Clinical Factors Related to Histopathologic Grade in Meningioma

Erna Kristiani[1], Michelle Agelica[2], Sally Suharyani[2], Kevin Dharmawan[2]

[1]*Department of Pathology Anatomy*
[2]*Faculty of Medicine Pelita Harapan University*

Citation : Kristiani Erna, Angelica Michelle, Suharyani Sally, Dharmawan Kevin. Clinical Factors Related to Histopathologic Grade in Meningioma**.** Medicinus. 2022 February; 10(2): 50-57
Keywords: Meningioma; Grade; Factor; Location; Size; Edema; Necrosis; Age; Gender
Correspondance : Erna Kristiani. Faculty of Medicine Univ. Pelita Harapan
E-mail : erna.Kristiani@uph.edu
Online First : June 2022

Abstract

Background: Meningiomas are the most common intracranial tumor of central nervous system tumors. Although the prevalence is lower, the WHO grade II and III meningiomas are more aggressive, with higher mitosis rates, are more likely to recur after surgery, and have lower survival rates. The ability to differentiate between WHO I and WHO II/ III meningiomas before surgery can contribute to a significant clinical benefit in helping the neurosurgeon doing the best management planning.

Methods: This is a retrospective cross-sectional study of meningioma patients in Siloam Hospital Lippo Village between 2014 – 2018. The sample will be recruited using consecutive sampling. The relationship between analyzed variables and meningioma grades will be investigated using a chi-square test if the data was eligible; otherwise, the Fisher-exact test will be performed.

Result: Ninety eight (69%) patients diagnosed as low grade meningioma, and 44 (31%) as high grade meningioma. Tumor location, size, edema, necrosis, age, and gender had significant results with $p \leq 0.05$. Multivariate results also show that all six variables have a significant relationship with each other.

Conclusions: Tumor location, size, edema, necrosis, age, and gender have a significant relationship to histopathological meningioma grade in patients at Siloam Hospital Lippo Village in 2014-2018.

Introduction

Meningioma is the most common primary tumor in the Central Nervous System (CNS) around 25,5% of all CNS neoplasms.[1,2] Meningioma originates from arachnoid, especially from the outer layers of arachnoid and arachnoid villi, which are also referred to as arachnoid cap cells and the distribution is spread throughout the CNS.[3]

Based on histopathological characteristics, the World Health Organization (WHO) divides meningioma into three grades, namely, grade I, II, and III. Among these three grades, grade I meningioma has the most frequent occurrences, while grade II and III only occur in 21-27,8% of all meningioma cases.[1]

Despite their lower prevalence rates, grade II and III meningioma are considered high-grade meningioma. This high-grade meningioma has a higher mitosis rate so that it develops more progressively, has a higher risk of recurrence, and a lower survival rate. Histologically grade III meningiomas are malignant with atypical nuclei.[3]

A variety of modalities can be used to support the diagnosis of meningioma, including computed tomography (CT scan) imaging and magnetic resonance imaging (MRI).[4] The standard management of meningioma is operative resection. However, patients with small lesions can be managed with Gamma Knife Surgery (GKS) and no longer candidates for operative surgery. Radiologically findings, such as an invasion of the brain, bone and peritumoral edema around the brain area are also related to high-grade meningioma, and if managed

with GKS, subsequent management will be complicated.[5,6]

Therefore, the ability to differentiate the grade of meningioma before treatment can contribute to a significant clinical benefit in assisting surgeons to develop an operative plan so that it runs as well as possible. Providing information about the tumor's grade can be useful intra-operatively because the surgeon has to decide considering the risks and benefits of more aggressive resection of the tissue around the tumor.[6,7]

The aim of this study is to examine the relationship between clinical factors and grades of meningioma because of its essential role in the clinical course and management of the disease.

Material And Methods

Samples are obtained from patient medical records with a diagnosis of meningioma at Siloam Hospital Lippo Village, which includes demographic data such as gender and age, clinical factors such as tumor location, tumor size, edema, necrosis, and also tumor pathology based on WHO grade between 2014 to 2018. Tumor location, size, edema, and necrosis were assessed through radiologic findings. For patients who did not undergo a histopathological examination of tumor tissue and incomplete clinical information are excluded. Statistical analysis was performed using SPSS 22.

