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Downregulation of miR-221, miR-143, and miR-22 in Meningioma: Diagnostic Performance in a Single-Center Case–Control Study

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ABSTRACT

AIM: To determine case–control differences in tissue miRNA expression and to quantify their ability to distinguish meningioma from nontumor dura.

MATERIAL and METHODS: Tissue samples from 45 intracranial meningioma cases (WHO grade I, n = 22; grade II, n = 23) and 26 dura controls were analyzed. miRNA expression levels were measured by quantitative real-time PCR (qRT-PCR), normalized to U6, and relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method. Group and grade comparisons were performed using appropriate parametric or nonparametric tests. Diagnostic performance was evaluated using receiver operating characteristic (ROC) and area under the curve (AUC) values, with optimal cut-off points determined by the Youden index. Sensitivity and specificity were reported.

RESULTS: Compared with controls, meningioma tissues showed significant downregulation of miR-221, miR-143, and miR-22 (all $p < 0.001$), whereas miR-145 showed borderline significance ($p = 0.052$). Diagnostic discrimination was highest for miR-221 (AUC, 0.912; cut-off, ≤0.19; sensitivity, 91.11%; specificity, 88.46%), followed by miR-143 (AUC, 0.810; cut-off, ≤0.24; sensitivity, 71.11%; specificity, 92.31%) and miR-22 (AUC, 0.771; cut-off, ≤0.36; sensitivity, 82.22%; specificity, 65.38%). No significant differences in expression were observed between grade I and grade II tumors for any miRNA.

CONCLUSION: Tissue miR-221, miR-143, and miR-22 are consistently downregulated in intracranial meningioma and demonstrate clinically meaningful diagnostic performance, with miR-221 showing the highest discriminatory accuracy. These findings support the potential integration of miRNA assays into tissue-based diagnostics and warrant multicenter validation to refine cut-off values and evaluate prognostic utility.

KEYWORDS: AUC, brain neoplasms, meningioma, microRNA

ABBREVIATIONS: AUC: Area under the curve, **miRNA:** MicroRNA, **qRT-PCR:** Quantitative real-time PCR, **ROC:** Receiver operating characteristic, **WHO:** World Health Organization

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INTRODUCTION

Meningiomas are extra-axial tumors arising from arachnoid cap cells and account for approximately 13%–26% of all intracranial tumors. They are more prevalent in females, and headache is among the most common presenting symptoms (17,21,22). Although most meningiomas are benign, a subset demonstrates aggressive behavior and recurrence that are not fully predicted by histopathological features alone (21,22).

Current diagnostic practice increasingly relies on an integrated approach. The 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS5) incorporates molecular criteria alongside morphology. Specifically, TERT promoter mutations and homozygous deletions of CDKN2A/B now warrant a WHO grade III designation, regardless of histology, owing to their strong association with early recurrence and poor clinical outcomes (14,16).

At the genomic level, meningiomas can be broadly classified into NF2-mutant and NF2–wild-type groups. The latter are enriched for alterations in genes such as *TRAF7*, *KLF4* (K409Q), *AKT1* (E17K), *PIK3CA*, and *SMO*, often displaying location-specific patterns (e.g., skull-base predilection) and pathway activation involving PI3K/AKT/mTOR or Hedgehog signaling. These alterations may co-occur, such as *TRAF7* mutations with *KLF4* or *AKT1*, and provide insights into tumor biology and therapeutic targets (1,3,6).

Beyond individual genetic alterations, epigenetic profiling has substantially improved risk stratification. DNA methylation–based classifications outperform histologic grading in predicting recurrence and have been translated into clinically relevant molecular groups. In addition, recurrent chromosomal losses—particularly of 1p and 14q—are common in higher-grade tumors and further refine prognostic assessment (4,7,18).

