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Clinical Investigation

Treatment of WHO Grade 2 Meningiomas With Stereotactic Radiosurgery: Identification of an Optimal Group for SRS Using RPA

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Purpose: This study assesses a large multi-institutional database to present the outcomes of World Health Organization grade 2 meningiomas treated with stereotactic radiosurgery (SRS). We also compare the 3-year progression-free survival (PFS) to that reported in the Radiation Therapy Oncology Group 0539 phase 2 cooperative group meningioma trial.

Methods and Materials: From an international, multicenter group, data were collected for grade 2 meningioma patients treated with SRS for demonstrable tumor from 1994 to 2019. Statistical methods used included the Kaplan-Meier method, Cox proportional hazards analysis, and recursive partitioning analysis.

Results: Two hundred thirty-three patients treated at 12 institutions were included. Patients presented at a median age of 60 years (range, 13-90), and many had at least 2 prior resections (30%) or radiation therapy (22%). Forty-eight percent of patients had prior gross total resection. At SRS, the median treatment volume was 6.1 cm^3 (0.1-97.6). A median 15 Gy (10-30) was delivered to a median percent isodose of 50 (30-80), most commonly in 1 fraction (95%). A model was developed using recursive partitioning analysis, with one point attributed to age >50 years, treatment volume >11.5 cm^3, and prior radiation therapy or multiple surgeries. The good-prognostic group (score, 0-1) had improved PFS ($P < .005$) and time to local failure ($P < .005$) relative to the poor-prognostic group (score, 2-3). Age >50 years (hazard ratio = 1.85 [95% confidence interval, 1.09-3.14]) and multiple prior surgeries (hazard ratio = 1.80 [1.09-2.99]) also portended reduced PFS in patients without prior radiation therapy. Two hundred eighteen of 233 patients in this study qualified for the high-risk group of Radiation Therapy Oncology Group 0539, and they demonstrated similar outcomes (3-year PFS: 53.9% vs 58.8%). The good-prognostic group of SRS patients demonstrated slightly improved outcomes (3-year PFS: 63.1% vs 58.8%).

Conclusions: SRS should be considered in carefully selected patients with atypical meningiomas. We suggest the use of our good-prognostic group to optimize patient selection, and we strongly encourage the initiation of a clinical trial to prospectively validate these outcomes.

Introduction

Meningiomas are the most common primary intracranial tumor, and treatment most commonly consists of surgical resection or stereotactic radiosurgery (SRS), with or without adjuvant radiation therapy in selected patients with high-grade tumors.[1-3] Many meningiomas arise sporadically, but they can also present as part of genetic syndromes. These include neurofibromatosis type 2 and multiple endocrine neoplasia type 1.[4,5] World Health Organization (WHO) grade 2 meningiomas comprise roughly 4.2% to 20% of all meningiomas, and they include characteristics such as a mitotic rate of 4 to 19 per 10 high-powered fields, brain invasion, or at least 3 of 5 specific histologic features.[1,6,7] WHO grade 2 meningiomas are not malignant (like WHO grade 3 meningiomas), but they may require a different treatment paradigm than WHO grade 1 meningiomas due to their increased aggressiveness and propensity to recur.[8]

Radiation-based options for meningiomas include both external beam radiation therapy and radiosurgery.[9-11] The European Organisation for Research and Treatment of Cancer (EORTC) 22042-26042 trial was a nonrandomized phase 2 and observational study that showed improved 3-year progression-free survival (PFS) for WHO grade 2 meningioma patients undergoing a complete resection when treated with adjuvant radiation therapy.[12] The EORTC-1308 trial seeks to build upon this foundation and is the first randomized trial assessing early adjuvant radiation therapy versus long-term active monitoring for patients with WHO grade 2 meningioma after complete surgical resection.[13] Radiosurgery has also demonstrated safety and efficacy for WHO grade 1 meningiomas.[14] Patients with WHO grade 2 tumors, however, demonstrated inferior tumor control of 50% in a large patient cohort.[15] These outcomes studies all assessed the extent of resection using Simpson criteria.[16]

The Radiation Therapy Oncology Group (RTOG) 0539 trial presented prospective 3-year PFS of patients with meningioma after surgical resection. Patients were split into 3 risk groups, as opposed to a direct division by WHO grade, and those in the intermediate-risk and high-risk groups received adjuvant external beam radiation therapy.[17,18] The 3-year PFS for these 2 groups were 93.8% and 58.8%, respectively. Patients in the high-risk group also demonstrated increased rates of local failure and reduced overall survival (OS), suggesting that further progress is required in the treatment of WHO grade 2 meningiomas.[17] Prevention of tumor recurrence is important for these patients, as recurrences often result in increased morbidity (including subsequent surgical interventions) and decreased survival.[19]

This study assesses a large multi-institutional database to present the outcomes of WHO grade 2 meningiomas treated with SRS and compares the 3-year PFS to that presented in RTOG 0539.[17] This is the largest such data set known to the authors, and we aim to stratify patients for potential treatment with SRS into good-prognostic and poor-prognostic groups to optimize patient selection.

Methods and Materials

Cohort development

A database of 271 patients with WHO grade 2 and 3 meningiomas treated with SRS was assessed, including patients treated from 1994 to April 2019. These patients had demonstrable tumor at the time of SRS, as opposed to treatments of resection beds. Grade 3 meningiomas were subsequently excluded from the data set, and all included patients had histologic confirmation of WHO grade 2 tumors. The data were collected by the International Radiosurgery Research Foundation, in accordance with best ethical and institutional review board–approved practices. Each institution obtained local institutional review board approval before data collection. An agreement to share deidentified patient data with the coordinating site is also in place. Finally, the coordinating site shared this deidentified data with the principal investigator of the study. All patients had a minimum of 6 months of clinical and radiographic follow-up, but most patients had much longer follow-up.

