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Supervised machine learning algorithms demonstrate proliferation index correlates with long-term recurrence after complete resection of WHO grade I meningioma

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OBJECTIVE Meningiomas are the most common primary intracranial tumor, and resection is a mainstay of treatment. It is unclear what duration of imaging follow-up is reasonable for WHO grade I meningiomas undergoing complete resection. This study examined recurrence rates, timing of recurrence, and risk factors for recurrence in patients undergoing a complete resection (as defined by both postoperative MRI and intraoperative impression) of WHO grade I meningiomas.

METHODS The authors conducted a retrospective, single-center study examining recurrence risk for adult patients with a single intracranial meningioma that underwent complete resection. Uni- and multivariate nominal logistic regression and Cox proportional hazards analyses were performed to identify variables associated with recurrence and time to recurrence. Two supervised machine learning algorithms were then implemented to confirm factors within the cohort that were associated with recurrence.

RESULTS The cohort consisted of 823 patients who met inclusion criteria, and 56 patients (6.8%) had recurrence on imaging follow-up. The median age of the cohort was 56 years, and 77.4% of patients were female. The median duration of head imaging follow-up for the entire cohort was 2.7 years, but for the subgroup of patients who had a recurrence, the median follow-up was 10.1 years. Estimated 1-, 5-, 10-, and 15-year recurrence-free survival rates were 99.8% (95% confidence interval [CI] 98.8%–99.9%), 91.0% (95% CI 87.7%–93.6%), 83.6% (95% CI 78.6%–87.6%), and 77.3% (95% CI 69.7%–83.4%), respectively, for the entire cohort. On multivariate analysis, MIB-1 index (odds ratio [OR] per 1% increase: 1.34, 95% CI 1.13–1.58, p = 0.0003) and follow-up duration (OR per year: 1.12, 95% CI 1.03–1.21, p = 0.012) were both associated with recurrence. Gradient-boosted decision tree and random forest analyses both identified MIB-1 index as the main factor associated with recurrence, aside from length of imaging follow-up. For tumors with an MIB-1 index < 8, recurrences were documented up to 8 years after surgery. For tumors with an MIB-1 index ≥ 8, recurrences were documented up to 12 years following surgery.

CONCLUSIONS Long-term imaging follow-up is important even after a complete resection of a meningioma. Higher MIB-1 labeling index is associated with greater risk of recurrence. Imaging screening for at least 8 years in patients with an MIB-1 index < 8 and at least 12 years for those with an MIB-1 index ≥ 8 may be needed to detect long-term recurrences.

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KEYWORDS meningioma; complete resection; gross-total resection; recurrence; MIB-1; Ki-67; oncology

ABBREVIATIONS CI = confidence interval; GBDT = gradient-boosted decision tree; GTR = gross-total resection; HR = hazard ratio; OR = odds ratio; SRS = stereotactic radiosurgery.

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Meningiomas are the most common benign intracranial tumors,[1] and radiological diagnosis rates have been increasing over the past decade.[2] Resection is the next most common intervention after observation,[3] and for WHO grade I tumors, gross-total resection (GTR) is associated with lower risk of progression on follow-up.[4–7] Defining a complete resection can be assessed intraoperatively, classically using the Simpson grading scale, or on postoperative MRI. Rates of local recurrence after GTR of a meningioma range from 7% to 23% at 5 years, from 13% to 39% at 10 years, and from 24% to 60% at 15 years.[7] In a study of parasagittal meningiomas, the recurrence rate after 25 years was 47% for the entire cohort and 38% after Simpson grade I/II resections.[8] However, historical studies examining recurrence after complete resection relied mostly on intraoperative surgical impression and did not consistently incorporate postoperative MRI results. Furthermore, intraoperative surgeon impression of the extent of resection does not always correlate with postoperative MRI findings, and extent of resection can be less favorable on early postoperative MRI when compared to a surgeon's Simpson grade.[9,10] Similarly, a small residual noted at the time of surgery may be missed on postoperative imaging, depending on MRI slice thickness and location.

For patients who undergo subtotal resection or who have a WHO grade II or III meningioma, long-term imaging follow-up is indicated given the higher risk of recurrence and/or progression. However, for WHO grade I tumors undergoing complete resection (as defined by both postoperative MRI and intraoperative impression), it is unclear what duration of imaging follow-up is reasonable. Furthermore, it is unclear what patient or tumor factors are associated with a higher risk of recurrence after complete resection of a WHO grade I tumor, which may indicate that longer follow-up is needed. In this study, we examined recurrence rates, timing of recurrence, and risk factors for recurrence in patients undergoing complete resection of WHO grade I meningiomas based on both postoperative MRI and intraoperative surgeon impression. These data can help guide neurosurgeons and neuro-oncologists to identify which patients are at risk of recurrence and may benefit from long-term follow-up.

