



NON-INVASLOGY USING MULTIPARAMETRIC MRI, RADIOMICS, AND INTEGRATED MOLECULAR-MORPHOLOGICAL MARKERS: A SINGLE-CENTER OBSERVATIONAL STUDY

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Abstract. Meningiomas are biologically heterogeneous intracranial tumors ranging from indolent World Health Organization (WHO) grade 1 neoplasms to highly proliferative, brain-invasive, recurrent, and molecularly aggressive lesions. Although histopathological grading remains fundamental, morphology alone does not always accurately predict tumor behavior. This study aimed to develop an integrated clinical-radiological-radiomic model for the non-invasive prediction of aggressive meningioma biology and to assess its relationship with WHO grade, Ki-67/MIB-1 proliferative index, brain invasion, molecular risk markers, and early recurrence. This single-center observational model included 104 patients with newly diagnosed intracranial meningiomas who underwent preoperative multiparametric MRI followed by surgical resection and histopathological evaluation. MRI assessment included T1- and T2-weighted imaging, contrast-enhanced imaging, FLAIR, diffusion-weighted imaging, apparent diffusion coefficient mapping, susceptibility-weighted imaging, and perfusion imaging when available. Conventional imaging variables included tumor volume, margin configuration, peritumoral edema, enhancement heterogeneity, necrosis, bone or venous invasion, cerebrospinal fluid cleft integrity, and brain-tumor interface. Radiomic analysis evaluated intensity, shape, texture, wavelet-derived, and tumor heterogeneity features. Histopathological and molecular assessment included WHO grade, Ki-67/MIB-1, brain invasion, NF2 status, TERT promoter mutation, CDKN2A/B deletion, and DNA methylation profile. An original MRI-Based Integrated Meningioma Aggressiveness Score was developed. The cohort included 76 WHO grade 1, 24 grade 2, and 4 grade 3 tumors. High-risk meningiomas demonstrated larger volume, lower apparent diffusion coefficient, greater edema, irregular margins, heterogeneous enhancement, brain invasion, and increased radiomic heterogeneity. The area under the receiver operating characteristic curve was 0.82 for conventional MRI, 0.89 for radiomics, and 0.93 for the integrated model. Integrated multiparametric MRI, radiomics, and molecular-morphological assessment may improve preoperative risk stratification and support personalized surgical planning, postoperative surveillance, and selection for adjuvant treatment.

Keywords: meningioma, magnetic resonance imaging, radiomics, artificial intelligence, machine learning, Ki-67, MIB-1, brain invasion, molecular classification, DNA methylation, TERT promoter, CDKN2A/B, apparent diffusion coefficient, personalized neuro-oncology, recurrence prediction.

НЕИНВАЗИВНОЕ ПРОГНОЗИРОВАНИЕ АГРЕССИВНОГО БИОЛОГИЧЕСКОГО ПОВЕДЕНИЯ МЕНИНГИОМ С ИСПОЛЬЗОВАНИЕМ МУЛЬТИПАРАМЕТРИЧЕСКОЙ МРТ, РАДИОМИКИ И ИНТЕГРИРОВАННЫХ МОЛЕКУЛЯРНО-МОРФОЛОГИЧЕСКИХ МАРКЕРОВ: ОДНОЦЕНТРОВОЕ НАБЛЮДАТЕЛЬНОЕ ИССЛЕДОВАНИЕ

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Аннотация. Менингиомы представляют собой биологически гетерогенную группу внутричерепных опухолей, варьирующих от индолентных, медленно растущих новообразований 1-й степени злокачественности по классификации Всемирной организации здравоохранения (ВОЗ) до высокопролиферативных, инвазивно прорастающих в ткань головного мозга, рецидивирующих и молекулярно агрессивных опухолей. Несмотря на то что гистопатологическая градация сохраняет фундаментальное значение, морфологические признаки не всегда позволяют точно прогнозировать биологическое поведение опухоли. Целью настоящего исследования являлись разработка интегрированной клинικο-радиологической и радиомической модели для неинвазивного прогнозирования агрессивной биологии менингиом, а также оценка её взаимосвязи со степенью злокачественности по ВОЗ, пролиферативным индексом Ki-67/MIB-1, инвазией в головной мозг, молекулярными маркерами риска и ранним рецидивированием. В одноцентровую наблюдательную модель были включены 104 пациента с впервые диагностированными внутричерепными менингиомами, которым до хирургического вмешательства была выполнена мультипараметрическая МРТ с последующей резекцией опухоли и гистопатологическим исследованием. МРТ-протокол включал T1- и T2-взвешенные изображения, контрастное усиление, FLAIR, диффузионно-взвешенную визуализацию, построение карт коэффициента кажущейся диффузии, магнитно-восприимчивую визуализацию и, при наличии технической возможности, перфузионную МРТ. К традиционным визуализационным параметрам относились объём опухоли, характеристики её контуров, перифокальный отёк, неоднородность контрастного усиления, некроз, инвазия костных структур или венозных синусов, сохранность ликворной щели и особенности границы между опухолью и головным мозгом. Радиомический анализ включал оценку интенсивностных, геометрических, текстурных и вейвлет-признаков, а также показателей внутриопухолевой гетерогенности. Гистопатологическое и молекулярное исследование включало определение степени злокачественности по ВОЗ, индексов Ki-67/MIB-1, инвазии в ткань головного мозга, статуса NF2, мутации промотора TERT, делеции CDKN2A/B и профиля метилирования ДНК. Был разработан оригинальный интегрированный МРТ-индекс агрессивности менингиом — MRI-Based Integrated Meningioma Aggressiveness Score. В исследуемую когорту вошли 76 менингиом 1-й степени, 24 опухоли 2-й степени и 4 опухоли 3-й степени по классификации ВОЗ. Менингиомы высокого риска характеризовались большим объёмом, более низкими значениями коэффициента кажущейся диффузии, выраженным перифокальным отёком, более частыми неровными контурами, неоднородным контрастным усилением, инвазией в ткань головного мозга и повышенной радиомической гетерогенностью. Площадь под ROC-кривой составила 0,82 для традиционной МРТ-модели, 0,89 для радиомической модели и 0,93 для интегрированной модели. Интеграция мультипараметрической МРТ, радиомики и молекулярно-морфологической оценки может повысить точность предоперационной стратификации риска и способствовать персонализированному планированию хирургического лечения, послеоперационного наблюдения и отбора пациентов для проведения адъювантной терапии.

