The Impact of MRI-Defined Extent of Resection Across Meningioma DNA Methylation Groups: Re-Evaluating Surgery in the Era of Meningioma Molecular Classification

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BACKGROUND AND OBJECTIVES: Extent of resection (EOR) is prognostic for meningioma outcomes. DNA methylation profiling can shed light on biological drivers and therapeutic vulnerabilities. The goal of this study was to re-evaluate the impact of EOR on clinical outcomes across meningioma DNA methylation groups.

METHODS: Patients with sporadic meningiomas who underwent resection from a multicenter, international cohort were retrospectively reviewed. Gross vs subtotal resection (GTR vs STR, respectively) was determined based on postoperative MRI. The Kaplan-Meier method, log-rank statistics, and multivariable Cox proportional hazard analyses were performed to evaluate the impact of EOR on local freedom from recurrence (LFFR) and overall survival (OS).

RESULTS: In total, 587 patients (Male: 195, Female: 392) underwent 644 surgeries for intracranial meningioma (GTR: 438, STR: 206), with 124 surgeries (19.3%) for recurrent intracranial meningiomas. The cohort included 375 (58.2%) World Health Organization (WHO) Grade 1, 202 (31.4%) WHO Grade 2, and 67 (10.4%) WHO Grade 3 meningiomas based on histological criteria. DNA methylation profiling was used to categorize meningiomas as Merlin-intact (N = 214, 33.2%), Immune-enriched (N = 236, 36.6%), or Hypermitotic (N = 194, 30.1%). GTR was associated with longer LFFR across all meningioma DNA methylation groups (Merlin-intact $P < .0001$; Immune-enriched $P = .013$; Hypermitotic $P = .001$) and was associated with longer OS for Hypermitotic meningiomas ($P = .0022$). In multivariable Cox proportional hazard analyses, EOR was significantly associated with LFFR across all DNA methylation groups and WHO grades but was significantly associated with OS only for Hypermitotic meningiomas (hazard ratio [GTR vs STR] 0.64, 95% CI 0.43-0.97, $P = .034$).

CONCLUSION: MRI-defined GTR is associated with improved LFFR across all meningioma DNA methylation groups and improved OS for patients with Hypermitotic meningiomas. These data continue to support maximal safe resection when feasible and demonstrate how molecular classification systems complement rather than supersede the prognostic impact of surgery.

KEY WORDS: Meningioma, Recurrence, DNA methylation, Extent of resection, Molecular classification

ABBREVIATIONS: BLM1, Baseline Model 1; **BLM2,** Baseline Model 2; **EOR,** extent of resection; **GTR,** gross total resection; **LFFR,** local freedom from recurrence; **OS,** overall survival; **STR,** subtotal resection; **WHO,** World Health Organization.

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Extent of resection (EOR) is consistently prognostic across all World Health Organization (WHO) meningioma grades.[1-5] Although the Simpson grade has historically been used to quantify EOR, groups such as the European Organization for Research and Treatment of Cancer and the Radiation Therapy Oncology Group have categorized EOR as gross total resection (GTR) or subtotal resection (STR) based on radiographic features to help differentiate surgical outcomes for clinical trials.[5,6] Nevertheless, maximal safe resection remains a cornerstone of meningioma treatment and provides tissue for diagnosis, relief of mass effect, and improved local control.

Recently, the WHO has implemented molecular criteria (eg, *CDKN2A/B* homozygous deletion, *TERT* promoter mutation) for meningioma grading, and there has been a concerted effort to develop molecular meningioma classification systems that incorporate genomic features to shed light on meningioma biological drivers, therapeutic vulnerabilities, and risk stratification. These molecular systems correlate with local freedom from recurrence (LFFR) and overall survival (OS).[7-14] DNA methylation profiling is an example of such a molecular risk stratification system, and prior work has identified 3 different DNA methylation groups, including Merlin-intact, Immune-enriched, and Hypermitotic meningiomas, that are associated with an increasing risk of recurrence.[11] As molecular classification systems such as this may become clinically implemented in the future to help risk-stratify meningiomas, it will be critical for neurosurgeons to understand the impact of EOR within different molecular groups to help guide surgical decision making. To address this, the goal of this retrospective, international cohort study was to re-evaluate the impact of EOR on LFFR and OS across meningioma DNA methylation groups.

METHODS

Study Design

This was an international retrospective cohort study that included WHO grade 1 to 3 meningiomas that were resected at 2 separate institutions (University of California, San Francisco = 295; University of Hong Kong = 349) from 1991 to 2022 and had available DNA methylation profiling data. Postoperative MRI was used to determine EOR, and cases were classified as either GTR if no residual tumor was present on MRI or STR if any residual tumor was present. As this was a multicenter study with deidentified patient data shared between sites, there was no centralized review of imaging including assessment of location. Sites defined meningioma EOR and recurrence based on radiology reports with an additional team member reviewing imaging and clinical documentation as confirmation. Patients were excluded if they had a diagnosis of NF2-related schwannomatosis. WHO grading was assigned using the contemporary WHO scale at the time of resection. For all tumors resected before 2021, WHO 2016 or earlier WHO grading criteria were used, which only relied on histological tumor features. Three tumors were resected after 2021, and these were graded according to WHO 2016 criteria for the study based on histological features for consistency purposes. As part of routine clinical care, all patients included in this study signed a written waiver of informed consent to contribute deidentified data to research. The Institutional Review Boards at each institution approved the study.