Treatment delivery

SRS was conducted using Gamma Knife units. Treatment was performed in a multidisciplinary fashion with a neurosurgeon, radiation oncologist, and medical physicist. Dose selection was at the discretion of the local team and considered prior radiation treatments (if any), target volume, neurologic condition, and collateral structures. Key data related to treatment delivery included the date of SRS, maximum tumor diameter, tumor volume, margin dose, maximum dose, treatment volume, percent isodose line used for the margin dose, number of fractions, and number of isocenters used.

Follow-up

After initial SRS, patients were typically followed at 6-month intervals for the first 2 years and yearly thereafter. Follow-up evaluations typically included both clinical and radiologic assessments. Assessment of tumor volumes and maximal diameters was performed at the time of SRS, as well as at each subsequent radiographic imaging. The formula abc/2 was used to approximate the tumor volume.[20] Tumor regression was also recorded and defined as a 20% or greater reduction in the volume of the targeted meningioma after SRS. Adverse radiation events included radiation necrosis (also recorded as symptomatic or asymptomatic) or intratumoral or peritumoral hemorrhage. An adverse radiation effect was determined as a progressive increase in the volume of a treated meningioma by at least 25% over time, along with peritumoral edema, which resolved or significantly decreased over the course of months.[21] Radiation necrosis was more specifically defined as biopsy-proven radiation necrosis or via consensus multidisciplinary review of imaging and clinical features at each participating site (including neurosurgery, radiation oncology, and radiology). Magnetic resonance imaging (MRI) was chiefly used to assess imaging features. Metabolic imaging such as positron emission tomography/computed tomography or magnetic resonance spectroscopy were used at the discretion of the treating physicians of each site.

Primary endpoints

The primary endpoint of the study was 3-year PFS. Notable secondary endpoints included 5-year PFS, 3-year OS, 5-year OS, and 3-year local control. PFS was primarily assessed using the Kaplan-Meier method, with censoring for death or disease progression and the initial time point of the date of SRS. Similarly, OS was assessed using the Kaplan-Meier method, with censoring for death and the initial time point of the date of SRS. Tumor progression was assessed by response assessment in neuro-oncology (RANO) criteria for meningiomas and considered as a binary endpoint, and time to local failure was analyzed via the Kaplan-Meier method (with censoring for disease progression).[22] The RANO criteria were applied at the time of data collection by each participating site. Planned subset analyses included (1) patients presenting for SRS with prior radiation therapy compared with those without and (2) a comparison of the 3-year PFS, 3-year OS, and 3-year local control to the corresponding risk groups of RTOG 0539.[23]

Gross total resection (GTR) was defined as resection of the entirety of the tumor based upon the intraoperative observations of the neurosurgeon or the absence of residual disease on the first postoperative neuroimaging study with contrast (typically an MRI). Subtotal resection (STR) was excision of a portion of the tumor but with intraoperative observations of residual tumor or evidence of residual tumor on the first postoperative neuroimaging study with contrast (again, typically an MRI). Assessment of STR or GTR was made based on imaging, the medical chart, and operative notes at the time of data collection and was performed at each participating site. All sites have had extensive experience participating in prospective and retrospective neuro-oncology studies.

Statistical methodology

Statistical assessment primarily consisted of the Kaplan-Meier method and Cox proportional hazards multivariate analysis. The Kaplan-Meier method was chiefly used to assess continuous variables (PFS, OS, and time to local failure) using the univariable log-rank test. The threshold for statistical significance was $P < .05$ in all cases. Other notable findings were termed "statistical trends." The Kaplan-Meier approach was used for assessment of the entire cohort, as well as subsets of the data. Two datapoints were missing in the data set (the extent of surgical resection for 1 patient and the presence or absence of symptoms at

diagnosis for another). When possible, all patients were included in statistical analyses, but in cases in which these variables with missing data were required, one or both of these patients were omitted from the analysis. Cox proportional hazards analysis was conducted at various points of the study. All Cox models incorporated censoring of PFS for death or disease progression. Overall concordance of the Cox model was recorded as a relative measure of the loss of fidelity with the elimination of variables. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs) in all cases.

Recursive partitioning analysis

Recursive partitioning analysis (RPA) was conducted using decision-tree analysis. Code was written in Python using open-source packages to conduct this statistical method.[24-26] Similar approaches have also been used with other programs and coding languages.[27,28] The RPA was developed for the endpoint of PFS as a continuous variable, and censoring of the data for death or disease progression was also incorporated into model construction. Censoring was incorporated by using the log-rank test as the criterion for node splitting, and a concordance index that accounted for censoring was used as a measure of the model's accuracy.[29-31]

First, potential predictive factors of PFS were assessed and determined to include treatment volume, maximum dose, margin dose, no new symptoms at the time of SRS, no prior radiation therapy to the target, multiple prior surgical resections, GTR (as opposed to STR), asymptomatic at diagnosis, age at SRS, sex, and location (convexity or parasagittal vs other). These variables were chosen because they were the key variables assessed in prior studies, and we sought to minimize overfitting by selecting a smaller initial set of variables for analysis.[15,17,18,32-34]

First, a correlation heatmap was generated to determine the relative correlations between variables. RPA was then conducted using a range of feature and selection criteria, so varied split, leaf, and maximum depth criteria were considered in potential models. The training set was used for model development, along with the validation set. The validation set served as a test of the accuracy of each potential model as it was constructed. After the highest-fidelity model for the validation set was selected, the test set was used to independently assess the model's accuracy. All variables selected via RPA were subsequently assessed via Cox hazards analysis to verify their predictive power for PFS.

