See the corresponding editorial in this issue, pp 472–474.

J Neurosurg 119:475–481, 2013

The impact of adjuvant stereotactic radiosurgery on atypical meningioma recurrence following aggressive microsurgical resection

Clinical article

Douglas A. Hardesty, M.D.,[1] Andrew B. Wolf, B.S.,[1] David G. Brachman, M.D.,[2] Heyoung L. McBride, M.D.,[2] Emad Youssef, M.D.,[2] Peter Nakaji, M.D.,[1] Randall W. Porter, M.D.,[1] Kris A. Smith, M.D.,[1] Robert F. Spetzler, M.D.,[1] and Nader Sanai, M.D.[1]

[1]Division of Neurological Surgery, Barrow Neurological Institute, and [2]Division of Radiation Oncology, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

Object. Patients with atypical meningioma often undergo gross-total resection (GTR) at initial presentation, but the role of adjuvant radiation therapy remains unclear. The increasing prevalence of stereotactic radiosurgery (SRS) in the modern neurosurgical era has led to the use of routine postoperative radiation therapy in the absence of evidence-based guidelines. This study sought to define the long-term recurrence rate of atypical meningiomas and identify the value of SRS in affecting outcome.

Methods. The authors identified 228 patients with microsurgically treated atypical meningiomas who underwent a total of 257 resections at the Barrow Neurological Institute over the last 20 years. Atypical meningiomas were diagnosed according to current WHO criteria. Clinical and radiographic data were collected retrospectively.

Results. Median clinical and radiographic follow-up was 52 months. Gross-total resection, defined as Simpson Grade I or II resection, was achieved in 149 patients (58%). The median proliferative index was 6.9% (range 0.4%–20.6%). Overall 51 patients (22%) demonstrated tumor recurrence at a median of 20.2 months postoperatively. Seventy-one patients (31%) underwent adjuvant radiation postoperatively, with 32 patients (14%) receiving adjuvant SRS and 39 patients (17%) receiving adjuvant intensity modulated radiation therapy (IMRT). The recurrence rate for patients receiving SRS was 25% (8/32) and for IMRT was 18% (7/39), which was not significantly different from the overall group. Gross-total resection was predictive of progression-free survival (PFS; relative risk 0.255, $p < 0.0001$), but postoperative SRS was not associated with improved PFS in all patients or in only those with subtotal resections.

Conclusions. Atypical meningiomas are increasingly irradiated, even after complete or near-complete microsurgical resection. This analysis of the largest patient series to date suggests that close observation remains reasonable in the setting of aggressive microsurgical resection. Although postoperative adjuvant SRS did not significantly affect tumor recurrence rates in this experience, a larger cohort study with longer follow-up may reveal a therapeutic benefit in the future.

(http://thejns.org/doi/abs/10.3171/2012.12.JNS12414)

Key Words • **atypical meningioma** • **stereotactic radiosurgery** • **adjuvant radiotherapy** • **gross-total resection** • **intensity modulated radiation therapy**

Atypical meningiomas (WHO Grade II) carry a substantially worse prognosis than their Grade I counterparts. In part due to revised WHO diagnostic criteria, the incidence of atypical meningiomas has increased over the last decade.[11] The optimal management of these lesions after initial resection has yet to be established, although options include observation, adjuvant traditional radiotherapy such as IMRT, and adjuvant

Abbreviations used in this paper: GTR = gross-total resection; IMRT = intensity modulated radiation therapy; PFS = progression-free survival; RR = relative risk; SRS = stereotactic radiosurgery; STR = subtotal resection.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

SRS.[3,4,6,10] Although the current literature on atypical meningiomas consists of relatively small case series, GTR has been associated with increased PFS in several studies.[5,6,8,9] However, this correlation may simply reflect disease severity at the time of presentation. Previous work has suggested that adjuvant radiation therapy may delay tumor recurrence following complete resection or STR.[1,8] The role of adjuvant SRS, however, is less clear. In 1 study, early adjuvant SRS after STR of atypical meningiomas improved local tumor control as compared with SRS after radiographic recurrence.[4] Other investigators have reported a suboptimal local control rate with SRS, although the ideal radiological dose or treatment algorithm has yet to be established.[2] To define the risk factors associated with postoperative atypical meningioma recurrence and further clarify the role of adjuvant SRS in the management of these lesions, we retrospectively reviewed all patients who underwent microsurgical resections of atypical meningiomas at our institution.

