P-ISSN 0215-7284
e-ISSN 25279106
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The Clinicopathological Profile and Recurrence of Meningioma at Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital

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Received : 05-04-2023
Accepted : 23-04-2023
Published : 31-01-2024

ABSTRACT

Background
Meningioma represents the most frequent primary intracranial tumor, and some subtypes may demonstrate aggressive characteristics with a correspondingly elevated risk of recurrence. To predict the likelihood of recurrence, clinical and pathological parameters are essential. More aggressive treatment strategies and strict follow-up can be implemented using these parameters. Therefore, this study aims to determine the clinicopathological characteristics of meningioma and its relationship with recurrence.

Method
This study adopted a retrospective cross-sectional approach using secondary data of meningioma cases from the archives of the Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital in 2019-2021. The clinical data were obtained through electronic medical records, and histopathological data assessment, including grade, mitosis, brain invasion, bone invasion, and dural invasion, were evaluated through microscopic examination.

Result
The data showed that a total of 219 cases of meningioma were reassessed. The mean age of patients was 45±11 years old, and the majority (88.1%) were female. The mean tumor size was 5±1.8 cm, with the most common tumor location being the skull base (71%) and 38.6% of cases showed radiological evidence of bone invasion. Subtotal resection was the treatment of choice for most patients (67.8%). CNS WHO grade 1 was found in 91.8% of cases, while Mitotic index ≥4/10 HPF, microscopic evidence of bone invasion, brain invasion, and dural invasion were found in 5%, 33.6%, 3.2%, and 16.8%, respectively. A minimum follow-up of 6 months was fulfilled by 71 cases, and 28% experienced recurrence/progression. These findings showed a significant association between the extent of resection (p=0.007) and tumor size (p=0.02) with the incidence of recurrence.

Conclusion
Clinical parameters such as the extent of resection and tumor size play a role in predicting the likelihood of meningioma recurrence. The predictive factors knowledge for meningioma recurrence is important in determining treatment strategies and follow-up.

Keywords: Clinicopathological, Meningioma, Progression, Recurrence

P-ISSN 0215-7284
e-ISSN 25279106
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INTRODUCTION

Meningioma is a tumor originating from the neoplastic proliferation of meningothelial cells in the arachnoid layer.[1] It is the most common intracranial neoplasm, accounting for approximately 39% of all intracranial tumors, with an incidence rate of 9.12 per 100,000 population.[1,2] Meningioma is known to have an increased incidence with age, and the median age at diagnosis is 66 years old.[3] It is more common in women than men, with a ratio of 2:1.[4] According to a retrospective study conducted by the Department of Neurology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, meningioma is the most common central nervous system (CNS) neoplasm, accounting for 45.1% of all intracranial tumors in 2014-2016.[5]

Meningioma can occur in the intracranial, intraspinal, or orbital areas. The most common locations include the convexity, parasagittal, skull base (sphenoid, frontobasal, and posterior fossa), parasellar/suprasellar, and intraventricular areas.[3] The growth is slow, with clinical symptoms varying depending on the location of the tumor. Clinical symptoms and signs occur due to mass compression of nearby brain and vascular structures. The symptoms include headache, seizures, focal cranial nerve deficits, and weakness.[1,3]

In the 5th edition of CNS Tumour Classification published in 2021, the World Health Organization (WHO) classifies meningioma into three grades. The grade determination is important in predicting tumor aggressiveness, risk of recurrence, survival, and guiding treatment management. CNS WHO grade 1 meningioma is a benign tumor with a low risk of recurrence and aggressive behavior. In contrast, CNS WHO grades 2 and 3 have a higher risk of recurrence and aggressive behavior.[1,6] The grade determination is based on the number of mitoses, brain invasion, atypical criteria, anaplastic criteria, and specific morphological subtypes. There are 15 histopathological subtypes of meningioma, with the most common subtypes being meningothelial, fibrous, and transitional. Most subtypes behave benign, except for certain more aggressive variants categorized as CNS WHO grade 2 and 3, namely chordoid, clear cell, papillary, and rhabdoid subtypes.[1]