Result

Univariate analysis

A total sample that fulfilled the inclusion and exclusion criteria from 2014-2018 is 142 individuals. From all samples, 53 (37,3%) were male, and 89 (62,7%) were female. Age <65 was 112 (78,9%) and ≥65 was 30 (21,1%). In MRI can be seen that tumor size <3,2 cm and ≥3,2 cm were 73 (51,4%) and 69 (48,6%), respectively. Tumor with edema was 58 (40,8%) and 84 (59,2%) without edema. On the other hand, sample with necrosis was 25 (17,6%) and 117 (82,4%) without necrosis. The most common tumor locations were in the cranial base region with 89 patients. 98 (69%) people suffer from low-grade meningioma and 44 (31%) suffer from high-grade meningioma.

As an illustration, we confirmed the radiological features with microscopic images in patients with grade II and III meningioma. (Figure 1 and 2).

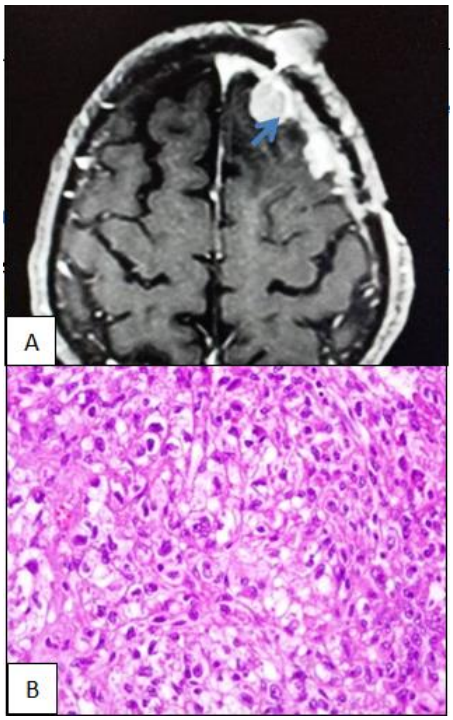
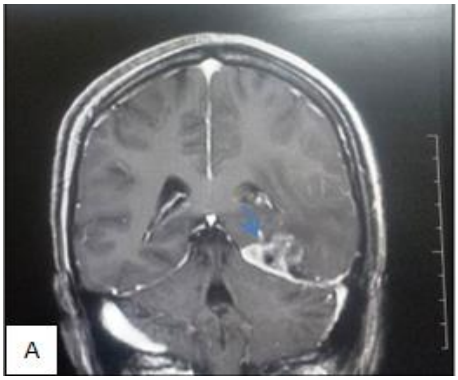


Figure1. A. MRI shows tumor mass in left frontal lobe with edema (arrow).
B. Histopathology appearance with atypical cells, confirmed as Meningioma WHO grade II.



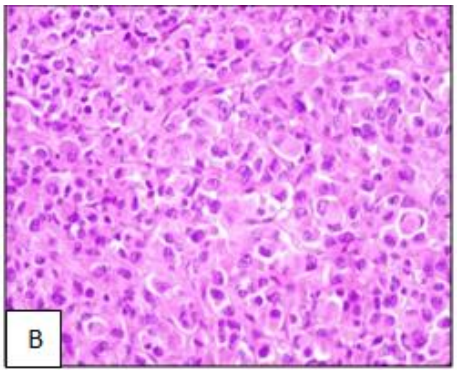


Figure2. A. MRI shows left occipital lobe tumor mass with central necrotic.
B. Histopathology appearance with anaplastic cells, confirmed as Meningioma WHO grade III.

Bivariate analysis

- **Relationship between Location and Grade of Meningioma**
  Most people who are diagnosed with high-grade meningioma were located in the parasagittal/falx/convection region, and low-grade meningioma was located in the cranial base region. This analysis was tested using Fisher-exact test and yielded a p-value <0.001.

- **Relationship of Size with Grade of Meningioma**
  Most people who are diagnosed with low-grade meningioma, are tumor size <3.2 cm. Thirty people with tumor size ≥3.2 cm are high-grade. These results were tested with Chi-square and produced a significant relationship with p=0.002.

- **Relationship of Edema with Grade Meningioma**
  Twenty-five (43,1%) tumor patients had edema with high-grade, and 19 (22.6%) people without edema were high-grade meningioma. This relationship was analyzed by Chi-square with a value of p = 0.009.

- **Relationship of Necrosis with Grade Meningioma**
  Patients with high-grade meningioma mostly had necrosis, which was 20 (80%), while 93 (79,5%) patients without necrosis had a low-grade meningioma. This relationship was analyzed by Chi-square with p<0,001.