Methods

Study Population

We identified all patients who underwent operations for atypical meningiomas between 1992 and 2011 at the Barrow Neurological Institute. Atypical meningiomas were diagnosed based on neuropathological analysis according to current WHO criteria; current criteria were retrospectively applied to older specimens. All patients underwent microsurgical resection with possible postoperative adjuvant radiotherapy or SRS. All adjuvant therapy was given within 6 months of surgery, prior to any clinical or radiographic tumor recurrence. Local tumor recurrence was defined as an increase in Gd-enhancing tissue within or adjacent to the resection cavity on postoperative MRI.

Data Collection

Hospital, outpatient clinic, and radiological records were reviewed. Clinical, radiographic, and outcome data were collected from inpatient and outpatient records. Characteristics identified for each case included age and Karnofsky Performance Status score at the time of surgery, prior surgery or radiation therapy, adjuvant therapy, tumor location, and time intervals between treatment modalities. To minimize splintering of the studied cohorts, Simpson Grade I and II resections were combined to represent tumors that were gross-totally resected. Statistical analysis of separate Simpson Grades was not possible due to small sample sizes. This study was approved by our institutional review board.

Radiosurgery was performed using either a Leksell Gamma Knife and Leksell Gamma Plan treatment planning software (Elekta Instruments) or CyberKnife system (Accuray). The decision to treat a patient using adjuvant radiosurgery was made on a case-by-case basis after consultation with our multidisciplinary tumor board, as well as case review at our weekly radiosurgical conference.

Statistical Analysis

Kaplan-Meier analysis with log-rank testing was used to compare PFS among groups of patients. The Fisher exact test was used to compare baseline characteristics between patient groups. A probability value < 0.05 was considered statistically significant.

Results

Demographics and Baseline Characteristics

We identified 228 unique patients undergoing 257 operations for atypical meningioma between 1992 and 2011. Patient demographics are detailed in Table 1. There was a slight female predominance (57%) in the study sample. A variety of tumor locations were noted including the convexity (n = 63, 28%), parasagittal lesions (n = 63, 28%), tumors of the skull base (n = 87, 38%), and other locations such as the spinal column or lateral ventricles (n = 15, 6.6%). The average age at first surgery was 62 years old (range 2–94 years old; Table 2). The MIB-1 proliferative index was available for 102 tumor specimens (40%) and ranged from 0.4% to 20.6%, with an average of 6.9%. Analysis of the extent of resection demonstrated GTR (Simpson Grades I and II) in 149 patients (58%); STRs therefore accounted for 42% of the overall group. Thirty-one patients (13.6%) had undergone previous resection of a Grade I meningioma at the site of the atypical meningioma. Twenty-five patients (11%) reported a history of radiotherapy of some type (either SRS or IMRT) prior to craniotomy for tumor resection.

Postoperative Follow-Up and Tumor Recurrence

The median postoperative clinical and radiographic follow-up duration was 52 months. During the follow-up period, 51 patients (22%) demonstrated radiographic evidence of disease progression. The median interval to progression was 20.2 months (range 3.7–86 months; Table 2). Thirty (59%) of the 51 patients underwent 36 operations for recurrent tumor; others were managed with salvage SRS (n = 7, 14%), IMRT (n = 1, 2%), or elected not to pursue additional treatment at the time of initial disease

TABLE 1: Patient demographics

Variable	All Patients	Adjuvant SRS	Adjuvant IMRT
no. of patients	228	32	39
female:male ratio	131:97	18:14	22:17
mean age ± SD (yrs)	62 ± 16	55 ± 19	55 ± 14
tumor location (%)			
convexity	63 (28)	3 (9.4)	10 (26)
parasagittal	63 (28)	12 (38)	14 (36)
skull base	87 (38)	17 (53)	9 (23)
other	15 (6.6)	3 (9.4)	2 (5.1)
mean MIB-1 index	6.9%	6.0%	7.6%
no. w/ tumor recurrence (%)	51 (22)	8 (25)	7 (18)
median follow-up (mos)	52	72	23*

* Statistically significant difference compared with all patients ($p < 0.05$).

