

## Chapter

# Diagnosis and Grading of Meningiomas

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## Abstract

Meningiomas are the most common primary brain tumors in adults. They are slow growing, mostly benign tumors affecting primarily older people. Meningiomas comprise a family of neoplasms that are most likely derived from the meningotheelial cells of the arachnoid cap cell. Current diagnosis of meningioma has been facilitated by MRI scans, and most patients with meningiomas have good prognosis without affecting the quality of life after successful treatment, like gross total resection (GTR). This chapter will briefly review the molecular basis, clinical diagnosis and grading of meningiomas and the treatment options.

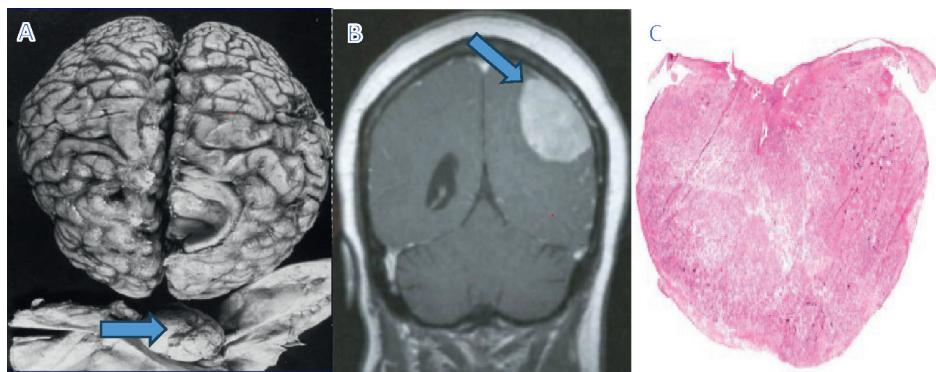
**Keywords:** meningioma, dura-based tumors, dural tail sign, DNA methylation, metastatic carcinoma

## 1. Introduction

Meningiomas are the most common primary brain tumors, which are primarily benign neoplasms affecting mainly elderly population with a median age of 66 years [1]. Meningioma occurs in the USA at an average annual age-adjusted rate of 8.58 cases per 100,000 population, accounting for 37.6% of CNS tumors. Although this tumor more commonly occurs in the elderly patients, it has a preference to affect the young population, especially women during pregnancy. This tumor is often described as an extra-axial tumor, but location of tumor still plays an important role in treatment and prognosis. As the improvement of diagnostic and treatment methods, this tumor should become a manageable neoplasm.

## 2. Incidence and etiology of meningiomas

Meningioma is the single most common tumor reported in patients older than 35 years. The incidence of meningioma is about 5.35 per 100,000 person years (3.17 in males and 7.19 in females), with a mean age at diagnosis of 64 years [1]. The incidence of meningioma is increasing, probably due to the incidental finding of this tumor by radiologic examination, as the technology becomes more advanced. Another



**Figure 1.**

Incidental finding of a meningioma during autopsy, arrow (A), tumor made a dent in brain tissue. (B) CT scan of a left frontal meningioma, the arrow indicates the dural tail. The tumor had mass effect to push the lateral ventricle. A gross picture of a resected meningioma attached to the dura (C).

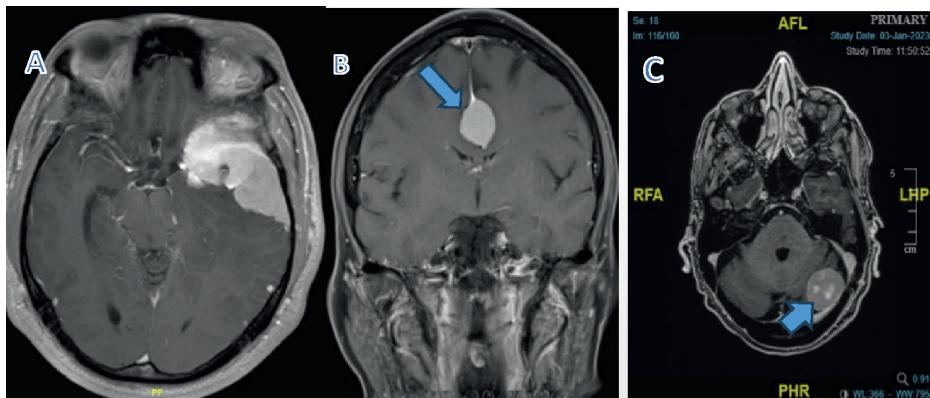
incidental finding of meningioma is by autopsy, in which removing the brain may lead to finding of meningioma attached to the skull (**Figure 1A**).