Methods

Study Design

This was a retrospective cohort study conducted at an academic medical center (University of California, San Francisco [UCSF] Medical Center). After we obtained approval from the UCSF IRB to conduct the study, the UCSF tumor registry was searched for adult patients who underwent a resection of an intracranial meningioma between 1990 and 2019. Inclusion criteria were patients who 1) were 18 years of age or older at the time of surgery, 2) were undergoing their first surgery for a WHO grade I meningioma, 3) underwent a GTR as defined by complete resection on postoperative MRI and based on surgeon impression (Simpson grade I/II resection), and 4) had an electronic medical record with available imaging and documentation of clinical outcomes. Patients were excluded from the study if they 1) had undergone a Simpson grade III–V resection, 2) had a diagnosis of neurofibromatosis type 2, 3) had undergone prior radiotherapy to the meningioma, 4) had multiple intracranial meningiomas at the time of surgery, or 5) developed an unrelated malignancy requiring systemic chemotherapy. Patients were not excluded if an additional meningioma was diagnosed on follow-up imaging after the date of surgery.

Patient and Tumor Variables

Patient variables included age, sex, date of first surgery, follow-up duration, history of radiation exposure, and date of death. Tumor variables included location (classified as convexity, skull base, intraventricular, or falx/parasagittal), tumor side (left/right), tumor dimensions (maximum diameters in axial, sagittal, and transverse planes) and volume (estimated using the "[length × width × height]/2" method), and MIB-1 labeling index. The MIB-1 labeling index was obtained from the pathology report, which specified the percentage of MIB-1 positivity based on immunohistochemical staining. Early in the study period, MIB-1 was obtained at the discretion of the attending neuropathologist, but later, MIB-1 was obtained in all patients with WHO grade I meningiomas. Surgical and clinical variables included Simpson grade, recurrence status, and date of recurrence. Simpson grade was gathered from operative reports when possible, and otherwise was interpreted retrospectively based on dictated surgeon impression in the operative report. For 18 patients, a distinction between a Simpson grade I and II resection was not available, but the primary surgeon had noted a complete resection. For *FOXM1* analysis, gene expression data were available for 50 of the patients within the cohort (NCBI gene expression omnibus accession no. GSE183656), which had been obtained previously.[11]

Clinical Outcomes of Interest

The main outcome of the study was tumor recurrence as diagnosed by imaging. Neuroradiologist and neurosurgeon agreement were required to consider growth on follow-up imaging as a recurrence. Follow-up imaging consisted of MRI or CT. In certain instances, imaging was obtained for other medical reasons. Other outcomes of interest included the diagnosis of an additional meningioma on follow-up surveillance.

Statistical Analysis

Demographic data and baseline characteristics were assembled and analyzed in the standard fashion. Recurrence-free survival was calculated using the Kaplan-Meier method. Uni- and multivariate Cox proportional hazards analyses were performed to identify variables associated with time to recurrence. Multivariate analyses were performed for variables with p values < 0.05 on univariate analysis. Two supervised machine learning algorithms based on decision trees (gradient-boosted decision trees [GBDTs] and random forests) were employed to determine the absolute importance of the 8 variables previously used in univariate analyses in predicting recurrence. These two algorithms have been previously validated for clinical risk

prediction.[12,13] For each machine learning algorithm, absolute importance measures for predicting recurrence were generated for all 8 variables. The most important variables for each machine learning model were then compared to the significant predictors as assessed by uni- and multivariate logistic regression.

The recursive partitioning algorithm in the statistical program JMP (version 15.0, SAS Institute Inc.) was used to determine optimal cutoffs for the MIB-1 index in predicting tumor recurrence. This partition algorithm searched all possible cutoffs of the continuous MIB-1 variable to best predict recurrence as a binary variable. The level of significance was 0.05 for all analyses. Statistical analyses were performed in JMP and RStudio (version 1.4.1106, RStudio Team 2021; https://www.rstudio.com/). Random forest and GBDT models were developed using the *randomForest* and *gbm* packages in R, respectively.

Results

Demographic, Tumor, and Clinical Characteristics

Of the 1879 patients who had a meningioma resected during the study period, 889 had a WHO grade I meningioma, and 823 of those patients met the remainder of the study's inclusion criteria. Patient demographics, tumor characteristics, and surgical variables are shown in Table 1. The median age of the cohort was 56 years, and 77.4% of the patients were female. The most frequent tumor location was the skull base (48.8%). Of the 805 patients with reported Simpson grade, 453 (56.3%) were Simpson grade I and 352 (43.7%) were grade II. The median tumor volume was noted to be 8.9 cm^3. Of the 313 patients with a documented MIB-1 labeling index, the median index was 2.5, and 296 patients (94.6%) had an index less than 8. The median duration of head imaging follow-up for the entire cohort was 2.7 years (Table 2). An analysis of patients with short-term follow-up (< 2 years) versus those with more long-term follow-up (≥ 2 years) revealed that most patient and tumor factors were no different between the two groups (Supplemental Table 1).

