**T.C.**

**BAHCESEHIR UNIVERSITY**

**GRADUATE SCHOOL OF EDUCATION**

**NEUROSCIENCE HEAD OF THE DEPARTMENT**

# EVALUATION OF H3K27ME3 EXPRESSION IN DIFFERENT ANATOMICAL LOCALISATIONS AND DIFFERENT HISTOLOGIC SUBTYPES IN MENINGIOMA CASES, ITS CORRELATION WITH RECURRENCE AND OTHER PROGNOSTIC PARAMETERS.

**MASTER'S THESIS**

**OMAR GALY**

**ISTANBUL 2023**

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**MASTER'S THESIS**

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**ISTANBUL 2023**

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## MASTER THESIS APPROVAL FORM

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| **Student's Name and Surname:** | Omar Galy |
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**Prof. Dr. Ahmet ÖNCÜ**

**Institute Director**

This thesis was read by us, quality and content as a Master's thesis has been seen and accepted as sufficient.

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## ABSTRACT

**Evaluation of H3K27me3 Expression in Different Anatomical Localisations and Different Histologic Subtypes in Meningioma Cases, Its Correlation with Recurrence and Other Prognostic Parameters.**

Galy, Omar
Master's Program in Neuroscience
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WHO classification of meningiomas has many limitations in predicting meningiomas' behaviour and prognosis, The diagnostic potential of H3k27me3 has been demonstrated for many tumours.

This study aimed to evaluate the expression of h3K27me3 in various anatomical localizations and various histologic subtypes of meningioma, as well as to determine the link between its expression and recurrence and free recurrence survival time.

112 cases from 2015 to 2022 were recruited from Goztepe Medical Park hospital, H3K27me3 was assessed by Immunohistochemistry, the cases were prepared and H3K27me3 was applied, Expression of H3K27me3 was assessed by two physicians, the data were collected, coded, and statistically analysed.

Most cases of meningioma retained more than 50% of H3K27me3 and no case showed total loss of expression. However, the difference of expression of H3K27me3 was not statistically significant neither among different WHO grades of meningioma (P=.211) nor among meningiomas in different localisations (.953) nor among different histologic subtypes of meningioma (.879). The expression of H3K27me3 was not different between de novo and recurrent meningiomas (.932). Loss of H3K27me3 was

not a risk factor for the incidence of recurrence, and it was not associated with free recurrence survival in meningioma.

Overall, H3K27me3 expression does not seem to be beneficial in the clinical diagnosis of meningioma. Moreover, it did not seem to show any potential to become an investigatory tool to determine the prognosis of meningioma.

**Keywords**: H3K27me3, Meningioma

# ÖZ

**Farklı Anatomik Lokalizasyonda Ve Farklı Histolojik Subtiplerdeki Meningioma Olgularında H3k27me3 Ekspresyonun Değerlendirilmesi, Rekürrens Ve Diğer Prognostik Parametrelerle Korelasyonu**

Galy, Omar

Sinirbilim Yüksek Lisans Programı

Tez Danışmanı: Ozlem Yapicier

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Meninjiomların Dünya Sağlık Örgütü 2021 sınıflandırması, meninjiomların davranışını ve prognozunu tahmin etmede birçok sınırlamaya sahiptir, H3K27me3'ün tanısal potansiyeli birçok tümör için gösterilmiştir.

Bu çalışmanın amacı, H3K27me3'ün çeşitli anatomik lokalizasyonlarda ve menenjiomun çeşitli histolojik alt tiplerinde ekspresyonunu değerlendirmenin yanı sıra ekspresyonu ile nüks ve nüks olmaksızın sağkalım süresi arasındaki bağlantıyı belirlemektir.

Çalışmada 2015-2022 yılları arasında Göztepe Medical Park hastanesinde ameliyat edilmiş 112 vakanın kesitlerine H3K27me3 uygulanmış ve H3K27me3 ekspresyonu iki patolog tarafından değerlendirilmiştir. Daha sonra tüm veriler toplanmış, kodlanmış ve istatistiksel olarak analiz edilmiştir.

Menenjiyom vakalarının çoğunda H3K27me3'ün ekspresyonunun %50'sinden fazlasını koruduğu ve hiçbir vakanın tamamen ekspresyon kaybı göstermediği saptandı. Bununla birlikte, H3K27me3 ekspresyonu farklı menenjiyom dereceleri arasında (P=.211), farklı lokalizasyonlardaki menenjiyomlar arasında (.953) veya

menenjiyomun farklı histolojik alt tipleri arasında (.879) istatistiksel olarak anlamlı değildi. H3K27me3 ekspresyonu de novo ve rekürren meningiomlar arasında da fark göstermedi (.932).

İstatistiksel veriler H3K27me3 kaybının nüks insidansı için bir risk faktörü olmadığı ve menenjiyomda nüks olmaksızın sağkalım ile ilişkili olmadığı yönündedir. Sonuç olarak, bulgular H3K27me3 ekspresyonun menenjiomun klinik biyolojik davranışında yol gösterici olmadığını düşündürmektedir.

Anahtar Kelimeler: H3K27me3, menenjiyom.

## ACKNOWLEDGMENTS

I would like to express my deepest appreciation to my supervisor Ozlem Yapicier Professor of pathology M.D. for her guidance, and additionally for her help and support during my illness. I would also love to show my gratitude to Mrs. Hatice Cirakoglu and Mr. Emircan Akman for the patience and extraordinary support they provided to me in the laboratory of pathology.

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| | |
|---|---|
| WHO | World Health Organization |
| CNS | Central Nervous System |
| HPF | High Power Fields |
| TERT | Telomerase Reverse Transcriptase |
| CDKN2A | cyclin-dependent kinase inhibitor 2A |
| CDKN2B | cyclin-dependent kinase inhibitor 2B |
| STAT6 | Signal Transducer and Activator of Transcription 6 |
| EMA | Epithelial Membrane Antigen |
| SSTR2A | somatostatin receptor 2A |
| NF2 | Neurofibromatosis type 2 |
| DNA | Deoxyribonucleic Acid |
| PAS | Periodic Acid-Schiff. |
| KLF4 | Krüppel-Like Factor 4. |
| TRAF7 | TNF Receptor-Associated Factor 7. |
| CEA | Carcinoembryonic Antigen. |
| NHERF1 | Na+/H+ Exchanger Regulatory Factor 1 |
| SMARCE1 | SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1 |
| PBRM1 | Polybromo-1 |
| BAP1 | BRCA1-associated protein 1 |
| SMO | Smoothened. |
| CPA | Cerebellopontine angle |
| MRI | Magnetic Resonance Imaging |
| CSF | Cerebrospinal Fluid |
| CT | Computerised tomography |
| EZH2 | Enhancer of Zeste Homolog 2 |

| | |
|---|---|
| PR | Progesterone Receptor |
| MPNSTs | Malignant Peripheral Nerve Sheath Tumors |
| GTR | Gross total resection |
| STR | Subtotal resection |
| RFS | Recurrence free survival |
| PFS | Progression free survival |
| GK | Gamma knife |
| HRP | Horseradish peroxidase |

# Chapter 1

# Introduction

## 1.1 Statement of The Problem

The meningioma grading system implemented by the WHO is an efficient tool for risk classification of meningiomas. and based on this classification, a decision regarding treatment is made, namely regarding whether radiotherapy is required or whether observation is sufficient. However, this classification has a lot of flaws because it can't completely anticipate the behaviour of the tumour, some meningiomas have a higher risk of recurrence, and this risk is irrespective of the histological grade of the tumour and the amount to which it was removed during surgery (Goldbrunner et al., 2016). and as a result, the WHO grading system can't always figure out the prognostic criteria like recurrence free survival and progression free survival. The inaccuracy of the WHO grading system in determining how a meningioma will behave, underscores the important requirement for the use of additional trustworthy biomarkers that can accurately reflect the behaviour of the tumour. Modifications of lysine 27 (K27) of histone H3 play an essential role in the development of tumours (Nowosielski et al., 2017a; Yoo & Hennighausen, 2012), the diagnostic and prognostic value of H3K27me3 were tested in meningioma and other tumours and the findings were diverse among different studies (Behling et al., 2021; Cai, Hou, et al., 2011; Cleven et al., 2016; Gauchotte et al., 2020; Maier et al., 2022). Trimethylation of H3K27 has the potential to be a novel and reliable biomarker (Katz et al., 2018), but further studying and testing of the diagnostic and prognostic value of H3K27me3 is required and needed.

## 1.2 Purpose of The Study

The purpose of this research is to evaluate the expression of h3K27me3 in various anatomical localizations and various histologic subtypes of meningioma, as well as to determine the link between its expression and recurrence and other free recurrence survival time.

### 1.3 Hypothesis/ Research Question

Is there a difference in the expression of h3K27me3 in meningioma depending on the location of the tumour and the histologic subtype? Is there a connection between the expression of H3K27me3 and the possibility of recurrence as well as free recurrence survival time?

### 1.4 Significance of The Study

trimethylation of H3K27 has been included into clinical diagnostic practice as an immunohistochemistry technique, and the loss of H3K27me3 has been linked to a bad prognosis. This study will assist to investigate the reproducibility of the prognostic value of H3K27me3 loss in combination with other factors, such as histological characteristics and the location of the tumour.

# Chapter 2

# Literature Review

## 2.1 Meningioma grading and Classification

Meningiomas are a class of neoplasms that are most likely formed from the meningothelial cells that are found in arachnid matter. (WHO Classification of Tumours Editorial Board, 2022). Following publishing in 1979, 1993, 2000, 2007, and 2016, the WHO categorization of tumours of the Central Nervous System, Fifth Edition, is the sixth version of the worldwide standard for the categorization of brain and spinal cord tumours. This edition is the fifth edition of the WHO Classification of Tumours of the Central Nervous System (Louis et al., 2021). The fifth edition of the WHO classification of tumours of the central nervous system introduces significant modifications. These modifications include a greater emphasis on the role of molecular diagnostics in CNS tumour classification, while at the same time maintaining a foundation in other well-established methods of tumour characterization, such as immunohistochemistry and histology (Louis et al., 2021). Meningiomas are now considered to be a single form of tumour that can have up to 15 subtypes. These histological subtypes are categorized into three grades, which usually represent the rate of growth and the chance of recurrence based on cytological characteristics (WHO Classification of Tumours Editorial Board, 2022).

**2.1.1 Meningioma grading.** A WHO grade 1 meningioma any predominant histology that is not rhabdoid, papillary, clear cell, chordoid, or chordoid. And does not fulfil the criteria of anaplastic or atypical meningiomas (Perry, 2018). Meningiomas can be classified into grades 2 and 3 according to WHO standards, and these standards are applicable to all subtypes of meningioma. But in order to make a diagnosis of atypical meningioma, the CNS grade 2 criteria need to be satisfied, and the CNS grade 3 criteria need to be satisfied in order to make a diagnosis of malignant meningioma (WHO Classification of Tumours Editorial Board, 2022). When there are 4 to 19 mitotic figures in 10 HPF of each 0.16 mm2 or when there is unequivocal brain invasion or when there is a specific morphological subtype or when there are at least 3 of 5 of the following symptoms, increased cellularity, small cells with a high N:C ratio, prominent nucleoli, sheeting, and foci of spontaneous necrosis, the criteria for CNS who grade 2 is met. When there are 20 or more mitotic figures in 10 consecutive

HPF of each 0.16 mm2, or when there is frank anaplasia, or when there is a TERT promoter mutation, or when there is homozygous deletion of CDKN2A and/or CDKN2B, then the CNS WHO grade 3 criteria has been fulfilled (WHO Classification of Tumours Editorial Board, 2022).

**2.1.2 Meningothelial meningioma.** Also known as syncytial or endothelial meningiomas, are the most prevalent histological subtype of meningioma. They are seen in approximately 60% of all meningiomas. Most commonly, they are associated with fibrous meningioma, which accounts for 40% of cases, but they can also occur alone, which accounts for 17% of cases (Backer-Grøndahl et al., 2012). Meningioma of the meningeal lining Epithelioid cells develop syncytia-like lobules in the meningothelial subtype of meningioma. Additionally, some of the nuclei inside the tumour seem to have nuclear holes and pseudo-inclusions. There is a striking similarity between the morphology of meningothelial meningioma cells and that of arachnoid cap cells. They have rich eosinophilic cytoplasm and are organized in lobules that can be delimited by thin collagen septa. They are mostly monomorphic. Although the borders between the cells are barely perceivable with light microscopy, giving the appearance of a syncytium, ultrastructural analyses have showed that the tumour cells have independent fragile processes, suggesting that the pattern is a pseudo-syncytium. This contradicts the findings of light microscopy, which provide the impression of a syncytium. Internal empty gaps, also known as nuclear holes, and pseudo-inclusions, also known as cytoplasmic invaginations, may be present in nuclei that range in shape from round to oval. When compared to their incidence in transitional, fibrous, and psammomatous meningiomas, the presence of whorls and psammoma bodies is extremely uncommon. AKT1 p.E17K mutations are often seen in meningothelial meningiomas. These mutations are usually associated with TRAF7 mutations, or PIK3CA and SMO mutations.(WHO Classification of Tumours Editorial Board, 2022).

**2.1.3 Fibrous meningioma.** The second most common histological subtype of meningioma, appearing in around fifty percent of all meningiomas. It is typically found along with meningothelial histology (for forty percent of cases) or alone seven percent of the time. They are the histological subtype of intraventricular meningioma that occurs most often (Backer-Grøndahl et al., 2012). The fibrous subtype of meningioma

is characterized by spindle cells arranged in a collagen-rich matrix in a parallel, storiform, or interlacing bundle pattern. Different quantities of intercellular collagen can be seen in the fascicles that tumour cells generate. Collagen deposition may be substantial, which raises the possibility of a single fibrous tumour as a possible differential diagnosis; however, only solitary fibrous tumours display nuclear staining for STAT6. EMA expression may be mild or absent, however, S100 staining may be surprisingly robust. In fibrous meningioma, however, the expression of SSTR2A is frequently robust and widespread, in contrast to that which is observed in schwannomas. In most cases, fibrous meningiomas exhibit the same genetic changes as transitional and psammomatous meningiomas, including deletion of the 22q gene and mutation of the NF2 allele that has been maintained. The DNA methylation characteristics of these meningiomas are similar to those of transitional and psammomatous meningiomas. They are often located near the convexity of the surface. (WHO Classification of Tumours Editorial Board, 2022).

**2.1.4 Transitional meningioma.** The transitional subtype of meningioma is characterized by the presence of transitional characteristics in addition to meningothelial and fibrous patterns. Lobular and fascicular areas are found near one another, with certain regions not being able to be definitively attributed to either of the two patterns. This subtype has a high frequency of whorl development as well as psammoma bodies. In addition to having comparable DNA methylation patterns, common 22q deletions and NF2 mutations are traits that are shared by transitional meningiomas, fibrous meningiomas, and psammomatous meningiomas respectively. They frequently originate from the convexity of the surface (WHO Classification of Tumours Editorial Board, 2022).

**2.1.5 Psammomatous meningioma.** Psammoma bodies are more common than viable tumour cells in the subtype of meningioma known as the psammomatous subtype. When separate psammoma bodies overlap with one another, it can lead to the formation of enormous, confluent calcified masses. The presence of actual meningioma cells may be extremely uncommon or almost non-existent, although immunohistochemistry for EMA or SSTR2A can indicate their presence. The fibrous or transitional subtypes are often the most appropriate classifications for non-calcified foci. Psammomatous meningiomas, fibrous meningiomas, and transitional

meningiomas all have similar molecular characteristics. These characteristics include 22q deletions, NF2 mutations, and epigenetic profiles. This subtype most frequently manifests itself in the thoracic spine area of women who are middle-aged or older in age (WHO Classification of Tumours Editorial Board, 2022).

**2.1.6 Angiomatous meningioma.** In the angiomatous subtype of meningioma, the intermixed meningioma cells are often outnumbered by the hyalinized tiny blood vessels that characterize this subtype. It is possible that genuine tumour cells will be difficult to locate and identify as meningioma cells due to the presence of many blood arteries. Blood vessels can have thin walls or thick walls, and their hyalinization level might vary. As is the case with the previously mentioned subtypes, angiomatous regions may also be intermixed with microcystic or even metaplastic areas, and the cells may exhibit degenerative nuclear atypia. It is possible for hyper-vascular instances to mimic haemangioblastoma; however, in most cases, inhibin expression is absent and SSTR2A positivity is present. There is a significant prevalence of chromosome 5 gain in angiomatous meningiomas, microcystic meningiomas, and metaplastic meningiomas. Angiomatous meningiomas, just like secretory and microcystic meningiomas, are frequently linked with cerebral oedema that is more than what would be expected for the size of the tumour (WHO Classification of Tumours Editorial Board, 2022).

**2.1.7 Microcystic meningioma.** A cobweb-like backdrop is produced on histology by the microcystic subtype of meningioma, which is characterized by the presence of microcysts created by cells with thin, elongated processes. The cysts have the potential to grow into macro-cysts, which can be detected macroscopically or radiologically. The presence of degenerative nuclear atypia in microcystic meningioma, like the presence of angiomatous nuclear atypia in angiomatous meningioma, might raise the suspicion of a higher grade of the tumour. On the other hand, microcystic meningiomas are almost never malignant. It is usual for there to be a gain of chromosome 5, as there is in angiomatous and metaplastic meningiomas. Microcystic regions can be coupled with these types of meningiomas. Cerebral oedema is common, and it is also common in meningiomas that are angiomatous and secretory (WHO Classification of Tumours Editorial Board, 2022).