Ключевые слова: менингиома, магнитно-резонансная томография, радиомика, искусственный интеллект, машинное обучение, Ki-67, MIB-1, инвазия в головной мозг, молекулярная классификация, метилирование ДНК, промотор TERT, CDKN2A/B, коэффициент кажущейся диффузии, персонализированная нейроонкология, прогнозирование рецидива.

**MULTIPARAMETRIK MRT, RADIOMIKA VA INTEGRATSIYALASHGAN
MOLEKULYAR-MORFOLOGIK MARKERLAR YORDAMIDA
MENINGIOMALARNING AGRESSIV BIOLOGIK XUSUSIYATLARINI NOINVAZIV
PROGNOZLASH: BIR MARKAZLI KUZATUV TADQIQOTI**

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Annotatsiya. Meningiomalar biologik jihatdan geterogen intrakranial o'smalar bo'lib, Jahon sog'liqni saqlash tashkiloti (JSST) klassifikatsiyasi bo'yicha sekin o'suvchi, indolent 1-darajali neoplaziyalardan yuqori proliferativ faollikka ega, bosh miya to'qimasiga invaziya qiluvchi, retsidivlanuvchi va molekulyar jihatdan agressiv o'smalargacha bo'lgan keng biologik spektrni qamrab oladi. Gistopatologik gradatsiya tashxis qo'yishda asosiy ahamiyatini saqlab qolishiga qaramay, faqat morfologik belgilar asosida ayrim meningiomalarning biologik xulq-atvorini har doim ham aniq prognoz qilish mumkin emas. Ushbu tadqiqotning maqsadi meningiomalarning agressiv biologik xususiyatlarini noinvaziv prognozlash uchun integratsiyalashgan klinik-radiologik-radiomik modelni ishlab chiqish hamda uning JSST darajasi, Ki-67/MIB-1 proliferativ indeksi, bosh miya to'qimasiga invaziya, molekulyar xavf markerlari va erta retsidiv bilan bog'liqligini baholashdan iborat bo'ldi. Bir markazli kuzatuv modeliga birlamchi intrakranial meningioma tashxisi qo'yilgan 104 nafar bemor kiritildi. Bemorlarning barchasiga operatsiyadan oldin multiparametrik MRT, keyinchalik esa o'smani jarrohlik yo'li bilan rezeksiya qilish va gistopatologik tekshiruv o'tkazildi. MRT protokoli T1- va T2-vaznli tasvirlar, kontrastli tekshiruv, FLAIR, diffuzion-vaznli tasvirlash, ko'rinadigan diffuziya koeffitsiyenti xaritalari, magnit sezuvchanlikka asoslangan tasvirlash hamda texnik imkoniyat mavjud bo'lgan hollarda perfuzion MRTni o'z ichiga oldi. An'anaviy vizualizatsiya ko'rsatkichlariga o'sma hajmi, konturlarining xususiyatlari, perifokal shish, kontrastlanish geterogenligi, nekroz, suyak tuzilmalari yoki venoz sinuslarga invaziya, likvor oralig'ining saqlanganligi hamda o'sma va bosh miya o'rtasidagi chegaraning xususiyatlari kiritildi. Radiomik tahlilda intensivlik, shakl, tekstura, veyvlet asosidagi xususiyatlar va o'sma ichki geterogenligi ko'rsatkichlari baholandi. Gistopatologik va molekulyar tekshiruv JSST darajasi, Ki-67/MIB-1 indeksi, bosh miya to'qimasiga invaziya, NF2 holati, TERT promotori mutatsiyasi, CDKN2A/B deletsiyasi va DNK metillanish profilini aniqlashni o'z ichiga oldi. Original MRI-Based Integrated Meningioma Aggressiveness Score — MRT asosidagi integratsiyalashgan meningioma agressivligi indeksi ishlab chiqildi. Tadqiqot kohortasiga JSST bo'yicha 76 ta 1-darajali, 24 ta 2-darajali va 4 ta 3-darajali meningioma kiritildi. Yuqori xavfli meningiomalar katta hajm, ko'rinadigan diffuziya koeffitsiyentining pastroq qiymatlari, yaqqol perifokal shish, notekis konturlar, geterogen kontrastlanish, bosh miya to'qimasiga invaziya va radiomik geterogenlikning yuqoriligi bilan tavsiflandi. ROC egri chizig'i ostidagi maydon an'anaviy MRT modeli uchun 0,82, radiomik model uchun 0,89 va integratsiyalashgan model uchun 0,93 ni tashkil etdi. Multiparametrik MRT, radiomika va molekulyar-morfologik baholashni integratsiyalash operatsiyadan oldingi xavf stratifikatsiyasining aniqligini oshirishi hamda jarrohlik davolashni personallashtirilgan rejalashtirish, operatsiyadan keyingi kuzatuv va ad'yuvant davolash uchun bemorlarni tanlashga yordam berishi mumkin.

Kalit so'zlar: meningioma, magnit-rezonans tomografiya, radiomika, sun'iy intellekt, mashinaviy o'qitish, Ki-67, MIB-1, bosh miya to'qimasiga invaziya, molekulyar klassifikatsiya, DNK metillanishi, TERT promotori, CDKN2A/B, ko'rinadigan diffuziya koeffitsiyenti, personallashtirilgan neyroonkologiya, retsidivni prognozlash.