TABLE 2: Comparison between patients with recurrent atypical meningiomas and all patients

Variable	All Patients	Patients w/ Recurrent Tumor
no. of patients	228	51
female:male ratio	131:97	27:24
mean age at first surgery ± SD (yrs)	62 ± 16	62 ± 16
tumor location (%)		
convexity	63 (28)	9 (18)
parasagittal	63 (28)	16 (31)
skull base	87 (38)	25 (49)
other	15 (6.6)	1 (2.0)
GTR (%)	149/258 (58)	17 (33)*
adjuvant SRS (%)	32 (14)	8/32 (25)
adjuvant IMRT (%)	39 (17)	7/39 (18)
mean MIB-1 index at 1st surgery	6.9%	8.6%
median tumor progression (mos)	none	20.2

* Statistically significant difference compared with all patients ($p < 0.05$).

progression (n = 9, 18%). Several patients (n = 4, 8%) were scheduled for additional resection, but had not yet undergone surgery at the time of data analysis. Of the 30 patients undergoing re-resection, 1 patient's tumor (3%) had progressed to malignant meningioma (WHO Grade III). The MIB-1 indices from the original versus the recurrent pathology did not differ significantly among patients whose atypical meningiomas went on to recur. Kaplan-Meier analysis using log-rank testing demonstrated a significant association between GTR of atypical meningiomas at first surgery and PFS, irrespective of adjuvant therapy (RR 0.255, $p < 0.0001$; Fig. 1).

Adjuvant SRS and PFS

Thirty-two patients underwent adjuvant SRS postoperatively, with 19 treated using Gamma Knife surgery and 13 using CyberKnife technology; two representative examples are demonstrated in Fig. 2. Target volumes ranged from 1.8 cm^3 to 45 cm^3 (mean 11.4 cm^3). Overall, 8 patients (25%) suffered progressive disease. Most patients (n = 22, 69%) who were treated with adjuvant SRS had undergone STR at the time of surgery. The median radiation dose was 14 Gy (range 11–16 Gy) to the 50% isodose line for Gamma Knife-treated patients while the dose for CyberKnife-treated patients ranged from 14–16 Gy in 1 fraction, to 21–27 Gy in 3 fractions, to 25 Gy in 5 fractions, depending on volume, location, and/or history of prior radiation therapy. There were no periprocedural complications associated with radiosurgical therapy. There was no association between adjuvant SRS and PFS in all patients using Kaplan-Meier analysis with log-rank testing (RR 1.0, $p = 0.99$; Fig. 3). Furthermore, a subgroup analysis of only patients with STRs failed to show a statistically significant PFS benefit for adjuvant SRS (RR 0.567, $p = 0.16$; Fig. 4). The combination of GTR and adjuvant SRS demonstrated a 100% rate of PFS over an average of 73 months of clinical follow-up, but the number of patients undergoing this therapy combination was small (n = 8) and the survival advantage was not statistically significant ($p > 0.05$) when compared with GTR alone.

Adjuvant IMRT and PFS

Thirty-nine patients underwent IMRT postoperatively. The median follow-up time for these patients was significantly shorter than for the population as a whole (23 vs 52 months, respectively; $p = 0.0057$) Slightly more than half of the 39 patients had undergone STRs (20 of 39, 51%). The median radiation dose was 54 Gy (range 54–59 Gy) in standard fractionation of 1.8–2 Gy per day. Seven patients (18%) suffered progressive disease despite IMRT.

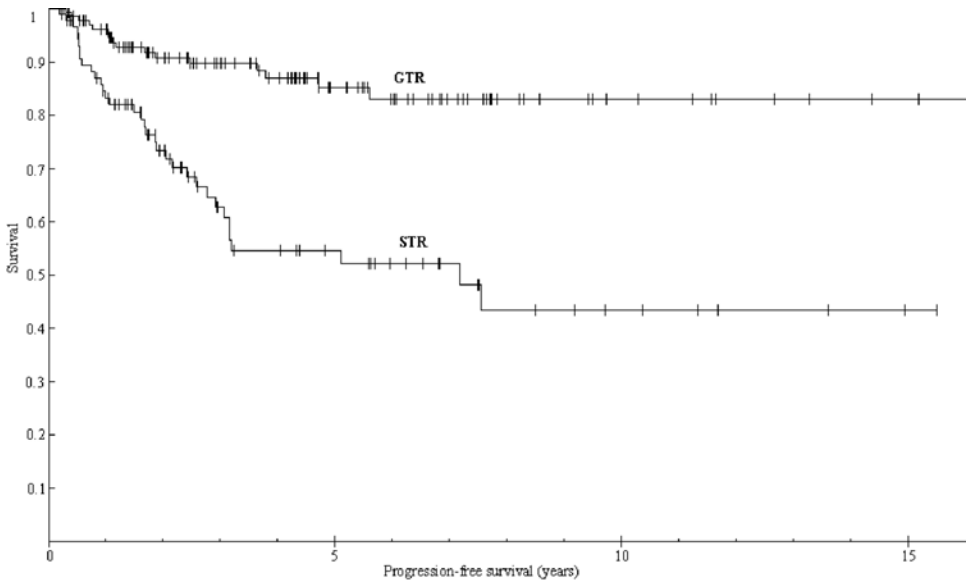

Fig. 1. Kaplan-Meier survival curve of GTR versus STR in all patients with atypical meningioma, regardless of adjuvant therapy. Log-rank testing demonstrated a significant difference between the groups favoring GTR (RR 0.255, $p < 0.0001$).