**2.1.8 Secretory meningioma.** The secretory subtype of meningioma is distinguished from other types of the disease by the presence of foci of gland-like epithelial development, PAS-positive eosinophilic secretions, and/or combination mutations in KLF4 and TRAF7. The eosinophilic secretions, also known as pseudo-psammoma bodies, test positive for a wide array of epithelial and secretory markers. CEA is one of these indicators. CEA and cytokeratin positivity can also be seen in the cells that surround the tumour. In some situations, elevated amounts of CEA can be seen in the blood; however, these levels tend to fall after resection but increase in the extremely rare instances when the cancer returns. It's very usual to have oedema around the tumour. This genetic subtype is distinguished by the presence of both the KLF4 p.K409Q mutation and the TRAF7 mutation. It may be possible to single out the KLF4 mutations in a few specific cases (WHO Classification of Tumours Editorial Board, 2022).

**2.1.9 Lymphoplasmacyte-rich meningioma.** A rare variant of meningioma known as lymphoplasmacyte-rich meningioma. In this form of the disease, large chronic inflammatory infiltrates prevail over the meningothelial component. Despite the name, plasma cells are not always present, and macrophages frequently predominate. It is possible that in certain instances it will be difficult to differentiate this subtype from inflammatory illnesses that present with patchy meningothelial hyperplasia (WHO Classification of Tumours Editorial Board, 2022).

**2.1.10 Metaplastic meningioma.** The metaplastic subtype of meningioma is characterized by the presence of localized or widespread mesenchymal components. These components might include osseous, cartilaginous, lipomatous, myxoid, and xanthomatous tissue, either alone or in combination. These changes are not known to have any clinical significance, and most of them do not represent genuine metaplasia. It is possible for the morphological characteristics of metaplastic meningioma to coincide with those of angiomatous and microcystic meningiomas, and gain of chromosome 5 is common in all three subtypes of meningiomas. It may be challenging to differentiate the ossification that occurs in metaplastic meningioma from the dystrophic ossification of psammoma bodies that occurs in psammomatous meningioma or from bone invasion. There is a possibility that remnants of the concentric inner structure of psammoma bodies or radiographic imaging of

neighbouring bone, respectively, might both contribute to the differentiating process (WHO Classification of Tumours Editorial Board, 2022).

**2.1.11 Chordoid meningioma.** The chordoid subtype of meningioma most closely resembles chordoma in appearance. It is characterized by cords or trabeculae of tiny, epithelioid (or less commonly spindled), variably vacuolated cells that are embedded in a mucin-rich matrix. Chordoid regions are frequently found intermingled with meningiomas that are more typical; nevertheless, instances of pure meningioma can occasionally be found. When they are present, chronic inflammatory infiltrates frequently take the form of discrete patches, although they may also be prominent. Patients with chordoid meningiomas may be younger than the usual age of presentation, which is around 45 years, although these tumours are often big and found in the supratentorial region of the brain. Chordoid meningiomas frequently do not exhibit any additional high-grade histological abnormalities; yet their recurrence rates are comparable to those of atypical meningiomas; as a result, they have been assigned to WHO grade 2. Epithelial differentiation with NHERF1-immunoreactive cytoplasmic micro-lumina was shown to be common in secretory meningiomas, according to the findings of one investigation. Extremely rarely, individuals will also have related haematological problems such anaemia or Castleman disease. However, DNA methylation patterns are overlapping with those of other meningioma subtypes, even though chromosome 2p deletions are overrepresented (WHO Classification of Tumours Editorial Board, 2022).

**2.1.12 Clear cell meningioma.** The clear cell subtype of meningioma is characterized by a mostly pattern-less or sheeting architecture, and its cells range from round to polygonal shapes. Clear cell meningiomas also include significant glycogen-rich cytoplasm, as well as perivascular and interstitial collagen. On occasion, the perivascular and interstitial collagen will condense into vast acellular zones of collagen or create brilliantly eosinophilic collagen that resembles amianthoid. It demonstrates substantial PAS-positive and diastase-sensitive cytoplasmic glycogen, however the whorl formation is not very clear, and psammoma bodies are not very noticeable. The cerebellopontine angle and the spine, and more specifically the cauda equina area, are common locations for clear cell meningiomas to develop. Additionally, younger individuals, such as children and young people, are more likely to be affected by this

condition. Because clear cell meningiomas are linked to more aggressive behaviours, such as recurrence and the occasional seeding of cerebrospinal fluid, they have been classified as WHO grade 2. However, this classification is provisional until bigger studies establish that clear cell meningiomas have higher rates of recurrence. Both germline mutations (found in families) and somatic mutations of SMARCE1 are quite frequent, and immunohistochemistry reveals that practically all cases demonstrate a loss of nuclear SMARCE1 expression (WHO Classification of Tumours Editorial Board, 2022).

**2.1.13 Papillary meningioma.** The presence of a significant perivascular pseudopapillary pattern is what distinguishes the papillary subtype of meningioma from the other subtypes. In the papillary subtype of meningioma, cancerous meningioma cells arrange themselves in a pseudo-rosette-like pattern around the thin-walled blood veins. The presence of cells with rhabdoid cytomorphology grouped in a papillary architecture in certain meningiomas is consistent with a genetic and molecular relationship between the papillary and rhabdoid subtypes of meningioma. There have been cases of papillary meningiomas seen in both children and adults. It is not uncommon for these tumours to be accompanied with peritumoral oedema as well as bone hyperostosis or destruction. Additionally, cyst development may be observed. There is a correlation between a papillary growth pattern and brain invasion as well as aggressive clinical behaviour such as dissemination and metastasis, most commonly to the lung. In the absence of any other traits that are characteristic of higher grades, focal papillary architecture alone is not sufficient for classifying tumours as CNS WHO grade 2 or 3. In some meningiomas, the cells have a rhabdoid cytomorphology, and they are grouped in a papillary architecture. Papillary and rhabdoid meningiomas contain the same genetic changes, which is consistent with the infrequently found morphological overlap between the two types of tumours. Papillary meningiomas are more likely to have a mutated or deleted copy of PBRM1, whereas rhabdoid meningiomas are more likely to have a single instance of this mutation. In a similar vein, BAP1 mutations or deletions, which are frequently discovered in rhabdoid meningiomas, have also been described in papillary meningiomas or rhabdoid meningiomas with partly papillary features. These mutations or deletions are then typically paired with modifications in PBRM1, which are seen in rhabdoid

meningiomas with partly papillary features (WHO Classification of Tumours Editorial Board, 2022).

**2.1.14 Rhabdoid meningioma.** The presence of rhabdoid cells is what distinguishes the rhabdoid subtype of meningioma from other types. Rhabdoid cells are described as swollen cells that have eccentric nuclei, open chromatin, macro-nucleoli, and significant eosinophilic paranuclear inclusions. These inclusions can take the form of identifiable whorled fibrils or compact and waxy spheres. Rhabdoid characteristics are typically already present at the time of the first resection, however they may become more noticeable after a recurrence. The vast majority of rhabdoid meningiomas exhibit significant rates of cell proliferation in addition to other histological hallmarks of malignancy. The fact that original cohorts of rhabdoid meningiomas included tumours with high rates of recurrence and mortality lends credence to the classification of this condition as a WHO grade 3 tumours of the central nervous system. Most of the tumours in those cohorts fulfilled the criteria for categorization as CNS WHO grade 3 anaplastic/malignant meningioma, in accordance with rhabdoid cytology. This was the case regardless of whether they had rhabdoid cytology. However, a significant number of rhabdoid meningiomas have now been identified based on rhabdoid cells alone, even though they do not match the other criteria for CNS WHO grade 3. Of them, fifty percent have CNS WHO grade 1 features and the other fifty percent have CNS WHO grade 2 features. This work suggests that rhabdoid meningiomas should be graded similarly to non-rhabdoid meningiomas; however, the authors cautioned that some of these tumours may still behave aggressively, and that close patient follow-up is required. A meta-analysis showed that patient outcome is strongly correlated with CNS WHO grade, independent of the rhabdoid features. There may be a connection between these two categories of meningiomas since certain meningiomas feature cells that have a rhabdoid cytomorphology and are organized in a papillary architecture. As part of the BAP1 tumour predisposition syndrome, a subgroup of rhabdoid and/or papillary meningiomas can occur in people who have germline mutations in the BAP1 gene. people with this condition are more likely to develop uveal and cutaneous melanoma, mesothelioma, and renal cell carcinoma, amongst other types of tumours, in their lifetime. It is important to note that the immunohistochemical disappearance of BAP1 expression in this context was related with a clinical behaviour that was aggressive

(consistent with CNS WHO grade 3), in these tumours. In addition, as was mentioned before in the section titled "Papillary meningioma," there is a possibility that rhabdoid and papillary meningiomas share some of the same histological and genetic characteristics (WHO Classification of Tumours Editorial Board, 2022).

**2.1.15 Atypical meningioma.** An atypical meningioma is defined as an intermediate-grade meningioma that exhibits increased mitotic activity, brain invasion, and/or at least three of the following characteristics: high cellularity, small cells with a high NC ratio, prominent nucleoli, sheeting (uninterrupted pattern-less or sheet- like growth), and foci of spontaneous (non-iatrogenic) necrosis. According to the findings of a major clinicopathological study, the threshold for increased mitotic activity is set at 22.5 mitoses per mm2. Nuclear atypia is frequently regarded to be degenerative in nature and is not connected with patient outcome; despite this, the term "atypical meningioma" is not an accurate description of the condition. Clinical risk factors for atypical meningioma include being male, having the tumour located outside of the base of the skull, and having previous surgery. Even after undergoing a complete resection, atypical meningiomas have been shown to have a high recurrence incidence; bone involvement may be linked with an even higher risk of recurrence. Meningioma invasion of the brain is characterized by irregular, tongue-like protrusions of tumour cells into underlying GFAP-positive parenchyma. There is no intervening leptomeninges during this stage of the disease. Since the pia has not been broken, extension via the perivascular Virchow-Robin gaps does not represent brain invasion. This kind of perivascular spread and hyalinization is most frequently seen in youngsters and has the potential to be confused with meningio-angiomatosis. Meningiomas with extra high-grade characteristics are more likely to cause brain invasion than other types of meningiomas. Despite this, the existence of brain invasion in otherwise benign appearing meningiomas that have had clinically entire resection is still debatable since it has been associated with recurrence rates that are comparable to those of other central nervous system tumours (WHO Classification of Tumours Editorial Board, 2022).

**2.1.16 Anaplastic meningioma.** Anaplastic meningioma is a type of high-grade meningioma that has overtly malignant cytomorphology (anaplasia). It can: (a) resemble carcinoma, high-grade sarcoma, or melanoma; (b) display markedly elevated

mitotic activity; (c) harbor a TERT promoter mutation; and/or (d) have a homozygous CDKN2A and/or CDKN28 deletion. In a study that involved 116 individuals, significantly high mitotic activity was defined as a mitotic count that was greater than or equal to 12.5 mitoses per mm 2. Only one to three percent of meningiomas are classified as anaplastic. Most of these tumours exhibit extensive necrosis and can infiltrate brain tissue. Using immunohistochemical or genetic testing, a meningothelial origin can be verified in certain cases of anaplastic astrocytoma. Because the course of malignancy in meningiomas is a continuum of growing anaplasia, it can be difficult to pinpoint the moment at which a meningioma is considered to have crossed the line from atypical to anaplastic. The repeatability between observers is excellent for the mitotic count but only mediocre for the detection of overt anaplasia. Regardless of any other histological characteristics, the presence of a TERT promoter mutation is associated with a significant probability of recurrence and a short interval before advancement of the disease. In the same vein, having a homozygous deletion of CDKN2A and/or CDKN2B is linked to high-grade histology, an increased likelihood of recurrence, and a shorter amount of time before advancement. Loss of H3 p.K28me3 (K27me3) is related with a lower overall survival and is found in around 10-20% of anaplastic meningiomas (WHO Classification of Tumours Editorial Board, 2022).

### 2.2 Meningioma and Localisation

Meningiomas are most frequently seen in the intracranial, intraspinal, or orbital regions of the body. The most common locations for tumours are the cerebral convexities, sphenoid ridges, olfactory grooves, parasellar/suprasellar areas, petrous ridges, optic nerve sheath, posterior fossa, and tentorium. Epidural and Intraventricular localizations are quite rare. The thoracic area is the most common location for spinal meningiomas. The mutation spectrum is strongly associated with the location of the tumour. For instance, skull base meningiomas carry mutations in AKT1, TRAF7, SMO, and/or PIK3CA, meanwhile convexity meningiomas and the majority of spinal meningiomas often carry a 22q deletion and/or NF2 mutations. Thus, we realise that tumour location is significantly linked with the mutation spectral range. The convexity and other locations outside of the skull base are the most prevalent places where higher grade meningiomas originate. While rare primary meningiomas can develop outside of the neuraxis (WHO Classification of Tumours Editorial Board, 2022).

**2.2.1 Parasagittal meningioma.** Twenty to thirty percent of all meningiomas are classified as parasagittal meningiomas. (Mathiesen, 2020) NF-2 mutations are almost always present in parasagittal meningiomas. In most clinical series, they tend to be more biologically aggressive than other types of meningiomas. Meningiomas of WHO grades II and III are highly represented, and most of the tumours are of a substantial size. (Magill, et al., 2018) Traditionally, Olivecrona established a categorization of parasagittal meningiomas based on a subdivision of the superior sagittal sinus into thirds, the anterior third, the middle third, and the posterior third. This division was based on Olivecrona's observations of the anatomy of the sinus. The anterior third extends all the way to the pre-Rolandic fissure, the middle third contains the peri-Rolandic region, and the posterior third terminates in the confluence of sinuses (Olivecrona, 1934). Focal neurologic deficit, epilepsy, and a rise in intracranial pressure are all symptoms of this condition. Although focal symptoms are a natural consequence of the localisation of lesions, three syndromes can be distinguished from one another. Frontal tumours have the potential to grow to huge proportions while gradually causing mental symptoms. Depression, personality disorders, cognitive deterioration over time, and burnout syndrome are some of the conditions that may belong to this group. (Mathiesen, 2020)

**2.2.2 Convexity meningioma.** Convexity meningiomas account for between 17% and 23% of all cases of intracranial meningiomas. (Morokoff et al., 2008) (Kamitani et al., (2001) reported that most patients with convexity meningiomas bigger than 2 or 3 cm in diameter manifested with spells of focal or generalized epileptic seizures, localised neurological impairments, or nonspecific headaches. This was the case for most of the patients. Contrarily, patients whose convexity meningiomas were less than 2 centimetres in size did not display any symptoms. Convexity meningiomas are more likely to express NF2 mutations and loss of heterozygosity of chromosome 22, this association between tumour location and genotype may help in the candidate selection process for future clinical trials that target specific oncogenic mutations (Bi et al., 2016).

**2.2.3 Sphenoid ridges.** 11–20% of all cases of cerebral meningiomas are shown to originate in the sphenoid wing (Güdük et al., 2019). Meningiomas of the sphenoid wing can be categorized as either globoid tumours with a nodular shape or as en plaque tumours, which are flat and spread throughout the entire sphenoid ridge. There are

three subtypes of globoid tumours that may be classified according to their location: medial, middle, and lateral (Nakamura et al., 2006). Meningiomas of the sphenoid wing arise from the outer arachnoid meningeal epithelial cells and grow slowly (American Academy of Ophthalmology., 2012).

Sphenoid wing meningiomas have a wide range of ophthalmic presentations related t -o their underlying tumour sites. Via bone, the cavernous sinus, or the superior orbital fissure the tumour may spread from the intracranial region into the orbit. It is possible for them to manifest with gradually worsening signs of an orbital or temporal fossa mass, such as temporal fullness, globe displacement, proptosis, reduced extraocular motility and ptosis. Visual field abnormalities, atrophy or optic disc oedema can be caused by tumours that are located close to the optic nerve or the sella or the optic. Furthermore, chemosis and eyelid oedema are frequently seen in patients (American Academy of Ophthalmology., 2012). NF2 mutation or 22q deletion is an independent factor that is related with recurrence in WHO grade 1 sphenoid wing meningiomas(Sakai et al., 2022).

**2.2.4 Olfactory grooves meningioma.** Meningiomas of the olfactory groove originate in the arachnoid cap cells of the dura, which are found in the anterior cranial fossa, directly above the cribriform plate. do not manifest any clinical signs during the early stages of tumour development, which results in a larger tumour size at the time of diagnosis (Ikhuoriah et al., 2022). Olfactory groove meningiomas are uncommon type of meningiomas that are both benign and slow growing. They account for 2% of all primary brain tumours, 4%-18% of all intracranial meningiomas, and 34% of all meningiomas that arise in the anterior cranial fossa (Ikhuoriah et al., 2022) Many patients do not experience any symptoms until the tumour has grown to a considerable size of more than 4 centimetres, at which point the tumour may compress the adjoining structures such as the frontal lobe, optic nerve, and optic chiasma. Clinical presentation and diagnosis typically take place in the late stage because many patients do not experience symptoms until this point. (Chiang & Goh, 2017; Welge-Luessen et al., 2001) Headaches, mental state changes (including personality changes), loss of short-term memory, and a lack of desire are frequent complaints reported by patients who have this condition. In addition to visual impairment, possible presenting symptoms include seizure activity and loss of smell (Cohen-Gadol, 2016a).