TABLE 1. Patient demographics and tumor characteristics

Variable	Value
No. of patients	823
Median age at resection (IQR, range), yrs	56 (47–66, 8–99)
Median tumor volume (IQR, range), cm^3*	8.9 (3.2–28.4, 0.03–280.6)
Median max tumor diameter (IQR, range), cm†	3.2 (2.2–4.6, 0.5–11.3)
Sex, n (%)	
F	637 (77.4)
M	186 (22.6)
Prior radiation exposure, n (%)	18 (2.2)
Side, n (%)	
Lt	373 (45.3)
Rt	324 (39.4)
Midline	126 (15.3)
Tumor location, n (%)	
Skull base	402 (48.8)
Convexity	250 (30.4)
Falx/parasagittal	159 (19.3)
Intraventricular	12 (1.5)
Simpson grade, n (%)‡	
I	453 (56.3)
II	352 (43.7)
MIB-1/Ki-67 index, n (%)§	
<8	296 (94.6)
≥8	17 (5.4)
Median MIB-1/Ki-67 index (IQR, range)	2.5 (1.9–4.0, 0–18.1)

* n = 764.
† n = 779.
‡ n = 805.
§ n = 313.

Postoperative Outcomes and Recurrences

Of the 823 total patients, 56 (6.8%) had tumor recurrence on follow-up verified by both a neuroradiologist and neurosurgeon. The median time to tumor recurrence was 4.4 years. The median overall imaging follow-up time for the subgroup of patients who had a recurrence was 10.1 years. Additionally, 9 patients (1.1% of the cohort) were diagnosed with a secondary, remote intracranial meningioma on follow-up imaging after surgery (Table 2).

The median times to recurrence for skull base, convexity, and falx/parasagittal meningiomas were 4.4, 3.0, and 4.6 years, respectively. Figure 1 shows overall recurrence-free survival for the cohort and distribution of times to documented recurrence. Estimated 1-, 5-, 10-, and 15-year recurrence-free survival rates were 99.8% (95% confidence interval [CI] 98.8%–99.9%), 91.0% (95% CI 87.7%–93.6%), 83.6% (95% CI 78.6%–87.6%), and 77.3% (95% CI 69.7%–83.4%), respectively, for the entire cohort. For skull base tumors, estimated 1-, 5-, 10-, and 15-year recurrence-free survival rates were 100% (no events), 89.8% (95% CI 84.5%–93.5%), 78.4% (95% CI 70.3%–84.8%), and 72.4% (95% CI 60.8%–81.6%). For convexity tumors, estimated 1-, 5-, 10-, and 15-year recurrence-free survival rates were 100% (no events), 94.3% (95% CI 88.4%–97.3%), 92.7% (95% CI 85.7%–96.4%), and 89.2% (95% CI 77.5%–95.2%). Finally, for falx/parasagittal tumors, estimated 1-, 5-, 10-, and 15-year recurrence-free survival rates were 99.1% (95% CI 94.0%–99.9%), 88.5% (95% CI 78.3%–94.3%), 81.7% (95% CI 69.2%–89.9%), and 68.6% (95% CI 46.8%–84.5%). There were no recurrence events for patients undergoing complete resection of an intraventricular meningioma (n = 12) who had a median imaging follow-up of 0.4 years.

Of the 56 patients with tumor recurrence on follow-up, 11 (19.6%) were symptomatic. Recurrences were treated in 48 cases (85.7%), with 38 of these treatments consisting of either stereotactic radiosurgery (SRS) or fractionated radiotherapy, 8 cases treated with surgery alone, and 2 cases treated with surgery and adjuvant SRS. Of the 8 patients not treated at recurrence, 4 were lost to follow-up while the remainder did not have continued progression or new symptoms.

TABLE 2. Tumor recurrence by location

Variable	Skull Base	Convexity	Falx/Parasagittal	Intraventricular	Total
No. of patients	402	250	159	12	823
Recurrences, n (%)	34 (8.5)	9 (3.6)	13 (8.2)	0 (0)	56 (6.8)
Median time to recurrence (range), yrs	4.4 (1.1–20.7)	3.0 (1.8–11.8)	4.6 (0.9–12.6)	—	4.4 (0.9–20.7)
Median yrs of imaging follow-up (range)	2.8 (0.0–30.8)	3.0 (0.0–27.7)	2.5 (0.0–20.3)	0.4 (0.0–7.6)	2.7 (0.0–30.8)
Symptomatic at recurrence, n (%)*	5 (14.7)	3 (33.3)	3 (23.1)	—	11 (19.6)
Visual changes	3	1	1	—	5
Hearing changes	1	0	0	—	1
Weakness	0	2	2	—	4
Headaches	0	0	1	—	1
Gait changes	0	0	2	—	2
Cognitive changes	0	0	2	—	2
Facial pain/paresthesias	1	0	0	—	1
Multiple meningiomas at recurrence, n (%)	4 (11.8)	2 (22.2)	3 (23.1)	—	9 (16.1)
Received treatment for recurrence, n (%)	30 (88.2)	8 (88.9)	11 (84.6)	—	48 (85.7)
SRS or RT only	25	7	7	—	38
Surgery only	5	1	2	—	8
Surgery + SRS	0	0	2	—	2

RT = radiation therapy.
* Patients with multiple symptoms at recurrence had each symptom counted.