Exposure to ionizing radiation is the primary and established risk factor for meningioma, especially those who were exposed in childhood. In addition, several findings suggested a risk association between hormone and meningioma, including the greater incidence of meningioma in women than in men, and the presence of hormonal receptors in some meningiomas, as well as a modestly increased risk associated with endogenous and exogenous hormone. Hormone-related risk of meningiomas was also found in patients treated with progestin, and patients with uterine fibroid, endometriosis, and breast cancer. Other attempts to link specific chemicals, diet, occupation, head trauma, and mobile phone use with meningioma have been inconclusive so far [1].

### 3. Clinical presentation of meningiomas

Clinical presentation of meningiomas varies based on the location of the tumor. Headache is a common symptom, and it may worsen with time. When tumor affects the brain surface (cortex), seizure may occur. In some elderly patients with cerebral atrophy, the symptoms may be mild, as there is more space for tumor growth until it reaches the surface of the brain. When the tumor compresses cranial nerves, especially in skull base meningiomas, nerve-damage-related symptoms may occur. As an example, the anterior fossa meningioma compresses the olfactory nerve leading to loss of smell, while compressing the optic nerve may lead to blurred, or double vision, or even blindness, and exophthalmos (**Figure 2A**). While tumors in the sella turcica region may cause visual field defect due to optic chiasm damage as well as abnormal hormonal expression by compressing the pituitary gland.

In the current WHO Classification of CNS tumors [1], meningiomas have 3 grades, primarily based on histopathological evaluation and their clinical behavior. These gradings are closely related to the clinical behavior of meningiomas including the recurrence rate. Grades 1, 2 and 3 meningiomas have 5-year recurrence rate of 12%, 41%, and 56% [2], respectively.



**Figure 2.**  
Middle cerebral fossa tumor with an en plaque meningioma, with no dual tail (A); parafalcine meningioma is close to superior sagittal sinus, arrow (B); uncommon cerebellar meningioma with dural tail sign, arrow (C).

Meningiomas often have dural invasion, and to prevent tumor recurrence, resection of a segment of dura is necessary (**Figure 1C**).

#### 4. Location of meningiomas

As with most diseases in central nerve system (CNS), location is an important factor in clinical presentation and treatment of brain tumors. In meningiomas, location is not only related to the treatment option, but also has some genetic background, and affects the prognosis. The most common locations of meningiomas include the cerebral convexities, in association with the falx cerebri and/or venous sinuses, olfactory grooves, sphenoid ridges, tentorium, and posterior fossa. Intraventricular and epidural locations are uncommon. Especially the intraventricular meningioma, the origin the tumor is still a mystery. Most spinal meningiomas occur in the thoracic spine. Of note, convexity meningiomas and most of the spinal meningiomas carry a 22q deletion and/or NF2 mutations. Whereas skull base meningiomas harbor mutations in AKT1, TRAF7, SMO, and /or PIK3CA. High grade meningiomas more commonly arise from the convexity and other non-skull base sites. Rare primary meningiomas arise outside the CNS, including the lung, or skin.

Although it is called dura-based tumor, as a matter of fact, there are two more layers of membrane between dura and brain, they are arachnoid and pie membrane, collectively called “leptomeninges”.

#### 5. Molecular genetics of meningiomas

Monosomy of chromosome 22 is the most common genetic abnormality found in meningiomas, with more than half of the tumors showing allelic losses in 22q12.2. This region encodes the NF2 gene. Initiation and malignant progression of NF2-driven meningiomas has been confirmed by animal models. While those meningiomas without NF2 mutation, mutations of AKT1 and p.E17K have been found. Since those mutations have been discovered in other cancers, they are considered as an

oncogenic deriver. Additional genetic changes occur in higher grade meningiomas, with losses of 1p, 6p/q, 10q, 14q, and 18p/q; as well as less frequently losses of 2p/q, 3p, 4p/q, 7p, and 8p/q. In addition, *CDKN2A* and *CDKN2B* heterozygous or homozygous deletion have been reported. Moreover, *PIK3CA* mutations are associated with antihormone treatment. Women with meningioma who were under long-term progestin therapy carry *PIK3CA* mutations more frequently than those without hormone therapy, and high-dose antiandrogen treatment with cyproterone leads to an enrichment of *PIK3CA*-mutated skull base meningiomas [1].

