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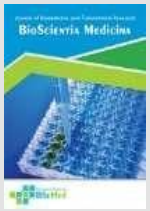

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Determinants of Recurrence in Intracranial Meningioma: A Decade of Experience with Surgical and Pathological Correlations in Bandung, Indonesia

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A B S T R A C T

Background: Intracranial meningiomas are common primary central nervous system tumors, mostly benign, yet recurrence remains a significant clinical challenge influencing patient prognosis. Understanding the characteristics and determinants of recurrence, particularly in specific populations, is crucial. Data on recurrent meningioma from developing countries like Indonesia are limited. This study aimed to describe the clinicopathological features and surgical management experience of recurrent intracranial meningiomas over a 10-year period at a tertiary referral hospital in Bandung, Indonesia. **Methods:** A retrospective analysis was conducted on all adult patients (≥18 years) surgically treated for recurrent intracranial meningioma at the Department of Neurosurgery, Dr. Hasan Sadikin General Hospital, Bandung, between January 2012 and December 2022. Patients with incomplete records were excluded. Data collected included demographics, clinical presentation, radiological findings (tumor location, bone infiltration, tumor invasion), surgical history (number of resections, time to recurrence), and histopathological results. Descriptive statistics were used for analysis. **Results:** Twenty-eight patients met the inclusion criteria. The cohort was predominantly female (n=24, 85.7%) with a median age of 46 years (range 26-67). The most common presenting symptoms were protrusion (n=11, 39.3%) and headache (n=7, 25.0%). Tumors were most frequently located in the parietal (n=10, 35.7%) and sphenoorbital (n=9, 32.1%) regions. Significant bone infiltration was observed in 75.0% (n=21) of cases. Tumor invasion into adjacent structures occurred in 21.4% (n=6), most commonly involving the cavernous sinus (n=2, 7.1% of total / 33.3% of invaded). The median time to recurrence detection was 36 months (range 6-144). Most patients (n=22, 78.6%) underwent two tumor removal surgeries during the study period. Based on available histopathology (n=17), meningothelial (n=10, 35.7% of total / 58.8% of available) and transitional (n=3, 10.7% of total / 17.6% of available) subtypes were the most common WHO Grade 1 diagnoses. One case each of atypical (Grade 2) and malignant (Grade 3) meningioma were identified. **Conclusion:** Recurrent intracranial meningiomas predominantly affected middle-aged females, often presenting with symptoms related to mass effect in parietal and sphenoorbital locations. High rates of bone infiltration and significant tumor invasion, particularly involving the cavernous sinus, were characteristic features. Recurrence was typically diagnosed within 3 years, with meningothelial and transitional subtypes being the most frequent histologies observed in this recurrent group. These findings underscore the complex nature of meningioma recurrence and highlight the need for tailored management strategies and long-term surveillance, particularly in cases with high-risk features like bone and sinus invasion.

1. Introduction

Meningiomas, neoplasms originating from the arachnoid cap cells of the meninges, are the most frequently diagnosed primary intracranial tumors, constituting a substantial portion, approximately 35-40%, of all primary brain tumors. The majority of these tumors, exceeding 80%, are classified as benign, corresponding to World Health Organization (WHO)

Grade 1, and are generally associated with a favorable prognosis following surgical resection. However, a clinically significant subset of meningiomas demonstrates more aggressive behavior, deviating from this benign course. Specifically, WHO Grade 2 (atypical) meningiomas account for 15-20% of cases, while Grade 3 (anaplastic/malignant) meningiomas represent 1-3% of all meningiomas. These higher grades are characterized by a markedly increased propensity for recurrence and are correlated with diminished overall survival rates, underscoring the critical impact of histological grading on patient prognosis. Despite advancements in neurosurgical techniques and adjuvant therapies, recurrence remains a paramount challenge in the long-term management of meningiomas, irrespective of the initial histological grade. This persistent risk of recurrence poses a significant clinical burden, necessitating ongoing surveillance and intervention strategies. Even following seemingly complete surgical removal, defined as Gross Total Resection (GTR), recurrence rates for WHO Grade 1 tumors are reported to range from 7-25% over extended follow-up periods. The likelihood of recurrence escalates substantially with higher-grade tumors; recurrence rates for Grade 2 and Grade 3 tumors can reach 30-50% and up to 100%, respectively. These statistics highlight the aggressive nature of higher-grade meningiomas and the inherent difficulty in achieving durable tumor control.[1-3]