Results

Patient cohort

The patient cohort considered in this study consisted of 233 patients from 12 institutions. The 12 institutions each contributed an average of 19 patients: 67, 45, 37, 19, 14, 14, 12, 11, 6, 5, 2, and 1 patients, respectively. There were 45% male patients and 55% female patients, presenting at a median age of 60 years (13-90) for SRS. The location of the treated meningioma varied, including the cerebral convexity (30%), parasagittal (37%), the skull base (33%), and ventricular (1%). Most patients initially presented with symptoms, including seizure (19%), headache (28%), or another neurologic deficit (66%). Thirty percent of patients had at least 2 resections before SRS, and GTR and STR rates were similar (48% and 52%, respectively). Twelve patients (5%) progressed from grade 1 to 2 between resections. Most meningiomas demonstrated necrosis on histologic assessment (63%), and brain invasion was reported in 35% of cases. Most patients had not undergone prior radiation therapy at the time of SRS (79%).

At the time of SRS, the median Karnofsky performance status was 90 (50-100), and patients presented at a median 25.4 months (0.4-262.9) after primary diagnosis. Patients received SRS at a median 12.1 months after the last resection (0.0-161.4). Patients were often treated with steroids (37%) or antiepileptics (34%) before SRS. Most patients did not have symptoms before SRS (59%), but many had a new neurologic deficit (31%). A median 12.5 (1-47) isocenters were used to treat a median tumor volume of 4.74 cm^3 (0.14-54.5). The median treatment volume was 6.1 cm^3 (0.1-97.6). Radiosurgery was delivered in one fraction for most cases (97%), and a median 15 Gy (10-30) was delivered to a median percent isodose of 50 (30-80; Table 1).

Treatment outcomes

At a median clinical follow-up of 37.6 months after SRS (6.0-281.7), 87% of patients were alive. A significant minority of patients (27%) had clinical follow-up of at least 5 years. The primary endpoint of 3-year PFS was 53.9%, and the 5-year PFS was 33.1% (Fig. 1). Three-year OS was 93.6%, and 5-year OS was 83.0%. Using the RANO criteria, 49% of patients experienced tumor progression after SRS, occurring at a median 18.5 months (1.1-90.1) after SRS.[22] Of these, 50% were biopsy-proven recurrences. Conversely, 34% of patients had tumor regression by the RANO criteria, occurring at a median 8.7 months (1.6-94.7) after SRS. Additional SRS, non-SRS radiation therapy, and resection were required in 36%, 13%, and 26% of patients, respectively (Table 2). PFS, OS, and time to local failure were stratified by early radiation therapy compared with late radiation therapy after the last surgical resection, using thresholds of 12 months, 6 months, and 3 months. No statistically significant differences were noted (Table E1). The only potential statistical trend consisted of potentially improved time to local failure in patients with radiation therapy at least 12 months after the last surgical resection, compared with early treatment ($P = .08$), but this finding is not definitive.

Table 1 Patient demographics, clinical presentation, and treatment details of SRS

Clinical characteristic		Treatment	
Patients	233	Median Karnofsky performance status at the time of SRS	90 (50-100)
Institutions	12	Tumor progression before SRS	186/232 (80.2%)
Sex		Treatment before SRS	
Male	105/233 (45.1%)	Steroids	85/233 (36.5%)
Female	128/233 (54.9%)	Antiepileptic medication	79/233 (33.9%)
Median age (y)	60 (13-90)	Median time from diagnosis (mo)	25.4 (0.4-262.9)
Location		Most recent surgical assessment	
Cerebral convexity	69/233 (29.6%)	Tumor volume at surgery (cm^3)	31.2 (1.15-392.8)
Parasagittal	86/233 (36.9%)	Maximum diameter at surgery (cm)	4.8 (1.8-8.9)
Skull base	76/233 (32.6%)	Postoperative median volume (cm^3)	2.1 (0-66.9)
Ventricular	2/233 (0.9%)	Postoperative maximum diameter (cm)	1.1 (0-16.5)
Symptoms at original presentation		Symptoms before SRS	
None	20/232 (8.6%)	None	137/233 (58.8%)
Seizure	44/232 (19.0%)	Headache	16/233 (6.9%)
Headache	66/232 (28.4%)	New seizure	15/233 (6.4%)
Other neurologic deficit	152/232 (65.5%)	New neurologic deficit	72/233 (30.9%)
Surgery before SRS		Other tumors	
At least 1	230/233 (98.7%)	Prior other irradiated intracranial tumors	10/233 (4.3%)
At least 2	70/233 (30.0%)	Other meningiomas	32/233 (13.7%)
Median mo from last surgery	12.2 (0-163.7)	Multiple tumors treated	19/233 (8.2%)
Peritumoral edema at diagnosis	95/219 (43.4%)	Median no. of isocenters	12.5 (1-47)
Degree of resection		No. of fractions	
Gross total resection	112/232 (48.3%)	1	227/233 (97.4%)
Subtotal resection	120/232 (51.7%)	>1	6/233 (2.6%)
Histologic features		Volume	
Necrosis present	127/202 (62.9%)	Median tumor volume (cm^3)	4.74 (0.14-54.5)
Brain invasion present	67/193 (34.7%)	Median maximum tumor diameter (cm)	2.6 (0.8-34.7)
Nuclear atypia present	60/187 (32.1%)	Median treatment volume (cm^3)	6.1 (0.1-97.6)
Median Ki-67 (%)	13 (2-40)		
Prior treatments		Dose	
No prior radiation therapy	183/233 (78.5%)	Median margin dose (Gy)	15 (10-30)
Prior stereotactic radiosurgery	14/233 (6.0%)	Median % isodose	50 (30-80)
Prior external beam radiation therapy	37/233 (15.9%)	Median maximum dose (Gy)	28 (18-53.5)

Abbreviation: SRS = stereotactic radiosurgery.