- **Relationship of Age with Grade Meningioma**
  Most patients who were ≥65 years-old had high-grade meningioma while patients <65 years-old had a low-grade meningioma. This relationship was analyzed by Chi-square with p=0,011.

- **Relationship of Gender with Grade Meningioma**
  A total of 23 (43.4%) men suffer from high-grade meningioma, and 21 (23.6%) women suffer from high-grade meningioma. The relationship between the two variables was carried out using chi-square test with p=0.014, which means there is a significant relationship between the two variables.

Multivariate analysis

All six variables, tumor location, size, edema, necrosis, age, and gender were tested in multivariate analysis of tumor grade with linier regression. The analysis result is shown in Table 1.

Table 1. Data analysis of meningioma patient at Siloam Hospital Lippo Village.

Characteristic	Frequency	Percentage (%)	Sig.	Exp (B)
Gender				
Male	53	37,3	0,024	0,231
Female	89	62,7		
Age				
<65	112	78,9	0,006	0,135
≥65	30	21,1		
Size (cm)				
<3,2	73	51,4	0,006	0,135
≥3,2	69	48,6		
Edema				
Yes	58	40,8	0,019	0,237
No	84	59,2		
Necrosis				
Yes	25	17,6	<0,001	0,035
No	117	82,4		
Location				
Cranial base	89	62,7	0,001	<0,001
Parasagittal/ falx/ convection	41	28,9		
Others	12	8,4		
Grade				
Low	98	69		
High	44	31		

Discussion

Grade I (low-grade) meningioma has a relatively good prognosis. In contrast, grade II and III (high-grade) meningioma have a worse prognosis and often require adjuvant therapy.[7] The ability to predict the tumor's grade will help the clinician provide a more accurate direction for the management, without waiting for a histological diagnosis, which sometimes requires a longer time.[6,7]

Lots of research that focuses on molecular characteristics using genomic and proteomic technology. However, these approaches require invasive procedures to take tissue samples, and usually, only a small portion of the sample can be analyzed and cannot reflect the composition and heterogeneity of the tumor.[1] Conversely, imaging tests that do not have invasive properties have great potential in assisting tumor stratification and guiding management because imaging examinations provide a more comprehensive picture of the whole tumor and help monitor the ongoing therapeutic response, development, and recurrence process.[6,7]

Relationship between Location and Grade of Meningioma

This study found a significant relationship between location and grade of meningioma ($p < 0.05$). These results are similar to previous studies which state that anatomic location is a risk factor for atypical and malignant meningioma, where there is a more significant increase in risk at non-base of skull tumor (27% vs. 12%; $p < 0.001$).[8]

Previous studies have suggested that meningioma in non-skull locations have a more aggressive nature. Previous studies using genomic analysis have shown that meningioma located in the area around the cerebral hemisphere and cerebellum often have higher grades and have more frequent NF2 gene mutations and / or lose chromosome 22 with concurrent genomic instability.[9]

A study by Hashimoto et al. showed that meningioma on the skull base had a significantly higher percentage of chromosome loss of 1p (20.31%) compared to meningioma in the non-skull base. These results suggest that genetics play an essential role where tumors in the skull base region tend to be at a minimum of genetic defects and have less aggressive biological properties.[10]

Relationship of Size with Grade of Meningioma

In this study, as many as 46.6% meningioma with size ≥3.2 cm were high grade, while 14.5% meningioma with size <3.2 cm experienced high grade, with significant differences. A study by Palaniandy et al. also showed similar results and found that high-grade meningioma had a mean tumor volume three times greater than low-grade meningioma. This result was also statistically significant ($p=0.001$).[3,5]

Relationship of Edema with Grade Meningioma

This study compares the percentage of meningioma accompanied by edema and without edema with high-grade tumors that are twice different. Hale et al. examined the relationship between degrees of edema divided into 4 degrees with meningioma grade.[17] The study results showed a significant correlation between edema and meningioma grade with a value of $p = 0.022$.