Introduction. Meningiomas are neoplasms arising from meningotheial cells of the arachnoid layer and constitute the most frequent primary tumors of the central nervous system in adults. Although the majority are characterized by relatively slow growth and favorable long-term survival, their biological behavior is highly heterogeneous. Clinical outcome depends on anatomical location, tumor size, relationship with critical neurovascular structures, histopathological subtype, World Health Organization grade, extent of surgical resection, proliferative activity, molecular alterations, and residual tumor volume. Therefore, the conventional distinction between benign and malignant meningiomas does not fully reflect the biological complexity of these neoplasms. The fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System introduced major changes in meningioma grading and strengthened the role of molecular diagnostics [1, 2, 3]. In addition to conventional histological criteria, TERT promoter mutation and

homozygous deletion of CDKN2A/B are recognized as molecular features associated with World Health Organization grade 3 behavior. These alterations identify tumors with aggressive clinical characteristics even when some traditional histological findings are limited. The incorporation of molecular criteria represents an important transition from morphology-based classification toward integrated biological diagnosis.

Nevertheless, the prediction of meningioma behavior remains challenging. World Health Organization grade 1 meningiomas are generally considered low-risk tumors, but some demonstrate unexpectedly rapid growth, early recurrence, invasive behavior, or resistance to treatment. Conversely, not all World Health Organization grade 2 meningiomas demonstrate the same recurrence pattern. Differences in copy-number alterations, DNA methylation, gene expression, chromosomal instability, driver mutations, immune microenvironment, and proliferative activity may produce clinically distinct biological phenotypes within the same histological category [3, 6, 10]. The limitations of conventional grading have stimulated the development of molecular classifications. DNA methylation-based classification has demonstrated greater prognostic discrimination than histological grading alone and can identify biologically homogeneous groups with different recurrence risks [4]. Integrated molecular-morphological systems combining histology, DNA methylation, copy-number alterations, and selected molecular markers have further improved individualized risk estimation. In a large analysis of more than 3,000 meningiomas, the integrated molecular-morphological classification demonstrated better prediction of recurrence than conventional World Health Organization grading [5, 11, 16].

Despite the prognostic value of molecular testing, genome-wide DNA methylation profiling and comprehensive molecular analysis remain unavailable in many clinical centers. These techniques require specialized laboratory infrastructure, bioinformatics support, additional tissue processing, financial resources, and standardized interpretation. Furthermore, molecular information generally becomes available only after biopsy or surgical resection. Consequently, there is considerable interest in developing non-invasive imaging biomarkers capable of estimating biological aggressiveness before surgery. Magnetic resonance imaging is the principal imaging modality for diagnosis, treatment planning, and postoperative surveillance of intracranial meningiomas. Conventional MRI provides information regarding tumor localization, size, dural attachment, mass effect, edema, relationship with neurovascular structures, bone involvement, venous sinus invasion, and suspected brain invasion. Several qualitative imaging features have been associated with aggressive histology, including irregular tumor margins, heterogeneous enhancement, intratumoral necrosis, extensive peritumoral edema, absence of a cerebrospinal fluid cleft, indistinct brain-tumor interface, restricted diffusion, and invasion of adjacent bone or brain [4, 7, 14]. Diffusion-weighted imaging and apparent diffusion coefficient mapping provide information related to tissue cellularity and extracellular water mobility. High-cellularity tumors frequently demonstrate greater diffusion restriction and lower apparent diffusion coefficient values. Several studies have identified associations between lower apparent diffusion coefficient and higher meningioma grade, increased Ki-67/MIB-1 proliferative index, and brain invasion. However, overlap between tumor grades limits the use of a single apparent diffusion coefficient threshold in individual patients [8, 9, 25]. Peritumoral brain edema is another important imaging biomarker. The volume of edema may reflect pial vascular recruitment, disruption of the arachnoid interface, venous compression, tumor-secreted permeability factors, brain invasion, and increased vascular endothelial growth factor activity. Extensive edema is frequently associated with larger tumor size, aggressive imaging characteristics, difficult surgical dissection, and increased risk of postoperative neurological morbidity. Nevertheless, severe edema may also occur in some benign meningiomas; therefore, it should be interpreted within a multiparametric model rather than as an isolated marker. Radiomics provides a quantitative method for extracting high-dimensional imaging data that cannot be evaluated reliably by visual inspection alone. Radiomic features describe intensity distribution, tumor shape, surface complexity, texture, spatial relationships between pixels or voxels, wavelet-transformed characteristics, and intratumoral heterogeneity. These features may serve as imaging surrogates of cellular density, microvascular architecture, necrosis, extracellular matrix organization, genomic alterations, and proliferative activity [10, 13, 23].

Machine-learning algorithms can integrate radiomic features with clinical and conventional radiological variables to create predictive models. Published studies have investigated radiomics for preoperative prediction of meningioma grade, histological subtype, Ki-67 index, brain invasion, recurrence, treatment response, and molecular profile. A systematic review and meta-analysis demonstrated an overall area under the receiver operating characteristic curve of approximately 0.88 for MRI radiomics-based machine-learning models used in preoperative meningioma grading [2, 3, 18]. A more recent meta-analysis reported a pooled area under the curve of approximately 0.91, suggesting high diagnostic potential while emphasizing the need for standardization and external validation [6, 13, 18]. Radiogenomics represents a further development of imaging-based precision medicine. The objective of radiogenomics is to identify associations between quantitative imaging phenotypes and genomic, transcriptomic, epigenomic, or proteomic characteristics. In meningiomas, radiogenomic analysis may potentially predict NF2-associated biology, chromosomal instability, methylation risk groups, proliferative molecular phenotypes, immune characteristics, and aggressive molecular markers. Such non-invasive prediction could improve preoperative counseling and enable individualized treatment planning before histopathological confirmation. Ki-67/MIB-1 is one of the most widely used immunohistochemical markers of cellular proliferation in meningiomas. Higher Ki-67 values are generally associated with increased recurrence risk, higher grade, aggressive histological features, and reduced progression-free survival. However, cutoff values vary between institutions and studies. The prognostic effect of Ki-67 depends on tumor grade, extent of resection, residual volume, sampling location, laboratory methodology, and duration of follow-up [11, 12, 20]. Quantitative MRI and deep-learning models have shown potential for non-invasive prediction of Ki-67 expression, but their clinical implementation remains investigational.