The factors that influence meningioma recurrence are complex and multifactorial. These determinants encompass a combination of tumor-related and patient-specific characteristics, including the extent of surgical resection (EOR), tumor grade, histological subtype, tumor location, proliferative index (quantified by markers such as Ki-67/MIB-1 labeling index), patient age, and increasingly, molecular and genetic markers. The extent of resection, historically assessed using the Simpson grading scale, has been established as a significant predictor of recurrence. Higher Simpson grades, indicative of less complete tumor removal, demonstrate a strong correlation with an elevated risk of recurrence. However, achieving GTR is not always feasible and can be particularly challenging in specific clinical scenarios. Tumors located at the skull base, those encasing critical neurovascular structures, or those exhibiting invasion into bone, dura, venous sinuses, or brain parenchyma often present formidable surgical obstacles to complete resection. The World Health Organization (WHO) classification system, a cornerstone of meningioma diagnosis and prognostication, underwent a significant update in 2021 (WHO CNS5). This revised classification scheme refines the grading of meningiomas by integrating not only traditional histological features, such as mitotic count, cellularity, specific architectural patterns, and brain invasion, but also specific molecular alterations. The incorporation of molecular markers, including TERT promoter mutation and homozygous CDKN2A/B deletion, aims to enhance the accuracy of prognostic assessments and better define higher-grade tumors. For instance, homozygous deletion of CDKN2A/B is now recognized as a criterion for Grade 3 classification, irrespective of histological appearance, due to its strong association with aggressive tumor behavior and increased recurrence risk. This exemplifies the growing recognition of the importance of molecular profiling in refining meningioma classification and predicting clinical outcomes. In addition to TERT promoter mutation and CDKN2A/B deletion, other molecular markers are emerging as important prognostic indicators in meningioma management. These include loss of chromosome 1p, BAP1 loss, and DNA methylation profiles. These markers provide additional layers of information that can help to stratify patients according to their risk of recurrence and guide treatment decisions.[4-7]

While a substantial body of research on meningioma recurrence has been conducted in North America and Europe, there remains a relative scarcity of data from developing countries, particularly within the Southeast Asian region. This disparity in research focus highlights a critical gap in our understanding of meningioma biology and clinical behavior across

diverse populations. Epidemiological and potentially pathogenetic differences may exist across ethnic groups, underscoring the need for population-specific studies. Factors such as genetic predisposition, environmental exposures, and access to healthcare resources could contribute to variations in meningioma incidence, clinical presentation, and outcomes. Therefore, a more comprehensive understanding of the specific characteristics, risk factors, and outcomes of recurrent meningiomas within the Indonesian population is crucial for optimizing local diagnostic and therapeutic strategies. Such knowledge can inform the development of tailored treatment protocols, improve patient management, and ultimately enhance clinical outcomes. Dr. Hasan Sadikin General Hospital in Bandung serves as a major tertiary referral center for neurosurgery in West Java, Indonesia. Its role as a high-volume center provides a valuable opportunity to study a significant cohort of patients with recurrent intracranial meningiomas.[8-10] This study aimed to retrospectively analyze the clinicopathological characteristics, radiological features, surgical management patterns, and recurrence timelines of patients treated for recurrent intracranial meningiomas at our institution over a ten-year period (2012-2022). By detailing our experience, we sought to identify potential determinants of recurrence within this specific cohort and contribute valuable data to the broader understanding of meningioma management, particularly within the Indonesian context.

2. Methods

This study employed a retrospective descriptive design to investigate the clinicopathological features, surgical management, and recurrence patterns of intracranial meningiomas. The study population comprised patients who underwent surgical resection for recurrent intracranial meningioma at the Department of Neurosurgery, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, a prominent national tertiary referral and teaching hospital.

The study period spanned from January 1st, 2012, to December 31st, 2022. All patients aged 18 years or older who underwent surgical resection for a pathologically confirmed recurrent intracranial meningioma within this timeframe were included in the study. For the purposes of this study, recurrence was defined as clinical and/or radiological evidence of tumor regrowth following a previous surgical resection for meningioma. Patients were excluded from the analysis if their medical records were incomplete, particularly if essential radiological, surgical, or histopathological data were missing. This exclusion criterion was implemented to ensure the availability of sufficient data for a comprehensive analysis of the variables of interest.