**2.2.5 Parasellar/sellar areas meningioma.** Any site along the dural skull base, such as planum sphenoidale, the tuberculum sellae, clinoid or anterior processes, cavernous sinuses, sphenoid wing, petroclival area, clivus or diaphragma sellae, might be the source of a meningioma in the sellar or parasellar region (Zada et al., 2016). Headaches, hydrocephalus, hypopituitarism, cranial nerve paresis, vision loss, proptosis, or any combination of these symptoms and signs may be the presentation of a sellar meningioma. Visual impairment is a common symptom of tuberculum sellae meningiomas, which first manifest as a bilateral superior quadrantanopsia and then progressively progress into a complete bitemporal hemianopsia. It has been noted that the presentation of an intrasellar meningioma can mimic an apoplexy of the pituitary gland (Kudo et al., 1997; Orakdöğen et al., 2004).

**2.2.6 petrous face meningioma.** Cerebellopontine angle (CPA) meningiomas arise from the petrous face of the temporal bone, which forms the lateral boundary of the CPA. They can be categorized into anterior, middle, and posterior, based on their attachment in relation to the internal acoustic meatus (Ali et al., 2020). Posterior fossa meningiomas form around 10% of all meningiomas. Fifty percent of them are located at the cerebellopontine angle (CPA), forty percent are tentorial or in the cerebellar convexity, nine percent are in the clival region, and six percent are near the foramen magnum(Ali et al., 2020). Patients usually present with symptoms associated with the cranial nerves, i.e. cerebellar dysfunction, hearing loss, malfunction of the facial nerve and trigeminal neuropathy are all examples of symptoms associated with the cranial nerves V, VI, VII, and VIII. In addition, the severity of the symptoms of compression of the pons, which might include obstructive hydrocephalus and gait disturbances in some of these individuals. (Mallucci et al., 1999; Pirouzmand et al., 2001).

**2.2.7 optic nerve sheath meningiomas.** They are rare, benign neoplasms that originate from the meningothelial cells of the meninges that surround the optic nerve. There is a meningeal sheath surrounding both the intra-orbital and intracanalicular parts of the optic nerve, therefore the tumour might originate from either of these areas (*Optic Nerve Sheath Meningioma - EyeWiki*, n.d.). They are responsible for one-third of all primary tumours of the optic nerve. The risk of developing optic nerve sheath meningioma is three times higher in women than it is in men, and the disease is most prevalent in adult women in their fourth or fifth decades of life (Shapey et al., 2013). Meningiomas of the optic nerve sheath have been linked to neurofibromatosis type 2,

according to research. Loss of the long arm of chromosome 22, which includes the portion of the chromosome that contains the NF2 gene, is the cytogenetic anomaly that is detected in meningiomas the most often (Kumar et al., n.d.). Visual impairment in the eye that's been impacted by optic nerve sheath meningioma often occurs gradually, without the patient experiencing any discomfort, and spreads throughout the entire field of vision. This tumour, if it is not treated, has the potential to cause total blindness (Parker et al., 2018). In individuals who have an Optic nerve sheath meningioma, the typical triad consists of optic atrophy, opto-ciliary shunt vessels and visual loss; however, most patients do not present with all three components (FRISEN et al., 1973).

**2.2.8 posterior fossa and tentorium meningioma.** Around thirty percent of all meningiomas detected in the posterior fossa are thought to have their origins in the tentorium cerebelli. This percentage accounts for roughly three to six percent of all meningiomas found within the brain itself. As is the case with other types of meningiomas, these tumours are more frequent in women of middle age. The sluggish development rate of tentorial meningiomas is one factor that contributes to their often-insidious clinical history. As a result, it is not uncommon for these tumours to reach a significant size before they are detected. Meningiomas of the medial tentorial region can show themselves clinically with a wide variety of signs and symptoms, depending on their size, precise position, the extent of any associated oedema, and whether they project into the supratentorial or infratentorial areas. Headaches and problems with walking gait are the symptoms that are seen most frequently. Alterations in mental state, visual abnormalities, and seizures are all quite typical symptoms. Additional symptoms such as dysphagia, hemiparesis, and trigeminal neuralgia have also been reported. (Conger & Cohen-Gadol, 2017).

**2.2.9 Parafalcine meningiomas.** account for 8.5% of all meningiomas found in the brain. Meningiomas of the parafalx originate the falx, and they are entirely covered by the cortex. They frequently develop bilaterally and have the potential to grow through the falx. They are most frequently present in the middle third of the superior sagittal sinus, namely around the middle third of the superior sagittal sinus (Cohen-Gadol, 2016). The clinical manifestations of a parafalcine meningioma change depending on where along the falx the tumour is located. Motor seizures, as well as sensory or contralateral hemiparesis/hemianesthesia, can be brought on by tumours

located close to the central sulcus. There is also a possibility of speech impairment. Headaches, blurry vision, and cognitive impairment may be caused by tumours that develop along the anterior portion of the falx. Those located in the posterior third might potentially produce visual disruptions (Cohen-Gadol, 2016).

**2.3 Meningioma Clinical manifestations**

Meningiomas are typically slow-growing tumours that can cause a variety of neurological deficits based on where the tumour is located. clinical signs and symptoms might occur from compression of neighbouring structures. Weakness, seizures, and headaches are common symptoms. even though it is not exclusive to meningiomas (WHO Classification of Tumours Editorial Board, 2022). Changes in personality, disorientation, and an altered state of awareness can be noted, especially in frontal or parasagittal meningiomas. Because of these symptoms, meningiomas are frequently mistaken in the beginning as dementia or depression. The list of possible diagnoses for a patient who presents with these symptoms is rather long and should include a variety of other intracranial pathologies(Buerki et al., 2018).

**2.4 Meningioma Epidemiology**

In the United States, the incidence of meningioma is 7.62 for every 100,000 people per year (Dolecek et al., 2015). According to estimates, the prevalence of meningioma is 97.5 for every 100,000 people in the United States (Wiemels et al., 2010). Primary brain tumours are a significant contributor to morbidity and death, even though they are far less common than secondary brain tumours caused by metastasis. Each year, doctors in the United States identify more than 70,000 new cases of primary brain and central nervous system tumours, including both malignant and benign types. Meningiomas make up 36.0% of them, while gliomas make up 28.6% of them. (Ostrom et al., 2015). While meningioma is the most common primary brain tumour found in adults, glioma is still the most common primary malignant brain tumour found in adults. (Ostrom et al., 2015). Meningiomas that are newly diagnosed are classed as WHO grade I tumours in 94.6% of cases, WHO grade II tumours in 4.2% of cases, and WHO grade III tumours in 1.2% of cases (Kshettry et al., 2015). Meningiomas are expected to recur in 10 to 32% of cases within 10 years, even after total removal (Adegbite et al., 1983; Mirimanoff et al., 1985).

**2.4.1 Meningioma and age.** Meningioma diagnoss often occur at 65 years of age. Meningioma incidence rates rise monotonically as people age, peaking at 51.3 cases per 100,000 people per year in those 85 and older (Ostrom et al., 2015).

**2.4.2 Meningioma and sex.** The incidence rate of meningioma in girls aged 0 to 19 years is almost equal to that in males aged 0 to 19 years, implying that the female-to-male incidence rate ratio is roughly 1.0. The female: male incidence rate ratio rises to about 2.0 in people 20 to 34 years old before peaking at 3.1 in people 35 to 44 years old. After then, this incidence rate ratio starts to decline, reaching a low of about 1.5 in those 85 or above (Wiemels et al., 2010).

**2.4.3 Meningioma and ethnicity.** Black Americans in the US had a 1.23-fold higher meningioma rate than non-Hispanic whites and a 1.21-fold higher rate than Asians and Pacific Islanders (Ostrom et al., 2015).

**2.5 Aetiology, Risk Factors and Prognosis**

Surgical resection, female gender, tumour size, and radiation were shown to be significant prognostic markers for benign meningioma, according to the findings of a major research that included 9000 patients. Radiotherapy, age, and resection were significant prognostic factors for malignant meningioma (Cahill & Claus, 2011).

**2.5.1 Molecular Aetiology.** To study genomic modifications in meningioma tumour genomes, Clark et al. performed whole-exome sequencing on fifty patients diagnosed with WHO grade I meningiomas. They found mutations in KLF4, SMO, NF2, AKT1 and TRAF7. This was done to examine genomic alterations in meningioma tumours (Clark et al., 2013). After the execution of whole-genome or whole-exome sequencing on 17 WHO grade I meningioma samples by Brastianos et al., validation sequencing was carried out on an additional 30 WHO grade I samples as well as 18 grade II/III samples. They discovered mutations that were comparable to those discovered by Clark et al., and they also discovered mutations in the genes AKT1, NF2, and SMO (Brastianos et al., 2013). The researchers Abedalthagafi et al. examined 150 meningiomas using array-comparative genomic hybridization, which was then followed by targeted sequencing of the genes NF2, AKT1, PIK3CA, SMO, KLF4 and TRAF7. They discovered that mutations in PI3K occur just as frequently as mutations in SMO and AKT1, and they also frequently co-occurred with mutations in TRAF7 (Abedalthagafi et al., 2016). Recent research has shown that 6%–7% of meningioma patients had mutations in the TERT gene promoter (Sahm et al., 2016).

**2.5.2 Inheritance.** In a case-control research, Claus et al. (2011) found that meningioma patients were four times more likely than controls to have a first-degree family history of meningioma. This information was gleaned from the patients' medical histories (Claus et al., 2011).

**2.5.3 Ionizing radiation.** Occupation, medical treatments (both diagnostic and therapeutic), and proximity to atomic bomb blasts are all potential avenues via which a person may be exposed to ionizing radiation (Walsh, 2020). Those who survived the atomic explosion of Hiroshima and Nagasaki are at an increased risk of developing meningioma, and this risk rises in proportion to the estimated dosage of radiation they were exposed to (Shimizu et al., 1989; Shintani et al., 1999). for doses of radiation that are in lower dose. Children in Israel who were treated with radiation therapy for scalp ringworm between the years 1948 and 1960 were found to have a higher relative risk for developing meningioma, according to one of the most well-known studies ever conducted on the relationship between ionizing radiation and the risk of meningioma (Sadetzki et al., 2002).

**2.5.4 Allergy and meningioma.** The results of a meta-analysis that Wang et al. (2011) performed on meningioma showed that eczema was associated with a 25% lower chance of developing meningioma (Wang et al., 2011). Moreover, a study carried out by Schoemaker et al., (2007). demonstrated a continuous inverse association between meningioma risk and the presence of hay fever, asthma, and eczema.

**2.5.5 Meningioma pathogenesis.** The biallelic deletion of the tumour suppressor gene neurofibromin 2 (NF2) is the genetic event that is observed the most frequently across all subtypes of meningioma. This gene is responsible for the production of the protein known as merlin, and its absence has been linked to a wide variety of cancers in the past. Some of these cancers include vestibular schwannoma and mesothelioma, as well as cancers of the kidney, breast, skin, prostate, and liver (Petrilli & Fernández-Valle, 2015). Since meningioma is linked to the genetic condition neurofibromatosis type II, NF2 loss was detected for the first time in this disease (Rouleau et al., 1987). In subsequent research, it was discovered that NF2 deletion is also a frequent occurrence in sporadic meningiomas and that it may account for as much as sixty percent of all cases (Ruttledge et al., 1994). The most common cause of these cases is a deletion, either focal or large-scale, of part or all of

chromosome 22 (which includes the NF2 gene) (Mérel et al., 1995). Meningiomas induced by NF2 loss are characterized by several distinctive clinical characteristics. It is more common for these tumours to develop in areas other than the base of the skull, such as the convexities, the posterior fosa, and the spinal cord (Kros et al., 2001). Additionally, they are more common in specific histologic variations like fibrous and transitional tumours.

**2.6 Meningioma Investigations**

Meningioma can be diagnosed based on the patient's medical history, the results of a physical exam, and radiological examinations (Buerki et al., 2018). The majority of meningiomas can be diagnosed by using standard H & E-stained sections. In some cases, however, the surprisingly broad morphologic spectrum that can be found makes diagnosis problematic, especially with some of the more uncommon or high-grade forms. Although rare and frequently poorly differentiated meningiomas may require ultrastructural or genetic studies to confirm the diagnosis, immunohistochemistry can usually resolve differential diagnose (Perry, 2018).

**2.6.1 MRI.** An MRI of the brain performed with contrast is the most effective radiological approach for diagnosing meningioma. Extra-axial lesions have a uniform enhancement, and they have a characteristic termed the dural tail. This can assist differentiate them from intra-axial lesions, which have a more diffuse enhancement. The venous sinus involvement may also be evaluated with the use of brain MRI. The cystic lesions in meningiomas, which may present a sign of an appearance similar to a mushroom, can also be found with the use of brain MRI. The invagination of the tumour in the brain parenchyma can be explained by this indication (Sotiriadis et al., 2015). Meningiomas often exhibit a hypointense lesion on T1-weighted imaging of the brain and a hyperintense lesion on T2-weighted imaging when seen on an MRI of the brain that does not include contrast. On T1 and T2 weighted images obtained from a non-contrast brain MRI, some meningiomas have the potential to appear as isointense. The CSF vascular cleft is another symptom that may be present and can be seen. It is possible to differentiate an extra-axial meningioma from an intra-axial lesion based on the presence of a cleft, which is an entrapment of cerebral cortical arteries that may be detected between the meningioma and the underlying cortex (Watts et al., 2014). It is possible that there will be calcifications as well as peritumoral brain oedema, which is often of the vasogenic kind. Oedema of the brain is a frequent complication that results

from the breakdown of the blood-brain barrier. It is responsible for the accumulation of protein-rich extracerebral fluid in the cerebral parenchyma, which ultimately results in vasogenic oedema (Hou et al., 2013). The MRI of the brain reveals the presence of oedema quite clearly as hyperintensity in T2-weighted images (B. W. Kim et al., 2011).

**2.6.2 Computerised tomography.** For individuals who are not candidates for an MRI, to visualize hyperostosis, or in situations with calcified meningiomas, a contrast-enhanced CT scan of the head may be helpful (Watts et al., 2014). The use of head CT scans is preferable for determining whether or not a tumor has calcifications and hyperostosis, as is the case with ossified meningiomas and meningioma en plaque (Baek et al., 2008).

**2.6.3 Digital subtraction angiography.** The feeding arteries of a meningioma can be seen with the help of digital subtraction angiography, often known as DSA (Papacci et al., 2015). Another radiological approach that may be utilized for surgical planning and post-operative follow-up is the positron emission tomography scan (Galldiks et al., 2017).

**2.6.4 MRI spectroscopy.** The use of MRI spectroscopy allows for the diagnosis of malignant meningiomas. It does this by contrasting the metabolic and chemical make-up of cancerous tumour tissue with that of healthy neural tissue. Through the examination of a wide variety of metabolites, MRI spectroscopy is able to evaluate the biochemical characteristics associated with the tumour. The levels of choline and creatinine in certain meningiomas are found to have increased while others have decreased (Watts et al., 2014).

**2.6.5 Genetic Karyotyping.** is a kind of genetic analysis that may be used to identify certain molecular and cytogenetic abnormalities. In certain cases of meningiomas, mutations in chromosome 22 for neurofibromatosis 2 are found, as well as the lack of a copy in chromosomes 1,10, and 14. Other genetic changes, such as those involving, AKT1, SMO, PRKAR1A, TRAF7, SUFU, KLF4, PIK3CA and POLR2A, have been documented in the scientific literature (Nowosielski et al., 2017b).

**2.7 Meningioma immunohistochemistry**

Epithelial membrane antigen (EMA) and progesterone receptor (PR) are currently the most frequently utilized IHC markers for the identification of

meningiomas, followed by CD34 for the diagnosis of SFT/HPC and S100 for the diagnosis of schwannoma. However, these indicators vary depending on the grades or subtypes of meningioma and have subpar sensitivities and specificities (Agaimy et al., 2014; Louis et al., 2016; Mezmezian et al., 2017). In recent studies, it has been demonstrated that newer markers, such as somatostatin receptor 2A (SSTR2A) for meningiomas, signal transducer and activator of transcription 6 (STAT6) for SFT/HPC, and SRYbox 10 (SOX10) for schwannomas, perform better in terms of diagnosis than traditional IHC markers (Ng et al., 2015; Schweizer et al., 2013)

**2.7.1 EMA**. The great majority of meningiomas exhibit patchy, frequently mild EMA expression and significant vimentin positivity; the latter is the most frequently used antibody for supporting a meningioma diagnosis. However, it has long been recognized that EMA lacks adequate sensitivity and specificity. Also, somatostatin receptor 2a (SSTR2a) has been described as another marker that is more sensitive and generally specific, except for neuroendocrine tumours where it exhibits strong immunoreactivity.(Menke et al., 2015).

**2.7.2 Cytokeratin.** Except for secretory meningioma, which highly produces cytokeratin in the cells surrounding the pseudo-psammoma bodies, cytokeratin is often negative or only focally positive. Alpha-1-antitrypsin, CA 19-9, immunoglobulins, CEA, and CA 19-9, which are normally negative in other kinds of meningioma, are also immunoreactive for the pseudo-psammoma bodies (Buhl et al., 2001)

**2.7.3 S-100.** The fibrous subtype is where variable S-100 protein expression is most frequently observed (Lusis et al., 2005).

**2.7.4 GFAP.** Most of the time, GFAP is negative, however, this stain can be helpful for revealing foci of brain invasion (Lusis et al., 2005).