Recursive partitioning analysis

An initial set of variables was determined for assessment, consisting of treatment volume, maximum dose, margin dose, no new symptoms at the time of SRS, no prior radiation therapy to the target, multiple prior surgeries, GTR (as opposed to STR), asymptomatic at diagnosis, age at SRS, sex, and location (convexity or parasagittal vs other). A correlation heatmap was generated, demonstrating significant correlation between margin dose and maximum dose. Maximum dose was eliminated from further assessment, as prescription dose has previously been identified as a potential correlate with tumor control.[14]

After splitting the data into training, test, and validation sets, RPA was conducted. This analysis identified 2 key threshold values: age >50 years and treatment volume >10 to 12 cm^3. These thresholds were then applied to the whole data set, in place of the corresponding continuous variables. Five variables consistently demonstrated high degrees of importance in the highest-fidelity models: age >50 years, multiple prior resections, treatment volume over 10 to 12 cm^3, no prior radiation therapy to the target, and asymptomatic at diagnosis. The treatment volume threshold was optimized, and 11.5 cm^3 was identified as the optimal threshold using Kaplan-Meier analysis.

Model development

These variables were assessed using multivariate Cox hazards analysis to verify the results of the RPA. Elimination of the 6 variables not included in the highest fidelity RPA models was accomplished without significant loss of

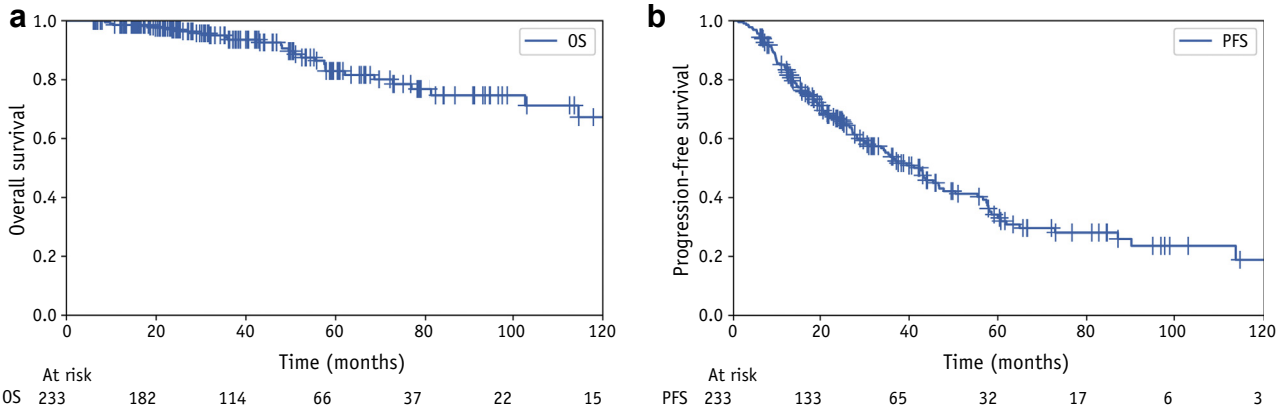

Fig. 1. Kaplan-Meier curves of overall survival (a) and progression-free survival (b) for the overall cohort are shown.

Table 2 Important treatment outcomes

Outcome	
Median clinical follow-up (mo)	37.6 (6.0-281.7)
Patients alive at last clinical follow-up	202/233 (86.7%)
Median radiographic follow-up	36.2 (6.0-279.3)
Tumor progression by RANO criteria	113/233 (48.5%)
Median time to progression (mo)	18.5 (1.1-90.1)
Tumor regression by RANO criteria	78/233 (33.5%)
Median time to regression (mo)	8.7 (1.6-94.7)
Adverse radiation effects	
None	203/233 (87.1%)
Asymptomatic radiation effects	14/233 (6.0%)
Symptomatic radiation effects	13/233 (5.6%)
Asymptomatic hemorrhage	2/233 (0.9%)
Symptomatic intracranial hemorrhage	1/233 (0.4%)
Median time to radiation effects (mo)	7.2 (1.8-69.9)
Treatments for adverse radiation effects	
Steroids	7/30 (23.3%)
Surgery	4/30 (13.3%)
Bevacizumab	6/30 (20.0%)
Other	1/30 (3.3%)
Any neurologic toxicity	48/233 (20.6%)
New cranial nerve palsy	
Resolved	8/233 (3.4%)
Permanent	9/233 (3.9%)
Median time to new cranial nerve palsy (mo)	33.9 (0.2-178.3)
Other new fixed neurologic deficit	23/233 (11.1%)
New seizures or epilepsy	25/233 (10.7%)
New anticonvulsant during follow-up	30/233 (12.9%)
Additional SRS	84/233 (36.1%)
Median time to SRS (mo)	20.9 (1.1-90.3)
Additional non-SRS radiation therapy	30/233 (12.9%)
Median time to non-SRS radiation therapy (mo)	33.8 (2.1-150.8)
Additional surgery	61/233 (26.2%)
Median time to surgery	27.7 (3.8-179.4)