Patient and Tumor Factors Associated With Recurrence

Recurrence-free survival differed significantly between falx/parasagittal and convexity meningiomas ($p < 0.05$, log-rank test; falx/parasagittal vs convexity odds ratio [OR] 2.58, 95% CI 1.10–6.04, $p = 0.03$) and between skull base and convexity meningiomas ($p < 0.05$, log-rank test; skull base vs convexity OR 2.50, 95% CI 1.2–5.22, $p = 0.015$; Fig. 2A, Table 3). There was also a significant difference in recurrence-free survival between meningiomas that underwent Simpson grade I and grade II resections ($p \leq 0.05$; Simpson grade II vs I OR 1.85, 95% CI 1.06–3.24, $p = 0.031$; Fig. 2B, Table 3). To statistically determine the MIB-1 index that best separated patients who would progress from those who would not, we performed recursive partitioning analysis for recurrence as the outcome of interest and identified an optimal split at an MIB-1 index score of 8. Comparing recurrence-free survival between meningiomas with MIB-1 labeling indices of < 8 and ≥ 8 yielded a statistically significant difference ($p < 0.01$; Fig. 2C). Given the interest in other molecular markers that may predict higher risk of recurrence on follow-up, we analyzed previously collected *FOXM1* expression, a marker of proliferation and poor clinical outcomes, for a subset of patients with available data (n = 50) and found that there was a higher level of *FOXM1* expression among patients who had a recurrence ($p = 0.017$; Supplemental Fig. 1).

Next, we examined whether MIB-1 scores changed during the 30-year study period due to factors such as changes in pathologists or MIB-1 quantification methods. To assess whether the time period may have impacted MIB-1 average scores, we split the study period in half (1989–2005 [n = 592] vs 2005–2019 [n = 231]) and MIB-1 scores were compared between the two groups. The median MIB-1 staining indices from 1989 to 2005 and from 2005 to 2019 were 2.8 (IQR 1.72–4.0) and 2.0 (IQR 2.0–4.0), respectively ($p = 0.396$). Thus, although multiple pathologists were part of the clinical care of these patients over this 30-year study period, there were no significant differences in the median MIB-1 score over time.

Uni- and multivariate analyses were then performed to examine predictors of recurrence as a binary outcome (Table 4). Univariate analysis found that tumor location, tumor volume, MIB-1 index, Simpson grade, and follow-up duration were all associated with documented recurrence. On multivariate nominal logistic regression analysis, MIB-1 index (OR per 1% increase: 1.34, 95% CI 1.13–1.58, $p = 0.0003$) and follow-up duration (OR per year longer: 1.12, 95% CI 1.03–1.21, $p = 0.012$) were both associated with recurrence.

A Cox proportional hazards analysis was then performed to examine factors associated with time to recurrence (Table 3). Univariate analysis showed that falx/parasagittal location ($p = 0.030$), skull base location ($p = 0.015$), tumor volume ($p = 0.017$), MIB-1 index ($p = 0.002$), and Simpson grade II resection ($p = 0.031$) were significantly associated with shorter recurrence-free survival. We then performed multivariate analysis using these significant variables, which demonstrated that only MIB-1 index was significantly associated with reduced time to recurrence (hazard ratio [HR] 1.22, 95% CI 1.08–1.37, $p = 0.001$). The multivariate Cox proportional hazards analysis was then repeated with the continuous MIB-1 index variable substituted with an MIB-1 index cutoff of 8, which yielded only an MIB-1 index ≥ 8 ($p = 0.003$) as significantly associated with recurrence (HR 5.03, 95% CI 1.72–14.71). To mitigate analysis biases related to limited follow-up, the same multivariate Cox proportional analysis was applied to the subgroup of patients