Data were meticulously extracted from a variety of sources to ensure a thorough and accurate representation of each patient's clinical course. These sources encompassed patient medical records, surgical logs, radiological reports and images, and pathology reports. Radiological images were primarily archived electronically, facilitating efficient data retrieval. A standardized data collection form was utilized to systematically record relevant information for each patient, ensuring consistency and minimizing the risk of data entry errors. The following variables were included in the data extraction process; Demographics: This category included age at the time of presentation for recurrence surgery and gender. Age was recorded in years, while gender was classified as either male or female; Clinical Presentation: The chief complaints or primary symptoms that led to the diagnosis of recurrence were documented. This encompassed a detailed description of the patient's symptoms as reported during clinical evaluation; Radiological Findings: Preoperative contrast-enhanced Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) scans were the primary sources of radiological data. These imaging modalities are standard hospital protocol for the evaluation of intracranial tumors. Tumor locations were categorized based on the primary anatomical sites involved. The specific locations included parietal,

frontal, sphenoorbital, temporal, sphenoid wing, and parasagittal regions. It is important to note that some tumors involved multiple contiguous regions, and in such cases, all involved locations were recorded. Bone infiltration was defined as the presence of tumor involvement or invasion into adjacent calvarial or skull base bone. This included the identification of hyperostosis (abnormal thickening of bone), erosion (destruction of bone tissue), or direct infiltration of the tumor into the bone, as visualized on imaging. Tumor invasion was defined as the extension of the tumor into specific adjacent structures. The structures of interest included the cavernous sinus, superior sagittal sinus, temporal muscle, external orbital muscle, falx cerebri, and brain parenchyma. The presence or absence of invasion into each of these structures was recorded; Surgical History: The total number of surgical procedures performed for meningioma removal was recorded for each patient. This included the initial surgery and all subsequent recurrence surgeries that occurred within the study period. It is important to note that an analysis of the extent of resection (EOR), such as Simpson grade, was not performed in this study due to inconsistencies in operative reporting over the ten-year study period; Time to Recurrence: Time to recurrence was calculated in months. This was determined by measuring the interval from the date of the preceding meningioma surgery to the date of radiological or clinical diagnosis of the recurrence that led to the surgery included in this study cohort; Histopathology: The results of the pathological examination of the recurrent tumor specimen were recorded. The diagnoses were based on the World Health Organization (WHO) classification criteria that were applicable at the time of diagnosis. The histological subtype and grade of the tumor were noted. In cases where multiple grades were identified during microscopic examination, the most severe grade was used for classification.

The collected data were compiled and organized using Microsoft Excel. Descriptive statistics were employed for the analysis of the data. Continuous variables, such as age and time to recurrence, were presented as median and range (minimum-maximum) to provide a measure of central tendency and variability. Categorical variables, including gender, symptoms, tumor location, presence of bone infiltration, specific sites of tumor invasion, number of resections, and histopathological subtype/grade, were presented as frequencies and percentages to illustrate the distribution of these variables within the study population. All statistical analyses were performed using Microsoft Excel.

3. Results

Table 1 summarizes the key demographic features of the patient cohort included in the study; Gender Distribution: The table shows a clear predominance of female patients. There were 24 female patients, representing 85.7% of the study population, while there were only 4 male patients, accounting for 14.3%. This indicates a strong female bias in the occurrence of recurrent intracranial meningiomas within this specific patient group. This observation aligns with the general understanding that meningiomas are more common in females than in males; Age at Recurrence Surgery: The median age at the time of surgery for recurrence was 46 years. The age range of the patients spanned from 26 to 67 years. The median age of 46 suggests that the "typical" patient requiring surgery for recurrent meningioma in this study was in their mid-forties. The median is a measure of central tendency that is less affected by extreme values than the mean (average), providing a robust representation of the central age within the group. The range of 26 to 67 years indicates that while the median age was 46, recurrent meningiomas affected patients across a broad age spectrum, from relatively young adults in their late twenties to older adults in their late sixties. This highlights that recurrence is a concern across a considerable portion of the adult lifespan.

Table 1. Demographic characteristics of patients.