Variables and Outcomes of Interest

Patient-related and treatment-related variables included age at the time of resection, sex, EOR, newly diagnosed vs recurrent presentation, postoperative radiotherapy, and length of follow-up. Postoperative radiotherapy consisted of stereotactic radiosurgery, fractionated radiotherapy, or intraoperative brachytherapy, which was typically reserved for recurrent high-grade meningiomas. Meningioma location was available for 290 tumors (45%) in the cohort as this feature was not reported across all sites. Clinical outcomes of interest included LFFR and OS from resection.

DNA Methylation Profiling and Analysis

A detailed account of the DNA methylation profiling and analysis methods have been previously reported.[11] DNA was extracted from all meningiomas included in the study and was processed on the Illumina Methylation EPIC BeadChip (WG-317-1003, Illumina) at the Molecular Genomics Core at the University of Southern California. Differentially methylated DNA probes were selected from a discovery cohort of 200 meningiomas from (University of California) using principal component analysis and scree/elbow plots, with a total of 2000 probes selected across the top 3 principal components. After DNA probe selection, the SeSAMe pipeline (Bioconductor v3.10) and k-means consensus clustering was used to assign the meningiomas to 3 DNA methylation groups. The optimal number of groups was analyzed using consensus matrices and indices, and validated the choice of 3 groups using the Kolmogorov-Smirnov test ($P < 2.2 \times 10^{-16}$). This analysis and statistical significance was confirmed in a validation cohort of 365 meningiomas from Hong Kong University. Although the DNA methylation probes alone did not identify a common genomic region or pathway underlying these groups, the DNA methylation groups were further characterized using DNA copy number status, RNA expression, chromatin accessibility, and cellular heterogeneity. This integrative analysis revealed that Merlin-intact meningiomas encode at least one functional copy of the NF2/Merlin tumor suppressor gene and have a favorable prognosis. Immune-enriched meningiomas have significant Immune cell infiltration and increased expression of human leukocyte antigen and meningeal lymphatic genes. Hypermitotic meningiomas are distinguished by convergent genetic and epigenetic mechanisms misactivating the cell cycle and have the worst clinical.[11] These DNA methylation groups are similar in nature to other molecular groups of meningiomas reported in the literature.[4,12,13,15]

Statistical Analysis

Statistical analyses were performed in JMP (version 16.0, SAS Institute Inc.) and R (version 4.4.0., R Foundation for Statistical Computing). Demographic data and baseline characteristics were assembled, and summary statistics were provided. The Kaplan-Meier method was used to evaluate the impact of EOR on LFFR and OS from the time of surgery, log-rank statistics were used to assess significance, and a LogNormal distribution was used for modeling of time-to-event estimates. Multivariable Cox proportional hazard analyses were performed for each DNA methylation group and each WHO grade and included age, sex, EOR, newly diagnosed vs recurrent presentation, and postoperative radiotherapy. To identify variables predictive of LFFR and compare the performance of various models, receiver operating characteristic (ROC) curve and area under the curve (AUC) analyses were performed using the *riskRegression* package in R. First, Cox models were constructed in a nested fashion to include a set of variables in a "baseline" model and a new model was

TABLE 1. Descriptive Statistics of Patients, Meningiomas, and Treatments for the Study Cohort

Feature	All patients	Merlin-intact	Immune-enriched	Hypermitotic
No. of patients	587	211	216	160
No. of surgeries	644	214	236	194
Median follow-up, y (IQR)	5.8 (2.1-9.5)	7.2 (3.1-10.7)	6.2 (2.3-9.4)	4.3 (1.7-8.1)
Median age at surgery (IQR)	57.6 (47.5-67.0)	55.7 (46.9-66.0)	55.3 (46.7-63.6)	60 (51.2-72.3)
Male	195 (33.2%)	53 (25.1%)	69 (31.9%)	72 (45%)
Female	392 (66.8%)	158 (74.9%)	147 (68.1%)	88 (55%)
Setting				
Newly diagnosed	520 (80.7%)	202 (94.4%)	196 (83.1%)	122 (62.9%)
Recurrent	124 (19.3%)	12 (5.6%)	40 (16.9%)	72 (37.1%)
Extent of resection				
Gross total resection	438 (68.0%)	152 (71%)	171 (72.5%)	115 (59.3%)
Subtotal resection	206 (32.0%)	62 (29%)	65 (27.5%)	79 (40.7%)
Postoperative radiotherapy (data unavailable for 2 cases)	133 (20.7%)	27 (12.7%)	35 (14.8%)	71 (36.8%)
Location[a] (data unavailable 354 cases)				
Convexity	80 (27.6%)	23 (24.5%)	31 (32.6%)	26 (25.7%)
Parasagittal/Falx	88 (30.3%)	19 (20.2%)	30 (31.6%)	39 (38.6%)
Skull Base	98 (33.8%)	48 (51.0%)	23 (24.2%)	27 (26.7%)
Other	24 (8.3%)	4 (4.3%)	11 (11.6%)	9 (9%)
World Health Organization grade				
1	375 (58.2%)	154 (72%)	153 (64.8%)	68 (35.1%)
2	202 (31.4%)	53 (24.8%)	62 (26.3%)	87 (44.8%)
3	67 (10.4%)	7 (3.2%)	21 (8.9%)	39 (20.1%)
DNA methylation group				
Merlin-intact	214 (33.2%)			
Immune-enriched	236 (36.6%)			
Hypermitotic	194 (30.1%)			

generated for each additional variable added. Then, for each model, an ROC curve and a set of time-dependent AUC values and 95% CIs were generated using 5-fold cross-validation. Finally, time-dependent AUC values were compared between models using Wald tests. The level of significance was set at $P < .05$ for all analyses.