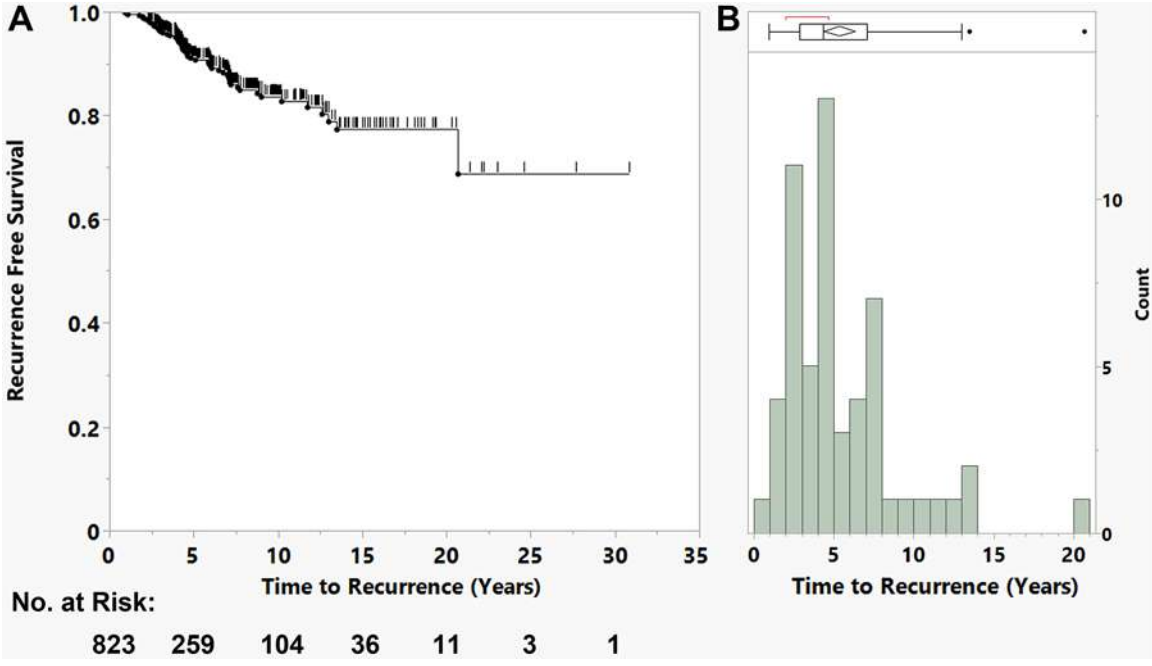

FIG. 1. Overall recurrence-free survival for the cohort. **A:** Kaplan-Meier curve of censored recurrence-free survival for the cohort. Estimated 1-, 5-, 10-, and 15-year rates of recurrence-free survival were 99.8% (95% CI 98.8%–99.9%), 91.0% (95% CI 87.7%–93.6%), 83.6% (95% CI 78.6%–87.6%), and 77.3% (95% CI 69.7%–83.4%) for the entire cohort. **B:** Histogram display of distribution of time to recurrence. At the top of the figure is a box plot with outliers. The *diamond* is a means diamond; i.e., the top and bottom of the diamond are a 95% CI for the mean. The *red line* denotes the densest region with half the values. Figure is available in color online only.

with at least 2 years of imaging follow-up. This analysis demonstrated that the MIB-1 index was still the only factor significantly associated with time to recurrence (HR 1.24, 95% CI 1.10–1.39, p = 0.0005).

Supervised machine learning algorithms were then implemented to identify factors within the cohort that were associated with recurrence. Two supervised machine learning algorithms based on decision trees (GBDT and

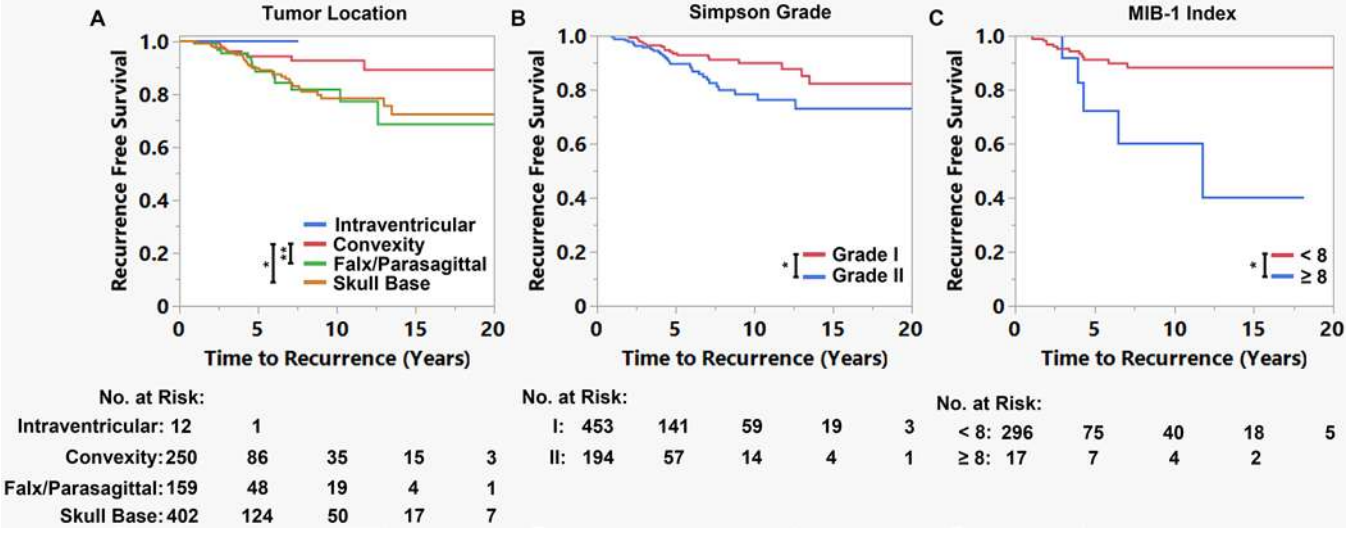

FIG. 2. Recurrence-free survival by tumor location, Simpson grade, and MIB-1 index score. **A:** When compared to convexity meningiomas, both falx/parasagittal and skull base meningiomas were at higher risk of recurrence on imaging follow-up (*p = 0.012, **p = 0.027). **B:** Simpson grade II resections were at higher risk of recurrence on follow-up compared to grade I resections (*p = 0.028). **C:** An MIB-1 index ≥ 8 was associated with increased risk of progression on follow-up (*p = 0.0026). Figure is available in color online only.