More recently, DNA methylation profiling has become one of the most promising molecular tests for CNS tumors, and DNA methylation will be a new classification of CNS tumors in the near future [3]. A European study found that DNA methylation-based meningioma classification captures more homogenous groups and has a higher power for predicting tumor recurrence and prognosis than the current WHO classification [3, 4].

*CDKN2A* and *CDKN2B* are tumor suppressor genes, and studies showed that *CDKN2A* homozygous deletion has occasionally been reported in atypical and anaplastic meningiomas and is considered as one of the genetic alterations commonly involved in their recurrence and malignant progression [5]. The homozygous deletion can be detected by the FISH method.

## 6. Neuroimaging

Neuroradiology is important in the diagnosis and planning the treatment of meningiomas and other brain tumors. Commonly, meningiomas are isodense to gray matter on noncontrast computed tomography (CT), and T1-weighted magnetic resonance imaging (MRI). They are contrast enhancing on MRI, and even small tumors (~3 mm) can be detected on MRI after administration of contrast agent. The “dural tail” sign on neuroimage is a very useful feature in the diagnosis of meningioma, or to confirm that the mass lesion is truly an extra-axial (**Figure 2**) [6]. Although some rare dura-based masses may have the same feature, they are very rare.

There is a special type of meningioma called “Meningiomas en plaque (MEP)”, which is a rare subtype of meningioma that comprises only 2–9% of all meningiomas. MEP are unique from the more common en masse meningiomas and are defined by their characteristic “carpet-like” invasion of adjacent bone, with extensive hyperostosis and dural thickening (**Figure 2A**).

## 7. Histopathological diagnosis and grading of meningiomas

### 7.1 Meningothelial whorl

A hallmark of meningiomas, composed of epithelial cells with conspicuous nuclear pseudo-inclusion, indistinct cellular borders aggregated into small sheet and large lobules, impart a syncytial feature, to concentric rings, which finally makes this characteristic histological feature, called “meningothelial whorl”. The central part may become hyalinized and calcified into psammoma body (**Figure 3A**).

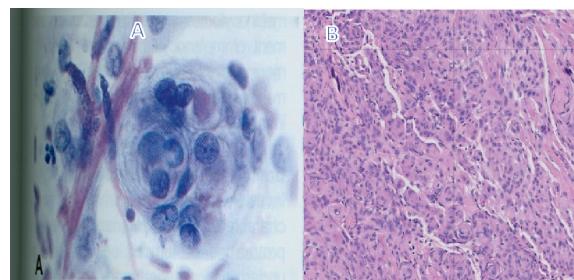
Diagnosis and grading of meningiomas mainly rely on histopathologic evaluation. Meningiomas have at least more than ten histologic subtypes, most are benign, but

some of them are associated with aggressive clinical behavior which need to be upgraded (grade 2 or 3), although rare, identifying those histological types is important for additional treatment and predicting the prognosis. The current grading system is based on WHO Classification of Central Nervous System Tumours [1].

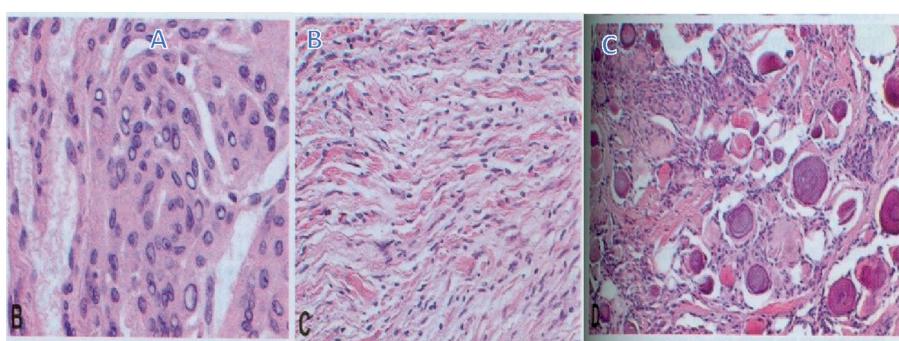
The grading of meningiomas dramatically changed in the late 90s. Since in a large-scale study, brain invasion (used to call it “malignant meningioma”) had been found not that “malignant” behavior clinically, and was downgraded as grade 2 atypical meningioma. The current WHO grading of meningiomas has 3 grades, as CNS WHO grade 1, 2 and 3 [1, 2].