Within this molecular framework, microRNAs (miRNAs) have emerged as promising biomarkers because they reflect pathway-level activity and can be reliably quantified from routine tissue samples. Although prior studies have linked miRNA dysregulation to meningioma biology and clinical behavior, actionable diagnostic thresholds remain limited (2,9). Building on this background, we investigated the expression of miR-221, miR-143, and miR-22, with miR-145 included as a comparator, in an expanded single-center cohort and assessed their diagnostic performance using ROC-derived cut-off values.

MATERIAL and METHODS

Subjects

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Practice Ethics Committee of the Eskisehir Osmangazi University Medical Faculty (approval date: May 5, 2021; Decision No. 14). Written informed consent was obtained from all participants. Tissue samples were collected from 45 patients diagnosed with intracranial meningioma between June 15, 2021, and August 15, 2023, at the Faculty of Medicine, Department of Neurosurgery. Control dura samples were obtained from 26 individuals who underwent decompressive craniectomy for cerebrovascular events.

Detection of miRNA Expression

Total microRNA was extracted using the Sanprep Column MicroRNA Mini-Preps Kit (Sangon Biotech Co., Ltd., Shanghai, China) according to the manufacturer's instructions. Complementary DNA was synthesized using the TaqMan Advanced miRNA cDNA Synthesis kit (Thermo Fisher Scientific, Inc.). Quantitative real-time PCR was performed with BrightGreen miRNA qPCR MasterMix (Applied Biological Materials, Vancouver, Canada) on a CFX96 Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., Hercules, California). miRNA-specific primers for miR-143 (#MI0000459), miR-145 (#MI0000461), miR-221 (#MI0000298), and miR-22 (#MI0000078) were obtained from OriGene Technologies (Beijing, China). Gene expression levels were normalized to U6 (#MP300001), and relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method (13).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25. Quantitative variables, including miRNA expression levels and age, were presented as mean ± standard deviation or median (Q1–Q3), as appropriate, whereas categorical variables were expressed as frequencies and percentages. The Shapiro–Wilk test was used to assess normality. Group comparisons were conducted using the Student *t* test or Mann–Whitney *U* test for normally and nonnormally distributed data, respectively. Gender distributions were compared using the chi-square test. Spearman correlation analysis was used to assess linear relationships between quantitative variables.

Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was used to quantify discriminatory ability. Optimal cut-off values were determined using the Youden index, and corresponding sensitivity and specificity values were reported. A p value < 0.05 was considered statistically significant. Because several miRNA expression variables exhibited skewed distributions, group comparisons and biological interpretations were primarily based on median values, which were considered more representative of qRT-PCR expression data.

RESULTS

Study Participants

A total of 45 meningioma samples (22 females and 23 males) and 26 non–tumor-associated dura mater samples (14 females and 12 males) were included in this study. Among the meningioma cases, 22 tumors were classified as WHO grade I and 23 as grade II. The mean age of the meningioma and control groups was 58.36 ± 11.16 and 56.28 ± 12.36 yr, respectively. There were no statistically significant differences in age or sex distribution between the case and control groups ($p > 0.05$). Detailed clinical and demographic characteristics of the study participants are summarized in Table I.

Comparison of miRNA Expression Levels between Case and Control Groups

Compared with non–tumor-associated dura controls, meningioma tissues exhibited significant downregulation of miR-221, miR-143, and miR-22 (all $p < 0.001$). In contrast, miR-145 showed only a borderline difference between the two groups ($p = 0.052$). miRNA expression levels in patients and controls are presented in Table II. Although mean expression values appeared higher for some miRNAs in the meningioma group, median values consistently indicated lower expression in tumor tissues, reflecting skewed distributions with outliers. Therefore, conclusions regarding miRNA downregulation were primarily based on median comparisons.

Comparison of miRNA Expression Levels between WHO Grade I and Grade II Meningiomas

No statistically significant differences in miRNA expression levels were observed between WHO grade I and grade II meningioma samples (all $p > 0.05$) (Table III).

ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis demonstrated that miR-143 yielded an AUC of 0.81, with a sensitivity of 71.11% and a specificity of 92.31%. The optimal cut-off value for miR-143 was ≤0.24, as determined by the Youden index. miR-22 showed an AUC of 0.771, with a sensitivity of 82.22% and a specificity of 65.38%, at an optimal cut-off value of ≤0.36. miR-221 demonstrated the highest diagnostic accuracy, with an AUC of 0.912, sensitivity of 91.11%, and specificity of 88.46%, at a cut-off value of ≤0.19. AUC values and corresponding cut-off points are summarized in Table IV. An overview of AUCs is presented in Figure 1, and sensitivities and specificities at the selected cut-off values are shown in Figure 2.

Collectively, these findings support miR-221 as a strong tissue-based diagnostic adjunct, with miR-143 providing high specificity and miR-22 contributing to sensitivity.

Table I: Clinical and Demographic Features of Patients and Controls

Variable	Control (n=26)	Case (n=45)	p-value
Female, n (%)	14 (53.8)	22 (48.9)	0.876
Male, n (%)	12 (46.2)	23 (51.1)	
Age, mean±SD	56.28±12.36	58.36±11.16	0.476
Age, median [Q1–Q3]	58 [50–62]	60 [52–66]	

Table II: Expression Levels of miRNAs in Patients and Controls

miRNA	Control Mean±SD	Control Median [Q1–Q3]	Case Mean±SD	Case Median [Q1–Q3]	p-value
miR-143	1.70±1.94	0.94 [0.35–2.64]	1.09±3.13	0.05 [0.03–0.33]	**<0.001**
miR-145	2.72±3.48	0.76 [0.30–4.50]	6.99±17.93	0.20 [0.08–1.90]	0.052
miR-22	2.69±4.44	1.22 [0.20–3.18]	3.73±13.33	0.06 [0.01–0.25]	**<0.001**
miR-221	2.46±2.65	1.31 [0.26–4.54]	0.11±0.23	0.05 [0.01–0.13]	**<0.001**

Table III: Expression Levels in Grade 1 vs Grade 2 Meningiomas

miRNA	Grade 1 Mean±SD	Grade 1 Median [Q1–Q3]	Grade 2 Mean±SD	Grade 2 Median [Q1–Q3]
miR-143	1.85±4.31	0.05 [0.03–1.47]	0.36±0.88	0.18 [0.05–0.24]
miR-145	8.16±18.48	0.36 [0.15–6.62]	5.87±17.73	0.20 [0.01–0.87]
miR-22	3.00±11.89	0.03 [0.00–0.30]	4.43±14.81	0.20 [0.02–0.25]
miR-221	0.16±0.32	0.04 [0.01–0.16]	0.06±0.07	0.05 [0.02–0.05]

Table IV: AUC and Cut-off Values for miRNAs

Test (Biomarker)	AUC	SE	p	95% CI for AUC	Cut-off / Sensitivity / Specificity
miR-143	0.810	0.051	**<0.001**	(0.709–0.910)	≤0.24 / 71.11% / 92.31%
miR-22	0.771	0.056	**<0.001**	(0.661–0.882)	≤0.36 / 82.22% / 65.38%
miR-221	0.912	0.041	**<0.001**	(0.831–0.992)	≤0.19 / 91.11% / 88.46%