Abbreviation: SRS = stereotactic radiosurgery.

the concordance of the resulting Cox model (0.65-0.64) (Fig. E1). Of the remaining 5 variables, asymptomatic at diagnosis demonstrated only a trend on Kaplan-Meier analysis toward improved PFS ($P = .09$); furthermore, due to it only applying to 20 patients, the confidence intervals were wide (Fig. E2). Because the variable applied to so few patients, it contributed little to a final stratification of the data, and it was therefore eliminated from the final model. Multiple prior surgical resections and prior radiation therapy were combined into a single variable at this stage because they both represented additional prior treatment to the atypical meningioma. The remaining variables were assessed via the Kaplan-Meier method: age >50 years ($P = .01$), treatment volume >11.5 cm^3 ($P = .10$), and prior radiation therapy or multiple resections ($P = .01$). Loss of concordance was minimal (0.64-0.62) on subsequent Cox hazards analysis including only these 3 variables, and because the resulting hazards ratios were similar among the 3 variables, each was assigned a value of 1 point in the subsequent score.

The model is demonstrated in Figure 2a. Good-prognostic group patients (score, 0-1) had improved PFS ($P < .005$) and time to local failure ($P < .005$) relative to the poor-prognostic group patients (score, 2-3; Fig. 2b). This translated to increased 3-year PFS (63.1% vs 41.9%) and 3-year local control (62.2% vs 42.1%). There was also a trend toward improved OS ($P = .09$), with increased 3-year OS (98.0% vs 87.7%). A flow diagram is also shown to demonstrate the clinical utility of this model (Fig. 2c).

Assessment of prior radiation therapy

The variables were then assessed in the patients with and without prior radiation therapy separately (Fig. 3). Age >50 years (HR = 1.85; 95% CI, 1.09-3.14) and multiple prior resections (HR = 1.80 [1.09-2.99]) again

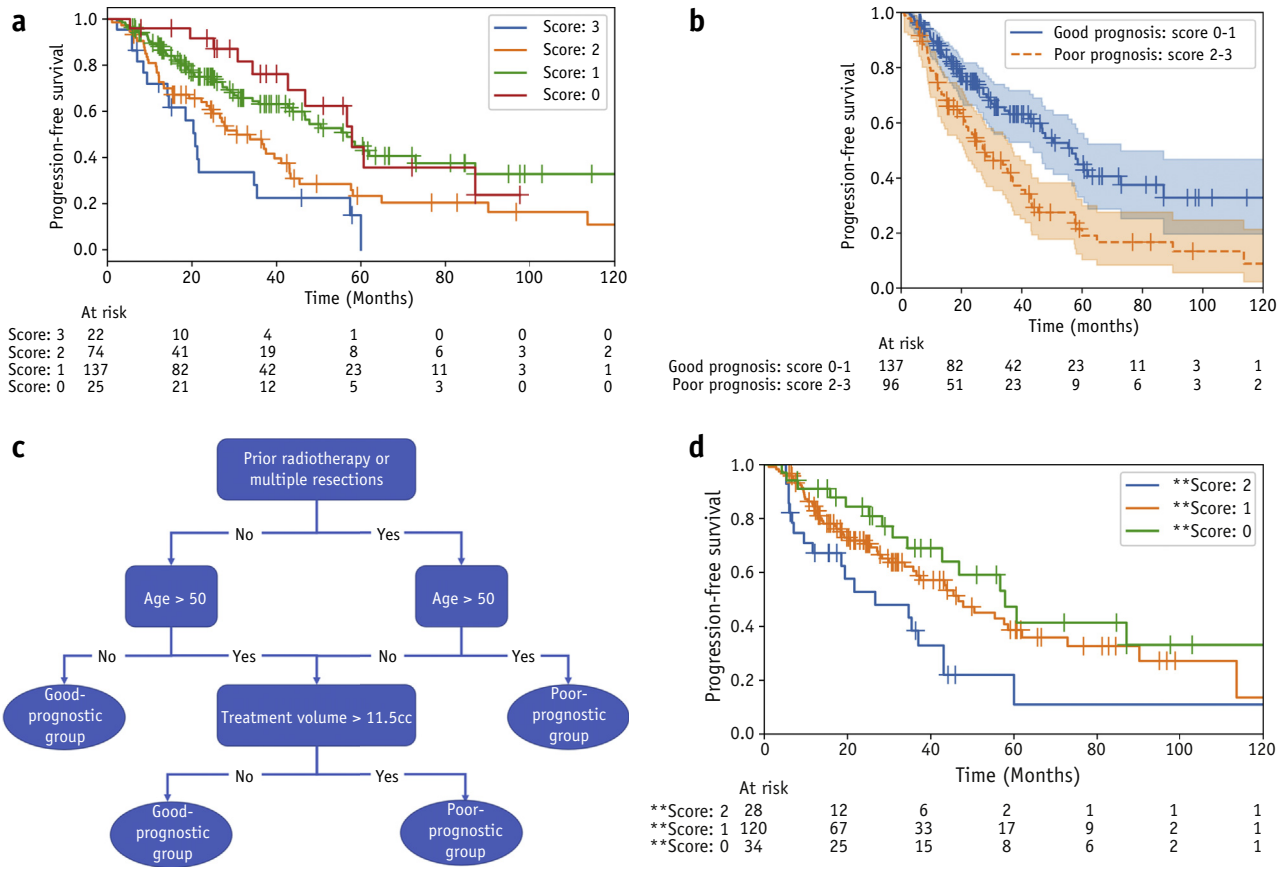

Fig. 2. Stratifications of the cohort are portrayed, with 95% confidence intervals for Kaplan-Meier plots. (a) First, progression-free survival is stratified by overall score (∗), which was defined as 1 point each for the following variables: age >50 years, treatment volume >11.5 cm^3, and prior radiation therapy or multiple surgical resections. (b) Next, the cohort is divided into a good-prognostic group (score, 0-1) and a poor-prognostic group (score, 2-3), using the same scoring system (∗; $P < .005$). (c) The flow diagram of the final model's clinical utility is shown. (d) Finally, the model was then applied to patients without prior radiation therapy, revealing 2 remaining key predictive factors. The resulting score (∗∗) was determined as 1 point each for age >50 years and multiple prior resections.