**2.7.5 Ki67.** Progesterone receptor and Ki-67 are two additional auxiliary indicators that are very helpful for grading and prognosis. Ki-67 labelling provides extra information regarding the proliferation index for several other tumour types as well (Lanzafame et al., 2000). However, the Ki-67 labelling index is most helpful in cases that are on the boundary between benign and atypical or atypical and anaplastic meningioma; it is primarily in these circumstances that Ki-67 and PR investigations are valuable (Nakasu et al., 2001)

**2.8 tumorigenesis and epigenetic modification**

The modification of histones, most prominently through the processes of methylation and acetylation, is one of the most important epigenetic determinants of gene expression and cellular differentiation. Histone H3 modifications, those involving lysine 27 (K27), play an essential part in the development of tumours (Wei et al., 2008)

**2.9 H3K27me3 and cancers**

It has been discovered that the trimethylation of lysine 27 (K27) of histone H3 plays a crucial role in the development of tumours by altering the repair of DNA damage, more specifically the repair of double-stranded DNA breaks through homologous recombination repair. (Gehring et al., 2009; Ngollo et al., 2017; Yoo & Hennighausen, 2012). Trimethylation of H3K27 and the subsequent silencing of genes in the region is mediated by the EZH2 subunit of the Polycomb repressive complex 2 (PRC2). This subunit also contributes to chromatin compaction and is involved in a variety of biological processes, including, proliferation, stem-cell plasticity, and cell differentiation (Margueron & Reinberg, 2011).

**2.9.1 Nasopharyngeal carcinoma.** Cai et al., (2011) examined the expression of H3K27me3 protein in nonneoplastic nasopharyngeal epithelial tissues and nasopharyngeal carcinoma (NPC) tissues using the techniques of Western blotting and immunohistochemistry (IHC). High expression of H3K27me3 was found to have a favourable association with a later T classification of the tumour, tumour metastasis, advanced clinical stage, and chemoradio-resistance, according to Cai et al., (2011) research. In addition, a high expression of H3K27me3 was found to be strongly connected with an NPC patient's decreased time of survival.

**2.9.2 Hepatocellular Carcinoma.** Cai, Hou, et al., (2011) utilized immunohistochemistry analysis (IHC) to investigate protein expression of H3K27me3 in hepatocellular carcinoma tissues from two distinct cohorts as well as comparable nontumorous hepatic tissues by means of tissue microarray. High expression of H3K27me3 in HCCs was substantially connected with poor differentiation, big tumour size, advanced clinical stage, vascular invasion, and multiplicity. In addition, high levels of H3K27me3 expression in HCC patients were found to be strongly connected with a decreased likelihood of survival (Cai, Hou, et al., 2011).

**2.9.3 Urothelial carcinoma of bladder.** Liu et al., (2013) investigated the expression of H3K27me3 protein in nonneoplastic nasopharyngeal epithelial tissues

and nasopharyngeal carcinoma (NPC) tissues using the techniques of Western blotting and immunohistochemistry (IHC). A high expression of H3K27me3 was found to be linked with the presence of lymph node metastases and multifocal tumours. Patients who had a high level of H3K27me3 expression in their tumours had a shorter time to cancer-specific survival (CSS) than patients who had a low level of H3K27me3 expression in their tumours. High expression of H3K27me3 was also a predictive predictor in individuals with grade 2 and grade 3 UCB in various subsets of patients who were being treated for the disease (Liu et al., 2013).

**2.9.4 Malignant peripheral nerve sheath tumours.** Cleven et al., (2016) investigated the possibility that H3K27me3 immunohistochemistry could serve both as a diagnostic and a prognostic marker for MPNSTs. They used tissue microarrays and performed H3K27me3 immunohistochemistry on primary MPNSTs and neurofibromas. They found that MPNST had a decreased level of H3K27me3, whereas expression levels were unchanged in neurofibromas. In addition, MPNSTs that had lost their H3K27 tri-methylation had a lower survival rate when compared to MPNSTs that still had their H3K27 tri-methylation intact (Cleven et al., 2016).

**2.9.5 Breast, prostate, and Pancreatic cancers.** (Wei et al., 2008) conducted an immunohistochemical study to investigate the association between trimethylation of H3K27 (H3K27me3) and clinical characteristics as well as prognosis in breast, ovarian, and pancreatic malignancies. They discovered that the expression of H3K27me3 was much lower in cancerous breast, ovarian, and pancreatic tissues compared to expression levels in normal tissues. In univariate survival analysis, H3K27me3 expression was found to have a substantial impact on the prognosis of patients with breast, ovarian, and pancreatic malignancies. Patients who had low expression of H3K27me3 had a significantly shorter overall survival time when compared to those patients who had high expression of H3K27me3. This was the case across all three types of cancer. The expression of H3K27me3 was found to be an independent predictive value for overall survival in a model that included multiple variables for each of the three forms of cancer. Based on these findings, they hypothesize that the presence of H3K27me3 expression serves as a predictive factor for the patients' clinical outcomes when they have breast, ovarian, or pancreatic cancer (Wei et al., 2008).

## 2.10 H3K27me3 And Meningioma

Katz et al., (2018) performed an immunohistochemical analysis on 232 individuals' meningiomas to examine the levels of H3K27me3. Trimethylation was identified in the tumour cells of 194 different patients. In 25 of the cases, the staining was only found in the vessels, and all the tumour cells were negative. In the end, 13 of the cases produced inconclusive staining patterns. They discovered that a significant association existed between the absence of the staining for H3K27me3 in all tumour cells and a more rapid progression. Complete loss of H3K27me3 staining is predictive of an increased risk of recurrence in meningiomas, specifically for the group of WHO grade I/II cases. This is true even when histological grade or the degree of resection is taken into consideration. The staining pattern did not further stratify for risk-related subgroups among WHO grade III cases, even though total loss of trimethylation also happened in some of those cases. However, a metanalysis Across 7 studies carried out by (Lu et al., 2022) showed that H3K27me3 loss was recorded in 213 of 2130 patients (10%)

**2.10.1 H3k27me3 expression in the different grades of WHO.** Behling et al., (2021) evaluated the prognostic significance of H3K27 histone trimethylation as well as its potential clinical utility in the "Tubingen meningioma cohort.". from 2003 to 2015 1268 cases were chosen, 163 of them were lost to follow up, other 79 cases were excluded and 1103 remained available. The mean follow-up time was approximately 40 months. H3K27me3 expression was associated with WHO grade of the tumour, as they discovered a decrease of trimethylation in 3.1% of meningiomas of grade I, 10.4% of meningiomas of grade II, and 17.7% of meningiomas of grade III. According to the results of the univariate analysis, the lack of H3K27me3 was a significant unfavourable prognostic factor. In the multivariate model, the significance of the H3K27me3 status was maintained (Behling et al., 2021). Another study carried by Jung et al., (2021) immunohistochemically assessed the prognostic implications of expression of H3K27me3 in 115 cases of WHO grade 2 and 26 cases of WHO grade 3. Loss of H3K27me3 was associated with shorter recurrence free survival and shorter overall survival, but not with WHO grade 3 meningioma. Multivariate analysis showed the H3K27me3 was significant for recurrence free survival and overall survival (Jung et al., 2021). In WHO grade 3 meningioma Maier et al., (2022) assessed the expression of H3K27me3. They immunohistochemically evaluated the presence of H3K27me3 in 40 WHO grade 3 meningioma cases, 20 were de novo and 20 were recurrent.

According to the results of a Cox proportional hazards regression analysis, the expression of H3K27me3 did not have a significant impact on overall survival (Maier et al., 2022). However, a study carried out by Gauchotte et al., (2020) in 66 cases of WHO grade 3 meningiomas showed that H3K27me3 loss was associated with shorter overall survival.

**2.10.2 H3K27me3 and extent of resection.** (Jung et al., 2021) found out that approximately 32% of gross total resection cases of meningioma showed H3K27me3 loss of expression, while loss of H3K27me3 was 36.1% in cases of subtotal resection. However, Katz et al., (2018) found out that H3K27me3 was lost in 12.4% of total resection cases and 6.5% of subtotal resection cases of meningioma.

**2.10.3 H3K27me3 expression among different histologic subtypes.** In the Tubingen meningioma cohort study (Behling et al., 2021) found variations of the H3K27me3 expression across the various histological subtypes. Anaplastic (16.7%) and rhabdoid (20%) meningiomas were shown to have the highest rate of trimethylation loss, followed by atypical (9.9%) and chordoid (14.3%) meningiomas in order of decreasing rate. In H3K27me3 was lost in 6.3% Fibroblastic cases their, 3.1% of meningothelial subtype cases and 4.3% of Psammomatous cases. There were no cases found of H3K27me3 loss in secretory meningiomas, metaplastic meningiomas, microcystic meningiomas, or angiomatous meningiomas. However, (Katz et al., 2018) found H3K27me3 loss highest in anaplastic subtype (30%), followed by atypical (13.4%), followed by chordoid and transitional respectively (12.5% and 10%). There were no cases found of H3K27me3 loss in secretory meningiomas, metaplastic meningiomas, lymphoplasmacyte-rich meningioma, psammomatous meningioma, fibrous meningioma, microcystic meningiomas, or angiomatous meningiomas.

**2.10.4 Localisation.** (Behling et al., 2021) discovered that in spinal meningiomas, H3K27me3 was lost in 0.8% of cases, but it was lost in 3.7% of cases in skull base tumours and 7.2% of cases in convexity/falx tumours.

**2.10.5 History of meningioma.** H3K27me3 loss is higher in recurrent cases of meningioma than de novo cases of meningioma. (Nassiri et al., 2021) Found H3K27me3 loss in 8.8% cases of de novo meningioma, while recurrent cases showed loss of H3K27me3 in 19.4% of the cases. While in Tubingen cohort study the loss of H3K27me3 was in 4% of the de novo cases and 11% of the recurrent cases. (Behling

et al., 2021). A study on H3K27me3 expression in grade 2 and grade 3 meningiomas showed almost no difference in H3K27me3 loss between de novo and recurrent cases of meningiomas (34% and 34.3 respectively) (Jung et al., 2021).

**2.10.6 Adjuvant therapy.** In a study in type 2 and 3 meningiomas carried out by Jung et al., (2021) it was shown that cases who received adjuvant therapy had a higher loss of H3K27me3 than cases who did not receive adjuvant therapy. Behling et al., (2021) also found similar findings.

**2.10.7 H3K27me3 expression in genders.** H3K27me3 loss is usually higher in males than females. Nassiri et al., (2021) found 18.3% loss among male cases while the loss was 11% among female cases. Behling et al., (2021) detected loss of H3K27me3 in 3.6% of female cases and 7.7% in male cases. Katz et al., (2018) detected loss of H3K27me3 among 11% of female cases, while the loss was 13.7% in male cases.

**2.10.8 H3K27me3 and prognosis.** Nassiri et al., (2021) discovered that a decrease of H3K27me3 predicted a worse prognosis with shorter durations to recurrence in their cohort, particularly for WHO grade 2 tumours which were enriched in their analysis. This was particularly true for the WHO grade 2 tumours. There was no difference in recurrence-free survival (RFS) between patients with retained H3K27me3 and those who had lost it for WHO grade 3 patients. After controlling for factors such as WHO grade, degree of resection, sex, age, and the recurrence status of the tumour, the researchers found that loss of H3K27me3 was not independently linked with Recurrence free survival. This was the conclusion they reached after doing a multivariable Cox regression analysis (Nassiri et al., 2021). During the univariate analysis done by Behling et al., (2021) the loss of H3K27me3 was found to be a significant negative prognostic factor for recurrence. In the multivariate model, the significance of the H3K27me3 status was maintained.

### 2.11 Meningioma Treatment

**2.11.1 Wait and see.** Magnetic Resonance Imaging (MRI) scans can be utilized to monitor and track small, asymptomatic meningiomas. The strategy can be used with elderly patients, individuals with serious problems, and patients with poor physical health (Deimling, n.d.).

**2.11.2 Surgery.** The main option for treatment for symptomatic meningiomas is surgical resection. The operation's aims are to relieve tumour-related symptoms and

enhance the quality of life (Saraf et al., 2011). When a patient's tumour has an apparent mass effect and elevated intracranial pressure, the tumour should be surgically removed. The factors that influence the surgical strategy are Benefits of surgery, dangers of surgery, biological properties of the tumour, clinical manifestations of the tumour mass, and patient preferences. Based on the patient's overall health, tumour location, age, tumour size, and symptoms, surgical risks were evaluated (Fathi & Roelcke, 2013). Meningiomas located in surgically difficult locations, such as the skull base, are more likely to only require subtotal resection. This is because the extent of resection is strongly correlated with tumour location (Perry, 2018).

**2.11.3 Radiation therapy.** Patients who have been diagnosed with WHO grade II or grade III meningioma, patients who have undergone partial resection, patients who have missed the opportunity for surgery for a variety of reasons, or patients who have a recurrence and are not candidates for resection, are all candidates for radiation therapy (Rockhill et al., 2007).

**2.11.4 Gamma knife.** Gamma Knife is useful in the case of small to medium-sized meningiomas that are found in sensitive or important parts of the brain, like the brainstem or optic nerve, where surgical removal would be challenging and dangerous (Kondziolka et al., 2008). for patients who are not good candidates for traditional surgery due to age, medical condition, or other factors. Studies have shown that Gamma Knife surgery can be a safe and effective treatment option for these patients (Shrieve et al., 1995). Gamma Knife surgery is a safe and effective treatment option for patients with recurrent or residual meningiomas (M. Kim et al., 2020). In a retrospective analysis that offered a 10-year follow-up and was one of the longest radiosurgically treated meningioma follow-up studies ever conducted. Lippitz et al.,(2020) found that after Gamma Knife treatment, there was a continually high level of local tumour control and a persistently low risk for adverse effects.

**2.11.5 Chemotherapy.** When surgical and radiotherapy options have been utilized, as in the case of recurrent or progressive meningiomas, drug therapy is the only option left. Non-benign meningiomas can be treated with a range of molecularly targeted medications as well as chemotherapeutic medicines. There is no consistently successful medicine found in different clinical investigations, even though several agents have demonstrated efficacy in preclinical research and some clinical uses (Nazem et al., 2020).

# Chapter 3

# Methodology

## 3.1 Research design

This study is a retrospective cohort study, and a blinded study since the raters were unaware of the specific clinical characteristics of the cases. To evaluate the expression of H3K27me3 expression loss in 112 cases of meningiomas, to evaluate the H3K27me3 expression a 4-teir scoring system was adopted, from 0 to 3 to cases where 0 was complete loss of expression, 1 was loss of more than 50%, 2 was retainment of more than 50% and 3 was total retainment of H3k27 trimethylation. The final rating of H3K27me3 expression was then compared between the different groups such as different localisations, histologic subtypes, the correlation between H3K27me3 and prognosis was also assessed.

**3.2 Target population and participants** Patients diagnosed with Meningioma and treated at Goztepe Medical Park hospital.

**3.2.1 Place of the study.** Bahcesehir University Pathology Lab.

**3.2.2 Recruitment of the cases.** Cases were recruited from the archive of Bahcesehir University Medical Park Hospital.

**3.2.3 Time of the study.** From January 2015 to December 2022

**3.2.4 Inclusion criteria:** cases diagnosed with Meningioma that are confirmed by MRI and Biopsy and who received treatment.

**3.2.5 Exclusion criteria.** Patients diagnosed with meningioma without MRI and Biopsy confirmations, or patients who did not receive treatment for the tumour.

**3.2.6 Sampling:**

***3.2.6.1 Sampling technique.*** Simple random sampling.

***3.2.6.2 Sample size:*** 112 biopsies from 111 patients.

**3.3 Data collection:**

**3.3.1 Data collection tools:**

Table 1.

*Collection tools used in the study*

| Collection tool | Brand and/or model |
|---|---|
| Tissue processing machine | Leica TP 1020 |
| Embedding machine | Leica EG 1150 H |

Table 1 (Cont.d)

*Collection tools used in the study*

| | |
|---|---|
| Microtome | SLEE type 5062 |
| Autoclave | Nuve |
| Microscope | Leica dm500 |
| Pre-treatment link machine | DAKO |
| Humidity chamber | Unknown brand |

Table 2.

*Substances used in the study*

| Substance | Brand and/or model |
|---|---|
| H&E | EnVision™ FLEX Hematoxylin |
| Wash buffer | EnVision™ FLEX Wash Buffer |
| Target retrieval solution | EnVision™ FLEX Target Retrieval Solution |
| Peroxidase-Blocking Reagent | EnVision™ FLEX Peroxidase-Blocking Reagent |
| Antibody H3K27Me3 | (MD48R) COMPANY: Medaysis RM0115 Rabbit dilution |
| HRP | EnVision™ FLEX /HRP |
| DAB+ Chromogen solution | EnVision™ FLEX DAB + Chromogen solution |
| Xylene | Unknown |
| Alcohol | Unknown |

### 3.3.2 Data collection procedure:

***3.3.2.1 preparing the slides and H3K27me3***. The tissues came in 10% formaldehyde were put in the tissue processing device and embedded in paraffin. Then the Tissues were made into paraffin blocks by embedding machine, were first cut in 3-micron thick sections on the microtome then deparaffinised using an autoclave in 70 degrees for 45 minutes then fixed with xylene and alcohol for ten minutes three times then washed with tap water then H&E stained. The prepared sections were examined under a microscope to confirm existence of tumour cells. For the

immunohistochemical staining determined later, a 3 micro-thick section is taken in the microtome again to prepare them for Immunohistochemistry. deparaffinised and dehydrated sections are taken into distilled water. Wash Buffer in concentration 1/20 was used to wash the slides are washed twice. Target Retrieval Solution was used as the pre-enzyme treatment in the study. Using a Pre-treatment link, we prepared Target Retrieval Solution with distal water in a tank and put the slide in the tank boiling it starting from 65 degrees up to 95 degrees for 20 minutes and then cooled it to 65 degrees again. The slides were washed twice again using a wash buffer. Then Peroxidase-Blocking Reagent was applied at room temperature for 5 minutes. Then the slides were washed again using a wash buffer. Then our antibody H3K27me3 was applied to the slides for an incubation period in a concertation of 1/30 for 45 minutes in a humidity chamber. The slides were washed twice again using a wash buffer. Horseradish peroxidase (HRP) was then applied for 20 minutes. Using a wash buffer the slides were again twice. Then DAB and Chromogen solution was applied for 10 minutes at room temperature. The slides were washed again twice with a wash buffer. Haematoxylin was then applied for counterstaining. The slides were then covered with mounting media and stuck with a coverslip on it. After that the slides were ready to be viewed by the raters by a microscope.

