ORIGINAL ARTICLE

Morphometric and Ki-67 proliferative index-related characteristics of meningiomas and their correlation with demographic, clinical, histopathological, and postoperative features

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ABSTRACT

Aim To investigate the correlations between tumour characteristics, symptoms, intraoperative findings, and outcomes in patient with meningioma.

Methods A retrospective study was conducted on 86 surgically treated patients at Department of Neurosurgery of Cantonal Hospital Zenica from 2010 to 2020. Patients with intracranial meningiomas underwent neurological evaluation and MRI scans to analyse tumour characteristics, including volume (TV), peritumoral brain oedema (PTBE) and oedema index (EI). Surgical treatment was performed, followed by postoperative MRI and outcome assessment. Intraoperatively, the tumour's relationship with cortex, pial membrane, skull bones, and sinuses was evaluated, and the extent of tumour resection was graded. Meningioma samples underwent histopathological analysis to assess the grade and regularity of borders, and Ki-67 labelling index was determined using immunohistochemistry.

Results Significant correlations were found between PTBE and Ki-67 expression ($p<0.001$), PTBE and vomiting/nausea ($p=0.002$), cognitive impairment ($p=0.047$), venous compression ($p=0.001$), cortical, pial and dural invasion ($p<0.05$), and the postoperative presence of oedema ($p=0.002$). Venous compression, cortical, pial, dural and bone invasion positively correlated with Ki-67 expression ($p<0.001$). Grade and tumour border positively correlated with Ki-67 expression ($p<0.001$). Oedema persistence postoperatively showed a positive correlation with Ki-67 expression ($p<0.001$).

Conclusion The study revealed significant correlations between Ki-67 expression and PTBE, with notable associations with clinical symptoms, tumour characteristics, and postoperative oedema presence.

Key words: brain oedema, brain neoplasms, morphometry, tumour volume, volumetry

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INTRODUCTION

Meningiomas, the most common primary benign tumours in the central nervous system, arise from arachnoid cells and are characterized by slow growth, often amenable to complete surgical resection, which confers a favourable prognosis for many patients (1,2). However, despite their general nature, the development of peritumoral brain oedema (PTBE) remains a significant clinical challenge in the management of meningiomas, influencing patient outcomes and necessitating close monitoring and follow-ups (5-8).

The Ki-67 proliferative index, a well-established marker of cellular proliferation, has become an invaluable tool for evaluating tumour aggressiveness and predicting clinical behaviour in various cancers, including meningiomas (1-4). The Ki-67 index has been associated with more aggressive tumour characteristics, such as higher grade and an increased risk of recurrence in meningiomas (4,5). Moreover, larger meningiomas are generally more metabolically active as they require a greater supply of nutrients for their growth. This increased metabolic demand is accompanied by an inflammatory process leading to heightened vascular permeability (9,10). Consequently, there is the occurrence of transudation of fluid components from blood vessels resulting in the formation of vasogenic oedema.

The complexity of the PTBE formation process is evident, and existing research suggests its multifactorial nature, considering various factors like venous stasis, thrombosis, compressive ischemia, and aggressive tumour growth (1). Given that the aforementioned factors are linked to the intracranial growth of meningiomas, it is expected that there is a correlation between the Ki-67 proliferative index and the volume of peritumoral oedema (1-3).

The aim of this study was to investigate a correlation between morphological characteristics of intracranial meningiomas and peritumoral brain oedema, and to examine the correlation between peritumoral oedema and the Ki-67 index. By investigating these factors, neurosurgeons can gain valuable insights that will assist them in making decisions regarding the treatment and postoperative patient management.

PATIENTS AND METHODS

Patients and study design

This retrospective study conducted at the Department of Neurosurgery, Cantonal Hospital Zenica (Bosnia and Herzegovina), involved 86 surgically treated patients in the period 2010-2020. Inclusion criteria were patients who had been diagnosed with intracranial meningioma and had undergone diagnostic evaluation, surgical treatment, and postoperative follow-up at the Department. Exclusion criteria were patients who had been surgically treated in another institution, with multiple expansive brain lesions or multicentric and multiple brain meningiomas, with any other brain abnormalities that could have affected the measurement results, with recurrent and/or previously treated intracranial meningiomas, who had previously undergone any craniotomy and/or craniectomy for reasons other than intracranial meningiomas, and patients who, for any reason, did not or could not have a preoperative magnetic resonance imaging of the brain and were operated based on CT scan.