RESULTS

Study Cohort

In total, 587 patients (Male: 195, Female: 392) underwent resection of 644 meningiomas (GTR: 438, 68%; STR: 206, 32%). Details of the study cohort are provided in Table 1. The cohort comprised 375 (58.2%) WHO grade 1, 202 (31.4%) grade 2, and 67 (10.4%) grade 3 meningiomas based on histological criteria. There were 124 surgeries (19.3%) for recurrent meningiomas. For patients with available meningioma location, 80 (27.6%) were convexity, 88 (30.3%) were parasagittal/falx, 98 (33.8%) were skull base, and 24 (8.3%) were classified as other locations.

DNA methylation profiling was used to categorize meningiomas as Merlin-intact (N = 214, 33.2%), Immune-enriched (N = 236, 36.6%), or Hypermitotic (N = 194, 30.1%). There was an association between the DNA methylation group and WHO grade (Pearson χ^2 $P < .0001$). Merlin-intact meningiomas consisted of

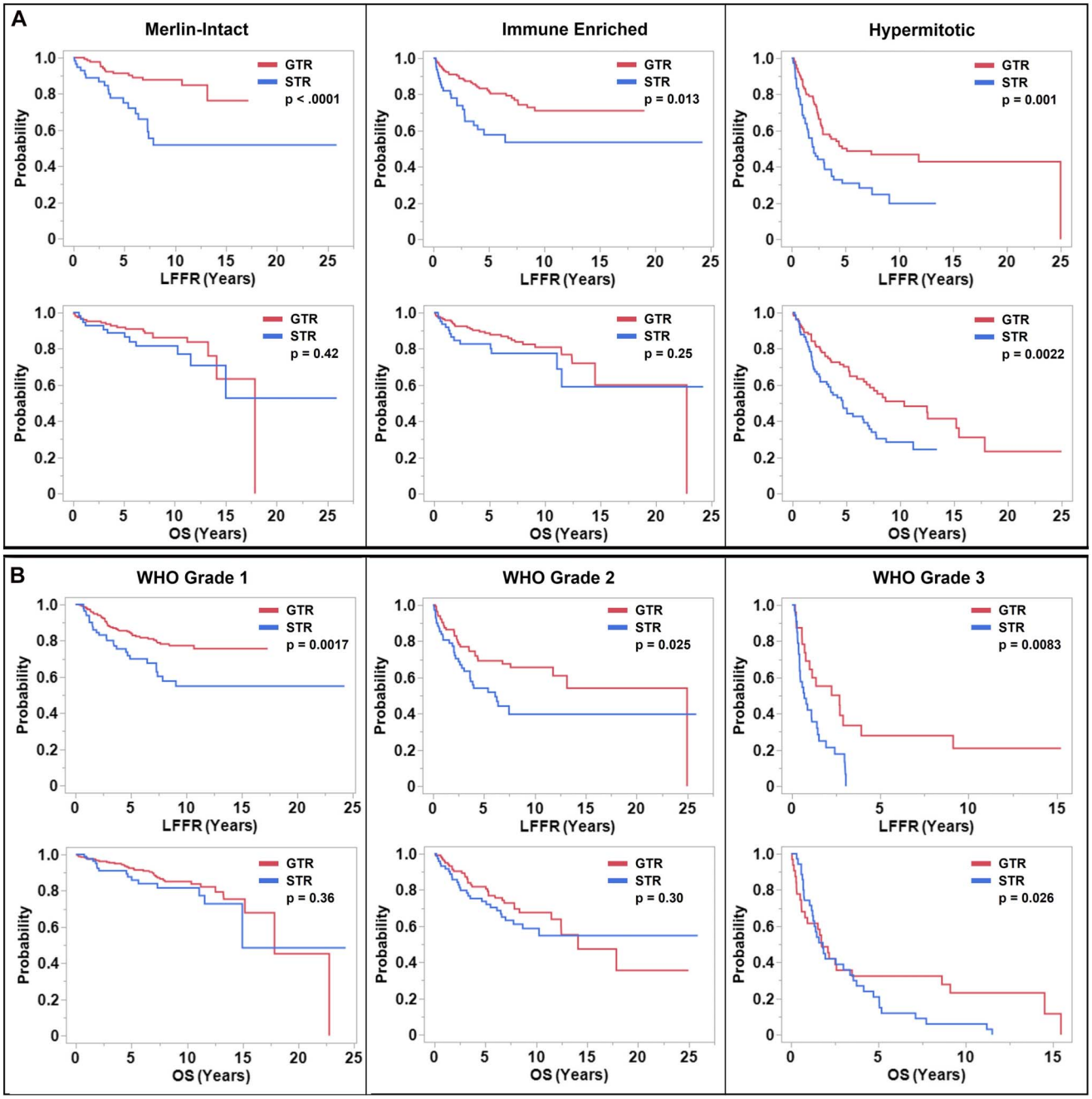


FIGURE 1. *Kaplan-Meier curves evaluating the impact of extent of resection on LFFR and OS by DNA methylation groups or WHO grade.* **A**, *GTR was significantly associated with longer LFFR across all DNA methylation groups (Merlin-Intact Log-rank P < .0001; Immune-enriched Log-rank P = .013; Hypermitotic Log-rank P = .001) and was associated with longer OS for patients with Hypermitotic meningioma (Log-rank P = .0022).* **B**, *GTR was significantly associated with longer LFFR across all WHO grades (Grade 1 Log-rank P = .0017; Grade 2 Log-rank P = .025; Grade 3 Log-rank P = .0083) and was associated with longer OS for patients with Grade 3 meningioma (Log-rank P = .026). GTR, gross total resection; LFFR, local freedom from recurrence; OS, overall survival; STR, subtotal resection; WHO, World Health Organization.*