demonstrated statistical significance in the no prior radiation therapy group, and the risk score using only these 2 variables is shown in Figure 2d. Only age >50 years (HR = 3.90 [1.43-10.67]) demonstrated significance in the prior radiation therapy group.

Comparison to RTOG 0539

RTOG 0539 enrolled 178 patients in the phase 2 trial of "Observation for Low-Risk Meningioma and of Radiotherapy for Intermediate and High-Risk Meningioma."[23] Patients were divided into 3 risk groups. Group 1 consisted of new WHO grade 1 meningiomas after GTR or STR. Group 2 consisted of recurrent WHO grade 1 meningiomas after GTR or STR, as well as new WHO grade 2 meningiomas after GTR. Finally, group 3 contained any WHO grade 3 meningioma, any recurrent WHO grade 2 meningioma, or a new WHO grade 2 meningioma after STR. Initial outcomes for the intermediate-risk group (group 2) demonstrated 3-year PFS of 93.8%, and the 3-year PFS of the high-risk group was 58.8%.[17,18]

The patient cohort considered in this study was divided using the same criteria as RTOG 0539, resulting in 14 patients who would have been candidates for RTOG 0539 group 2 (intermediate risk) and 218 patients who would have been candidates for group 3 (high risk). The first group of patients demonstrated 100.0% 3-year OS and 51.4% 3-year PFS. The second group has 93.1% 3-year OS and 53.9% 3-year PFS (Table 3). Within the high-risk group of RTOG 0539, a subgroup analysis demonstrated numerically inferior 3-year PFS for recurrent WHO grade 2 patients compared with initial WHO grade 3 patients (45.0% vs 64.7%). Due to the small numbers in this subgroup analysis, however, the (superior) results of the entire study cohort were used as a comparison to the results presented in this study.

Other notable predictive factors

Assessment of other notable predictive factors was conducted to assess the effect of histologic features on PFS. Overall, there was no significant evidence that Ki-67 (tested as a continuous and a dichotomized variable), necrosis, or

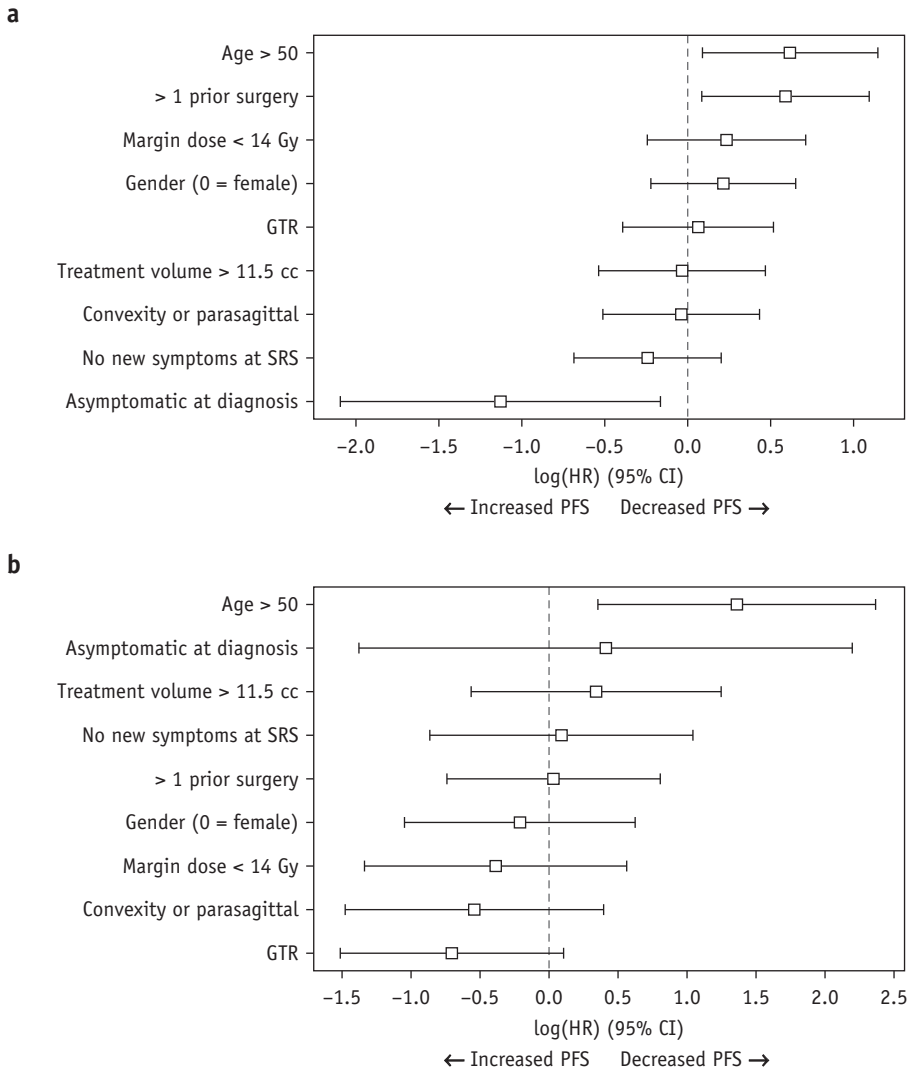

Fig. 3. Results of the multivariate Cox hazards analyses of progression-free survival (PFS) for the (a) no prior radiation therapy and (b) prior radiation therapy subsets are shown. *Abbreviations*: CI = confidence interval; GTR = gross total resection; SRS = stereotactic radiosurgery.