Atypical and malignant meningiomas are reported to infiltrate more frequently around the tissue.[3] This also underlies the occurrence of edema around the tumor, while grade I meningioma are less likely to develop edema. There are various etiologies proposed for the mechanism of edema, namely compressive ischemia due to disruption of the blood-brain barrier, vascular shunting due to parasitism of the micro vial vessels, mechanical venous obstruction, increased elevated hydrostatic pressure in the tumor, and the phenomenon of secretory excretory tumor cells.[18,19]

Relationship of Necrosis with Grade Meningioma

The incidence of necrosis in this study was significantly different where 45.4% of tumors with necrosis were high-grade meningioma, while those without necrosis were only 54.6%. A study by Backer et al. reported that necrosis was found in 23% of cases of meningioma spread in 11.9% grade I meningioma, 45.8% grade II meningioma, and 100% grade III meningioma.[20]

Necrosis comes from nutritional insufficiency and hypoxia due to high metabolic demands, which suggest that this condition is associated with more aggressive development. Necrosis can be found in small and large tumor foci. Hypoxic tumor cells involving necrotic tissue can show areas that have experienced differentiation and transformation of malignant cells.[21]

Relationship between age and grade of meningioma

In this study, a significant relationship was found between age and the incidence of high-grade meningioma, where the age group ≥65 years had a higher percentage of high-grade meningioma (50%) compared to the age group <65 years (35.9%). However, the results of other studies are still controversial. Some studies state a relationship between age and grade of meningioma, where age ≥65 years shows a significantly higher percentage suffering from high-grade meningioma.[22] However, other studies report conflicting results.[5]

The relationship between age and grade of meningioma is still not known. Zhou et al. found that the pediatric group had a higher risk of developing meningioma with a higher grade. The reason that can explain this relationship may be due to embryogenic abnormalities, such as genetic mutations. But in this study, there were no samples with pediatric age.[1]

Relationship of Gender with Grade of Meningioma

In this study, men tend to experience higher meningioma grade ($p < 0.05$). Liang et al. conducted a study of 1,239 cases and reported that men had a higher risk of developing high-grade meningioma, whereas, in that study, the ratio of men to women with high-grade meningioma was 21.7% compared to 12.9% $p < 0.001$.[23]

The reason between the male gender and the occurrence of high-grade meningioma are still not clear. Various studies have suggested that hormone levels, hormone receptors, and chromosomal abnormalities can affect the tendency of high tumor grade.[23,24] Other studies have also shown an inverse relationship between levels of progesterone receptor expression and tumor histology grading.[24]

Conclusion

In this study, we concluded that clinical factors such as, tumor location, size, edema, necrosis, age and gender have a significant relationship to histopathological meningioma grade. Predicting clinical factors can be useful for surgeons to plan treatment strategies.

Conflicts of Interest

The authors affirm no conflict of interest in this study.

Funding Sources

This study does not need any funding.

Acknowledgment

-

References

1. Zhou P, Ma W, Yin S, Li Y, Jiang S. Three risk factors for WHO grade II and III meningiomas: A study of 1737 cases from a single center. Neurology India. 2013; 61: 40-4. https://doi.org/10.4103/0028-3886.107928

2. Khampalikit I, Cheunsuchon P, Sitthinamsuwan B. Clinical Predictors of WHO Grades, Subtypes, and Atypical Histopathological Features of Meningiomas. J Med Assoc Thai. 2017; 100: 122-32.

3. Palaniandy K, Haspani MSM, Zain NRM. Prediction of histological grade and completeness of resection of intracranial meningiomas: role of peritumoural brain Edema. Malays J Med Sci. 2017; 24: 33-43. https://doi.org/10.21315/mjms2017.24.3.5

4. Li H, Zhao M, Jiao Y, *et al*. Prediction of High-Grade Pediatric Meningiomas: Magnetic Resonance Imaging Features Based on T1-Weighted, T2-Weighted, and Contrast- Enhanced T1 Weighted Images. World Neurosurgery. 2016; 91: 89-95. https://doi.org/10.1016/j.wneu.2016.03.079.

5. Magill ST, Young JS, Chae R, Aghi MK, Theodosopoulos PV, McDermott MW. Relationship between tumor location, size, and WHO grade in meningioma. Neurosurg Focus. 2018; 44: E4. https://doi.org/10.3171/2018.1.FOCUS17752

6. Coroller TP, Bi WL, Hyunh E, *et al*. Radiographic prediction of meningioma grade by semantic and radiomic features. PLoS ONE. 2017; 12: 1-15. https://doi.org/10.1371/journal.pone.0187908

7. Hale AT, Wang L, Strother MK, Chambless LB. Differentiating meningioma grade by imaging features on magnetic resonance imaging. J Clin Neurosci. 2018; 48: 71-5. https://doi.org/10.1016/j.jocn.2017.11.013

8. Kane AJ, Sughrue ME, Rutkowski MJ, *et al*. Anatomic Location Is a Risk Factor for Atypical and Malignant Meningiomas. Cancer. 2011; 117: 1272-8. https://doi.org/10.1002/cncr.25591