***3.3.2.2 rating the score of H3K27me3 expression***. The raters were separately asked to evaluate the expression of H3K27me3 expression loss in 112 cases of meningiomas, they were requested to give a score from 0 to 3 to cases where 0 was complete loss of expression, 1 was loss of more than 50%, 2 was retainment of more than 50% and 3 was total retainment of H3k27 trimethylation. After each rater evaluated the expression separately their scores were compared and they were requested to reevaluate the cases they disagreed on separately again, after that they were requested to discuss the remaining disagreed cases together and agree on a final rating.

**3.3.3 Data analysis procedure.** To measure the Interrater reliability Cohen's kappa coefficient was used. To compare categorial factors and the significance of difference between groups chi square test was used. When cases are normally distributed student's T-test was used for comparing quantitative parameters between groups and for determining the significance of variance between groups Levene's test was used. To test the distribution of cases in quantitative parameters Kolmogorov-

Smirnova was used. When cases were not normally distributed in the quantitative parameters Mann-Whitney U test was used. Kaplan–Meier estimates and log-rank test were used to estimate and compare distribution of Recurrence free survival between groups. P values are considered statistically significant when less than (0.05). All data were analysed using the 25$^{th}$ version of Statistical Package for Social Sciences (SPSS) by IBM.

**3.3.4 Validity and reliability.** An inter-rater reliability analysis was performed between the dependent samples of Rater 2 and Rater 1. For this purpose, the Cohens Kappa was calculated, which is a measure of the agreement between two dependent categorical samples.

### 3.4 Limitations

Sample size seems relatively not large enough, otherwise no remarkable obstacles or limitations were faced throughout the study.

# Chapter 4
# Findings

## 4.1 Characteristics of the study group.

**4.1.1 Sex.** There were 112 cases of meningiomas; 77 (68.8%) of those cases occurred in females, and 35 (31%) occurred in males. (See table 3)

**4.1.2 Grade.** As seen in (table 3) WHO grade 1 meningioma was the most common in this study accounting for 71.4% (80) while WHO Grade 2 and 3 together accounted for 29.6% of the cases where the first contributed for 20.5% (23 cases) and the later contributed for the remaining 8% (9cases).

**4.1.3 Histological subtype.** Table 3 demonstrates the distribution of meningioma among the different histological subtypes. Meningothelial subtype alone presented more than two thirds of the cases accounting for 70.5% of the cases (79 case), Transitional subtype came second with 10 cases (8.9%), followed by Anaplastic and Secretory accounting for 7.1% and 3.6% respectively. While Rhabdoid and Fibrous subtypes presented 1.8% of the cases each. Finally, Lymphoplasmactye-rich, Psammomatous, Angiomatous, Microcystic, Meningothelial-microcystic meningioma, Metaplastic and Chordoid subtypes presented only one case for each one of them (see table 1).

**4.1.4 Location.** The most common localisation for meningioma in this study was in the convexity, accounting for 45 cases (40.2%), Parasellar and sellar and spinal were the second and third most common locations accounting for 17% (19) and 11.6% (13) respectively. 7 cases were reported to be in Cerebellopontine angle and same in the sphenoid wing. 5 tumours were located in the olfactory groove, 4 were in the Parafacine and Falx, 3 in the cavernous sinus,2 in the parasagittal and also 2 in the Petrous face.1 case was located in the cerebellar area and the same was for the posterior fossa and tentorium area, foramen magnum, intraventricular area, and optic nerve sheath. (See table 3). However, there is a broader classification which classifies meningiomas into three classes: Intracranial, Skull-base, and spinal. In our study the Intracranial cases were 74 (66.1%), The skull base cases were 24 (21.4%) and the Spinal were 14 (12.5%), Figure (1) illustrates the percentages of the locations in the study.

**4.1.5 History of meningioma.** Approximately two thirds (67%) of the cases were de novo (75 cases) while 37 cases were recurrent (33%).

**4.1.6 Type of surgery.** 53.6% of the cases were treated with surgery alone, where 46.4 of the meningioma cases were treated with surgery and Gamma knife surgery.

**4.1.7 Extent of resection.** Most of the tumours were resected totally accounted for 82.1% while 17.9% were resected sub-totally.

**4.1.8 Adjuvant therapy.** 95.5% of the cases did not receive neither Radiotherapy nor chemotherapy (107 case), however 4 cases received only radiology and one case received both radiotherapy and chemotherapy and no case received only chemotherapy without radiotherapy.

**4.1.9 Recurrence.** Among 112 cases, recurrence occurred in 30.4% of them, however 69.6% of the cases did not reoccur again.

**4.1.10 H3K27me3 expression.** All the 112 cases of meningiomas retained H3K27me3 but in different rates, 38,4 of the cases completely retained the expression of H3K27me3 and they were rated as 3, 58% of the cases retained more than 50% of H3K27me3 expression as they were rated as 2, only 4 cases (3.6%) retained less than 50% of H3K27me3 and they were rated as 1, and no case showed total loss of H3K27me3.

Table. 3

*Characteristics of the study group*

| | Study group | |
|---|---|---|
| Characteristic | N | % |
| Sex | | |
| Female | 77 | 68.75 |
| Male | 35 | 31.25 |
| Grade | | |
| 1 | 80 | 71.43 |
| 2 | 23 | 20.54 |
| 3 | 9 | 8.04 |
| Histological subtype | | |
| Meningothelial | 79 | 70.54 |
| Transitional | 10 | 8.93 |

Table 3. (Cont.d)

| | | |
|---|---|---|
| Anaplastic | 8 | 7.14 |
| Secretory | 4 | 3.57 |
| Fibrous | 2 | 1.79 |
| Chordoid | 2 | 1.79 |
| Psammomatous | 1 | 0.89 |
| lymphoplasmacyte-rich | 1 | 0.89 |
| Metaplastic | 1 | 0.89 |
| Angiomatous | 1 | 0.89 |
| Microcystic | 1 | 0.89 |
| meningothelial + microcystic | 1 | 0.89 |
| Rhabdoid | 1 | 0.89 |
| Localisation | | |
| Convexity | 45 | 40.18 |
| parasellar and sellar | 19 | 16.96 |
| Spinal | 13 | 11.61 |
| cerebellopontine angle | 7 | 6.25 |
| sphenoid wing | 7 | 6.25 |
| olfactory groove | 5 | 4.46 |
| parafalcine and falx | 4 | 3.57 |
| cavernous sinus | 3 | 2.68 |
| Parasagittal | 2 | 1.79 |
| petrous face | 2 | 1.79 |
| posterior fossa and tentorium | 1 | 0.89 |
| foramen magnum | 1 | 0.89 |
| optic nerve sheath and chiasm | 1 | 0.89 |
| Cerebellar | 1 | 0.89 |
| Intraventricular | 1 | 0.89 |

Table 3. (Cont.d)

| | | |
|---|---|---|
| De novo or recurrent | | |
| De novo | 75 | 67,0 |
| Recurrent | 37 | 33,0 |
| Type of surgery | | |
| Open surgery | 60 | 53,6 |
| Open surgery and Gamma knife surgery | 52 | 46,4 |
| Extent of resection | | |
| Gross-total | 92 | 82,1 |
| Subtotal | 20 | 17,9 |
| Adjuvant therapy | | |
| NO adjuvant therapy | 107 | 95,5 |
| Radiotherapy | 4 | 3,6 |
| Radiotherapy and chemotherapy | 1 | ,9 |
| Recurrence | | |
| Yes | 34 | 30,4 |
| No | 78 | 69,6 |
| H3K27me3 | | |
| 1 | 4 | 3,6 |
| 2 | 65 | 58,0 |
| 3 | 43 | 38,4 |

Note. The percentages are within recurrence except H3K27me3 expression

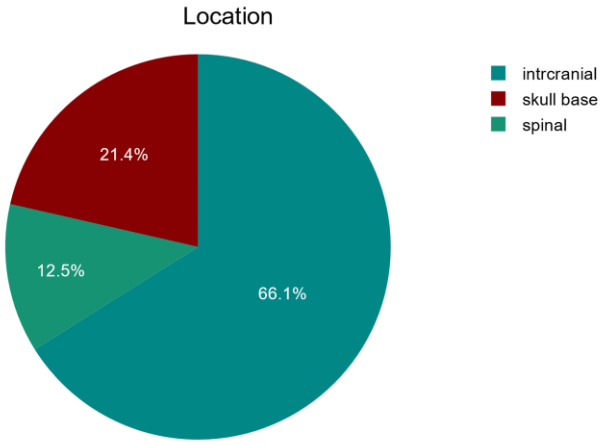



*Figure 1 Locations of meningioma.*

**4.2 Recurrence in different groups of the study**

Table 2 shows the rates of recurrence in different groups in the study, Chi square was used to determine the significance of the results, P value was considered significant when less than (.05).

**4.2.1 Recurrence and sex.** female cases accounted for 58% of recurrences (57%) while 41% of recurrences happened in males. While absence of recurrence was 68.8% in females and 31.1% in males. The relation between recurrence was insignificant as P value was .135 in a Chi square test.

**4.2.2 Recurrence in different Grades.** Recurrence occurred the most in Grade 1, Grade 1 accounted for 47.1 of the recurrences, followed by Grade 2 and Grade 3 accounting for 32.1 and 20.6% respectively. Absence of recurrence was the lowest in Grade 3 accounting for only 2.6%, while Grade 2 and 1 accounted for 15.4% and 82.1 respectively. However, in WHO Grade 1 the recurrence incidence was only 20%, in WHO Grade 2 was 47.8% and in WHO grade 3 was 77.8%. Chi square test was used to test the relation between Recurrence and WHO grades, the relation was significant as P Value was estimated to be (.000).

**4.2.3 Recurrence in different histological subtype.** 58.8% of recurrences occurred in meningothelial subtype, the second highest was Anaplastic subtype accounting for 17.6% of recurrences. Followed by Rhabdoid with 5.9% of recurrences. However Fibrous, secretory, angiomatous, transitional and chordoid presented with one recurrence for each one of them. While the remaining subtypes did not suffer from any recurrence. Absence of recurrence was highest in meningothelial accounting for

76.6% followed by transitional, Secretory and Anaplastic presenting for 11.5%, 3.8% and 2.6% of having no recurrences respectively.

**4.2.4 Recurrence in different Location.** 58.8% of the recurrences occurred in the convexity, followed by the sphenoid wing which accounted for 8.8% of the cases, however recurrences occurred in two cases located parasellar and sellar and the same in parasagittal and Parafacine and falx. There was only one incidence of recurrence in posterior fosa and tentorium, and the same in olfactory groove, spinal, cerebellar, cerebellopontine angle areas, no recurrences occurred in the remaining areas. Chi square was used to test significant and P value was found to be (.26), See table (4).

**4.2.5 Recurrence and history of meningioma.** Table (4) demonstrates the incidence of recurrence in de novo and recurrent meningiomas. The incidence of recurrence was profoundly more common in recurrent type of tumours accounting of 94.1% of all incidences of recurrence, however only 5.9% of recurrences occurred in the de novo type of meningioma. Chi square was used to test the relation between recurrence and history meningioma, there was a significance as P value was .000 and Null hypothesis was rejected.

**4.2.6 Recurrence in open surgery and Gamma knife surgery.** Table (4) shows the incidence of total recurrences in tumours treated with surgery and Gamma knife together and tumours treated with Gamma knife surgery. Incidence mostly happened in tumours treated with both surgery and Gamma knife accounting for 82.4% of total recurrences, while only 17.6% of recurrences occurred in the tumours treated with open surgery. Absence of recurrence was more common in cases treated with surgery accounting for 69.2% comparing cases treated with surgery and Gamma knife surgery which accounted for the remaining 30.8%. Chi square test showed that the results are highly significant as P value was as low as (.000).

**4.2.7 Recurrence and extent of resection.** Tumours resected totally presented 85.3% of total cases of recurrence, where tumours treated with subtotal resection presented 14.7% of total cases of recurrences, absence of recurrence was reported more in cases resected totally accounting for 80.8 of total cases of no recurrences, while 19.2% of cases that did not suffer from recurrence were treated with subtotal resection. Using Chi square to test significance of the previous findings, it is thought to be insufficient as P value was as high as (.565).

**4.2.8 Recurrence and adjuvant therapy.** Cases treated with no radiotherapy or chemotherapy presented 88.2 of total incidence of recurrence, while cases treated with radiotherapy and cases treated with radiotherapy and chemotherapy presented 8.8%, 2.2% (one case) of total incidence of recurrence respectively. However, having no recurrence was mostly in cases treated with no adjuvant therapy accounting for 98.7%, while cases treated with radiotherapy accounted for 1.3%. Chi square test showed that the findings aren't significant as P value was (.42).

**4.2.9 Recurrence and H3K27me3 expression.** Table (4) demonstrates the incidence of recurrence among the meningioma tumours with different rates of H3K27me3 expression, the incidence of recurrence was 25% with cases losing more than 50% of H3K27me3 expression, while 29.2% of cases expressing more than 50 % of H3K27me3 suffered from recurrence and 70.8% did not have recurrence, however 32.6% of cases with complete retainment of H3K27me3 expression suffered from recurrence while 67.4% did not have recurrence. Chi square value showed no significance as P value was as high as (.909).

Table 4

*Recurrence and characteristics of the study group.*

| | **Recurrence** | | | | |
|---|---|---|---|---|---|
| Characteristic | Yes | | No | | **P** |
| | N | % | N | % | |
| Sex | | | | | |
| Female | 57 | 58,8% | 77 | 68,8% | .135 |
| Male | 21 | 41,2% | 35 | 31,3% | |
| Histological subtype | | | | | |
| Microcystic | 1 | 2,9% | 0 | 0% | |
| meningothelial + microcystic | 0 | 0% | 1 | 1.3% | |
| Metaplastic | 0 | 0% | 1 | 1.3% | |
| Chordoid | 1 | 2.9% | 0 | 0% | |
| Meningothelial | 20 | 58.8% | 59 | 76.6% | |
| Transitional | 1 | 2.9% | 9 | 11.5% | .20 |

Table 4. (Cont.d)

| | | | | | |
|---|---|---|---|---|---|
| lymphoplasmacyte-rich | 0 | 0% | 1 | 1.3% | |
| Psammomatous | 0 | 0 | 1 | 1.3 | |
| Fibrous | 1 | 2.9 | 1 | 1.3 | |
| Angiomatous | 1 | 2.9 | 0 | 0 | |
| Secretory | 1 | 2.9 | 3 | 3.8 | |
| Rhabdoid | 2 | 5.9 | 0 | 0 | |
| Anaplastic | 6 | 17.6 | 2 | 2.6 | |
| Location | | | | | |
| Convexity | 20 | 58.8 | 25 | 32.1 | |
| Spinal | 1 | 2.9 | 12 | 15.4 | |
| parasellar and sellar | 2 | 5.9 | 17 | 21.8 | |
| cerebellopontine angle | 1 | 2.9 | 6 | 7.7 | |
| Parasagittal | 2 | 5.9 | 0 | 0 | .26 |
| sphenoid wing | 3 | 8.8 | 4 | 5.1 | |
| olfactory groove | 1 | 2.9 | 4 | 5.1 | |
| parafalcine and falx | 2 | 5.9 | 2 | 2.6 | |
| petrous face | 0 | 0 | 2 | 2.6 | |
| posterior fossa and tentorium | 1 | 2.9 | 0 | 0 | |
| foramen magnum | 0 | 0 | 1 | 1.3 | |
| cavernous sinus | 0 | 0 | 3 | 3.8 | |
| Intraventricular | 0 | 0 | 1 | 1.3 | |
| optic nerve sheath and chiasm | 0 | 0 | 1 | 1.3 | |
| Cerebellar | 1 | 2.9 | 0 | 0 | |

| | | | | | |
|---|---|---|---|---|---|
| optic nerve sheath and chiasm | 0 | 0 | 1 | 1.3 | |
| History of meningioma | | | | | |
| De novo | 2 | 5.9 | 73 | 93.6 | **.000** |
| Recurrent | 32 | 94.1 | 5 | 6.4 | |
| Type of surgery | | | | | |
| Open | 6 | 17.6 | 54 | 69.2 | **.000** |
| Open + Gamma knife | 28 | 82.4 | 24 | 30.8 | |
| Type of resection | | | | | |
| Gross total | 29 | 85.3 | 63 | 80.8 | .565 |
| Subtotal | 5 | 14.7 | 15 | 19.2 | |
| Adjuvant therapy | | | | | |
| No | 30 | 88.2 | 77 | 98.7 | |
| Radiotherapy | 3 | 8.8 | 1 | 1.3 | |
| Radiotherapy and chemotherapy | 1 | 2.9 | 0 | 0 | .42 |
| Chemotherapy | 0 | 0 | 0 | 0 | |
| Grade | | | | | |
| 1 | 16 | 47.1 | 64 | 82.1 | |
| 2 | 11 | 32.4 | 12 | 15.4 | .000 |
| 3 | 7 | 20.6 | 2 | 2.6 | |
| H3K27me3 expression | | | | | |
| 1 | 1 | 25 | 3 | 75 | |
| 2 | 19 | 29.2 | 46 | 70.8 | .909 |
| 3 | 14 | 32.6 | 29 | 67.4 | |

*Note. Chi square test was used to test significance, P value less than .05 is considered significant. The percentage is within recurrence except for* H3K27me3 *expression the percentage is withing* H3K27me3 *different grades.*

### 4.3 H3K27me3 expression in different grades of meningiomas

(Table 5) demonstrates the H3K27me3 expression among the different WHO grades of meningioma. 41.3% of WHO grade 1 meningioma cases retained H3K27me3 expression completely, while 56.3% retained more than 50% of the expression and only 2.5% retained less than 50% of the expression. However, WHO grade 2 meningioma cases retained expression completely in 39.1% of the cases and retained more than 50% of the expression in 52.2% of the cases and retained less than 50% of the expression in 8.7% of the cases. While in WHO grade 3 meningioma cases 88.9% of the cases retained more than 50% of the expression of H3K27me3, while the remaining 11.1% showed full retainment of expression of H3K27me3, no case of Grade 3 showed retainment of expression of H3K27me3 of less than 50%.