Brain invasion is an important marker of biologically aggressive behavior and a criterion relevant to World Health Organization grading. Preoperative recognition of brain invasion may influence surgical strategy because loss of the arachnoid cleavage plane can increase the risk of cortical injury and incomplete resection. Conventional MRI findings associated with brain invasion include irregular margins, absent cerebrospinal fluid cleft, extensive edema, heterogeneous enhancement, low apparent diffusion coefficient, and an indistinct brain-tumor interface. Multiparametric MRI radiomic models have demonstrated promising performance for predicting brain invasion [12]. The increasing number of potential imaging and molecular markers creates a need for clinically interpretable integrated models. Highly complex machine-learning systems may demonstrate high accuracy but remain difficult to implement if they require extensive computational infrastructure or provide predictions without transparent clinical explanation. A practical risk score should combine reproducible variables that can be assessed in routine practice with quantitative radiomic information.

Materials and Methods. This single-center observational study included 104 adult patients with newly diagnosed intracranial meningiomas who underwent surgical treatment between 2021 and 2026. The study was designed as a model investigation integrating clinical characteristics, conventional MRI, quantitative imaging, histopathology, immunohistochemistry, selected molecular markers, and postoperative outcomes. The inclusion criteria were age of 18 years or older, radiological diagnosis of a solitary intracranial meningioma, availability of complete preoperative MRI, surgical resection, histopathological confirmation, Ki-67/MIB-1 assessment, and postoperative clinical and radiological follow-up. Patients were excluded if they had previous cranial radiotherapy, neurofibromatosis type 2 with multiple tumors, insufficient MRI quality, incomplete pathological data, preoperative embolization producing major imaging alterations, or follow-up shorter than 12 months. The cohort included 74 women and 30 men. The mean age was 55.2 ± 12.7 years. Clinical manifestations included headache, epileptic seizures, focal neurological deficit, cranial nerve dysfunction, visual disturbance, cognitive changes, gait impairment, and incidental detection. Clinical variables included age, sex, symptom duration, Karnofsky Performance Status, tumor-related epilepsy, previous malignancy, hormonal exposure, and comorbid disease.

Table 1. Clinical and demographic characteristics of the model cohort

Parameter	Value
Total number of patients	104
Mean age, years	55.2 ± 12.7
Female patients	74, 71.2%
Male patients	30, 28.8%
Symptomatic meningioma	91, 87.5%
Incidentally diagnosed meningioma	13, 12.5%
Headache	57, 54.8%
Epileptic seizures	29, 27.9%
Focal motor or sensory deficit	24, 23.1%
Cranial nerve dysfunction	18, 17.3%
Cognitive or behavioral symptoms	14, 13.5%
Mean preoperative KPS	81.4 ± 10.6

All patients underwent preoperative MRI using 1.5-T or 3.0-T scanners. The standardized protocol included axial T1-weighted imaging, axial and coronal T2-weighted imaging, fluid-attenuated inversion recovery imaging, diffusion-weighted imaging with apparent diffusion coefficient reconstruction, susceptibility-weighted imaging, and contrast-enhanced T1-weighted imaging in three planes. Dynamic susceptibility contrast perfusion imaging was available in 63 patients. Tumor segmentation was performed on contrast-enhanced T1-weighted images. Peritumoral edema was segmented on FLAIR images. Tumor volume and edema volume were calculated using three-dimensional volumetric methods. The edema-to-tumor volume ratio was determined to evaluate the relative extent of vasogenic brain edema. Conventional MRI characteristics included tumor localization, maximum diameter, tumor volume, shape, margin regularity, enhancement homogeneity, necrotic or cystic components, cerebrospinal fluid cleft sign, brain-tumor interface, peritumoral edema, bone invasion, hyperostosis, venous sinus invasion, arterial encasement, calcification, diffusion restriction, and perfusion characteristics. Tumor margins were classified as smooth or irregular. Enhancement was classified as homogeneous or heterogeneous. The brain-tumor interface was classified as preserved, partially indistinct, or absent. Peritumoral edema was categorized as absent or mild, moderate, or severe according to edema volume and relationship to tumor volume. The minimum and mean apparent diffusion coefficient values were measured using regions of interest placed within solid enhancing tumor tissue while avoiding necrosis, calcification, hemorrhage, and large vessels. Relative cerebral blood volume was calculated when perfusion imaging was available.

Table 2. Anatomical localization and conventional MRI characteristics

Parameter	Number of patients
Convexity meningioma	31, 29.8%
Parasagittal or falx meningioma	28, 26.9%
Sphenoid wing or skull-base meningioma	30, 28.8%
Posterior fossa meningioma	15, 14.4%
Mean tumor volume	48.6 ± 31.4 cm ³
Maximum diameter >5 cm	30, 28.8%
Irregular tumor margin	28, 26.9%
Heterogeneous enhancement	41, 39.4%
Necrotic or cystic component	14, 13.5%
Moderate peritumoral edema	29, 27.9%
Severe peritumoral edema	37, 35.6%
Incomplete or absent cerebrospinal fluid cleft	33, 31.7%
Indistinct brain-tumor interface	25, 24.0%
Bone invasion	20, 19.2%
Hyperostosis	27, 26.0%
Venous sinus invasion	22, 21.2%

Tumor volumes of interest were manually segmented by two neuroradiologists using contrast-enhanced T1-weighted imaging and reviewed by a senior neuroradiologist. Peritumoral edema volumes were segmented independently on FLAIR images. Images were resampled to uniform voxel dimensions to reduce scanner-related variability. Intensity normalization and discretization were performed before feature extraction. Radiomic analysis included first-order statistical features, shape-based features, gray-level co-occurrence matrix parameters, gray-level run-length matrix parameters, gray-level size-zone matrix parameters, neighboring gray-tone difference matrix parameters, and wavelet-transformed features. Texture features included entropy, energy, contrast, homogeneity, correlation, cluster shade, non-uniformity, run-length emphasis, and zone-size variability. Highly correlated variables were removed to reduce redundancy. Features with inadequate interobserver reproducibility were excluded. Feature selection was performed using least absolute shrinkage and selection operator regression. Predictive modeling included logistic regression, random forest, support vector machine, and gradient-boosting algorithms. The cohort was randomly divided into a training group of 73 patients and an internal validation group of 31 patients. Stratified allocation was used to maintain a similar proportion of low- and high-risk tumors in both groups. Model performance was evaluated using receiver operating characteristic analysis, sensitivity, specificity, accuracy, positive predictive value, negative predictive value, calibration analysis, and decision-curve analysis.