9. Clark VE, Erson-Omay EZ, Serin A, *et al*. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013; 339: 1077-80. https://doi.org/10.1126/science.1233009

10. Hashimoto N, Rabo CS, Okita Y, *et al*. Slower growth of skull base meningiomas compared with non–skull base meningiomas based on volumetric and biological studies. J Neurosurg. 2012; 116: 574-80. https://doi.org/10.3171/2011.11.JNS11999

11. Hwang WL, Marciscano AE, Niemierko A, *et al*. Imaging and extent of surgical resection predict risk of meningioma recurrence better than WHO histopathological grade. Neuro- Oncology. 2016; 18: 863-72. https://doi.org/10.1093/neuonc/nov285

12. Liu Y, Chotai S, Chen M, Jin S, Qi S-T, Pan J. Preoperative radiologic classification of convexity meningioma to predict the survival and aggressive meningioma behavior. Plos One. 2015;1: 1-13. https://doi.org/10.1371/journal.pone.0118908

13. Tan LA, Boco T, Johnson AK, *et al*. Magnetic resonance imaging characteristics of typical and atypical/anaplastic meningiomas-case series and literature review. Br J Neurosurg. 2014;29:77-81. https://doi.org/10.3109/02688697.2014.957647

14. Tang Y, Dundamadappa SK, Thangasamy S, *et al*. Correlation of apparent diffusion coefficient with Ki-67 proliferation index in grading meningioma. Am J Roentgenol. 2014;202:1303-8. https://doi.org/10.2214/AJR.13.11637

15. Toh CH, Castillo M, Wong aMC, *et al*. Differentiation between classic and atypical meningiomas with use of diffusion tensor imaging. Am J Neuroradiol. 2008;29:1630-5. https://doi.org/10.3174/ajnr.A1170

16. Watanabe Y, Yamasaki F, Kajiwara Y, *et al*. Preoperative histological grading of meningiomas using apparent diffusion coefficient at 3T MRI. Eur J Radiol. 2013;82:658-63. https://doi.org/10.1016/j.ejrad.2012.11.037

17. Hale AT, Wang L, Strother MK, Chambless LB. Differentiating meningioma grade by imaging features on magnetic resonance imaging. J Clin Neurosci. 2018; 48: 71-5. https://doi.org/10.1016/j.jocn.2017.11.013

18. Huang RY, Bi WL, Griffith B, *et al*. Imaging and diagnostic advances for intracranial meningiomas. J Neurooncol. 2019; 21: 44-61. https://doi.org/10.1093/neuonc/noy143

19. Hou J, Kshettry VR, Selman WR, Bambakids NC. Peritumoral brain edema in intracranial meningiomas: the emergence of vascular endothelial growth factor–directed therapy. Neurosurg Focus. 2013; 35: 1-10. https://doi.org/10.3171/2013.8.FOCUS13301

20. Backer-Grøndahl T, Moen BH, Torp SH. The histopathological spectrum of human meningiomas. Int J Clin Exp Pathol. 2012; 5: 231-42.

21. Goes P, Santos BFO, Suzuki FS, *et al*. Necrosis is a consistent factor to recurrence of meningiomas: should it be a stand-alone grading criterion for grade II meningioma? J Neurooncol. 2018; 137: 331-6. https://doi.org/10.1007/s11060-017-2721-4

22. Lin BJ, Chour KN, Kao HW, *et al*. Correlation between magnetic resonance imaging grading and pathological grading in meningioma. J Neurosurg. 2014; 121: 1201-8. https://doi.org/10.3171/2014.7.JNS132359

23. Abdelzaher E, El-Gendi SM, Yehya A, Gowil AG. Recurrence of benign meningiomas: Predictive value of proliferative index, BCL2, p53, hormonal receptors and HER2 expression. Br J Neurosurg. 2011; 25: 707-13. https://doi.org/10.3109/02688697.2010.522743

24. Tao Y, Liang G, Li Z, Wang Y, Wu A, Wang H, *et al*. Clinical features and immunohistochemical expression levels of androgen, estrogen, progesterone and Ki-67 receptors in relationship with gross-total resected meningiomas relapse. Br J Neurosurg. 2012; 26: 700-4. https://doi.org/10.3109/02688697.2012.685780

Author's Statement

The authors declared that all the images and figures in this manuscript is/are author's own work and/or has obtained necessary permission to re-use the content from the authors and publisher of respective materials.

Erna Kristiani