Generalizability

In this study, we observed a lower recurrence rate in those patients with AM who received adjuvant RT, regardless of extent of resection status. Our observed recurrence rate of AM in the

cohort of patients who did not receive adjuvant RT is in step with other retrospective review reports. This study reports the highest number of patients who received adjuvant RT hitherto reported in the literature. Patients had an acceptable risk profile from adjuvant RT. Location of meningioma, tumor size, age of patient, and MIB proliferative status did not relate to recurrence-free survival. We hypothesize that adjuvant RT reduced recurrence rate of AM in our population due to the relatively higher proportion of patients receiving high-dose external beam radiation therapy (>50 Gy) and longer length of follow-up in our comparative cohorts. Based on our observations, we endorse the consideration of the use of adjuvant RT after resection of AM, regardless of extent of resection. We await the continued results of other prospective trials that will further elucidate the role of adjuvant RT in AM. Additionally, it will be important to further define the best treatment for patients with AM if recurrence does occur.

CONCLUSION

AMs have a higher risk of recurrence than standard meningiomas, regardless of extent of resection. We observed lower recurrence rate in patients who received adjuvant RT after resection of AMs, and this occurred with an acceptable risk profile. We await the results of the prospective, randomized studies currently underway for further direction regarding the role of adjuvant RT in resected cranial AMs.

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Supplemental Digital Content 1. Table. Summary of patients characteristics (including no RT group, n = 170).

Supplemental Digital Content 2. Table. Number of RT cases by surgeon.

Supplemental Digital Content 3. Table. Number of adjuvant RT cases for each surgeon.

Supplemental Digital Content 4. Table. Simpson grade resections for each surgeon.

Supplemental Digital Content 5. Table. Number of recurrences for each surgeon.