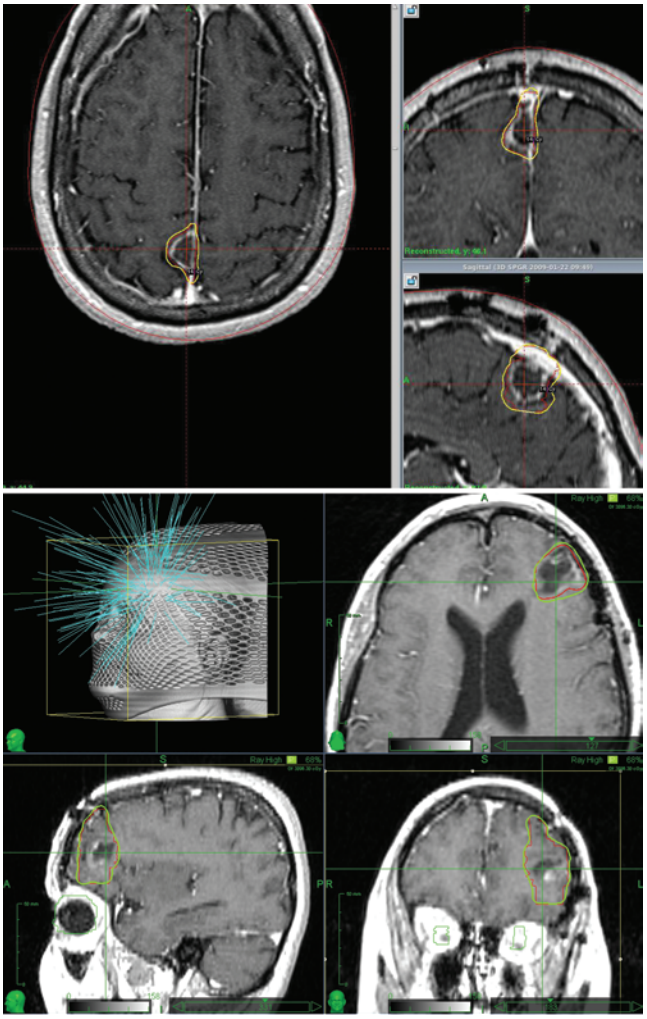

Fig. 2. Two representative radiosurgery plans for adjuvant therapy. **Upper:** Gamma Knife surgical plan for a 6.2-cm^3 target treated with 14 Gy at the 50% isodose line and resulting in 98% coverage. The *yellow outline* represents the 68% isodose line. The *red outline* is the tumor bed as identified by hand by the treating radiosurgery team. The *crosshairs* are the epicenter of the lesion. **Lower:** CyberKnife plan of a gross-totally resected 13.9-cm^3 tumor treated with 21 Gy at the 68% isodose line in 3 fractions, yielding 98% coverage of the target volume. The *green outline* represents the 68% isodose line, the *red outline* the tumor bed, and the *crosshairs* the lesion epicenter.

There was 1 patient who suffered cranial wound breakdown as a complication of IMRT, requiring operative reconstruction. Using Kaplan-Meier analysis with log-rank testing, there was no association between adjuvant IMRT and PFS in all patients (RR 0.717, p = 0.45; Fig. 5) nor was there an association in subgroup analysis of only patients with STR (RR 1.27, p = 0.55; Fig. 6). A comparison between adjuvant IMRT and adjuvant SRS yielded no differences in PFS between the 2 modalities (RR 0.715, p = 0.52). Lastly, the combination of GTR and adjuvant IMRT produced a 100% rate of PFS over an average of 14 months of clinical follow-up, but the number of patients undergoing this therapy combination was small (n = 15) and the survival advantage was not statistically significant (p > 0.05) when compared with GTR alone.