Surgical intervention is still the standard therapy for meningioma with the primary goal of total resection of the tumor mass, including dural and bone. Furthermore, radiotherapy may be considered when total resection cannot be achieved. Therefore, the extent of resection classified as Simpson grade can indicate recurrence in addition to the WHO histopathological grade.[7]

Meningioma is the most common primary brain tumor, but studies on meningioma in Indonesia is still limited. Therefore, this study aims to determine clinicopathological characteristics and recurrence of meningioma at Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital.

METHOD

This was a retrospective analytical study of patients diagnosed with meningioma at the Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital for 3 years. The inclusion criteria were patients diagnosed between January 2019 to December 2021. The exclusion criteria were cases reviewed from other hospitals and cases with unavailable, suboptimal, or non-representative slides. The sampling technique was consecutive, selecting all samples that met the inclusion and exclusion criteria.

This study collected clinical and pathological data, including age, gender, tumor location, tumor size, radiological evidence of bone invasion, the extent of tumor resection, duration of follow-up, recurrence/progression, histopathological grade, histopathological subtype, mitosis, brain invasion, and microscopic bone invasion. Clinical data were obtained from pathology request forms and electronic health records.

A senior pathologist re-evaluated histopathology specimens from stained slides of hematoxylin and eosin (HE). The data were analyzed using statistical analysis tests with SPSS version 26.0. A comparative analysis of numerical data was performed using an independent t-test for normally distributed data or a Mann-Whitney U-test for non-normally distributed data. Meanwhile, comparative analysis of categorical data was performed using a chi-square test or Fisher's exact test when the chi-square test requirements were not met. Results were considered statistically significant when the p-value was <0.05.

RESULT

From January 2019 to December 2021, 251 cases of brain tumors diagnosed with

Maj Patol Indones 2024; 33(1): 715-723
DOI: 10.55816/mpi.v33i1.598

P-ISSN 0215-7284
e-ISSN 25279106
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meningioma were found. Out of the 251 cases initially considered for reassessment, ten cases were slide reviews from other hospitals, ten cases which slides were unavailable, eleven cases were the same patients, and one cases had a suboptimal and non-representative slide. Therefore, 219 cases were reassessed, and Table 1 shows the clinicopathological characteristics. The average age of patients diagnosed with meningioma was 45±11 years old, with a higher proportion of females (88.1%) diagnosed than males (11.9%). The most common tumor location was found in the skull base (71%).

Table 1. Clinicopathological characteristics of meningioma.

Parameter	Result
Age (years old),	
mean ±SD	45±11
Gender	
Male	26 (11.9%)
Female	193 (88.1%)
Size (cm)	
mean ±SD, n=173	5±1.8
<2 cm	7 (4%)
2-4 cm	46 (26.6%)
>4 cm	120 (69.4%)
Tumor location, n=219	
Skull base	154 (71%)
Non-skull base	63 (29%)
Radiological bone invasion, n=197	76 (38.6%)
Extent of Resection, n=205	
Total resection	66 (32.2%)
Subtotal resection	139 (67.8%)
Histopathological grade	
Grade 1	201 (91.8%)
Grade 2	16 (7.3%)
Grade 3	2 (0.9%)
Follow-up duration (months),	
median (minimum-maximum)	2 (0-40)
Mitosis, n=219	
≥4/10 HPF	11 (5%)
<4/10 HPF	208 (95%)
Brain invasion, n=219	
Invasive	7 (3.2%)
Non-Invasive	212 (96.8%)
Microscopic bone invasion, n=219	
Invasive	73 (33.6%)
Non-Invasive	146 (66.4%)
Dural invasion, n=219	
Invasive	37 (16.8%)
Non-Invasive	182 (83.2%)
Recurrence/progression, n=71	
Recurrence/progression	20 (28%)
Non-Recurrence/ Non-progression	51 (72%)