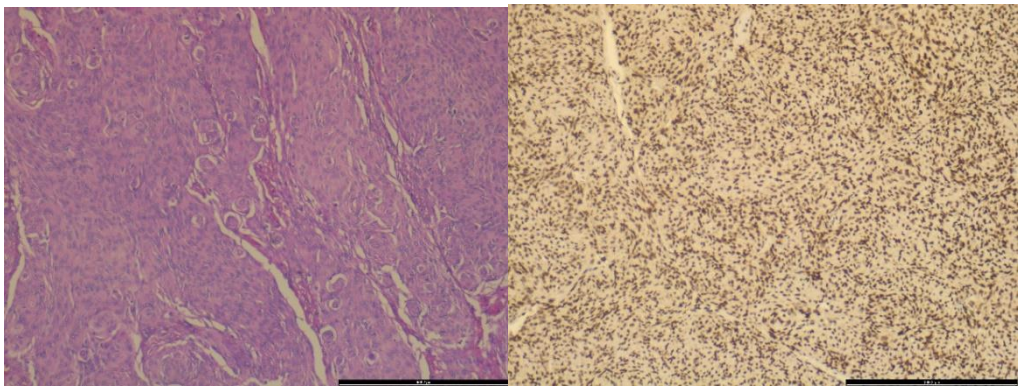
Table 5

*H3K27me3 expression in different WHO grades of meningiomas*

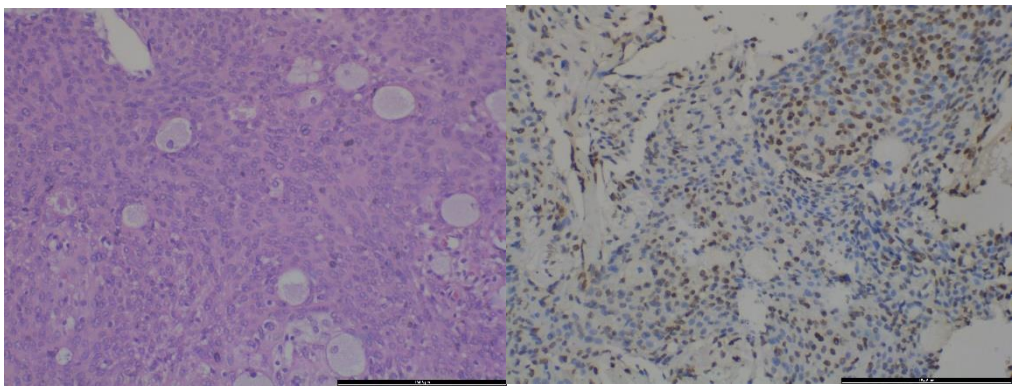
| | H3K27me3 expression | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | P |
| WHO Grade | *N* | % | *N* | % | *N* | % | |
| 1 | 2 | 2.5 | 45 | 56.3 | 33 | 41.3 | .211 |
| 2 | 2 | 8.7 | 12 | 52.2 | 9 | 39.1 | |
| 3 | 0 | 0 | 8 | 88.9 | 1 | 11.1 | |

*Chi Square was used to test significance, P value is considered significant when less than (.05). the percentages are within grades*

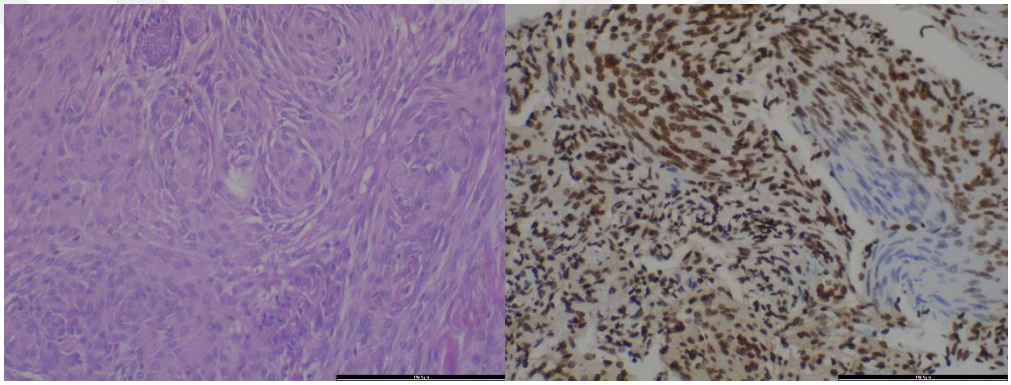
**A** **B**



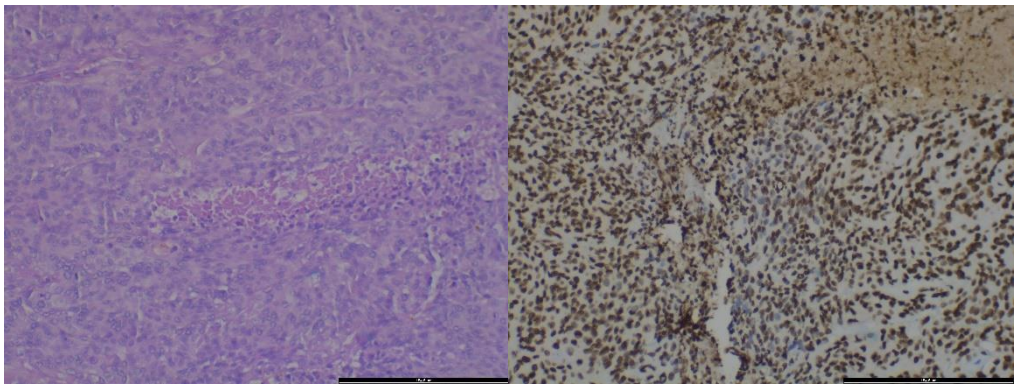
**C** **D**



**E** **F**



**G** **H**



**I** **J**

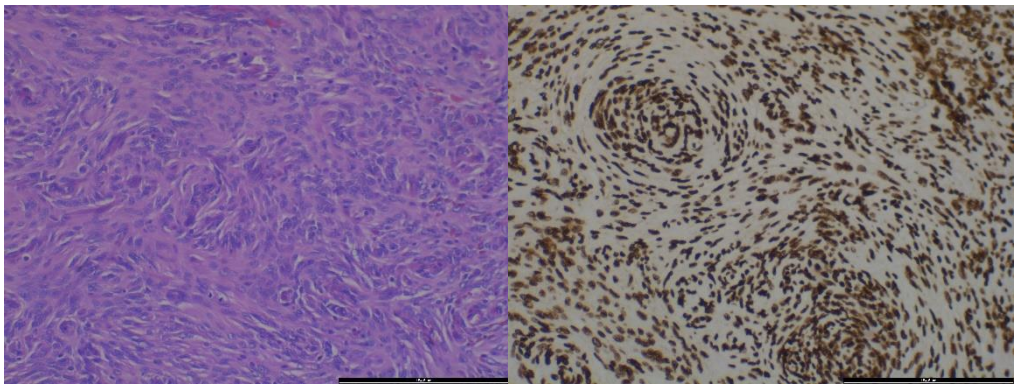


*Figure 2 H3K27me3 expression in different grades. (A) Grade 1 meningioma with H+E staining, (B) shows Grade 1 meningioma with score 3 of H3K27me3 expression (x10 magnification). (C) Grade 2 meningioma with H+E staining, (D) Grade 1 meningioma with score 1 of H3K27me3 expression (x20 magnification). (E) Grade 1 meningioma with H+E staining, (F) Grade 1 meningioma with score 2 of H3K27me3 expression (x20 magnification). (G) Grade 3 anaplastic meningioma with H+E staining. (H) Grade 3 meningioma with score 2 of H3K27me3 expression (x20 magnification). (I) Grade 2 meningioma with H+E staining. (J) Grade 2 meningioma with score of 3 of H3K27meh expression.*

### 4.4 H3K27me3 expression in different localisations

Table (6) demonstrates the expression of H3K27me3 in different localisations, Tumours located in the convexity, showed complete retainment of H3K27me3 (rated 3) in 44.44% of the cases, more than 50% (rated 2) in 53.33% of the cases and less than 50% (rated 1) only in one case. In Spinal Meningioma cases, 69.23% of the cases retained more than 50% of H3K27me3 while 30.77% showed complete retainment, no case showed less than 50% of retainment. In parasellar amd Sellar meningioma cases, 57.89% of the cases retained more than 50% of H3k2meh while 30.77% of the cases showed complete retainment and only two cases showed less than 50% expression of H3K27me3. In cerebellopontine angle cases, 4 cases retained more than 50% of H3K27me3 while one cases retained less than H3K27me3 and another one case showed complete retainment of H3K27me3. There were two cases of Parasagittal meningioma, one case showed complete retainment of H3K27me3 and the other showed retainment of 50%. In sphenoid wing meningioma, 57.14% of the cases showed complete retainment while 42.86 showed more than 50% of retainment.

Meningiomas located in the olfactory groove showed complete retainment of H3K27me3 in 60% of the cases and retainment of more 50% in 40% of the cases. Parafalcine and Falx meningioma, 25% of the cases showed complete retainment and 75% of the cases showed retainment of more than 50%. In Petrous face meningioma there were two cases, one case showed complete retainment and the other showed retainment of more than 50%. In Posterior fosa and tentorium, foramen magnum, Intraventricular and optic sheath there was only one case in each location and all of them showed retainment of more than 50%. There was only one case of Cerebellar meningioma it showed complete retainment of H3K27me3. In Cavernous sinus meningioma there were 3 cases only and all of them showed retainment of more than 50% of H3K27me3 expression. A $Chi^2$ test was performed between Location and H3K27me3 expression. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the $Chi^2$ test were not met. There was no statistically significant relationship between Location and H3K27me3 expression, The calculated p-value of .953 is above than the defined significance level of 5%. The $Chi^2$ test is therefore not significant, and the null hypothesis is not rejected. However, when H3K27me3 expression was compared between three localisations, Intracranial, skull-Base and Spinal. 54.05% of intracranial cases retained more than 50% of H3K27me3, 41.89% showed complete retainment and approximately 4% showed loss of more than 50%. In Spinal meningioma 74.43% showed retainment of more than 50%, 28.75% showed complete retainment of H3k27 trimethylation and no case showed loss of more than 50%. In skull-Based meningiomas, 62.5% retained more than 50% of H3K27me3, 33.33% showed total retainment and 4.17% showed retainment of less than 50%. See table (7). A $Chi^2$ test was performed between Location and H3K27me3 expression. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the $Chi^2$ test were not met. There was no statistically significant relationship between Location and H3K27me3 expression, The calculated p-value of .729 is above than the defined significance level of 5%. The $Chi^2$ test is therefore not significant, and the null hypothesis is not rejected.

Table 6.

*H3K27me3 expression in different localisations.*

| | H3K27me3 expression |
|---|---|

| | 1 | | 2 | | 3 | | |
|---|---|---|---|---|---|---|---|
| Location | N | % | N | % | N | % | P value |
| Convexity | 1 | 2.22% | 24 | 53.33% | 20 | 44.44% | .953 |
| Spinal | 0 | 0% | 9 | 69.23% | 4 | 30.77% | |
| parasellar and sellar | 2 | 10.53% | 11 | 57.89% | 6 | 31.58% | |
| cerebellopontine angle | 1 | 14.29% | 4 | 57.14% | 2 | 28.57% | |
| Parasagittal | 0 | 0% | 1 | 50% | 1 | 50% | |
| sphenoid wing | 0 | 0% | 3 | 42.86% | 4 | 57.14% | |
| olfactory groove | 0 | 0% | 2 | 40% | 3 | 60% | |
| parafalcine and falx | 0 | 0% | 3 | 75% | 1 | 25% | |
| petrous face | 0 | 0% | 1 | 50% | 1 | 50% | |
| posterior fossa and tentorium | 0 | 0% | 1 | 100% | 0 | 0% | |
| foramen magnum | 0 | 0% | 1 | 100% | 0 | 0% | |
| cavernous sinus | 0 | 0% | 3 | 100% | 0 | 0% | |
| optic nerve sheath and chiasm | 0 | 0% | 1 | 100% | 0 | 0% | |
| Cerebellar | 0 | 0% | 0 | 0% | 1 | 100% | |
| Intraventricular | 0 | 0% | 1 | 100% | 0 | 0% | |

Note. Chi square was used, P value is considered significant when it is less than (.05)

Table 7.

*H2k27me3 expression in Intracranial, spinal, and skull-base meningiomas.*

| | H3K27me3 | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | |
| Location | N | % | N | % | N | % | P |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Spinal | 0 | 0 | 10 | 71.43 | 4 | 28.57 | .729 |
| Intracranial | 3 | 4.05 | 40 | 54.05 | 31 | 41.89 | |
| Skull-base | 1 | 4.17 | 15 | 62.5 | 8 | 33.33 | |

Note. Chi square test was used to test relation, relation is considered significant when P value is less than .05.

**4.5 H3K27me3 expression in different histologic subtypes.**

Table (8) demonstrates the expression of H3K27me3 in different histologic subtypes. In cases of meningothelial subtype, 56.96% of cases showed retainment of more than 50% (rated 2) of H3K27me3, while 37.97% showed retainment of 100% (rated 3), however only 5.06% showed loss of more than 50% (rated 1). In Anaplastic meningiomas, 87.5% showed retainment of more than 50% and only one case showed complete retainment, and no case showed retainment of less than 50%. In transitional meningioma, 60% of cases showed retainment of more than 50% and 40% showed complete retainment. Psammomatous, Lymphoplasmacyte-rich, angiomatous and meningothelial with microcystic had only one for each subtype and it showed complete retainment. There were two fibrous meningiomas one showed complete retainment and the other showed retainment of more than 50%. Rhabdoid, Microcystic and Metaplastic subtypes all had one case for each one of them, and each case showed retainment of more than 50%. Among 4 cases of secretory meningioma, three cases showed complete retainment and one case showed retainment of more than 50%. There were also two cases of Chordoid meningioma, and they both showed retainment of more than 50% of H3K27me3. A $Chi^2$ test was performed between Histologic subtype and H3K27me3 expression. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the $Chi^2$ test were not met. There was no statistically significant relationship between Histologic subtype and H3K27me3 expression, The calculated p-value of .879 is above than the defined significance level of 5%. The $Chi^2$ test is therefore not significant, and the null hypothesis is not rejected.

Table 8.

H3K27me3 *expression in different histologic subtypes.*

| | H3K27me3 expression | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | |
| Histologic subtype | \ N | % | n | % | N | % | P valu e |
| Meningothelial | 4 | 5.06 % | 4 5 | 56.96 % | 3 0 | 37.97 % | .879 |
| Anaplastic | 0 | 0% | 7 | 87.5% | 1 | 12.5% | |
| Transitional | 0 | 0% | 6 | 60% | 4 | 40% | |
| Psammomatous | 0 | 0% | 0 | 0% | 1 | 100% | |
| lymphoplasmacyte -rich | 0 | 0% | 0 | 0% | 1 | 100% | |
| Fibrous | 0 | 0% | 1 | 50% | 1 | 50% | |
| Metaplastic | 0 | 0% | 1 | 100% | 0 | 0% | |
| Angiomatous | 0 | 0% | 0 | 0% | 1 | 100% | |
| Secretory | 0 | 0% | 1 | 25% | 3 | 75% | |
| Microcystic | 0 | 0% | 1 | 100% | 0 | 0% | |
| meningothelial + microcystic | 0 | 0% | 0 | 0% | 1 | 100% | |
| Rhabdoid | 0 | 0% | 1 | 100% | 0 | 0% | |
| Chordoid | 0 | 0% | 2 | 100% | 0 | 0% | |

*Note. Note. Chi square was used, P value is considered significant when it is less than (.05)*

### 4.6 H3K27me3 expression in De novo and recurrent meningioma

Table (9) illustrates the expression of H3K27me3 in De novo and recurrent meningioma. In de novo cases, 4% showed expression of less than 50%, while 57% showed expression of more than 50% and 38.67 showed complete retainment of H3K27me3. In recurrent cases, only one case showed expression of less than 50%, while 59.46% of the cases showed expression of more than 50%, 37.84% of the cases showed complete retainment. A $Chi^2$ test was performed between De novo or recurrent and H3K27me3. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the $Chi^2$ test were not met. There was no statistically significant relationship between De novo or recurrent and H3K27me3. The calculated p-value of .932 is above than the defined significance level of 5%. The $Chi^2$ test is therefore not significant, and the null hypothesis is not rejected.

Table 9.