Discussion

Our analysis of the largest single-institution series of atypical meningiomas with long-term follow-up demonstrates an overall recurrence rate of 22%, with median recurrence at 20.2 months, despite aggressive microsurgical resection. As expected, GTR was strongly predictive of a prolonged PFS, validating previous reports advocating aggressive resection of these tumors using modern microsurgical techniques.[5,6,8,9] Gross-total resection can be challenging at the skull base, and 38% of patients in our series had atypical meningiomas involving the cranial base. At least 1 report has suggested that a non–skull base location is a risk factor for atypical meningioma.[7] While this remains a possibility, the relatively large number of skull base atypical meningiomas in this series may also reflect the cranial base referral patterns of our institution.

Neither adjuvant SRS, nor adjuvant IMRT, were associated with a PFS benefit for all patients or for those patients with STR. While these findings dispute prior work indicating that adjuvant SRS significantly impacts the clinical outcome of patients with atypical meningioma,[4] a trend toward increased PFS for patients with subtotally resected tumors undergoing SRS was observed (RR = 0.567), but did not reach statistical significance (p = 0.16). Similarly, although the cohort that underwent the combination of GTR and adjuvant radiation therapy with either SRS or IMRT showed no recurrences (0 of 23), this did not yield a statistically significant improvement in clinical outcomes when compared with GTR alone (p = 0.80). A combined Kaplan-Meier curve of all treatment modalities summarizes our observations (Fig. 7). These trends may reflect a Type II error due to the small number of patients undergoing adjuvant therapy, although a larger sample size would be needed to make this assessment. Another explanation could be a lead-time bias, in which patients treated with adjuvant therapy receive additional cranial imaging and are diagnosed with recurrence earlier than patients only undergoing resection. Controlling the number and timing of postoperative imaging examinations, however, was beyond the scope of this study's design. Similarly, this analysis was not sufficiently powered to compare the relative impact of IMRT versus SRS for patients with atypical meningioma. Importantly, despite similar demographics and recurrence rates between these two populations, patients with larger treatment volumes were generally referred for IMRT instead of SRS at our institution. Preoperative and postoperative MRI was available for independent review (instead of relying on the official radiographic report) in less than 50% of patients; thus formal volumetric analysis was not possible. However, patients with more discrete, nodular residual disease were generally more likely to receive SRS, while patients with en plaque residual at the brain-tumor interface were more commonly selected for IMRT. Because these differences in recurrence patterns could belie underlying differences in tumor biology, direct comparison of these two modalities is limited.

The retrospective nature of this study also limits the conclusions to be drawn from these observations. Baseline characteristics for patients undergoing adjuvant ther-

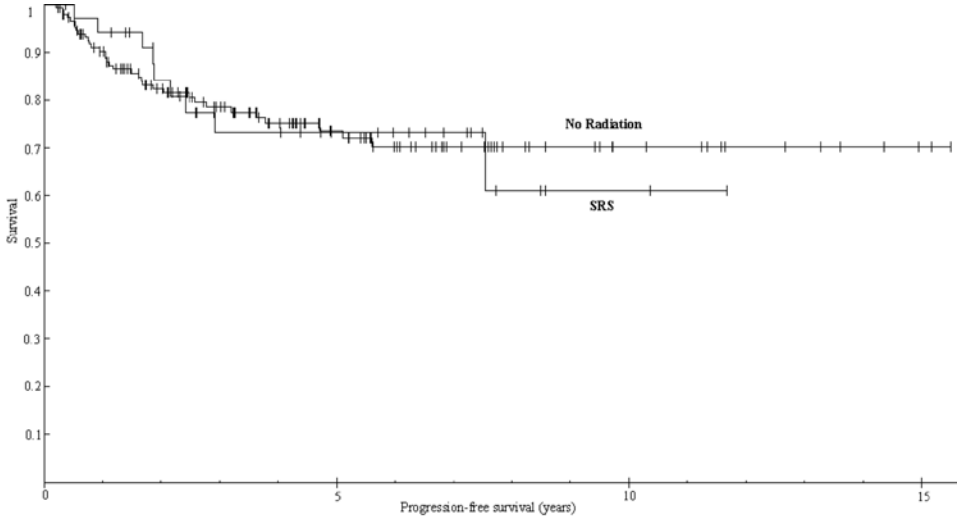

Fig. 3. Kaplan-Meier curve of adjuvant SRS compared with no radiation in all patients. Log-rank testing demonstrated no significant differences between groups.