Tumor size data were available for 173 cases with a mean largest diameter of 5±1.8 cm. More than half of the cases (61.2%) were large-sized tumors (>4 cm). The median follow-up radiological examination after surgery was 2 months, ranging from 0-40 months. Radiologic evidence of bone invasion was found in 76 cases (38.6%). More than half of patients (63.5%) had a subtotal resection. Furthermore, microscopic reassessment showed that most cases had a low histopathologic grade of 91.8%. The number of cases with ≥ 4/10 HPF mitosis, brain invasion, dural invasion, and microscopic bone invasion was found in 5%, 3.2%, 16.8%, and 33.6% of cases, respectively. The most common subtype was meningothelial at 52%, and followed by mixed and atypical subtype, as shown in Figure 1.

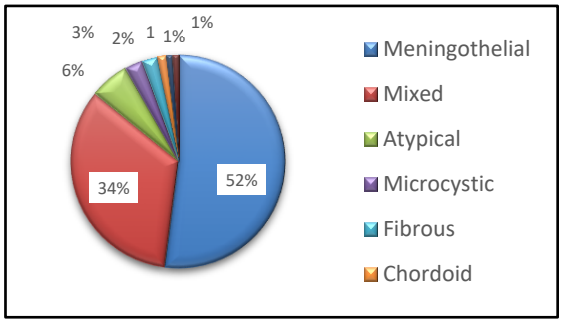

Figure 1. Histological subtypes of meningioma.

Data on follow-up of 6 months were available for 71 cases, of which 20 cases (28%) experienced recurrence and 51 cases (72%) did not experience recurrence. The incidence of recurrence was most frequent at 7-12 months after surgery, as shown in Figure 2. There was no significant difference (p=0.137) in the mean age of patients between recurrence (42±14.5 years old) and non-recurrence groups (46±10.6 years old). Furthermore, there was no significant difference in gender between recurrence and non-recurrence groups (p=0.66).

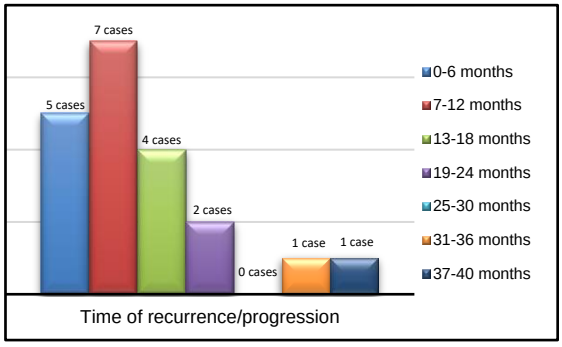

Figure 2. Months to recurrence/progression.

Clinicopathological characteristics of meningioma in the two groups are summarized in Table 2. There was a significant association between the extent of resection and recurrence (p=0.007). There was no significant difference

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(p=0.117) in the mean tumor size between recurrence (5.3±1.3 cm) and non-recurrence groups (4.6±1.8 cm). However, there was a significant difference in tumor size between the groups when the tumor size was categorized into (≤4 cm and >4 cm). Recurrence incidence was higher in high-grade meningioma (33.3%) than in low-grade (27.4%).

Table 2. Clinicopathological characteristics of meningioma in recurrence/progression and non-recurrence/progression cases.