154 (72%) WHO grade 1, 53 (24.7%) grade 2, and 7 (3.3%) grade 3 tumors with GTR and STR performed in 152 (71%) and 62 (29%) cases, respectively. Immune-enriched meningiomas consisted of 153 (64.8%) WHO grade 1, 62 (26.3%) grade 2, and 21 (8.9%) grade 3 meningiomas with GTR and STR performed in 171 (72.5%) and 65 (27.5%) of cases, respectively. Hypermitotic

TABLE 2. Estimated 1-year, 5-year, and 10-y LFFR and OS Across Meningioma DNA Methylation Subgroups

		All patients		Merlin-intact		Immune-enriched		Hypermitotic	
N = 644	Estimated	GTR	STR	GTR	STR	GTR	STR	GTR	STR
LFFR[a]	1-y	94.3% (92.1%-95.9%)	82.9% (78.1%-86.9%)	99.1% (96.6%-99.8%)	92.1% (83.9%-96.3%)	94.6% (90.9%-96.9%)	85.3% (76.3%-91.2%)	87.2% (80.9%-91.6%)	72.9% (63.7%-80.4%)
	5-y	79.0% (75%-82.5%)	53.5% (46.5%-60.4%)	92.4% (87.3%-95.6%)	71.5% (59.2%-81.2%)	81.5% (75.1%-86.6%)	61.4% (48.6%-72.7%)	56.3% (47.0%-65.1%)	31.3% (21.8%-42.7%)
	10-y	68.2% (62.7%-73.2%)	38.9% (31.3%-47.0%)	84.8% (76.3%-90.7%)	58.0% (43.4%-71.4%)	72.2% (63.6%-89.5%)	48.5% (34.2%-63.1%)	39.6% (29.7%-50.5%)	16.9% (9.6%-28.1%)
OS[b]	1-y	95.1% (93.1%-96.5%)	92.0% (88.2%-94.6%)	97.0% (93.6%-98.6%)	97.1% (90.5%-99.2%)	96.2% (93%-98.0%)	93.9% (86.6%-97.3%)	90.6% (85.1%-94.2%)	86.9% (79.3%-92.0%)
	5-y	82.3% (78.7%-85.4%)	68.6% (62.4%-74.2%)	89.6% (84.1%-93.4%)	85.6% (75.3%-92.0%)	86.6% (81.0%-90.7%)	79.9% (68.7%-87.8%)	65.8% (57.3%-73.3%)	46.9% (37.2%-56.9%)
	10-y	73.1% (68.2%-77.4%)	53.5% (45.9%-61.0%)	84.0% (76.4%-89.5%)	75.9% (62.1%-85.8%)	79.4% (71.7%-85.4%)	70.3% (55.7%-81.7%)	50.6% (40.8%-60.3%)	27.6% (18.7%-38.7%)

GTR, gross total resection; LFFR, local freedom from recurrence; OS, overall survival; STR, subtotal resection.
[a]Log-rank *P*-values for GTR vs STR: all Patients, $P < .0001$; Merlin-intact, $P < .0001$; Immune-enriched, $P = .013$; Hypermitotic, $P = .001$.
[b]Log-rank *P*-values for GTR vs STR: all Patients, $P < .0001$; Merlin-intact, $P = .42$; Immune-enriched, $P = .25$; Hypermitotic, $P = .0022$.

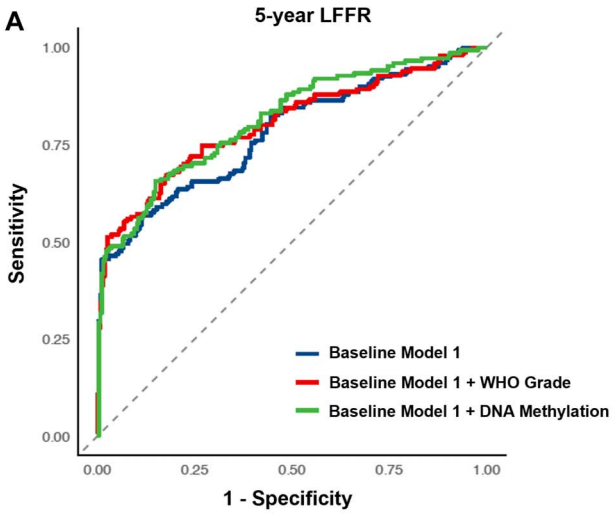
meningiomas consisted of 68 (35.0%) WHO grade 1, 87 (44.9%) grade 2, and 39 (20.1%) grade 3 tumors with GTR and STR performed in 155 (59.3%) and 79 (40.7%) of cases, respectively. Postoperative radiotherapy was given for 27 (12.7%) Merlin-Intact, 35 (14.8%) Immune-enriched, and 71 (36.8%) Hypermitotic meningiomas. DNA methylation groups were associated with significant differences in LFFR and OS (**Supplemental Digital Content 1** [http://links.lww.com/NEU/E633]). Furthermore, DNA methylation groups were associated with ROC curve AUC values ranging from 63.9% to 79.5% for predicting 5-year and 10-year LFFR (**Supplemental Digital Content 1** [http://links.lww.com/NEU/E633]).