Features	Details	Frequency (n)	Percentage (%)
Demographics	**Gender**		
	Male	4	14.3%
	Female	24	85.7%
	Age at Recurrence Surgery (years)		
	Median	46	-
	Range	26 - 67	-

Table 2 presents a comprehensive overview of the clinical features observed in the study cohort; Clinical Presentation: The most frequent primary symptom was protrusion (proptosis) (11 patients, 39.3%), followed by headache (7 patients, 25.0%), and then Blurred Vision (3 patients, 10.7%). Other less frequent symptoms included Weakness (Focal Deficit) (2 patients, 7.1%), Seizure (2 patients, 7.1%), and Decrease of Consciousness (2 patients, 7.1%). The high prevalence of protrusion, likely referring to the bulging of the eye, suggests a significant involvement of the orbital region in these recurrent meningiomas. This is further supported by the radiological findings later in the table. Headache being the second most common symptom is consistent with the general presentation of intracranial tumors, where mass effect can lead to increased intracranial pressure. Blurred vision symptoms also point to involvement of the visual pathways or structures surrounding the eye. The presence of weakness, seizures, and decreased consciousness indicates that recurrent meningiomas can cause significant neurological morbidity, depending on their location and impact on the brain; Radiological Features: The most common location was Parietal (10 patients, 35.7%), closely followed by Sphenoorbital (9 patients, 32.1%). Frontal (8 patients, 28.6%), Temporal (7 patients, 25.0%), and "Sphenoid Wing" (6 patients, 21.4%) were also involved. The predominance of parietal and sphenoorbital locations suggests that recurrent meningiomas in this cohort frequently arise in these regions. Parietal tumors can affect motor and sensory functions, while sphenoorbital tumors can involve the orbit and cranial nerves. The involvement of frontal, temporal, and sphenoid wing locations indicates the diverse anatomical origins of recurrent meningiomas. The table footnote clarifies that tumor locations are not mutually exclusive, meaning some tumors involved multiple regions. A high proportion (21 patients, 75.0%) showed evidence of bone infiltration. This is a significant finding, as bone infiltration can make surgical resection more challenging and increase the risk of recurrence. It suggests that these recurrent tumors often have an aggressive growth pattern involving the skull. Tumor invasion into specific structures was observed in 6 patients (21.4%). This indicates that in a subset of patients, the tumor extended beyond its primary location into adjacent critical structures. This invasion can complicate surgical removal and increase the risk of neurological deficits. The most common site of invasion was the "Cavernous Sinus" (2 patients, 33.3% of invaded, 7.1% of total), followed by "Superior Sagittal Sinus," "Temporal Muscle," "External Orbital Muscle," and "Falx Cerebri" (1 patient each, 16.7% of invaded, 3.5% of total). Invasion of the cavernous sinus is particularly concerning due to the presence of critical cranial nerves and blood vessels, making surgical management complex. Invasion into other sites like the superior sagittal sinus, temporal muscle, etc., also presents surgical challenges and potential for complications; Surgical & Recurrence Data: The majority of patients (22 patients, 78.6%) had undergone 2 tumor resections (initial + 1st recurrence), while 6 patients (21.4%) had undergone 3 tumor resections (initial + 2 recurrences). This data highlights the recurrent nature of meningiomas. Most patients required a second surgery, and a significant minority required a third surgery, indicating the difficulty in achieving permanent tumor control in some cases. The median time to recurrence was 36 months, with a range from 6 to 144 months. The median of 36 months (3 years) provides a central tendency for the time it takes for recurrence to occur.

This suggests that close follow-up is crucial for at least the first 3 years after initial surgery. The wide range (6 to 144 months) indicates that recurrence can occur relatively early (within 6 months) or very late (up to 12 years) after the initial surgery. This emphasizes the need for long-term surveillance; Histopathology (Recurrent Tumor): Histopathology data was available for 17 patients (60.7%), but not available for 11 patients (39.3%). The missing histopathology data for a significant portion of patients is a limitation of the study, as it restricts the ability to fully characterize the tumor biology in all cases. Of the cases with available histopathology, most were Grade 1 (15 patients, 88.2% of available, 53.6% of total). There were also Grade 2 (Atypical) and Grade 3 (Malignant) cases (1 patient each, 5.9% of available, 3.5% of total). The majority of recurrent tumors were still WHO Grade 1, indicating that even benign meningiomas can recur. The presence of Grade 2 and Grade 3 tumors in the recurrence group suggests that some tumors can become more aggressive over time (malignant transformation) or that higher-grade components were initially missed. Among the Grade 1 tumors, the most common subtype was "Meningothelial" (10 patients, 66.7% of Grade 1, 35.7% of total), followed by "Transitional" (3 patients, 20.0% of Grade 1, 10.7% of total), "Microcystic" (1 patient, 6.7% of Grade 1, 3.5% of total), and "Fibroblastic" (1 patient, 6.7% of Grade 1, 3.5% of total). This provides a breakdown of the specific histological variants within the most common grade. Different subtypes may have slightly different growth patterns or recurrence risks, although this study doesn't directly explore those differences.