Parameter	Recurrence/Progression (n=20)	Non-recurrence/Progression (n=51)	p-value
Age (years old), mean ±SD	42±14,5	46±10,6	0.137
Gender			
Male	1 (14.3%)	4 (85.7%)	0.66
Female	29 (29.7%)	45 (70,3%)	
Tumor size, mean ± SD	5.3±1.3 cm	4.6±1.8 cm	0.117
≤4 cm	3 (12.0%)	22 (88.0%)	**0.02**
>4 cm	17(37)	29 (63%)	
Location			
Skull base	13(27.1%)	35(72.9%)	0.769
Non-skul base	7(30.4%)	16(69.9%)	
Radiological bone invasion			
Invasive	8 (32%)	17 (68%)	0.597
Non-invasive	12 (26.1%)	34(73.9%)	
Extent of Resection			
Total resection	1 (5%)	19 (95%)	**0.007**
Subtotal resection	19 (37.3%)	32 (62.7%)	
Histopathological grade			
Low	17 (27.4%)	45 (72.6%)	0.7
High	3 (33.3%)	6 (69.6%)	
Microscopic invasion of bone			
Invasive	7 (29.2%)	17 70.8%)	0.9
Non-invasive	13 (28.3%)	33(71.7%)	
Mitosis			
<4/10 HPF	17 (26.2%)	48(73.8%)	0.34
≥4/10 HPF	3 (50%)	3 (50%)	
Brain invasion			
Invasive	2 (50%)	2 (50%)	0.314
Non-invasive	18 (26.9%)	49 (73.1%)	
Dural invasion			
Invasive	3(25%)	9 (75%)	1.00
Non-invasive	17(28.8%)	42(71.2%)	

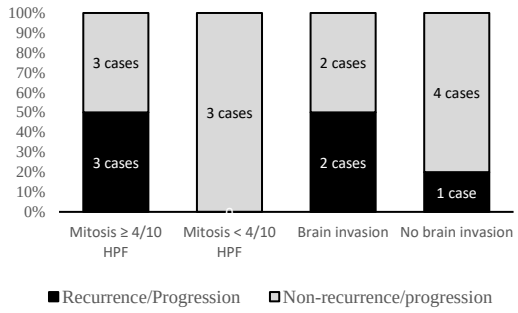

Figure 3. Mitosis and brain invasion were associated with recurrence/progression and non-recurrence/ progression in high-grade meningioma (CNS WHO grade 2 and 3).

Even though there was no significant association between mitosis and brain invasion with recurrence in all cases, the incidence of recurrence was elevated in cases of high-grade meningioma (CNS WHO grade 2 and 3) with mitosis ≥ 4/10 HPF (50%) and brain invasion (50%). Recurrence incidence in non-brain invasive high-grade meningioma was only 20%, and there was non-recurrence in cases with mitosis <4/10 HPF, as shown in Figure 3.

DISCUSSION

Meningioma is the most common primary intracranial tumor.[1,2] The number of cases diagnosed at the Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital during 2019-2021 was 251 cases, approximately 84 cases/year. This number is consistent with data from the Central Brain Tumor Registry of the United States (CBTRUS) in 2021, showing a meningioma percentage of 39% for all primary intracranial tumors with an incidence rate of 9.12 per 100,000 population.[2] There were 71 cases that met the minimum follow-up duration of 6 months with complete clinical data, where 20 cases (28%) experienced recurrence.

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This aligns with the study by Violaris et al,[17] Romani et al,[8] and He et al[12] which ranges from 21.5 to 34.9%. Recurrence rate increases with the increase in histopathological grade, with CNS WHO grades 1, 2, and 3 meningioma having a recurrence rate of 7-25%, 29-52%, and 50%-94%, respectively.[18] In this study, low grade meningioma recurred in 17 cases (27,4%) and high-grade meningioma recurred in 3 cases (33.3%). A retrospective study by Haddat et al[19] assessing recurrence in CNS WHO grade 1 meningioma showed a lower recurrence rate (10.9%). This could be attributed to the timely detection and diagnosis, which enables earlier management while the tumor is still small, allowing for total resection with a reduced risk of recurrence. Another possibility could also be due to many cases without complete follow-up data.