## 8. CNS WHO grade 1 meningiomas

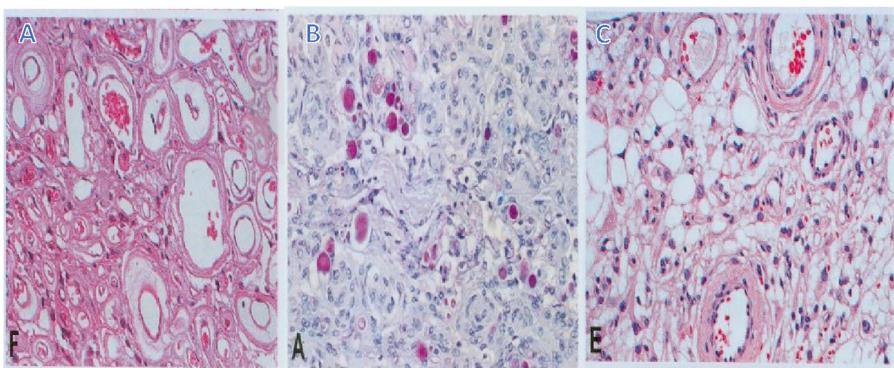
The most common histopathological type of meningiomas is meningotheelial type (characterized by meningotheelial whorls) and transitional type (**Figure 3**) [3]. The tumor cells are often in a nodular pattern, compared to the sheet-like pattern in more aggressive tumors. Sometimes, those types can be found mixed. Other WHO grade 1 types of meningiomas include psammoma body type (mostly occurs in female patients and thoracic spine), microcystic, angiomyomatous, and secretory (**Figures 4 and 5**). The diagnosis of grade 1 meningioma is based on presence of mitoses less than 4/10 High power view (HPV). Besides, bone and dural invasion are



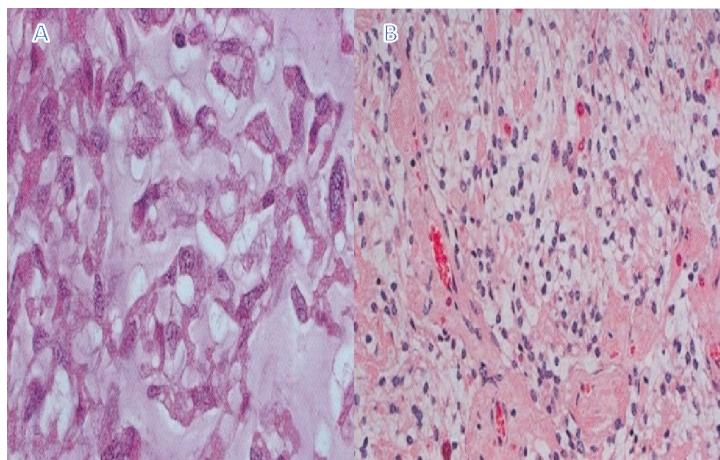
**Figure 3.**  
Meningotheelial whorl (A) is the diagnostic hallmark for meningioma H&E X400. Meningotheelial meningioma with numerous meningotheelial whorls (B, H&E X200).



**Figure 4.**  
Nuclear pseudo inclusion body is another histopathologic feature of meningioma (A). Fibrous meningioma with fibrous-like cells (B), psammoma body meningioma (C). All H&E X200.



**Figure 5.**  
Angiomatous (A), secretory (B) and microcystic (C) are other subtypes of grade 1 meningiomas. All H&E X200.



**Figure 6.**  
Brain invasion is a diagnostic criterion for atypical meningioma. The tumor cells show penetrating rather than pushing feature into brain parenchyma (A H&E stain X200), confirmed by immunostaining of GFAP (brown color on the right indicating the brain parenchyma) (B, IHC stain X200).

still considered as grade 1 tumor. However, if the mitoses are more than 4 but less than 20 per 10 HPF, or the tumor has brain invasion, the tumor should be upgraded to WHO grade 2 atypical meningioma (**Figure 6**).