nuclear atypia affected PFS. There was a trend toward reduced PFS with brain invasion, but this did not achieve statistical significance ($P = .18$).

Patient symptoms did meet the threshold for significance, however. Patients with no symptoms at the time of SRS demonstrated improved OS ($P = .03$) and patients who were asymptomatic at diagnosis showed a trend toward improved PFS ($P = .09$).

Toxicity

Patients in this cohort experienced any neurologic toxicity in 21% of cases. Only 11% of patients experienced a new, fixed neurologic deficit, however. New seizures or epilepsy presented in 11% of patients, requiring the initiation of anticonvulsants during follow-up in 13% of cases. Adverse radiation effects were reported in 30 cases, including asymptomatic radiation effects (6%) and symptomatic radiation effects (6%). These occurred at a median 7.2 months (1.8-69.9) after SRS, and treatment most commonly consisted of steroids (23%), bevacizumab (20%), or open surgery (13%). The 4 patients who underwent surgical treatment had symptomatic radiation necrosis (n = 3) or symptomatic intracranial hemorrhage (n = 1).

Discussion

Overall, patients demonstrated favorable 3-year OS (93.6%) and 3-year PFS (53.9%) after SRS for WHO grade 2 meningiomas, comparable with the results of the high-risk group from RTOG 0539. A model was developed to stratify patients into a good-prognostic group (score, 0-1) and a poor-prognostic group (score, 2-3) to aid in patient selection for SRS. In particular, patients with age >50

Table 3 Key treatment outcomes of good-prognostic SRS group, poor-prognostic SRS group, and external beam radiation therapy outcomes from RTOG 0593

Groups	N*	3-y PFS, %	3-y OS, %	3-y local control, %
SRS: good-prognostic group	137	63.1	98.0	62.2
SRS: poor-prognostic group	96	41.9	87.7	42.1
RTOG 0539: intermediate-risk	48	93.8	96	3-y local failure: 4.1†
RTOG 0539: high-risk	51	58.8	78.6	68.9
SRS: intermediate-risk candidates for RTOG 0539	14	51.4	100.0	51.4
SRS: high-risk candidates for RTOG 0539	218	53.9	93.1	53.7

Abbreviations: RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery.

The SRS intermediate-risk and high-risk candidates for RTOG 0539 consider patients who would have qualified for the intermediate and high-risk groups of RTOG 0539, respectively.

* N indicates the number of patients evaluated for the primary endpoint (3-year progression-free survival).

† Indicates that this value is different than the column header. In this box, the 3-year local failure rate is reported, as opposed to the 3-year local control.

years, multiple prior resections or prior radiation therapy, and treatment volume >11.5 cm^3 demonstrated reduced PFS. Age >50 years and multiple prior resections also portended reduced PFS for patients without prior radiation therapy.

The most direct comparison for the outcomes of this study is those of RTOG 0539. The intermediate-risk group of RTOG 0539 included 16 recurrent WHO grade 1 tumors and 36 patients with WHO grade 2 meningioma after GTR.[18] The high-risk group of RTOG 0539 was composed of 11 initial WHO grade 2 cases, 17 initial WHO grade 3 cases, 8 recurrent WHO grade 2 cases, 5 recurrent WHO grade 3 cases, and 12 patients with recurrence on imaging only.[17] Only 14 patients in this study would have qualified for the intermediate-risk group of RTOG 0539, and the overall outcomes of this study were very comparable with those of the high-risk group of RTOG 0539 (3-year PFS 53.9% vs 58.8%). Specifically, patients in this study who would have qualified for the high-risk group of RTOG 0539 also demonstrated similar values for the primary endpoint of 3-year PFS (53.9% vs 58.8%). The good-prognostic group of SRS patients may even have slightly improved outcomes (3-year PFS 63.1% vs 58.8%).

This data set did not contain grade 3 meningiomas like the high-risk group of RTOG 0539, so one could question whether their inclusion may have led to a reduction in 3-year PFS. A post hoc analysis of the high-risk RTOG 0539 group actually demonstrated decreased 3-year and 5-year PFS in recurrent WHO grade 2 tumors compared with newly diagnosed WHO grade 3 meningiomas (45.0% vs 64.7% and 30.0% vs 58.2%, respectively). There were few patients included in this post hoc analysis, but this comparison describes the vast majority of WHO grade 3 tumors included in RTOG 0539, as there were only 5 total patients with recurrent WHO grade 3 meningiomas included. Overall, these details further indicate that the data set considered in this study is comparable to that of the high-risk portion of RTOG 0539, as opposed to the intermediate-risk group. Therefore, the results of treatment of atypical meningiomas (especially those termed "high-risk" by RTOG 0539) with SRS indicate that SRS should be considered in appropriately selected patients.