Methods

Neurologic symptoms and signs were evaluated by anamnesis and neurologic examination. Patients underwent magnetic resonance imaging of the head with contrast, magnetic angiography and venography (MRI, Siemens Magnetom Avanto, Munich, Germany). MRI data were used to analyse the morphological characteristics of intracranial meningiomas. The morphologic features analysed were tumour volume, peritumoral brain oedema and tumour margins.

To measure morphological characteristics of meningiomas, IMPAX system was used (Impax version 6.5.1.144, AGFA HealthCare N.V., Belgium). The formula for measuring the volume of a spheroid (each tumour is approximately spherical in shape) was used to determine the tumour volume (TV) and volume of peritumoral brain oedema (PTBE): $V=4/3\pi \times a/2 \times b/2 \times c/2$ (12). The measurement included the coronal (Figure 1a), axial (Figure 1b), and sagittal (Figure 1c) diameters, for assessing the cumulative value of TV and PTBE. Subsequently, measurements of the same tumour diameters were taken to calculate VT. By subtracting the TV value from the cumulative value (TV+PTBE), the PTBE value

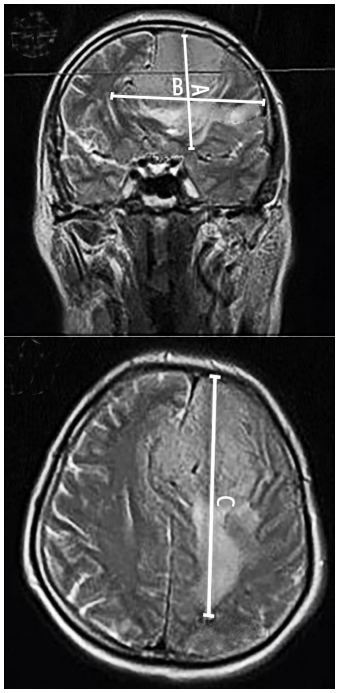

Figure 1. Measurements for the volume of peritumoral oedema (PTBE): A) coronal diameter; B) axial diameter; C) sagittal diameter (Department of Neurosurgery, Cantonal Hospital Zenica, 2022)

was obtained. The relationship between TV and PTBE was evaluated by calculating the oedema index (EI): EI = (TV + PTBE)/(TV) (11-13). To analyse the size of the tumour, T1 sequences with contrast were used, while the size of the oedema was analysed on T2 sequences. The measurements were in cm^3.

The patients underwent surgical treatment using surgical microscope (Carl Zeiss, OPMI Pentero 900, Oberkochen, Germany), and an ultrasonic aspirator (Söring Sonoca 300, Quickborn, Germany). Intraoperatively, the tumour's relationship was evaluated to the cortex, pial membrane, indicating invasiveness, as well as its proximity to the skull bone. The presence of venous compression by the meningioma on the cerebral veins was also observed, potentially impeding the normal exchange of interstitial fluid and resulting in consequent oedema. The extent of tumour resection was graded according to the Simpson grading system: I - complete surgical removal of the tumour with resection of the dural attachment and removal of the affected bone; II - complete macroscopic removal of the tumour with coagulation of the dural attachment; III - complete macroscopic removal of the intradural tumour without coagulation or resection of the dural attachment; IV - partial tumour resection, while V represents tumour biopsy (14). In the postoperative period, all patients spent at least 24 hours in the Intensive Care Unit.

Meningioma samples underwent histopathological analysis, immunohistochemistry, and assessment of Ki-67 labelling index. Formalin-fixed (4%) paraffin-embedded blocks were sectioned (3-5 μm), mounted on poly-L-lysine-coated slides, and incubated overnight at 45 °C. Slides were deparaffinized, rehydrated, and subjected to antigen retrieval using citrate buffer. Endogenous peroxidase activity was blocked, followed by incubation with anti-human Ki-67 antibody. Positive staining was quantified by determining the percentage (%) of tumour cells showing staining in high-power fields, focusing on regions with intense staining - hot spots.