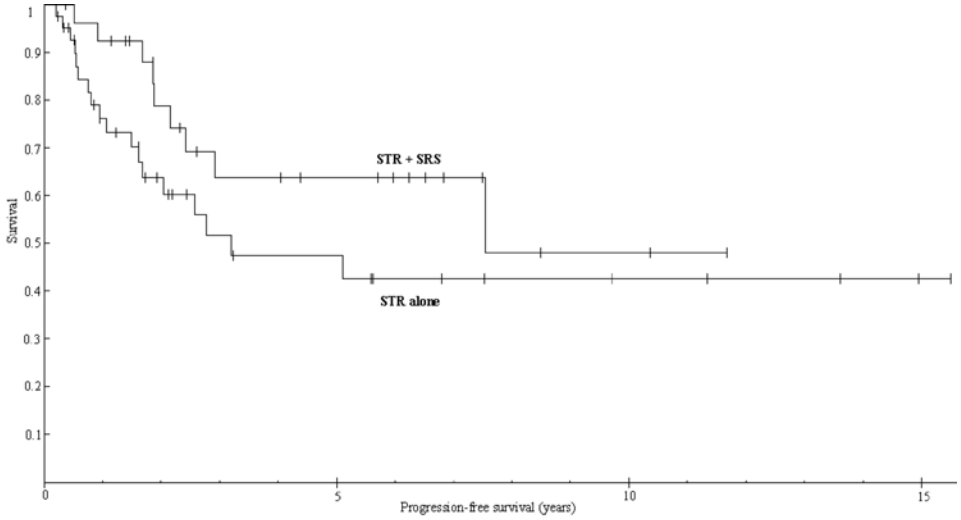

Fig. 4. Kaplan-Meier curve of adjuvant SRS compared with no radiation in patients with STRs. Log-rank testing demonstrated no significant differences between groups.

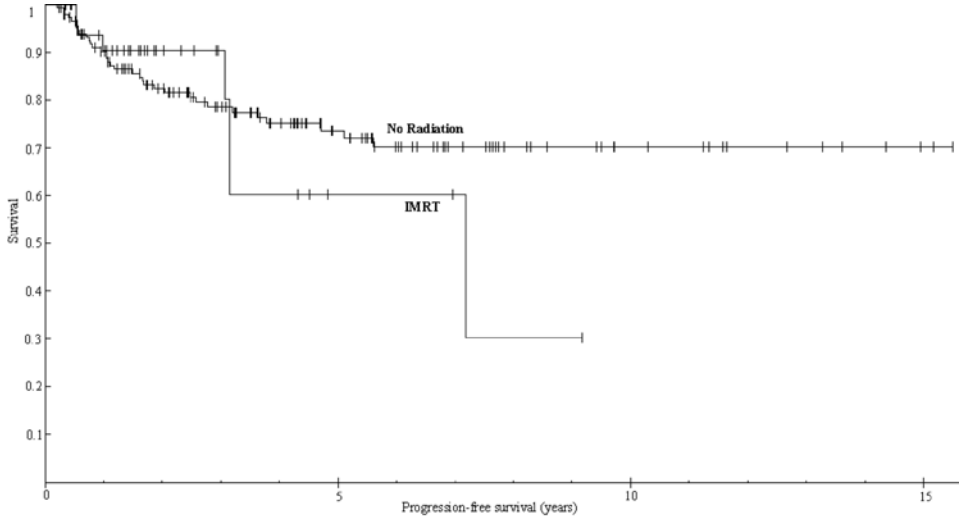

Fig. 5. Kaplan-Meier curve of adjuvant IMRT compared with no radiation in all patients. Log-rank testing demonstrated no significant differences between groups.