TABLE 3. Uni- and multivariate analysis of characteristics associated with time to recurrence

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Sex				
F	1.0 (ref)		—	—
M	1.48 (0.83–2.65)	0.186	—	—
Age at resection, yrs	1.00 (0.98–1.02)	0.762	—	—
Tumor location				
Convexity	1.0 (ref)		1.0 (ref)	
Falx/parasagittal	2.58 (1.10–6.04)	**0.030**	0.42 (0.04–3.95)	0.446
Skull base	2.50 (1.20–5.22)	**0.015**	1.90 (0.42–8.56)	0.406
Tumor side				
Lt	1.0 (ref)		—	—
Rt	1.15 (0.65–2.02)	0.637	—	—
Midline	0.77 (35–1.74)	0.534	—	—
Tumor volume	1.01 (1.00–1.01)	**0.017**	1.01 (0.99–1.02)	0.423
MIB-1/Ki-67 index	1.18 (1.06–1.30)	**0.002**	1.22 (1.08–1.37)	**0.001**
MIB-1/Ki-67 index grouped				
<8	1.0 (ref)		—	—
≥8	4.29 (1.53–12.06)	**0.006**	—	—
Simpson grade				
I	1.0 (ref)		1.0 (ref)	
II	1.85 (1.06–3.24)	**0.031**	1.60 (0.47–5.48)	0.456
Prior radiation exposure	0.61 (0.08–4.42)	0.624	—	—

Boldface type indicates statistical significance.

random forests) were employed to determine the absolute importance of the 8 variables previously used in univariate analyses in predicting recurrence. Aside from imaging follow-up duration, the MIB-1 index was the main factor associated with recurrence using these two separate algorithms (Fig. 3).

Discussion

Key Results

This study aimed to identify rates of recurrence following a complete resection of an intracranial WHO grade I meningioma as defined by MRI and by intraoperative

TABLE 4. Uni- and multivariate nominal regression analysis of factors associated with recurrence

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Sex, F vs M	0.71 (0.39–1.30)	0.27		
Age at resection, by yr	0.99 (0.97–1.01)	0.15		
Tumor location, vs convexity				
Falx/parasagittal	2.38 (0.99–5.72)	0.052	0.30 (0.03–3.03)	0.31
Skull base	2.47 (1.17–5.25)	**0.018**	1.92 (0.41–9.00)	0.41
Tumor side, vs lt				
Rt	1.27 (0.71–2.29)	0.42		
Midline	1.03 (0.45–2.37)	0.94		
Tumor volume, by cm^3	1.01 (1.00–1.02)	**0.027**	1.01 (0.99–1.02)	0.55
MIB-1 index, by increase of 1%	1.28 (1.11–1.48)	**0.0011**	1.34 (1.13–1.58)	**0.0003**
Simpson grade, II vs I	1.92 (1.08–3.41)	**0.025**	2.02 (0.53–7.63)	0.29
Follow-up duration, by yr	1.17 (1.12–1.22)	**<0.0001**	1.12 (1.03–1.21)	**0.012**

Boldface type indicates statistical significance.

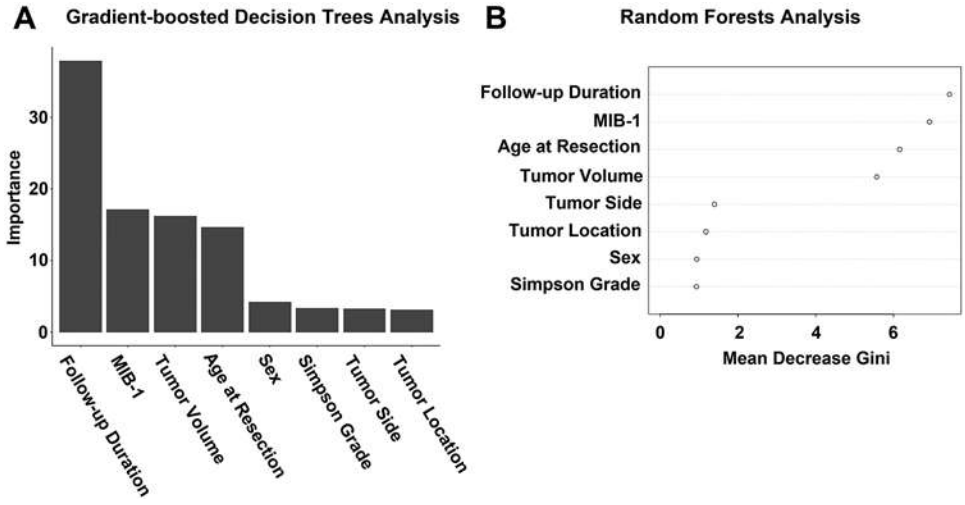

FIG. 3. Results of supervised machine learning algorithms based on decision trees to identify variables associated with recurrence. **A:** Absolute importance of variables in predicting recurrence based on GBDTs. Importance of variables is ranked from left to right. **B:** Absolute importance of variables in predicting recurrence based on random forests. Variables with a greater mean decrease in the Gini index signify a variable of higher importance. Besides imaging follow-up duration, MIB-1 was the main factor associated with recurrence in both analyses.