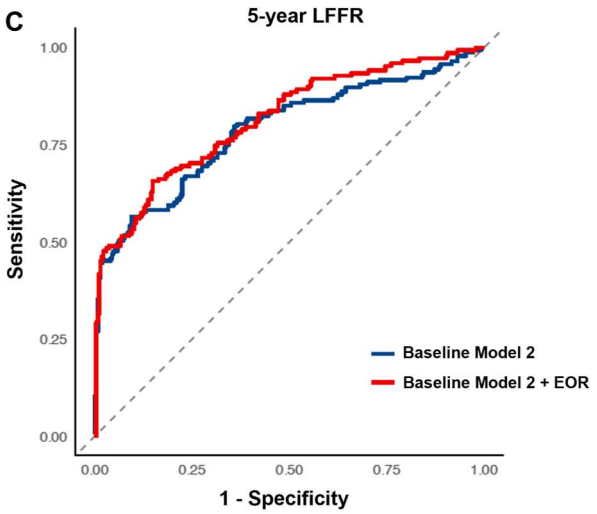
Impact of EOR on LFFR and OS Across Meningioma DNA Methylation Groups

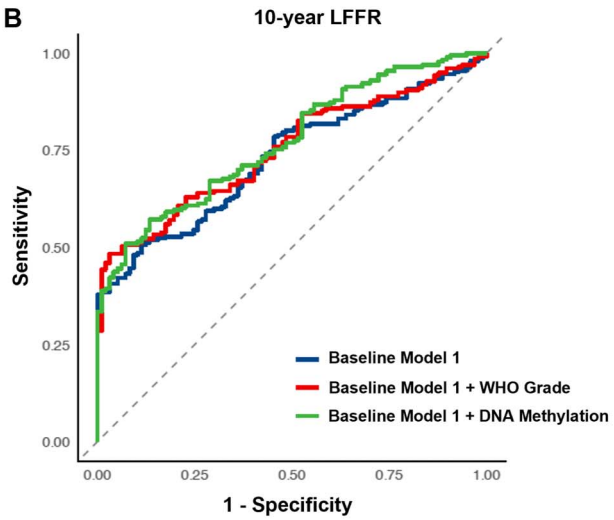
On Kaplan-Meier analyses, GTR was associated with longer LFFR across all meningioma DNA methylation groups (Log-rank: Merlin-intact $P < .0001$; Immune-enriched $P = .013$; Hypermitotic $P = .001$) and was associated with longer OS for Hypermitotic meningiomas (Log-rank: $P = .0022$) (Figure 1). Estimated 1-year, 5-year, and 10-year LFFR after GTR vs STR across meningioma DNA methylation groups are presented in Table 2. GTR was associated with longer LFFR across all histological WHO grades (Log-rank: Grade 1 $P = .0017$; Grade 2 $P = .025$; Grade 3 $P = .0083$) and was associated with longer OS for Grade 3 meningiomas (Log-rank: $P = .026$) (Figure 2). Estimated 1-year, 5-year, and 10-year LFFR after GTR vs STR across WHO grades are presented in Table 3.

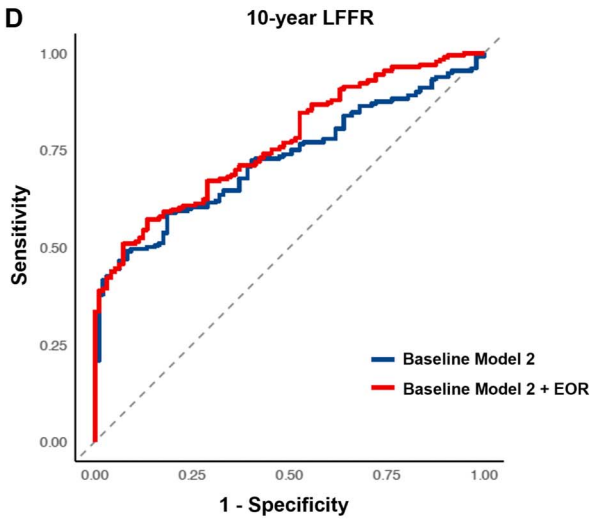
On multivariable Cox proportional hazard analyses adjusted for age, sex, newly diagnosed vs recurrent presentation, and postoperative radiotherapy, EOR was significantly associated with LFFR across all meningioma DNA methylation groups and WHO grades but was significantly associated with OS only for Hypermitotic meningiomas (hazard ratio [GTR vs STR] 0.64, 95% CI 0.43-0.97, $P = .034$) (Tables 4 and 5). Details for each individual multivariable Cox proportional hazards model within each individual DNA methylation group or WHO grade are displayed in **Supplemental Digital Content 2** (http://links.lww.com/NEU/E634). Interaction analyses (**Supplemental Digital Content 2** [http://links.lww.com/NEU/E634]) demonstrated that older age significantly decreased LFFR for Merlin-intact tumors, and female patients within the Immune-enriched subgroup had significantly increased LFFR. In addition, older age was associated with significantly decreased OS for Merlin-intact tumors, and recurrent tumors for Immune-enriched and Merlin-intact tumors were associated with significantly decreased OS as well.