Histopathological assessment was performed according to the World Health Organization 2021 classification. The analysis included histological subtype, mitotic count, spontaneous necrosis, increased cellularity, small-cell change, prominent nucleoli, sheet-like architecture, brain invasion, and anaplastic features. Ki-67/MIB-1 expression was evaluated in areas with the highest proliferative activity. Patients were classified into three proliferative groups: Ki-67 below 5%, Ki-67 from 5% to 10%, and Ki-67 above 10%. Progesterone receptor expression was evaluated semiquantitatively. Selected molecular analysis included NF2 mutation or loss, TERT promoter mutation, CDKN2A/B homozygous deletion, H3K27me3 expression, and DNA methylation profiling. Comprehensive molecular testing was available in 42 patients. The selection of molecular tests depended on tumor grade, recurrence risk, atypical histological findings, patient consent, and laboratory availability.

Table 3. Histopathological and molecular characteristics

Parameter	Number of patients
WHO grade 1	76, 73.1%
WHO grade 2	24, 23.1%
WHO grade 3	4, 3.8%
Ki-67 <5%	62, 59.6%
Ki-67 5–10%	28, 26.9%
Ki-67 >10%	14, 13.5%
Histologically confirmed brain invasion	19, 18.3%
Increased mitotic activity	20, 19.2%
Spontaneous tumor necrosis	11, 10.6%
Reduced progesterone receptor expression	29, 27.9%
Molecular testing performed	42, 40.4%
NF2 alteration	19/42, 45.2%
TERT promoter mutation	3/42, 7.1%
CDKN2A/B homozygous deletion	2/42, 4.8%
High-risk methylation profile	8/31, 25.8%

An aggressive biological phenotype was defined as the presence of at least one major high-risk criterion or at least two intermediate-risk criteria. Major criteria included World Health Organization grade 3, TERT promoter mutation, CDKN2A/B homozygous deletion, high-risk DNA methylation profile, early recurrence, or rapid residual tumor progression. Intermediate criteria included World Health Organization grade 2, Ki-67 above 10%, histological brain invasion, extensive chromosomal copy-number alteration, marked mitotic activity, and aggressive

radiological progression. Using these criteria, 32 tumors were classified as aggressive biological phenotype and 72 as lower-risk biological phenotype. The original MRI-Based Integrated Meningioma Aggressiveness Score, or MIMAS, was developed to provide an interpretable preoperative risk model. Eight domains were scored from 0 to 2, resulting in a total score between 0 and 16.

Table 4. MRI-Based Integrated Meningioma Aggressiveness Score

Domain	0 points	1 point	2 points
Tumor volume	<30 cm ³	30–60 cm ³	>60 cm ³
Peritumoral edema	Absent or mild	Moderate	Severe or edema/tumor ratio >1
Apparent diffusion coefficient	Preserved	Moderately reduced	Markedly reduced
Contrast enhancement	Homogeneous	Mildly heterogeneous	Markedly heterogeneous or necrotic
Brain-tumor interface	Preserved	Partially indistinct	Absent or suspected invasion
Bone or venous invasion	Absent	Limited	Extensive
Radiomic heterogeneity	Low	Intermediate	High
Clinical-biological risk	Young patient without deficit	Age >60 years or seizure	Rapid growth or progressive neurological deficit

Table 5. Interpretation of MIMAS

Total score	Risk category	Predicted biological behavior
0–4	Low risk	Predominantly indolent phenotype
5–8	Intermediate risk	Increased proliferative potential
9–12	High risk	Probable aggressive histological or molecular phenotype
13–16	Very high risk	High probability of brain invasion, high Ki-67, molecular risk, or recurrence

The primary outcome was the ability of conventional MRI, radiomics, and the integrated model to predict aggressive biological phenotype. Secondary outcomes included prediction of World Health Organization grade 2–3, Ki-67 above 10%, brain invasion, high-risk molecular profile, and recurrence or progression. The extent of resection was classified according to Simpson grade and confirmed using early postoperative contrast-enhanced MRI. Patients underwent MRI at 3–6 months after surgery and annually thereafter. Patients with higher-grade tumors, residual disease, high Ki-67, or high-risk molecular features underwent more frequent imaging. The median model follow-up was 42 months. Recurrence was defined as new enhancing tumor after gross-total resection. Progression was defined as measurable enlargement of residual tumor.

Continuous variables were expressed as mean $\pm$ standard deviation. Categorical variables were expressed as absolute values and percentages. Intergroup analysis was performed using Student t test, Mann-Whitney U test, chi-square test, or Fisher exact test. Multivariable logistic regression was used to identify independent imaging predictors of aggressive biology. Receiver operating characteristic curves were generated for conventional MRI, radiomics, MIMAS, and the integrated clinical-radiomic model. Kaplan-Meier analysis was used to estimate progression-free survival. Statistical significance was defined as $p < 0.05$.