AUC: Area Under the Curve, **SE:** Standard Error, **CI:** Confidence Interval

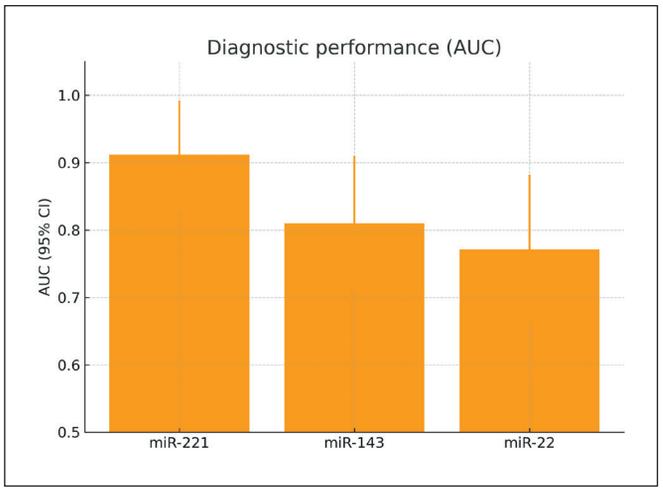

Figure 1: Diagnostic performance of miRNAs expressed as area under the curve (AUC) values. miR-221 demonstrated the highest discriminatory accuracy compared with miR-143 and miR-22.

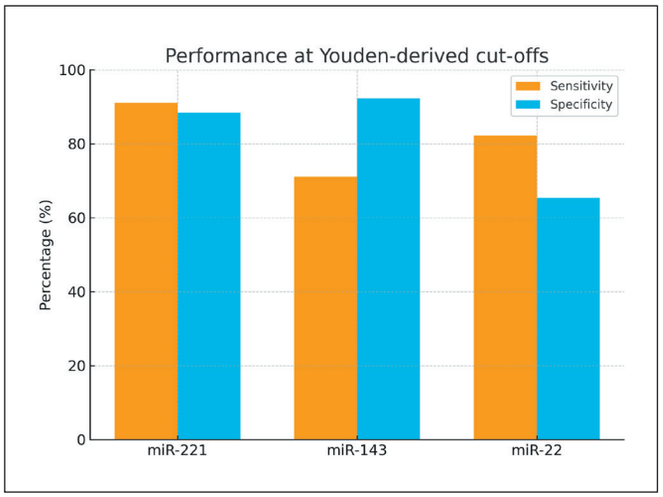

Figure 2: Sensitivity and specificity of miRNAs at Youden-derived optimal cut-off values. miR-221 showed balanced sensitivity and specificity, whereas miR-143 demonstrated higher specificity.

DISCUSSION

Meningiomas originate from arachnoid membrane cells and account for approximately 13%–26% of intracranial tumors. Although generally considered benign, meningiomas exhibit the second-highest morbidity rate after glial tumors. They typically grow slowly and are sometimes detected incidentally on radiologic imaging. The WHO Classification of Tumours of the Central Nervous System categorizes meningiomas into three histological grades and 15 subtypes to aid prognostic stratification. Approximately 90% of meningiomas are classified as WHO grade I (benign), 5%–7% as grade II (atypical), and 1%–3% as grade III (anaplastic) (21).

Meningiomas were among the earliest solid tumors investigated for genetic abnormalities, an important step toward understanding their biological behavior. Genetic insights may inform diagnosis, treatment, and preventive strategies. Familial studies indicate that first-degree relatives of patients with meningioma have an approximately twofold increased risk of developing the disease, although no consistent excess risk has been demonstrated among distant relatives at the population level (15). While this information has limited immediate diagnostic utility, it supports a heritable component that intersects with known somatic alterations and epigenetic programs in meningioma biology.

In the present cohort, tissue miR-221, miR-143, and miR-22 were significantly downregulated in meningioma samples compared with dura controls (all $p < 0.001$), whereas miR-145 showed only a borderline difference ($p = 0.052$). From a diagnostic perspective, miR-221 demonstrated the strongest discriminatory ability (AUC, 0.912; cut-off, ≤0.19; sensitivity, 91.11%; specificity, 88.46%), followed by miR-143 (AUC, 0.810; cut-off, ≤0.24; sensitivity, 71.11%; specificity, 92.31%) and miR-22 (AUC, 0.771; cut-off, ≤0.36; sensitivity, 82.22%; specificity, 65.38%). No significant differences were observed between WHO grade I and grade II tumors for any miRNA, indicating that while these markers may support diagnosis, they are insufficient for grading when used alone.