Using 5-fold cross-validation, 2 baseline multivariable models (Baseline Model 1, BLM1; Baseline Model 2, BLM2) were created to predict 5-year and 10-year LFFR. DNA methylation groups, WHO grade, or EOR were then introduced into these models to determine their impact on ROC AUC for predicting 5-year and 10-year LFFR. Using a baseline model including age, sex, postoperative radiotherapy, newly diagnosed vs recurrent presentation, and EOR (BLM1), incorporating DNA methylation groups into the model significantly improved the ROC AUC for both 5-year and 10-year LFFR (5-year LFFR: ΔAUC 0.035, $P = .001$; 10-year LFFR: ΔAUC 0.041, $P = .005$; Figure 2A and 2B). When using BLM1 and incorporating WHO grade into the model, the ROC AUC improved for 5-year LFFR but did not reach significance for 10-year LFFR (5-year LFFR: ΔAUC 0.024, $P = .024$; 10-year LFFR: ΔAUC 0.021, $P = .085$; Figure 2A and 2B). To evaluate the impact of EOR, a second baseline model including age, sex, postoperative radiotherapy, newly diagnosed vs recurrent presentation, and









Time	Model	AUC (95% CI)
5-year	BLM1	0.778 (0.730-0.827)
	BLM1+WHO Grade	0.803 (0.756-0.850)
	BLM1+DNA Methylation	0.814 (0.770-0.858)
10-year	BLM1	0.730 (0.670-0.790)
	BLM1+WHO Grade	0.751 (0.693-0.810)
	BLM1+DNA Methylation	0.771 (0.715-0.826)

Variables in baseline model 1 (BLM1): Age, Sex, Adjuvant RT, Recurrence Status, EOR

Time	Comparison	ΔAUC (95% CI)
5-year	BLM1+WHO Grade vs. BLM1	0.024 (0.003-0.046, p=0.024)
	BLM1+DNA Methylation vs. BLM1	0.035 (0.014-0.056), p=0.001)
10-year	BLM1+WHO Grade vs. BLM1	0.021 (-0.003-0.046, p=0.085)
	BLM1+DNA Methylation vs. BLM1	0.041 (0.013-0.069, p=0.005)

Variables in baseline model 1 (BLM1): Age, Sex, Adjuvant RT, Recurrence Status, EOR

Time	Model	AUC (95% CI)
5-year	BLM2	0.788 (0.739-0.837)
	BLM2+EOR	0.814 (0.770-0.858)
10-year	BLM2	0.726 (0.666-0.787)
	BLM2+EOR	0.771 (0.715-0.826)

Variables in baseline model 2 (BLM2): Age, Sex, Adjuvant RT, Recurrence Status, DNA Methylation Group

Time	Comparison	ΔAUC (95% CI)
5-year	BLM2+EOR vs. BLM2	0.026 (0.002-0.050, p=0.035)
10-year	BLM2+EOR vs. BLM2	0.044 (0.013-0.076, p=0.005)

Variables in baseline model 2 (BLM2): Age, Sex, Adjuvant RT, Recurrence Status, DNA Methylation Group

FIGURE 2. *Assessing the impact of DNA methylation group, WHO grade, and EOR on AUC for multivariable models predicting 5-year and 10-year LFFR. DNA methylation groups were incorporated into BLM1, which resulted in significantly increased 5-year* **A** *and 10-year* **B** *LFFR AUC. EOR was incorporated into BLM2, which resulted in significantly increased 5-year* **C** *and 10-year* **D** *LFFR AUC. AUC, area under the receiver operating characteristic curve; BLM1, Baseline Model 1; BLM2, Baseline Model 2; EOR, extent of resection; LFFR, local freedom from recurrence; RT, radiotherapy; WHO, World Health Organization.*

DNA methylation groups was created (BLM2), and the impact of incorporation of EOR was assessed. Incorporation of EOR significantly improved the ROC AUC for 5-year and 10-year LFFR (5-year LFFR: ΔAUC 0.026, $P = .035$; 10-year LFFR: ΔAUC 0.044, $P = .005$; Figure 2C and 2D).

DISCUSSION

Surgical resection is a cornerstone of meningioma management. Maximal safe resection of large meningiomas, when feasible, is recommended by groups such as the European Association of Neuro-Oncology and the International Consortium of Meningiomas.[4,5] Indeed, there is substantial evidence supporting the prognostic benefits of surgical resection for meningiomas, regardless of which definitions (ie, Simpson grade or MRI-defined GTR/STR) are used.[1-3,16-18] Such evidence has evolved from single surgeon experiences to include multicenter series and phase 2 clinical trials evaluating the prognostic value of GTR. Recent meningioma molecular risk stratification systems have also demonstrated the value of EOR in nomograms predicting outcomes such as LFFR and OS.[10,14,19] However, detailed analyses illustrating the varying impact of EOR across molecular risk stratification systems remain sparse.

With the recent implementation of molecular features in the WHO 2021 meningioma grading criteria, it is likely that many of the recent molecular stratification systems will enter clinical practice. Prior DNA methylation profiling by our group has led to the identification of 3 molecular groups of meningioma, with genomic features that are similar when compared with integrated molecular classification systems by other authors.[4,11-13,15] As such, we sought to evaluate EOR's impact on LFFR and OS within each individual DNA methylation group compared with histological classifications. This study demonstrates that GTR significantly correlates with longer LFFR within Merlin-intact, Immune-enriched, and Hypermitotic meningiomas and affects OS for the Hypermitotic subgroup. This was demonstrated both with multivariable analyses within each DNA methylation subgroup and using a 5-fold cross-validation model in which either the DNA methylation group or EOR was incorporated into a baseline model, which led to a significant ΔAUC for predicting 5-year and 10-year LFFR. Such results continue to support maximal safe resection, when feasible, even in the era of meningioma molecular classification.