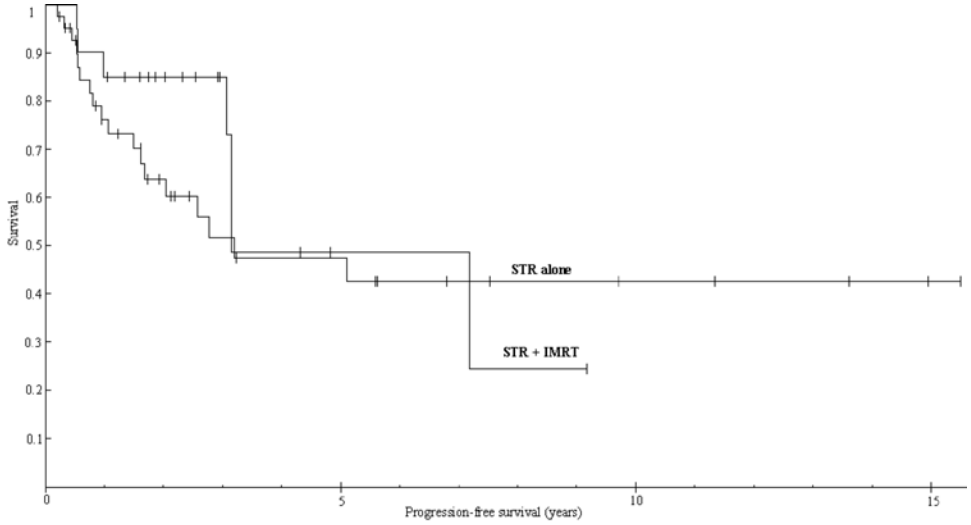

Fig. 6. Kaplan-Meier curve of adjuvant IMRT compared with no radiation in subtotally-resected patients. Log-rank testing demonstrated no significant differences between groups.

apy were similar to those for patients who did not receive further therapy, but a selection bias for referral to adjuvant therapy cannot be ruled out. Taken together, the disparity between our current findings and that of the sole prior retrospective adjuvant radiotherapy study[4] suggest that a prospective, randomized clinical trial would be worthwhile, at the least for patients with STRs, and possibly for those with GTRs. However, until such a trial, the appropriate role of adjuvant SRS remains unclear. Although we observed no SRS-related complications, the choice to undergo adjuvant SRS should be made on a case-by-case basis, as we find no evidence to support the universal application of this management paradigm.

At the time of repeat resection, only 1 patient had undergone transformation to a malignant meningioma, 7 months after the first microsurgical resection followed by adjuvant SRS. Overall, an additional craniotomy procedure for tumor recurrence was tolerated well. Over half of the 30 patients undergoing re-resection (n = 17, 57%) had no further recurrence after the second operation (median follow-up 29.5 months, range 3–258 months). Therefore, for most cases we agree that atypical meningioma recurrence should first be treated surgically, when possible, instead of with salvage SRS or IMRT. Several retrospective studies have suggested that adjuvant IMRT increases PFS and a large, multicenter trial is underway to address this issue (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0539).[1,4] However, no study to

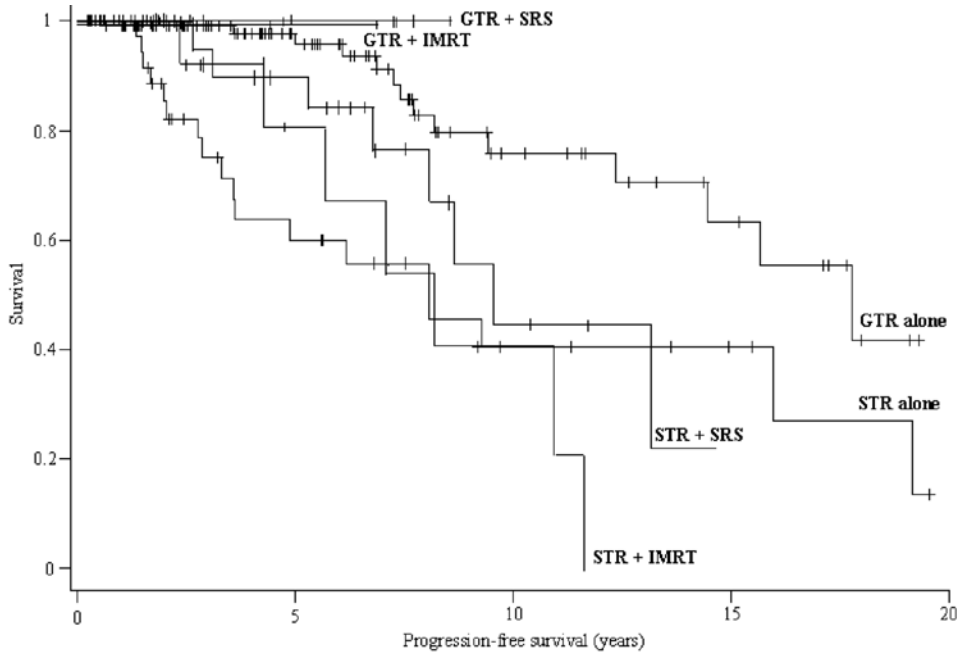

Fig. 7. Kaplan-Meier curve summarizing all treatment combinations. The addition of adjuvant therapy (either SRS or IMRT) to GTR did not yield a PFS benefit compared with GTR alone as determined by log-rank testing.

date has compared adjuvant IMRT or SRS to a strategy of watchful waiting with repeat microsurgical resection at the time of recurrence.