Biological Interpretation

miR-22. Although miR-22 upregulation has been reported in several malignancies and linked to metabolic reprogramming—particularly via repression of ATP-citrate lyase (ACLY) and modulation of *de novo* lipogenesis—our data demonstrate reduced miR-22 expression in meningioma tissue compared with dura controls (20,23). This discrepancy highlights the content-dependent nature of miRNA regulatory networks and underscores the importance of tissue-matched controls in biomarker development.

miR-143. Consistent with previous reports describing tumor-suppressive functions through modulation of KRAS/MAPK signaling and ERK5-dependent transcriptional programs, miR-143 expression was lower in meningioma tissues than in controls (5,19,25). The absence of grade-dependent differences suggests that miR-143 loss may represent an early or lineage-stable event rather than a driver of histologic progression.

miR-145. Prior studies in meningioma have reported downregulation of miR-145 in higher-grade tumors and inhibitory effects on cellular proliferation and migration in experimental models (11). Across multiple cancer types, miR-145 is generally regarded as a tumor suppressor (24). The borderline case–control difference observed in our study may reflect biologic heterogeneity, sample size limitations, or platform-related effects and warrants confirmation in larger cohorts.

miR-221/222 axis. Members of the miR-221/222 family are frequently upregulated and proproliferative in many epithelial cancers through repression of tumor suppressors such as $p27^{Kip1}$ and PTEN (10,12). In malignant meningioma models, inhibition of miR-221/222 enhances radiosensitivity and reduces radiation-induced invasiveness by relieving PTEN suppression (8). In contrast, the reduced miR-221 expression observed in our meningioma samples relative to dura controls

suggests lineage-specific regulation and raises the possibility that miR-221 downregulation reflects tissue identity rather than tumor aggressiveness.

Clinical Implications and Limitations

The observed downregulation of miR-221, miR-143, and miR-22, together with their ROC-derived thresholds, supports their potential use as tissue-based adjuncts to conventional histopathological diagnosis. Integration of these markers with current molecular frameworks, including DNA methylation classes and chromosomal alterations, may further enhance diagnostic and predictive accuracy (4,7,14,18). Key limitations of this study include its single-center design, lack of longitudinal outcome data, and absence of an external validation cohort. In addition, potential confounding effects of pre-analytical variables, such as ischemia time or embolization, cannot be fully excluded.

Future studies should pursue multicenter validation, evaluate associations with tumor recurrence and other prognostic outcomes, and assess multimarker panels that integrate miRNAs with genomic and epigenomic features to develop clinically actionable diagnostic and prognostic models. The use of non–tumor-associated dura mater obtained during decompressive craniectomy for cerebrovascular events represents a pragmatic and ethically feasible control strategy in neurosurgical research. Nevertheless, ischemia, inflammation, or acute pathological processes may influence miRNA expression independently of tumor biology. Such effects are expected to introduce nonspecific biological variability and would likely bias results toward underestimation rather than overestimation of tumor-specific differences. Multicenter studies incorporating alternative control tissues will be valuable for further validation.

CONCLUSION

Our findings identify miR-221, miR-143, and miR-22 as promising tissue-based diagnostic biomarkers for distinguishing intracranial meningioma from non-tumor–associated dura mater. Further multicenter validation and integration with established molecular classifiers are required before routine clinical implementation.

Declarations

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Disclosure: The authors declare no conflict of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: EO, ST, EE
Data collection: ST, EO, EE
Analysis and interpretation of results: ZO, EO, HO
Draft manuscript preparation: ST, EO
Critical revision of the article: SA, AA
Other (study supervision, fundings, materials, etc...): EO, AA
All authors (ST, EO, EE, ZO, SA, HO, AA) reviewed the results and approved the final version of the manuscript.

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