Table 2. Clinical characteristics of patients with recurrent intracranial meningioma (N=28).

Features	Details	Frequency (N)	Percentage (%)
Clinical presentation	**Primary Symptom**		
	Protrusion (Proptosis)	11	39.3%
	Headache	7	25.0%
	Blurred Vision	3	10.7%
	Weakness (Focal Deficit)	2	7.1%
	Seizure	2	7.1%
	Decrease of Consciousness	2	7.1%
Radiological features	**Primary Tumor Location**		
	Parietal	10	35.7%
	Sphenoorbital	9	32.1%
	Frontal	8	28.6%
	Temporal	7	25.0%
	Sphenoid Wing	6	21.4%
	Bone Infiltration Present	21	75.0%
	Tumor Invasion Present	6	21.4%
	Site of Invasion (n=6):		
	Cavernous Sinus	2	33.3% of invaded / 7.1% of total
	Superior Sagittal Sinus	1	16.7% of invaded / 3.5% of total
	Temporal Muscle	1	16.7% of invaded / 3.5% of total
	External Orbital Muscle	1	16.7% of invaded / 3.5% of total
	Falx Cerebri	1	16.7% of invaded / 3.5% of total
Surgical & recurrence data	**Total Number of Tumor Resections**		
	2 Times (Initial + 1st Recurrence)	22	78.6%
	3 Times (Initial + 2 Recurrences)	6	21.4%
	Time to Recurrence (months)		
	Median	36	-
	Range	6 - 144	-
Histopathology (Recurrent Tumor)	**Data Availability (N=28)**		
	Available	17	60.7%
	Not Available	11	39.3%
	WHO Grade (N=17)		
	Grade 1	15	88.2% of available / 53.6% of total
	Grade 2 (Atypical)	1	5.9% of available / 3.5% of total
	Grade 3 (Malignant)	1	5.9% of available / 3.5% of total
	Grade 1 Subtypes (N=15)		
	Meningothelial	10	66.7% of Grade 1 / 35.7% of total
	Transitional	3	20.0% of Grade 1 / 10.7% of total
	Microcystic	1	6.7% of Grade 1 / 3.5% of total
	Fibroblastic	1	6.7% of Grade 1 / 3.5% of total

4. Discussion

The demographic analysis of this study cohort brings to the forefront a notable characteristic, the striking predominance of female patients. In this group of individuals who underwent surgery for recurrent intracranial meningioma, females constituted a substantial 85.7% of the total, while males represented a considerably smaller fraction at 14.3%. This pronounced gender imbalance is not an isolated finding, rather, it aligns with a significant body of existing literature and clinical observations that consistently demonstrate a higher incidence of meningiomas in females compared to males across various populations and geographical locations. This well-established gender disparity in meningioma occurrence has intrigued researchers and clinicians for many years, prompting extensive investigation into the underlying etiological factors that might account for this phenomenon. While a single, definitive explanation has remained elusive, the current prevailing hypotheses and ongoing research strongly suggest that hormonal influences play a pivotal, albeit complex, role. Meningiomas, as tumors arising from the arachnoid cap cells of the meninges, often exhibit a unique biological characteristic, the expression of receptors for both estrogen and progesterone. These steroid hormone receptors are intracellular proteins that bind to specific hormones, triggering a cascade of cellular signaling pathways that can ultimately influence cell growth, proliferation, and differentiation. The presence of estrogen and progesterone receptors in meningioma cells strongly implies that these hormones, which play fundamental roles in female reproductive physiology, may also be involved in the development and progression of meningiomas. Estrogen, the primary female sex hormone, is known to have a variety of effects on cell growth and proliferation in different tissues. Progesterone, another key female hormone, also exerts diverse effects on cellular function, often modulating or counteracting the actions of estrogen. The intricate interplay between these hormones and their receptors within meningioma cells is a subject of intense research. It is hypothesized that fluctuations in hormone levels throughout a woman's life may contribute to variations in meningioma behavior. These hormonal fluctuations are a natural and inherent part of the female experience, occurring during key physiological events such as menstruation, pregnancy, and menopause. The menstrual cycle is characterized by cyclical changes in estrogen and progesterone levels. While the precise impact of these monthly hormonal fluctuations on meningioma growth is not fully understood, it is conceivable that they could create a microenvironment that either promotes or inhibits tumor cell proliferation. Pregnancy is a period of dramatic hormonal shifts, with significant increases in both estrogen and progesterone. Some clinical observations suggest that meningiomas may exhibit accelerated growth during pregnancy, potentially due to the elevated hormone levels. However, this is not a universal finding, and further research is needed to clarify the relationship between pregnancy, hormonal changes, and meningioma growth. Menopause marks another significant hormonal transition in a woman's life, with a decline in estrogen and progesterone production. The impact of menopause on meningioma behavior is also complex and not fully resolved. Some studies suggest that the hormonal changes associated with menopause may influence tumor growth or recurrence risk, while others have not found a clear correlation. To gain a more nuanced understanding of the precise relationship between gender, hormones, and meningioma recurrence, further research is essential. One promising avenue of investigation involves detailed hormonal profiling of tumor tissue. This would entail measuring the levels of estrogen and progesterone receptors, as well as the expression of enzymes involved in hormone metabolism, within meningioma cells. Correlating these tumor-specific hormonal profiles with the patient's hormonal status (e.g., premenopausal, postmenopausal, hormone replacement therapy) could provide valuable insights into how hormonal factors influence tumor behavior. Advanced techniques such as immunohistochemistry,