surgeon impression. We found that the median time to recurrence was 4.4 years, ranging from 1 year to over 20 years from initial surgery. However, the median imaging follow-up in this cohort of 823 patients was short (2.7 years), suggesting that some providers or patients may forego long-term imaging follow-up in this clinical context. Imaging was the primary form of detecting recurrence as fewer than 20% of patients were symptomatic at the time of documented regrowth, yet more than 85% of patients subsequently underwent intervention. Only longer follow-up and a higher MIB-1 labeling index were significantly associated with recurrence on multivariate analysis. Using recursive partitioning, a threshold MIB-1 index of 8 was the best cutoff for predicting recurrence in this cohort.

Meningioma Recurrence Risk After GTR

Reported rates of recurrence among meningiomas vary depending on tumor grade, characteristics, and surveillance practices at each institution. Overall, recurrence risk after a GTR of a meningioma is not negligible. Indeed, a Response Assessment in Neuro-Oncology (RANO) review noted recurrence risk rates at 5, 10, and 15 years to be 7%–23%, 20%–39%, and 24%–60%, respectively, after GTR of a meningioma.[7] A further study by Pettersson-Segerlind et al. demonstrated that 38% of parasagittal meningiomas that underwent Simpson grade I/II resections recurred after 25 years of follow-up.[8] The estimated recurrence risk was similar in the current study despite a strict definition of complete resection, including both surgeon impression and postoperative MRI assessment. This large cohort, therefore, verifies prior reports that typically relied on surgeon impression alone to define the extent of resection.

Proliferation Index as a Predictor of Recurrence

Higher MIB-1 labeling index has been found to correlate with both the risk of meningioma recurrence after resection and poorer clinical outcomes across multiple studies.[14,15] This remains true when only studying WHO grade I meningiomas, although such studies did not limit analysis to only those patients undergoing a complete resection.[6,16] Although tumor location and tumor volume were significant for recurrence risk on univariate analysis, we found that neither was significant on multivariate analysis. Other studies examining WHO grade I meningioma outcomes after either GTR or subtotal resection similarly reported no association between location and tumor progression.[5] These findings suggest that it is intrinsic meningioma biology that dictates long-term recurrence risk. Molecular grouping of meningiomas appears to predict recurrence-free survival better than extent of resection, treatment with radiation, or WHO grade.[17]

Of the 313 patients with available MIB-1 index scores in the present cohort, the median value was 2.5%, and only 17 (5.4%) had a result of 8 or greater. In their cohort of 239 WHO grade I meningiomas, Haddad et al. reported a mean MIB-1 index of 3.3 with a range of 0.0–18.11.[6] Marciscano et al. reported a median MIB-1 index of 1.9% in a group of 71 meningiomas without atypical features, with 13 of them having an index of at least 3%.[18] Oya et al. reported that, among 205 WHO grade I meningiomas, 37 (18%) had an MIB-1 index greater than 3%.[19] While the cutoff determined in this study appears to be on the higher end of the ranges previously reported, it is important to note that MIB-1 index as a continuous variable was predictive of recurrence. In practice, the cutoff itself could be a helpful tool for clinicians.

Proposed Imaging Paradigm

One goal of the study was to determine the minimum length of imaging follow-up based on risk factors of recurrence after complete resection of a WHO grade I meningioma. Recurrence for the cohort was documented from

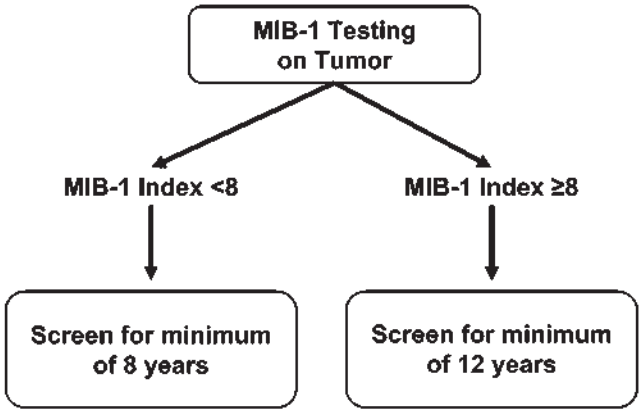

FIG. 4. Recommended minimum duration of imaging follow-up based on current cohort. MIB-1 testing is recommended at the time of surgery to obtain a proliferation index. For tumors with an index < 8, at least 8 years of annual screening is recommended. For tumors with an index ≥ 8, at least 12 years of annual screening is recommended.