The patients were postoperatively assessed with the Glasgow Outcome Scale (15) grading from 1 (death outcome) to 5 (resolution of clinical symptoms).

A follow-up MRI was performed after 3 months. The MRI scan was conducted using the same protocol as the preoperative evaluation, with a focus on assessing the presence or absence of oedema.

Statistical analysis

Descriptive statistics methods were used: percentages, mean value, standard deviation (SD), minimum and maximum value, and 95% confidence interval (CI). Deviations from the normal distribution for the examined variables were determined using the Kolmogorov-Smirnov test. From the methods of comparative statistics, nonparametric data were used: $\chi 2$-test, as well as Spearman Rho correlation coefficient. The level of statistical significance was set to ≤ 0.05.

RESULTS

Of the 86 patients, 33 (38.4%) were male and 53 (61.6%) were female (p=0.031). The majority of patients 31 (36.0%) fell into the 61-70 years category, followed by 51-60 years 26 (30.2%) and 71-80 years 15 (17.4%) (p<0.001), implying varying risks of developing meningiomas among different age groups (Table 1).

Most patients had a headache preoperatively (51.2%, p=0.829). Frontal meningiomas were

Table 1. Demographic and morphometric characteristic of 86 patients with meningioma

Variable		No (%) of patients	p
Demographic data			
Gender	Male	33 (38.4)	0.031
	Female	53 (61.6)	
Age (years)			<0.001
	21-40	2 (2.3)	
	41-50	9 (10.5)	
	51-60	26 (30.2)	
	61-70	31 (36.0)	
	71-80	15 (17.4)	
	>81	3 (3.5)	
Clinical data			
Headache	Yes	44 (51.2)	0.829
	No	42 (48.8)	
Vomiting/nausea	Yes	8 (9.3)	<0.001
	No	78 (90.7)	
Hemiparesis	Yes	27 (31.4)	0.001
	No	59 (68.6)	
Epileptic seizure	Yes	16 (18.6)	<0.001
	No	70 (81.4)	
Cognitive impairment	Yes	7 (8.1)	<0.001
	No	79 (91.9)	
Dysphasia	Yes	8 (9.3)	<0.001
	No	78 (90.7)	
Venous compression	Yes	31 (36.0)	0.010
	No	55 (64.0)	
Total		**86 (100.0)**	

most frequent (34.9%) (p<0.001). Most patients had left-sided meningioma 45 (52.4%), while 27 (31.4%) were right-sided and 14 (16.3%) occupied both sides. Dural invasion was the most common, 55 (64.0%). Simpson grade I resection was performed with 63 (73.3%) meningiomas, grade II with 20 (23.3%) and grade III with 1 (3.5%) meningioma (p<0.001) (Table 2).

Histopathological findings were also examined and 68 (78.1%) patients had grade I meningioma. Borders of resected tumours were clear in 56 (65.1%) and irregular in 30 (34.9%) meningiomas (p<0.001).

Postoperatively, most patients were graded with GOS 5 in 55 (64.0%) (p<0.001). There were no patients with GOS 2 grade. Oedema presence was evaluated on postoperative MRI imaging three months after resection. Most patients, 47 (54.6%) (p<0.001), showed absence of oedema (Table 2).

The mean tumour volume was 53.69±54.4 cm^3, indicating significant variability in tumour size among patients, with most tumours likely being smaller in size (p<0.001). The EI mean value of 3.61±3.53 was found, indicating different levels of oedema among patients (p<0.001). The PTBE average value was 107.30±167.15 cm^3.