quantitative polymerase chain reaction (qPCR), and mass spectrometry can be employed to achieve a comprehensive assessment of the hormonal milieu within meningiomas. While hormonal influences are strongly implicated in the gender disparity observed in meningioma incidence, it is crucial to acknowledge that other factors may also contribute to this phenomenon. The etiology of meningiomas is likely multifactorial, involving a complex interplay of genetic, environmental, and other biological determinants. Therefore, it is imperative to explore potential contributing factors beyond hormonal influences to gain a more complete understanding of the observed gender differences. Genetic factors are known to play a role in the development of various types of tumors, and meningiomas are no exception. Certain genetic syndromes, such as neurofibromatosis type 2 (NF2), are associated with an increased risk of developing meningiomas. NF2 is caused by mutations in the NF2 gene, which encodes a tumor suppressor protein called merlin. However, NF2 accounts for only a small proportion of all meningiomas. The majority of meningiomas are sporadic, meaning they occur without a clear family history. Nevertheless, subtle genetic variations or predispositions that are more prevalent in females could potentially contribute to the higher incidence of meningiomas in this gender. Large-scale genomic studies comparing meningiomas in male and female patients could be instrumental in uncovering such underlying genetic factors. These studies could employ techniques such as genome-wide association studies (GWAS), exome sequencing, and whole-genome sequencing to identify genetic variants that are associated with meningioma risk and that exhibit gender-specific differences. Identifying specific genes or genetic pathways involved in meningioma development could provide new targets for therapeutic intervention. In addition to hormonal and genetic factors, other gender-specific biological differences might also contribute to the observed disparity in meningioma incidence. These differences could encompass a wide range of physiological and molecular processes, including variations in immune responses, metabolic pathways, or the expression of growth factors and signaling molecules. For instance, differences in the way male and female brains respond to cellular stress or DNA damage could potentially influence the likelihood of tumor development. Furthermore, variations in the microenvironment surrounding meningioma cells, such as differences in the composition of the extracellular matrix or the presence of specific immune cells, could also play a role. Investigating these complex biological differences requires a multidisciplinary approach, integrating techniques from molecular biology, immunology, and neurobiology. It is essential to emphasize that while the female predominance observed in this study aligns with general trends reported in the literature, it is crucial to interpret this finding within the specific context of the population under investigation. The epidemiology of meningiomas can vary across different ethnic groups, geographical regions, and populations, reflecting the influence of diverse genetic, environmental, and lifestyle factors. Different ethnic groups may harbor distinct genetic predispositions to meningiomas. Variations in the prevalence of specific genetic variants or mutations could influence the incidence and characteristics of meningiomas within a population. For example, certain populations may have a higher frequency of specific polymorphisms in genes involved in hormone metabolism or DNA repair, which could affect meningioma risk. Environmental factors, such as exposure to radiation, certain chemicals, or infectious agents, have been implicated in the development of various types of cancer, including meningiomas. Differences in environmental exposures across populations could contribute to variations in meningioma incidence. For instance, occupational exposures, dietary habits, or exposure to environmental pollutants may vary significantly between different regions. Lifestyle factors, such as smoking, alcohol consumption, and obesity, have also been associated with an increased risk of certain cancers. Variations in these lifestyle factors across populations could contribute to differences in meningioma risk. Therefore, extrapolating the findings

of this study, particularly the observed gender disparity, to other populations should be done with caution. It is imperative to conduct further research in diverse ethnic and geographic groups to comprehensively characterize the gender-related aspects of meningioma recurrence. Large-scale epidemiological studies, international collaborations, and meta-analyses can provide a more robust understanding of the global patterns of meningioma incidence and the factors that contribute to gender differences across different populations.[11-15]