0.93 to 20.7 years after surgery. When examining subgroups of patients with minimum imaging follow-up durations of 2, 5, 10, and 15 years, recurrence risk rates were 11.3% (53/467 patients), 15.5% (43/278 patients), 22.2% (28/126 patients), and 23.9% (11/46 patients), respectively. Thus, longer imaging follow-up appeared to increase the percentage of patients with documented recurrence, consistent with the logistic regression and supervised machine learning analyses.

As MIB-1 index was the only variable on multivariate Cox proportional hazards and nominal logistic regression analyses associated with recurrence, which was confirmed as significant on random forest and GBDT analysis, a proposed imaging paradigm was developed taking this variable into account (Fig. 4). For tumors with an MIB-1 index < 8, recurrences were documented up to an imaging follow-up of 8 years. Thus, imaging screening for at least 8 years identified 100% of recurrences for patients with an MIB-1 index < 8 and 48 (85.7%) of 56 recurrences within the entire cohort. For tumors with an MIB-1 index ≥ 8, recurrences were documented up to an imaging follow-up of 12 years. Thus, imaging screening for at least 12 years identified 100% of recurrence for patients with an MIB-1 index ≥ 8 and 52 (92.9%) of 56 recurrences within the entire cohort.

In general, there is a lack of guidance on the duration of postoperative surveillance needed for WHO grade I meningiomas undergoing complete resection. Prior consensus reports have suggested imaging annually or every 2 years up to 9 years after resection, with consideration of stopping afterward.[20] Based on the results of this study, longer follow-up may be needed. A general recommendation would be to proceed with annual screening for 2–5 years when recurrence risk is greatest (based on Fig. 1) and then space them out to every 2 years after that. The MIB-1 index appears to be a good differentiator of recurrence risk on follow-up, yet even for patients with an MIB-1 proliferation index < 8, recurrences were still noted as long as 8 years. This study provides guidance on what we believe is the "minimal" length of follow-up needed in this patient population (Fig. 4). Ideally, even longer follow-up can be pursued; longer follow-up may allow for earlier SRS treatment of asymptomatic recurrence as opposed to more complex management of larger, symptomatic recurrences.

The median follow-up duration of only 2.7 years in this cohort suggests that either patients or surgeons are electing to stop screening early, and actual recurrence rates may be underestimated due to this. Thus, these data may help neurosurgeons counsel patients on the long-term risk of recurrence and need for long-term imaging follow-up, regardless of whether a complete resection was achieved. As with other areas of meningioma management such as the treatment of incidental meningiomas,[21] interventions including recommended imaging follow-up durations should be data driven. Future studies should continue to investigate molecular markers that guide imaging follow-up paradigms in a data-driven manner.

Study Limitations

This study is a retrospective study and was limited by recall bias. We could only evaluate patients who had adequate documentation of pre- and postoperative examinations and available imaging. Furthermore, over the study period, postoperative MR images may have been obtained with different slice thicknesses, which could not be controlled for. Given the retrospective nature of the study, we could not standardize imaging follow-up or ensure MIB-1 testing for all patients in the cohort. Thus, recurrence rates may be underestimated due to shorter follow-up or patients following up elsewhere.

Conclusions

In this retrospective study of WHO grade I meningiomas undergoing complete resection, estimated 1-, 5-, 10-, and 15-year rates of recurrence-free survival were 99.8%, 91.0%, 83.6%, and 77.3%, respectively. The median time to recurrence was 4.4 years, and longer follow-up was associated with increased diagnosis of recurrence. Furthermore, most recurrences were detected on imaging, and most patients were asymptomatic. These data demonstrate the importance of long-term follow-up even for patients considered "low risk" after a complete resection of a meningioma. Longer follow-up may allow for earlier SRS treatment of asymptomatic recurrence as opposed to more complex management of larger, symptomatic recurrences. The MIB-1 labeling index may help predict which patients are at greater risk of recurrence after a complete resection.

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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: Morshed. Acquisition of data: Morshed, Nguyen, Dalle Ore, Cummins, Saggi, Chen, Choudhury, Ravi, Raleigh. Analysis and interpretation of data: Morshed, Nguyen, Saggi. Drafting the article: Morshed, Nguyen, Magill, McDermott, Theodosopoulos. Critically revising the article: Morshed, Nguyen, Chen, Choudhury, Raleigh, Magill, McDermott, Theodosopoulos. Reviewed submitted version of manuscript: Morshed, Nguyen, Dalle Ore, Cummins, Saggi, Chen, Choudhury, Raleigh, Magill, McDermott, Theodosopoulos. Approved the final version of the manuscript on behalf of all authors: Morshed. Statistical analysis: Morshed, Nguyen, Saggi. Study supervision: Morshed, Theodosopoulos.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Table 1 and Fig. 1. https://thejns.org/doi/suppl/10.3171/2022.4.JNS212516.

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