TABLE 3. Estimated 1-year, 5-year, and 10-y LFFR and OS Across Meningioma WHO Grades

		All patients		WHO Grade 1		WHO Grade 2		WHO Grade 3	
N = 644	Estimated	GTR	STR	GTR	STR	GTR	STR	GTR	STR
LFFR[a]	1-y	94.3% (92.1%-95.9%)	82.9% (78.1%-86.9%)	97.4% (95.3%-98.6%)	95.1% (89.6%-97.7%)	96.1% (92.1%-98.1%)	92.4% (85.5%-96.2%)	71.2% (54.8%-83.5%)	41.1% (28.3%-55.3%)
	5-y	79.0% (75%-82.5%)	53.5% (46.5%-60.4%)	85.8% (81.5%-89.3%)	72.3% (62.5%-80.4%)	78.6% (71.1%-84.6%)	71.8% (61.7%-80.1%)	31.1% (16.3%-51.2%)	2.8% (0.7%-11.4%)
	10-y	68.2% (62.7%-73.2%)	38.9% (31.3%-47.0%)	75.7% (69.1%-81.2%)	55.4% (42.7%-67.5%)	64.6% (54.5%-73.5%)	58.3% (46.1%-69.5%)	17.2% (6.5%-38.4%)	0.4% (0.04%-4.3%)
OS[b]	1-y	95.1% (93.1%-96.5%)	92.0% (88.2%-94.6%)	98.2% (96.4%-99.1%)	98.2% (94%-99.5%)	96.1% (92.1%-98.1%)	92.4% (85.5%-96.2%)	64.1% (49.7%-76.3%)	74.9% (61.6%-84.7%)
	5-y	82.3% (78.7%-85.4%)	68.6% (62.4%-74.2%)	90.5% (86.9%-93.3%)	87.5% (79.6%-92.6%)	78.6% (71.1%-84.6%)	71.8% (61.7%-80.1%)	30.4% (18.2%-46.2%)	15.6% (8%-28.2%)
	10-y	73.1% (68.2%-77.4%)	53.5% (45.9%-61.0%)	83.5% (78%-87.8%)	77.1% (65.3%-85.7%)	64.6% (54.5%-73.5%)	58.3% (46.1%-69.5%)	18.7% (9.1%-34.5%)	4.1% (1.3%-12.4%)

GTR, gross total resection; LFFR, local freedom from recurrence; OS, overall survival; STR, subtotal resection; WHO, World Health Organization.
[a]Log-rank *P*-values for GTR vs STR: all Patients, $P < .0001$; Grade 1, $P = .0017$; Grade 2, $P = .025$; Grade 3, $P = .0083$.
[b]Log-rank *P*-values for GTR vs STR: all Patients, $P < .0001$; Grade 1, $P = .36$; Grade 2, $P = .3$; Grade 3, $P = .026$.

TABLE 4. Multivariable Cox Proportional Hazards Analyses Evaluating the Effect of Meningioma EOR on LFFR Across WHO Grades and DNA Methylation Subgroups

LFFR	HR (95% CI)[a]	*P* value
WHO Grade 1	0.48 (0.30-0.79)	.0036
WHO Grade 2	0.56 (0.34-0.91)	.019
WHO Grade 3	0.42 (0.19-0.90)	.026
Merlin-intact	0.17 (0.08-0.36)	<.0001
Immune-enriched	0.52 (0.30-0.90)	.0202
Hypermitotic	0.58 (0.39-0.88)	.0095

EOR, extent of resection; HR, hazard ratio; LFFR, local freedom from recurrence; WHO, World Health Organization.
[a]Adjusted HR from multivariable Cox proportional hazard analyses evaluating the effect of EOR (gross total resection vs subtotal resection) on LFFR within each separate DNA methylation group or WHO grade adjusted for age, sex, newly diagnosed vs recurrent presentation, and postoperative radiotherapy.

Importantly, these findings do not guide surgical approach selection between traditional transcranial and minimally invasive techniques such as endoscopic methods or keyhole craniotomies. Surgical approaches should be tailored to each patient to maximize resection while minimizing morbidity. In addition, it is difficult to draw conclusions regarding the selection of adjuvant therapies that may benefit patients with meningioma including radiotherapy, radiosurgery, or novel systemic agents based on the present data given its retrospective nature and lack of standardized adjuvant therapy selection across sites. Ongoing clinical trials are assessing the value of postoperative radiotherapy for patients with WHO grade 2 meningiomas treated with GTR (European Organization for Research and Treatment of Cancer 1308/ROAM, NRG-BN003). Molecular classification systems may also provide insight into patients who may be responsive to radiotherapy treatment.[10] There are also new trials beginning to assess targeted inhibitors for high-grade meningiomas, including cyclin-dependent kinase inhibitors (NCT03220646, NCT02523014, NCT02933736, NCT03434262). The results from these trials will continue to guide selection of adjuvant therapy and interpretation of trial results in the context of molecular classification systems will be needed.

TABLE 5. Multivariable Cox Proportional Hazards Analyses Evaluating the Effect of Meningioma EOR on OS Across WHO Grades and DNA Methylation Subgroups

OS	HR (95% CI)[a]	*P* value
WHO Grade 1	0.78 (0.42-1.46)	.43
WHO Grade 2	0.73 (0.44-1.23)	.23
WHO Grade 3	1.01 (0.56-1.81)	.97
Merlin-intact	1.12 (0.46-2.74)	.81
Immune enriched	0.84 (0.43-1.67)	.63
Hypermitotic	0.64 (0.43-0.97)	.034

EOR, extent of resection; HR, hazard ratio; OS, overall survival; WHO, World Health Organization.
[a]Adjusted HR from multivariable Cox proportional hazard analyses evaluating the effect of EOR (gross total resection vs STR) on OS within each separate DNA methylation group or WHO grade adjusted for age, sex, newly diagnosed vs recurrent presentation, and postoperative radiotherapy.