### 8.1 Meningothelial meningioma

The tumor is composed of numerous meningothelial whorls, as is categorized as grade 1 meningioma (**Figure 3**).

### 8.2 Fibrous meningioma

The tumor cells in this type of meningioma have spindle-cell features (**Figure 4B**), with collagen matrix surrounding the tumor cells. Some cases require immunohistochemical (IHC) stain to be distinguished from solitary fibrous tumor (SFT).

### **8.3 Transitional meningioma**

Transitional meningioma is a mixture of both meningotheelial and fibrous types, with focal whorls and psammoma bodies. This is the most common type of meningioma in practice.

### **8.4 Psammomatous meningioma**

This subtype of meningioma mostly arises in the thoracic spine with female predominance and numerous Psammomatous calcification (**Figure 4C**).

### **8.5 Angiomatous meningioma**

This subtype includes numerous capillary blood vessels with hyalinized vascular wall (**Figure 5A**). In some cases, nuclear atypia may be observed, which is not considered as a factor for higher grade, but a degenerative change.

### **8.6 Secretory meningioma**

This subtype is characterized by round, eosinophilic periodic acid-Schiff (PAS)-positive, and carcinoembryonic antigen (CEA)-immunoreactive secretion (**Figure 5B**).

### **8.7 Microcystic meningioma**

The microcystic change in this subtype is made by vacuolated tumor cells. Like with other brain tumors, microcystic feature is usually a sign of low-grade tumor, even in some cases, nuclear atypia and pleomorphism may be present, but it is not considered as a high grade feature (**Figure 5C**).

### **8.8 Metaplastic meningioma**

This rare subtype may occasionally contain bone or cartilaginous, and lipomatous tissue, with no clinical significance.

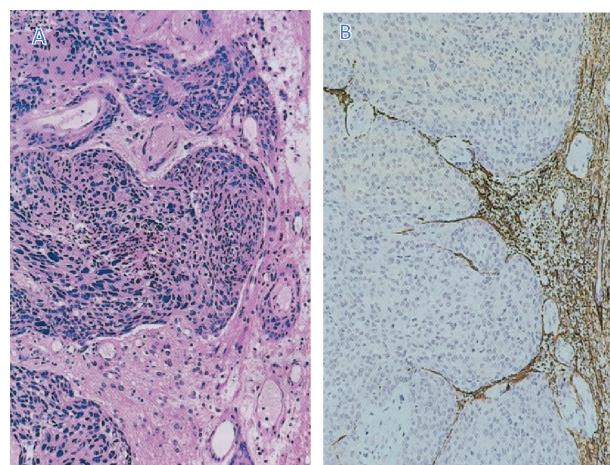
### **8.9 Lymphoplasmacytic-rich meningioma**

This rare subtype contains marked chronic inflammatory infiltrations, oftentimes obscuring the neoplastic meningioma cells, and makes the diagnosis challenging. However, in most meningiomas, some lymphocytes are always present.

### **8.10 CNS WHO grade 2 atypical meningiomas**

Atypical meningiomas are associated with increased recurrence rate and seeding by cerebrospinal fluid (CSF), which need to be closely followed and adjuvant therapy might be necessary. The diagnoses of atypical meningiomas become more frequent, from 5–25% [6].

Specific histological subtypes related to atypical meningiomas include chordoid and clear cell types (**Figure 7**). In addition, brain invasion is one of the diagnostic criterion for atypical meningioma. Another diagnostic criterion for WHO grade 2



**Figure 7.**  
*Chordoid (A, H&E stain X400) and clear cell meningioma (B, H&E stain X200).*

meningioma is increased mitoses more than 4/10 HPV but less than 20/10HPV. This needs careful microscopic evaluation [1]. Sometime, brain invasion needs immunohistochemical stain to be confirmed (**Figure 6**). Other less common histological criteria for atypical meningioma include focal necrosis, loss of nodular pattern with replacement of sheeting architecture, macronuclei, and small cell formation [6].