The mean age at diagnosis of meningioma was 45±11 years old. This result is consistent with Pant et al[6] with a mean age of 44.58. In other studies, the mean age at diagnosis is 55-65 years old.[8,10,17] Reddy et al[20] and Mubeen et al[4] found that the most common age group for meningioma is between 40-60 years old. The incidence of meningioma increases with age, with a median of 66 years old.[3] It is rare in children, with a percentage of 0.4-4.1% of all childhood tumors.[21] Furthermore, there was no significant difference (p=0.137) in the mean age between recurrence (42±14.5 years old) and non-recurrence groups (46±10.6 years old). This result is consistent with the studies by Mirian and Violaris et al.[15,17] However, Romani et al[8] showed that older age tended to have a lower recurrence rate. In contrast, Lee et al[22] showed that older age was associated with recurrence in univariate analysis.

The proportion of female patients was higher than males, with a ratio of 1:7.4. In some studies, the proportion of cases in women is more than 50% (62.3%-75%).[14,17,23] CBTRUS data also shows a tendency for meningioma to occur in women more than men.[2] This tendency is related to the role of hormones in meningioma pathogenesis.[3,20] There was no significant association (p=0.66) between gender and recurrence in this study, consistent with the studies by Romani et a,[8] Mirian et al,[15] and violaris et al.[17.] However, Lee et al[22] showed different results in the univariate analysis where male gender was associated with recurrence incidence.

The average tumor size in this study was 5±1.8 cm. In a study conducted by Magill et al[10] the average size of meningioma was found to be 3.8±1.8 cm. There was no significant difference (p=0.117) in the average tumor size between recurrence (5.3±1.3 cm) and non-recurrence groups (4.6±1.8 cm). However, there was a significant difference in size when the tumor was categorized into two groups (p=0.02). Romani et al[8] showed no association between tumor size and recurrence. Studies by Lee et al[22] and Ildan et al[9] found an association between tumor size and recurrence, where larger size increases the likelihood of tumor cell infiltration into the arachnoid membrane and brain tissue.[24]

The tumor location was mostly in the skull base (71%). In the studies by Romani et al,[8] Magill et al,[10] and Behling et al[25] the proportion in the skull base was 51.5%, 52%, and 59%, respectively. There was no significant association (p=0.769) between tumor location and recurrence in line with Romani et al,[8] Mirian et al,[15] Violaris et al,[17] and Spille et al.[26] However, tumor location can affect recurrence when total resection is difficult to achieve.[17]

The radiological finding of bone invasion was found in 76 cases (38.6%). This result is consistent with the numbers reported by Zwirner et al,[27] Ko et al,[28] and He et al[12] which ranged from 19.9 to 55.3%. Statistical analysis showed no significant association between radiological bone invasion and recurrence in this study (p=0.597). He et al[12] also showed no significant association between bone invasion on radiological examination and recurrence. Meanwhile, Ildan et al[9] showed that bone changes in osteolysis destruction are more associated with recurrence than hyperostosis. Bone invasion in meningioma can be diagnosed using Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), which are then confirmed histopatho-logically after surgery.[7]

Surgery is the primary treatment modality for meningioma and total resection should be performed when possible. In this study, only one-third of cases were totally resected (32.2%). The extent of resection is greatly influenced by the location of the tumor, involvement of arterial veins and cranial nerves, and invasion into surrounding brain tissue. Total resection is often difficult in skull base meningioma, such as the cavernous sinus, sellar tuberculum, cerebellopontine angle, and petroclival region. Tumors in the convexity/

Maj Patol Indones 2024; 33(1): 715-723
DOI: 10.55816/mpi.v33i1.598

P-ISSN 0215-7284
e-ISSN 25279106
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parasagittal area require relatively more simple surgical techniques.[29] There was a significant relationship between the extent of resection and recurrence incidence (p-value=0.004). This aligns with studies conducted by Violaris et al[17] and Garcia-Segura et al.[30] The most accepted predictor of recurrence is the Simpson grading system, which classifies the extent of resection into grades I-V and can assess tumor invasion into venous sinuses, dura mater, and bone.[17]