H3K27me3 *expression in De novo and recurrent meningioma.*

| | H3K27me3 immunoexpression | | | | | | |
|---|---|---|---|---|---|---|---|
| History of meningioma | < 50% | | >50% | | 100% | | P value |
| | N | % | N | % | n | % | |
| De novo | 3 | 4 | 43 | 57.33 | 29 | 38.67 | .932 |
| Recurrent | 1 | 2.7 | 22 | 59.46 | 14 | 37.84 | |

*Note. Chi square test was used to test the significance of relationship, it is considered significant when P value is less than .05.*

### 4.7 the rate of recurrence in different Age, Ki67 and PR

Table (10) shows a comparison of recurrence in different Age, Ki67 and PR. The mean age of patients who suffered from recurrence of meningioma was 57.29 years old, and the mean age of patients who did not have a recurrence of meningioma was

55.10 years old. The mean of Ki67 retainment was 8.38% in patients who suffered from recurrence, and it was 4.14 in patients who did not have a recurrence, The mean of PR retainment was 39.94 in patients who suffered from a recurrence, and 58.69 in patients who did not have a recurrence. T test showed significant differences between the two means having a recurrence and not having a recurrence of Ki67 where P value was (.001), however it was insignificant in the means of age and PR where P value was (.474 and .007) respectively.

Table 10.

*Comparison of recurrence in different Age, Ki67 and PR*

| | Recurrence | | | | | |
|---|---|---|---|---|---|---|
| | Yes | | No | | Levene's test | T Test |
| | N | Mean | N | Mean | | |
| Age | 34 | 57.29 | 78 | 55.10 | .871 | .474 |
| Ki67 | 34 | 8.38 | 78 | 4.14 | .000 | .001 |
| PR | 34 | 39.94 | 78 | 58.69 | .311 | .007 |

*Note: there is a significance of variance between groups when P value is more than (.05) in Levene's test. In T test there is significance when P value is less than (.05)*

**4.7.1 Age distribution of patients with a recurrence.** Figure (3) shows the age distribution in cases with recurrence. The ages of patients who had a recurrence were normally distributed, distribution was tested using Kolmogorov-Smirnova where P value was (.200).

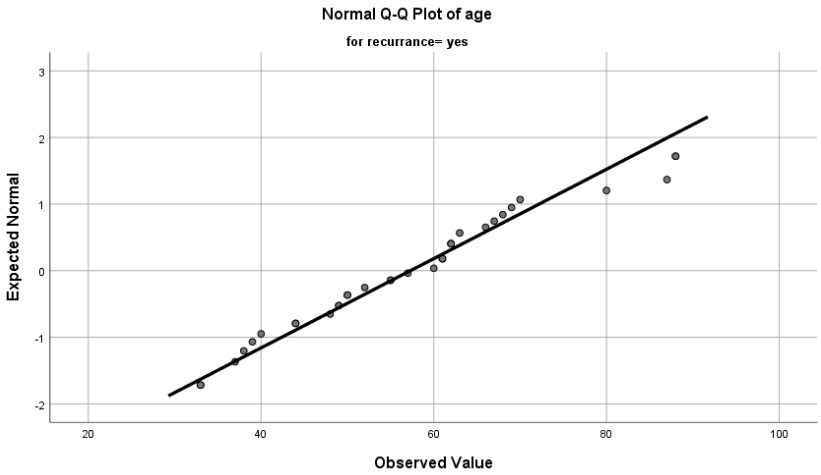



*Figure 3. Age distribution in cases with recurrence.*

**4.7.2 Age distribution of patients with no recurrence**. Figure (4) shows the age distribution in cases with no recurrence. The ages of patients who did not have a recurrence were normally distributed, distribution was tested using Kolmogorov-Smirnova where P value was (.200).

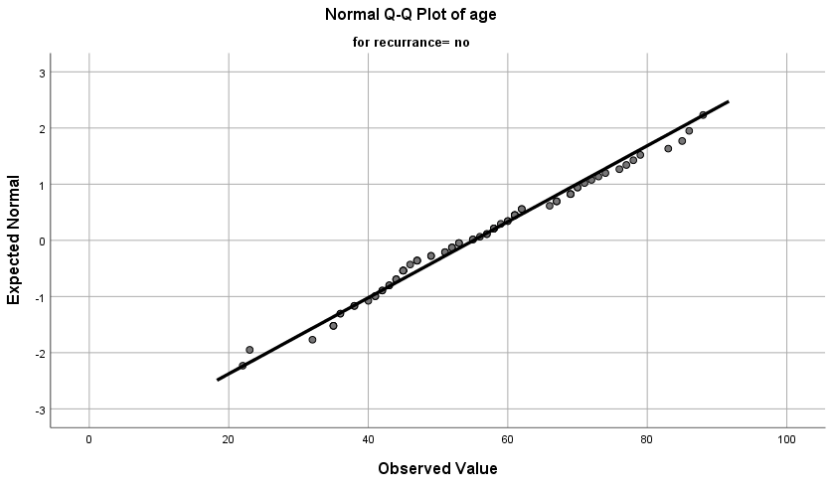



*Figure 4. age distribution in cases with no recurrence.*

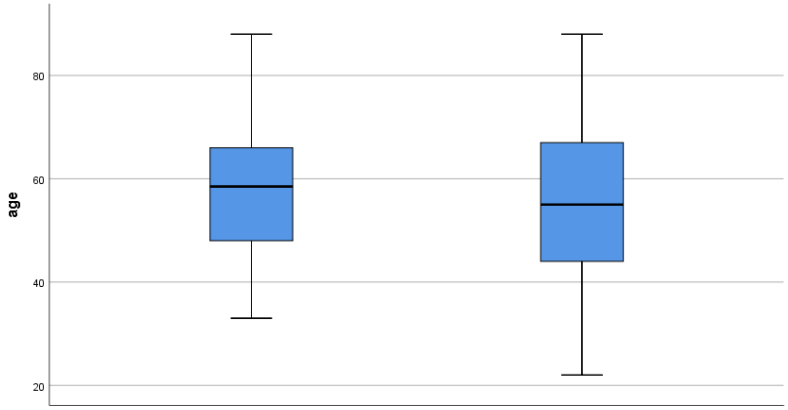



*Figure 5. Comparison of Age distribution between recurrence and no recurrence cases.*

**4.7.3 Ki67 expression distribution in cases where recurrence occurred.** Figure (6) demonstrates the distribution of Ki67 expression among the cases with a recurrence of meningioma. The expression Ki67 is normally distributed as seen in figure (6) and confirmed by Kolmogorov-Smirnova test (P=.14).

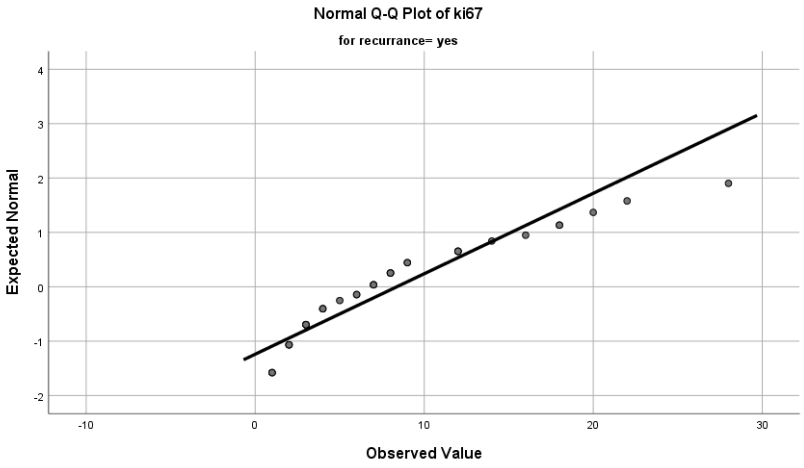



*Figure 6 Ki67 expression distribution in cases where recurrence occurred.*

**4.7.4 Ki67 expression distribution in cases where recurrence did not occur.** Figure (7) demonstrates the distribution of Ki67 expression among the cases with no recurrence of meningioma. The expression Ki67 is not normally distributed as seen in figure (8) and confirmed by Kolmogorov-Smirnova test (P=.000).

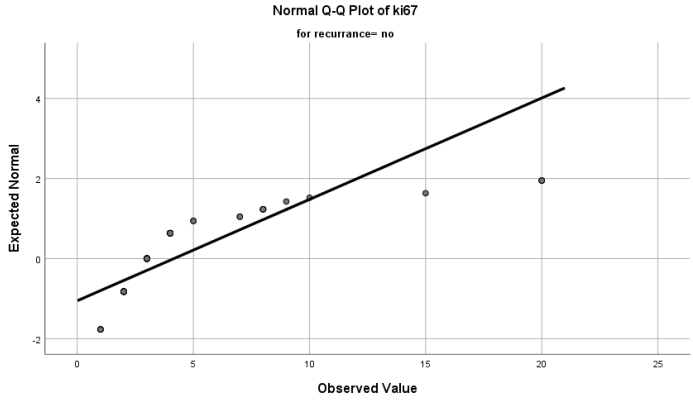



*Figure 7 Ki67 expression distribution in cases where recurrence did not occur.*

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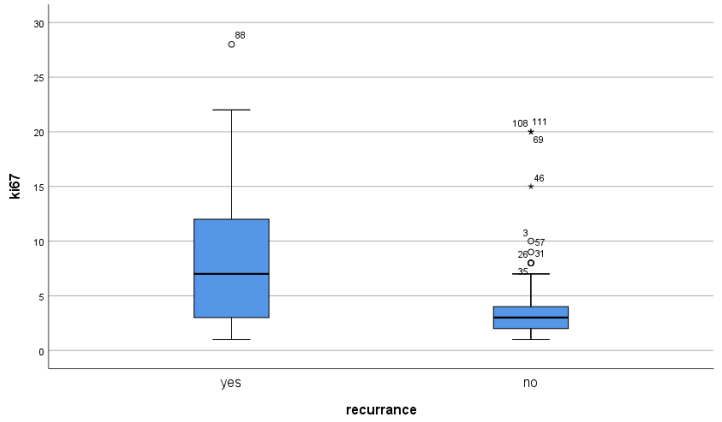


*Figure 8. Comparison of Ki67 distribution between recurrence and no recurrence cases.*

**4.7.5 PR expression distribution in cases where recurrence occurred.** Figure (9) demonstrates the distribution of PR expression among the cases with a recurrence of meningioma. The expression PR is normally distributed as seen in figure (8) and confirmed by Kolmogorov-Smirnova test (P=.18).

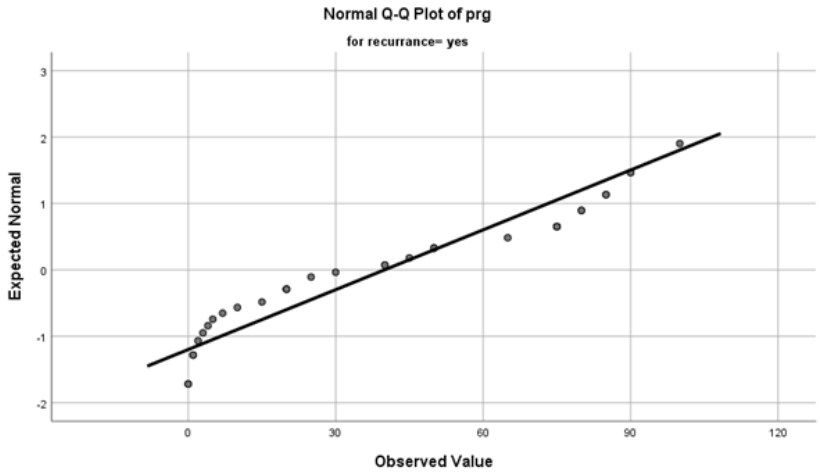


*Figure 9. expression distribution in cases where recurrence occurred.*

**4.7.6 PR expression distribution in cases where recurrence did not occur.** Figure (10) demonstrates the distribution of PR expression among the cases with a recurrence of meningioma. The expression PR is not normally distributed as seen in figure (11) and confirmed by Kolmogorov-Smirnova test (P=.000).

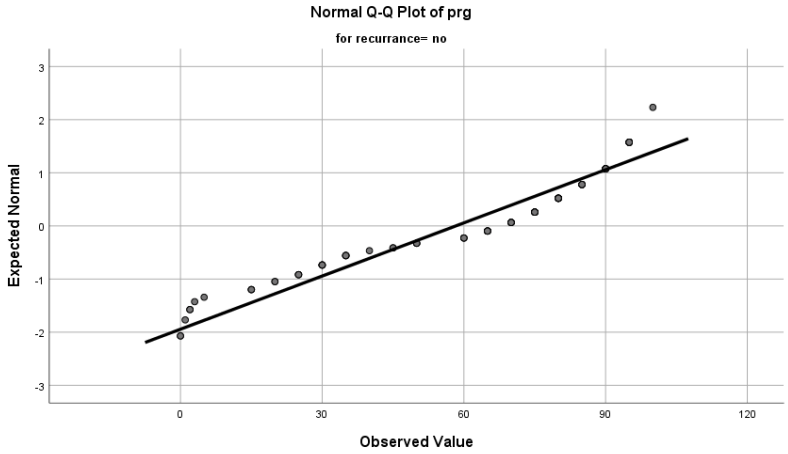


*Figure 10. PR expression distribution in cases where recurrence did not occur.*

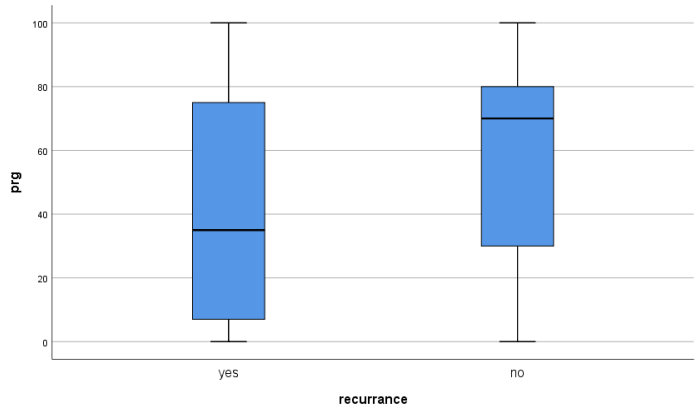


*Figure 11. Comparison between PR in recurrence and no recurrence cases*

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**4.7.7 Ki67 and PR expression in cases with recurrence and with no recurrence.** Table (11) demonstrates the mean rank of Ki67 and PR in cases with recurrence and without recurrence. The mean rank of Ki67 expression is 73.1 in patients who suffered from a recurrence, and 49.26 with patients who did not have a recurrence. Moreover, the mean rank of expression of PR in patients who suffered from a recurrence was 44.04 while the mean rank in patients who did not have recurrence was 71.93. using Mann Whitney U test, the association between expression of Ki67 and recurrence is considered significant as P value was as low as (.000).

Table 11.

*Ki67 and PR in recurrence and non-recurrence cases of meningiomas.*

| | Recurrence | N | Mean Rank | P. value |
|---|---|---|---|---|
| Ki67 | Yes | 34 | 73.1 | .000 |
| | No | 78 | 49.26 | |
| PR | Yes | 34 | 44.04 | .007 |
| | No | 78 | 71.93 | |

*Note. Mann Whitney U test was used, P value < .05 is considered significant*

## 4.8 Survival

**4.8.1 Free recurrence survival in different Who grades of meningiomas.** Table (12) demonstrates the means and medians of free recurrence survival of different WHO grades of meningiomas using the Kaplan Meir method, the mean time of free

recurrence survival drops as the Grade upgrades, in WHO grade 1 meningioma the mean of time before developing a recurrence is 18.188 months while it drops to 13.091 months and 11.286 months in WHO Grade 2 and 3 respectively. However, the Median of time of free recurrence survival is 9 months in Grade, 8 months in Grade 2 and 9 months in Grade 3, Log rank test was used to test the significance of the result and P value was (.382).

Table 12.

*Free recurrence survival by month in different Who grades of meningiomas*

| | | Mean | | | Median | | P |
|---|---|---|---|---|---|---|---|
| | | 95% confidence interval | | | | | value |
| Grade | estimate | Std.error | Lower bound | Upper bound | Estimate | Std.error | .382 |
| 1 | 18.188 | 4.452 | 9,462 | 26,913 | 9,000 | 2,400 | |
| 2 | 13.091 | 3.561 | 6,111 | 20,071 | 8,000 | 1,101 | |
| 3 | 11.286 | 3.061 | 5,287 | 17,285 | 9,000 | 5,237 | |

*Note. Log rank was used to test the difference between the groups, it is considered significant when P value is less than (.05).*

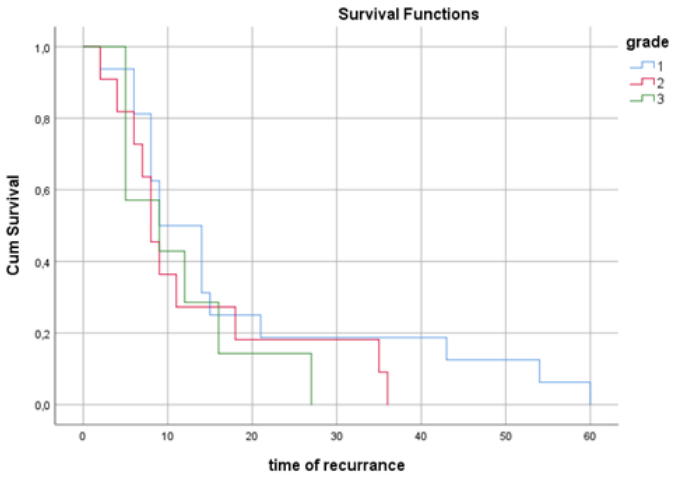


*Figure 12. Free recurrence survival in different Who grades of meningiomas.*

**4.8.2 Free recurrence survival in de novo and recurrent meningiomas** Table (13) demonstrates the means and medians of free recurrence survival in de novo and recurrent meningiomas using the Kaplan Meir method, the mean of free recurrence survival in de novo cases is 11.5 months while the mean of free recurrence survival in

de novo cases is 11.5 months and the median is 8 months, while the mean of free recurrence survival in recurrent cases is 15.344 months and the median is 9 months. Log rank test was used to test the significance of the result and P value was (.846).