## 9. Histopathologic subtypes of WHO grade 2 meningiomas

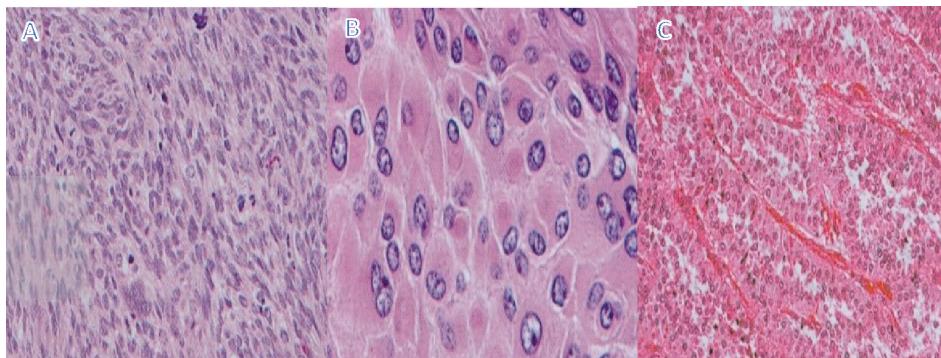
### 9.1 Chordoid meningioma

This subtype of meningioma was named for its resemblance to the bone tumor, chordoma. Most cases are large, supratentorial masses and hard to resected. This tumor is composed of foamy or vacuolated “physaliferous-like” cells, often mixed with other types of meningiomas, making it hard to diagnose (**Figure 7A**).

### 9.2 Clear cell meningioma

This tumor is another subtype of grade 2 meningioma, it has a strong predilection to the spinal cord, and posterior fossa, as well as a younger age at presentation, and even happens in infants, children, and young adults [6]. The tumor is composed of sheets of cells with clear cytoplasm (**Figure 7B**), with almost no whorl and psammoma bodies. Immunohistochemical stains are usually required to separate it from metastatic clear cell renal cell carcinoma.

Brain invasion is another diagnostic criterion for CNS WHO grade 2 atypical meningioma. The brain invasion used to be called “malignant meningioma”. It became less important after a large-scale study [2]. However, it carries some risk for recurrence, so it was categorized into grade 2 tumor. Careful evaluation of brain invasion is important in daily practice, and sometime immunohistochemical stains are required to differentiate true invasion from push artifact (**Figure 6**).



**Figure 8.**  
*Anaplastic (grade 3) meningioma with increased mitoses (A, H&E X200), Rhabdoid meningioma (B, H&E X400) and papillary meningioma (C, H&E X200).*

## 10. CNS WHO grade 3 anaplastic meningioma

Grade 3 meningioma is essentially a malignant tumor, with increased recurrence rate and CSF seeding, as well as a poor prognosis. Although rare, identifying this type of tumor is very important. The specific histological subtypes related to anaplastic meningioma include rhabdoid and papillary (**Figure 8B** and C) meningiomas. In addition, mitoses more than 20/10HPV is considered as anaplastic feature (**Figure 8A**). Besides, their morphology can resemble carcinoma, sarcoma or even melanoma [3]. Molecular analysis plays an important role in assistance for diagnosis and predicting the prognosis of the anaplastic meningiomas, including telomerase reverse transcriptase (TERT) promoter mutation and homozygous deletion of *CDKN2A* and/or *CDKN2B* [3].

### 10.1 Rhabdoid meningioma

It is an aggressive meningioma with an ill-defined eosinophilic cytoplasmic inclusion, globular or fibrillar in texture. Often with necrosis and active mitotic activity (**Figure 8B**). In tumor pathology, almost all tumors with rhabdoid features have aggressive behavior and poor prognosis.

### 10.2 Papillary meningioma

This rare subtype of meningioma, like other papillary tumors, has a fibrovascular core, and the tumor cells have a perivascular arrangement of epithelial tumor cells resembling the pseudo rosettes of ependymoma (**Figure 8C**). This subtype of tumor has a potential to recurrence and metastasis to other organs [6]. Extracranial metastases to lung, pleura, bone and liver are rare but most often associated with CNS WHO grade 3 meningiomas. In one series, the incidence of metastases from all meningiomas was 0.67%, with a greater incidence in CNS WHO grade 2 and grade 3 meningiomas [1].