Table 2. Tumour characteristics and follow-up

Variable		Values	p
MRI findings (No; %)			
Localization	Basal	6 (7.0)	<0.001
	Falx	21 (24.4)	
	Frontal	30 (34.9)	
	Occipital	2 (2.3)	
	Parietal	11 (12.8)	
	PCA	1 (1.2)	
	Sphenoid wing	1 (1.2)	
	PCF	5 (5.8)	
	Temporal	9 (10.5)	
Side	Right	27 (31.4)	<0.001
	Left	45 (52.4)	
	Both	14 (16.3)	
Intraoperative findings (No; %)			
Cortical and pial invasion	Yes	42 (48.8)	0.829
	No	44 (51.2)	
Dural invasion	Yes	55 (64.0)	0.010
	No	31 (36.0)	
Sinus invasion	Yes	28 (32.6)	0.001
	No	58 (67.4)	
Bone invasion	Yes	20 (23.3)	<0.001
	No	66 (76.7)	
Simpson's classification	I	63 (73.3)	<0.001
	II	20 (23.3)	
	III	3 (3.5)	
Histopathological findings (No; %)			
Grade	I	68 (78.1)	<0.001
	II	17 (19.8)	
	III	1 (1.2)	
Tumour border	Clear	56 (65.1)	
	Irregular	30 (34.9)	
Ki-67 Mean±SD (Min – Max)	0.09±0.12 (0.01–0.7)		<0.001
Morphometric data Mean±SD (Min – Max)			
TV (cm3)	53.69±54.4 (1.24–222.02)		<0.001
PTBE (cm3)	107.3±167.14 (0 – 1000)		<0.001
EI	3.62±3.52 (1 – 14)		<0.001
Postoperative evaluation and follow up (No; %)			
GOS	1	2 (2.3)	<0.001
	2	0 (0)	
	3	7 (8.1)	
	4	22 (25.6)	
	5	55 (64.0)	
Oedema presence	Yes	39 (45.4)	<0.001
	No	47 (54.6)	
Total		**86 (100.0)**	

Min, minimum; Max, maximum; MRI, magnetic resonance imaging; PCA, pontocerebellar angle; PCF – posterior cranial fossa; PTBE, peritumoral brain oedema; EI, oedema index; TV, tumour volume; GOS, Glasgow Outcome Scale;

The TV demonstrates a statistically significant positive correlation with PTBE (R=0.527; p<0.001), suggesting that larger tumour volume often accompanies greater PTBE. The EI also exhibits a statistically significant positive correlation with the Ki-67 proliferation index (R=0.488; p<0.001) (Figure 2) and PTBE (R=0.911; p<0.001). These correlations indicate that a higher EI was often associated with increased tumour proliferation and a larger PTBE volume. The Ki-67 proliferation index showed a

Table 3. Correlation between observed variables

Variable	Tumour volume (TV)		Peritumoral brain oedema (PTBE)		Oedema index (EI)		Ki-67	
	R	p	R	p	R	p	R	p
Demographic data								
Gender	0.040	0.712	0.110	0.315	0.117	0.283	0.118	0.281
Age	0.171	0.116	0.024	0.827	0.052	0.633	0.125	0.252
Clinical data								
Headache	0.092	0.400	0.025	0.819	0.001	0.993	0.076	0.486
Vomiting/nausea	0.324	0.002	0.121	0.266	0.007	0.946	0.008	0.941
Hemiparesis	0.071	0.518	0.015	0.890	0.085	0.438	0.008	0.944
Epi	0.037	0.733	0.014	0.901	0.022	0.843	0.075	0.494
Cognitive impairment	0.215	0.047	0.234	0.030	0.116	0.290	0.048	0.658
Dysphasia	0.144	0.185	0.184	0.089	0.264	0.014	0.206	0.057
Venous compression	0.344	0.001	0.531	0.000	0.537	<0.001	0.370	<0.001
MRI findings								
Localization	0.181	0.096	0.017	0.876	0.050	0.645	0.035	0.749
Side	0.164	0.132	0.003	0.977	0.018	0.872	0.127	0.243
TV	-	-	0.527	<0.001	0.280	0.009	0.385	<0.001
EI	0.280	0.009	0.911	<0.001			.488	<0.001
PTBE	0.527	<0.001	-	-	0.911	<0.001	.468	<0.001
Intraoperative findings								
Cortical and pial invasion	0.297	0.005	0.581	<0.001	0.609	<0.001	0.617	<0.001
Dural invasion	0.307	0.004	0.554	<0.001	0.577	<0.001	0.438	<0.001
Sinus invasion	0.209	0.053	0.274	0.011	0.261	0.015	0.360	0.001
Bone invasion	0.186	0.087	0.369	<0.001	0.356	0.001	0.294	0.006
Simpson's classification	0.070	0.523	0.127	0.244	0.233	0.031	0.129	0.238
Histopathological findings								
Grade	0.214	0.048	0.341	0.001	0.356	0.001	0.528	<0.001
Tumour border	0.321	0.003	0.603	<0.001	0.578	<0.001	0.612	<0.001
Postoperative evaluation and follow up								
GOS	-0.111	0.311	-0.318	0.003	-0.357	0.001	-0.213	0.049
Oedema presence	0.328	0.002	0.743	<0.001	0.760	<0.001	0.596	<0.001