We suggest the use of our good-prognostic group category for optimizing patient selection, and we strongly encourage the initiation of a phase 2 clinical trial assessing 3-year PFS to prospectively analyze these outcomes. To our knowledge, this analysis presents the first such stratification of grade 2 meningiomas using RPA, and this subgroup likely identifies patients most likely to benefit from this treatment approach. Additionally, the median follow-up time of 37.6 months after SRS may be insufficient to demonstrate a translation of improved PFS to an OS benefit in the good-prognostic group. For this reason, it is unknown whether the outcomes demonstrated in this study may also result in an OS benefit at a longer duration of follow-up. Similarly, long-term follow-up is needed to definitively understand the effect of adjuvant radiation therapy on OS in patients with atypical meningiomas.

Regardless of whether this PFS benefit translates to improved OS, the effect of improved PFS must be weighed against the morbidity of tumor recurrence and salvage therapy. Significant variation exists in delineations of the region at risk for radiation therapy, with no set consensus regarding treatment volumes.[35] Naturally, such differences could affect toxicity. It is also possible that improved reproducibility and prognostication of the meningioma grading system allows for a more accurate and consistent comparison of meningiomas, resulting in the consistent findings of improved PFS with adjuvant radiation therapy.[1,6,7]

One potential concern could be whether the age criterion influences PFS due to its effect on OS; however, the time to local failure was also improved in the good-prognostic group, and the OS only demonstrated a trend toward improvement. This may point to different underlying tumor biology or other reasons why younger patients may be better SRS candidates.[36-38] Further investigation into this underlying reason is undoubtedly required.

The finding that multiple prior resections or prior radiation therapy was a strong predictor for reduced PFS is an intuitive finding that matches other results in the literature. Hwang et al determined that imaging characteristics and the extent of surgical resection were better predictors of meningioma recurrence than WHO grade in their retrospective review of 144 patients.[39] Other predictors of progression in the literature include subtotal resection, parafalcine/parasagittal location, peritumoral edema, high mitotic index, high MIB-1 labeling index, tumor size, and

certain cytokines (eg, hepatocyte growth factor).[40-45] It may be that the relative effects of the histologic predictors were dampened because this data set specifically assessed patients with WHO grade 2, leading to increased homogeneity of these factors compared with other studies. The importance of prior disease recurrence, however, is consistent throughout the literature.[17] The novel treatment volume threshold of 11.5 cm^3 addresses the inherent difficulties in treating larger tumors (potentially especially with radiosurgery). However, the fact that this variable did not maintain statistical significance within the subgroup analyses of prior radiation therapy and no prior radiation therapy suggests that its influence on PFS is likely less than that of patient age and a history of multiple prior treatments.

A separate consideration for patients with recurrent WHO grade 2 meningiomas concerns the potential for repeat resection. Optimal patient selection for additional surgical resection remains to be determined, but small retrospective studies have demonstrated potential benefit for additional surgical intervention.[46,47] Even so, subsequent tumor recurrence rates remain high, suggesting a potential benefit for patients in our "good-prognostic group" with the addition of SRS.

Assessment for other notable predictors of patient outcomes yielded 2 significant conclusions: (1) Tumor histology failed to further stratify patients within this cohort of WHO grade 2 meningiomas, and (2) patient symptoms may be important predictors of survival. Due to the relative rarity of WHO grade 2 meningiomas, most studies concerning asymptomatic meningiomas have considered tumors of varying histologic grades. Two studies have demonstrated an increased rate of complications with resection of asymptomatic meningiomas, suggesting the value of a more restrictive surgical threshold for elderly patients.[33,48] Our results corroborate those of Yano et al, who found that about 63% of asymptomatic meningiomas did not exhibit tumor growth, and only 6% of patients experienced symptoms during the observation period of the study.[34] Finally, larger tumors may have increased likelihood for being WHO grade 2 on final pathology, so this factor should also be considered before making a decision regarding potential surgical resection.[32] Overall, it appears that many patients with asymptomatic meningiomas may be candidates for observation, due to the minimal effect of these tumors on survival and low rates of development of further symptoms.

One limitation of this study is that the RTOG 0539 trial enrolled patients immediately after surgery, but the patients in this cohort received SRS at a median 12 months after the last resection. In other disease sites, differences in the time from primary diagnosis or last treatment have been linked to survival outcomes, but no such differences in outcomes were noted in this study.[49] In RTOG 0539, gross tumor volume was defined as the tumor bed on postoperative MRI, inclusive of any nodular enhancement.[17] This likely resulted in larger gross tumor volumes than those used in this study. Furthermore, because this study included only patients with demonstrable tumor at SRS, it is likely that the patients treated in this study were even higher risk than those in RTOG 0539. In this setting, the encouraging results presented in this study occurred despite this difference that likely favored patients in RTOG 0539. Next, the comparison to RTOG 0539 is imperfect owing to the differences in their inclusion criteria in the high-risk and intermediate-risk groups, compared with WHO grade. Overall, however, there are sufficient similarities to draw meaningful conclusions from comparing these 2 cohorts. Additionally, the median number of MRI scans per patient during this period of follow-up was not available. We urge future investigators to consider reporting this variable in subsequent publications as an additional descriptor of the follow-up paradigm. Finally, our modeling efforts were applied to a moderately sized data set. External and prospective validation of the model should be undertaken.

Conclusions

SRS should be considered in carefully selected patients with atypical meningiomas. We suggest the use of our good-prognostic group category for optimizing patient selection, and we strongly encourage the initiation of a clinical trial to prospectively analyze these outcomes. Patients with age $\leq$50 year, up to 1 prior resection, and no prior radiation therapy would likely be appropriate candidates.

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