## 11. Other dura-based tumors like meningioma

Both solitary fibrous tumor (SFT) and hemangiopericytoma (HPC) used to be subtypes of meningiomas. They have been separated from meningioma due to

different molecular genetics and immunohistochemical staining patterns. Those two tumors are positive for CD34 and with nuclear expression of STAT6 by immunohistochemical stain and both have fusion of *NAB2* and *STAT6*. Currently, these two tumors are considered as one entity with different presentation, while SFT is in the benign end, the HPC is more aggressive and has frequent recurrence [1]. In addition, they may occur in the other organs of the human body.

## 12. Metastatic carcinomas to meninge and meningioma

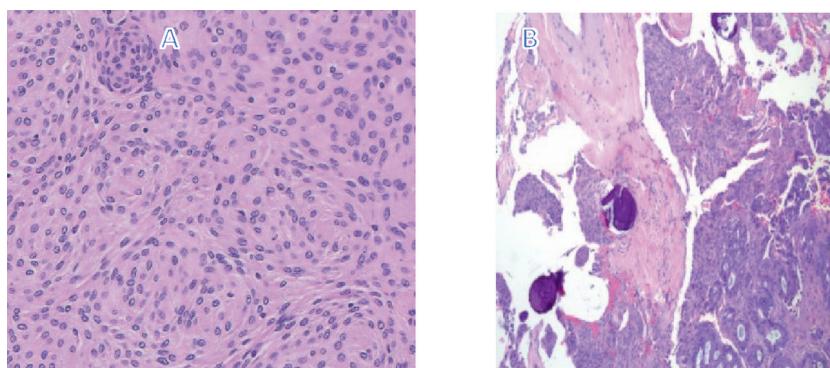
Both breast cancer and prostate cancer have great potential to metastasis to dura. The breast cancer, followed by lung adenocarcinoma are the tumors documented most likely to metastasizes into meningioma, probably due to the hormonal reason. Those so-called collision tumors may cause some diagnostic difficulty, and immunohistochemical stains are required to detect the primary tumor (**Figure 9B**).

### 12.1 Skull-base meningiomas

Skull-base meningioma has its growth and histopathologic characteristics with different treatment methods. It leads to functional disturbance which significantly alters the quality of life. Although no being set up as a subtype, it is worth mentioning here.

The skull base is the floor, or base, of the skull located behind the eyes and nose, composed of five bones – the frontal, ethmoid, sphenoid, temporal and occipital – that provide support to the bottom of the brain, and contains many bony structures, blood vessels and nerves. The skull base is also called “fossa” and are separated into 3 fosses, including anterior, middle and posterior fosses. The anterior and middle fosses usually referred as “supratentorial”. While the posterior fossa (inferior tentoria) contains cerebellum, part of brainstem and 4th ventricle, meningiomas may happen in posterior fossa although relatively uncommon (**Figure 2C**). Middle cerebral fossa meningioma may cause hearing loss or ringing in the ears, memory loss or weakness of arms and legs. Due to the complex bony structure, vessels and nerves, complete resection (GTR) of skull-base meningiomas may sometimes be challenging.

Middle cerebral fossa tumors may cause memory loss, and hearing defect, while posterior fossa tumors can lead to hearing defect, and dizziness.



**Figure 9.**  
Skull-base meningioma is with incomplete whorl as a nodule (A, H&E X200), a collision tumor of metastatic adenocarcinoma of lung primary into meningioma (B, H&E X200).

Skull base meningiomas may have different histopathologic features compared to the convexity meningiomas, such as, skull-base meningioma has less well-formed meningotheelial whorls (**Figure 9A**), compared to complete meningotheelial whorls as seen in (**Figure 3A and B**), probably due to its growth condition, but the incomplete larger nodules resemble the whorls (**Figure 9A**).

### 13. Clinical management of meningiomas

Management of meningiomas varies based on several factors, including the extent and severity of symptoms and signs, tumor size and location. Some meningiomas are asymptomatic while other tumors can cause location-specific neurologic deficits, general non-specific symptoms or both. Location-specific symptoms can result in visual disturbances, hearing loss, aphasia, hemiparesis or hemi-sensory changes. More generalized symptoms that frequently occur include headache, nausea/vomiting, dizziness, and seizures. Seizures occur in 30–40% of meningioma patients [7].