R, Spearman Rho correlation coefficient; GOS, Glasgow Outcome Scale

statistically significant positive correlation with PTBE (R=0.468; p<0.001), which indicates that greater tumour proliferation may be linked to a larger PTBE volume. These correlations indicate that a higher EI often accompanies greater tumour proliferation and a larger PTBE.

The TV exhibited significant positive correlations with vomiting/nausea (R=0.324; p=0.002), cognitive impairment (R=0.215; p=0.047), venous compression (R=0.344; p=0.001), cortical and pial invasion (R=0.297; p=0.005), dural invasion (R=0.307; p=0.004), and presence of oedema (R=0.328; p=0.002). These findings indicate that an increase in TV leads to heightened expression of the symptoms and intraoperative findings. The PHD demonstrated a significant positive correlation (R=0.214; p=0.048), as did the tumour border (R=0.321; p=0.003) with TV, suggesting that an increase in TV was associated with a higher grade and irregularity of the tumour border (Table 3).

Significant positive correlations were observed between peritumoral brain oedema (PTBE) and gender (R=0.110; p=0.315) as well as age (R=0.024; p=0.827), implying that females and older individuals exhibit higher PTBE values. Cognitive impairment exhibited a significant positive correlation with PTBE (R=0.234; p=0.030), indicating that higher PTBE volumes resulted in cognitive impairment. Cortical and pial invasion (R=0.581; p<0.001), dural invasion (R=0.554; p<0.001), sinus invasion (R=0.274: p=0.011), and bone invasion (R=0.369; p<0.001) showed significant positive correlations with PTBE. The Glasgow Outcome Scale (GOS) demonstrated a negative correlation with PTBE (R= -0.318; p=0.003), suggesting a poorer postoperative patient status with higher PTBE values (Table 3).

Intraoperative findings of cortical and pial invasion (R=0.609; p<0.001), dural invasion (R=0.577; p<0.001), sinus invasion (R=0.261; p=0.015), and bone invasion (R=0.356; p=0.001) were significantly positively correlated with EI, suggesting their contribution to elevated levels of oedema. Tumour grade (PHD) and tumour border exhibited a significant positive correlation with EI (R=0.356; p=0.001 and R=0.578; p<0.001, respectively). Additionally, the presence of oedema on control MRI after 3 months demon-

strated a significant positive correlation with EI (R=0.760; p<0.001), implying that the presence of oedema is associated with higher preoperative values of EI (Table 3).

Venous compression exhibited significant positive correlations with Ki-67 expression (R=0.370; p<0.001), indicating that the presence of venous compression may be associated with higher levels of Ki-67 expression. Cortical and pial invasion showed significant positive correlations with Ki-67 expression (R=0.617; p<0.001), suggesting that the invasion of cortical and pial regions was associated with increased expression of Ki-67. Grade (PHD) demonstrated a significant positive correlation with Ki-67 expression (R=0.528; p<0.001), suggesting that higher tumour grade was associated with increased expression of Ki-67. The tumour border also exhibited significant positive correlations with Ki-67 expression (R=0.612; p<0.001), indicating that a more extensive tumour border may be associated with higher expression levels of Ki-67. Oedema presence showed significant positive correlation with both Ki-67 expression (R=0.596; p<0.001), suggesting that the presence of oedema on control MRI after 3 months was associated with higher expression levels of Ki-67 (Table 3).