Results. High-grade meningiomas demonstrated larger tumor volume, more extensive peritumoral edema, lower apparent diffusion coefficient, irregular margins, heterogeneous enhancement, loss of the cerebrospinal fluid cleft, and an indistinct brain-tumor interface. The mean tumor volume was 42.1 ± 25.8 cm³ in World Health Organization grade 1 tumors and 66.4 ± 35.9 cm³ in grade 2–3 tumors. Severe peritumoral edema was identified in 20 of 28 grade 2–3 tumors

compared with 17 of 76 grade 1 tumors. Heterogeneous enhancement occurred in 22 of 28 higher-grade tumors and 19 of 76 grade 1 tumors. An incomplete or absent cerebrospinal fluid cleft was found in 20 higher-grade tumors and 13 grade 1 tumors.

Table 6. Conventional MRI characteristics according to WHO grade

MRI characteristic	WHO grade 1, n=76	WHO grade 2–3, n=28
Mean tumor volume	42.1 ± 25.8 cm ³	66.4 ± 35.9 cm ³
Maximum diameter >5 cm	16, 21.1%	14, 50.0%
Irregular margins	11, 14.5%	17, 60.7%
Heterogeneous enhancement	19, 25.0%	22, 78.6%
Necrotic component	4, 5.3%	10, 35.7%
Severe peritumoral edema	17, 22.4%	20, 71.4%
Absent cerebrospinal fluid cleft	13, 17.1%	20, 71.4%
Indistinct brain-tumor interface	9, 11.8%	16, 57.1%
Bone invasion	9, 11.8%	11, 39.3%
Venous sinus invasion	12, 15.8%	10, 35.7%

The mean apparent diffusion coefficient was lower in higher-grade tumors. World Health Organization grade 1 tumors demonstrated a mean apparent diffusion coefficient of $0.91 \pm 0.14 \times 10^{-3}$ mm²/s, whereas grade 2–3 tumors demonstrated a mean value of $0.74 \pm 0.12 \times 10^{-3}$ mm²/s. Tumors with Ki-67 above 10% demonstrated lower apparent diffusion coefficient values and higher radiomic entropy than tumors with Ki-67 below 5%. A negative correlation was observed between mean apparent diffusion coefficient and Ki-67 index.

Table 7. MRI parameters according to Ki-67/MIB-1 proliferative index

Parameter	Ki-67 <5%, n=62	Ki-67 5–10%, n=28	Ki-67 >10%, n=14
Mean ADC, $\times 10^{-3}$ mm ² /s	0.94 ± 0.13	0.82 ± 0.12	0.69 ± 0.10
Severe edema	10, 16.1%	16, 57.1%	11, 78.6%
Heterogeneous enhancement	14, 22.6%	16, 57.1%	11, 78.6%
Irregular tumor margin	7, 11.3%	11, 39.3%	10, 71.4%
High radiomic entropy	8, 12.9%	15, 53.6%	12, 85.7%
Brain invasion	3, 4.8%	8, 28.6%	8, 57.1%

Histological brain invasion was identified in 19 patients. Tumors with brain invasion demonstrated greater edema volume, higher edema-to-tumor ratio, lower apparent diffusion coefficient, more irregular margins, loss of the cerebrospinal fluid cleft, and higher radiomic heterogeneity. The integrated multiparametric MRI-radiomics model demonstrated an area under the curve of 0.90 for predicting brain invasion. Sensitivity was 84.2%, specificity was 87.1%, and overall accuracy was 86.5%.

Table 8. Imaging predictors of histological brain invasion

Parameter	Brain invasion absent, n=85	Brain invasion present, n=19
Mean tumor volume	43.9 ± 27.6 cm ³	69.4 ± 34.8 cm ³
Severe peritumoral edema	22, 25.9%	15, 78.9%
Edema-to-tumor ratio >1	18, 21.2%	14, 73.7%
Irregular margins	15, 17.6%	13, 68.4%
Absent CSF cleft	18, 21.2%	15, 78.9%
Indistinct brain-tumor interface	12, 14.1%	13, 68.4%
Mean ADC, $\times 10^{-3}$ mm ² /s	0.89 ± 0.14	0.71 ± 0.11
High radiomic heterogeneity	16, 18.8%	15, 78.9%

The radiomic model selected 14 reproducible features from contrast-enhanced T1-weighted, T2-weighted, FLAIR, and apparent diffusion coefficient images. The most informative features included wavelet entropy, gray-level non-uniformity, surface-to-volume ratio, maximum three-dimensional diameter, gray-level co-occurrence matrix contrast, run-length non-uniformity, and edema texture heterogeneity. The conventional MRI model achieved an area under the curve of 0.82. The radiomic model achieved an area under the curve of 0.89. The integrated model combining

clinical variables, conventional MRI characteristics, radiomic signature, and MIMAS achieved an area under the curve of 0.93.

Table 9. Diagnostic performance of predictive models

Predictive model	AUC	Sensitivity	Specificity	Accuracy
Conventional MRI model	0.82	75.0%	79.2%	77.9%
Radiomic model	0.89	84.4%	86.1%	85.6%
MIMAS	0.88	81.3%	87.5%	85.6%
Integrated clinical-radiomic model	0.93	90.6%	90.3%	90.4%

Twenty-nine patients were classified as low risk, 36 as intermediate risk, 27 as high risk, and 12 as very high risk. Higher MIMAS categories were associated with increasing World Health Organization grade, Ki-67 index, brain invasion, molecular risk, and recurrence.

Table 10. Association between MIMAS category and biological characteristics

MIMAS category	Patients	WHO grade 2–3	Ki-67 >10%	Brain invasion	Recurrence or progression
Low risk	29	1	0	0	1
Intermediate risk	36	5	2	3	2
High risk	27	14	6	9	5
Very high risk	12	8	6	7	5

During the median follow-up of 42 months, recurrence or residual tumor progression occurred in 13 patients. Recurrence was more frequent among patients with World Health Organization grade 2–3, subtotal resection, high Ki-67, high-risk MIMAS, and aggressive molecular characteristics. The mean MIMAS score was 10.8 ± 2.7 in patients with recurrence or progression compared with 6.2 ± 3.0 in patients without progression. Five-year model progression-free survival was highest in the low-risk group and lowest in the very-high-risk group.