Meningioma management can include observation by monitoring the tumor with regular imaging. Some meningiomas are followed by observation, particularly those that are small, incidental, and asymptomatic in nature. For larger, symptomatic tumors or for tumor progression or in tumor recurrence, the two most common treatment modalities include surgery and radiation therapy. Chemotherapy is becoming a more common treatment modality in recurrent meningiomas with an increase in molecular testing for targeted treatment.

Surgical resection is the primary treatment modality in symptomatic tumors. Careful consideration is required to determine if symptoms can be localized to the tumor or associated peritumor edema. The tumor location, amount of safe resection and the patient's overall health, including medical comorbidities, age, and performance status are used to determine the surgical risk vs. benefit for tumor resection. The surgical approach varies based on tumor size and location. Meningiomas that are located along the convexity of the calvaria vault are more accessible but are also associated with an increased risk of vascular injury in midline convexity tumors due to the proximity to major venous sinuses like the superior sagittal sinus. Meningiomas that grow along the base of the skull also pose an increased risk of a neurologic deficit given the proximity and involvement of cranial nerves and vessels that transverse the skull at its base [8].

The second common treatment approach includes radiotherapy. Radiotherapy is typically considered as the primary treatment if the tumor is not able to be safely resected based on the location, size, or when a patient is a poor surgical candidate to obtain disease control. Additionally, radiation therapy is also considered post-surgically if maximal resection is not achieved, tumor has recurrence or in cases of inoperable locations, and high grades. Radiosurgery or stereotactic radiotherapy in single or multiple doses may be appropriate in small tumors whereas external beam radiotherapy is more appropriate for recurrent, multiple or extensive lesions with a dose of up to 70 Gy for grade 2/3 meningiomas [9].

The use of chemotherapy in meningiomas remains an area of unmet need. Chemotherapy is typically used in the treatment of recurrent meningioma supported by national comprehensive cancer network (NCCN) guidelines, with several options including sunitinib, bevacizumab, octreotide, and combination therapy like bevacizumab combined with everolimus. Additional research is needed to identify potential targeted treatment based on the molecular characteristics and the genetic mutations previously associated with meningiomas including *NF2*, *SMO*, *TERT*, and *TRAF7* [9].

Symptom management in meningiomas can be challenging. Several common neurological symptoms seen in this patient population include seizures, headaches and mood disorders. Brain tumor-related seizures can be treated with anti-epileptic medication or surgery to reduce tumor burden and to relieve associated mass effect. Anticonvulsant is typically recommended in patients with brain tumor who have experienced at least one seizure. There is no consensus on antiepileptic medication selection as several factors must be taken into consideration including age, psychological history and drug-drug interactions. New generation of anticonvulsants like levetiracetam, lacosamide, clobazam and vigabatrin are typically used as the first line with fewer drug-drug interactions [10]. Headaches are usually multifactorial but a high percentage of headaches in brain tumors are associated with vasogenic edema. As such, careful consideration of treatment options must be exercised when treating headaches. Corticosteroids effectively reduce cerebral edema and are often used in patients with brain tumor. Dexamethasone is often chosen for its long biological half-life, and low mineralocorticoid activity [11]. Mood disorders are also commonly seen in brain tumor patients. Mood disorder can be related to the direct tumor effect on neurologic functions, although the exact relationship between mood and tumor location remains unclear. Additionally, mood disorders can be triggered or exacerbated by medications, including steroids and antiepileptic medications like levetiracetam, making these disorders challenging to treat effectively. Typical medications used in the meningioma include antidepressants (SSRIs), antipsychotics, mood stabilizers or anxiolytic agents [11].

In conclusion, meningiomas are very common primary brain tumors. Its molecular genetics, clinical presentation, diagnosis and grading have been studied for a while, and the standard of care has been well-established. New information, especially molecular information becomes more and more commonly used in our practice, which provides new insight into this tumor. We believe as more information helps us to understand this tumor, it will become a manageable tumor soon.

## Abbreviations

CNS	Central nervous system
CSF	Cerebrospinal fluid
SSS	Superior sagittal sinus
MRI	Magnetic resonance imaging
CT	Computed tomography
WHO	World Health Organization
FISH	Fluorescent in situ hybridization
GTR	Gross total resection
HPV	High power view
MEP	Meningioma en plaque
IHC	Immunohistochemical stain
GFAP	Glial fibrillary acidic protein
NF2	Neurofibromatosis 2

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