The pathological characteristics evaluated were histopathological grade, number of mitoses, microscopic bone invasion, brain invasion, and dural invasion. Most cases in this study were WHO grade 1 CNS tumors (91.8%). This result is consistent with the findings of previous studies, ranging from 80 to 90%.[4,8,17,25,31] Statistical analysis showed no significant association (p-value=0.7) between histopathological grade and recurrence. Previous studies by Mubeen et al[4] and Holleczek et al[21] showed an association between both groups. In contrast, Mirian et al[15] found slightly different results, with a significant univariate between histopathological grade and recurrence but a non-significant multivariate analysis. This discrepancy may be due to the many grade 1 meningioma cases without follow-up data after tumor resection. As a national referral center, Dr. Cipto Mangunkusumo Hospital has led to most patients only receiving surgery and being followed up at their original hospital.

The histopathological grade of meningioma is one of the prognostic indicators for the complication. A study by He et al[12] found a significant relationship between histopathological grade and recurrence of skull base meningioma. Clinicians determine the therapy type based on this parameter, and recurrence rate increases with grade. However, the WHO grade is unreliable as the main information relates to recurrence.[12,21,32] Several histomorphological criteria determine the histopathological grade in meningioma, including mitosis, brain invasion, signs of atypia, and anaplasia, as shown in Figure 4.[1] This complex and subjective classification system often leads to interobserver variations, especially in borderline cases.[32]

Based on the fifth edition of CNS tumor classification in 2021, it has been determined that there are fifteen subtypes of meningioma. Most subtypes demonstrate benign behavior and are classified into the CNS WHO grade 1 category. At the same time, some exhibit more aggressive behavior with a higher recurrence rate and are categorized into higher grades such as chordoid, clear cell, atypical, papillary, rhabdoid, and anaplastic. The most commonly found subtypes are meningothelial, fibrous, and transitional.[1] The most common subtype in this study was meningotelial in line with the studies by Mubeen et al,[4] Violarist et al,[17] and J et al.[31] Aside from single subtypes, mixed meningioma with several subtypes was also frequently found (33.8%). Meanwhile, the mixture consist of common subtypes such as meningothelial with other rarer subtypes such as secretory, angiomatous, metaplastic, and microcystic (Figure 5).

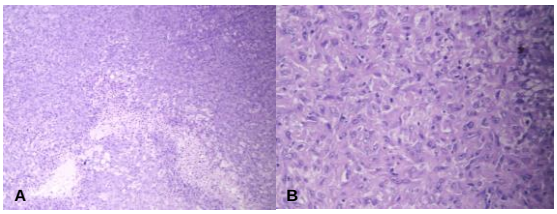

Figure 4. Anaplastic meningioma with hypercellular tumor, necrotic area, and 25/10 HPF mitosis. A. Hypercellular tumor with necrosis, H&E,100 times, B. Mitosis, H&E, 400 times.

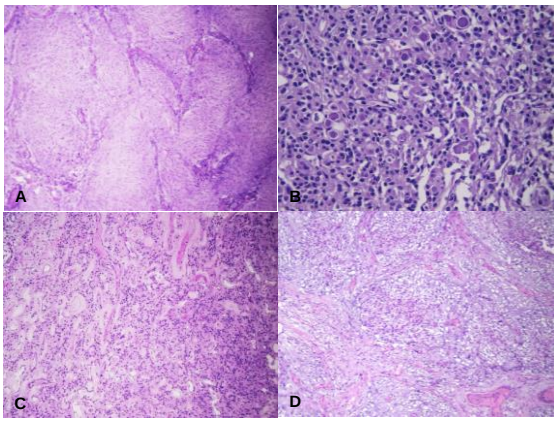

Figure 5. Meningioma subtypes. A. Meningothelial, H&E,100 times. B. Secretory, H&E,400 times. C. Angiomatous, H&E,100 times. D. Microcystic, H&E,100 times.