DISCUSSION

The study examined the relationships among PTBE, TV, and EI in meningiomas and complex interplay of these variables and their clinical implications. Significant variations were observed in TV with a wide range of values 1.24–222.02 cm^3 (mean 53.69±54.4 cm^3), indicating substantial heterogeneity in tumour sizes. The main tumour volume was 27.81 cm^3 in Bečulić et al. study (7). The median tumour and oedema volumes were 13.73 cm^3 at Hess at al. (16). The EI had a mean of 3.62±3.52 (range 1-14), reflecting varying degrees of oedema involvement. PTBE in a study of Ahmeti et al. (17) demonstrated considerable variability; it is in agreement with the results of our study (range 0-1000 cm^3), highlighting the diverse nature of oedema presence. Tumour volume in the group with PTBE was significantly larger than in those without oedema according to Li et al. (18).

A positive correlation was found between TV and EI, indicating that larger tumours are often associated with increased oedema. Monitoring TV and EI can provide insights into the severity of PTBE. Bečulić et al. (7) noted a positive correlation between PTBE and TV. Simis et al. (9) found a larger volume of PTBE correlated with the larger tumour volume of meningiomas. The correlation of TV with the size of PTBE partly implies that larger tumours destroy the leptomeninges and cerebral cortex by their mass effect, enabling the direct transfer of oedema fluid to the white matter resulting in vasogenic oedema (10).

TV showed a positive correlation with the Ki-67 proliferation index in our study, suggesting that larger tumours tend to have a higher proliferation rate. This has implications for prognosis and treatment decisions. The positive correlation between tumour volume and Ki-67 proliferation rate was also confirmed in other studies (19) explaining that tumours with Ki-67 ≤3.19% were 2 cm smaller than tumours with Ki-67 >3.195%. A moderate correlation was found between the tumour size and Ki-67 (20). Our results showed a positive correlation of TV with PTBE volume, indicating that larger tumours are associated with greater peritumoral oedema.

This study also highlighted gender differences in meningioma occurrence and identified age categories with higher prevalence, contributing to understanding of the disease demographics. Overall, these findings provide important insights into tumour characteristics and guide clinical decision-making. The correlation between Ki-67 proliferation index and PTBE is confirmed by previous investigations (7,11, 13-15).

Higher TV is proved to correlate with incidence of preoperative symptoms (17,21), confirming this study's results. Ahmeti et al. (17) showed independency between TV and brain invasion as opposed to this study.

No correlation between PTBE and gender and age were found in some studies (22-24), contrary to our results and the results of Lee et al. (25). Simis et al. (9) found a positive correlation between PTBE and headache and seizures. Cognitive deficits, palsy and seizure were significantly more present preoperatively in patients with PTBE than in patients without PTBE, Ahmeti et al reported. (17) Brain invasion strongly correlated with PTBE in Ahmeti et. al (17), matching this study. Loewenstern et al. (26) did not observe a

coincidence between headache and PTBE. Reportedly, a higher rate of cognitive deficits in patients with frontal meningiomas and PTBE (27) and an increased risk for palsy and aphasia in patients with PTBE were found (28). Some studies showed that meningiomas with higher PTBE, irregular margins and invasive behaviour were associated with higher Simpson grade (30).

Opposing the presented study, no correlation with GOS and PTBE volume was found in other studies (17,30). Bečulić et al. (7) showed a statistically significant correlation with higher Ki-67 and irregular tumour margins. Same studies found no statistically significant difference between males and females and their Ki-67 values, as well as between Ki-67 value and pial and cortical invasion, matching the results reported in this study (17,30).

The study is limited by its retrospective design and singular institutional scope, thereby restricting generalizability. The observational nature of the findings, in conjunction with the limited 3-month follow-up period, may not adequately account for long-term variations in patient conditions.

In conclusion, the study demonstrates positive correlations between TV, PTBE, EI, and the Ki-67 proliferation index, suggesting that larger tumours are associated with higher oedema levels and increased proliferation rates. These findings provide valuable insights into tumour characteristics, enhancing our understanding of tumour behaviour, prognosis, and supporting informed treatment decisions. This study unveils a novel finding, emphasizing the critical consideration of postoperative oedema persistence in the realm of brain tumour management. Further research is warranted to explore the predictive role of Ki-67 in monitoring postoperative oedema and developing effective strategies to address this aspect of brain tumour treatment. EI and Ki-67 proliferation index in clinical assessments can contribute to more comprehensive evaluations and improved outcomes for patients with brain tumours, underscoring the need for continued investigations in neuro-oncology.

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