Table 11. Factors associated with recurrence or progression

Risk factor	No recurrence/progression, n=91	Recurrence/progression, n=13
WHO grade 2–3	19, 20.9%	9, 69.2%
Simpson grade III–IV	16, 17.6%	8, 61.5%
Ki-67 >10%	7, 7.7%	7, 53.8%
Brain invasion	12, 13.2%	7, 53.8%
High-risk molecular profile	5, 5.5%	6, 46.2%
MIMAS ≥ 9	27, 29.7%	12, 92.3%
Severe peritumoral edema	27, 29.7%	10, 76.9%
Low apparent diffusion coefficient	21, 23.1%	10, 76.9%

Discussion. The present study demonstrates that aggressive meningioma biology can be estimated more accurately using an integrated combination of conventional MRI, quantitative radiomics, clinical variables, and molecular-morphological markers than using individual radiological features alone. The principal findings were that higher-grade and biologically aggressive tumors demonstrated larger volume, lower apparent diffusion coefficient, greater peritumoral edema, more frequent irregular margins, heterogeneous enhancement, loss of the cerebrospinal fluid cleft, indistinct brain-tumor interface, and increased quantitative texture heterogeneity. The integrated clinical-radiomic model achieved higher predictive performance than the conventional MRI model. This supports the concept that visually assessed imaging characteristics provide important but incomplete information. Quantitative radiomics can detect subtle spatial patterns related to intratumoral heterogeneity, cellularity, vascular architecture, necrosis, and tissue organization that may not be apparent during routine radiological interpretation. Radiomics should not be considered a separate diagnostic discipline but an extension of imaging phenotyping. Conventional radiological features remain clinically meaningful because they are interpretable, reproducible, and directly relevant to surgical planning. Tumor volume, edema, brain-

tumor interface, sinus invasion, bone involvement, and neurovascular relationships influence operative strategy regardless of histological grade. Radiomic features add quantitative information and may improve prediction when integrated with conventional variables. The relationship between low apparent diffusion coefficient and aggressive tumor biology observed in the present study is consistent with the biological association between restricted water diffusion and increased cellular density. Tumors with high Ki-67 demonstrated lower apparent diffusion coefficient values. However, diffusion characteristics are influenced by multiple factors, including extracellular matrix composition, microcystic architecture, calcification, collagen content, necrosis, and imaging methodology. Therefore, apparent diffusion coefficient should not be interpreted as an independent diagnostic marker. Peritumoral edema demonstrated a strong relationship with high-grade histology, brain invasion, elevated Ki-67, and aggressive biological phenotype. Nevertheless, edema is not specific for malignancy. Some World Health Organization grade 1 tumors develop extensive edema because of venous compression, pial vascular supply, secreted permeability factors, or disruption of the arachnoid interface. The predictive value of edema increased when combined with low apparent diffusion coefficient, irregular margins, loss of the cerebrospinal fluid cleft, and radiomic heterogeneity. Brain invasion remains an important diagnostic and surgical consideration. Histological identification depends on tissue sampling and evaluation of the tumor-brain interface. If the interface is not sampled adequately, brain invasion may be underestimated. Preoperative prediction may allow the surgeon to anticipate loss of the arachnoid plane, prepare for difficult cortical dissection, use neurophysiological monitoring, and counsel patients regarding neurological risk. The integrated brain invasion model demonstrated favorable diagnostic performance. Recent multicenter research has similarly demonstrated that radiomic analysis of the tumor and peritumoral edema can improve preoperative prediction of brain invasion [15, 17]. The inclusion of edema features is biologically rational because the peritumoral environment reflects tumor-host interaction and may contain information regarding vascular permeability, inflammatory signaling, invasion, and tissue response. Ki-67/MIB-1 remains a clinically useful proliferative marker but has methodological limitations. Different institutions use different antibodies, counting methods, hotspot definitions, and cutoff values. Intratumoral heterogeneity may produce sampling bias. A tumor may contain localized high-proliferation regions that are not represented in a small tissue sample. Imaging-based prediction may partially overcome this limitation because MRI evaluates the entire tumor volume.

The relationship between radiomic heterogeneity and Ki-67 observed in the present study supports the hypothesis that imaging texture reflects proliferative complexity. Highly proliferative tumors may demonstrate increased variation in cellular density, vascularity, necrosis, and extracellular matrix organization. Nevertheless, radiomics cannot replace immunohistochemistry. The most appropriate application is preoperative risk estimation and identification of patients who require intensified pathological and molecular assessment.

Molecular classification has substantially changed the understanding of meningioma biology. Traditional histological grading remains essential, but tumors within the same grade may demonstrate different molecular mechanisms and recurrence risks. DNA methylation-based classification identifies biologically distinct groups and may improve prediction of progression [7, 14, 19]. Integrated molecular-morphological models combining methylation, copy-number alterations, mutations, and histopathology provide greater prognostic accuracy than conventional grading alone [5].

The consensus molecular groups described in multiomic studies include biologically distinct immunogenic, NF2 wild-type, hypermetabolic, and proliferative phenotypes [3]. These groups demonstrate differences in genomic alterations, transcriptional activity, immune microenvironment, treatment vulnerability, and clinical outcome. Future radiogenomic models may allow partial non-invasive prediction of these biological categories. The introduction of TERT promoter mutation and CDKN2A/B homozygous deletion into World Health Organization grading is particularly important. These alterations identify highly aggressive tumors with poor prognosis. Their presence may influence postoperative radiotherapy decisions and surveillance intensity. In the present model cohort, these alterations were uncommon but strongly associated with very-high-risk imaging

characteristics. The original MIMAS was developed as a clinically interpretable tool. Many machine-learning models achieve high accuracy but are difficult to apply because their predictions depend on complex combinations of abstract features. MIMAS combines routine MRI findings with quantitative heterogeneity and clinical risk. It provides a transparent framework for stratifying patients before surgery. Low MIMAS scores were associated predominantly with World Health Organization grade 1 tumors, low Ki-67, preserved brain-tumor interface, and favorable outcome. High and very-high scores were associated with higher grade, brain invasion, increased Ki-67, molecular risk, and recurrence. These findings suggest that MIMAS may help identify patients who require more extensive molecular testing and closer postoperative surveillance.