Mitosis ≥4/10 HPF was only found in 11 (5%) cases, with the highest mitotic count being 27 mitoses/10 HPF. Statistical analysis showed no significant association between mitosis and recurrence (p=0.34). This is inconsistent with Olar et al[33] where a higher mitotic count is associated with recurrence in a larger sample size.[33] Studies by Champeux et al[13] and Bertero et al[34] showed that increased mitotic activity in WHO grade 2 meningioma is associated with

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DOI: 10.55816/mpi.v33i1.598

P-ISSN 0215-7284
e-ISSN 25279106
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recurrence. In a different study, Champeux et al[23] showed that mitotic count is not associated with recurrence in WHO grade 1 CNS tumors. According to WHO, mitosis is one of the parameters used in determining the grade of meningioma.

Brain invasion was only found in 7 cases (3.2%). Behling et al[25] and Spille et al[26] reported a higher incidence of brain invasion at 6.7% and 7%, respectively. The discrepancies may be due to the failure to remove the invasive part of the tumor in cases with subtotal resection. This study had no significant relationship (p=0.314) between brain invasion and recurrence in line with Spille and Bertero et al.[26,34] The predictive value of brain invasion is still debated in many studies. Other studies by Kim et al,[35] Champeux et al,[13] and Garcia-Segura et al[30] showed a relationship between brain invasion and recurrence in high-grade meningioma.

This study found microscopic bone invasion in 76 cases (38.6%). There was no significant association (p=0.9) between microscopic bone invasion and recurrence in line with Haddad et al.[19] However, it differs from the study by Kim et al[35] where bone invasion is associated with recurrence in high-grade meningioma.

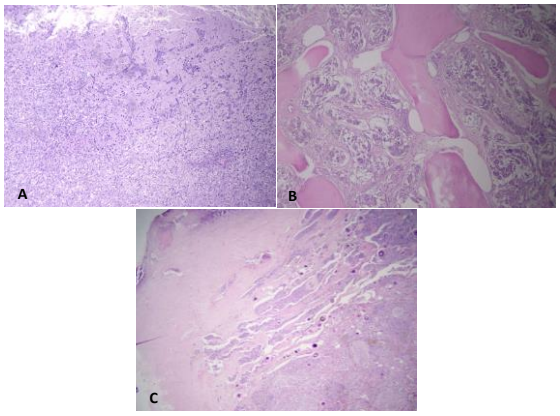

Figure 6. A. Brain invasion, H&E, 100 times. B. Bone invasion, H&E,100 times. C. Invasion of duramater, H&E,40 times.

The dural invasion was found in 37 cases (16.8%) and previous studies found a higher percentage, from 46.2% to 63%.[36] This difference may be because of most cases were subtotal resections, resulting in an inadequate sample size for evaluating dural invasion. This study also had no significant association (p=1.00) between dural invasion and recurrence in line with Murase et al.[37] Study on dural invasion is limited because it does not meet the morphological criteria for histo-pathological grading of meningioma. However, recurrence often occurs in the duramater of the resection area, which may be due to the presence of residual tumor cells on a microscopic level.[37]

CONCLUSION

In this study, the proportion of females diagnosed with meningioma was higher than males. The most common histopathological grade was CNS WHO grade 1 meningioma, with an overall recurrence rate of 28%. Furthermore, the most common histological subtype was meningothelial, and the least were chordoid, transitional, and anaplastic. The strongest association was found between the extent of resection and tumor size with recurrence. There was no association between age, gender, tumor location, radiological evidence of bone invasion, histopathological grade, mitosis, dural invasion, and brain invasion with recurrence.

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P-ISSN 0215-7284
e-ISSN 25279106
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Maj Patol Indones 2024; 33(1): 715-723
DOI: 10.55816/mpi.v33i1.598