The median age of patients who underwent surgery for recurrent meningioma in this study was 46 years, with the ages spanning from 26 to 67 years. This median age presents an interesting point of comparison when juxtaposed with observations derived from other studies, particularly those conducted within Western populations, where the peak incidence of meningiomas is frequently reported to occur later in life, typically within the sixth or seventh decade. The somewhat younger median age observed in this Indonesian cohort prompts speculation about the potential underlying factors contributing to this difference, and several possibilities warrant careful consideration. One plausible explanation is that genuine variations exist in the age distribution of meningioma development and, subsequently, recurrence across different ethnic or geographic populations. It is conceivable that genetic variations, environmental influences, or lifestyle factors that are more prevalent within the Indonesian population could potentially contribute to an earlier onset of meningiomas or a higher propensity for recurrence at a younger age. Genetic predispositions, which can influence an individual's susceptibility to various diseases, may differ across ethnic groups, potentially affecting the age at which meningiomas develop. Similarly, variations in environmental exposures, such as dietary habits, occupational hazards, or exposure to specific toxins, could play a role in modulating meningioma risk and age of onset. Furthermore, lifestyle factors, including patterns of physical activity, smoking habits, or reproductive patterns, may also contribute to differences in the age distribution of meningiomas. Another potential explanation for the younger median age in this study lies in variations in healthcare access and referral patterns. It is conceivable that patients within this specific setting might present for medical evaluation at an earlier stage of symptom development, leading to earlier diagnosis and treatment of recurrent tumors. Factors such as the availability of healthcare facilities, the efficiency of the referral system, and the timeliness of diagnostic procedures can all influence the stage at which patients seek medical attention. If patients in this Indonesian cohort have relatively prompt access to healthcare and are referred for neurosurgical evaluation without significant delay, it could contribute to the earlier detection of recurrent tumors. Increased awareness of meningioma symptoms, both among patients and healthcare providers, could also play a significant role in earlier detection. When individuals are well-informed about the potential signs and symptoms of meningiomas, they may be more likely to seek medical attention promptly, leading to earlier diagnosis. Similarly, if healthcare providers are vigilant in recognizing and investigating potential meningioma symptoms, it can facilitate timely identification of recurrent tumors. Furthermore, it is essential to acknowledge that the specific characteristics of the study population itself, including potential selection biases, could exert an influence on the observed age distribution. This study is a retrospective analysis conducted at a single center, and as such, the patient cohort may not be fully representative of the broader Indonesian population. Factors such as the hospital's referral patterns, the socioeconomic status of the patients treated at the institution, or specific inclusion and exclusion criteria employed in the study could introduce biases that affect the age distribution of the study sample. For instance, if the hospital serves a predominantly younger population or if the study design preferentially included younger patients, it could skew the median age towards a lower value. It is