The impact of EOR across meningioma molecular classification systems has been mixed. Our group has previously reported a gene expression biomarker that refines meningioma risk stratification compared with all other classification systems. Across the 3 gene expression risk groups (Low, Intermediate, and High), EOR differentiated LFFR with MRI-defined GTR and STR 5-year LFFR rates of 96.1% vs 80.3% for the low-risk group, 80.5% vs 54.9% for the intermediate-risk group, and 30% vs 9.8% for the high-risk group.[10] Similarly, using an integrated molecular classification system incorporating mitotic count, copy number variation, or *CDKN2A/B* mutation status, Driver et al[14] found that MRI-defined GTR vs STR differentiated progression-free survival for their Integrated grade 1 and 2 tumors but not for Integrated grade 3 tumors ($P = .38$). However, other studies that have implemented Simpson-grade defined EOR have not found the same impact. Maas et al[8] reported an integrated risk scoring system incorporating DNA methylation, copy number alterations, and histological analysis for which Simpson-grade defined EOR was not prognostic in a Cox proportional hazards model for time to recurrence. Similarly, in a prior study by Sahm et al[9] from the Heidelberg group in Germany, Simpson grade was not prognostic when accounting for 6 different DNA methylation subgroups. Finally, a study from the Toronto group by Nassiri et al[12] reported that Simpson grade was not associated with recurrence-free survival in a multivariable analysis using an integrative molecular classification system. When taking into account our results in the context of these prior studies, it appears that the prognostic impact of EOR may vary by the particular molecular classification system being used. These results also bring into question the use of Simpson grade over an MRI-based GTR vs STR designation for defining EOR in the context of molecular classification systems. Additional multicenter studies will be needed to clarify these points.

Thus, a question remains as to whether the Simpson grade provides any additional utility over MRI-defined GTR, particularly when implementing molecular classification systems. Future work should examine these 2 definitions of EOR with specific separation of Simpson 1 vs 2 vs 3 vs 4/5 grades and comparisons with an MRI-defined binary definition of GTR vs STR. These comparisons should also be made across different molecular classification systems including those based on DNA methylation groups, copy number variation and other DNA alterations, and gene expression risk groups. Furthermore, the impact of EOR on survival from surgery should be evaluated in all subgroups to comprehensively assess EOR's impact on clinical outcomes.

Comparisons with DOTATATE positron emission tomography-computed tomography EOR may also be considered in the context of such studies. Ueberschaer et al.[20] used DOTATATE positron emission tomography-computed tomography to demonstrate unexpected tumor remnants in 40.5% of Simpson grade 1/2 resections with MRI noting some cases with persistent residual as well. This suggests that DOTATATE imaging may surpass MRI in detecting residual disease and could be used to better define EOR. The impact of postoperative MRI-negative/DOTATATE-positive sites on recurrence risk is unclear and requires further studies. Such data would help guide intraoperative decision-making, which may become even more relevant if radiomics or liquid biopsy provide molecular information in the preoperative setting. These results could also guide clinical trial methodology for future studies implementing molecular stratification of meningiomas as part of their selection criteria.

Limitations

This study was limited due to its retrospective nature. The median follow-up was 5.8 years for the cohort, and it should be noted that longer follow-up may be needed to detect recurrences for low-grade meningiomas. In addition, the study may be underpowered to detect survival differences in patients with Merlin-intact and Immune-enriched meningiomas, which generally have a more favorable survival outcome when compared with Hypermitotic tumors.[13] In this study, clear imaging evidence of residual tumor was needed to define a resection as subtotal, but there may be the potential for "borderline" cases to be categorized differently between observers. As central imaging review was not possible and given that not all sites provided details on tumor location, these data were only available for 45.7% of the cohort, which limited the ability to evaluate the impact of EOR stratified by both the DNA methylation group and location. This is a significant limitation of the cohort as tumor locations may affect surgical strategy and the possibility of a GTR. Of note, prior work has suggested that different molecular groups of meningiomas may have a predisposition for forming in certain locations.[4,21,22] In addition, this study's generalizability to the NF2-related schwannomatosis population is limited, as these patients were excluded and can only fall under Immune-enriched or Hypermitotic DNA methylation subgroups.

CONCLUSION

In conclusion, MRI-defined GTR is associated with improved LFFR across all meningioma DNA methylation groups and improved OS for patients with Hypermitotic meningiomas. These results were comparable with those observed across histological WHO grades, supporting the continued pursuit of maximal safe resection in the era of meningioma molecular classification.

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Supplemental Digital Content 1. **Figure 1**. Impact of DNA methylation Groups on LFFR and OS. **A**, Kaplan-Meier curves demonstrating the impact of DNA methylation groups on LFFR (Log-rank $P < .0001$) with reported 1-year, 2-year, 5-year, 10-year, and 15-year estimated probabilities of LFFR. **B**, Kaplan-Meier curves demonstrating the impact of DNA methylation groups on OS (Log-rank $P < .0001$) with reported 1-year, 2-year, 5-year, 10-year, and 15-year estimated probabilities of LFFR. **C**, DNA methylation groups were associated with ROC curve AUC values ranging from 63.9% to 79.5% for predicting 5-year and 10-year LFFR.

Supplemental Digital Content 2. **Table 1**. Multivariable Cox proportional hazards models for LFFR by the DNA methylation group and WHO Grade. **Table 2**. Multivariable Cox proportional hazards models for OS by the DNA methylation group and WHO Grade. **Table 3**. Multivariable Cox proportional hazards models for LFFR with interaction effects between the DNA methylation group and clinical variables. **Table 4**. Multivariable Cox proportional hazards models for OS with interaction effects between the DNA methylation group and clinical variables.