Table 13.

*Free recurrence survival in de novo and recurrent meningiomas.*

| | Mean | | | | Median | | |
|---|---|---|---|---|---|---|---|
| | | | 95 Confidence interval | | | | |
| De novo or recurrent | Estimate | Std. error | Upper bound | Lower bound | Estimate | Std. error | P value |
| De novo | 11,500 | 3,500 | 4,640 | 18,360 | 8,000 | . | .846 |
| Recurrent | 15,344 | 2,616 | 10,215 | 20,472 | 9,000 | ,702 | |

*Note. Log rank was used to test the difference between the groups, it is considered significant when P value is less than (.05).*

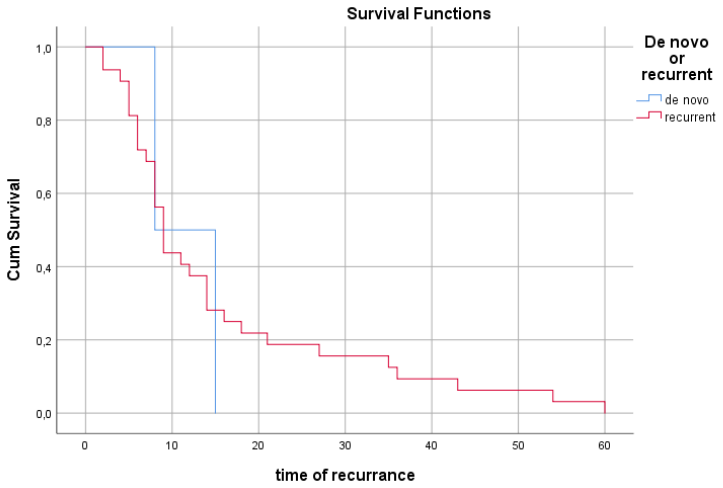


*Figure 13. Free recurrence survival in de novo and recurrent meningiomas.*

**4.8.3 Free recurrence survival and H3K27me3 expression.** Table (14) demonstrates the means and medians of free recurrence survival in cases with different expressions of H3K27me3 using the Kaplan Meir method. Cases rated 1 had a free recurrence survival mean of 2 months and a median of 2 months, while cases rated with a score 2 of expression had a free recurrence survival mean of 16.263 months and a median of 9 months. And cases rated with a score 3 of expression had a free recurrence survival mean of 14.5 months and a median of 9 months, Log rank test was

used to test the significance of the result and P value was (.000). however, there was only one case of meningioma rated with 1 in H3K27me3 that suffered recurrence and when Kaplan Meir method was used after excluding that case the P value of Log rank test was (.761).

Table 14.

*Free recurrence survival and* H3K27me3 *expression.*

| | Mean | | | | Median | | |
|---|---|---|---|---|---|---|---|
| | | | 95% confidence interval | | | | |
| Final rating | Estimate | Std. error | lower bound | upper bound | estimate | Std. error | P. Value |
| 1 | 2,000 | ,000 | 2,000 | 2,000 | 2,000 | . | |
| 2 | 16,263 | 3,787 | 8,840 | 23,686 | 9,000 | ,717 | .761 |
| 3 | 14,500 | 3,088 | 8,448 | 20,552 | 9,000 | 2,806 | |

*Note. Log rank was used to test the difference between the groups, it is considered significant when P value is less than (.05).*

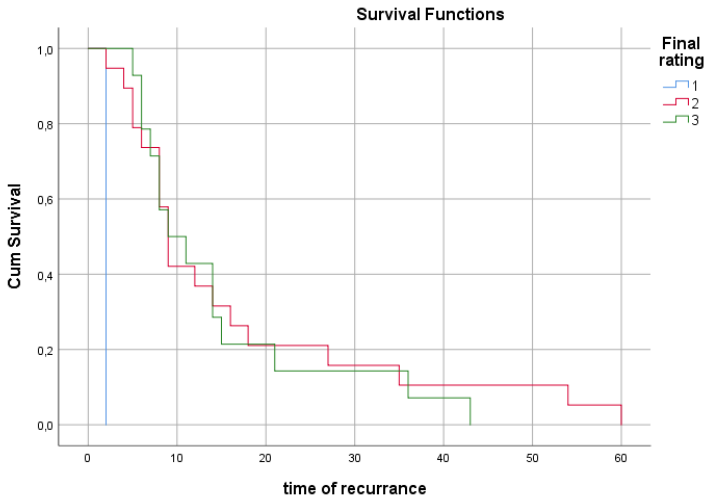


*Figure 14. Free recurrence survival and H3K27me3 expression.*

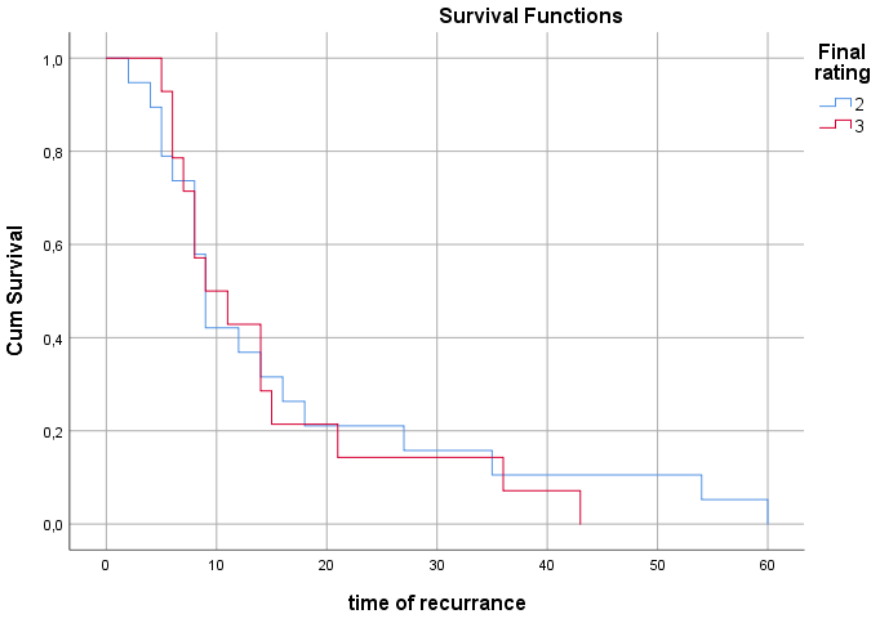


*Figure 15. Free recurrence survival and H3K27me3 expression of cases rated 2 and 3*

# Chapter 5

# Discussion And Conclusion

## 5.1 Discussion of Findings for Research Questions

**5.1.1 H3K27me3 expression.** In previous studies, 3-teired or 4-teired rating system was used, where 3 was complete retainment and 0 was complete loss of H3K27me3 expression or 2 was complete retainment and 0 was complete loss, and then comparison was primarily made in dichotomous manner between retainment and complete loss (Katz et al., 2018; Nassiri et al., 2021). In this study we used a 4-teired rating system to evaluate the expression of H3K27me3, where complete retainment was rated 3, retainment of more than 50% was rated 2, retainment of less than 50% was rated 1 and complete loss was rated 0. In this study all the 112 cases of meningiomas retained H3K27me3 but in different rates, 38,4 of the cases completely retained the expression of H3K27me3, 58% of the cases retained more than 50%, only 4 cases (3.6%) retained less than 50% of H3K27me3. In total there was more loss than retainment, as only 38.4% showed complete retainment, and the remaining 61.4% of cases showed different degrees of loss and no case showed total loss of H3K27me3.This study showed a different result regarding retainment to loss ratio comparing to previous studies where complete retainment was more common and complete loss was present. (Gauchotte et al., 2020; Katz et al., 2018; Nassiri et al., 2021). Complete loss did not exist among the 112 cases while it was 10% in a study conducted by Lu et al., (2022) in 2150 cases of meningioma. Most of the cases in our study showed retainment in more than 50% of H3k27 trimethylation. It seems that complete loss of H3K27me3 is not common to find.

**5.1.2 H3K27me3 in WHO grades.** Complete retainment of H3k27 trimethylation did not show big difference between WHO grade 1 and 2 meningiomas, as 41.3% of WHO grade 1 meningioma cases retained H3K27me3 expression completely and 39.1% in WHO grade 2 meningiomas, and not a big difference was noted in cases where more than 50% of H3k27 trimethylation was retained, as 56.3% of Grade 1 and 52.2 of grade 2 retained more than 50% of the expression. However, In Grade 1 meningiomas only 2.5% retained less than 50% of the expression. While in WHO grade 2 meningioma 8.7% cases retained less than 50% of H3k27 trimethylation. While in WHO grade 3 meningioma cases 88.9% of the cases retained more than 50% of the expression of H3K27me3, while the remaining 11.1% showed

full retainment of expression of H3K27me3, no case of Grade 3 showed retainment of expression of H3K27me3 of less than 50%. Chi square test did not prove any significance of the relation between H3K27me3 and WHO grades as P value was .211. our finding regarding relation between H3K27me3 and WHO grades is opposed to the finding of Behling et al., (2021); Katz et al., (2018); Nassiri et al., (2021) where there was a difference of expression of H3K27me3 between grade 1 and 2. In our study there is no relationship between expression of H3K27me3 and WHO grades of meningioma.

**5.1.3 H3K27me3 in histologic subtypes.** In the most common subtype of meningioma meningothelial subtype, 56.96% of cases showed retainment of more than 50% (rated 2) of H3K27me3, while 37.97% showed retainment of 100% (rated 3), however only 5.06% showed loss of more than 50% (rated 1). These findings are consistent with the finding of Katz et al., (2018). Since they both showed retainment of K27meh among all the cases of the meningothelial subtype with absence of complete loss of H3k27 trimethylation. In the malignant subtype Anaplastic meningiomas, all the cases showed retainment of more than 50% or complete, no case showed retainment of less than 50%, which indicates that the retainment of expression of H3k27 trimethylation is high. These findings are different to the findings of Maier et al., (2022) where they found retainment of more than 50% was 29.5% and less than 50% was 55.7% and cases of complete loss was 14.7%. Transitional subtype of meningioma showed a high level of complete retainment of H3k27 trimethylation when compared to meningothelial and anaplastic, as 40% of the cases showed complete retainment and the remaining 60% of cases showed retainment of more than 50%, and no case showed expression of less than 50%. However, the highest rate of complete retainment was within secretory subtype, 75% of the cases of secretory meningioma showed complete retainment and 25% showed retainment of more than 50%. There was no statistically significant relationship between Histologic subtype and H3K27me3 expression as the Chi square test did not show any significance (P= .879). In this study there is no obvious relation between H3K27me3 expression loss and Histologic subtypes of meningioma.

**5.1.4. H3K27me3 in locations.** Meningiomas located intracranially had a high percentage of total retainment cases, 41.89% of intracranial meningiomas showed total retainment, 54.05% showed retainment of more than 50% and 4% showed total loss. This number of total retainment is almost similar to the finding of (Hua et al., 2023)

where it was 51.6% and it was also the location with the highest percentage of total retainment. This might suggest that Intracranial meningiomas are the most likely to have a total retainment of H3k27 trimethylation. Spinal meningiomas showed a low percentage of complete retainment compared intracranial meningioma having only 28.75% of its cases showing total retainment, and 74.43% showing retainment of more than 50% and no case showed retainment less than 50%. A study done by (Jung et al., 2021) also showed zero cases of complete loss in spinal meningiomas where all the other locations had complete loss cases, in our study there was no complete loss among all cases, but spinal meningiomas were the only location with zero cases with less than 50%. This might indicate that Spinal Meningiomas are the unlikeliest among all the locations to have complete loss. Skull-based meningiomas had a higher percentage of total retainment than spinal meningiomas and less than intracranial meningiomas, having 33.33% of its cases showing total retainment, 62.5% showing retainment of more than 50% and only 4.17% with retainment less than 50%. Skull based meningiomas have less total retainment cases and slightly more cases having loss of more than 50% of H3K27me3 than Intracranial. Similar results were observed in a study done by Hua et al., (2023). This might suggest that Skull-base meningiomas have a higher rate of loss and a lower rate of retainment of H3K27me3 than Intracranial. However, A $Chi^2$ test was performed between Location and H3K27me3 expression. There was no statistically significant relationship between Location and H3K27me3 expression, The calculated p-value of .729 is above than the defined significance level of 5%. The $Chi^2$ test is therefore not significant, and the null hypothesis is not rejected. Thus, there is no strong relation between H3K27me3 expression loss and anatomical localisations of meningioma.

**5.1.5 Recurrence in H3K27me3.** The incidence of recurrence increased as the percentage of H3k27 trimethylation increased. The incidence of recurrence was 25% with cases retaining less than 50% of H3K27me3 expression and increased to 29.2% in cases retaining more than 50 % of H3K27me3 and increased to 32.6% in cases with complete retainment of H3K27me3 expression. Chi square test showed no significance as P value was as high as (.909). The absence of relationship between H3k27 trimethylation loss and risk of recurrence in our study might be due to the absence of cases with complete loss of expression, as it was found by Katz et al., (2018) that cases with complete loss of expression had an increased risk of having a recurrence.

However, in our study H3K27me3 loss is not associated with increased risk of recurrence.

**5.1.6 Free recurrence survival in H3K27me3.** Kaplan Meir method was used to assess the free recurrence survival in cases with different H3K27me3. Cases rated 1 had a free recurrence survival mean of 2 months and a median of 2 months, while cases rated with a score 2 of expression had a free recurrence survival mean of 16.263 months and a median of 9 months. And cases rated with a score 3 of expression had a free recurrence survival mean of 14.5 months and a median of 9 months. Free recurrence survival in cases with a loss of less than 50% is longer than free recurrence survival in cases with total retainment. Log rank test was used to test the significance of the result and P value was (.000). however, there was only one case of meningioma rated with 1 in H3K27me3 that suffered from recurrence and when Kaplan Meir method was used after excluding that case the P value of Log rank test was (.761). Loss of H3k27 trimethylation is unlikely to be associated with shorter free recurrence survival.

**5.1.7 Recurrence and free recurrence survival in de novo and recurrent and in different WHO grades.** The history of meningioma was so decisive to having a recurrence, The incidence of recurrence was profoundly more common in recurrent type of tumours accounting of 94.1% of all incidences of recurrence, however only 5.9% of recurrences occurred in the de novo type of meningioma. 86.48% of recurrent cases suffered from a recurrence, while among de novo cases only 2.6% had a recurrence. Chi square was used to test the relation between recurrence and history meningioma, there was a significance as P value was .000 and Null hypothesis was rejected. The incidence of recurrence was higher in recurrent meningioma that de novo meningiomas. However, the free recurrence survival was shorter de novo was shorter than recurrent meningiomas, the mean of free recurrence survival in de novo cases is 11.5 months while the mean of free recurrence survival in de novo cases is 11.5 months and the median is 8 months, while the mean of free recurrence survival in recurrent cases is 15.344 months and the median is 9 months. Log rank test was used to test the significance of the result and P value was (.846). The expression of H3k27 trimethylation in de novo and recurrent meningiomas showed close rates of retainment and loss, however, the calculated p-value of .932 is above than the defined significance level of 5%. The $Chi^2$ test is therefore not significant, and the null hypothesis is not

rejected. These results can add to the literature where there is opposing results regarding expression of H3K27me3 in de novo or recurrent meningiomas, these results are similar to the findings of a study on H3K27me3 expression in grade 2 and grade 3 meningiomas which showed almost no difference in H3K27me3 loss between de novo and recurrent cases of meningiomas (34% and 34.3 respectively) (Jung et al., 2021). But different to the results found in another study where H3K27me3 loss is higher in recurrent cases of meningioma than de novo cases of meningioma. (Nassiri et al., 2021) Found H3K27me3 loss in 8.8% cases of de novo meningioma, while recurrent cases showed loss of H3K27me3 in 19.4% of the cases. While in Tubingen cohort study the loss of H3K27me3 was in 4% of the de novo cases and 11% of the recurrent cases. (Behling et al., 2021). In different WHO grades, the recurrence incidence was increasing as the Grade increase and the relation was found to be significant when Chi square test was used as P value was as low as (.000). high WHO grade was also a poor prognostic factor when free recurrence survival was calculated using Kaplan Meir, the mean of free recurrence survival was shorter as the grade increases, however the Log rank test did not show high significance of the relation as P value was as high as (.382). these findings regarding the prognosis and the WHO grading are fully consistent with parameters upon which the basis of the WHO classification of meningiomas in the WHO classification of tumours of the nervous system was made. (WHO Classification of Tumours Editorial Board, 2022).

**5.2 Conclusions**

Most cases of meningioma showed retainment of more than 50% H3K27me3 immunoexpression and there was no case of total loss. However, the difference of expression of H3K27me3 was not statistically significant neither among different WHO grades of meningioma nor among meningiomas in different localisations nor among different histologic subtypes of meningioma. The expression of H3K27me3 was not different between de novo and recurrent meningiomas. Loss of H3K27me3 was not a risk factor for incidence of recurrence, and it was not associated with free recurrence survival in meningioma.

Overall, H3K27me3 expression does not seem to be beneficial in the clinical diagnosis of meningioma. Moreover, it does not seem to show any potential to become a reliable investigatory tool to determine the prognosis of meningioma.

### 5.3 Recommendations

Further studies with bigger sample size and longer follow up period are needed to determine the diagnostic and prognostic value of H3K27me3 in meningioma.

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