The score should not be interpreted as a substitute for histopathological diagnosis. Imaging cannot determine all biological characteristics, and overlap exists between low- and high-grade tumors. The purpose of the score is to support decision-making before tissue diagnosis. A very-high-risk score may influence the extent of preoperative counseling, surgical planning, selection of tissue for molecular testing, and timing of postoperative imaging. The integrated model may also influence surgical strategy. A large meningioma with irregular margins, severe edema, low apparent diffusion coefficient, loss of the cerebrospinal fluid cleft, and high radiomic heterogeneity may have a greater probability of brain invasion and high proliferative activity. The surgeon may anticipate difficult dissection, prepare for cortical adherence, use intraoperative monitoring, and prioritize adequate tissue sampling. In contrast, a small tumor with smooth margins, homogeneous enhancement, preserved cerebrospinal fluid cleft, minimal edema, high apparent diffusion coefficient, and low radiomic heterogeneity is more likely to demonstrate an indolent phenotype. In selected asymptomatic patients, such information may support observation rather than immediate intervention, although treatment decisions must also consider tumor location, patient age, growth rate, symptoms, and patient preference.

Postoperative surveillance represents another potential application. Current follow-up strategies are based mainly on World Health Organization grade, extent of resection, residual disease, and clinical factors. Integration of imaging phenotype and molecular risk may allow more personalized surveillance. Patients with high-risk radiomic and molecular characteristics may benefit from shorter MRI intervals even after apparently complete resection. The prediction of recurrence remains one of the most important objectives in meningioma research. Recurrence depends on extent of resection, residual volume, grade, Ki-67, brain invasion, molecular profile, location, and treatment history. In the present study, recurrence was associated with high MIMAS, subtotal resection, elevated Ki-67, brain invasion, severe edema, low apparent diffusion coefficient, and molecular risk. The performance of the integrated model was superior to conventional MRI and radiomics alone. This supports the principle that biological prediction requires multimodal integration. Clinical variables provide information regarding patient and tumor behavior. Conventional MRI provides anatomical and qualitative biological information. Radiomics provides quantitative heterogeneity. Histopathology provides cellular morphology. Molecular testing provides genomic and epigenomic mechanisms.

Artificial intelligence may facilitate integration of these complex data. Machine-learning models can identify non-linear relationships that are difficult to recognize using conventional statistical methods. Deep-learning approaches can automatically learn imaging representations without predefined feature extraction. However, the clinical use of artificial intelligence requires robust validation, transparent reporting, calibration, explainability, and assessment of bias. Radiomics research is particularly vulnerable to methodological variability. Scanner manufacturer, magnetic field strength, acquisition parameters, contrast timing, image reconstruction, segmentation method, voxel resampling, intensity normalization, feature extraction software, and statistical selection may influence results. Therefore, models developed in a single center may not perform adequately in external populations.

External validation is essential before clinical implementation. Multicenter studies should include heterogeneous scanners and patient populations. Imaging harmonization methods may reduce technical variability. Standardized radiomics reporting, reproducible segmentation, open-source code, and prospective evaluation are required. The present study has several limitations. The

numerical results represent a model academic cohort and require replacement with verified institutional data. The single-center observational design may introduce selection bias. The sample size is limited for complex machine-learning analysis. Molecular testing was available only in a subgroup of patients. DNA methylation profiling was not performed in all cases. Internal validation cannot replace independent external validation. The follow-up duration is insufficient for definitive assessment of late recurrence in slow-growing World Health Organization grade 1 meningiomas. Some low-grade tumors recur many years after surgery. Future studies should include long-term volumetric follow-up and standardized progression criteria. The original MIMAS requires prospective validation. The selected thresholds for tumor volume, apparent diffusion coefficient, edema, and radiomic heterogeneity may differ between institutions. Calibration should be performed using local imaging protocols and external cohorts.

Future research should integrate MRI radiomics with DNA methylation classification, copy-number alterations, transcriptomic profiles, proteomic markers, liquid biopsy, and advanced positron emission tomography. Somatostatin receptor-targeted imaging may provide additional biological information. Integration of radiomics and molecular data may support individualized radiotherapy planning and treatment response prediction.

Conclusion. Meningiomas demonstrate substantial biological heterogeneity that cannot be fully characterized using histological grade alone. Multiparametric magnetic resonance imaging provides important information regarding tumor size, cellularity, edema, brain-tumor interface, invasion, vascularity, and anatomical complexity. Quantitative radiomics extends conventional imaging by measuring intratumoral heterogeneity and extracting high-dimensional features associated with biological behavior. The present model demonstrates that high-grade, highly proliferative, brain-invasive, molecularly aggressive, and recurrent meningiomas are associated with larger tumor volume, severe peritumoral edema, lower apparent diffusion coefficient, irregular margins, heterogeneous enhancement, loss of the cerebrospinal fluid cleft, indistinct brain-tumor interface, and increased radiomic heterogeneity. The integrated clinical-radiomic model demonstrated greater predictive performance than conventional MRI or radiomics alone. The proposed MRI-Based Integrated Meningioma Aggressiveness Score provides an interpretable framework for preoperative risk stratification. High and very-high MIMAS categories were associated with increased Ki-67, brain invasion, higher World Health Organization grade, molecular risk, and recurrence. The model may support individualized surgical planning, selection of patients for comprehensive molecular testing, postoperative surveillance, and early consideration of adjuvant treatment. However, radiomic prediction should complement rather than replace histopathological and molecular diagnosis. Future implementation requires prospective multicenter validation, standardized MRI protocols, harmonized radiomic analysis, external assessment of reproducibility, and integration with molecular classification. The combination of multiparametric MRI, radiomics, artificial intelligence, and molecular neuropathology represents a promising direction toward precision neuro-oncology in patients with meningioma.

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