Conclusions

Our findings in this large series of WHO Grade II atypical meningiomas do not demonstrate a significant overall survival or PFS benefit from adjuvant SRS, even among patients whose tumors have been subtotally resected. In the future, additional molecular studies of these tumors may help stratify patients whose tumor biology predisposes them to recurrence or predicts radiosensitivity. These specific subsets of patients with atypical meningioma may uniquely benefit from adjuvant radiotherapy. Although our results do not support the utility of routine adjuvant radiotherapy for all atypical meningiomas, only a prospective study could adequately settle this controversy.

Disclosure

Dr. Spetzler serves as a consultant to Zeiss; has direct stock ownership in Boston Scientific, DicomGrid, EmergeMD, Neurovasx, Synergetics, Stereotaxis, RSB Spine, iCo Therapeutics, and Katalyst/Kogent; and has received royalties from Codman and Stryker.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sanai, Hardesty, Brachman, McBride, Youssef, Nakaji, Porter, Smith, Spetzler. Acquisition of data: Hardesty, Wolf. Analysis and interpretation of data: Sanai, Hardesty, Wolf. Drafting the article: Sanai, Hardesty, Wolf. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sanai. Statistical analysis: Hardesty. Administrative/technical/material support: Sanai. Study supervision: Sanai.

References

1. Aghi MK, Carter BS, Cosgrove GR, Ojemann RG, Amin-Hanjani S, Martuza RL, et al: Long-term recurrence rates of atypical meningiomas after gross total resection with or without postoperative adjuvant radiation. **Neurosurgery 64:**56–60, 2009
2. Attia A, Chan MD, Mott RT, Russell GB, Seif D, Bourland JD, et al: Patterns of failure after treatment of atypical meningioma with gamma knife radiosurgery. **J Neurooncol 108:** 179–185, 2012
3. Bria C, Wegner RE, Clump DA, Vargo JA, Mintz AH, Heron DE, et al: Fractionated stereotactic radiosurgery for the treatment of meningiomas. **J Cancer Res Ther 7:**52–57, 2011
4. Choi CY, Soltys SG, Gibbs IC, Harsh GR, Jackson PS, Lieberson RE, et al: Cyberknife stereotactic radiosurgery for treatment of atypical (WHO grade II) cranial meningiomas. **Neurosurgery 67:**1180–1188, 2010
5. Goyal LK, Suh JH, Mohan DS, Prayson RA, Lee J, Barnett GH: Local control and overall survival in atypical meningioma: a retrospective study. **Int J Radiat Oncol Biol Phys 46:** 57–61, 2000
6. Jo K, Park HJ, Nam DH, Lee JI, Kong DS, Park K, et al: Treatment of atypical meningioma. **J Clin Neurosci 17:**1362–1366, 2010
7. Kane AJ, Sughrue ME, Rutkowski MJ, Shangari G, Fang S, McDermott MW, et al: Anatomic location is a risk factor for atypical and malignant meningiomas. **Cancer 117:**1272–1278, 2011
8. Mair R, Morris K, Scott I, Carroll TA: Radiotherapy for atypical meningiomas. Clinical article. **J Neurosurg 115:**811–819, 2011
9. Palma L, Celli P, Franco C, Cervoni L, Cantore G: Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. **J Neurosurg 86:**793–800, 1997
10. Pearson BE, Markert JM, Fisher WS, Guthrie BL, Fiveash JB, Palmer CA, et al: Hitting a moving target: evolution of a treatment paradigm for atypical meningiomas amid changing diagnostic criteria. **Neurosurg Focus 24(5):**E3, 2008
11. Willis J, Smith C, Ironside JW, Erridge S, Whittle IR, Everington D: The accuracy of meningioma grading: a 10-year retrospective audit. **Neuropathol Appl Neurobiol 31:**141–149, 2005

Manuscript submitted February 29, 2012.
Accepted December 13, 2012.
Preliminary results of this study were presented at the Arizona Neurosurgical Society Meeting in Marana, Arizona, on October 29, 2011.
Please include this information when citing this paper: published online February 8, 2013; DOI: 10.3171/2012.12.JNS12414.
Address correspondence to: Nader Sanai, M.D., Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 310 North Third Avenue, Phoenix, Arizona 85013. email: nader.sanai@bnaneuro.net.