paramount to acknowledge the inherent limitations of a single-center retrospective study and to emphasize the need for further research to definitively establish whether there are significant age-related differences in meningioma recurrence between Indonesian and other populations. Large-scale, population-based studies, encompassing diverse geographic regions and ethnic groups within Indonesia, are essential to provide a more comprehensive and representative picture of meningioma epidemiology. These studies should employ rigorous methodologies to minimize bias and control for potential confounding factors, allowing for more robust conclusions about age-related trends in meningioma recurrence. International collaborative efforts, pooling data from multiple centers and countries, can also contribute valuable insights into the global patterns of meningioma age distribution and the factors that influence these patterns. The clinical presentation of recurrent meningiomas in this study exhibited considerable diversity, with the specific symptoms experienced by patients varying depending on the location and size of the tumor, as well as the involvement of surrounding neurological structures. Despite this variability, several key symptoms emerged as particularly prominent, providing valuable insights into the common clinical manifestations of recurrent meningiomas. The most frequently reported chief complaint among patients in this study was protrusion, observed in 39.3% of cases. This symptom likely reflects the relatively high proportion of tumors located in the sphenoorbital region, a complex anatomical area situated at the base of the skull, encompassing the bony cavity that houses the eye (orbit) and surrounding structures. Meningiomas arising in the sphenoorbital region can exert pressure on the eye and its associated tissues, leading to proptosis, which is characterized by the abnormal protrusion or bulging of the eye from the orbit. The degree of proptosis can vary depending on the size and extent of the tumor, and it may be accompanied by other ocular manifestations. The close proximity of the sphenoorbital region to the optic nerve, which transmits visual information from the eye to the brain, and other critical structures involved in vision, such as the extraocular muscles that control eye movement, explains why visual disturbances were relatively common in this cohort. Blurred vision, reported in 10.7% of patients, can result from compression or invasion of the optic nerve, leading to impaired visual acuity. Other potential visual symptoms associated with sphenoorbital meningiomas include diplopia (double vision), visual field defects (loss of specific portions of the visual field), and decreased visual acuity. Headache was another prevalent symptom among patients in this study, reported by 25.0% of cases. Headache is a common and often nonspecific symptom associated with a variety of intracranial tumors, including meningiomas. The underlying mechanisms responsible for headache in meningioma patients are multifactorial, but one of the primary contributing factors is the mass effect of the tumor. As the tumor grows within the confined space of the skull, it can exert pressure on surrounding brain tissue, blood vessels, and meninges, leading to an increase in intracranial pressure. This elevated pressure can trigger headache, which may vary in intensity, frequency, and character. The location of the headache may also provide clues about the location of the tumor, although this is not always the case. Other neurological symptoms were reported less frequently in this study, each observed in 7.1% of patients. These included weakness (focal deficit), decreased level of consciousness, and seizures. These symptoms indicate that recurrent meningiomas can indeed cause significant neurological morbidity, and the specific nature of these symptoms is largely dependent on the location of the tumor and the extent to which it compresses or invades the surrounding brain tissue. Weakness or focal deficit suggests involvement of the motor pathways in the brain. A decreased level of consciousness implies a more significant impact on overall brain function. Seizures arise from abnormal electrical activity. The variability observed in the clinical presentation of recurrent meningiomas in this study underscores the paramount importance of a

thorough and meticulous neurological examination in all patients suspected of harboring these tumors. A comprehensive neurological assessment allows clinicians to identify specific neurological deficits, assess cognitive function, and evaluate sensory and motor skills. In addition to the neurological examination, comprehensive radiological evaluation is equally crucial for the accurate diagnosis, localization, and characterization of recurrent meningiomas. Advanced imaging techniques, such as magnetic resonance imaging (MRI) with contrast enhancement and computed tomography (CT) scans, provide detailed anatomical information about the tumor's size, location, extent of invasion, and relationship to surrounding structures. These imaging studies are essential for surgical planning, treatment decisions, and monitoring tumor recurrence.[16-20]

5. Conclusion

This retrospective study of recurrent intracranial meningiomas in a cohort of Indonesian patients reveals several key clinicopathological and surgical characteristics. The patient group was predominantly female, aligning with the established gender disparity observed in meningioma incidence globally. The median age at recurrence surgery was 46 years, which is somewhat younger than the typical age of presentation in Western populations, suggesting potential variations in the disease's natural history across different ethnic or geographical groups. Clinically, the most common presenting symptoms were protrusion and headache, reflecting the frequent involvement of tumors in the sphenoorbital region and the general mass effect associated with intracranial tumors. Radiological findings highlighted the predilection of recurrent meningiomas for the parietal and sphenoorbital regions, with a high incidence of bone infiltration and a notable proportion of cases exhibiting tumor invasion into adjacent structures, including the cavernous sinus. The recurrence patterns observed in this study underscore the challenging nature of meningioma management, with most patients requiring multiple surgical interventions. The median time to recurrence was 36 months, emphasizing the need for prolonged follow-up due to the potential for both early and late recurrences. Histopathological analysis revealed that the majority of recurrent tumors were WHO Grade 1, with meningothelial and transitional subtypes being the most common. These findings contribute valuable insights into the specific characteristics of recurrent intracranial meningiomas within the Indonesian population. They highlight the importance of considering population-specific factors in the diagnosis, treatment, and long-term management of this challenging condition. Further research, particularly large-scale, population-based studies and international collaborations, is warranted to validate and expand upon these observations, ultimately leading to improved patient care and outcomes.

6. References

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